Effects of Dopamine $D_1$-like and $D_2$-like Agonists in Rats that Self-Administer Cocaine

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ABSTRACT
The reinforcing effects of $D_1$-like and $D_2$-like agonists, and their capacity to modify cocaine self-administration, were compared in rats with extensive cocaine self-administration experience. Cocaine (0.01–1.0 mg i.v.) dose-dependently maintained responding under a fixed ratio (FR) 5 schedule of reinforcement, and an inverted U-shaped function characterized the relationship between unit dose and self-administration behavior. When substituted for cocaine, the $D_1$-like agonists SKF 82958 (0.001–0.032 mg i.v.) and SKF 77434 (0.001–0.1 mg i.v.) did not maintain responding above levels observed during saline substitution. In contrast, the $D_2$-like agonists quinuclidine (0.001–0.1 mg i.v.) and 7-hydroxy-dipropylaminotetralin (7-OH-DPAT; 0.01–0.32 mg i.v.) reliably maintained i.v. self-administration behavior that was characterized by inverted U-shaped dose-effect functions. Pretreatment with the $D_1$-like agonists SKF 82958 and SKF 77434 (0.1–1.0 mg/kg i.p.) shifted the dose-effect function for cocaine self-administration downward, whereas pretreatment with the $D_2$-like agonists quinuclidine (0.01 mg/kg i.p.) and 7-OH-DPAT (0.32–1.0 mg/kg i.p.) shifted the cocaine dose-effect function to the left. Effects of $D_1$-like and $D_2$-like agonists on patterns of responding maintained by cocaine (0.32 mg i.v.) also differed: $D_1$-like agonists increased the latency to the first response but did not otherwise alter patterns of cocaine self-administration, whereas $D_2$-like agonists increased the intervals between self-administered cocaine injections. The results suggest that $D_2$-like agonists, but not $D_1$-like agonists, have prominent reinforcing effects and enhance the effects of self-administered cocaine in rats with extensive cocaine self-administration experience. Consequently, $D_2$ receptor-related neuronal mechanisms may be especially important in mediating the abuse-related effects of cocaine.

Drug self-administration procedures have been useful for investigating the neurobiological and pharmacological mechanisms underlying the reinforcing effects of cocaine, and such information may lead to the development of new and effective medications for cocaine abuse and dependence (Mello and Negus, 1996; Mendelson and Mello, 1996). Cocaine nonspecifically blocks the reuptake of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin (Taylor and Ho, 1978); however, the reinforcing effects of cocaine have been most compellingly related to its action as an indirect dopamine agonist (Wise and Bozarth, 1987; Koob, 1992). In this regard, the potency with which many monoamine reuptake inhibitors serve as i.v. reinforcers is highly correlated with their binding to the dopamine transporter (Ritz et al., 1987; Bergman et al., 1989). Moreover, in contrast to selective dopamine reuptake inhibitors, selective norepinephrine and serotonin reuptake inhibitors have not been shown to produce reinforcing effects in drug self-administration procedures.

Studies with direct dopamine receptor agonists offer another pharmacological method for elucidating the neurobiological mechanisms underlying the abuse-related effects of cocaine. In contrast to cocaine or other dopamine reuptake inhibitors, which increase the activation of dopamine receptors nonspecifically, direct dopamine agonists can be used to selectively activate $D_1$-like ($D_1$, $D_3$) or $D_2$-like ($D_2$, $D_3$, $D_4$) receptors which, in turn, have different anatomical and functional characteristics. For example, $D_1$-like agonists modulate the expression of dynorphin and Substance P within striatopallidal neurons, whereas $D_2$-like agonists regulate enkephalin expression within striatopallidal neurons (Gerfen et al., 1990). In addition, $D_1$ receptors are positively coupled with adenylyl cyclase through stimulatory G-proteins, whereas $D_2$ receptors are negatively coupled to adenylyl cyclase through inhibitory G-proteins (Schwartz et al., 1992). Moreover, adaptations in these different systems occur in response to chronic cocaine administration (Terwilliger et al., 1991; Nestler and Aghajanian, 1997). Thus, studies with selective

ABBREVIATIONS: 7-OH-DPAT, 7-hydroxy-dipropylaminotetralin; FR, fixed ratio; $A_{50}$, dose calculated to produce 50% of the measured effect; TO, timeout.
D₁-like and D₂-like agonists may provide one way to clarify the roles of distinct neural pathways and molecular mechanisms involved in cocaine addiction. Although it is generally believed that both D₁-like and D₂-like receptor mechanisms may be involved in the reinforcing and other behavioral effects of cocaine, recent studies suggest that D₁-like and D₂-like agonists have differing profiles of cocaine-related actions. On the one hand, both D₁-like and D₂-like agonists have been reported to maintain i.v. self-administration in animals previously trained to self-administer cocaine (Woolverton et al., 1984; Self and Stein, 1992; Caine and Koob, 1993, 1995; Weed and Woolverton, 1995; Nader and Mach, 1996), and this is consistent with findings that both D₁-like and D₂-like receptor blockers seem to antagonize cocaine self-administration behavior (Bergman et al., 1990; Caine and Koob, 1994). On the other hand, D₁-like agonists may not maintain responding as robustly or under as wide a range of conditions as was reported for cocaine and D₂-like agonists (Grech et al., 1996). In addition, in both rats and monkeys, D₁-like agonists may attenuate the ability of cocaine to reinitiate responding after extinction of cocaine self-administration whereas D₂-like agonists appear to enhance this effect of cocaine (Self et al., 1996; Barrett-Larimore and Spealman, 1997). These latter results agree with previous findings that D₂-like agonists produced leftward shifts in the dose-effect function for cocaine self-administration (Caine and Koob, 1995; Caine et al., 1997). The effects of D₁-like agonists on cocaine self-administration are unknown, but, based on results from the studies described above, D₁-like agonists may differ qualitatively from D₂-like agonists in the manner by which they modify the abuse-related effects of cocaine.

The present study was designed to further evaluate differing roles of D₁-like and D₂-like receptors in mediating the abuse-related effects of cocaine by systematically comparing the effects of D₁-like and D₂-like agonists in rats trained to self-administer cocaine. First, D₁-like or D₂-like agonists were substituted for cocaine in rats with extensive cocaine self-administration experience to rigorously evaluate and compare the reinforcing effects of these agents. Second, modification of the reinforcing effects of cocaine by D₁-like and D₂-like agonists was studied by assessing the effects of pretreatments on full dose-effect functions for cocaine self-administration. In general, the results of this study suggest that D₂-like agonists, but not D₁-like agonists, maintain self-administration and enhance the effects of self-administered cocaine in rats with extensive cocaine self-administration training. These results are consistent with those from parallel studies in which the cocaine-discriminative stimulus generalized to D₂-like agonists, but not D₁-like agonists, in rats with extensive cocaine discrimination training (Caine et al., unpublished observations).

Materials and Methods

Animals

Cocaine self-administration studies were conducted in 32 male Wistar rats (Charles River, Wilmington, MA). The rats weighed approximately 350 g at the start of the study and were maintained in the range of 400 to 600 g with once-daily feedings of standard rat chow (Rat Diet 5012; PMI Feeds, Inc., St. Louis, MO). Bacon-flavored biscuits (Bio-Serve, Frenchtown, NJ) were also provided once or twice weekly, primarily for enrichment. Each rat was housed individually with free access to water in a temperature- and humidity-controlled facility that was maintained on a 12-h light/dark cycle (lights on from 7:00 AM to 7:00 PM). Behavioral testing generally began toward the end of the light cycle (4:00 PM to 6:00 PM). Animal maintenance and research were conducted in accordance with the guidelines provided by the National Institutes of Health Committee on Laboratory Animal Resources, and all protocols were approved by the Institutional Animal Care and Use Committee. The health of the rats was periodically monitored by consulting veterinarians.

Apparatus

Drug self-administration studies were conducted in experimental chambers (21 cm × 29.5 cm × 24.5 cm) placed within sound-attenuating cubicles equipped with a house light and an exhaust fan. Each chamber contained three response levers. On one wall of the chamber, two levers were located on either side of a pellet receptacle, 3 cm above the grid floor and 1.5 cm from the side walls. During preoperating training, responding on either of these two levers was maintained by 45-mg food pellets (A/R Rodent Pellets; P. J. Noyes Co., Lancaster, NH) that were delivered by a pellet dispenser (ENV-203) to the food receptacle located between the two levers and 2 cm above the floor. A third lever, which was used for drug-maintained responding, was located on the center of the opposite wall, 3 cm above the floor. A single white stimulus light located above each lever was used to indicate that responding had scheduled consequences.

A single-channel fluid swivel (Lomir Biomedical, Malone, NY) was mounted on a balance arm above the chamber and attached to a spring lead with an inner Tygon tubing. The other end of the swivel was connected to an infusion pump that permitted automated delivery of i.v. drug injections for specified durations (see below). The infusion pump (PHM-100; 3.3 rpm motor) and all other components of the operant chambers and associated hardware were supplied by MED Associates Inc. (Georgia, VT). Scheduling of experimental events and data collection were accomplished with a DOS-based microcomputer system that was equipped with programs written in MED Associates MedState Notation.

Drug Self-Administration Procedures

Summary of Groups and Procedures. All rats were first allowed to respond in 2-h drug self-administration sessions (5–6 days per week) with a single unit dose of cocaine (0.32 mg per injection; approximately 1.0 mg/kg/injection). After stable self-administration behavior was established (see below), the rats were divided into two groups of 16 rats each. One group of rats was trained further, with a multiple-component drug self-administration procedure. In this procedure, the unit dose of cocaine was varied during the test session to obtain cocaine self-administration dose-effect functions. After stable cocaine dose-effect functions were established (see below), D₁-like and D₂-like dopamine agonists were either substituted for cocaine or administered as pretreatments to cocaine self-administration, until at least eight rats had been tested with each of the following dopamine agonists: SKF 82958, SKF 77434, quinelorane, and 7-hydroxy-dipropylaminotetralin (7-OH-DPAT). The benzazepine D₁-like agonist SKF 82958 was extensively studied, because this agent was previously shown to maintain responding, and additionally, to attenuate cocaine’s reinstating effects after extinction of cocaine self-administration in both rats and monkeys (Weed and Woolverton, 1995; Grech et al., 1996; Self et al., 1996; Barrett-Larimore and Spealman, 1997). SKF 77434, a relatively low-efficacy D₁ dopamine agonist, was reported to support drug self-administration in rats, but not in primates (Self and Stein, 1992; Weed and Woolverton, 1995). For comparison with D₁-like agonists, the D₂-like agonists quinelorane and 7-OH-DPAT were chosen, because these drugs maintained responding and/or enhanced the effects of self-administered cocaine in both rats and monkeys (Caine and Koob, 1995; Parsons et al., 1996; Nader and Mach, 1996; Caine et al., 1999b).
Rats in the second group were pretreated with dopamine agonists before cocaine self-administration sessions that were identical with training sessions (see below) until at least six rats had been pretreated with each of the following compounds: SKF 82958, SKF 77434, R-6-Br-APB, SKF 81297, and quinolinole. Compared with SKF 82958 and SKF 77434, respectively, both R-6-Br-APB and SKF 81297 have high selectivity and efficacy at D1 receptors. These compounds were included to expand the number of D1-like agonists that were evaluated. Rats were randomly assigned to different substitution drugs or pretreatment drugs in a counterbalanced fashion until the designated group size was obtained for each test drug. Typically, all doses of a drug were tested in a rat before that rat was assigned a new drug for substitution or pretreatment tests. Data were analyzed and presented only for rats in which tests with all doses of a drug had been completed (within-subjects, Latin square-based design).

Preoperative Training. Lever responding was initially shaped by using food reinforcement. During daily 1-h sessions of food availability, the stimulus lights were illuminated above the two levers located on either side of the pellet receptacle, and rats were trained to press either of these two levers under a fixed ratio (FR 1) schedule of food reinforcement. Food training continued until rats earned 100 food pellets in a single session. Rats were then implanted with an i.v. catheter for drug self-administration studies.

Surgery. Rats were anesthetized with an isofluorane/oxygen vapor mixture and prepared with chronic indwelling i.v. catheters as previously described (Caine et al., 1993), with minor modifications (Emmett-Oglesby et al., 1993). Each catheter consisted of a 13-cm length of Silastic tubing fitted to a 22-gauge guide cannula that was bent at a right angle. The guide cannula was encased in dental cement anchored with a 0.5-inch-diameter circular nylon mesh. The tubing was passed s.c. from the animal’s back to the right external jugular vein. All animals were allowed to recover for approximately 7 days before they were given access to i.v. cocaine. After surgery, a prophylactic dose of ticarcillin (20 mg/kg, i.v.) was delivered for 5 days to forestall infection. Thereafter, catheters were flushed daily with sterile physiological saline containing heparin (3 USP U/0.1 ml). If blood could not be withdrawn through the catheter, then catheter patency was tested by administering a solution containing 25 mg/ml ketamine and 1.25 mg/ml midazolam (0.05–0.1 ml, i.v.). Animals with patent catheters exhibited prominent signs of sedation and responding maintained by i.v. cocaine injections under a cue light above the drug self-administration lever was illuminated, and responding on that lever was maintained by i.v. cocaine injections under a FR 1 timeout (TO) 20-s schedule of reinforcement. Under this schedule, completion of the response requirement produced an i.v. infusion of the unit dose of cocaine and initiated a 20-s TO period during which the cue light was turned off and responses had no scheduled consequences. In subsequent training sessions, the response requirement was gradually increased to a FR 5. Each rat was trained until cocaine self-administration behavior stabilized, with stability defined as three consecutive sessions during which there was less than 10% variation in the total number of cocaine reinforcers earned per session.

Multiple-Component Cocaine Self-Administration Training. A procedure for rapid assessment of responding maintained by different doses of cocaine was adapted from a previous study (Caine and Koob, 1995). These multiple-component sessions consisted of three or four 20-min components separated by 2-min TO periods. Dose-effect functions were determined by increasing the volume of cocaine injections in successive components so that 0-, 17-, 56-, or 178-µl injections were delivered in approximately 0, 1, 3, 2, and 10 s, respectively. Drug solutions consisted of 0.56 mg/ml cocaine, 1.78 mg/ml cocaine, or 5.6 mg/ml cocaine, yielding unit doses of 0, 0.01, 0.032, 0.10, 0.32, and 1.0 mg total cocaine per injection (approximately 0.032–3.2 mg/kg/injection). During any one session, different doses of cocaine were always presented in an ascending order, and an injection of the cocaine dose available during each component was noncontingently administered at the beginning of the component. Substitution or pretreatment testing began after drug self-administration behavior stabilized, with stability defined as three consecutive multiple-component sessions during which the dose that maintained peak responding remained stable within a half log-unit range.

Each rat, test drugs were evaluated by studying overlapping ranges of doses across three or four sessions. Each drug was initially substituted for cocaine in two consecutive sessions. If levels of responding maintained by any dose of the substitution drug were observed to be above levels observed during saline substitution, then the substitution drug was studied in the third consecutive session. However, if during the first two substitution sessions with a drug, no dose of the substitution drug maintained responding above levels observed during saline substitution, then multiple-component cocaine self-administration sessions were resumed, and stable cocaine-maintained behavior was re-established before a third session with the substitution drug. For subjects in which self-administration behavior occurred during the third drug substitution test only, the experiment was continued for an additional (fourth) drug substitution test.

Pretreatment Tests. The doses of cocaine available for self-administration during multiple-component sessions were determined by pseudorandom design such that sessions began with unit doses of 0, 0.01, 0.032, or 0.1 mg cocaine. Occasionally, 2-h single-component sessions of cocaine self-administration (see below) or multiple-component sessions of saline availability (0, 17, 56, 178 µl) were interspersed with multiple-component sessions of cocaine self-administration. Pretreatments were administered i.p. (1 ml/kg) immediately before the test session, and included the following drugs and doses: SKF 82958 (0.1, 0.32 mg/kg); SKF 77434 (0.32, 1.0 mg/kg); quinolone (0.0032, 0.01 mg/kg); 7-OH-DPAT (0.01–0.32 mg/injection). In each rat, test drugs were evaluated by studying overlapping ranges of doses across three or four sessions. Each drug was initially substituted for cocaine in two consecutive sessions. If levels of responding maintained by any dose of the substitution drug were observed to be above levels observed during saline substitution, then the substitution drug was studied in the third consecutive session. However, if during the first two substitution sessions with a drug, no dose of the substitution drug maintained responding above levels observed during saline substitution, then multiple-component cocaine self-administration sessions were resumed, and stable cocaine-maintained behavior was re-established before a third session with the substitution drug. For subjects in which self-administration behavior occurred during the third drug substitution test only, the experiment was continued for an additional (fourth) drug substitution test.
providing a sensitive behavioral baseline for the evaluation of pretreatment effects (Caine et al., 1993; Caine and Koob, 1993, 1994). Each pretreatment test was preceded by a baseline session (i.e., a session during which the total number of cocaine reinforcers deviated by ≤ 10% from the most recent session in which no pretreatment was administered). Drugs were administered i.p. (1 ml/kg) immediately before the test session and included SKF 82958 and SKF 81297 (0.032–3.2 mg/kg), SKF 77434 (0.1–3.2 mg/kg), R-6-Br-APB (0.032–1.0 mg/kg), and quinolone (0.0003–0.032 mg/kg). In this set of studies, each dose of a pretreatment drug was tested once in each rat. Doses were administered in a pseudorandom order except for the highest dose of each drug, which was tested last.

**Data Analysis.** Data from multiple-component test sessions were expressed as the total number of drug injections obtained in each 20-min component. For each rat, multiple determinations were averaged. For comparison with data from substitution tests or pretreatment tests, baseline values were averaged from three recent multiple-component self-administration sessions that spanned the entire cocaine dose range, and in which no pretreatments were administered. Reinforcing effects of a drug during substitution test sessions were analyzed with a one-way within-subjects ANOVA using drug dose as the factor. Significant main effects were followed by pair-wise comparisons of responding maintained by saline, with those maintained by each drug dose. Pretreatment effects on the cocaine self-administration dose-effect function were analyzed with a two-way within-subjects ANOVA by using pretreatment dose and cocaine dose as factors. Significant main effects were followed by pair-wise comparisons of each cocaine dose under baseline conditions, with the same cocaine dose under each pretreatment condition. Pretreatment effects on the latency to the first response or the mean interinfusion interval during single-component self-administration sessions were analyzed by a one-way within-subjects ANOVA using pretreatment dose as the factor. Significant main effects were followed by pair-wise comparisons of each drug pretreatment dose with saline pretreatment. The criterion for significance was p < .05 for all analyses (main effects followed by Duncan pair-wise comparisons).

Data from single-component test sessions were expressed as the total number of injections delivered during the 2-h session. A50 values were defined as the dose of a pretreatment drug that decreased the number of cocaine injections obtained in a session to 50% of baseline values. A50 values were generally determined by linear interpolation of a portion of the log dose-effect function for each rat. In three instances, A50 values were determined by extrapolation from values that did not exceed 50% of the maximal effect. Group means and confidence intervals were then calculated from the individual A50 values.

**Drugs.** Cocaine was provided by the National Institute on Drug Abuse, National Institutes of Health. All other drugs (SKF 82958, SKF 77434, R-6-Br-APB, SKF 81297, quinolone, 7-OH-DPAT) were obtained from Research Biochemicals International (Natick, MA). All drugs were dissolved in physiological saline, and, with the exception of cocaine, the saline was warmed to assure dissolution. All doses refer to the weights of the respective salts (cocaine, HCl; quinolone, 2 HCl; all other drugs, HBr).

**Results**

**Effects of Cocaine, D1-like Agonists, or D2-like Agonists Alone (Fig. 1).** Cocaine dose-dependently and reliably maintained responding when the unit dose of cocaine was varied in 20-min components of multiple-component test sessions. Across a 100-fold range of unit doses (0.01–1.0 mg/injection), cocaine produced a stable, inverted U-shaped dose-effect function that is characteristic of drug self-administration data (Fig. 1, left panel). Intermediate doses of cocaine (0.032 and 0.1 mg/injection) maintained the highest levels of cocaine self-administration (10.5 ± 4.4 and 12.2 ± 1.2 injections/20-min component, respectively), which were significantly different from levels produced by saline substitution (p < .01). In comparison with intermediate doses of cocaine, lower (0.01 mg/injection) and higher doses (0.32 and 1.0 mg/injection) maintained lower levels of self-administration that were not statistically different from those observed during saline substitution. However, self-administration of high doses of cocaine differed qualitatively from responding maintained by saline, in that high doses of cocaine produced response patterns characterized by regular interinfusion intervals throughout the entire response period (for more detail, see Fig. 4, below).

When substituted for cocaine, SKF 82958 and SKF 77434 did not consistently maintain drug self-administration behavior, and rates of responding maintained by SKF 82958 and SKF 77434 were not significantly different from rates of responding maintained by saline (p > .05; Fig. 1, middle panel). Inspection of data from individual rats indicated that, in a few instances, D1-like agonists maintained responding above levels typically observed during saline substitution. For example, four rats earned a maximum of between four and nine injections of SKF 82958 (0.001 or 0.0032 mg/injection) and two rats earned a maximum of six injections each of SKF 77434 (0.0032 or 0.032 mg/injection) in a single self-administration component. However, these modest levels of self-administration were not observed during repeated determinations at these doses of SKF 82958 and SKF 77434 in these same rats, and the maximum average value across multiple determinations for an individual rat was 4.0 injections of SKF 77434 and 5.5 injections of SKF 82958.

In contrast to the effects of the D1-like agonists, i.v. injections of the D2-like agonists quinolone and 7-OH-DPAT consistently maintained responding above saline levels and produced inverted U-shaped dose-effect functions (Fig. 1, right panel). Maximal self-administration of the D2-like agonists was maintained by 0.032 mg/injection quinolone (13.7 ± 2.4 injections/20 min component) and 0.1 mg/injection 7-OH-DPAT (6.5 ± 1.0 injections/20-min component). These doses, as well as the next lower dose of each drug, maintained levels of self-administration significantly higher than those observed during saline substitution (p < .05). Inspection of individual data indicated that some dose or doses of quinolone reliably maintained responding above...
saline levels in every rat tested, and 7-OH-DPAT produced this effect in seven of eight rats tested.

Effects of Pretreatment with D<sub>1</sub>-like or D<sub>2</sub>-like Agonists on Cocaine Self-Administration (Fig. 2). Pretreatment with the D<sub>1</sub>-like agonists SKF 82958 and SKF 77434 dose-dependently decreased self-administration of cocaine doses that maintained maximal self-administration behavior, resulting in a downward shift in the cocaine dose-effect function (Fig. 2, left panels). The lower doses of SKF 82958 (0.1 mg/kg) or SKF 77434 (0.32 mg/kg) almost completely eliminated responding maintained by 0.032 mg/injection cocaine, whereas the next higher dose of each D<sub>1</sub>-like agonist significantly decreased responding maintained by both 0.032 and 0.1 mg/injection cocaine. Higher doses of SKF 82958 (1.0 mg/kg) and SKF 77434 (3.2 mg/kg) produced more severe disruptions of behavior and were studied only in experiments with self-administration of a single dose of cocaine (see below).

The effects of both quinelorane and 7-OH-DPAT on cocaine self-administration were dose-dependent. A low dose of quinelorane (0.0032 mg/kg) suppressed responding maintained by 0.032 mg/injection cocaine, but did not alter self-administration of other doses of cocaine. A higher dose of quinelorane (0.01 mg/kg) increased responding in the presence of the cocaine-associated cue-light alone and during availability of a low dose of cocaine (0.01 mg/injection). However, responding maintained by higher doses of cocaine (0.1–0.32 mg/injection) was decreased, resulting in a leftward shift of the cocaine dose-effect function. The effects of a broader dose range of quinelorane pretreatments on the self-administration of a single dose of cocaine (0.32 mg/injection) were further explored in additional experiments (see below). Pretreatment with 7-OH-DPAT (0.32–1.0 mg/kg) produced effects similar to those produced by the higher dose of quinelorane (Fig. 2, right panels). Responding in the presence of the cocaine-associated cue light alone and during availability of the lowest dose of cocaine (0.01 mg/injection) was increased by both doses of 7-OH-DPAT (0.32 and 1.0 mg/kg), resulting in a leftward shift of the cocaine dose-effect function.

Effects of Pretreatment with D<sub>1</sub>-like or D<sub>2</sub>-like Agonists on Patterns of Self-Administration Maintained by a Single Dose of Cocaine (Figs. 3 and 4). Both D<sub>1</sub>-like and D<sub>2</sub>-like agonists decreased self-administration of a dose of cocaine on the descending limb of the cocaine dose-effect function (0.32 mg/injection). When this dose of cocaine was available under control conditions (saline pretreatment), rats self-administered an average of 24.5 ± 0.9 injections in 2 h, and drug intake was distributed evenly throughout the session. Pretreatment with R-6-Br-APB, SKF 77434, SKF 82958, SKF 81297, or quinelorane dose-dependently decreased the number of cocaine injections that were self-administered (Fig. 3). The D<sub>2</sub>-like agonist quinelorane was approximately 2 log units more potent in decreasing cocaine self-administration than were the D<sub>1</sub>-like agonists, whereas potency did not differ significantly among the latter drugs (Table 1).

Although all of the dopamine agonists decreased cocaine self-administration, there were qualitative differences in the effects of D<sub>1</sub>-like and D<sub>2</sub>-like agonists on the patterns of cocaine-maintained responding. For example, the D<sub>1</sub>-like agonist SKF 82958 dose-dependently increased the latency to the first lever response, and slightly decreased interinfusion intervals after responding was initiated (Fig. 4, top panels). In contrast, the D<sub>2</sub>-like agonist quinelorane dose-dependently...
increased both the latency to the first response, and the intervals between cocaine injections during self-administration bouts (Fig. 4, top and bottom panels).

Visual inspection during initial experiments with higher pretreatment doses of SKF 82958 or quinolone revealed the occurrence of intense stereotypies that precluded further self-administration testing. SKF 82958 (3.2 mg/kg) in combination with cocaine (0.32 mg/injection) produced rapid circling movements, prolonged rearing accompanied by side-to-side head movements, and explosive jumping. In some cases, the lever was activated during a stereotypic whole body movement (i.e., jumping). In contrast to the effects of SKF 82958, the D2-like agonist quinolone (0.1 mg/kg), in combination with cocaine (0.32 mg/injection), produced intense focused stereotypies that were characterized by persistent sniffing and licking of the grid floor or the lever. Repetitive paw, head, and oral movements also occasionally resulted in lever responses that continued throughout the session, including during the postreinforcer TO periods.

**Discussion**

**Self-Administration of D2-like Agonists.** In the present study, direct dopamine agonists with high affinity for D2-like receptors maintained i.v. drug self-administration in cocaine-trained subjects in a manner consistent with previous findings in primate and rodent species. For example, a broad range of dopamine D2-like agonists differing in potency and selectivity for D2-like receptors have been shown to reliably maintain self-administration behavior in cocaine-experienced monkeys (Woolverton et al., 1984; Grech et al., 1996; Nader and Mach, 1996). Similarly, in rats with cocaine self-administration experience, the selective D2-like agonists quinpirole and 7-OH- DPAT have been shown to maintain responding with performance described by inverted U-shaped dose-effect functions characteristic for drug self-administration behavior (Caine and Koob, 1993, 1995). The present results extend the latter observations to include the selective D2-like agonist quinolone.

**Self-Administration of D1-like Agonists.** Although the reinforcing effects of D2-like agonists in the present experiments are consistent with previous findings, results with D1-like agonists in this study differ markedly from those in earlier reports. For example, Self and Stein (1992) previously reported that both the D1-like partial agonist SKF 77434 and the full agonist SKF 82958 maintained i.v. self-administration in rats. Moreover, several D1-like agonists (SKF 82958, R-6-Br-APB, SKF 81297) were found to maintain responding under selected conditions in monkeys (Weed and Woolverton, 1995; Grech et al., 1996). However, in the present experiments, SKF 82958 and SKF 77434 clearly did not maintain i.v. self-administration in cocaine-experienced rats. The reasons for these qualitatively different findings are not immediately obvious, but probably do not include dose selection, inasmuch as the doses tested here included all of the doses previously reported to be effective in rats (Self and Stein, 1992).

Differences in behavioral history and schedule parameters may have contributed to the different effects of D1-like agonists in the present and previous studies. For example, rats in the present study had extensive experience with extinction of self-administration behavior during availability of saline injections or low nonreinforcing doses of cocaine, or during illumination of the cue lights in the absence of any injections, before self-administration tests with direct dopamine agonists. Consequently, the separation between levels of cocaine-maintained responding and responding during saline substitution was greater in rats in the present study (>10-fold) than in previous studies (≤3-fold; Self and Stein, 1992). In addition, the FR value was higher and the postreinforcer TO was longer in this study than in previous studies (>10-fold) than in previous studies (≤3-fold; Self and Stein, 1992).

Differences in behavioral history and schedule parameters may have contributed to the different effects of D1-like agonists in the present and previous studies. For example, rats in the present study had extensive experience with extinction of self-administration behavior during availability of saline injections or low nonreinforcing doses of cocaine, or during illumination of the cue lights in the absence of any injections, before self-administration tests with direct dopamine agonists. Consequently, the separation between levels of cocaine-maintained responding and responding during saline substitution was greater in rats in the present study (>10-fold) than in previous studies (≤3-fold; Self and Stein, 1992). In addition, the FR value was higher and the postreinforcer TO was longer in this study than in previous studies of D1-like agonist self-administration in rats. Such schedule parameters may play an important role in drug self-administration studies. For example, increased FR and TO values previously have been shown to attenuate self-administration of low

### Table 1

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<th>Drug</th>
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<tr>
<td>SKF 81297</td>
<td>2.41</td>
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**Fig. 4.** Comparison of the effects of pretreatments with the D1-like agonist SKF 82958 or the D2-like agonist quinolone on patterns of responding maintained by 0.32 mg/injection cocaine. Abscissae (top panels), dose of pretreatment drug in mg/kg (log scale). Points above “S” show data obtained after saline pretreatment. Ordinate (top left panel), latency from the start of the session to the first lever press in minutes. Ordinate (top right panel), average interval that separated cocaine infusions in minutes. Values shown are group means (± S.E.), calculated from single determinations in each of the same eight rats. Asterisks indicate significant differences from responding after saline pretreatment by Duncan’s pair-wise comparison after a significant main effect of dose (*p < .01, **p < .005). The bottom panel shows event records from self-administration sessions of a representative rat to illustrate the qualitative differences in the effects of the D1-like and D2-like agonist pretreatments on cocaine self-administration. Horizontal lines denote time, and each downward tick represents the delivery of one cocaine injection. The type of pretreatment is printed above each event record.
doses of cocaine in rats (Caine and Koob, 1994). Furthermore, in previous studies in monkeys, the reinforcing effects of the D_{2-like} agonist SKF 81297 were clearly evident under a fixed-ratio schedule, but not under a more demanding second-order schedule of reinforcement. In contrast, cocaine and D_{2-like} agonists maintained self-administration under both schedules (Grech et al., 1996). In conjunction with such previous findings, the present results support the view that the range of conditions across which D_{1-like} agonists maintain self-administration behavior may be more limited than for cocaine or for D_{2-like} agonists.

**Modification of Cocaine Self-Administration by Pretreatment with D_{2-like} Agonists.** Consistent with previous findings, pretreatment with D_{2-like} agonists shifted the dose-effect function for cocaine self-administration to the left (Caine and Koob, 1995; Caine et al., 1997, 1999). The effects of D_{2-like} agonists on cocaine self-administration depended on the pretreatment dose as well as the unit dose of cocaine. A low dose of quinelorane slightly suppressed responding maintained by a low cocaine-dose, an effect that may be due to a preferential action at D_{2-like} autoreceptors to reduce postsynaptic dopaminergic tone (Eilam and Szechtman, 1989; De poortere et al., 1996). In contrast, higher doses of quinelorane or 7-OH-DPAT, which presumably increase postsynaptic D_{2-like} dopaminergic receptor activation, increased responding maintained by low cocaine doses and dose-dependently increased interjection intervals during self-administration of a higher dose of cocaine (0.32 mg/injection). This profile of effects is characteristic for D_{2-like} agonists in rats (Caine and Koob, 1993, 1995; Parsons et al., 1996; Caine et al., 1997), and similar effects of quinelorane and 7-OH-DPAT have recently been observed in rhesus monkeys (Caine et al., 1999). Collectively, these findings suggest that pretreatment with D_{2-like} agonists may augment the reinforcing effects of cocaine.

Behavioral effects of D_{2-like} agonists other than enhancement of cocaine’s reinforcing effects also probably contributed to the modification of cocaine self-administration in the present study. For example, in addition to increasing the self-administration of low doses of cocaine, quinelorane and 7-OH-DPAT also increased responding maintained by the cocaine-associated cue light alone, suggesting that the D_{2-like} agonists at least partly affected response rates independently of interactions with cocaine. There are at least three likely explanations for these effects of D_{2-like} agonists in the absence of cocaine. First, D_{2-like} agonists produce cocaine-like discriminative stimulus effects (see Caine et al., 1999a), and these discriminative stimulus effects may have elicited responding even in the absence of cocaine. Second, D_{2-like} agonists may have enhanced the conditioned-reinforcing effects of cocaine-associated stimuli such as the cocaine-associated cue light (Robbins and Everitt, 1992). Third, D_{2-like} agonists may have increased low rates of responding as a result of their rate-altering effects on schedule-controlled behavior (Bergman et al., 1995). Thus, in the absence of cocaine or when low doses of cocaine were available for self-administration, multiple effects of D_{2-like} agonists may have contributed to an increase in responding. In combination with higher doses of cocaine, D_{2-like} agonists apparently supplemented the behavioral effects of self-administered cocaine.

**Modification of Cocaine Self-Administration by Pretreatment with D_{1-like} Agonists.** In contrast to the effects of D_{2-like} agonists on cocaine self-administration, the D_{1-like} agonists SKF 77434 and SKF 82958 decreased responding maintained by a broad range of doses of cocaine, and produced downward shifts in the cocaine dose-effect function. Notably, the D_{1-like} agonists SKF 77434 and SKF 82958 have been reported to differ in agonist efficacy, yet had similar effects on cocaine self-administration in the present study. These findings are consistent with previous results indicating that efficacy-based differences in behavioral effects of D_{1-like} agonists may be a less relevant factor for the modification of cocaine’s effects in rats than in monkeys. In monkeys, for example, low-efficacy D_{1-like} agonists including SKF 38393 and SKF 75670, such as the D_{1-like} receptor blocker SCH 39166, have been shown to surmountably antagonize the behavioral effects of self-administered cocaine, resulting in rightward shifts in dose-effect functions for cocaine self-administration (Katz and Witkin, 1992; Bergman and Rosenzweig-Lipson, 1992). In rats, however, the low-efficacy agonist SKF 77434 produces behavioral effects that are qualitatively similar to those produced by high-efficacy agonists including SKF 82958 (see Waddington et al., 1995, for review). In view of the similar agonist effects of SKF 77434 and SKF 82958 in rats, the present results suggest that reductions in cocaine self-administration produced by D_{1-like} agonists, in contrast to those produced by D_{1} receptor blockers, may not be surmountable by increased doses of cocaine (Bergman et al., 1990; Caine and Koob, 1994).

As with D_{2-like} agonists (see above), behavioral effects of D_{1-like} agonists that are unrelated to the reinforcing effects of cocaine also probably contributed to altered cocaine self-administration in the present study. For example, doses of SKF 82958 and SKF 77434 that decreased cocaine self-administration in the present study also were shown to decrease responding maintained by food in drug discrimination studies in rats (Terry et al., 1994; Caine et al., unpublished observations). In addition, doses of D_{1-like} agonists that decrease cocaine self-administration in rhesus monkeys also decreased food-maintained responding during the same test sessions (Caine et al., 1999). In the present study, the pattern of cocaine self-administration after pretreatment with D_{1-like} agonists was characterized by an increased latency to initiate cocaine self-administration, followed by responding that was similar to baseline performance. In view of the above findings, this pattern of behavior likely resulted from a nonselective, albeit transient, disruption of behavior. The relationship between such behavioral disruption by D_{1-like} agonists and their modification of cocaine’s reinforcing effects is currently unknown. Accordingly, further studies designed to assess the selectivity of D_{1-like} agonist-induced decreases in cocaine self-administration are warranted.

**Implications for Neurobiological Mechanisms Underlying Cocaine’s Reinforcing Effects.** The different effects of D_{1-like} and D_{2-like} agonists in assays of cocaine self-administration and cocaine discrimination may support the results of previous studies aimed at identifying the neuroanatomical and molecular bases of the abuse-related effects of cocaine. For example, D_{2-like} agonists, but not D_{1-like} agonists, regulate gene expression within striatopallidal neurons (Gerfen et al., 1990), and a critical role for the ventral pallidum in cocaine self-administration has been proposed...
In addition, D₁-like agonists inhibit adenyl cyclase through activation of inhibitory G proteins, whereas D₂-like receptors are positively linked to adenyl cyclase through stimulatory G proteins. Inhibitory G proteins have been proposed as a common signal-transduction mechanism for the reinforcing effects of abused drugs, and inactivation of inhibitory G proteins in the nucleus accumbens attenuates some behavioral effects of self-administered cocaine (Self et al., 1994; Self and Nestler, 1995). The present results and those from a companion study of cocaine discrimination (Caine et al., unpublished observations) indicate that D₂-like agonists produce prominent reinforcing effects and cocaine-like discriminative stimulus effects in cocaine-trained animals. Consequently, these findings support previous results and suggest that D₂ receptor-expressing pathways (e.g., striatopallidal neurons) and D₂ receptor-linked molecular events (e.g., inhibitory G proteins) may be especially important in mediating the abuse-related effects of cocaine.

Summary. In the present study, D₁-like and D₂-like dopamine agonists produced different behavioral effects in rats trained under a FR schedule of cocaine-maintained responding. When substituted for cocaine, D₂-like agonists dose-dependently and reliably maintained i.v. self-administration, whereas D₁-like agonists failed to consistently maintain responding. When administered as pretreatments, D₂-like agonists increased self-administration of low doses of cocaine and also appeared to enhance the behavioral effects of higher doses of cocaine. In contrast, D₁-like agonists only decreased self-administration across a broad range of doses of cocaine. The present results are consistent with results of a companion study in rats trained to discriminate cocaine from saline (Caine et al., unpublished observations), in which D₂-like agonists readily substituted for and enhanced the effects of cocaine under a wider range of conditions than did D₁-like agonists. Collectively, these findings suggest that the behavioral effects of cocaine overlap with those of D₂-like agonists to a greater extent than with those of D₁-like agonists.

Acknowledgments

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References
