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Behavioral Effects of Intrastriatal Caffeine Mediated by Adenosinergic Modulation of Dopamine

SHEENA A. JOSSELYN AND RICHARD J. BENINGER[1]

Department of Psychology, Queen's University, Kingston, Canada, K7L 3N6

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JOSSELYN, S. A. AND R. J. BENINGER. *Behavioral effects of intrastriatal caffeine mediated by adenosinergic modulation of dopamine*. PHARMACOL BIOCHEM BEHAV **39**(1) 97–103, 1991.—Although caffeine is generally classified as a psychomotor stimulant, the neurotransmitter systems mediating its effect on behavior have not yet been established. Mounting evidence suggests possible involvement of adenosinergic and/or dopaminergic (DA) systems. To evaluate these possibilities, four experiments examined circling behavior in rats following unilateral intrastriatal microinjections of: 1) caffeine alone; 2) the adenosine agonist, 2-chloroadenosine (2-CADO) alone; 3) caffeine with 2-CADO pretreatment; and 4) caffeine with pretreatment of the DA receptor antagonist, *cis*-flupenthixol. Each experiment consisted of seven test sessions; the first and seventh were preceded by no treatment, the second and sixth by control microinjections (saline or *cis*-flupenthixol) and the third, fourth and fifth by drug microinjections. Results showed that 10.0 and 20.0 but not 1.0 μg of caffeine produced a significant contraversive bias in circling behavior, while 2.0 and 5.0 but not 1.0 μg doses of 2-CADO produced significant ipsiversive circling. Rats pretreated with central 2-CADO or *cis*-flupenthixol (in doses that did not influence circling bias when administered alone) prior to caffeine (10.0 μg) failed to exhibit a contraversive bias. Taken together, the present studies provide compelling support for the suggestion that the motor effects of intrastriatal caffeine are mediated by the antagonism of endogenous adenosine which, in turn, functionally increases DA.

Caffeine Adenosine Dopamine Striatum Circling behavior Rat

CAFFEINE is among the most widely consumed behaviorally active compounds (2) and has been used (some would argue abused) since antiquity (24). Although generally classed as a psychomotor stimulant (44,45), the precise neuropharmacological characterization of this common substance remains incomplete. Efforts to define the neurotransmitter actions underlying the stimulant effects of caffeine have implicated an antagonism of the endogenous neuromodulator adenosine (11, 19–21, 33, 46). Thus application of adenosine inhibits the spontaneous firing of central neurons, while caffeine application reverses this slowing (14,26); adenosine depresses locomotor activity and operant responding (1, 15, 42, 50), which can be reversed by methylxanthines such as caffeine or theophylline (16, 26, 27, 34, 48, 55); and a correlation has been demonstrated between the potency of ten methylxanthines to stimulate locomotor activity and their respective potencies as inhibitors of binding of adenosine receptor ligands (11, 46, 54).

An underlying dopaminergic mediation of the excitatory effects of caffeine has also been hypothesized. Although caffeine has no direct interactions with the dopamine (DA) receptor (35,52), contradictory evidence regarding the effect of caffeine on central DA has been reported. Thus data obtained from in vitro studies have reported caffeine to increase the release of DA in mice (52) and rats (6), decrease DA release (9,17) or exert no effect (32). Additionally, caffeine and theophylline have been reported to reduce DA turnover, an effect shared by amphetamine (9).

Mounting behavioral evidence demonstrates that the consequences of caffeine administration are similar to those produced by the DA agonist, amphetamine. Thus caffeine-induced hyperactivity in rodents can be partially blocked by the DA receptor antagonist pimozide (18,52), prevented by alpha-methyl-para-tyrosine (AMPT) but reinstated upon administration of L-DOPA (55). Haloperidol-induced catalepsy was reported to be dose-dependently reversed by theophylline (8), while haloperidol reportedly antagonized the stimulation of respiration induced by theophylline (35).

Rotational behavior following unilateral manipulations of DA provides an index of lateralized striatal DA activity (25,43). Unilateral imbalances of DA produced via lesion, electrical stimulation or intracerebral drug injections result in a directional bias with rats typically rotating away from (contraversive to) the side of greater DA activity (43). For example, amphetamine or apomorphine, when unilaterally injected directly into the striatum, produced contraversive rotation (25,31), while similar administration of the DA antagonist haloperidol evoked ipsilateral circling in rats receiving systemic apomorphine (10).

[1]Requests for reprints should be addressed to Richard J. Beninger.

Experiments investigating caffeine and adenosine using the rotational paradigm have drawn uncertain conclusions as to the neuropharmacology of caffeine's effects, specifically caffeine's relationship to adenosine and DA. Systemic caffeine has been found to produce intense contraversive rotation in rats with unilateral denervation of the nigrostriatal pathway (7,23), an effect shared by L-DOPA and apomorphine (23,49). Furthermore, caffeine enhanced the rotation induced by L-DOPA and apomorphine (22,23). The intensive contraversive circling evoked by caffeine was partially blocked by DA antagonists in rats (30,53) and, in similarly prepared mice, was decreased by AMPT (53). No circling, however, has been reported following unilateral striatal administration of caffeine in otherwise intact rats, although apomorphine was effective (30). The authors concluded that the effect of caffeine was dependent on receptors rendered supersensitive due to denervation.

Green et al. (28) reported ipsiversive circling following unilateral striatal injection of 5′-N-ethylcarboxamide adenosine (NECA), an adenosine agonist, in intact rats pretreated with subcutaneous apomorphine. The authors suggested that NECA had interfered with the action of apomorphine in the ipsilateral striatum leaving the contralateral striatum unaffected and presumably with higher DA activity. Thus the rat circled ipsiversively. However, no rotation was observed following intrastriatal NECA administration in rats not also pretreated with apomorphine.

The present study was designed to more closely define the involvement of and relationship between intrastriatal caffeine, adenosine and DA in the rotational biases observed in otherwise intact rats. We demonstrate for the first time that intrastriatal caffeine produces a contralateral bias in the rotational behavior observed in intact rats and that this effect is blocked by intrastriatal pretreatment with either an adenosine agonist or a dopamine antagonist.

METHOD

Animals

Male Wistar rats (Charles River, Canada) were individually housed in hanging wire cages and maintained in a controlled environment on a 12-h light/dark cycle (lights on at 0600 h). Food and water were continuously available in the home cages. Animals weighed between 300 and 360 g at the time of surgery.

Surgeries

Each animal was anaesthetized with sodium pentobarbital (60 mg/kg, IP), placed in a stereotaxic device and surgically prepared with chronic indwelling guide cannulae (0.64 mm diam) aimed at the anterodorsal region of the striatum; coordinates were 0.26 mm posterior to bregma, 3.0 mm lateral to the midline and 3.5 mm ventral to the surface of the skull with the incisor bar set at 3.2 mm below the horizontal plane passing through the interaural line (41). The cannulae were anchored to the skull with stainless-steel screws and dental cement. When not in use, the guide cannulae were occluded with wire pins. Following surgery, rats were allowed to recover for 1 week before further experimental manipulations.

Apparatus

Three circular wooden-bottomed arenas (30.0 cm dia.) with wire mesh sides (30.0 cm high) were used for testing rotational behavior.

Drugs

Caffeine (Sigma), 2-chloroadenosine (2-CADO) (Research Biochemical Incorporated), *trans*-flupenthixol and *cis*-flupethixol (H. Lundbeck A/S) were dissolved daily in normal saline.

Central Injections

A Hamilton microsyringe (10.0 μl) mounted in an infusion pump (Sage Instruments Pump Model 355) was used to infuse the drug at a rate of 1.0 μl per minute. Injection cannulae (0.31 mm dia.) made of stainless steel tubing were cut to extend 1.0 mm beyond the tips of the guide cannulae and were attached to the microsyringe by plastic tubing. The injection cannulae were maintained in position following injection for an additional min to ensure diffusion of the drug.

Behavioral Evaluation

Four experiments (using a unique set of rats for each) adhered to the same general protocol. All rats were observed for circling behavior following seven treatments: 1) no injection; 2) control injection; 3), 4), 5), three drug injections; 6) replication of control; and 7) replication of no injection. Test sessions occurred every 72 h between the hours of 0900 to 1300. The number of complete ipsiversive and contraversive rotations were manually counted for two time periods (0–5 and 15–20 min).

The order of treatments in each of the four experiments is shown in Table 1. The first experiment examined the effects of caffeine (1.0, 10.0, 20.0 μg in 1.0 μl) on circling, the second the effects on the adenosine agonist, 2-CADO (1.0, 2.0, 5.0 μg in 1.0 μl). In each case the three drug doses were given in a counterbalanced order. The third and fourth were interaction experiments which attempted to block the effect of caffeine established in the first experiment. The adenosine agonist, 2-CADO was centrally administered 15 min before caffeine in the third experiment, while *cis*-flupenthixol was similarly administered in the fourth experiment. Thus, in the third and fourth experiments, the third and fifth treatments involved caffeine (10.0 μg) preceded 15 min earlier by vehicle (saline or *trans*-flupenthixol in Experiments 3 and 4, respectively); the fourth treatment sessions involved injection of caffeine (10.0 μg) preceded by 2-CADO (1.0 μg; Experiment 3) or *cis*-flupenthixol (20.0 μg; Experiment 4). In addition, the second and sixth treatment sessions for the fourth experiment were *cis*-flupenthixol (20.0 mg).

Circling scores were determined for each session by calculating the ratio of ipsilateral over total turns with scores under 0.5 indicative of a contraversive bias and those over 0.5 representing an ipsiversive bias. Following behavioral testing, cannulae placements were verified histologically.

RESULTS

Rats were included in subsequent statistical analyses if the cannula tip was between 5.8 and 7.0 mm in the ventral coordinate, 2.2 and 4.2 mm lateral and within 0.75 mm of the posterior coordinate (Fig. 1). The number of rats surgically prepared and the number conforming to the above guidelines for experiments 1–4 was 17 or 21, 17 of 18, 15 of 15 and 11 of 14, respectively.

Student *t*-tests for correlated measure performed on the no-injection scores from the first and seventh sessions of each of the four experiments did not reveal any significant differences within each experiment; scores were, therefore, averaged. Similarly, as the control injection scores from the second and sixth sessions from all experiments did not differ, they too were averaged. Circling score means (±SEM) for these sessions ranged from 0.48 (±0.04) to 0.63 (±0.02).

Experiment 1: Caffeine-Induced Circling

Experiment 1 evaluated the effects of caffeine doses of 1.0, 10.0 and 20.0 μg delivered in a volume of 1.0 μl. A one-way

TABLE 1

OUTLINE OF EXPERIMENTAL PROTOCOL

	Treatment Session						
Experiment	1	2	3	4	5	6	7
1*	no injection	1.0 μl saline	1.0 μg caffeine	10.0 μg caffeine	20.0 μg caffeine	1.0 μl saline	no injection
2*	no injection	1.0 μl saline	1.0 μg 2-CADO	2.0 μg 2-CADO	5.0 μg 2-CADO	1.0 μl saline	no injection
3	no injection	1.0 μl saline	1.0 μl saline + 10.0 μg caffeine	1.0 μg 2-CADO + 10.0 μg caffeine	1.0 μl saline + 10.0 μg caffeine	1.0 μl saline	no injection
4	no injection	20.0 μg c-flu	20.0 μg t-flu + 10.0 μg caffeine	20.0 μg c-flu + 10.0 μg caffeine	20.0 μg t-flu + 10.0 μg caffeine	20.0 μg c-flu	no injection

*The three doses in sessions 3, 4 and 5 were given in a counterbalanced order across rats. Abbreviations: 2-chloroadenosine (2-CADO); *cis*-flupenthixol (c-flu); *trans*-flupenthixol (t-flu).

Rats with unilateral chronic indwelling cannulae aimed at the striatum received microinjections according to the schema presented above. Following injections rats were behaviorally evaluated for circling bias.

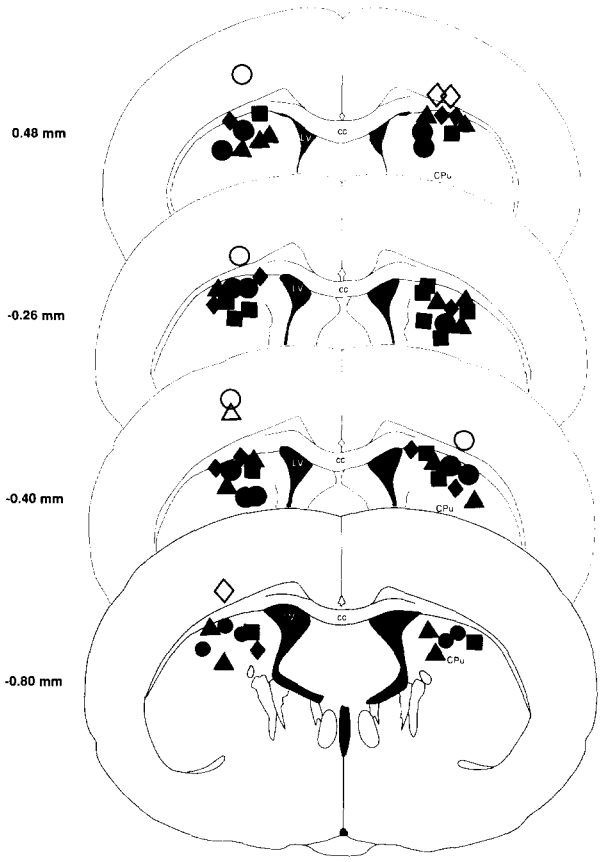

FIG. 1. Cannulae placements for rats completing experiments. Filled symbols (circles, triangles, squares and diamonds for Experiments 1 through 4, respectively) represent the tips of the cannulae for those deemed to be accurate placements, while open symbols represent those with inaccurate placements. Coronal sections were reproduced from Paxinos and Watson (41). Number beside each section indicates the distance in mm anterior to bregma.

analysis of variance (ANOVA) for repeated measures on the five circling scores (no injection, control injection and the three doses of caffeine) revealed a significant effect of treatment, $F(4,64) = 65.21$, $p<0.001$. Dunnett's tests comparing the vehicle treatment to all others revealed that rats receiving 10.0 and 20.0 μg showed significantly lower circling scores, indicating a tendency to circle contraversively (Fig. 2). The mean number (±SEM) of total (10 min) turns for each treatment were as follows: 9.32 (±0.48), 9.56 (±0.52), 9.18 (±0.51), 11.00 (±0.76) and 11.65 (±0.81). A repeated measure ANOVA revealed a significant effect of treatment, $F(4,64) = 3.58$, $p<0.01$.

Experiment 2: 2-CADO-Induced Circling

Doses of 1.0, 2.0 and 5.0 μg in a volume of 1.0 μl of the adenosine agonist, 2-CADO were examined. A one-way ANOVA

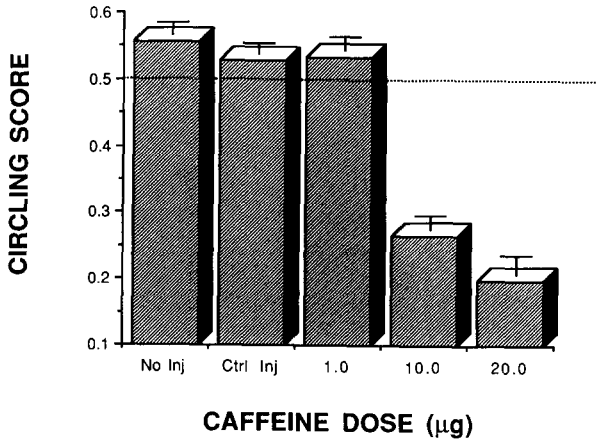

FIG. 2. Circling induced by caffeine. Mean (±SEM) circling scores for rats in Experiment 1. The bars represent no injection (No Inj), control injection (Ctrl Inj; saline) and injections of 1.0, 10.0 and 20.0 μg caffeine. The horizontal dotted line at 0.5 represents no circling bias: scores above this line are indicative of an ipsiversive circling bias while scores below are indicative of a contraversive bias. A significant contraversive circling bias was produced by 10.0 and 20.0 μg of caffeine (*$p<0.01$). n = 17.

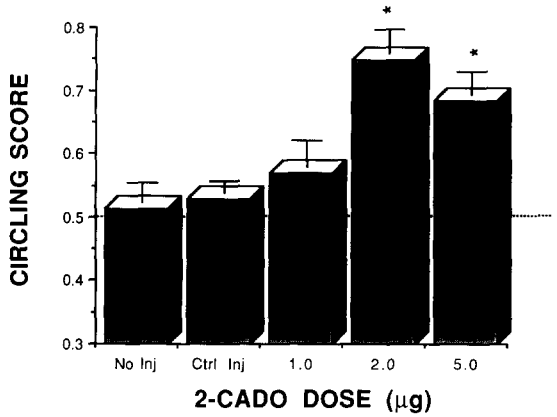

FIG. 3. Circling induced by 2-chloroadenosine (2-CADO). Mean (+SEM) circling scores for rats receiving no injection (No Inj) and microinjections of saline (control injection; Ctrl Inj) and 1.0, 2.0 and 5.0 μg of 2-CADO. A significant ipsiversive bias was produced by 2.0 and 5.0 μg of 2-CADO (*$p<0.01$). n = 17.

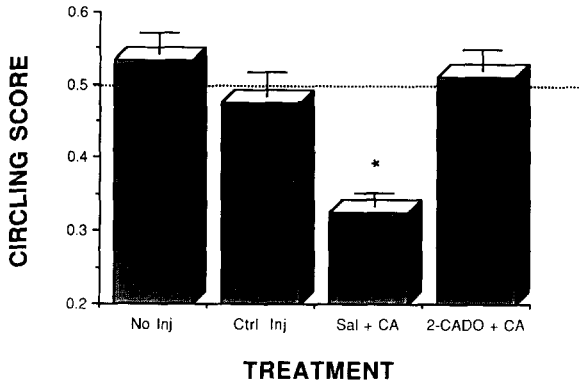

FIG. 4. The contralateral circling bias induced by caffeine is blocked by 2-CADO pretreatment. Mean (+SEM) circling scores for no injection (No Inj), control injection (Ctrl Inj; saline), saline (Sal) followed 15 min later by 10.0 μg caffeine (CA) and 2-CADO (1.0 μg) followed 15 min later by caffeine (10.0 μg). Saline pretreatment did not block the contraversive circling bias produced by caffeine (*$p<0.01$) but this bias was blocked by 2-CADO pretreatment. n = 15.

revealed a significant effect of treatment, $F(4,64) = 8.96$, $p<0.001$. Post hoc analysis showed that the two higher doses of 2-CADO produced significantly higher scores demonstrating an ipsiversive circling bias, an effect opposite in direction to that observed with caffeine (Fig. 3). The mean number (±SEM) of turns for the five treatments were: 9.32 (±0.41), 9.97 (±0.59), 8.82 (± 0.56), 8.09 (±0.41) and 7.65 (±0.59). A one-way ANOVA showed a significant effect of treatment, $F(4,64) = 3.58$, $p<0.01$.

Experiment 3: 2-CADO Versus Caffeine-Induced Circling

If the rotational response to caffeine critically involved the antagonism of adenosine, it should have been possible to prevent the contraversive circling bias with intrastriatal coadministration of an adenosine agonist. The third experiment examined the effect of coadministration of caffeine and 2-CADO. Circling scores (±SEM) for drug sessions 1 and 3 (saline followed by caffeine) were 0.32 and 0.33, respectively, and did not differ significantly from each other according to a *t*-test for correlated measures and were averaged. The resulting four circling scores (no injection, control injection, saline followed by caffeine and 2-CADO followed by caffeine) were analyzed with an ANOVA. A significant effect of treatment was found, $F(3,42) = 13.35$, $p<0.001$. Post hoc analysis revealed that the circling scores for the saline followed by caffeine treatment were significantly lower, replicating the contraversive circling effect of caffeine. When caffeine was preceded by 2-CADO, no significant circling bias was seen. Thus a dose of 2-CADO that did not produce a significant circling bias when administered alone (in Experiment 2) completely blocked the caffeine effect when given in conjunction with it (Fig. 4). These results suggest that caffeine may produce its behavioral effects by antagonizing adenosine.

The mean number (±SEM) of turns for each treatment were as follows: 9.53 (±0.27), 8.63 (±0.49), 9.93 (±0.65) and 7.93 (±0.62). A significant effect of treatment, $F(3,42) = 4.32$, $p<0.01$, was revealed by an ANOVA.

Experiment 4: DA Antagonist Versus Caffeine-Induced Circling

If the effects of caffeine were on dopaminergic neurons, a blockade of DA receptors should have modified the rotational behavior produced by caffeine. To test this hypothesis, Experiment 4 was designed similar to Experiment 3 and using the DA receptor blocker *cis*-flupenthixol in an attempt to antagonize the contraversive circling bias produced by caffeine. Thus the second and sixth treatments in Experiment 4 were a dose of *cis*-flupenthixol that produced no circling bias when administered alone and the three drug injection sessions were as follows: 1) *trans*-flupenthixol (20.0 μg), the biologically inactive geometric isomer of *cis*-flupenthixol followed 15 min later by caffeine (10.0 μg); 2) *cis*-flupenthixol (20.0 μg), the biologically active DA antagonist, followed by caffeine (10.0 μg); 3) repeat of condition 1 above. Mean circling scores for drug conditions 1 and 3 (0.31 and 0.30, respectively) did not differ according to Student's *t*-tests and were averaged. An ANOVA performed on the four circling scores [no injection, 20.0 μg *cis*-flupenthixol alone, *trans*-flupenthixol (20.0 μg) followed by caffeine (10.0 μg) and *cis*-flupenthixol (20.0 μg) followed by caffeine (10.0 μg] showed a significant treatment effect, $F(3,30) = 5.34$, $p<0.01$. Dunnett's tests comparing all the treatment scores to *cis*-flupenthixol alone showed a significantly lower circling score (indicative of a contraversive circling bias) in the *trans*-flupenthixol followed by caffeine condition. When caffeine was preceded by *cis*-flupenthixol, no significant circling bias was seen. Thus *cis*-flupenthixol administered before caffeine completely blocked the contraversive circling produced by caffeine (Fig. 5).

Analysis of variance performed on total turns across treatments [8.50 (±0.65), 8.57 (±0.35), 9.30 (±0.67) and 9.15 (±0.57)] revealed no significant effect.

DISCUSSION

In each of the four experiments, the three drug treatment sessions were bracketed by no injection and control injection treatments. The circling scores obtained from the predrug and postdrug no injection and control injection sessions did not differ significantly from one another and, further, most averaged roughly 0.5, indicating no directional bias. Thus chronic cannulation, control injections and a history of several central drug treat-

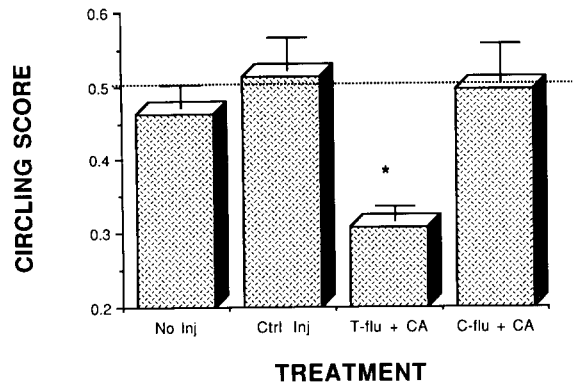

FIG. 5. The contralateral circling bias induced by caffeine is blocked by *cis*-flupenthixol pretreatment. Mean (+SEM) circling scores for no injection (No Inj), control injection (Ctrl Inj; 20.0 μg *cis*-flupenthixol), caffeine (CA; 10.0 μg) after pretreatment with *trans*-flupenthixol (T-flu; 20.0 μg) and caffeine (10.0 μg) following pretreatment with *cis*-flupenthixol (C-flu). Pretreatment with *trans*-flupenthixol did not block the contraversive circling bias produced by caffeine (*$p<0.01$) but this bias was completely blocked by *cis*-flupenthixol. n = 11.

ments did not significantly affect circling bias. This finding is in agreement with previous experiments employing a similar paradigm to evaluate circling effects in the frontal cortex (3, 37, 38, 47) and further attests to the reliability of this method of studying circling bias.

Experiments 1, 3 and 4 demonstrated that intrastriatal caffeine induced a contraversive circling bias in otherwise intact rats. This finding is contrary to that of Herrera-Marshitz et al. (30) who reported that while intrastriatal caffeine produced dose-dependent contraversive rotation in rats with denervated striata, similar administration of caffeine (50.0–100.0 μg) failed to produce rotational behavior in otherwise intact rats. There are several possible explanations for this discrepancy. Firstly, the differences between the dose range tested in the Herrera-Marschitz study (50.0–100.0 μg) and that used in the present study (1.0–20.0 μg) may account for contradictory results. This speculation is supported by the finding that the dose-response curve for the effects of systemic caffeine on locomotor activity is an inverted U (5, 12, 13).

The instrumentation used to evaluate the effect of caffeine may also be a possible source of this discrepancy. Herrera-Marschitz et al. (30) used an automated circular bowl rotometer to record the number of turns per min and at times counted as many as 9000 contraversive turns following caffeine in lesion rats. The present study relied on direct observation to count the number and direction of rotations and at times counted fewer than ten circles per five-minute period. Perhaps an effect of this small magnitude was not detected in the previous studies. Although the present number of rotations is comparatively small, caffeine's influence on circling was reliably demonstrated, dose-dependent, replicated and was shown to be sensitive to the blocking effect of 2-CADO or the DA antagonist. The circling described in the present paradigm was not of the compulsive nose-to-tail variety described by some authors (30) but rather a slow continuous or noncontinuous wide rotation not accompanied by postural deviations.

Thirdly, Herrera-Marschitz et al. (30) used the number of contralateral rotations as the dependent measure, while the present study focused on circling bias by comparing the number of ipsiversive rotations to the total number of rotations. In this way, a rat would exhibit a contraversive bias even if as few as four contraversive and one ipsiversive rotation were counted (circling score = 1/5 = 0.20). If four contraversive and four ipsiversive rotations were counted, a circling score of 0.5, indicative of no circling bias, would be given. By focusing on the number of contraversive rotations alone, the differences in ratio of rotations would be overlooked.

The adenosine agonist 2-CADO was observed to dose-dependently induce an ipsiversive rotational bias. Green et al. (28) found that NECA, also an adenosine agonist, produced similar results in rats that were cotreated with subcutaneous apomorphine, but failed to find that NECA alone, in otherwise untreated rats, produced circling behavior. Again, the source of this discrepancy may be the use of different measuring techniques.

The third experiment demonstrated that the contraversive circling bias evoked by caffeine was prevented by pretreatment with an adenosine agonist that, when administered alone, produced no effect on circling (see Experiment 2). Green et al. (28) attempted to block the circling resulting from intrastriatal NECA and subcutaneous apomorphine with theophylline (100 mg/kg, IP). These authors found that the total number of rotations was significantly decreased by theophylline administration but found complicating motor effects with animals receiving all three drugs. The present results are in general agreement with those of Green et al. (28) and provide clear evidence for an adenosinergic mediation of the behavioral action of intrastriatal caffeine.

The fourth experiment demonstrated that control injections of *cis*-flupenthixol (20.0 μg) did not affect circling bias. This is in agreement with previous findings of Costall et al. (10) that *cis*-flupenthixol, when not given in conjunction with peripheral apomorphine, induced no rotation. The finding that *cis*-flupenthixol was able to block the effects of caffeine on circling suggests that the behavioral effects of caffeine may be mediated by dopamine. This is in excellent agreement with biochemical data showing that caffeine enhances DA release (6, 9, 51). As the results of Experiment 3 show that caffeine acts via adenosinergic receptors, results are also in agreement with biochemical data showing that adenosine inhibits synthesis and release of DA from striatal slices in the rat (29,39) and synaptosomes (36) and as measured by in vivo voltammetry (40).

In the field of drug addiction, many authors have focused on the ability of most addictive substances to reward behavior via an enhancement of DA function (4). The present results, by demonstrating a caffeine-DA link, help to substantiate caffeine's inclusion in this category and further infer a possible role for adenosine in the etiology and perhaps treatment of addictions.

In summary, the results showed that intrastriatal caffeine caused a contraversive bias in circling behavior that was blocked with either an adenosine agonist or DA antagonist. This suggests that the mechanism for the behavioral action of intrastriatal caffeine may be an inhibition of adenosine and subsequent increase in DA function. These results suggest that the behavioral effects of intrastriatal caffeine are ultimately mediated by DA.

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