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Adenosine agonists CGS 21680 and NECA inhibit the initiation of cocaine self-administration

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Abstract

Administration of the adenosine antagonist caffeine will facilitate the reinstatement of cocaine self-administration responding. This suggests that adenosine receptors may play a role in the motivational systems that regulate cocaine-seeking behaviors. If so then adenosine agonists may act to block cocaine self-administration. To test this hypothesis, the effects of the nonselective adenosine agonist NECA and of the A_{2A} selective agonist, CGS 21680 on the self-administration of cocaine were determined. In these experiments, rats were allowed to obtain intravenous cocaine infusions (0.6 mg/kg/infusion) delivered under a Fixed Ratio 5 schedule. Treatment with either NECA or CGS 21680 in comparison to vehicle administration reduced the number of infusions received per session. This, primarily, was due to a marked increase in the latency for delivery of the first cocaine infusion. Responding after drug-induced delays tended to be at control levels. Adenosine agonists are known to have sedative effects and these actions might play a role in NECA and CGS 21680-induced increases in latencies for cocaine delivery. These results indicate that the administration of adenosine agonists may inhibit cocaine-seeking behaviors. The degree to which these actions are on motivational systems as opposed to involving less specific effects remains to be fully elucidated.

Keywords: Cocaine; Self-administration; Adenosine receptors

1. Introduction

Caffeine has adenosine A_1 and A_{2A} receptor antagonist effects at doses that produce behavioral stimulation (Fredholm, 1995). This agent has been shown to reinstate extinguished cocaine self-administration behavior in rats (Schenk et al., 1996; Worley et al., 1994) and mice (Kuzmin et al., 1999). In mice, the administration of either 1,3-dipropyl-8-cyclopentyl xanthine (DPCPX) or 8-cyclopentyl theophylline (8-CPT), both selective adenosine A_1 receptor antagonists, partially blocks the extinction of responding for self-administered cocaine (Kuzmin et al., 1999). Low doses of cocaine and caffeine when administered in combination appear to have additive actions that lead to the induction of conditioned place preference (Beddingfield et al., 1998). Thus, there seems to be a few studies that suggest adenosine receptors may be involved in the regulation of the neuronal systems associated with both the motivation to self-administer cocaine and with the mediation of cocaine's reinforcing actions.

Adenosine A_1 receptors exist in moderate concentrations in the hippocampus, substantia nigra, thalamic nuclei, and cerebral and cerebellar cortices (Fastborn et al., 1987; Goodman and Snyder, 1982; Rivkees et al., 1995; Snowhill and Williams, 1986). Binding of the adenosine A_2 selective agonist, [^{3}H]CGS 21680 has been found to be highly concentrated in the caudate–putamen, nucleus accumbens, and olfactory tubercle (Jarvis and Williams, 1989; Johansson and Fredholm, 1995). This compound, at higher concentrations, has also been found to bind in other brain regions including the cerebral cortex, hippocampus, and

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thalamus (Johansson and Fredholm, 1995). There is some evidence that CGS 21680 binds to sites in the hippocampus and cerebral cortex that are distinct from the striatal A_{2A} receptor (Johansson and Fredholm, 1995).

Reverse transcription-polymerase chain reaction techniques suggest that adenosine A_{2A} receptor messenger RNA is distributed widely throughout the brain (Dixon et al., 1996). High concentrations of A_{2A} mRNA, however, appear to be restricted to the striatum, nucleus accumbens, and olfactory tubercle (Dixon et al., 1996; Svenningsson et al., 1997). Adenosine A_{2A} receptor mRNA is found to a large extent in neurons that co-express dopamine D_2 and preproenkephalin A mRNA (Fink et al., 1992; Svenningsson et al., 1997). This is of interest because the nucleus accumbens has been implicated in the mediation of cocaine's rewarding actions and the activation dopamine D_2-like family receptors promotes the reinstatement of cocaine self-administration (De Vries et al., 1999; Self et al., 1996; Wise et al., 1990).

The effects of adenosine agonists on cocaine self-administration do not appear to have been examined. In this study, the effects of the adenosine agonist, 5′-*N*-carboxamido adenosine (NECA) and (2-(*p*-(carboxyethyl)-phenethylamino)-5′-*N*-ethyl-carbamido adenosine (CGS 21680) on cocaine self-administration were determined. NECA is a nonselective adenosine agonist that has 1.2-fold greater selectivity for A_2 receptors than for A_1 receptors in the brain tissue (Hutchison et al., 1989). CGS 21680 has approximately 140-fold greater selectivity for A_2 receptors than for the A_1 receptor (Hutchison et al., 1989). This compound has been determined to have a 160-fold greater selectivity specifically for the A_{2A} receptor than for the A_1 receptor in rat striatal membranes (Kim et al., 1994). In striatal tissues, CGS 21680 potently stimulates cyclic AMP formation, but does not inhibit electrically stimulated dopamine release (Lupica et al., 1990). These actions are consistent with those of a selective adenosine A_2 agonist.

2. Methods

These experiments were conducted with the approval of the Institutional Animal Care and Use Committee at the Boston University School of Medicine.

2.1. Apparatus

Test sessions in the cocaine self-administration experiments were conducted in two-lever operant chambers (MED Associates, St. Albans, VT). The operant chamber ($23 \times 23 \times 40$ cm) is housed inside a sound-attenuating chamber with a clear plastic window located on a center door. The operant chamber contains two levers placed 7.54 cm above a grid floor and two lights located 5.5 cm above the levers. The experimental programs were controlled and the data were collected by an IBM compatible computer using MED-PC software.

2.2. Animals

Male Wistar rats (Taconic, Germantown, NY) were used in each of these experiments. These animals ranged in weight between 350 and 425 g. They were housed individually in hanging wire cages under a 12-h light/dark cycle. The effects of NECA were tested in four rats. Five rats were used in the CGS 21680 experiments.

2.3. Cocaine self-administration

During the catheter implantation procedure, animals were first anesthetized with a 50 mg/kg (ip) dose of pentobarbital. Supplementary doses of chloral hydrate, 80/kg (ip) were administered as needed. A silastic catheter (Plastics One, Roanoke, VA) was implanted surgically into the right external jugular vein and was extended into the right atrium. The free end of the catheter was threaded subcutaneously and exited via an incision made on the scalp (Depoortere et al., 1993). The cannula assembly was then affixed to the skull with stainless steel screws and cranioplastic cement. Animals received postsurgical care for 5 days.

After recovery from surgery catheters were checked for patency each morning by infusing 0.1 ml of 10 U/ml heparinized saline. After infusion, the syringe was drawn back and checked for blood. If blood could not be drawn, 0.1–0.3 ml of 10 U/ml heparin solution was infused and drawn back until blood appeared. Streptokinase (0.5 ml) dissolved in 30 U/ml heparin solution was infused after the completion of every daily self-administration session. Food intake was restricted to allow the animals to maintain but not gain body weight.

Prior to surgery, rats were handled daily for 2 weeks and then trained to lever press for food reward (45 mg Noyes pellets). Approximately 6 days after surgery, rats were shaped to self-administer the training dose (0.3 mg/kg/infusion) of cocaine on a Continuous Reinforcement (CRF) schedule for a minimum of 5 days. Infusion volumes of 0.1 ml were delivered over 6-s long periods. Prior to each session, a 3-s primer injection was infused to displace the heparinized saline and fill the catheter with drug. When animals were reinforced, a stimulus light flashed for 6 s followed by a 20-s timeout. Lever presses during this period were not reinforced. A second lever in the chamber was inactive; lever presses were counted but were not reinforced. Rats were advanced to a Fixed Ratio 5 (FR5) reinforcement schedule and the dose of cocaine administered was increased to 0.6 mg/kg/infusion when 28 reinforcements in a 3-h session had been reached on the CRF schedule for 3 consecutive days. On the FR5 schedule, rats were limited to a maximum of 160 reinforcements in a 3-h session. The criterion for stable baseline was met when the number of reinforcements obtained per sessions varied by less than 20% for 3 consecutive days. Sessions were conducted daily excluding weekends

2.4. Drugs

Cocaine and NECA (Research Biochemicals International, Natick, MA — RBI), were dissolved in 0.9% saline solution. CGS 21680 (RBI) was dissolved in a 10% ethanol solution. In one experiment, either NECA (5, 7.5, 10, 20 μg/kg) or vehicle (saline) was administered intraperitoneally 15 min prior to the start of test sessions. Either CGS 21680 (0.05, 0.1, 0.2, 0.4 mg/kg ip) or vehicle, in a second experiment, were injected 10 min prior to the start of test sessions. Test agents were administered following a random order crossover design. In most cases, animals were tested twice with the same dose.

2.5. Data analysis

Repeated measures ANOVAs were used to compare baseline vs. vehicle (control) data and drug treatments and vehicle data (SigmaStat Statistical Software, 1997). When appropriate, vehicle and drug treatment data were compared using Dunnett's test.

3. Results

No significant difference [$F(1,3)=0.04$; $P=.85$] was detected between the mean number of cocaine infusions delivered after vehicle administration (35.6 ± S.D. 6.7) and during baseline conditions (35.3 ± S.D. 3.6) in the NECA treatment experiment. The mean number of cocaine infusions obtained under baseline conditions (34.6 ± S.D. 6.7) and following injection of vehicle (37.9 ± S.D. 9.0) also were not significantly different [$F(1,4)=4.4$; $P=.1$] for animals during the CGS 21680 experiment. After the administration of either NECA or CGS 21680, the mean number of cocaine infusions obtained per session was decreased significantly in a dose-dependent manner (Fig. 1) [NECA: $F(4,12)=14.9$; $P<.001$; CGS 21680: $F(4,16)=27.8$; $P<.001$].

Mean vehicle treatment and baseline condition latencies for the delivery of the first cocaine infusion did not differ significantly in either the NECA [$F(1,3)=0.49$; $P=.53$] or CGS 21680 [$F(1,4)=6.4$; $P=.6$] experiments. The administration of either NECA [$F(4,12)=16.1$; $P<.001$] or CGS

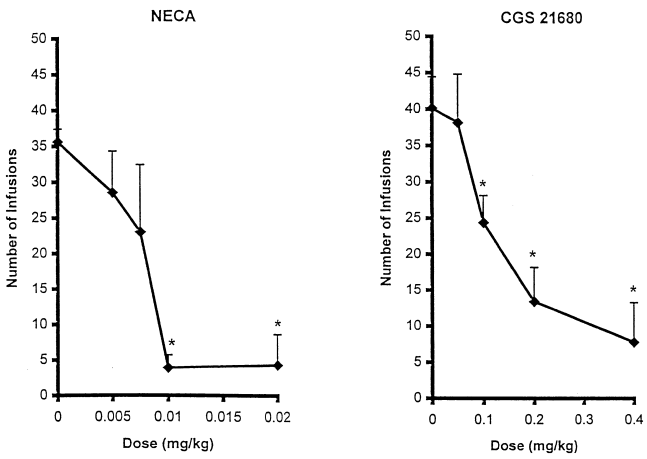

Fig. 1. Mean cocaine infusions self-administered during a 3-h session as a function of either NECA or CGS 21680 dose. *$P<.05$ from vehicle treatment.

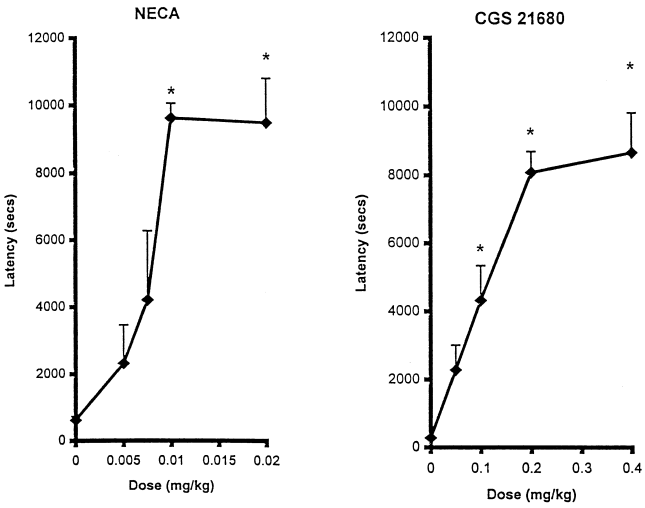

Fig. 2. Mean latencies for the delivery of the first cocaine reinforcement as a function of either NECA or CGS 21680 dose. *$P<.05$ from vehicle treatment.

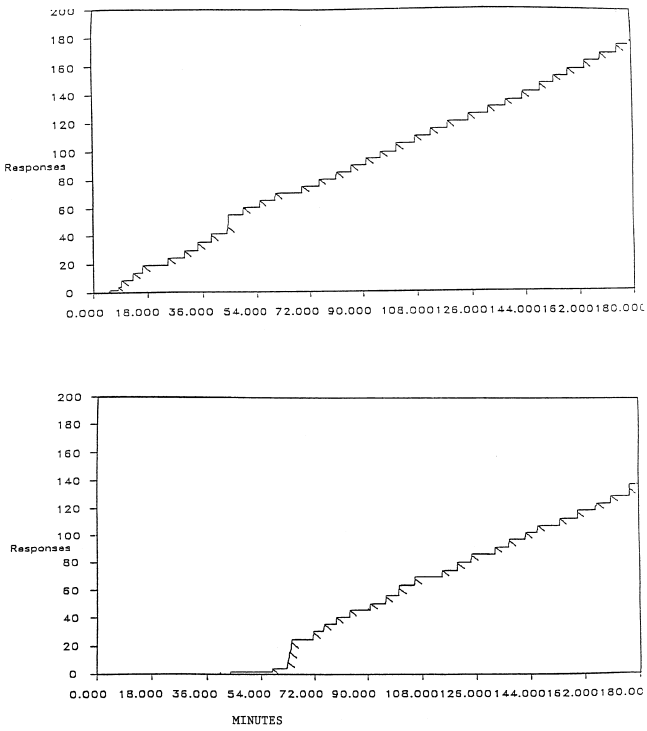

Fig. 3. Representative cumulative record samples for responses during a cocaine self-administration vs. time in minutes after injection of vehicle (top) and NECA 0.005 mg/kg (bottom).

21680 [$F(4,16)=38.5$; $P<.001$] treatment resulted in a significant increase in latencies above values obtained for vehicle treatment (Fig. 2). Thus, reductions in the number of cocaine infusions received after either NECA or CGS 21680 administration are, in a large part, due to initial delays in responding.

Compared to rates of responding on the active lever, animals pressed the inactive lever at rates that were many times lower, indicating that responding was being regulated by reinforcement with cocaine. In some instances, particularly following the administration of higher doses of either NECA or CGS 21680, animals would not lever press for cocaine during the entire test session. When animals did start to respond after the injection of either of these agents, then the rates of cocaine self-administration were typically similar to the rates observed during baseline and vehicle treatment sessions. As examples of this, representative cumulative records for animals self-administering cocaine after saline or NECA administration or after vehicle or CGS 21680 administration are shown in Figs. 3 and 4, respectively. In the records shown in Fig. 3 for an animal in the NECA treatment group, response rates soon reached 0.88 presses/min following saline administration, while after administration of a 0.005-mg/kg dose of NECA, a rate of 1.0 presses/min was quickly attained after responding commenced. In Fig. 4, the record shows a rate of 1.3 presses/min, which was attained shortly after the administration of vehicle and that the same response rate was reached after the administration of a 0.1-mg/kg dose of CGS 21680.

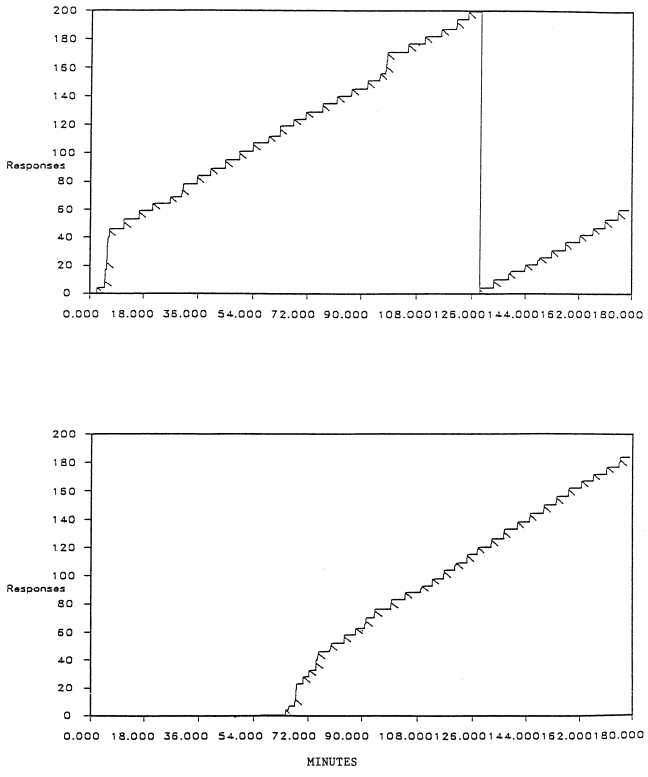

Fig. 4. Representative cumulative record samples for responses during a cocaine self-administration vs. time in minutes after injection of vehicle (top) and CGS 21680 0.1 mg/kg (bottom).

4. Discussion

NECA and CGS 21680 produced similar effects on cocaine self-administration behavior, blocking the initiation of self-administration, but not markedly altering rates of self-administration responding from control values once responding commenced. In this respect, the actions of these agents resemble those previously reported for the cyclic AMP specific phosphodiesterase inhibitors rolipram and Ro 20-1724 (Knapp et al., 1998) and the dopamine D_1 receptor agonists, SKF 77434 (Knapp et al., 1997) and SKF 82958 (Caine et al., 1999).

The results of this study are consistent with the notion that the stimulation of adenosine receptor systems may reduce cocaine-seeking behaviors. The extent to which these effects are attributable to nonspecific effects of either of the adenosine agonists tested in this study is not yet clear. NECA and CGS 21680 both produce hypotensive effects that may contribute to the inhibitory actions of these agents on the initiation of responding for cocaine (Casati et al., 1995; Hutchison et al., 1989). In Sprague–Dawley rats, the ED_{50} for NECA-induced depression of locomotor activity has been reported to be 0.005 mg/kg sc (Holtzman, 1991). This suggests that even the lowest dose of NECA administered in the present study may have significant locomotor-depressant actions. The ED_{50} for the locomotor-depressant effects of CGS 21680 has been found to be 0.2 mg/kg ip (Rimondini et al., 1997). Thus, at the two lowest doses of this agent found in the present study to significantly increase the latency for the delivery of the first cocaine infusion, locomotor activity may not be markedly decreased. It was also observed in the present investigation that while NECA administration frequently produced sedation, animals treated with CGS 21680 appeared to be alert during testing. Other investigators have indicated that rats did not seem to be sedated by the administration of CGS 21680 at doses as high as 2 mg/kg ip (Rimondini et al., 1997).

In many instances, animals would not respond during the entire test sessions after the administration of either NECA or CGS 21680. This usually occurred after the administration of the highest doses of these agents used in this study. More typically, following the administration of either NECA or CGS 21680, animals began responding after a period of delay at rates close to control values. If animals had experienced drug-induced debilitation after the administration of either NECA or CGS 21680, then it might be expected that initial responses would be irregular or would have occurred with less frequency than was observed under baseline conditions.

CGS 21680 has been reported to have an elimination half-life of only 15 min after the intravenous administration of a 0.3-mg/kg dose of this agent (Chovan et al., 1992).

Mean latencies for the delivery of the first cocaine infusion exceeded 1 h when animals were injected with a 0.1-mg/kg dose of CGS 21680 and exceeded 2 h when higher doses were administered. Thus, responding for cocaine may have started in animals treated with CGS 21680 only after this agent had been substantially cleared from the plasma.

NECA has been shown to produce a modest degree of catalepsy in female rats at doses close to the highest dose of this compound used in this study (Martin et al., 1993). The ED_{50} for NECA-induced catalepsy was found to be 0.15 mg/kg ip, which is well above the doses of this agonist administered in the present investigation. In female rats, modest levels of catalepsy were produced by CGS 21680 at a dose slightly greater than 0.3 mg/kg ip (Martin et al., 1993). The dose–response curve in these animals for the cataleptic effects of CGS 21680 was found to be flat. In male Sprague–Dawley rats, the ED_{50} was found to be 2 mg/kg ip for catalepsy induced by CGS 21680 (Rimondini et al., 1997). Thus, it is unlikely that the inhibition of responding for cocaine produced by the administration of CGS 21680 can be attributed to the cataleptic actions of this agent.

Findings from a few studies suggest that the inhibitory effects of NECA and CGS 21680 on responding for cocaine are not due to drug-induced response impairment. Response latencies on a brain stimulation reward task were found to not be significantly altered by the administration of CGS 21680 at 0.1, 0.3, and 3 mg/kg ip doses (Baldo et al., 1999). This suggests that significant impairment of responding is not produced by CGS 21680 within this range of doses. When condition avoidance responding (CAR) was measured during an hour-long test session, NECA reduced responding by only about 10% at 0.01 mg/kg ip and by 60% at 0.1 mg/kg (Martin et al., 1993). CGS 21680 reduced avoidance responding by 25% at a 0.3-mg/kg dose and by about 45% at a 1-mg/kg dose. Baseline CAR response rate in these experiments were at least 54 responses per hour. These results suggest that, unlike neuroleptic agents, adenosine agonists do not produce complete elimination of conditioned avoidance responding. They also indicate that animals should be capable of making five lever responses within an hour after the administration of either NECA or CGS 21680 at the highest doses of these agents tested in the present study, even though mean latencies for delivery of the first cocaine infusion in this investigation exceeded 2 h at these doses.

Rats with a prior history of exposure to NECA will self-administer this agent at doses ranging between 0.001 and 0.01 mg/kg/infusion (Sahraei et al., 1999). This result indicates that rats can perform lever-pressing tasks while under the influence of NECA and that this compound may produce rewarding effects. In rats responding on a variable ratio of 15 for food, response rates were found to be a little under 0.5 lever presses per second following a 0.01mg/kg ip dose of NECA and declined to zero at an approximately 0.02 mg/kg dose of this agonist (Logan and Carney, 1984). This suggests that the lowest dose of NECA found here to significantly increase the latency for delivery of the first cocaine infusion may not completely block high rates of operant responding.

NECA administration may delay responding for cocaine by serving as a rewarding substitute for cocaine. However, this explanation seems unlikely because the effects of administering a rewarding agonist rarely results in complete cessation of lever pressing followed by normal rates of pressing once responding is initiated. In contrast to NECA, animals will not self-administer low doses of CGS 21680 (Sahraei et al., 1999). Injection of either CGS 21680 and the adenosine A_{2A} agonist 2-[(2-aminoethylamino)carbonylethyl phenylethylamino]-5′-*N*-ethylcarboxyamido adenosine produced an elevation in brain stimulation reward thresholds (Baldo et al., 1999). These results suggest that adenosine A_{2A} receptors may play a negative modulatory role in neuronal systems that have been implicated in mediating the rewarding effects of cocaine (Kornetsky and Bain, 1990).

At present, the mechanism through which adenosine agonists act to inhibit cocaine-seeking behavior is uncertain. The administration of dopamine D_2 receptor agonists promotes reinstatement of cocaine self-administration responding (De Vries et al., 1999; Self et al., 1996; Wise et al., 1990) suggesting that D_2 receptors can play a role in the initiation of cocaine-seeking behavior. Infusion of CGS 21680 into the nucleus accumbens produces an elevation in gamma amino butyric acid levels in the ventral pallidum (Ferre et al., 1994). Similar effects occur when the dopamine D_2 receptor antagonist raclopride is infused into the nucleus accumbens (Ferre et al., 1994). Thus, activation of A_{2A} receptors in the nucleus accumbens may lead to effects that resemble those produced by dopamine D_2 antagonists. It is possible then that adenosine agonists inhibit cocaine-seeking behavior by functionally antagonizing D_2 receptor system activity. There is evidence that administration of the raclopride blocks responding for cocaine-associated cues in animals that have received a priming dose of cocaine (Weissenborn et al., 1996). However, it is not yet clear how dopamine D_2-like receptors in the nucleus accumbens influence cocaine-seeking behaviors that are initiated by environmental stimuli alone rather than by pharmacological agents. This needs to be kept in mind because external cues are the factors that most likely caused animals to start responding for cocaine in the present study.

It should be noted that binding studies suggest that CGS 21680 has approximately a 160-fold greater selectivity for adenosine A_{2A} receptor than for the A_1 receptor (Kim et al., 1994). Thus, the selectivity of this agent is not great enough to exclude the possibility that CGS 21680 in behavioral experiments has activity at the A_1 receptor. Findings in mice that the administration of the adenosine A_1 receptor antagonists DPCPX and 8-CPT partially prevents the development of extinction of responding for self-administered cocaine (Kuzmin et al.,

1999) suggests that A_1 receptor might play a role in regulating cocaine-seeking behavior. Adenosine A_1 and A_2 selective agonists have been shown to act synergistically in mice to produce locomotor depression (Nikodijevic et al., 1991). This suggests the possibility that adenosine A_1 and A_2 could interact to influence responding for cocaine.

The results of this study suggest that adenosine agonists can have inhibitory actions on the motivational systems associated with cocaine self-administration. Evidence from other studies presented above suggests that nonspecific behavioral impairment may not account for the long delays that occur before animals began self-administering cocaine in this study. Future investigations using central infusions of adenosine agonists and the administration of adenosine kinase inhibitors that activate only central adenosine systems may help to further establish just how specific are the effects of adenosine agonists on cocaine-seeking behavior.

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