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Dopaminergic Mechanism for Caffeine-Produced Cocaine Seeking in Rats

Thomas A. Green, M.S., and Susan Schenk, Ph.D.

Systemic administration of caffeine reinstates extinguished cocaine self-administration behavior in rats, but the mechanism mediating this behavioral effect has not been established. The present study examined the role of adenosinergic A2 and dopaminergic mechanisms in caffeine-produced cocaine seeking. Following extinction of cocaine self-administration, experimenter-administered injections of caffeine (1.25–20 mg/kg) and theophylline (1–10 mg/kg) dose-dependently reinstated extinguished cocaine-seeking behavior. Administration of the adenosinergic A2 antagonist, 3,7-dimethyl-1-propargylxanthine (DMPX; 0.546–2.18 μg/kg), failed to produce cocaine seeking. Pretreatment with doses of the adenosine A1/A2 agonist 5′-N-ethylcarboxamidoadenosine (NECA; 0.003–0.03 mg/kg) that were below those that produced marked sedation failed to block reinstatement. These data suggest that methylxanthine-produced cocaine seeking is not due to adenosine A2 receptor antagonism. In contrast, pretreatment with the dopaminergic D1-like antagonist SCH 23390 (0.005–0.02 mg/kg) or the D2-like antagonist eticlopride (0.03–0.3 mg/kg) produced a dose-dependent attenuation of caffeine-produced reinstatement at doses that did not decrease cocaine self-administration. These findings suggest that dopaminergic mechanisms underlie the ability of caffeine to reinstate extinguished cocaine-taking behavior.

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KEY WORDS: *Relapse; Reinstatement; Drug seeking; Caffeine; Cocaine; Adenosine; Dopamine; Drug abuse*

A high rate of relapse to cocaine abuse continues to be a major deterrent to effective long-term treatment. In the laboratory, exposure to cocaine (Jaffe et al. 1989) and caffeine (Rush et al. 1995) produce cocaine craving in experienced users. These effects have been modeled in animals (see Markou et al. 1993 for review) to examine the mechanisms underlying the ability of exposure to some drugs to initiate drug seeking. Ultimately it is hoped that identification of these mechanisms will lead to more effective pharmacotherapies to prevent relapse to cocaine abuse.

One procedure (de Wit and Stewart 1981) examines the ability of various stimuli to reinstate extinguished drug-taking behavior. Experimenter-administered injections of indirect dopaminergic agonists such as cocaine, amphetamine, and methylphenidate (Schenk and Partridge 1999), as well as a number of direct dopaminergic D2-like receptor agonists including bromocriptine (Wise et al. 1990), 7-OH-DPAT (Self et al. 1996) and quinpirole (Self et al. 1996; De Vries et al. 1999) led to cocaine seeking. The dopamine transporter blocker GBR 12909 and the cocaine analogs WIN 35,428 and RTI-55 (Schenk et al. 2000) also produced cocaine seeking. A dissociation between a role of dopamine D1-like and D2-like receptors has been suggested since D2-like,

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but not D1-like, agonists reinstated extinguished cocaine-taking behavior (Self et al. 1996; DeVries et al. 1999). Further, D1-like agonists and antagonists, but not D2-like antagonists, attenuated reinstatement of cocaine-seeking behavior in rats (Self et al. 1996) and in squirrel monkeys (Khroyan et al. 2000).

Reinstatement of extinguished cocaine-taking behavior was also produced following administration of caffeine to laboratory rats (Worley et al. 1994; Self et al. 1996; Schenk et al. 1996; Schenk and Partridge 1999). The primary effect of low doses of caffeine is blockade of adenosine receptors with secondary effects on a number of neurochemical systems (see Daly 1993 for review), and many of the behavioral effects of caffeine and other methylxanthines are correlated with their potency as adenosine antagonists (Snyder et al. 1981; Katims et al. 1983; Mumford and Holtzman 1991b). Secondary to this effect at adenosine receptors, caffeine also has effects on dopaminergic substrates (Fuxe et al. 1998) via interactions between adenosine A2 and dopamine D2 receptors (Ferre et al. 1991, 1993; Dasgupta et al. 1996; Fuxe et al. 1998). The ability of caffeine to reinstate extinguished cocaine-taking behavior might be related to these effects, particularly in light of the hypothesized role of activation of dopamine D2 receptors in cocaine seeking.

The present study was undertaken to examine the contribution of adenosinergic and dopaminergic mechanisms in caffeine-produced cocaine seeking. The ability of adenosine antagonists to produce cocaine-seeking behavior and of dopamine antagonists to attenuate cocaine seeking was measured.

METHODS

Subjects

Male Sprague-Dawley rats (Harlan, TX) weighing 325–350 g were used. They were housed individually in hanging polycarbonate cages. The humidity and temperature controlled colony at Texas A&M University was kept in a 24-h lights-on condition. Food and water were freely available except during testing. Experimental protocols were in strict accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the Texas A&M University Institutional Laboratory Animal Care Committee.

Surgery

A Silastic catheter was implanted in the right jugular vein. Briefly, the rats were deeply anesthetized with ketamine (60.0 mg/kg) and pentobarbital (20.0 mg/kg). The external jugular vein was isolated and the catheter was inserted. The distal end (22 ga stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler's screws with dental acrylic. Each day, the catheters were infused with 0.1 ml of a sterile saline solution containing heparin (30.0 U/ml), penicillin G potassium (250,000 U/ml) and streptokinase (8000 IU/ml) to prevent infection and the formation of clots and fibroids. The rats were allowed five days after surgery for recovery.

Self-Administration

Self-administration testing was carried out in operant chambers (Med Associates, ENV-001) equipped with two levers. Depression of one lever (the active lever) resulted in an intravenous infusion of cocaine HCl, dissolved in sterile physiological saline with heparin (0.5 U/ml). Depression of the other lever (the inactive lever) was without programmed consequence. Drug delivery and data acquisition were controlled by the OPN software package (Spencer and Emmett-Oglesby 1985). Cocaine deliveries were made by mechanical pumps (Razel, Model A with 1 rpm motor equipped with 20.0 ml syringes). These pumps delivered 0.1 ml infusions over a 12 s duration. A stimulus light located above the active lever was illuminated during each 12 s infusion. Responses emitted during infusions were without programmed consequences.

Acquisition of cocaine self-administration proceeded during daily 2-h tests. Each test began with an experimenter-delivered infusion of cocaine. Thereafter, cocaine infusions (0.5 mg/kg/infusion) were delivered according to an FR-1 schedule of reinforcement by depression of the active lever. Criteria for acquisition consisted of at least 30 reinforced responses during the 2-h session and a ratio of active:inactive lever responses of at least 2:1. These criteria were generally achieved within 5–10 days. The response requirements were then increased to FR-5 and 2-h daily tests were conducted until there was less than 20% variation in the number of active lever responses across three consecutive days. At that time, behavior was considered stable. The cocaine infusion was always paired with the illumination of a stimulus light located directly above the active lever.

Drug-Produced Cocaine Seeking

Once responding on the FR-5 schedule was stable, the ability of various drug primes to elicit drug-seeking behavior was measured. This test was conducted in a single session consisting of three phases. The first phase was a 1-h period of cocaine self-administration (0.5 mg/kg/infusion, FR-5 schedule of reinforcement) in which the light stimulus was paired with cocaine infusions. After the 1-h period, the cocaine solution was replaced with saline and responding was monitored for 3 h. During this extinction phase (phase 2), the light stimulus that had been paired with cocaine was presented

on an FR-5 schedule along with the saline infusion. At the start of the third phase, in which again saline but not cocaine was available, groups of animals (n = 5–7 per group) received an injection of caffeine (1.25–20.0 mg/kg), the adenosine A1/A2 antagonist, theophylline (1.0–10.0 mg/kg) or the adenosine A2 antagonist, 3,7-Dimethyl-1-propargylxanthine (DMPX; 0.546–2.18 μg/kg). The ability of the drug to elicit cocaine seeking, defined as the number of responses made on the lever that previously resulted in the delivery of cocaine, was determined. As with other phases of this test, coincident with each saline infusion was the illumination of the light stimulus. Responding was monitored for 3 h following the injection.

The ability of each of the three drugs to reinstate extinguished cocaine-taking behavior was measured in a separate group of rats. The effects of multiple doses were determined in each subject and the order of doses was randomly assigned. Between each reinstatement test, there were at least two daily self-administration sessions during which responding was reinforced with cocaine infusions (0.5 mg/kg/infusion) and the illumination of the light stimulus according to an FR-5 schedule.

Additional groups (n = 4–6 per group) received an injection of the dopamine D1-like antagonist, SCH 23390 (0.005–0.020 mg/kg), the dopamine D2-like antagonist, eticlopride (0.03–0.30 mg/kg), or the adenosine A1/A2 agonist, 5′-N-Ethylcarboxamidoadenosine (NECA; 0.003–0.03 mg/kg) prior to the caffeine (20.0 mg/kg) injection at the start of Phase 3. As above, separate groups of rats were used for each drug test and the order of testing of the various doses of each drug was randomly assigned. All pretreatments with the exception of SCH 23390 were administered 30 min prior to caffeine. SCH 23390 was administered 15 min prior to caffeine.

Because there was a decrease in responding produced by pretreatment with the dopamine antagonists, the specificity of this effect was determined in other groups of rats trained to self-administer cocaine. On a test day, animals (n = 4/group) were pretreated with the higher doses of SCH 23390 (0.02 mg/kg; 15 min pretreatment), eticlopride (0.1 or 0.3 mg/kg; 30 min pretreatment) or vehicle prior to a 60-min cocaine self-administration session (0.5 mg/kg/infusion). Doses were assigned according to a Latin Square design. The number of responses produced by drug-treated groups was compared with the number of responses under control conditions.

Locomotor Activity

A limited number of tests were conducted in order to determine whether the doses of DPMX used in the reinstatement tests were behaviorally relevant. Locomotor activity was measured in an automated Digiscan 16 system. The system included four optical beam activity monitors (Model E61-32; Coulbourn Instruments Inc., Lehigh Valley, PA) comprised of 16 vertical and 32 horizontal infrared sensors. Each monitor (40 × 40 × 30.5 cm) was completely enclosed and had air holes drilled in the top panel. A Coulbourn E61-58 multiplexer analyzer was located in an adjacent laboratory to monitor beam breaks and to track the simultaneous interruptions of optical beams. All testing was carried out in the dark between 10:00 A.M. and 2:00 P.M. White noise was continuously present throughout testing.

Separate groups of drug-naïve rats (n = 8 per group) were injected with saline or 10.9 μg/kg of the A2 agonist N^6 - [2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)-ethyl]adenosine and placed into the activity apparatus for 15 min. They were then injected with either saline or 2.18 μg/kg of the A2 antagonist DMPX. This was the highest dose of DPMX administered for the reinstatement tests. Activity was measured for an additional 45 min following the injection.

Drugs

All drugs were dissolved in 0.9% saline solution and were mixed daily prior to each test. Cocaine HCl (National Institute of Drug Abuse) was mixed in individual syringes according to the body weight of each animal. Intravenous infusions were in a volume of 0.1 ml/infusion. Caffeine (Sigma Chemical Co., St. Louis, MO), theophylline, eticlopride, NECA, DPMA, DMPX (RBI, Natick, MA) and SCH 23390 (Medication Development Division of NIDA) were dissolved in 0.9% saline and were administered in a volume of 1.0 ml/kg. All drug weights refer to the salt.

Data Analysis

Responses produced during Phase 3 of the reinstatement tests were analyzed using 2-factor repeated measures Analyses of Variance for each experiment. The effects of SCH 23390 and eticlopride on responding maintained by cocaine were analyzed by comparing responses to those produced following administration of the vehicle control. Locomotor activity data were analyzed using a 2-way ANOVA (DPMX Dose × DPMA Dose). Planned comparisons were used to compare each dose to the appropriate control. All data are expressed as the average number of active lever responses (±) S.E.M. Results were deemed significant at $p < .05$ for a 1-tailed test.

RESULTS

Cocaine-Seeking Behavior Produced by Methylxanthines

Figure 1 shows the number of responses produced during Phase 1 (60-min self-administration) and Phase 2 (extinction responding during the 3-h period following

the replacement of cocaine solution with saline) for a representative group of rats (n = 6) from the present study. During Phase 1, responding is high and by the end of Phase 2, fewer than 15 responses per hour are produced.

Figure 2 shows the number of responses produced following administration of various doses of caffeine (panels A–C), theophylline (panels D–F), or DMPX (panels G–I) at the start of Phase 3. Administration of caffeine or theophylline, reinstated extinguished responding in a dose-dependent manner. Administration of DPMX failed to reinstate extinguished cocaine-taking behavior.

Separate ANOVAs (Dose × Hour) were conducted on the number of responses made following injection of each of the three drugs at the start of phase 3. There was a main effect of Caffeine Dose ($F_{5,24} = 4.807$, $p < .005$), Hour ($F_{2,60} = 38.088$, $p < .001$) and an interaction between Caffeine Dose and Hour ($F_{10,48} = 5.007$, $p < .001$). Contrasts revealed that caffeine doses of 5.0 ($p < .05$), 10.0 ($p < .05$) and 20.0 ($p < .01$) mg/kg significantly increased responding over saline levels during the first hour following the injection, while only the 10.0 ($p < .01$) and 20.0 ($p < .05$) mg/kg doses increased responding during the second hour.

Theophylline Dose was also significant ($F_{3,24} = 9.17$, $p < .001$) as was Hour ($F_{2,56} = 13.67$, $p < .001$) and the interaction between these two factors ($F_{6,36} = 7.10$, $p < .001$). Contrasts of the individual hour data revealed that responding following the 10.0 mg/kg dose was significantly greater than responding following vehicle for all three hours of reinstatement (first two hours $p < .01$, third hour $p < .05$). The 3.0 mg/kg dose, however, only increased responding during the second hour ($p < .05$).

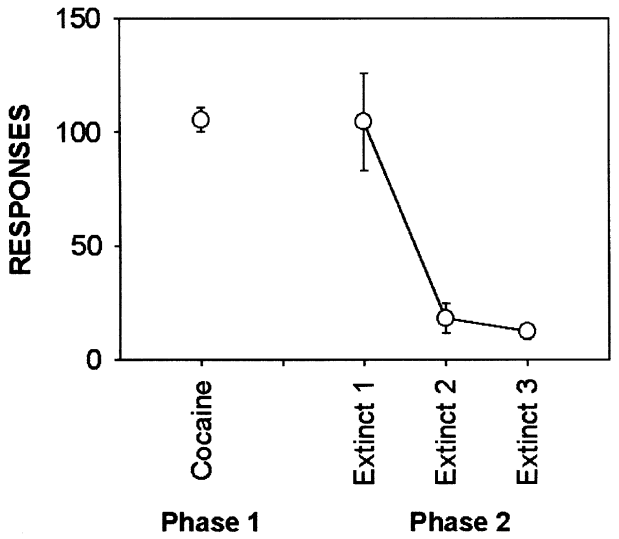

Figure 1. Representative data for cocaine responding (Phase 1) and extinction of responding (Phase 2) for test sessions. Each point represents mean responses ± S.E.M. over a 60-min period (n = 6).

The adenosine A2 antagonist, DMPX, failed to reinstate extinguished responding at the doses tested ($F_{3,18} = 0.243$, NS). To ensure that behaviorally relevant doses of DMPX had been employed, the ability of 2.18 μg/kg DMPX (the highest dose tested) to elicit locomotor activity was determined. The effect of prior administration of a single dose of the A2 agonist, DPMA, was also determined. Figure 3 shows that DMPX elicited hyperlocomotion and that this effect was blocked by treatment with 10.9 μg/kg DPMA. An ANOVA (DMPX Dose X DPMA Dose) revealed a significant interaction ($F_{1,28} = 11.97$, $p < .005$). Tukey post hoc comparisons revealed that DMPX-induced hyperactivity ($p < .01$) was significantly attenuated by DPMA treatment ($p < .01$).

Effect of NECA on Caffeine-Produced Cocaine-Seeking Behavior

A separate group of rats was pretreated with the non-selective A1/A2 agonist NECA 30 min prior to caffeine at the start of Phase 3 (data not shown). Although high doses of NECA (0.01 and 0.03 mg/kg) completely suppressed caffeine-induced reinstatement, the rats were visibly sedated and noticeably hypothermic following administration, suggesting a non-specific rate-suppressant effect. One rat died following administration of the 0.03 mg/kg dose.

Effects of Dopaminergic Antagonists on Caffeine-Induced Cocaine-Seeking Behavior

The effects of pretreatment with the selective dopamine D1-like antagonist, SCH 23390, on caffeine-induced reinstatement are presented in Figure 4 (panels A–C). An ANOVA (SCH 23390 Dose × Hour) revealed a significant Dose × Hour interaction ($F_{6,18} = 4.66$, $p < .005$). Planned comparisons of these data revealed a significant decrease in caffeine-produced reinstatement during the first hour following pretreatment with 0.02 mg/kg SCH 23390 ($p < .05$) and a near-significant decrease during the second hour following drug administration ($p = .075$). The 0.01 mg/kg dose of SCH 23390 showed a near-significant decrease in responding for the first hour ($p = .055$) as well as during the second hour ($p = .075$). Responses on the inactive lever were infrequent and not significantly altered by SCH 23390.

The effects of pretreatment with the selective dopamine D2-like antagonist, eticlopride, on caffeine-induced reinstatement are presented in Figure 4 (panels D–F). An ANOVA (Eticlopride Dose × Hour) revealed a significant Dose × Hour interaction ($F_{6,24} = 8.13$, $p < .001$). Planned comparisons of these data revealed that the 0.3 mg/kg dose decreased responding throughout the three hour reinstatement period (first hour $p < .001$, second and third hours $p < .05$) while the 0.1 mg/kg dose decreased responding only during the first 2 hours (first

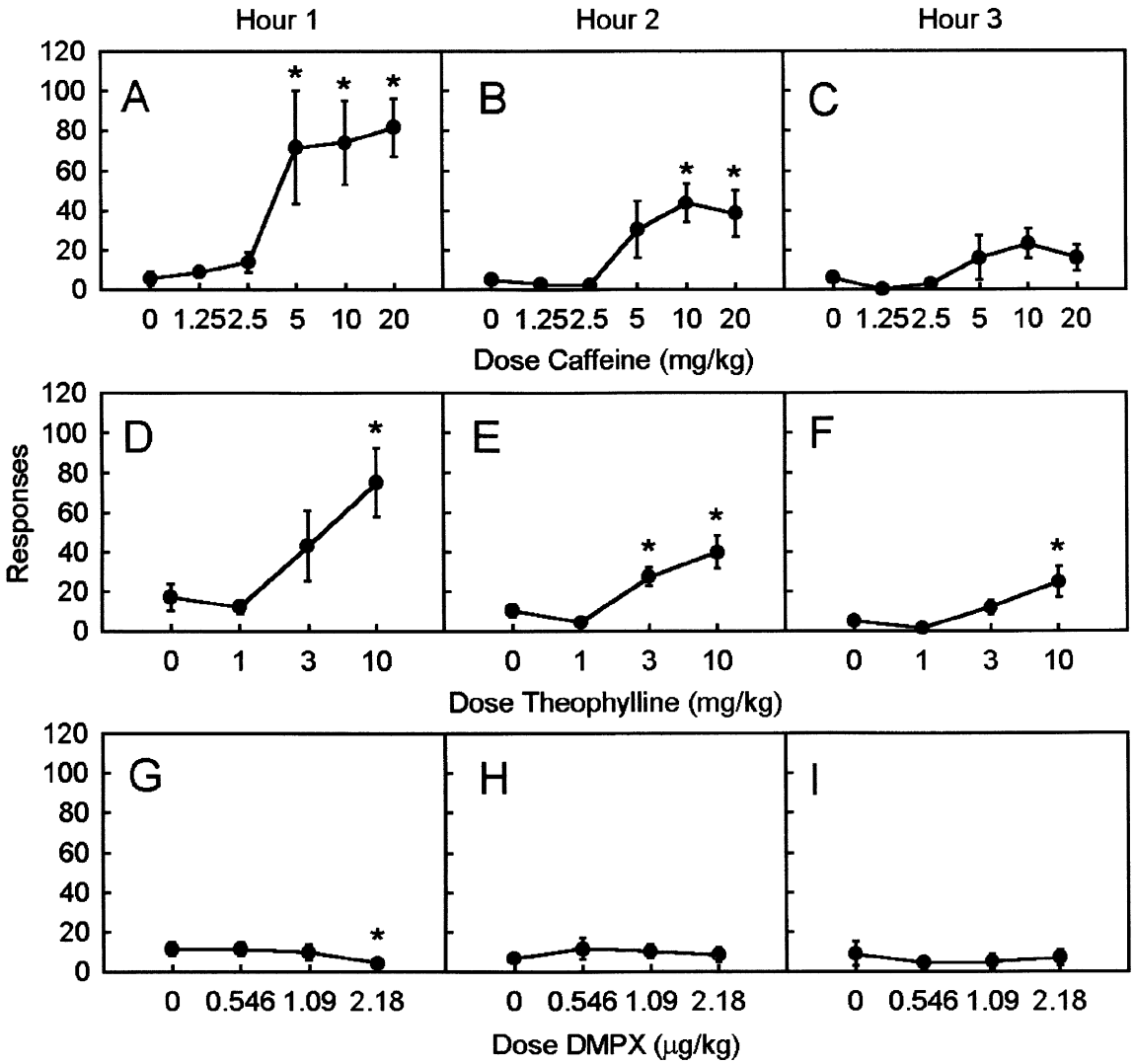

Figure 2. Responses for test trials of reinstatement of cocaine responding with caffeine (A–C), theophylline (D–F), or DMPX (G–I). Rats were administered caffeine (0–20 mg/kg, IP; n = 5), theophylline (0–10 mg/kg; n = 7) or DMPX (0–2.18 μg/kg; n = 7) at the beginning of Phase 3. Each point represents mean responses ± S.E.M. for a 60-min period. Asterisks (*) denote statistical significance ($p < .05$) from control responding.

hour $p < .005$, second hour $p < .05$). Responses on the inactive lever were again infrequent and not significantly altered by eticlopride.

Effects of Dopaminergic Antagonists on Cocaine Self-Administration

The effects of pretreatment with SCH 23390 (0.02 mg/kg) and eticlopride (0.1 and 0.3 mg/kg) on cocaine self-administration are depicted in Figure 5. During the 60-min session, rats pretreated with vehicle emitted an average of 141 ± 20 responses on the active lever. Pretreatment with 0.02 mg/kg SCH 23390, the dose that attenuated caffeine-produced cocaine seeking, produced a non-significant increase in responding for cocaine ($t = -1.40$, $p = .255$). Furthermore, in contrast to effects of eticlopride on caffeine-produced reinstatement, pretreatment with the 0.1 mg/kg dose of eticlopride produced an increase in cocaine self-administration ($t = 26.87$, $p < .001$). Pretreatment with the highest dose of eticlopride (0.3 mg/kg), however, produced a marked decrease in responding maintained by cocaine ($t = -12.31$, $p < .005$).

DISCUSSION

Caffeine and theophylline produced a dose-dependent reinstatement of extinguished cocaine-taking behavior with relative potencies similar to those at adenosinergic receptors (Snyder et al. 1981). A selective A2 adenosine antagonist, however, failed to produce drug seeking,

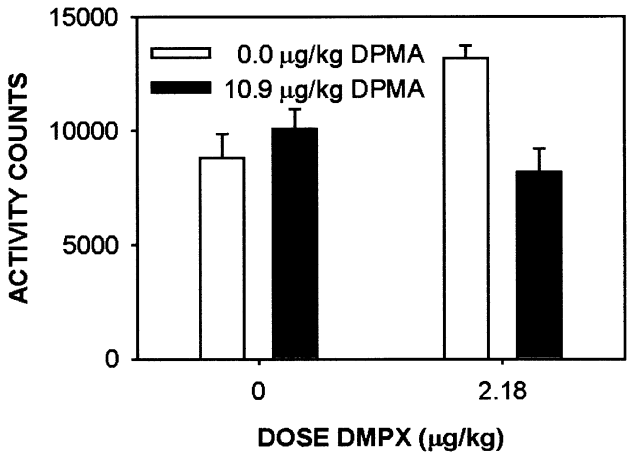

Figure 3. Effect of DMPX and/or DPMA on locomotor activity (n = 8 per group). Rats were habituated to testing apparatus for 15 min with or without 10.9 μg/kg DPMA before being injected with saline or 2.18 μg/kg DMPX. Activity was then recorded for 45 min. Data are expressed as mean photocell interrupts ± S.E.M.

even at a dose that produced hyperactivity. Only doses of a non-selective adenosine A1/A2 receptor agonist that produced non-specific effects blocked caffeine-produced cocaine seeking. The ability of caffeine to produce cocaine-seeking behavior was, however, attenuated by pretreatment with doses of dopaminergic antagonists that did not produce a nonspecific rate-suppressant effect.

Although a primary effect of low doses of caffeine is antagonism of adenosine receptors (Daly 1993), a secondary effect of adenosine A2 antagonism is a disinhibition of dopamine D2 receptors (Dasgupta et al. 1996; Fuxe et al. 1998). Cocaine seeking has been attributed to activation of dopamine D2-like receptors (Self et al. 1996) which raises the possibility that caffeine-produced cocaine seeking might similarly be due to adenosine A2/dopamine D2 interactions. If so, the selective A2 antagonist DMPX would have been expected to produce cocaine seeking comparable to effects produced by caffeine. The failure of a behaviorally relevant dose of DMPX to produce cocaine seeking suggests that the ability of dopamine antagonists to attenuate caffeine-induced cocaine seeking occurs via non-adenosinergic A2 mechanisms.

It is possible that both A1 and A2 receptor antagonism might be required to elicit drug-seeking behavior. If so, one would have expected the non-selective adenosinergic agonist, NECA, to block caffeine-induced cocaine seeking. However, the NECA-induced antagonism of caffeine-produced cocaine seeking was obtained only following administration of doses that produced noticeable lethargy, prostrate posture and extreme hypothermia. These results suggest that the decrease in caffeine-produced cocaine seeking seen with NECA pretreatment is due to a non-specific rate-suppressant effect.

Dopaminergic mechanisms underlying caffeine-produced cocaine seeking were demonstrated in groups that received pretreatment with the selective dopaminergic antagonists, SCH 23390 and eticlopride. In previous studies, it was shown that these drugs produce sedative effects, raising the possibility that the decrease in cocaine seeking was due to non-specific effects. In order to assess this possibility, effects of SCH 23390 and eticlopride on cocaine self-administration were assessed. Doses of these drugs that decreased caffeine-produced cocaine seeking increased cocaine self-administration, suggesting that the decrease in cocaine seeking was specific. It has been shown that higher doses of antagonists are required to decrease cocaine self-administration than to decrease responding maintained by non-drug reinforcers (Corrigall and Coen 1991; Caine and Koob 1994) which raises the possibility that cocaine self-administration counteracted possible sedative effects of the dopamine antagonists that would still be apparent when administered in combination with caffeine, as in the reinstatement tests. This possibility was not, however, assessed in the present study. Taken together, these findings suggest that dopaminergic antagonism, independent of adenosine A2 antagonism, mediates caffeine-produced cocaine seeking.

Other studies have also suggested that some behavioral effects of caffeine are produced independent of adenosine A2 antagonism. For example, discriminative stimulus effects of a low dose of caffeine were not blocked by administration of several adenosine analogs (Holtzman 1991). Additionally, some potent adenosinergic antagonists did not mimic caffeine's ability to produce rotational behavior in unilaterally lesioned animals (Garrett and Holtzman 1995; Fenu and Morelli 1998) or to increase thresholds for reinforcing brain stimulation (Mumford and Holtzman 1991a).

It is noteworthy that the subjects in the present study received substantial exposure to cocaine through self-administration prior to the reinstatement tests. Exposure to cocaine has been repeatedly demonstrated as a sufficient condition for the development of behavioral and neurochemical sensitization to subsequent administration of a variety of stimulants (Akimoto et al. 1990; Elmer et al. 1996). Although repeated administration of caffeine was ineffective in sensitizing rats to the behavioral effects of caffeine itself, preexposure rendered rats supersensitive to the behavioral effects of cocaine (Schenk et al. 1989; Horger et al. 1991). These findings suggest that repeated caffeine administration produced neuroadaptations in systems underlying the behavioral response to cocaine, and raise the possibility that the reverse condition is also true; that repeated exposure to cocaine via self-administration renders subjects more responsive to some of the effects of caffeine.

Consistent with this hypothesis, caffeine produced a contraversive bias in unilaterally 6-OHDA lesioned ani-

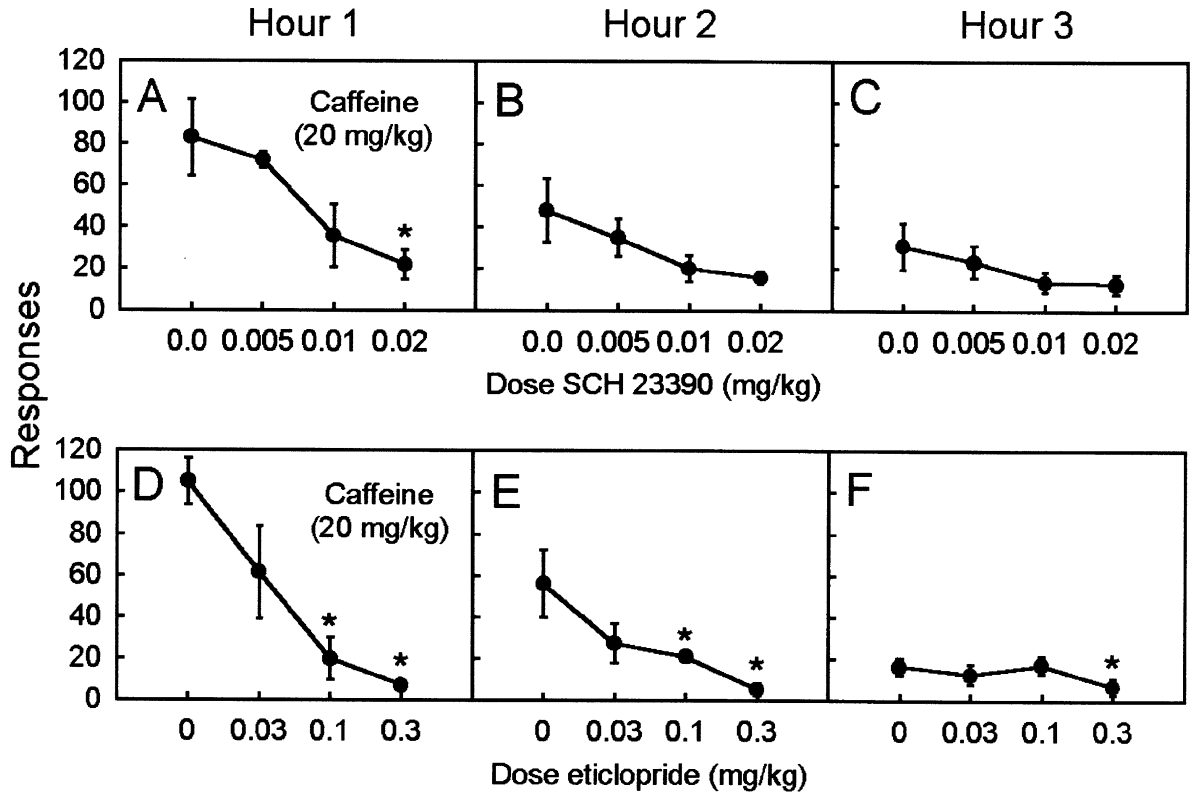

Figure 4. Effect of SCH 23390 (panels A–C) or eticlopride (panels D–F) on caffeine reinstatement of cocaine seeking for hours 1–3. Rats were pretreated with SCH 23390 (0–0.02 mg/kg; n = 4) or eticlopride (0–0.3 mg/kg; n = 5) 15 or 30 min before reinstatement, respectively. Drug-seeking behavior was elicited with caffeine injection (20 mg/kg). Each point represents mean responses ± S.E.M. for a 60-min period. Asterisks (*) denote statistical significance ($p < .05$) from control responding.

mals only when the subjects were first sensitized with dopaminergic agonists (Fenu and Morelli 1998). Coupled with the findings that potent nonxanthine adenosinergic antagonists did not produce rotational behavior (Garrett and Holtzman 1995; Fenu and Morelli 1998), caffeine might exert this effect through a non-adenosinergic A2 mechanism that becomes sensitized following preexposure to dopamine agonists. A similar mechanism might underlie caffeine-produced cocaine seeking.

Although administration of the A2 antagonist, DMPX, failed to reinstate extinguished cocaine-taking behavior, locomotor activation was produced. This effect was mediated by adenosine A2 antagonism since concurrent administration of the A2 agonist, DPMA, blocked DMPX-produced hyperactivity. The differential effects of DMPX on drug seeking and locomotor activation might be due to the different drug histories of the animals, but a more likely explanation is that hyperactivity and drug seeking are differentially dependent on adenosinergic mechanisms. A third possibility is that the increase in locomotor activity produced by DPMX interfered with the ability of the animal to perform the lever press operant. This interpretation is unlikely, however, since doses of caffeine (Worley et al. 1994) and other drugs (Schenk and Partridge 1999; Schenk et al. 2000) that produced reinstatement also increase locomotor activity.

Other findings have also provided evidence for a dissociation of the mechanisms underlying behavioral effects of methylxanthines. For example, pretreatment with DPMX increased locomotor activity but, unlike caffeine or theophylline, it failed to alter thresholds for reinforcing electrical brain stimulation (Mumford and Holtzman 1990; Baldo et al. 1999). Similarly, pretreatment with the selective $A2_A$ antagonist SCH 58261 produced locomotor stimulation (Svenningsson et al. 1997), but failed to delay extinction of cocaine self-administration in mice (Kuzmin et al. 1999) or to induce rotational behavior in rats (Fenu and Morelli 1998). Finally, pretreatment with the nonxanthine adenosinergic antagonist, CGS 15943, produced locomotor stimulant effects (Holtzman 1991) but failed to alter operant responding maintained by electrical brain stimulation (Mumford and Holtzman 1991a).

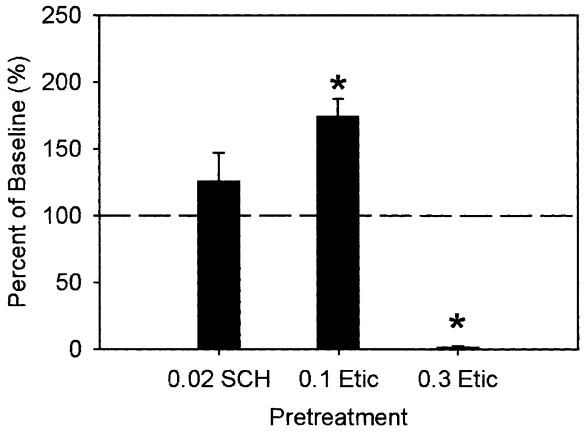

Figure 5. Effect of SCH 23390 and eticlopride pretreatment on cocaine self-administration. Rats were pretreated with SCH 23390 (0.02 mg/kg; IP; 15 min pretreatment) or eticlopride (0.1 or 0.3 mg/kg; IP; 30 min pretreatment) before cocaine self-administration (0.5 mg/kg/infusion; 60 min session; n = 4). Data are presented as mean ± S.E.M. responses as a percentage of baseline responding. Asterisks (*) denote significant difference in responding from baseline.

In summary, the present results suggest that caffeine-produced cocaine seeking is not mediated by adenosinergic A2 antagonism, but is contingent upon dopaminergic mechanisms. The nature of the interaction between caffeine and dopamine is not well understood, but warrants further investigation to determine whether they become more apparent following experience with cocaine self-administration, as in the present study.

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REFERENCES

Akimoto K, Mamamura T, Kazahaya Y, Akiyama K, Otsuki S (1990): Enhanced extracellular dopamine level may be the fundamental neuropharmacological basis of cross-behavioral sensitization between methamphetamine and cocaine—an in vivo dialysis study in freely moving rats. Brain Res 507:344–346

Baldo BA, Koob GF, Markou A (1999): Role of adenosine A2 receptors in brain stimulation reward under baseline conditions and during cocaine withdrawal in rats. J Neurosci 19:11017–11026

Caine SB, Koob GF (1994): Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. J Pharmacol Exp Ther 270:209–218

Corrigall WA, Coen KM (1991): Cocaine self-administration is increased by both D1 and D2 dopamine antagonists. Pharmacol Biochem Behav 39:799–802

Daly JW (1993): Mechanism of action of caffeine. In Garattini S (ed), Caffeine, Coffee, and Health. New York, Raven Press, Ltd., pp 97–149

Dasgupta S, Ferre S, Kull B, Hedlund PB, Finnman UB, Ahlberg S, Arenas E, Fredholm BB, Fuxe K (1996): Adenosine $A2_A$ receptors modulate the binding characteristics of dopamine D2 receptors in stably cotransfected fibroblast cells. Eur J Pharmacol 316:325–331

De Vries TJ, Schoffelmeer AN, Binnekade R, Vanderschuren LJ (1999): Dopaminergic mechanisms mediating the incentive to seek cocaine and heroin following long-term withdrawal of IV drug self-administration. Psychopharmacology 143:254–260

Elmer GI, Brockington A, Gorelick DA, Carrol FI, Rice KC, Matecka D, Goldberg SR, Rothman RB (1996): Cocaine cross-sensitization to dopamine uptake inhibitors: unique effects of GBR12909. Pharmacol Biochem Bevav 53:911–918

Fenu S, Morelli M (1998): Motor stimulant effects of caffeine in 6-hydroxydopamine-lesioned rats are dependent on previous stimulation of dopamine receptors: a different role of D_1 and D_2 receptors. Eur J Neurosci 10:1878–1884

Ferre S, Herrera-Marschitz M, Grabowska-Anden M, Casas M, Ungerstedt U, Anden NE (1991): Postsynaptic dopamine/adenosine interaction: II. Postsynaptic dopamine agonism and adenosine antagonism of methylxanthines in short-term reserpinized mice. Eur J Pharmacol 192:31–37

Ferre S, O'Connor WT, Fuxe K, Ungerstedt U (1993): The striopallidal neuron: a main locus for adenosine-dopamine interactions in the brain. J Neurosci 13:5402–5406

Fuxe K, Ferre S, Zoli M, Agnati LF (1998): Integrated events in central dopamine transmission as analyzed at multiple levels. Evidence for intramembrane adenosine A_{2A}/dopamine D_2 and Adenosine A_1/dopamine D_1 receptor interactions in the basal ganglia. Brain Res Rev 26:258–273

Garrett BE, Holtzman SG (1995): Does adenosine receptor blockade mediate caffeine-induced rotational behavior? J Pharmacol Exp Ther 274:207–214

Holtzman SG (1991): CGS 15943, a nonxanthine adenosine receptor antagonist: effects on locomotor activity of non-tolerant and caffeine-tolerant rats. Life Sci 49:1563–1570

Horger BA, Wellman PJ, Morien A, Davies BT, Schenk S (1991): Caffeine exposure sensitizes rats to the reinforcing effects of cocaine. Neuroreport 2:53–56

Jaffe JH, Cascella NG, Kumor KM, Sherer MA (1989): Cocaine-induced cocaine craving. Psychopharmacology 97:59–64

Katims JJ, Annau Z, Snyder SH (1983): Interactions in the behavioral effects of methylxanthines and adenosine derivatives. J Pharmacol Exp Ther 227:167–173

Khroyan TV, Barrett-Larimore RL, Rowlett JK, Spealman RD (2000): Dopamine D1- and D2-like receptor mechanisms in relapse to cocaine-seeking behavior: effects of selective antagonists and agonists. J Pharmacol Exp Ther 294:680–687

Kuzmin A, Johansson B, Zvartau EE, Fredholm BB (1999):

Caffeine, acting on adenosine A1 receptors, prevents the extinction of cocaine-seeking behavior in mice. J Pharmacol Exp Ther 290:535–542

Markou A, Weiss F, Gold LH, Caine SB, Schulteis G, Koob GF (1993): Animal models of drug craving. Psychopharmacology 112:163–182

Mumford GK, Holtzman SG (1990): Methylxanthines elevate reinforcement threshold for electrical brain stimulation: role of adenosine receptors and phosphodiesterase inhibition. Brain Res 528:32–38

Mumford GK, Holtzman SG (1991a): Do adenosinergic substrates mediate methylxanthine effects upon reinforcement thresholds for electrical brain stimulation in the rat? Brain Res 550:172–178

Mumford GK, Holtzman SG (1991b): Qualitative differences in the discriminative stimulus effects of low and high doses of caffeine in the rat. J Pharmacol Exp Ther 258:857–865

Rush CR, Sullivan JT, Griffiths RR (1995): Intravenous caffeine in stimulant drug abusers: subjective reports and physiological effects. J Pharmacol Exp Ther 273:351–358

Schenk S, Valadez A, Horger BA (1989): Caffeine preexposure sensitizes rats to the motor activating effects of cocaine. Behav Pharmacol 1:447–451

Schenk S, Worley CM, McNamara C, Valadez A (1996): Acute and repeated exposure to caffeine: effects on reinstatement of extinguished cocaine-taking behavior in rats. Psychopharmacology 126:17–23

Schenk S, Partridge B (1999): Cocaine-seeking produced by experimenter-administered drug injections: dose-effect relationships in rats. Psychopharmacology 147:285–290

Schenk S, Partridge B, Shippenberg TS (2000): Reinstatement of extinguished drug-taking behavior in rats: effect of the kappa-opioid receptor agonist U69593. Psychopharmacology 151:85–90

Self DW, Barnhart WJ, Lehman DA, Nestler EJ (1996): Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. Science 271:1586–1589

Snyder SH, Katims JJ, Annau Z, Bruns RF, Daly JW (1981): Adenosine receptors and behavioral actions of methylxanthines. Proc Natl Acad Sci 78:3260–3264

Spencer Jr DG, Emmett-Oglesby MW (1985): Parallel processing strategies in the application of microcomputers to the behavioral laboratory. Behav Res Methods Instrum 17:294–300

Svenningsson P, Nomikos GG, Ongini E, Fredholm BB (1997): Antagonism of adenosine A_{2A} receptors underlies the behavioral activating effect of caffeine and is associated with reduced expression of messenger RNA for NGFI-A and NGFI-B in caudate-putamen and nucleus accumbens. Neuroscience 3:753–764

Wise RA, Murray A, Bozarth MA (1990): Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. Psychopharmacology 100:355–360

de Wit H, Stewart J (1981): Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology 75: 134–143

Worley CM, Valadez A, Schenk S (1994): Reinstatement of extinguished cocaine-taking behavior by cocaine and caffeine. Pharmacol Biochem Behav 48:217–221