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Effects of Tunnel Maze Complexity on Caffeinic Hyperactivity in the Rat

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OETTINGER, R., J. R. MARTIN, E. ROSENBERG AND K. BÄTTIG. *Efffects of tunnel maze complexity on caffeinic hyperactivity in the rat.* PHARMACOL BIOCHEM BEHAV **23**(1) 85–90, 1985.—The study investigated effects of caffeine on spontaneous tunnel locomotion without consummatory reward. The stimulant effects consisted in delayed intrasession habituation, and they differed in magnitude according to dosage and the complexity of the tunnel arrangements. In a simple hexagonal tunnel without choice points, 16 mg/kg BW produced greater stimulation than other doses, and this most efficient dose became less effective if tunnels were arranged according to the radial maze paradigm. No stimulation was obtained if an open field was incorporated into the maze. Caffeine also had no effect on open field behavior, but it tended to improve the efficiency of radial arm maze patrolling, and it significantly depressed exploration of short tunnel arms branching from the radial arms in favor of exploration of the more distant radial tunnel ends.

Caffeine Tunnel maze Spatial learning Anxiety Locomotor activity Rat

CAFFEINE is a psychotropic drug widely used by humans and as such, has been investigated in animals in diverse behavioral test paradigms. The behavioral effects of caffeine have been most extensively studied in various activity-measuring devices, including photocell cages, running wheels, and straight runways. In general, the effect of caffeine on locomotor activity is an inverted U-shaped function of the dose given [11, 12, 19, 28, 33].

In stimulus discrimination paradigms, an optimal dose of caffeine that enhances discrimination has sometimes [20,29], but not always [16] been demonstrated. Furthermore, operant responding under a DRL schedule is found to be increased at an optimal caffeine dose, but the number of reinforcements received is concomitantly reduced [32, 33, 36]. Thus the activity enhancement induced with caffeine administration does not always work to the benefit of the experimental subject. In relatively simple exploration tests, such as an open field or a holeboard, caffeine has been found to enhance activity [5,11], but whether exploratory behavior is also altered is unclear due to the confounding of exploratory behavior and locomotor activity [30]. To date, the effects of caffeine have not been thoroughly evaluated in more complex maze situations (see [8,17] for reviews).

Towards this goal a Dashiell-type tunnel maze was used in the present experiment [1]. This test paradigm permitted the automatic measurement of locomotion by means of photobeam units. The level of maze complexity was varied by using a hexagonal tunnel without choice points (A), a symmetrical tunnel arrangement with multiple choices designed so as to evaluate the efficiency of radial arm patrolling (B), and a third maze which included in addition to complex choices an open field allowing to measure effects on anxiety (C). The rats tested in this study were not food or water deprived in order to avoid bias by caffeine effects on consummatory motivation as suggested by Merkel *et al.* [24]. An initial experiment was done to investigate the stimulant effect of several caffeine doses on locomotion in the no choice hexagonal tunnel maze configuration. The most efficient dose was then selected and used in a subsequent experiment designed to compare the effects between the three mazes.

METHOD

Animals

The 150 female Wistar rats used in this investigation were obtained from the Kleintierfarm Madoerin (Fuellinsdorf, Switzerland). Female rats were chosen for this study because earlier investigations [2,22] showed that female rats are more active in this behavioral testing system than their male counterparts and that this difference is due only to a modest extent to increases of locomotor activity on the oestrus day. These subjects were selected from a larger group of 200 animals on the basis of activity measurements obtained in a pretest. The pretest lasted 4.5 minutes, was carried out several weeks before the experiment and involved the measurement of locomotion in a half segment of the outermost tunnel of the maze. The most active and inactive animals were eliminated in order to get an approximatively normal distribution of locomotor activity for the remaining animals. These animals were assigned to the different groups so as to achieve a balance for activity levels. Throughout the study the rats were group-housed (8–10 per cage) in Macrolon IV cages in animal quarters with a 12:12 hour light-dark cycle with light onset at 6:00 a.m. Temperature and humidity were controlled (22°C, 50% relative humidity). Food pellets No. 890 (Nafag AG, Gossau, Switzerland) and tap water were available ad lib in the home cage. The rats were approximately 3.5 months old at the time of testing and weighed 215

to 270 grams. All subjects were extensively handled prior to the start of behavioral testing.

Apparatus

The tunnel maze with multiple optional barriers shown at the bottom left of Fig. 1 was used. Forty-two infrared photocell units were distributed uniformly throughout the tunnels as is also shown in Fig. 1. They were interfaced to a PDP11/34 computer system. The diagonal diameter of the maze was 1.4 m. The tunnels were 8 cm wide and 15 cm high. The ceiling and side walls were fitted together to form a unit that could be lifted from the floor to permit easy removal of the subject and subsequent cleaning of the floor (Fig. 1). The ceiling, walls, and floor were lined with dark grey PVC plastic. The three maze configurations used in the present study are shown in Fig. 1. Configuration A included only the outermost hexagonal tunnel with a single barrier to prevent the animal from completely circling. The subject was placed in this outer tunnel through a door in the maze ceiling. Configuration B consisted of 6 symmetrical segments in the form of a radial arm maze with each arm leading from the covered, 750 cm^2 central arena to the periphery of the maze and including a short blind alley halfway to the periphery. For this configuration the subject was placed into the central arena through the ceiling opening at the start of the testing session. Subsequently the central arena was covered by a low wooden lid. Configuration C was produced by dividing the maze into two equal sectors such that in order to pass from one sector to the other the subject had to cross an open field obtained by transformation of the central arena. This was done by removing the central arena ceiling and inserting a hexagonal side wall 55 cm high with a 60 W incandescent bulb 43 cm above the floor.

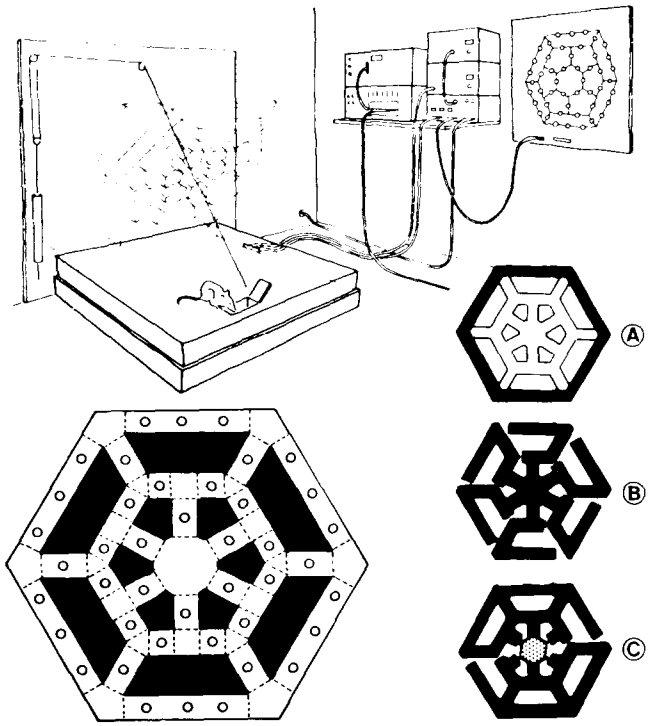

FIG. 1. Overview of the tunnel maze system (top), with the ground plan (bottom left) and the 3 maze configurations (bottom right). Possible barrier positions are indicated by dotted lines, photocell units by open circles (ground plan).

Statistical Analysis

The data were analyzed using the BMDP82 statistical software package [13]. BMDP-program 7D was used for description of groups with histograms and analysis of variance (ANOVA). This program controls for the assumption of homogeneity of variances and offers test statistics for within group variances which are not assumed to be equal [7]. In the case of correlated data (e.g., the development of habituation over a trial) an ANOVA procedure including a repeated measures design was used (BMDP-program 2V). Because the F-test is rather sensitive to a violation of the variance-covariance matrix symmetry [37], corrections were made for the degree of freedom of the numerator of the F ratio in the case of repeated factors according to the method described by Box [6].

Procedure

All testing was done during the light portion of the light-dark cycle with testing beginning at least one hour after light onset and ending at least one hour prior to light offset. In order to eliminate any possible effects of the time factor, the experimental design was counterbalanced for time effects. The subjects were injected interperitoneally (IP) with saline vehicle or caffeine (anhydrous caffeine, Fluka AG Buchs, Switzerland) at doses of 8, 16, or 32 mg/kg BW. The injected rat was then placed into a holding cage for 15 minutes before being placed into the tunnel maze system. At the end of the 30-minute test session the subject was removed and the maze floor thoroughly wiped with a cloth dampened with warm water to eliminate odor trails. Each subject was injected and tested only once. The order of experimental conditions was counterbalanced across days. In the first experiment 60 rats were randomly divided into 4 equal groups that were injected with saline or caffeine (8, 16, or 32 mg/kg BW) prior to testing in configuration A.

This experiment was done to determine an optimal dose of caffeine to be used in enhancing locomotor activity in the tunnel maze system used in our laboratory with the female Wistar rats.

In the second experiment 90 rats were randomly divided into 6 equal groups. Half of the subjects were injected with 16 mg/kg BW caffeine and the remainder with saline vehicle. According to a 2×3 design, a caffeine group and a saline group were tested in each of the three configurations (A, B, and C). The procedure used was identical to that previously described.

Behavioral Variables

Total locomotor activity provided by the number of photobeam interruptions per trial was determined in all three tunnel maze configurations (A, B, C). Changes in this measure over the session were the basis of the measurement of intratrial habituation. Open field activity, an index of "emotionality," could be measured only in the 2-sector configuration (C). Both the number of crossings of the central illuminated open field and the time spent in this open arena were determined separately for the 6 successive time intervals composing a test trial. To measure spatial cognitive abilities the efficiency of patrolling the tunnel maze system within the 6-arm radial configuration (B) was analyzed using different

parameters. In contrast to the radial maze test introduced by Olton and Samuelson [27], the tunnel maze used in this investigation consisted of dark tunnels which included angles and a short blind alley halfway from the center to the periphery of the maze rather than straight elevated runways. In order to adequately describe how a rat chooses among the 6 symmetrical tunnels of the radial maze arrangement, the following analysis was performed. For each tunnel an entry point, a point in the middle, and one at the end were defined as three different criteria for exploration of a given tunnel. As variables, the total number of arm entries required to reach the defined points in all 6 arms, the amount of locomotor activity to reach the entry criteria for all 6 arms for a first time and for a second time, the number of blind alley entries, the number of repetitive choices of an already visited tunnel, the sequential position of a first repetitive tunnel visit, and the elapsed time until entry criteria for all 6 arms were reached for a first time and for a second time were defined. Furthermore, to control for the existence or the development of simple turning strategies (e.g., choice of tunnels in clockwise direction) the distribution of the 6 theoretically possible choices (e.g., +1 as the neighbor arm in clockwise direction, etc.) were analyzed. As a measurement of strategy, the relative frequency of the most frequent choice direction was determined individually, averaged per group, and separately analyzed for reaching all kinds of the defined places for entering a radial tunnel both to reach the entry criteria of the 6 arms for a first time and for a second time.

RESULTS

Experiment 1

In the first experiment using only configuration A, the effect of the 3 dosages of caffeine on total locomotor activity and on the rate of intrasession habituation was evaluated by performing separate analyses of variance for each dose in comparison to the common saline control group (Fig. 2a). The doses of 8 mg/kg, $F(1,28)=6.35$, $p<0.05$, and 16 mg/kg, $F(1,28)=9.90$, $p<0.005$, but not 32 mg/kg produced a significant increase of total activity for all 5 test intervals combined. For the 16 mg dose level the drug × interval interaction reached the level of significance, $F(1,112)=6.96$, $p<0.01$. Considering the drug effects across the 5 separate test intervals, no significance was obtained with any dose for the first interval. With 8 mg/kg significance was obtained for the third and the following intervals (all F's>3.94, $p<0.05$), with 16 mg/kg already for the second and the following intervals (F's>4.29, $p<0.05$). According to these results, the 16 mg/kg dose of caffeine was chosen for Experiment 2.

Experiment 2

Figure 2b shows the locomotion (total activity) data in the same way as for the previous experiment. The single dose of 16 mg/kg, chosen as the most efficient dose in the first experiment, differentially affected total activity with respect to the chosen maze configuration. The effect was most pronounced and similar in magnitude to the first experiment with maze configuration A, which was again included in the testing design to match the testing situation in the first experiment, $F(1,28)=24.91$, $p<0.001$. The effect was smaller but still significant with the 6-arm radial configuration B, chosen so as to increase alley length and choice complexity, $F(1,28)=11.49$, $p<0.01$. No significant effect was obtained with maze configuration C (including a small open field),

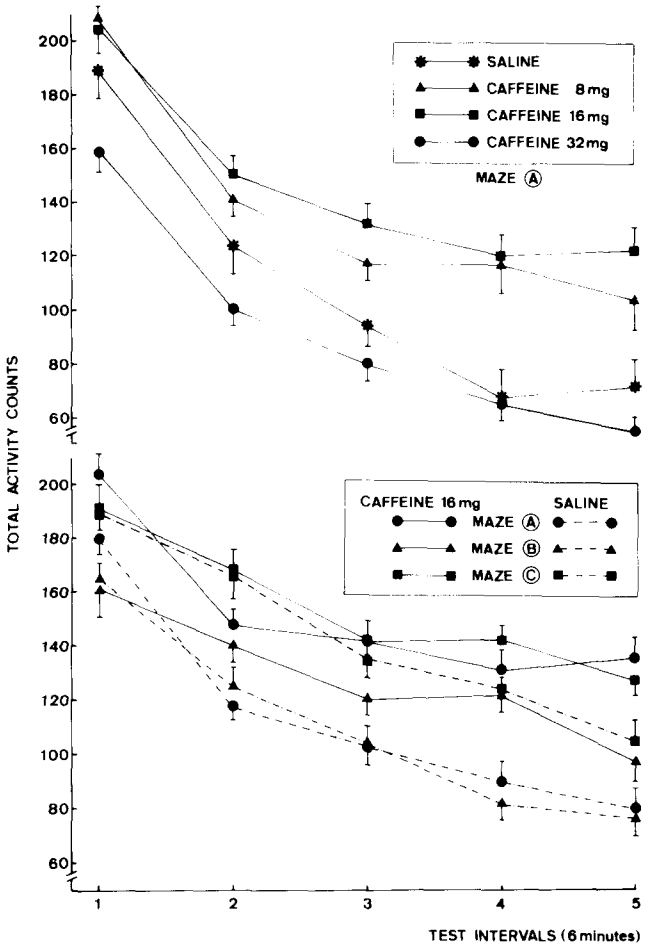

FIG. 2. Dose-response curves from Experiment 1: Intrasession habituation for the successive 6-minute time intervals are plotted for the 3 dosages and the saline control group (top). For the most powerful stimulatory dose of caffeine (16 mg), the development of intrasession habituation in 3 tunnel maze configurations differing in complexity are plotted in the lower graph.

which was chosen so as to include an element of situational anxiety. On the other hand, for this open field configuration the level of activity for the saline group was significantly greater than for the other two maze configurations (both F's>13.78, $p<0.001$).

The process of habituation across the successive test intervals reached significance for all groups (all F's>55.16, $p<0.001$).Within intervals, the drug-saline difference reached significance with maze A for all intervals (all F's>5.98, $p<0.05$) and with maze B for the fourth and fifth interval (both F's>13.50, $p<0.001$). The drug × interval interaction reached significance for maze configuration B only $F(1,112)=5.52$, $p<0.05$.

The aspect of open field anxiety addressed with configuration C was estimated by the development of the number of open field crossings across the five test intervals. In contrast to the gradual decrease of locomotor activity, the number of open field crossings increased about threefold from the beginning to the end of the testing session. There was no difference between saline and caffeine groups in this respect, as only the interval factor, $F(1,112)=5.98$, $p<0.05$,

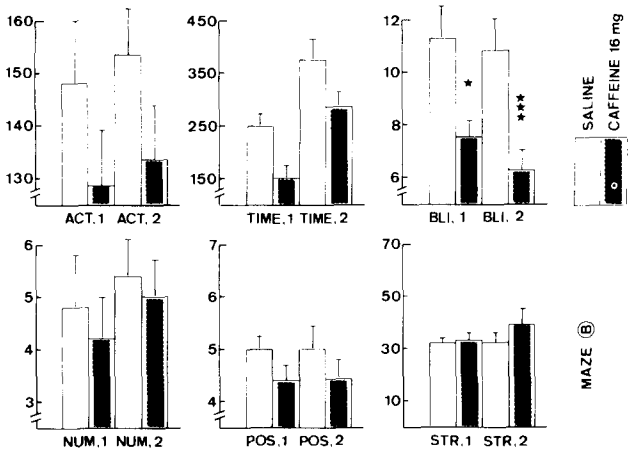

FIG. 3. Spatial learning in the 6-arm radial maze configuration: activity to reach all arms for a first (ACT, 1) and a second time (ACT, 2), time required to reach all arms a first (TIM, 1) and a asecond time (TIM, 2), number of blind alley visits after reaching all 6 arms a first time (BLI, 1) and a second time (BLI, 2), number of repetitive arms entries after reaching all 6 arms a first (NUM, 1) and a second time (NUM, 2), sequential position of a first repetitive arm entry in the first (POS, 1) and the second sequence (POS, 2), and the relative use of strategies after reaching all 6 arms for a first (STR, 1) and a second time (STR, 2).

but neither the drug factor nor the interaction reached significance. A gradual increase of time spent in the open field paralleled the increase of the number of crossings, and significance again was reached for the interval factor, $F(1,112)=4.28$, $p<0.05$, but neither for the drug factor nor for the interaction.

The aspects of spatial distribution of locomotion and choice behavior were approached with the 6-arm radial configuration B, using different parameters as shown in Fig. 3. All statistical operations resulted in equal differentiations regardless of whether arm visits to the entry, to the middle, or to the end served as criteria. Figure 3 showing all data for the entry criteria is therefore representative for all three analyses. Of the four closely related parameters, the activity counts until all 6 arms were entered at least once, the time needed to reach this criterion, the number of repetitive arm entries up to this criterion, and the ordinal number of the first repetitive arm entry, the first three tended to suggest an improvement of patrolling efficiency by caffeine. This picture remained similar for the data collected until the animals reached the criterion for entering all 6 arms a second time and again regardless of whether entries only to the initial, middle, or end parts of the arms were considered. However, this tendency suggesting a caffeine induced improvement in repetition free patrolling of the six radial arms failed to reach significance. The frequencies of the different directional choice possibilities (one or two arms away, clockwise or counterclockwise, and straight ahead) were highly similar for the two groups. This is indicated in Fig. 3 by data showing the average frequencies of the most often selected possibility.

Contrasting these negative results with respect to the efficiency of patrolling the 6 radial arms, caffeine decreased the number of entries into the small side alleys situated halfway between the central arena and the periphery of the maze, and this decrease was significant both for the first and the second tour to all 6 radial arms $F(1,28)=4.09$, $p<0.05$; $F(1,28)=9.12$, $p<0.01$.

DISCUSSION

The present investigation was concerned with the effects of caffeine on complex maze locomotion, exploratory efficiency, and open field anxiety as well as on the habituation of tunnel maze behavior. An initial experiment was done in order to investigate the stimulant effect of several caffeine doses on locomotion in the no choice hexagonal tunnel maze configuration. As pointed out, caffeine's effect on activity generally results in an inverted U-shaped function of dose, as has been shown by many different laboratories and reviewed by Calhoun [8]. Interestingly, for the simple activity-measuring devices the caffeine doses reported to produce the most pronounced stimulatory effects are highly comparable. Using a rectangular activity cage, Dews [12] has described highly stimulatory effects for 10 and 20 mg/kg caffeine in mice. In a study by Marriott [21], caffeine in doses of 12.5 and 25 mg/kg significantly increased the activity levels in a running wheel. The results obtained from the first experiment of the present study are therefore in complete agreement with the findings of other authors, as caffeine in doses of 8 and 16 mg/kg produced clear stimulatory effects on overall locomotor activity for the 30-minute testing session, whereas the 32 mg/kg dose did not. Furthermore, the results of the first experiment showed a reduction of the rate of intrasession habituation for the 16 mg/kg dose of caffeine so that the drug/saline difference in the activity scores becomes progressively greater for the successive time intervals, supporting thus the interpretation given by Estler *et al.* [14] that caffeine acts by retarding the habituation process. These authors found that whereas activity in a photocell cage rapidly declined in a control group in the initial 30 minutes of the testing session, that of a chronically caffeine treated group declined relatively slowly. That caffeine's effects on habituation could highly depend on the surrounding conditions is suggested by the findings of Ward [35], who described an increased tactile startle without an alteration of habituation of this response.

The second experiment of this study was therefore addressed to the influence of environmental complexity on the stimulatory properties of the most efficient dose of caffeine as defined in Experiment 1 (16 mg/kg). In a relatively monotonous situation (maze configuration A), the stimulatory effect of caffeine was seen for earlier test intervals than in the more complex arrangements (B, C). The latter finding is probably due to the higher stimulus density offered by the more complex configurations which led to higher baseline activity levels in the control animals, so that caffeine's stimulatory effects were "masked." In the study by Marriott [21], caffeine in a dose previously shown to produce dramatic activity enhancement in a running wheel produced no increase of activity, defined as the number of arm entries, in a Y-maze that was not familiar to the subject. The reason for this finding probably lies in the unfamiliarity of the animals with the environment leading to relatively high motor activity levels of control individuals, most likely resulting from an enhanced exploratory component of motor activity. However, interactions of additional dose levels, age, and sex with the more complex mazes cannot be completely excluded.

In the 2-sector maze configuration (C) there was no stimulatory effect on activity observed over the testing ses-

sion, but this situation also produced greater activity in the controls than the other tunnel configurations. It is likely that the illuminated open field in the center of this arrangement is responsible for this result, perhaps by increasing an activity component associated with anxiety (a stress of a milder form than would be produced by fear). The open field in the center of the maze could then represent a challenging situation leading to increased nonspecific locomotor activity. On the other hand, the present results provide no evidence that behavioral aspects related to anxiety, as measured by the frequency of crossings through an illuminated arena and the time spent there, might be affected by caffeine in a dose that clearly produced increased motor activity. With the same tunnel configuration chlordiazepoxide was seen to depress open field anxiety in a way dissociated from the effects on tunnel locomotion [23]; it seems that for this particular type of anxiety caffeine has no apparent effect. For caffeine, there is not much literature dealing with possible changes in anxiety-related behavioral parameters. Gupta *et al.* [18], using an open field test, also found no effects of caffeine (6.25, 12.5, 25.0, 50.0, 100.0 mg/kg) on "emotional freezing" or on the defecation rate. More recently, File and Hyde [15] tested several compounds in a social interaction test of anxiety in which the brightness of illumination and the familiarity to the test arena were manipulated. Social interaction served as an indicator of the anxiety level, with a higher anxiety level leading to less social interaction. In this test, caffeine decreased social interaction while increasing motor activity. The effects described by the authors were similar to those produced by the stimulant amphetamine. Based on the definitions given, caffeine was proposed to have an anxiety-producing effect, as was apparent in the reduction of social interaction. However, this does not exclude the possibility that this test could be biased by caffeine's stimulatory effects on motor activity. On the other hand, Beer *et al.* [4] noted a clear anxiolytic property of the methylxanthines (caffeine, theophylline, theobromine) in a conflict test with electric shocks to produce anxiety. Thus, it seems likely that the baseline level of reactivity in an anxiety-measuring situation is an important factor in determining the behavioral effects seen after caffeine treatment, and could, at least in part, explain the controversial data reported from different laboratories concerning anxiety.

The detailed analysis of a rat's choice pattern in the radial maze arrangement (B) used in this study allows an evaluation of possible behavioral effects of caffeine on spatial cognitive performance. For efficient patrolling behavior a rat must establish a cognitive concept which permits the avoidance of repetitive entries of the most recently visited arms. Caffeine clearly increased the total number of arms visited during the test session, reflecting the higher level of locomotor activity. But there is clear evidence that caffeine also worked to the benefit of the animal in terms of spatial cognitive performance. The number of blind alley entries up to the time when all six arms had been visited for a first, and subsequently for a second time, was significantly reduced. Such a reduction of blind alley visits normally develops with increasing experience of a rat tested for several days in the same radial configuration [25]. Furthermore, the activity scores and intervals required to reach these performance criteria were non-significantly lowered by caffeine. It is obvious from our analysis of choice sequences that caffeine did not principally alter the animals' strategy of problem solving. The radial tunnel maze has been shown earlier to represent a very sensitive instrument for detection of cognitive alterations that are not related to locomotor activity. Lesions in the dorsal hippocampus for example, led to a decreased patrolling efficiency, whereas locomotor activity remained unchanged [26]. From the literature it is not clear whether caffeine has an action on higher cognitive functions in the rodent. Although in a number of studies [9, 31, 34) caffeine did in fact improve learning and memory in different test paradigms, other investigators failed to observe any such improvements [3,10]. A semichronic study using the radial tunnel maze configuration could help in characterizing caffeine's presumed cognitive effects.

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