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European Journal of Pharmacology 373 (1999) 135–140

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The effect of caffeine in animal models of learning and memory

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Received 21 December 1998; received in revised form 22 March 1999; accepted 30 March 1999

Abstract

In the present investigation we studied the effect of caffeine on memory task inhibitory avoidance and habituation to a new environment. Caffeine impaired retention scores in mice submitted to inhibitory avoidance and habituation when administered 30 min before training at the doses of 10–30 mg/kg. These effects cannot be explained by state-dependency since the administration of caffeine 30 min before the test session did not reverse the effect of pre-training caffeine administration, but can more probably be explained by an impairment in the acquisition or by interference with attentional processes. On the other hand, caffeine improved the inhibitory avoidance (but not habituation) retention scores when administered immediately after the training or 30 min before the test session at the doses of 1–30 mg/kg or 3–10 mg/kg, respectively. These results suggest that caffeine differentially affects the different stages of memory processing and that this effect depends on particularities of the memory task under study.

Keywords: Memory; Learning; Caffeine; Avoidance, inhibitory; (Mouse); Habituation

1. Introduction

It is generally believed that caffeine and related xanthines improve learning and memory. On the other hand, an accurate review of studies on this subject shows that there is a controversy about it. While many studies suggest an improving effect of caffeine either in animal (Paré, 1961; Rahmann, 1963; Flexner and Flexner, 1975; Roussinov and Yonkov, 1976; Flood et al., 1978; Yonkov and Roussinov, 1983; Valzelli et al., 1986; Molinengo et al., 1995; Cestari and Castellano, 1996; Howell et al., 1997) or in human (Calev, 1994; Riedel and Jolles, 1996; Riedel et al., 1995; Pollina and Calev, 1997) models of learning and memory, other studies report that caffeine does not affect memory (Loke, 1988; Loke et al., 1985; Furusawa, 1991; Hudzik and Wenger, 1993; Smith et al., 1994) or even impairs it (Bartus, 1979; Izquierdo et al., 1979; Erikson et al., 1985; Terry and Phifer, 1986; Kant, 1993; Sansone et al., 1994; Pan, 1995; Fisher and Guillet, 1997).

A possible reason for this controversy could be that caffeine does not present a general improving effect on all kinds of memory and that its effect may not be the same in all the phases of memory processing. Despite the large number of studies concerning the effect of caffeine on memory in the literature, none of them presented a systematic study of the effects of caffeine on memory considering the specific stage of memory storage that is affected and the specificities of each memory task. In addition, in some of these investigations the effect of caffeine on memory was not the main subject of study but one observation made in parallel with other items.

In the present investigation, we systematically studied the effect of caffeine on acquisition, consolidation and retrieval of two animal memory tasks. We chose inhibitory avoidance and habituation because these memory tasks represent quite different type of learning, sufficient to test the effect of caffeine on different learning situations. Further, in the inhibitory avoidance task the nature of the stimulus (footshock) is strong enough to allow the animals to learn to avoid the dark compartment after only one training trial. Thus, this is task ideal for studies of the effect of caffeine in different stages of memory formation. On the other hand, the habituation task uses less stressful stimuli and is acquired by the animals in five trials. Once again the contrast between the two tasks makes them

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0014-2999/99/$ - see front matter
PII: S0014-2999(99)00225-3

suitable to test the critical differences of the behavioral situations causing different effects of caffeine on memory.

2. Materials and methods

2.1. Animals

Data for a total of 372 adult male Swiss mice (26–32 g) from our own breeding stock were used. The animals were maintained in a temperature-controlled room (22 ± 2°C) on a 12/12 h light/dark cycle (lights on 7:00 AM) with food and water available ad libitum. All the behavioral experiments were conducted between 7:00 AM and 12:00 noon. The animals were maintained in Plexiglas home cages (60 cm × 25 cm × 25 cm) and the same 12 cagemate mice were maintained until the end of the experiments.

2.2. Materials

Caffeine (Sigma) was dissolved in saline (0.9% NaCl) and administered i.p. in a volume of 0.1 ml/10 g body weight.

2.3. Procedures

The animals of the same cages were chosen in a randomized manner to compose groups of 12 mice each that were submitted to the different schedules of drug administration and returned to the same home cage after the end of the experimental procedures.

Twenty four groups of mice received saline or 1, 3, 10, 30 or 100 mg/kg caffeine, respectively, and were submitted to an inhibitory avoidance task with a 48 h training-test interval. The following drug administration schedules were carried out: (1) 30 min before training; (2) immediately after training; (3) 30 min before the test; (4) 30 min before training and 30 min before the test. The inhibitory avoidance task apparatus consisted of an automated 23 cm × 50 cm × 23 cm shuttle-box (GEMINI Avoidance System, San Diego Instruments, San Diego, CA) with a dark front glass and a floor made of parallel 2 mm caliber stainless steel bars spaced 5 mm apart. The box is divided into an illuminated compartment and a dark compartment of the same size by a wall with a guillotine door. An adaptation box restrains the space of the light compartment to the dimensions of 10 cm × 12 cm × 10 cm. In the training session the animal was placed in the illuminated compartment facing the closed door. After the animal turned around 180° the door was opened and the latency to enter the dark compartment was computed. Animals that took more than 30 s to enter the dark compartment in the training session were eliminated from the experiment and replaced with others in order to maintain 12 animals per group. After entering the dark compartment the animal received a 0.15 mA footshock, 1 s, and was returned to its home cage. The test session was similar to the training session except that the animal received no footshock and a limit of 600 s for latency of entries into the dark compartment was imposed. The latency of entry into the dark compartment in the test session was taken as a measure of retention (adapted from Da Cunha et al., 1990).

Two additional groups of animals received saline or 30 mg/kg caffeine 30 min before each of the five sessions of habituation to a new environment. Five additional groups of mice received saline or 3, 10, 30 or 100 mg/kg caffeine, respectively, immediately after each of the sessions of habituation to a new environment. The habituation sessions consisted of allowing the animal to freely explore a habituation box (20 cm × 50 cm × 20 cm) with three infrared light beams pointing to photocells for 5 min. The number of times the animal crossed the lines and the number of rearings were computed. A decrease in these exploration scores was taken as a measure of retention (Netto et al., 1986).

2.4. Statistical analysis

The inhibitory avoidance data were analyzed by one-way Kruskal–Wallis analysis of variance (ANOVA) followed by the Mann–Whitney *U*-test. The habituation data were analyzed by two-way ANOVA taking the number of the session as a repeated measure, and the differences between groups were evaluated by the post-hoc Duncan test.

3. Results

All groups of animals presented similar latencies to enter the dark compartment in the training session: mean = 11.6 ± 0.33 s; median (Q25/75) = 10.4 (7.3/14.8); one-way ANOVA, $F(23,264) = 1.25$, $P > 0.2$. Control animals learned to avoid the dark compartment since their latencies to enter the dark compartment in the test session were significantly higher than the latencies to enter the dark compartment in the training session ($U \leq 20$, $P < 0.003$, Mann–Whitney test). Fig. 1A shows the retention scores (test session latencies) of the animals that received caffeine 30 min before the training session. Caffeine administration at doses higher than 10 mg/kg significantly impaired memory acquisition in a dose-dependent manner (Kruskal–Wallis ANOVA $H(5,72) = 42.16$, $P \leq 0.001$, followed by the Mann–Whitney *U*-test, $P \leq 0.05$). As can be seen in Fig. 1B, post-training caffeine administration at the doses of 1 to 30 mg/kg improved memory consolidation (Kruskal–Wallis ANOVA $H(5,72) = 30.64$, $P \leq 0.001$, followed by the Mann–Whitney *U*-test, $P \leq 0.05$). The same effect was not obtained with the administration of 100 mg/kg caffeine, which did not affect retention. As can be seen in Fig. 1C, the administration of 3 or 10 mg/kg caffeine 30 min before the test session improved memory retrieval (Kruskal–Wallis ANOVA $H(5,72) =$

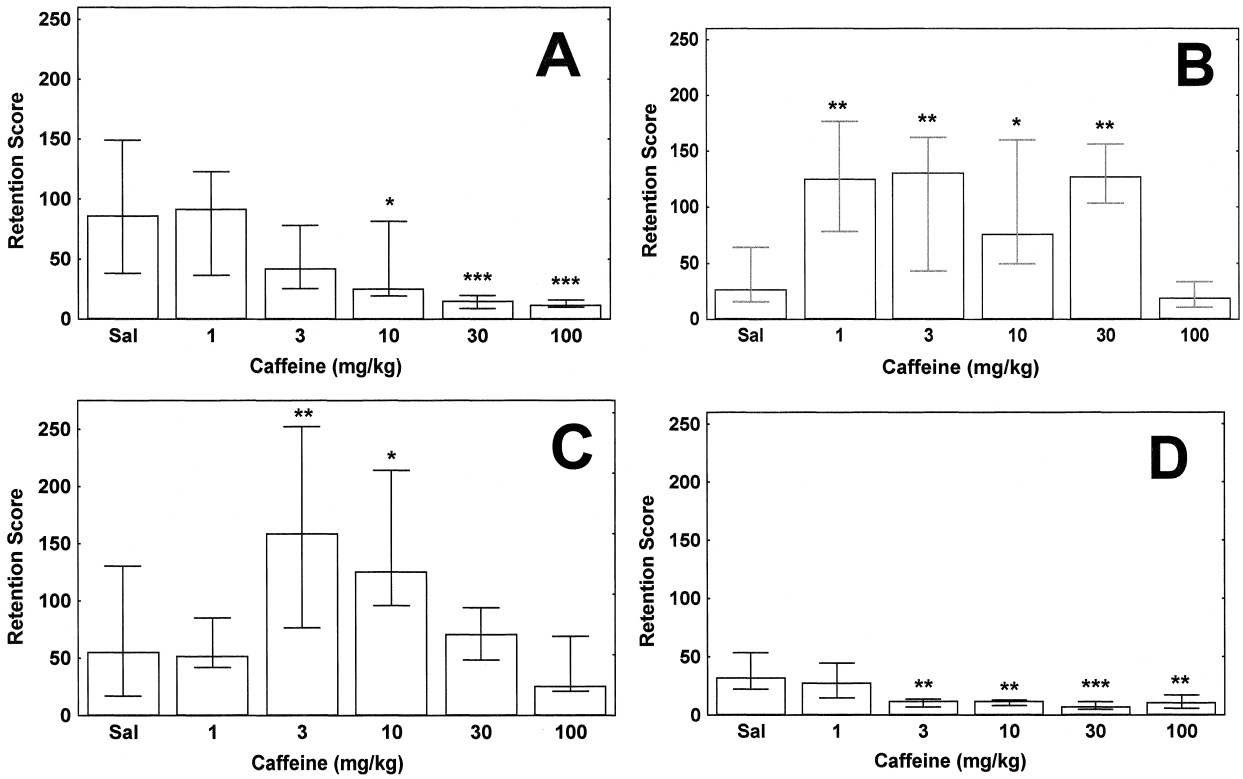

Fig. 1. Effect of i.p. caffeine administration on the memory of inhibitory avoidance in mice. Columns indicate the median (±interquartile range) latency to enter the dark compartment in the test session. Groups of 12 animals each received vehicle or caffeine 30 min before the training session (A), immediately after training (B), 30 min before the test session (C) or 30 min before training and 30 min before the test (D). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.05$ compared to the saline group, Mann–Whitney *U*-test after the Kruskal–Wallis ANOVA.

23.32, $P \leq 0.001$, followed by the Mann–Whitney *U*-test, $P \leq 0.05$). On the other hand, at the doses of 1, 30 or 100 mg/kg caffeine did not affect the test session scores. The results presented in Fig. 1D show that the impairing effect of pre-training caffeine administration was not caused by a phenomenon of dependency on the drug state since the pre-test caffeine administration did not reverse the amnesia caused by the pre-training caffeine administration: the animals receiving 3–100 caffeine 30 min before the training and 30 min before the test session presented lower retention scores compared to the control group (Kruskal–Wallis ANOVA $H(5,72) = 26.89$, $P \leq 0.001$, followed by the Mann–Whitney *U*-test, $P \leq 0.05$).

The scores for habituation of the three groups of animals to an open field are presented in Fig. 2. One-way ANOVA of the data obtained with pre-training caffeine administration showed that the crossing scores of the groups receiving caffeine (Fig. 2A) were significantly higher than the scores of the control group ($F(1,24) = 9.16$ $P \leq 0.01$). As the baseline scores of the animals differed, it was difficult to analyze the differences in the decrease in locomotor activity as an indication that caffeine altered habituation. For this reason these data were analyzed by two-way ANOVA taking the second day to the fifth day of training as a repeated measure and the first day scores as a covariate. This analysis showed that 30 mg/kg pre-training caffeine administration did not affect habituation: the animals significantly decreased their crossing scores denoting habituation ($F(3,72) = 9.58$, $P \leq 0.001$), but the caffeine treatment did not affect it ($F(1,23) = 2.78$, $P = 0.10$) and did not interact significantly with the repeated measure ($F(3,72) = 1.26$, $P \geq 0.2$). On the other hand, rearing scores were not affected by pre-training caffeine treatment on the first training day ($F(1,24) = 0.13$, $P \geq 0.2$, one-way ANOVA). As can be seen in Fig. 2B, two-way ANOVA taking the day of training as a repeated measure showed a significant decrease in the scores for rearing ($F(4,96) = 4.81$; $P \leq 0.01$) denoting habituation. This analysis also showed that pre-training 30 mg/kg caffeine administration impaired habituation ($F(1,24) = 9.53$, $P \leq 0.001$) and also significantly interacted with the repeated measure ($F(4,96) = 5.96$, $P \leq 0.001$).

The data about the effect of post-training administration of caffeine on habituation were not complicated by the fact that caffeine could affect both performance and/or memory retention: since caffeine was administered after training, only memory consolidation would be affected by treatment. One-way ANOVA showed that the crossing ($F(4,60) = 0.24$, $P \geq 0.2$) and rearing scores ($F(4,60) = 0.23$, $P \geq 0.2$) of caffeine-treated animals did not differ between groups. As can be seen in Fig. 2C and D, in this experiment the animals also denoted habituation decreas-

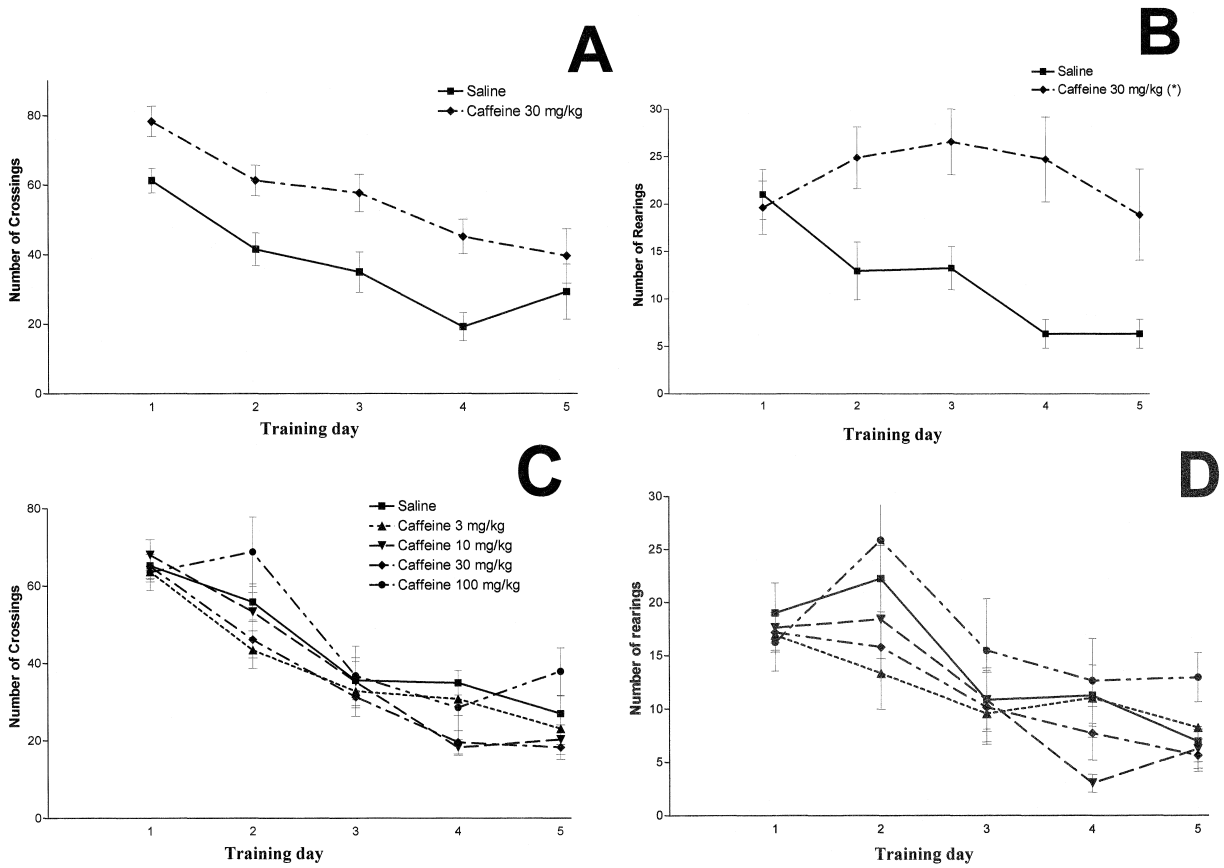

Fig. 2. Effect of i.p. caffeine administration on the habituation of rats to a new environment. Groups of 12 animals each received vehicle or caffeine 30 min before the training session (A and B) or immediately after training (C and D). The habituation scores, locomotor activity (crossings, A and C) and rearings (B and D), are expressed as mean ± S.E.M. $^{*}P < 0.05$, two-way ANOVA followed by the Duncan test.

ing their scores for crossing ($F(4,240) = 114.14$, $P \leq 0.001$) and rearing ($F(4,240) = 28.40$, $P \leq 0.001$). The caffeine treatment did not affect it directly (crossing: $F(4,60) = 1.15$, $P = 0.19$; rearing: $F(4,60) = 1.14$, $P \geq 0.2$) but presented a tendency to interact with the repeated measure (crossing: $F(16,240) = 2.24$, $P \leq 0.01$; rearing: $F(16,240) = 1.59$, $P = 0.07$).

4. Discussion

In the present study we address the discrepant data about the effects of caffeine reported in literature by looking for answers to the following questions: (1) Can these discrepancies be explained by differential effects of caffeine on specific stages of memory formation? (2) Can different effects of this drug on different kinds of learning explain them?

The results presented above suggest that caffeine does present different effects on different stages of memory processing and that these effects depends on the characteristics of the memory task. The administration of a drug before the training session of a memory task can affect performance, attention, and/or memory acquisition, impairing the distinction of which process was affected. This seems to be the case for the results obtained with the administration of caffeine before the habituation sessions. As shown in Fig. 2, caffeine administration can increase the exploratory behavior of the animal in an open field. In an attempt to minimize the effect of caffeine on performance the crossing scores of the first of the five habituation sessions were used as a covariate in a two-way ANOVA (see Fig. 2). From this analysis we concluded that pre-training caffeine administration did not affect memory acquisition expressed by the decrease in the ambulatory (crossing) behavior. On the other hand, rearing scores, another exploratory behavior that decreases as a function of habituation (Netto et al., 1986), were not affected by the first pre-training administration of caffeine, but if we consider the decrease of rearing scores in the subsequent sessions to be an index of habituation, then the results suggest that pre-training administration of caffeine impairs habituation. The results of this experiment suggest that caffeine may impair memory acquisition. The results obtained from inhibitory avoidance experiments (see Fig. 1A) suggest more solidly an impairing effect of caffeine on memory acquisition: the effect was dose-dependent and caffeine did not alter the scores of the animals in the

training sessions but only the retention scores in the test session. However, an effect of caffeine on attention cannot be ruled out.

The present results and the results reported by Pan (1995) and Fisher and Guillet (1997) suggest that these two different memory tasks may present different sensitivities but, despite differences between them, both tasks are susceptible to the memory impairing effect of pre-training caffeine administration. The conclusion is the same if we compare these data with the pre-training effect of caffeine on other tasks (Izquierdo et al., 1979; Kant, 1993) and even in other species (Bartus, 1979; Sansone et al., 1994) including humans (Erikson et al., 1985; Terry and Phifer, 1986). Sansone et al. (1994) reported that lower doses of pre-training caffeine were ineffective in impairing memory retention, as also observed in our study. The lack of a dose–effect study may explain some reports of ineffectiveness of pre-training caffeine administration on memory (Loke, 1988; Loke et al., 1985; Furusawa, 1991; Hudzik and Wenger, 1993; Smith et al., 1994).

The literature reports that some drugs that impair memory when administered before the training session can improve it when the same drug is administered again before the test session, a phenomenon known as state-dependency (Quirarte et al., 1994). This phenomenon seems not to occur with caffeine since, as shown in Fig. 1D, the administration of this drug before the training test did not reverse the amnesic effect of pre-training caffeine administration on inhibitory avoidance.

At this point, one conclusion may be drawn from these data: when administered at appropriate doses before training, caffeine impairs most kinds of learning. This effect can be observed in different memory tasks, using quite different kinds of stimuli. But, more important than this, we could find no report in the literature showing that caffeine administration before a learning trial can improve memory, in contrast to the general belief that caffeine has a generalized beneficial effect on learning and memory. Another important point to consider is that the impairing effect of caffeine on memory seems to be stronger than its improving effect on memory consolidation since the caffeine administered to the animals before training will still be present in their blood after training, thus affecting memory consolidation. This prevalence of the pre-training effect is also observed in relation to the improving effect of caffeine on memory retrieval: pre-test caffeine administration did not reverse its pre-training impairing effect.

Although caffeine did not affect the scores of the animals in the training session of the inhibitory avoidance task and this effect on rearing scores in the first training session of the habituation task did not affect the decrease of this scores in the subsequent sessions (habituation), we cannot rule out the possibility that the impairing effect of pre-training caffeine treatment is due to factors other than memory acquisition. On the other hand, the results obtained with the administration of caffeine immediately after the training session can more consistently be attributable to an effect on memory consolidation since the animals were not under the effect of the drug during the training. As can be seen in Fig. 1B, the post-training caffeine treatment at the doses of 1 to 30 mg/kg, but not 100 mg/kg, improved memory consolidation. Caffeine administration after the habituation sessions did not improve retention at any of the tested doses but presented a tendency ($P = 0.07$) to do that (see Fig. 2B). The improving effect of caffeine on the consolidation of the inhibitory avoidance task in mice was also observed by Cestari and Castellano (1996) and other authors observed this effect in other models of learning and memory (Flexner and Flexner, 1975; Flood et al., 1978; Molinengo et al., 1995). Roussinov and Yonkov (1976) and Yonkov and Roussinov (1983) reported an improving effect of caffeine when administered 5 min before the training session in a multi-chamber maze in mice. In those studies caffeine was most probably available in effective plasma concentrations only after the training session. On the other hand, our results contrast with the study of Yonkov (1985) reporting an improving effect of caffeine when administered immediately after training to rats submitted to the habituation to an open field. The lack of effect of the highest dose of caffeine on inhibitory avoidance could be explained by the inverted-U-shaped dose effect curve observed for most of the known drugs that improve memory consolidation (McGaugh, 1973).

Taken together, the results of the present investigations and of other studies lead us to the second general conclusion of this work: caffeine can improve memory consolidation, but only at moderate (lower) doses and this effect cannot be extrapolated to all learning situations, i.e., it depends on the particularities of the memory task.

The improving effect of caffeine on memory retrieval (Fig. 1C) was also observed in other studies, including an animal model of dementia (Valzelli et al., 1986) and also in a study with humans (Riedel et al., 1995). These studies agree with our conclusion that caffeine improves memory retention but few reports are available to allow a generalization of this conclusion for all kinds of learning situations.

The present results also emphasize some particularities of the effect of caffeine on learning and memory that were not systematically addressed in previous studies: (1) the administration of higher doses of caffeine before a training sessions impairs memory retention; (2) caffeine can improve memory consolidation, but only at moderate (lower) doses and this effect cannot be generalized to all learning situations; (3) pre-test caffeine administration at moderate doses improves memory retrieval; (4) the impairing effect of pre-training caffeine administration on memory cannot be reversed by its improving effect on memory consolidation or retrieval. These conclusions contribute to clarifying the previous controversy about the effect of caffeine on learning and memory.

Acknowledgements

This work was supported by CNPq, PRONEX and Fundação Vitae-Andes-Antorchas.

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