Pharmacology Biochemistry & Behavior, Vol. 30, pp. 809–815. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Behavioral Effects of Acute and Chronic Administration of Caffeine in the Rat

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Received 12 October 1987

FILE, S. E., H. A. BALDWIN, A. L. JOHNSTON AND L. J. WILKS. *Behavioral effects of acute and chronic administration of caffeine in the rat.* PHARMACOL BIOCHEM BEHAV **30**(4) 809–815, 1988.—This study investigated the effects of acute and chronic caffeine treatment on behavior in the social interaction, holeboard and home-cage aggression tests and on proconvulsant actions with pentylenetetrazol. Acutely-treated rats received an IP injection of caffeine (20 or 40 mg/kg). Chronically-treated rats received caffeine in their drinking water for 21 days (50 or 100 mg/kg/day) followed by an injection of caffeine on the test day (20 or 40 mg/kg respectively). Acutely, the higher dose of caffeine (40 mg/kg) decreased levels of social interaction. In the holeboard test, 20 mg/kg of acute caffeine increased motor activity whilst 40 mg/kg reduced head-dipping behavior. In the home-cage aggression test, acute caffeine (40 mg/kg) reduced offensive aggressive behaviors. After chronic treatment with caffeine none of these behaviors differed significantly from controls. After both acute and chronic treatment, caffeine (20 and 40 mg/kg) was proconvulsant with pentylenetetrazol.

Caffeine Tolerance Anxiety Aggression Seizures Locomotor activity Exploration

THE methylxanthine caffeine is widely consumed both in the form of caffeine-containing beverages and foods and in various over-the-counter and prescription medicines [4].

Clinically, caffeine increases anxiety, nervousness and tenseness in healthy volunteers [5, 22, 27] and in patients with panic anxiety disorder [3]. It decreases fine motor coordination [22], whilst improving performance in various learning and cognitive function tests [13]. Caffeine was also found to decrease aggression in healthy volunteers [6] and in psychiatric patients [11].

In rats, caffeine has been demonstrated to decrease levels of social interaction in the social interaction test [14]. These effects are in the opposite direction to those of benzodiazepines and other clinically effective anxiolytic drugs [12] and in the same direction as the effects of drugs causing anxiety in man [10, 16, 17, 20, 24]. Caffeine increases locomotor activity in mice [26] and decreases aggressive mouse-killing behavior in isolated rats [25]. In high doses (200 mg/kg) caffeine produces tonic-clonic seizures in both rats [8] and mice [23].

Because the chronic consumption of caffeine is such a widespread phenomenon, it is important to know which of its behavioral effects are retained by chronic treatment. Tolerance to the increase in locomotor activity produced by caffeine in rats has been shown after 2 weeks of chronic treatment [7,19]. Holtzman [21] treated rats with 160 mg/kg/day caffeine in the drinking water for 11 weeks and found tolerance to the increase in locomotor activity produced by a challenge dose of caffeine, but no cross tolerance to amphetamine.

In this study, we have investigated the effects of acute and chronic caffeine treatment in the social interaction [12], holeboard [18], in the home-cage aggression [17] tests, and on the incidence of pentylenetetrazol (PTZ)-induced convulsions. Acutely-treated rats were tested after an intraperitoneal (IP) injection of caffeine (20 or 40 mg/kg). The two doses of caffeine were chosen on the basis of previous studies showing that they were behaviorally active. To determine the effects of chronic treatment with caffeine rats were given caffeine in the drinking water (approximately 50 or 100 mg/kg/day respectively) for 21–26 days and then tested after injection of caffeine (20 or 40 mg/kg respectively). Chronic treatment was administered in the drinking water for several reasons: (1) the brain levels of caffeine would be reasonably constant throughout the day; this is not the case with a single bolus administration, (2) this method of administration would be less stressful to the rat than daily injections, (3) most previous studies involving chronic caffeine treatment used this route of administration, thus our results would be comparable with these. The two chronic doses chosen (50 and 100 mg/kg/day in drinking water) were roughly equivalent to the acute IP injection doses (20 and 40 mg/kg), and on the test day, 30 min before testing, acutely- and chronically-treated rats received identical IP injections.

Thus the chronically-treated rats were tested in the presence of approximately the same dose of caffeine that they had been exposed to for the previous three weeks.

METHOD

Animals

Male hooded Lister rats (Olac Ltd., Bicester, U.K.) weighing 130–175 g at the start of the experiment were housed in a room with an 11 hr light: 13 hr dark cycle (lights on at 06:00) and allowed free access to food and water. Initially rats were housed in groups of eight, they were then singly housed for 7 days before their first test.

Drugs

Drug solutions. Caffeine and pentylenetetrazol (PTZ) were dissolved in distilled water in concentrations to give an IP injection volume of 2 ml/kg. Control-treated rats received distilled water alone.

During chronic treatment caffeine was dissolved in the rats' drinking water. Control treated rats received untreated drinking water.

Drug treatment.

Acute treatment. Rats received a single injection of caffeine (20 or 40 mg/kg IP), or control, at times before each test, as specified for each procedure below (n=7–9 per group).

Chronic treatment. Animals received caffeine in their drinking water (approximately 50 or 100 mg/kg/day), or control, for up to 26 days. At times before each test, which were identical to the acutely-treated rats, they received an injection of caffeine (20 or 40 mg/kg IP), or control, respectively (n=7–10 per group).

During chronic treatment, the presence of caffeine in the drinking water had no significant effect on daily water consumption. The rats were weighed and the volume of water consumed was measured (approximately 22 ml/rat) daily. The concentration of caffeine in the drinking water was adjusted each day to achieve the approximate doses of 50 and 100 mg/kg/day (approximately 0.5 and 1.0 mg of caffeine/ml of water).

Test Order

Acute caffeine. Pairs of rats were tested in the social interaction test 30 min after an acute injection of caffeine (20 or 40 mg/kg) or control. Immediately after testing, one of each pair was placed in the holeboard apparatus. Two separate groups of rats were tested in the home-cage aggression test and for PTZ-induced seizures. In both cases rats received an acute injection of caffeine or control 30 min before the test.

Chronic caffeine. On the 22nd day of chronic treatment rats were tested in the social interaction test 30 min after receiving an acute caffeine (20 or 40 mg/kg) or control injection. Immediately after testing, one of each pair was placed in the holeboard apparatus. Chronic treatment was resumed and on the 24th day of treatment the same rats were scored in the home-cage aggression test 30 min after an injection of caffeine or control. Chronic treatment was continued until the 26th day of treatment when rats were tested for PTZ-induced seizures 30 min after receiving an injection of caffeine or control.

Social Interaction Test

The test arena was a dimly-lit (56.5 radiometric lux) wooden box, 60×60×35 cm. Motor activity and rears were measured by the breaking of infrared photobeams positoned 4.5 and 11 cm from the floor respectively. A camera was mounted vertically over the box and the rats were observed on a monitor in an adjacent room. The time spent in social interaction was scored using keyboards linked to a Control Universal microcomputer.

The rats were allocated to pairs on the basis of similar weight (±10 g). Both members of a pair always received the same drug treatment. Two days before testing, pairs of rats were placed into the test arena for 7.5 min and the day before testing, rats spent 7.5 min in the arena alone. Thus the rats were familiar with both the apparatus and their partner.

On the test day, pairs of rats were placed into the arena for 7.5 min. The duration of the following social behaviors were scored by two independent observers who were blind to the drug treatment: sniffing, following, grooming, mounting, boxing, wrestling, kicking or pushing the partner. Passive body contact (when the rats were sitting or lying in contact with each other, but without interacting) was scored separately. At the end of each trial the box was thoroughly wiped clean with a damp cloth. Rats were tested in an order randomized for drug treatment between 07.30 and 12.00 hr.

Holeboard

The holeboard was a wooden box, 60×60×35 cm, with four holes of 3.8 cm diameter equally spaced in the floor. Motor activity and rearing were measured by the breaking of photobeams positioned 4.5 and 11 cm from the floor respectively. Photobeams below the surface of the holes provided measures of the number of head-dips and the time spent head-dipping. All measures were entered directly into a Control Universal microcomputer.

Rats were placed individually into the centre of the holeboard for a 7.5 min test period. The box was thoroughly wiped clean with a damp cloth after each trial.

Home-Cage Aggression Test

The test of aggressive behavior was carried out in cages measuring 38×25×18 cm, with wire grid floors and tops. The frequencies of various behaviors were recorded by scorers using keyboards linked directly to a Control Universal microcomputer.

The test was carried out by introducing an identically housed intruder into the home-cage of a singly housed resident and observing the ensuing behavior during a six-minute bout. The pairs were chosen on the basis of weight (±10 g) and no rat had the same partner as in the social interaction test. In the groups which received acute caffeine treatment, drug-treated rats were matched versus untreated opponents and only the behaviors of the drug-treated animals were scored. For each drug treatment, two groups of rats were tested, one in which residents received drug treatment and the other in which intruders received drug treatment. In the groups tested after chronic caffeine treatment, both the resident and the intruder received identical drug treatment and the behavior of both animals was scored simultaneously. Two scorers, who were blind to drug treatment, were allocated to record the frequencies of the following behaviors, in either the resident or the intruder: self-grooming, sniffing and grooming of partner, aggressive grooming of partner, kicking or pushing of partner, wrestling, boxing and submission.

PTZ-Induced Seizures

Animals were observed in cages measuring 38×25×18

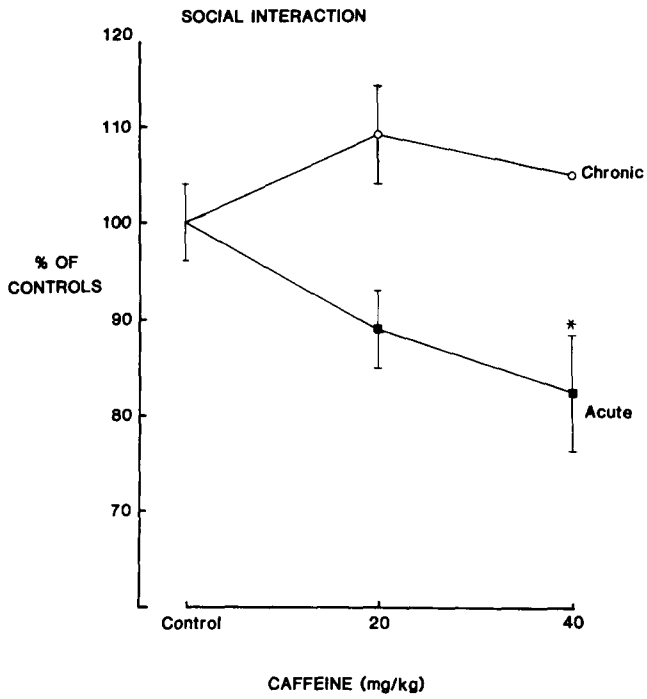

FIG. 1. Time spent in active social interaction by pairs of rats, as a percentage of controls for each group. Acutely-treated rats (closed squares) were tested following an injection of control (n=8) or caffeine (20 or 40 mg/kg, n=9 for both). Chronically-treated rats (open circles) received control (n=6) or caffeine (50 or 100 mg/kg/day, n=6 and 8 respectively) in the drinking water, for 21 days, and were tested on day 22 following an injection of control or caffeine (20 or 40 mg/kg) respectively. Raw control scores: Acute=260.2 (±10.7) sec; chronic=179.5 (±12.6) sec. *$p<0.05$, significantly different from own controls (Duncan's tests following ANOVA and ANCOVA).

TABLE 1

THE EFFECT OF CAFFEINE TREATMENT ON MOTOR ACTIVITY IN PAIRS OF RATS IN THE SOCIAL INTERACTION TEST

Caffeine Treatment	Control	Low Dose 20 mg/kg	High Dose 40 mg/kg
Acute	768.8 (34.6) n=8	764.7 (30.5) n=9	767.7 (33.9) n=9
Chronic	515.8 (21.3) n=6	623.5 (41.9)* n=6	656.9 (19.8)† n=8

Values are significantly different from controls: *$p<0.05$, †$p<0.01$ (Duncan's Multiple Range tests following ANOVA).

Mean (±SEM) motor scores per 7.5 min test are presented for acutely- and chronically-treated rats.

TABLE 2

THE EFFECT OF CAFFEINE TREATMENT ON THE NUMBER OF REARS BY PAIRS OF RATS IN THE SOCIAL INTERACTION TEST

Caffeine Treatment	Control	Low Dose 20 mg/kg	High Dose 40 mg/kg
Acute	73.1 (4.0) n=8	52.7 (4.1)* n=9	52.6 (3.9)* n=9
Chronic	60.0 (5.1) n=6	65.0 (5.9) n=6	75.5 (4.6) n=8

Values are significantly different from control: *$p<0.01$ (Duncan's Multiple Range tests following ANOVA).

Mean (±SEM) motor scores per 7.5 min test are presented for acutely- and chronically-treated rats.

cm, with wire grid floors and tops, in which the rats had been housed singly for at least seven days.

Before each test a pilot experiment was performed in control-treated rats from each experiment to obtain a sub-convulsant dose of PTZ (i.e., that produced myoclonic jerks in an undrugged rat, but did not normally produce full tonic-clonic seizures). The doses chosen were 30 mg/kg PTZ for the acute caffeine treatment groups and 35 mg/kg for the chronically treated groups (see the Results and Discussion sections for details).

Each rat received a single PTZ injection and was then immediately returned to its home-cage and a stop-clock started. The following measures were obtained: latency to the first myoclonic jerk; number of myoclonic jerks; latency to a full tonic-clonic seizure (further myoclonic jerks following a full seizure were not scored). In cases when tonic-clonic seizure activity was not observed, the trial was ended after 10 min. The rats were killed immediately after the experiment.

Statistical Analyses

The data from the holeboard experiment were analysed using analysis of variance (ANOVA). For the social interaction test, motor scores and rears were analysed using ANOVA. If motor activity was unaffected social interaction scores were analysed using ANOVA; if motor scores were significantly affected, social interaction scores were analysed using analysis of covariance (ANCOVA) with time spent in social interaction as the dependent variable and motor activity as the covariate. Post hoc comparisons were made using Duncan's Multiple Range tests. The aggression data were analysed using Mann-Whitney U-tests. Mann-Whitney U-tests were used to compare the number of myclonic jerks and latencies obtained in the PTZ-induced seizures experiment and the number of rats that seized were compared using Fischer Exact Probability tests.

RESULTS

Social Interaction

Acute caffeine. Acute administration of caffeine produced a dose-dependent decrease in the time spent in active social interaction, which was significantly different from controls at the 40 mg/kg dose, $F(2,23)=3.1$, $p=0.07$, Duncan's: 40 mg/kg, $p<0.05$ (see Fig. 1). Motor activity was not affected by caffeine in this test (see Table 1). Both doses of caffeine significantly decreased the number of rears compared with controls, $F(2,23)=8.4$, $p<0.005$; Duncan's tests: 20 mg/kg, $p<0.01$; 40 mg/kg, $p<0.01$ (see Table 2).

Chronic caffeine. When rats that had been chronically-treated with caffeine in the drinking water for 21 days, were injected with caffeine and tested in the social interaction test, there was no significant effect on social interaction (see Fig. 1) or rearing activity compared with controls (see Table 2). However both doses of caffeine produced a significant increase in motor activity in this test, $F(2,17)=6.9$, $p<0.01$; Duncan's: 20 mg/kg, $p<0.05$; 40 mg/kg, $p<0.01$ (see Table 1).

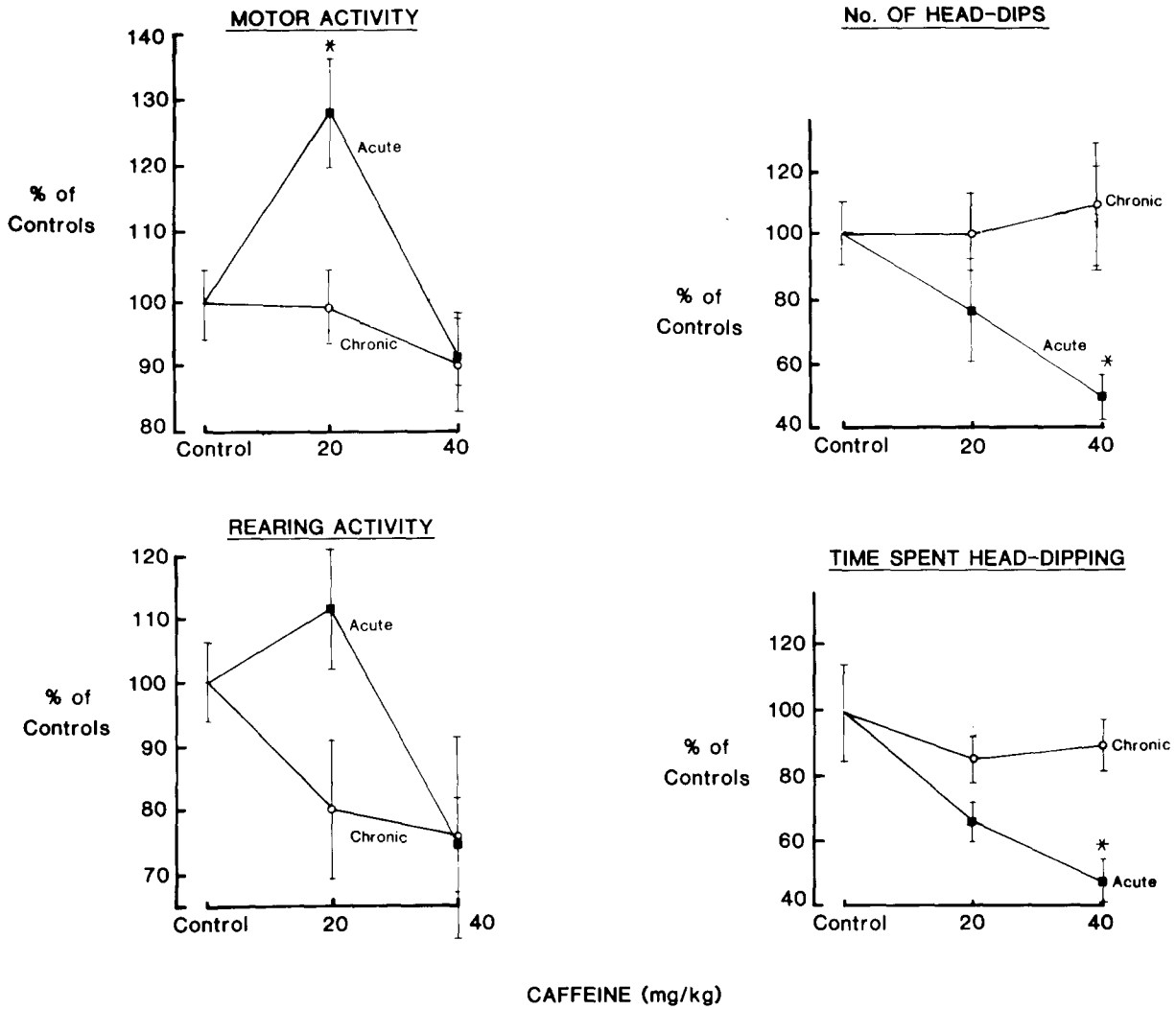

FIG. 2. Behavior of rats in the holeboard, as percentage of controls for each group. Acutely-treated rats (closed squares) were tested following an injection of control (n=7) or caffeine (20 or 40 mg/kg, n=8 for both). Chronically treated rats (open circles) received control (n=7) or caffeine (50 or 100 mg/kg/day, n=8 for both) in their drinking water for 21 days, and were tested on day 22 following an injection of control or caffeine (20 or 40 mg/kg) respectively. Raw control scores: Acute group—motor activity=270.6 (±26.3), numbers of rears=23.4 (±3.2), number of head-dips=17.7 (±1.4), time spent head-dipping=19.6 (±2.6); Chronic group—motor activity=371.0 (±19.2), number of rears=26.9 (±1.8), number of head-dips=46.0 (±6.2) and time spent head-dipping=45.7 (±2.6). *$p<0.05$, significantly different from own controls (Duncan's tests following ANOVA).

Holeboard

Acute caffeine. The low dose of caffeine (20 mg/kg) significantly increased motor acticity whilst 40 mg/kg had no significant effect compared with controls, $F(2,20)=6.9$, $p<0.01$, Duncan's: 20 mg/kg, $p<0.05$. Neither dose had a significant effect on rearing activity. The high dose of caffeine (40 mg/kg) significantly decreased the number of head-dips compared with controls, $F(2,20)=4.6$, $p<0.05$, Duncan's: 40 mg/kg, $p<0.01$ and significantly decreased the time spent head-dipping compared with controls, $F(2,20)=3.3$, $p=0.06$, Duncan's: 40 mg/kg, $p<0.05$ (see Fig. 2).

Chronic caffeine. Injection of caffeine in rats treated chronically had no significant effect on motor activity, rearing activity, number of head-dips or time spent head-dipping (see Fig. 2).

Home-Cage Aggression Test

Acute caffeine. In the drug-treated residents, caffeine (40 mg/kg IP) produced significant decreases in the frequencies of kicking and pushing ($p<0.05$) and aggressive grooming ($p<0.05$) compared with controls (see Table 3). The low dose of caffeine (20 mg/kg had no effect in these rats. In the drug-treated intruders caffeine (20 and 40 mg/kg) had no effect.

Chronic caffeine. Caffeine injection in chronically-treated rats no effects significant at $p<0.05$.

PTZ-Induced Seizures

Acute caffeine. The subconvulsant dose of PTZ, chosen on the basis of a pilot experiment on 4 of the control-treated

TABLE 3

THE EFFECTS OF CAFFEINE TREATMENT ON THE FREQUENCY OF BEHAVIORS IN THE HOME-CAGE AGGRESSION TEST

		n	Self-Groom	Sniff, Groom	Submit	Kick, Push	Agg Groom	Wrestle	Box
				Residents					
	Control	10	3.4 ±1.0	82.2 ±8.3	7.9 ±1.8	14.7 ±3.6	6.8 ±2.0	19.4 ±4.2	11.9 ±2.5
Acute	Caf 20 mg/kg	10	4.4 ±3.4	79.3 ±8.6	5.9 ±1.4	14.0 ±2.7	2.9 ±1.1	24.7 ±4.7	10.5 ±1.4
	Caf 40 mg/kg	10	3.6 ±2.0	87.6 ±9.9	3.6 ±1.1	6.3* ±2.6	1.0* ±0.7	15.0 ±4.4	4.9 ±1.4
	Control	8	8.1 ±3.2	106.9 ±10.5	8.6 ±2.3	26.9 ±7.1	4.8 ±2.4	30.0 ±4.4	6.6 ±3.1
Chronic	Caf 20 mg/kg	8	7.0 ±4.6	113.8 ±8.7	5.6 ±1.8	22.4 ±3.9	3.7 ±1.1	34.9 ±6.6	5.9 ±0.9
	Caf 40 mg/kg	8	8.0 ±2.7	94.4 ±11.5	5.9 ±2.5	11.6 ±3.8	2.3 ±0.5	18.9 ±7.1	3.8 ±1.8
				Intruders					
	Control	10	0.9 ±0.2	19.8 ±3.0	5.2 ±1.4	30.5 ±4.5	5.1 ±1.3	8.5 ±2.5	2.9 ±1.2
Acute	Caf 20 mg/kg	10	0.4 ±0.3	21.1 ±2.8	4.9 ±1.5	16.3 ±2.5	2.3 ±1.0	4.1 ±1.0	3.1 ±1.0
	Caf 40 mg/kg	10	0.9 ±0.4	23.0 ±3.3	6.7 ±1.5	17.1 ±4.6	2.2 ±1.0	4.8 ±1.6	2.2 ±1.1
	Control	9	1.1 ±0.4	20.1 ±3.6	13.0 ±3.9	26.9 ±4.8	1.8 ±0.6	14.8 ±4.2	3.4 ±1.5
Chronic	Caf 20 mg/kg	9	1.4 ±0.8	22.3 ±3.2	14.5 ±2.9	31.1 ±5.6	0.8 ±0.4	9.1† ±3.5	2.8 ±0.8
	Caf 40 mg/kg	9	0.3† ±0.2	18.4 ±3.3	6.6† ±1.9	21.0 ±5.6	0.9 ±0.5	9.0 ±3.3	1.6 ±1.0

Values are significantly different from control: *$p<0.05$, †$p<0.10$ (Mann-Whitney U-tests).
The mean (±SEM) frequencies of occurrence per 6 min test are presented for acutely and chronically treated rats.

rats, was 30 mg/kg. As can be seen in Fig. 3, none of the control rats had full tonic-clonic seizures (0/8), whilst all had myoclonic jerks. Caffeine had no significant effect on the latency to the first myoclonus, or on the number of myoclonic jerks, but produced a significant increase ($p<0.05$) in the number of rats having full tonic-clonic seizures compared with controls (see Fig. 3).

Chronic caffeine. The subconvulsant dose of PTZ chosen for the chronic caffeine experiment was 35 mg/kg. In the pilot experiment 2 control-treated rats were given 30 mg/kg of PTZ, but whilst neither rat had full tonic-clonic seizures, one also had no myoclonic jerks. Therefore the dose of PTZ was increased to 35 mg/kg at which dose all had myoclonic jerks without full tonic-clonic seizures. However, during the experiment, two of the control-treated rats experienced full seizures (2/12). Injection of caffeine in chronically-treated rats had no significant effect on the latency to the first myoclonus or the number of myoclonic jerks, but produced a significant increase ($p<0.05$) in the number of rats having full tonic-clonic seizures compared with controls (see Fig. 3). The implications of using a higher dose of PTZ for this part of the experiment are considered in the Discussion section.

DISCUSSION

In this study we have demonstrated the effects of acute administration of caffeine in the home-cage aggression test, on PTZ-induced seizures and in the holeboard, as well as repeating the finding that caffeine (40 mg/kg) reduces social interaction in the social interaction test [14].

In the drug-treated residents, acute caffeine treatment (40 mg/kg) produced significant decreases in kicking and pushing and aggressive grooming when they were confronted with an untreated rat intruding into their home territory. Kicking and pushing and aggressive grooming are considered to be offensive behaviors. As no changes were detected in the other behavioral measures in this test for acutely-treated rats these changes represent a specific decrease in offensive behaviors for the dominant animals. Acute caffeine has been shown to decrease aggressive behaviors both clinically [6] and in rats [25]. In intruder rats, as a consequence of their subordinate

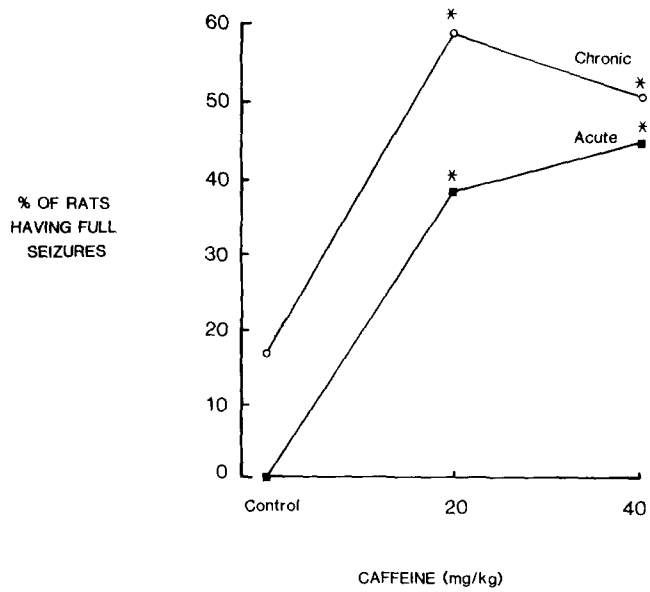

FIG. 3. Number of rats having full tonic-clonic seizures in response to a subconvulsant dose of PTZ as a percentage of controls for each group. Acutely-treated rats (closed squares) were injected with control (n=8) or caffeine (20 or 40 mg/kg, n=8 and 9 respectively) 30 min before testing. Immediately before the test these rats received an injection of PTZ (30 mg/kg). Chronically-treated rats (open circles) received (n=12) or caffeine (50 or 100 mg/kg/day, n=12 for both) in their drinking water for 25 days. On day 26 they were injected with control or caffeine (20 or 40 mg/kg), respectively, 30 min before testing. Immediately before testing these rats received an injection of PTZ (35 mg/kg). Raw control scores: acute=0/8; chronic=2/12. *$p<0.05$, significantly different from own controls (Fischer Exact Probability tests).

status, aggressive behaviors may already have been too suppressed to show a further caffeine-induced decrease.

Both doses of acute caffeine treatment were significantly proconvulsant with PTZ shown by an increase in the number of rats having full tonic-clonic seizures compared with PTZ-treated controls. There were, however, no significant effects of caffeine on the latency to the first myoclonic jerk or the number of myoclonic jerks. Very high doses of acute caffeine have previously been demonstrated to produce tonic-clonic seizures in both rats [8] and mice [23].

In the holeboard, 20 mg/kg acute caffeine significantly increased motor activity, whilst 40 mg/kg had no effect on motor activity but decreased head-dipping. Thus, whilst the lower dose of caffeine had a stimulant effect, the higher dose produced a decrease in exploratory behaviors.

The changes in the social interaction, holeboard and home-cage aggression tests after acute treatment were no longer found in the chronically-treated group. It should however, be noted that the control levels for the acute and chronic caffeine experiments were different for some of the behaviors. In the case of social interaction, the control level for the chronic caffeine experiment was significantly lower than for the acutely treated rats (control levels: acute experiment 260.2±10.7; chronic experiment 179.5±12.6 sec/7.5 min). The different control levels could have contributed to caffeine's lack of effect in the social interaction test after chronic treatment. However, we commonly experience variations in the levels of social interaction of control groups and in another study acute administration of caffeine (40 mg/kg) decreased social interaction compared with control levels that were not significantly different from that of our chronic study (control level 211.1±15.0; caffeine 40 mg/kg 170.4±16.4 sec/7.5 min) (unpublished observations). In addition, control-treated rats often have social interaction scores of about 180 sec/7.5 min and these are consistently reduced by various other compounds (FG and PTZ papers have means of 175). There were also differences between the acute- and chronically-treated controls on levels of rearing and motor activity (both in the social interaction test and holeboard), and on head-dipping behavior in the holeboard. These changes are probaly due to the fact that it was necessary to change the photocells in this apparatus between the two experiments, and not because the actual behavioral activity of the rats was different. Why then did chronic treatment abolish the behavioral effects of caffeine in these tests? One possibility is that chronic caffeine administration could have produced a permanent shift in the levels of the behaviors measured, perhaps due to an upregulation of receptors, and this shift was merely being masked by the administration of caffeine on the test day. However, in another experiment, rats were chronically-tested with the same doses of caffeine (50 or 100 mg/kg/day) or vehicle control for 21 days and then tested in the social interaction test and holeboard, undrugged, on the day after cessation of chronic treatment [1]. In that experiment there were no differences from controls for the chronically-treated rats, showing that permanent shift in these behaviors had not occurred. We cannot, however, exclude the possibility that these rats may have also been undergoing some withdrawal effects due to cessation of chronic treatment. The stimulant properties of the methylxanthines are well documented [26] and tolerance to the increase in locomotor activity after chronic treatment has been demonstrated previously [7, 19, 21]. It therefore seems that the lack of effects of chronic caffeine on social interaction, exploration and aggression are more likely to reflect the development of tolerance than to be explained by baseline shifts.

There was no apparent tolerance to the proconvulsant effect of caffeine with PTZ after chronic treatment. As explained in the Results section, a slightly higher dose of PTZ was used in the chronic treatment experiment (35 mg/kg) compared with the acute caffeine experiment (30 mg/kg). This higher dose did produce tonic-clonic seizures in two of the control rats (2/12). Despite this, after chronic treatment, both doses of caffeine still significantly increased the number of rats having full tonic-clonic seizures compared with PTZ-treated controls. However, the interpretation of this data is limited because these rats were probably nearer to their seizure threshold due to the increased dose of PTZ. Thus, whilst we cannot be sure whether partial tolerance had developed, these results do show that after 3 weeks of treatment complete tolerance had not occurred to the proconvulsant effect of caffeine.

If we are correct that there is no tolerance to the proconvulsant effects of caffeine, this suggests that the neurochemical pathways that mediate this response may be different from those mediating it's other behavioral effects. There is evidence that the convulsant effects of caffeine are mediated by its action at the BDZ receptors [23],whereas its stimulant effect is thought to be mediated by antagonism at adenosine receptors [26]. However binding studies with various ligands for these sites, before and after chronic caffeine treatment, have yielded conflicting data [2]. Therefore, as yet, tolerance to a particular behavioral effect of caffeine cannot be attributed to a specific change in the binding properties of any particular receptor.

ACKNOWLEDGEMENTS

We would like to thank Peter Mabbutt and Jackie Walker for their expert technical assistance. S.E.F. is a Wellcome Trust Senior Lecturer, H.A.B. is supported by an SERC CASE award, A.L.J. is supported by a postgraduate award from the Department of Education, N. Ireland and L.J.W. is supported by the MRC.

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