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Interactive Effects of Caffeine, 2-Chloroadenosine and Haloperidol on Activity, Social Investigation and Play Fighting of Juvenile Rats

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HOLLOWAY, W. R., JR. AND D. H. THOR. *Interactive effects of caffeine, 2-chloroadenosine and haloperidol on activity, social investigation and play fighting of juvenile rats.* PHARMACOL BIOCHEM BEHAV **22**(3) 421–426, 1985.—The effects of caffeine, 2-chloroadenosine and haloperidol and their interaction on activity, social investigation, and two measures of play fighting (crossover and pinning), were investigated in juvenile male rats. Caffeine (20 mg/kg) increased activity, decreased crossover and pinning, but had no effect on social investigation. Both 2-chloroadenosine (0–10 mg/kg) and haloperidol (0–10 mg/kg) depressed activity, social investigation, crossover and pinning. When given together in varying dosages, caffeine and 2-chloroadenosine had behavioral effects suggestive of a competitive interaction between the two drugs. In contrast, the effects of haloperidol were not appreciably altered by simultaneous caffeine treatment. These results suggest that the influence of caffeine and 2-chloroadenosine on activity, social investigation and play fighting involve interaction with adenosine receptors.

Rat Juvenile Pre-pubertal Social investigation Activity Play fighting Pin Crossover Caffeine 2-Chloroadenosine Haloperidol Adenosine receptor

ADENOSINE is an endogenous neuromodulatory substance which binds to high and low affinity receptors (A1 and A2, respectively) in the brain and periphery (see [6, 7, 26] for reviews). Adenosine and adenosine analogs typically inhibit firing rates of neurons and have been shown to suppress behavioral activity and some forms of experimentally induced seizures (e.g., [9, 18, 29]), induce moderate analgesia and hypothermia [9, 28, 29], and decrease escape behaviors [28], heart rate and blood pressure (e.g., [18,26]). Adenosine receptors are present in the brain at birth, as evidenced by biochemical [10,19] and pharmacological methods [11, 12, 13], increasing in number during lactation and the prepubertal period. Methylxanthines, including caffeine, are competitive antagonists of adenosine biochemically, and have been shown to interfere with the behavioral effects of adenosine analogs in the adult (e.g., [9, 18, 28, 29] and infant [12].

The pharmacological regulation of behaviors of rats between weaning and puberty has been of increasing interest [30]. There is some suggestion that this may be a neurochemically unique period, at least in the rat, evidenced in part by reduced behavioral responsiveness to amphetamine in prepubertally aged subjects. However, little is known about the effects of adenosine agonists or antagonists on behaviors of the juvenile. Recent finding indicate that the actions of many drugs (e.g., opioids, antipsychotics, benzodiazepines, antidepressants, coronary vasodilators and nonsteroidal anti-inflammatory agents) may include some alteration of adenosine function [26]. In earlier studies we found that caffeine increased locomotor activity of rats, regardless of age [14, 16, 32]. However, pinning, an index of play fighting behavior which occurs with relatively high frequency between weaning and puberty (e.g., [14, 20, 22, 23, 27, 35]), was depressed in a dose dependent manner by caffeine [14,16], as was crossover, a measure of play initiation [32]. Social investigation of another juvenile was not influenced by caffeine until the male subjects were at least 44 days old, when the drug caused an increase in social investigation. Subsequent studies have linked this caffeine-induced increase in social investigation to the presence of gonadal testosterone [17].

The following experiments provide evidence that the effects of caffeine and 2-chloroadenosine (adenosine antagonist and agonist, respectively) on behaviors of juvenile rats involve interaction with adenosine receptors. Haloperidol, which was found to have behavioral effects similar to 2-chloroadenosine, was used to indicate pharmacological specificity of the interactive effects of caffeine and 2-chloroadenosine.

METHOD

Subjects

Male Long-Evans hooded rats from our colony were used as subjects. The rats were born to nulliparous females (day of birth=Day 0) and reared in litters of nine with food and water always available. At weaning (Day 21) subjects were

ear punched and housed together with males from another litter. Lights were on a 12:12 light/dark cycle (lights on at 2:00 p.m.).

Treatment

On the day before testing subjects were weighed and isolated in plastic cages (41×51×22 cm) with food and water always available. Twenty hr later each rat was injected subcutaneously (SC) on the dorsolateral surface with the appropriate drug dosage and returned to its cage. When two drugs were administered, one was injected immediately after the other. Twenty min later, cage quadrants entered by the subject in 2 min were counted. Immediately thereafter a juvenile intruder was placed in the subject's cage. Social investigation of the intruder by the subject, and two play fighting behaviors exhibited by the subject (pinning and crossover) were recorded. Except for the first study (2-Chloroadenosine (1)), where the test period was 10 min long, all observations of social investigation and play fighting lasted 6 min. Social investigation was noted whenever the subject's head was directed toward the intruder (<2 cm) and he was following, sniffing or otherwise actively investigating the intruder. Because the intruder typically engaged in very little investigation of the resident, investigative behaviors by the intruder (including mutual grooming) were not recorded. Pinning was easily discerned, occurring when one rat was held inverted with the other rat standing over him. Crossover was recorded whenever the resident's body completely traversed the trunk of the intruder, regardless of direction of approach. Virtually all crossovers involved the resident moving over the dorsal surface of the intruder.

Social investigation and pinning were recorded on paper tape using hand activated switches. Crossover frequency was recorded at 1 min intervals during the observation. Intruders were unfamiliar, group-housed males similar in age to the subjects. In nearly all cases an intruder was used only once on any test day. Testing was done in dim red light in the last half of the dark period.

2-Chloroadenosine and Haloperidol Dose Curves

2-Chloroadenosine (1). Male rats 44–47 days old were used as subjects, receiving a SC injection of vehicle, 0.1 or 1 mg/kg 2-chloroadenosine (2-CA) (n=6/dose) prior to testing. Crossover frequency was not recorded in this experiment. The 2-CA (Sigma) was dissolved in 0.9% NaCl vehicle and injected in the volume of 1 ml/kg.

2-Chloroadenosine (2). Male rats 27–35 days old received SC injections of 0, 0.1, 1, and 10 mg/kg 2-CA before testing (ns=10 in the 0, 0.1 and 1 mg/kg groups, n=6 in the 10 mg/kg group). Subjects were derived from 20 litters but were assigned to treatment without regard to litter.

Haloperidol. Subjects were male rats (36–41 days old) and received 0, 0.01, 0.1, 1.0 or 10 mg/kg haloperidol before testing (n=9/dose). Haloperidol (Haldol, McNeil Laboratories, Injectable 5 mg/ml) was diluted in 0.9% NaCl vehicle immediately before use and injected in the volume 2 ml/kg. Subjects were from 10 litters but treatment was not nested within litter.

2-Chloroadenosine-Caffeine Interactions

Subjects were male rats (27–35 days old) given successive SC injections of 2-CA and caffeine. The following 11 groups were formed, determined by the 2-CA-caffeine dose combinations (mg/kg): 0–0, 0.1–0, 1–0, 10–0, 0–20, 0.1–20, 1–20, 10–20, 1–10, 1–30 and 1–40. Except for the 10–0 group where n=6, all groups contained 10 subjects. Anhydrous caffeine (Sigma) and 2-CA were dissolved in 0.9% NaCl vehicle solutions. All doses were given in the volume 2 ml/kg except for the 40 mg/kg caffeine dose where the injection volume was 4 ml/kg. Using these 2-CA-caffeine dose combinations we were able to determine if increasing doses of caffeine could reverse the effects of 2-CA (i.e., the 1–0, 1–10, 1–20, 1–30 and 1–40 groups, with the 0–0 and 0–20 groups serving as referents) and also whether caffeine could shift the dose response curve of 2-CA to the right (i.e., the 0–0, 0.1–0, 1–0, 10–0, 0–20, 0.1–20, 1–20 and 10–20 dose combinations). Subjects were from 20 litters. Rats in the 0–0, 0.1–0, 1–0 and 10–0 dose groups were the same subjects described in 2-Chloroadenosine (2) experiment above.

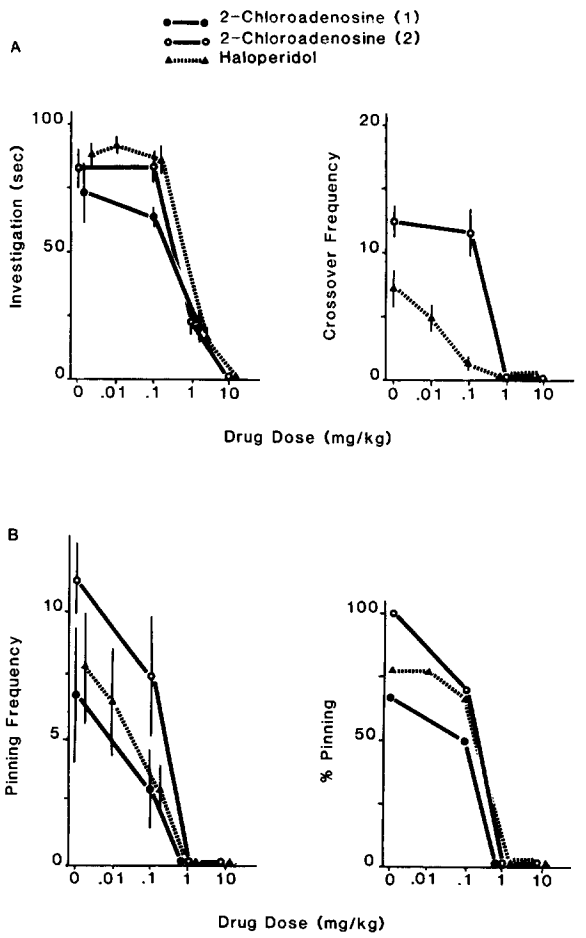

FIG. 1. (A and B) Behaviors of juvenile rats receiving increasing doses of 2-chloroadenosine or haloperidol. The 2-chloroadenosine data are from two different experiments, 2-Chloroadenosine (1) and 2-Chloroadenosine (2). In experiment 2-Chloroadenosine (1), crossover frequency was not recorded. With the exception of % subjects engaging in pinning (% Pinning), all data are expressed as mean±SE.

Haloperidol-Caffeine Interactions

Male rats 34–39 days old, from 15 litters, were tested after receiving two successive injections of one of the following haloperidol-caffeine dose combinations (mg/kg): 0–0, 0–20,

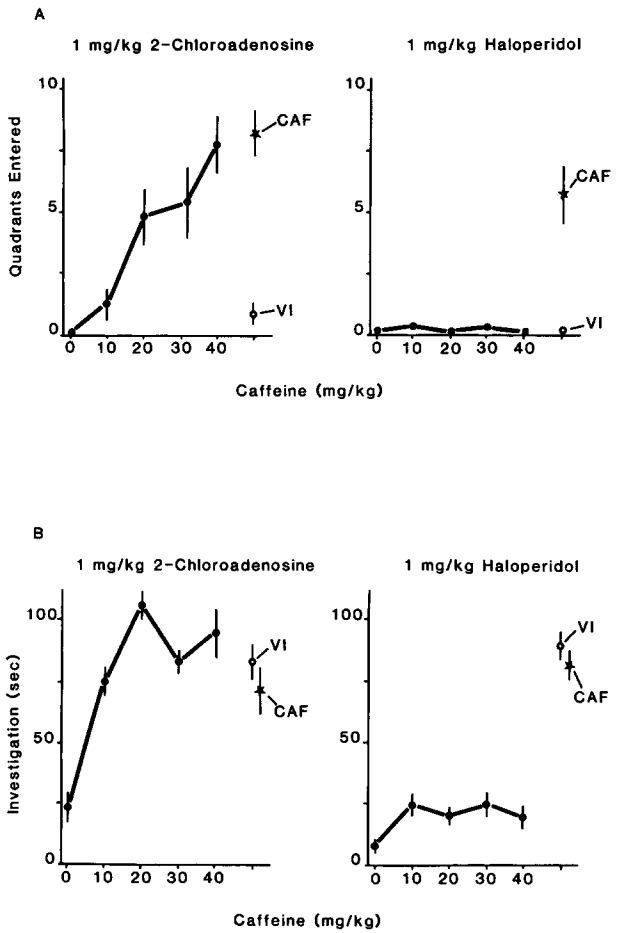

FIG. 2. Cage Quadrants Entered (A) and Investigation Duration (B) by juvenile rats receiving 1 mg/kg 2-chloroadenosine (left panel) or 1 mg/kg haloperidol (right panel) in combination with one of five doses of caffeine. Included for reference are data from subjects receiving only vehicle (VI) or only 20 mg/kg caffeine (CAF). All data are expressed as mean±SE.

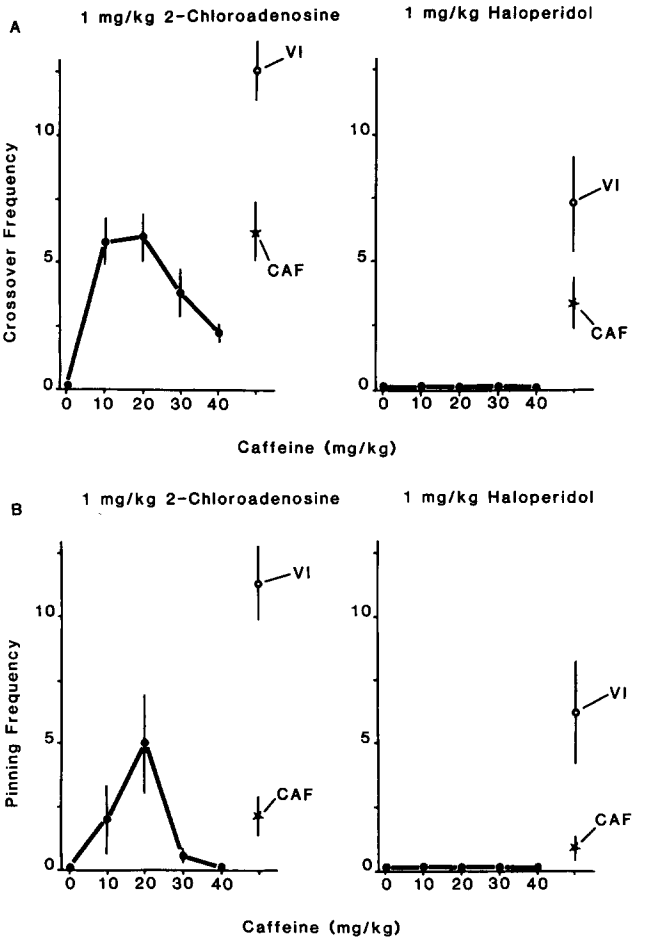

FIG. 3. Crossover Frequency (A) and Pinning Frequency (B) by juvenile rats receiving either 1 mg/kg 2-chloroadenosine (left panel) or 1 mg/kg haloperidol (right panel) in combination with one of five doses of caffeine. Included for reference are data from subjects receiving only vehicle (VI) or only 20 mg/kg caffeine (CAF). All data are expressed as mean±SE.

1–0, 1–10, 1–20, 1–30 or 1–40 (n=9/dose combination). These dose combinations enabled us to determine if caffeine could reverse the behavioral depressant effect of haloperidol. Haloperidol and caffeine solutions were injected in the volume 2 ml/kg and 4 ml/kg respectively.

RESULTS

2-Chloroadenosine and Haloperidol Dose Curves

The 2-CA and haloperidol dose curves for mean duration of social investigation, mean frequencies of crossover and pinning and % subjects engaging in pinning were analyzed by 1-way ANOVAs or χ^2 tests, where appropriate, and are presented in Fig. 1. The two drugs had very similar behavioral effects, each causing a dose dependent depression in all behaviors observed. With the exception of pinning frequency in the 2-Chloroadenosine (1) and Haloperidol experiments, where $F(2,15)=3.37$, $p=0.07$ and $F(4,40)=4.97$, $p<0.05$, respectively, the F's for all ANOVAs ranged from 10.9–85.5, ps<0.005. Subjects receiving 1 or 10 mg/kg of either 2-CA or haloperidol did not engage in pinning or crossover. Although social investigation was significantly reduced by 1 mg/kg doses of each drug ($p<0.05$), this behavior was only completely suppressed by the 10 mg/kg doses. Cage quadrants entered during the activity test were recorded for all subjects but the group means were uniformly low, ranging from 0–1.2±0.8.

2-Chloroadenosine-Caffeine Interactions

These data indicate that caffeine can reverse the effects of a single dose (1 mg/kg) of 2-CA (left panels of Figs. 2 and 3) and that the dose curves for 2-CA are shifted to the right by caffeine (Fig. 4). Both results suggest a competitive interaction between caffeine and 2-CA.

Included in Figs. 2 and 3 (left panels) are data from subjects who received only vehicle (VI) or only 20 mg/kg caffeine (CAF). Rats in the CAF group had higher cage quadrants entered scores and lower mean crossover and pinning frequencies relative to subjects in the VI group, ts$(18)=6.6$, 3.75 and 5.23, ps<0.005, respectively. There was no effect of caffeine on social investigation. These data replicate other work [14, 17, 32].

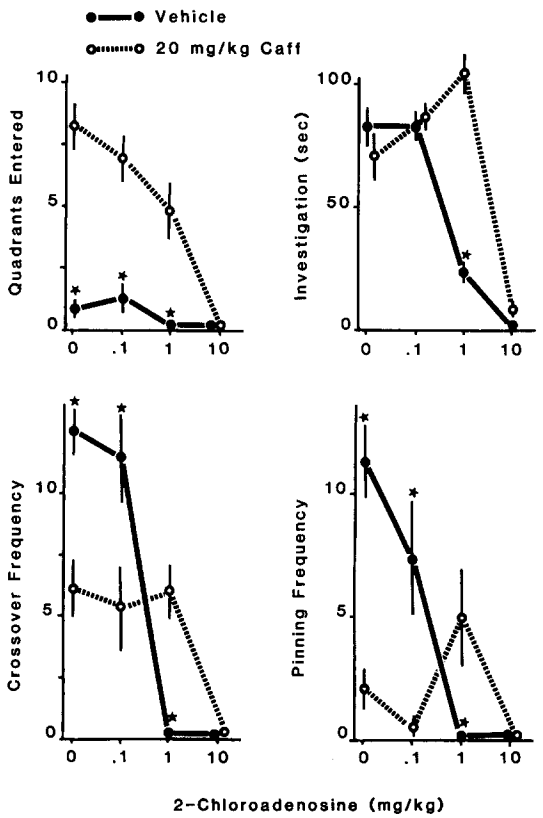

FIG. 4. Behaviors (mean±SE) of juvenile rats receiving either vehicle or 20 mg/kg caffeine in conjunction with one of four doses of 2-chloroadenosine. A star denotes 2-chloroadenosine groups that differed significantly ($p<0.05$) from the comparable 2-chloroadenosine dose group also given 20 mg/kg caffeine.

The left panels of Figs. 2 and 3 describe the interactive effect of caffeine and 2-CA. For cage quadrants entered (Fig. 2A left panel), caffeine alleviated the depressant effects of 2-CA, $F(5,54)=10.2$, $p<0.001$. The 40 mg/kg caffeine dose, when given with 1 mg/kg 2-CA, produced a level of activity equal to that found in control subjects receiving 20 mg/kg caffeine (the CAF group). Similarly, caffeine reversed the depressant effect of 2-CA on social investigation, $F(5,54)=15.2$, $p<0.001$. This reversal was evident in the 10 mg/kg caffeine group (Fig. 2B, left panel), which did not differ from the group that received only the vehicle (VI). Somewhat different displacement curves were observed for both crossover and pinning, presumably because both caffeine and 2-CA suppress these behaviors. Increasing the dose of caffeine partially reversed the 2-CA induced decrease in each behavior (see Figs. 3A and B, left panels). Crossover and pinning frequency increased when 10 and 20 mg/kg caffeine were given with 1 mg/kg 2-CA; however the frequencies of both behaviors fell at the 20 and 40 mg/kg caffeine doses. All caffeine dose groups differed significantly from the VI group for both behaviors ($p<0.01$). Significance was still observed when the VI group was excluded from the analyses of the caffeine dose, $Fs(4,45)=8.9$ and 3.8, $ps<0.05$, indicating the reliability of the inverted U functions observed for mean crossover and pinning frequencies. Thus, for cage quadrants entered, social investigation, crossover and pinning, caffeine partially or completely reversed the depressant effects of 2-chloroadenosine.

Similar results were obtained when 20 mg/kg caffeine or vehicle was given to subjects receiving increasing doses of 2-CA (See Fig. 4), i.e., the 2-CA dose curves for cage quadrants entered, social investigation, crossover and pinning behavior were shifted to the right by simultaneous administration of caffeine. These effects were reflected in significant interactions for the four behaviors, $Fs(3,68)=7.99$, 18.6, 11.24 and 11.81, $p<0.001$, respectively. The inverted U function noted above when caffeine was used to reverse 2-CA's effect on pinning was also evident when 2-CA was used to reverse the effect of caffeine. Although the dose curve for 2-CA's depressant effect on crossover was shifted to the right by caffeine, there was no inverted U function.

Haloperidol-Caffeine Interactions

These data are presented in the right panels of Figs. 2 and 3 and provide evidence of pharmacological specificity for the 2-chloroadenosine-caffeine interactions noted above. Because so few subjects receiving both caffeine and haloperidol entered cage quadrants during the activity test or exhibited pins or crossovers, these data were analyzed using χ^2 tests. All subjects engaged in social investigation, so these data were evaluated by a 1-way ANOVA.

There was little indication that caffeine could reverse the depressant effects of 1 mg/kg haloperidol. Regardless of caffeine dose, only 5 of 45 haloperidol treated subjects entered one or more cage quadrants (1, 2 and 2 in the 0, 10 and 30 mg/kg caffeine dose groups, respectively). A χ^2 test comparing all treatment groups (combined) with those receiving only 20 mg/kg caffeine (8 of 9 entered one or more cage quadrants) was highly significant, $\chi^2(1)=20.8$, $p<0.001$. See Fig. 2A, right panel, for mean activity scores. Similarly, no subject receiving both haloperidol and caffeine engaged in crossover or pinning, $\chi^2(1)=47.0$ and 33.6 respectively, $ps<0.001$, when compared with the VI group, who received only vehicle (Fig. 3A and 3B, right panel).

Rats in all caffeine-haloperidol dose combinations engaged in less ($p<0.01$) social investigation than subjects who received vehicle (Fig. 2B, right panel). When only groups receiving both caffeine and 1 mg/kg haloperidol were considered, an increase in social investigation was evident, $F(4,40)=3.54$, $p<0.05$, with subjects in the 10 and 30 mg/kg caffeine groups differing significantly ($p<0.01$) and rats in the 20 and 40 mg/kg caffeine groups differing marginally ($p<0.10$) from subjects receiving only haloperidol. Thus, for social investigation, increasing doses of caffeine partially reversed the effects of haloperidol. These effects, however, were small and not dose dependent.

Relative to the VI group, 20 mg/kg caffeine (CAF group) increased cage quadrants entered and suppressed crossover and pinning, $ts(16)=3.8$, 1.7, 2.5, $ps<0.01$, <0.10 and <0.05, respectively. The drug had no effect on social investigation of a novel juvenile, $t(16)=0.6$.

DISCUSSION

These results suggest that adenosine receptors function to modulate activity and social behaviors of rats during the prepubertal period. Caffeine, an adenosine receptor antagonist, reversed the effects of a fixed dose of the adenosine receptor agonist, 2-chloroadenosine, and similarly, caffeine reduced the behavioral effectiveness of 2-chloroadenosine (i.e., shifted the 2-chloroadenosine dose curve to the right). The

pharmacological specificity of these actions was demonstrated by the inability of caffeine to reverse the depressant actions of haloperidol, a dopaminergic receptor antagonist, whose effects on locomotor activity, social investigation and play-fighting resembled those of 2-chloroadenosine.

Although adenosine receptor subtypes (e.g., A1 and A2) have different affinities for adenosine and adenosine analogs (including 2-chloroadenosine), they appear to have very similar affinities for caffeine [8]. As discussed by Daly and colleagues [8], the receptor populations involved with caffeine's behavioral effects depend on both the levels of endogenous adenosine in a brain region and the affinities of the receptor populations for adenosine. Thus, it is possible that different adenosine receptor populations are involved in the regulation of each behavior. Several of the present findings indicate this may be true. Crossover and pinning behaviors had different 2-CA dose curves than did social investigation; no rat engaged in either measure of play fighting at the 1 mg/kg dose, whereas all subjects engaged in social investigation at this dose, although at a lower level than controls. Similarly, different competition curves for the behaviors were observed when caffeine was used to reverse the effects of 2-CA. The 2-CA induced decrease in social investigation was effectly reversed at the 10 mg/kg caffeine dose, whereas the highest levels of play fighting were observed at the 20 mg/kg dose of caffeine (decreasing at higher doses of the drug). Alternatively, these different response patterns to caffeine and 2-chloroadenosine may reflect the different morphologies of the behaviors observed and be unrelated to activity of any specific population of adenosine receptors.

Agonists and antagonists of dopaminergic, noradrenergic, cholinergic (only antagonists have been used), purinergic, serotonergic and opioid receptors decrease play fighting when given by single injection [1, 2, 3, 4, 5, 14, 16, 21, 24, 32, 33]. Two drugs, apomorphine and morphine, have been found to modestly increase play when given by this method. Taken together these data suggest that play fighting, a complex behavior, is influenced by several neurochemical systems and its normal expression depends on a finely tuned equilibrium of neural activity. Distortion of this balance with either agonists or antagonists of several neurotransmitters typically depresses play fighting. Although a large number of drugs have been used, in few instances have the pharmacological specificity of their effects on play been determined (see [25,35] for more extensive reviews). The present data suggest that caffeine and 2-chloroadenosine alter play via interactions with adenosine receptors. Elsewhere [34], we have reported that withdrawal from chronic scopolamine exposure increases social play (scopolamine depresses play when given by single injection). Those data are consistent with development of cholinergic receptor supersensitivity induced by chronic receptor blockade, and suggest that scopolamine effects on play may involve blockade of muscarinic receptors. Additional studies using cholinergic agonists and antagonists together are needed to establish the pharmacological specificity of this effect. In an extensive series of experiments using a number of drugs specific for noradrenergic and dopaminergic receptors, Beatty and colleagues [4] attempted, without success, to reverse the inhibitory effect of amphetamine on play fighting. However, if amphetamine acts through multiple neurotransmitter systems to influence play, blocking any one may have little or no influence on the drug's action. Additional studies using specific agonists and antagonists given together are needed to determine which, if any, of these drug effects are pharmacologically specific and which, if any, represent a nonspecific disruption of play fighting.

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