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Learning Impairment in the Radial-Arm Maze Following Prolonged Cannabis Treatment in Rats

Alexander Stiglick and Harold Kalant

Department of Pharmacology, University of Toronto, Toronto, and Addiction Research Foundation of Ontario, Toronto, Canada M5S 2S1

Abstract. Chronic oral administration of cannabis extract to rats (daily Δ^9-tetrahydrocannabinol dose 20 mg/kg) was examined in three experiments for its residual effect on radial-arm maze learning following a 1-month drug-free period. Learning a simple eight-arm maze was significantly impaired in rats treated for either 6 months (Experiment I) or 3 months (Experiment II) with the drug. In Experiment III, animals that received the extract for 3 months exhibited significant learning deficits on a much more difficult 12-arm radial maze. The results demonstrate that the deleterious effects of cannabis on radial-arm maze learning are probably due to a tendency toward increased vigilance and perseveration, possibly combined with an impaired utilization of spatial cues.

Key words: Chronic cannabis – Learning – Radial-arm maze – Rat

Previous studies from our laboratory have demonstrated that prolonged administration of *Cannabis sativa* to rats can produce residual learning deficits. For example, acquisition of Hebb-Williams maze performance is retarded in rats that have been intubated daily for 6 months with cannabis extract in a dose providing 20 mg/kg Δ^9-tetrahydrocannabinol (THC) (Fehr et al. 1976). More recently, Fehr et al. (1979) reported that the same drug treatment disrupted the learning of a complex one-way active avoidance task. The disruption appeared to be correlated with irregular spike-like waves in electrical recordings from the dorsal hippocampus. All of these effects of the drug were observed at least 1 month after the last treatment.

Although the nature of the learning impairment produced by cannabis is not known, it is possible that the residual effects of long-term treatment resemble the changes that accompany hippocampal dysfunction. This idea is supported by the fact that alteration of hippocampal functioning results in impaired learning of the Hebb-Williams maze (Kimble 1978), and also in deficits in active avoidance (Schmaltz 1971).

The purpose of the present study was to examine the nature of the learning disability further, by using the radial-arm maze developed by Olton and his associates. Learned behavior on this maze is disrupted by lesions to the hippocampus or to its extrinsic pathways (Olton and Samuelson 1976; Olton et al. 1977, 1978; Olton and Werz 1978). In Experiment I, learning of a relatively simple eight-arm radial maze was examined in rats treated for 6 months with cannabis extract (THC dose 20 mg/kg). In Experiments II and III animals were treated for 3 months with the same daily dose and tested either on the eight-arm maze or on a much more difficult 12-arm radial maze.

Offprint requests to: Dr. H. Kalant

Experiment I

Materials and Methods

The subjects were 30 naive male Wistar rats weighing 120–130 g at the beginning of drug treatment. Rats of this weight are considered immature, since they are only about 40 days old. All animals were caged individually, exposed to a normal light-dark cycle, and given free access to both food and water until they attained a weight of 330–340 g. After this their weights were maintained at this level by giving each subject three or four standard rat chow pellets per day and monitoring body weights at least twice per week. This procedure was designed to provide adequate motivation in the radial maze, and also to keep the rats from becoming too large for testing.

Cannabis Extract. Dried cannabis leaf material (marijuana), obtained from the Department of National Health and Welfare, Ottawa, was extracted with ethanol and the extract was analyzed by gas-liquid chromatography (GLC) and thin-layer methods. The preparation and analysis procedures are described in earlier reports from our laboratory (Fehr et al. 1976, 1979; Fehr 1977). The extract used in Experiment I contained 28.5% THC and 10.0% cannabinol (CBN), expressed as dry weight of extract. The cannabidiol content was negligible, possibly because of its naturally low quantities in cannabis material, although the extraction procedure may have lowered it further. The final ethanolic extract was stored under nitrogen in an air-tight bottle at 4° C until required for intubation. It was analyzed by GLC at least every 3 months and was never found to contain significantly less THC than was measured originally.

Different leaf material was used for Experiments II and III, but all of the final extracts had two- or three-times more THC than CBN. Extract used in Experiment II was 17.0% THC and 4.9% CBN, while that in Experiment III contained 10.0% THC and 5.0% CBN. The lower cannabinoid content of the material used in the latter two experiments was due to lower amounts in the original dried leaf material.

In each experiment the ethanolic extract was dried, then dissolved in olive oil to give a concentration of 10 mg/ml solution THC, and the same supply of olive oil served as the control substance for rats in the vehicle groups. New solutions were made every 1–2 weeks.

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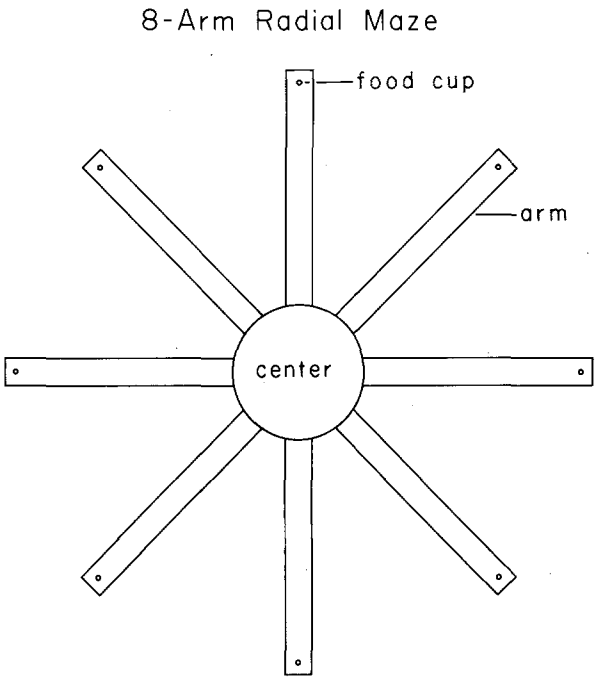

Fig. 1. Schematic diagram of eight-arm radial maze

Radial-Arm Maze. The eight-arm radial maze (Fig. 1) was similar to that described by Olton and Samuelson (1976). The apparatus consisted of a round central platform elevated 50 cm above the floor, with eight radiating arms attached to it at equal distances from each other. The center platform was made from plywood 2 cm thick and 34 cm in diameter. The plywood arms were 86 cm long and 9 cm wide equipped with walls made of light aluminum sheet about 1 mm in thickness. The walls were 5 cm high for most of their length, but were increased to approximately 10 cm on one side of each arm where it joined the centre platform, to deter the animal from going from one arm to another without first traversing the center platform. A well 2 cm in diameter and 1 cm deep was drilled 4.5 cm from the end of each arm to serve as a food cup for a single 45 mg Noyes pellet that was used to bait each arm. The test room had low illumination supplied by three 40 W light bulbs 1 – 2 m above the floor of the room. A white plywood barrier (122 × 91 cm) was placed between the observer and the maze, since pilot work showed that, without this barrier, the rats were often deterred from entering the arms closest to the scorer. There were numerous visual cues scattered around the room, such as a sink, shelves, and other objects.

Intubation Procedure. The rats were randomly assigned to either the cannabis group ($N = 16$) or the vehicle group ($N = 14$). Cannabis-treated rats received daily gavage of the extract in olive oil in a dose that provided 20 mg THC/kg body weight, while rats in the vehicle group were given the same volume of olive oil only. All subjects received their respective treatments for 180 days (6 months), and then the drug was withdrawn abruptly. The rats were then permitted to stay in their home cages for another 30 days to allow clearance of residual cannabinoids from the body before testing on the maze began.

Testing Procedure. At the start of the session for each animal, one Noyes pellet was placed at the end of each arm in the food cup. On test day 1 only, another pellet was put at the starting position of each arm, just inside the entrance from the center platform. This was done to encourage the rat to explore the maze without the shaping procedure always considered necessary by other investigators (e.g., Olton 1977; Olton and Werz 1978; Alfano and Petit 1981).

One rat at a time was put into the middle of the center platform with its head always pointing away from the experimenter. Each test was terminated when the animal obtained all the food pellets in the maze (maximum eight pellets) or when 10 min had elapsed, whichever occurred first. An entry into an arm was scored whenever a rat had all four paws fully into an arm, even if the subject did not go to the end of the arm to obtain the food. The animals were tested in the maze every other day for a total of 15 test days.

Dependent Measures and Statistical Treatment. Three measures of learning ability were taken and analyzed statistically:

1) The mean number of correct responses for each group was measured for every test day and analyzed collectively by an analysis of variance. Correct responses were defined as the number of arms entered only once out of the first eight entries made. This definition was used because the optimal strategy for the rat, of course, was to visit each arm only once to obtain all eight pellets.

2) The mean number of errors made by subjects in each group over the 15-day test period was compared by analysis of variance. Errors were defined as the number of arms that a rat entered more than once in a session to obtain all pellets. For example, a poorly performing rat that made 40 entries to obtain the eight pellets received an error score of 32, reflecting the number of redundant or unnecessary entries, and could have a correct score of 1 – 7. On the other hand, an animal that performed very well and obtained all eight pellets by visiting each arm only once received an error score of 0, and its correct score was a perfect 8.

3) A criterion of perfect performance was used as an overall measure of learning ability on the radial-arm maze. An animal reached criterion on the first day it achieved a perfect score. Thus, a quantal measure was obtained each day as the cumulative number (or percent) of rats in each group to reach criterion, either on that day or on any previous day or days. This measure of learning was then used to compare the groups by regression analysis, to determine if either the slopes or intercepts (height) of the curves of the two groups were significantly different.

Two other measures were taken to assess whether related changes in behavior were produced by the drug treatment:

1) The tendency for subjects to exhibit perseveration of responding was assessed by measuring the number of perseverative errors exhibited by each animal. This type of response occurred whenever a rat re-entered one of the two arms most recently visited during the same test. The number of perseverative responses was expressed as a percentage of the total errors and subjected to analysis of variance.

2) To measure general activity levels, the average rate of entry into the arms was calculated for each rat as the total number of arms entered/total time to complete each test. Scores for every test day were analyzed collectively by analysis of variance.

Results

As shown in Fig. 2, control rats gained weight significantly more rapidly than cannabis-treated animals for the first

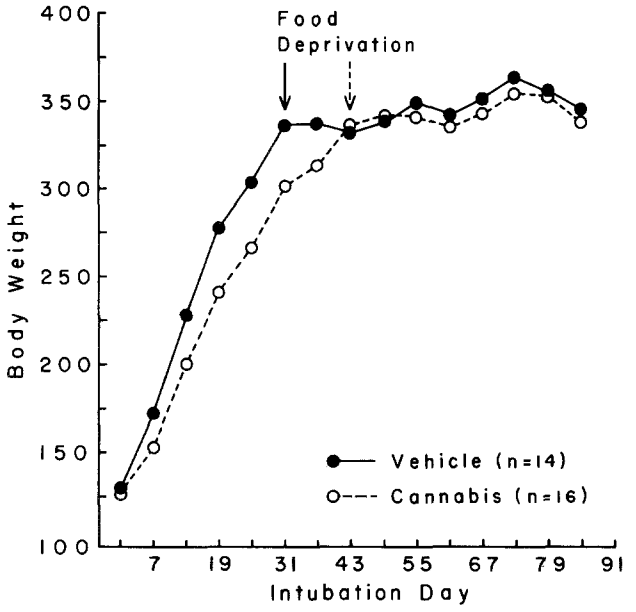

Fig. 2. Body weights of cannabis-treated and control rats during the first 3 months of intubation. Cannabis animals received daily gavage with a dose of cannabis extract providing THC 20 mg/kg in olive oil. Controls received only olive oil. Food restriction (*arrows*) was started when subjects attained a weight of 330–340 g

5 weeks, during which both groups were on ad libitum feeding (results of regression analysis $F = 1683.74$, df 1, 216, $P < 0.001$). This is consistent with reduction of food intake by cannabis treatment, as reported by Sofia and Barry (1974). As the controls reached the criterion weight for food restriction while the cannabis group continued ad libitum intake, the difference disappeared (Fig. 2) within 10–14 days. For the remaining 4.5 months of intubation, as well as the 1-month post-treatment waiting period and the 1.5-month learning period, the two groups were at the same weight. Essentially similar results were found in Experiments II and III.

Although no shaping was used in this study, only one cannabis-treated rat did not learn to run down the arms to obtain food. This rat was discarded after it failed to leave the center platform for 6 consecutive test days. In general, the cannabis-treated rats appeared more reluctant than controls to leave the center platform on test day 1: Four animals in the cannabis group and one rat in the vehicle group could not be scored on that day, since they failed to make at least eight entries in the time allowed. Therefore, data from day 1 were not included in the statistical analyses.

When analyses of variance were applied to the remaining data (until day 15) subjects in the cannabis group made fewer correct entries (significant main effect of group $F = 7.30$, df 1, 27, $P < 0.01$) and more errors ($F = 4.25$ df 1, 27, $P < 0.05$) than vehicle controls, as shown in Fig. 3a, b. These significant effects make it unnecessary to consider the daily variability among subjects in each group: Therefore, SE are omitted from the figures to maintain clarity.

The slower learning of cannabis-treated rats was confirmed by the cumulative percentage of rats in each group that achieved at least one perfect score on any test day (Fig. 3c). Subjects in the vehicle group reached this criterion in fewer days than the cannabis-treated animals (mean 7.4 and 9.1 days, respectively). This is reflected as a significant

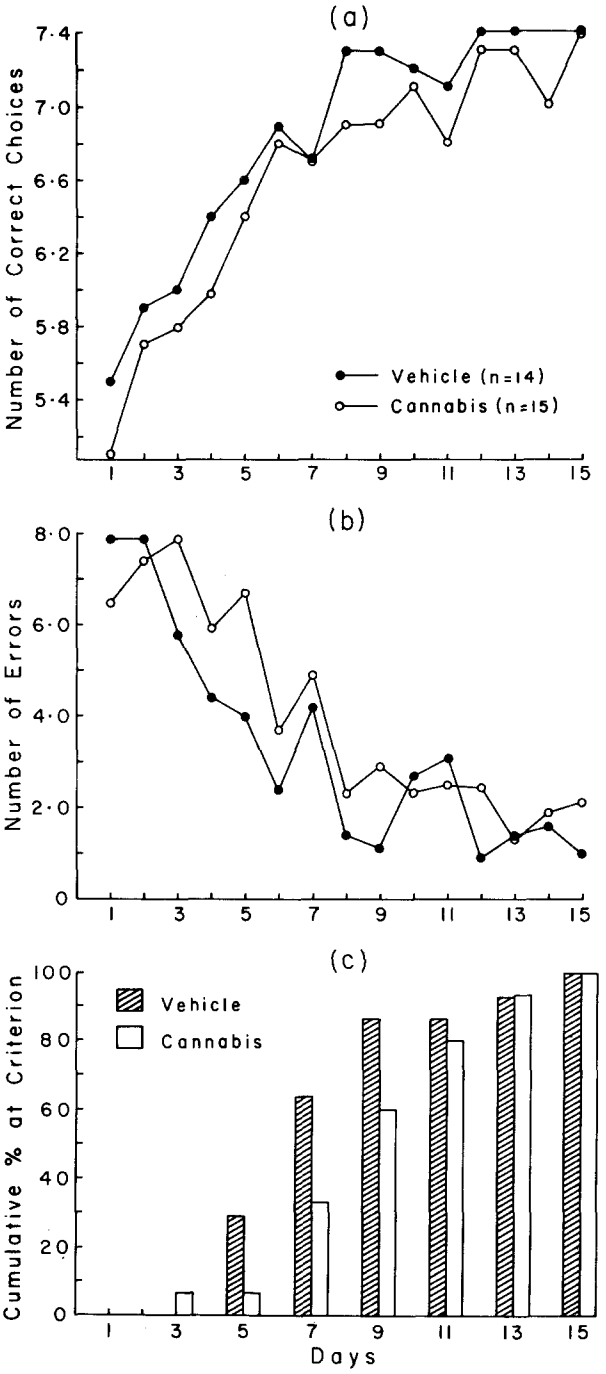

Fig. 3a–c. Acquisition of eight-arm radial maze performance by cannabis-treated and control rats. Cannabis animals had received daily gavage during 6 months with a dose of cannabis extract providing THC 20 mg/kg in olive oil. Controls received only olive oil. Tests began 30 days after the last gavage. **a** Correct performance scores on successive test days. **b** Error scores (incorrect entries) on successive tests. **c** Cumulative percentage of each group attaining criterion of one or more perfect performances

difference in intercept between the two groups ($F = 44.8$, df 1, 9, $P < 0.005$) by regression analysis.

A higher percentage of errors was due to perseverative responses in the cannabis group (10.37%) than in the vehicle group (7.21%) over the last 14 days of testing, but this effect was not statistically significant ($F = 2.28$, df 1, 27, $P < 0.14$).

Analysis of the rate of entry into the arms revealed that both groups of subjects increased their rates significantly over the 15-day test period (trial effect $F = 28.10$, df14,378, $P < 0.001$), but the overall rate exhibited by cannabis-treated subjects was lower than the rate of vehicle controls (significant main effect of group $F = 5.70$, df1, 27, $P < 0.02$; group-×-trial interaction not significant).

Discussion

On three measures of ability, a subtle but significant learning impairment was exhibited by animals that had received chronic intubation with cannabis extract for 6 months. In addition, rats in the cannabis group took a longer time to obtain food in the maze than vehicle-treated subjects, as shown by the difference in rates of entry into the arms. This impairment was evident for at least 1 month of testing on the radial maze, or more than 2 months after the last drug administration. In rats the half-life of THC and its metabolites is approximately 21 h (Klausner and Dingell 1971). Therefore, it is extremely unlikely that the learning impairment in the present study was due to residual drug in cannabis-treated rats. This view is supported by the fact that the same subjects were still impaired on other behavioral tests more than 4 months after the last drug administration. These results will be reported separately.

Experiment II

Materials and Methods

The subjects were 45 naive male Wistar rats weighing approximately 125 g when drug treatment began. Subjects in the cannabis ($N = 16$) and vehicle ($N = 15$) groups were intubated, food-deprived, and tested using the procedures outlined in Experiment I, except that the intubation period lasted only 90 days (3 months). A third group of subjects, the sham-intubation group ($N = 14$) was intubated daily with the gavage tube only (i.e., nothing was passed through the tube). This group was included to control for the possibility that chronic administration of the vehicle substance (olive oil) may produce a facilitation of learning in the vehicle-treated animals.

Except for these changes, materials and methods were identical to those in Experiment I.

Results

Even without shaping, almost all rats learned to obtain food in the maze very quickly. However, on test day 1 many subjects, especially in the cannabis group, appeared reluctant to leave the center platform. Four of the cannabis-treated rats made fewer than eight entries on that day, whereas only one rat in each control group failed to enter every arm of the maze. On subsequent tests, this hesitation to explore the maze was reduced in all but one rat in the vehicle group, which was discarded after failing to leave the center platform for 6 consecutive days.

As shown in Fig. 4, subjects in the cannabis group performed more poorly than animals in the other groups, while the control groups did not differ significantly from each other (for sham versus vehicle comparisons, all statistical tests were not significant). Analysis of variance on data of days 2–15 revealed that the cannabis-treated rats made fewer correct choices ($F = 16.24$, df 2, 42, $P < 0.001$) and more errors ($F = 8.81$, df 2, 41, $P < 0.001$) than control subjects. Moreover rats in the cannabis group required more days to achieve at least one perfect score (mean 9.3 days) than either sham (mean 5.2 days) or vehicle (mean 4.6 days) controls (signifi-

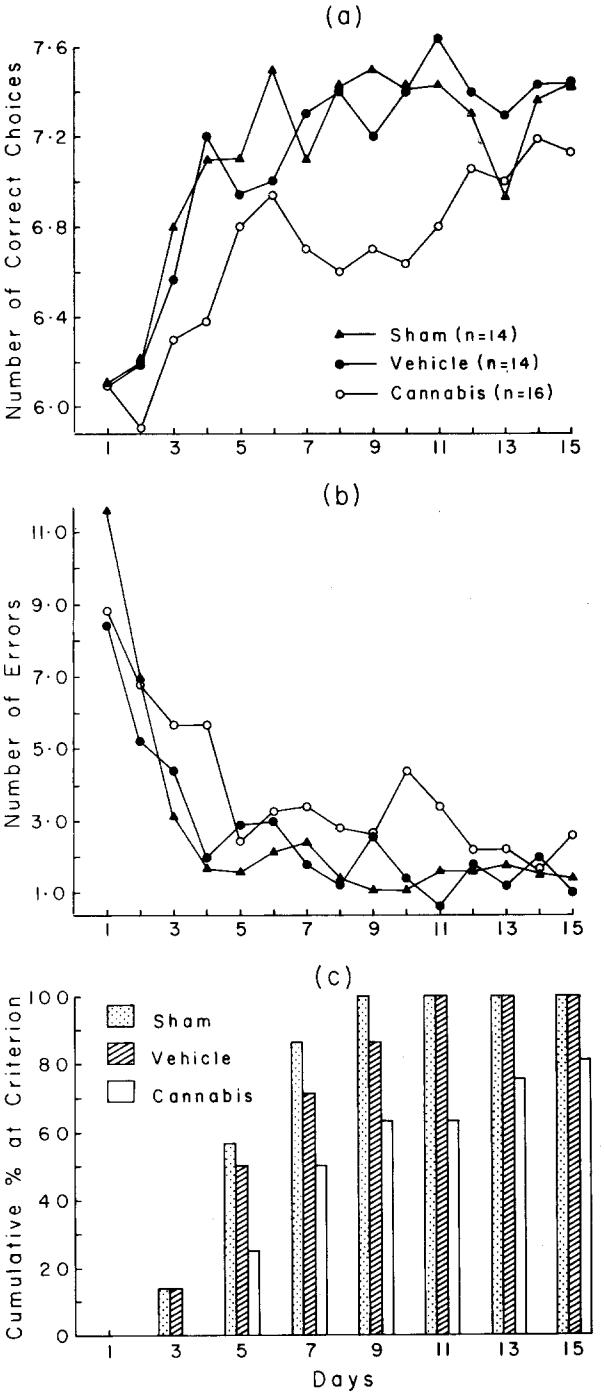

Fig. 4a–c. Acquisition of eight-arm radial maze performance by cannabis-treated and control rats. Cannabis animals had received daily gavage during 3 months with a dose of cannabis extract providing THC 20 mg/kg in olive oil. Vehicle controls received only olive oil. Sham controls had the gavage tube passed daily, but received nothing through it. Tests began 30 days after the last gavage. **a** Correct performance scores on successive test days. **b** Error scores (incorrect entries) on successive tests. **c** Cumulative percentage of each group attaining criterion of one or more perfect performances

cant intercept difference among the data from each group $F = 18.90$, $df\,2,38$, $P < 0.001$).

On the last 14 test days, the cannabis-treated rats made a higher percentage of perseverative errors (12.30% of total errors) than either sham (8.30%) or vehicle (7.22%) controls but this effect did not reach the 5% level of significance ($F = 2.52$, $df\,2,41$, $P < 0.09$).

All groups of rats significantly increased their rates of entry into the arms over the course of testing (trial effect $F = 41.57$, $df\,14,574$, $P < 0.001$), but the rates were lower in the cannabis group than in the control groups (significant effect of group $F = 6.55$, $df\,2,41$, $P < 0.003$; group-×-trial interaction was not significant).

Discussion

This experiment demonstrates that 3 months of treatment with the same dose of cannabis extract produced a long-term impairment of learning ability in the rat. The subjects in the cannabis group performed more poorly and took longer to make choices than rats in both control groups, whereas the latter were not significantly different from each other. This means that the difference in ability between cannabis- and vehicle-treated subjects was due to the deleterious effects of cannabis, not to a beneficial effect of the vehicle substance.

It is evident from these data that the impairment produced by only 3 months of cannabis administration is very similar to the effects of the 6-month treatment in Experiment I. Of course, the definition of a minimum effective duration of treatment must be qualified by the minimum daily dose of THC (or other cannabinoid) required to produce these effects. In a previous report from our laboratory, no residual impairment was observed after THC dosage of 10 mg/kg daily for 3 months (Fehr et al. 1976). Taken together, the data suggest that a daily THC dose closer to 20 mg/kg may be necessary, but does not yet establish a lower limit of exposure to produce learning impairment in rats.

Despite the significant learning deficits, many cannabis-treated subjects were able to perform well on the eight-arm radial maze by the last test day. In Experiment III, naive subjects were tested on a much more difficult 12-arm maze in an attempt to increase the disparity between experimental and control subjects.

Experiment III

Materials and Methods

The subjects were 30 naive male Wistar rats weighing approximately 125 g when drug treatment was started. The rats were randomly assigned to either the cannabis ($N = 15$) or vehicle ($N = 15$) groups, then were intubated and food-deprived using the procedures outlined in Experiment II. Because the performance of sham-intubated and vehicle rats was virtually identical in Experiment II, sham-intubated controls were not included in this experiment. Cannabis treatment was again for 3 months at a daily dose providing 20 mg THC/kg.

The materials and methods were identical to those of Experiment II, except for the following changes:

1) The radial maze had 12 radiating arms attached to a center platform that was 50 cm in diameter. Each arm was 86 cm long and 10 cm wide, equipped with a small light and a photocell that were on opposite walls 3 cm above the floor of the arm and 21.5 cm from the center platform. A single 1.2 W red light bulb, visible only to the experimenter, was located under the center platform. This light was activated whenever a rat crossed in front of the photocell on any arm. This provided a more objective criterion of arm entry than was used previously.

2) After the 90-day intubation period the subjects stayed in the home cage for 35 days before testing began.

3) On test day 1 only, there was one extra Noyes pellet located at the starting position of each arm, thus providing 12 free pellets, in addition to the pellets at the end of each arm in the food cups. Every test was terminated when the subjects obtained all the food pellets in the food cups or when 12 min had elapsed, whichever occurred first.

4) Correct responses were defined as the number of arms entered only once out of the first 12 entries made. Hence, a perfect score was 12/12, with an error score of 0 (no arms entered more than once).

Results

On test day 1, a few rats in each group appeared reluctant to leave the center platform. Two animals in the cannabis group and three rats in the vehicle group could not be scored on that day because they made fewer than 12 entries. However, on subsequent days, all subjects learned to obtain food without a shaping procedure.

In general, the 12-arm maze was much more difficult to learn than the eight-arm maze used in previous experiments. Nevertheless, subjects in the vehicle group still learned more quickly than animals in the cannabis group (Fig. 5). Analysis of variance on data of days 2–15 showed that rats in the cannabis group made fewer correct choices ($F = 5.08$, $df\,1,28$, $P < 0.03$) and made more errors ($F = 4.72$, $df\,1,28$, $P < 0.04$) than vehicle controls. In addition, the cannabis-treated subjects were less able to reach a criterion of at least one perfect score than controls over all test days. By the final test day, only two cannabis-treated animals had reached this criterion, compared with eight animals in the control group ($N = 15$ for each group). This difference is shown in Fig. 5c, and is reflected by a significant difference in the intercepts between the curves from the two groups ($F = 25.26$, $df\,1,21$, $P < 0.001$). Comparison of Fig. 5 (12-arm maze) with Figs. 3 and 4 (eight-arm maze) reveals that the use of the 12-arm radial maze did not increase the disparity between rats in the cannabis and vehicle groups, except with respect to the days-to-criterion score.

The occurrence of perseverative responding was not appreciably different between cannabis-treated (4.00% of total errors) and vehicle-treated (3.72%) subjects in this experiment. In addition, the rate of entry into the arms was not significantly different between the two groups.

Discussion

The 12-arm radial maze produced an increase in task complexity, relative to the eight-arm maze, but did not increase the difference between the treatment and control groups with respect to correct or error scores. This is in contrast to the effects of hippocampal lesions reported by Olton and his colleagues, who have shown that the disparity between hippocampal-lesioned and control rats increases dramatically when the maze task is made more difficult by the addition of more arms (Olton 1977; Olton et al. 1977).

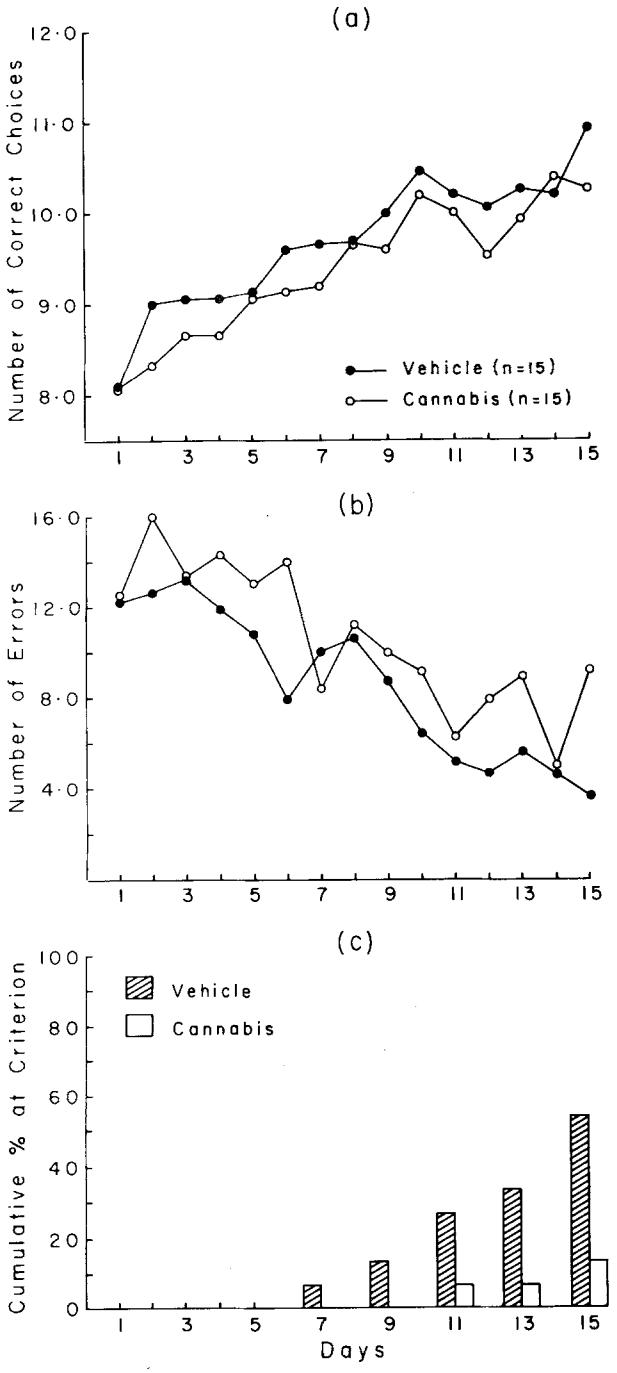

Fig. 5a—c. Acquisition of 12-arm radial maze performance by cannabis-treated and control rats. Cannabis animals had received daily gavage during 3 months with a dose of cannabis extract providing THC 20 mg/kg in olive oil. Tests began 35 days after the last gavage. **a** Correct performance scores on successive test days. **b** Error scores (incorrect entries) on successive tests. **c** Cumulative percentage of each group attaining criterion of one or more perfect performances

Whatever interpretation is advanced to explain the present data, it seems clear that the demonstrated effects of chronic cannabis administration are not a function of task complexity alone in the radial-arm maze.

General Discussion

The results of the present experiments confirm previous reports from our laboratory which showed that 6 months of cannabis treatment produces long-term impairment of certain learning abilities in the rat. Learning impairment can be produced by as little as 3 months of treatment, as long as the cannabis extract is adjusted to provide a daily dose of 20 mg THC/kg. This effect is not unique to cannabis; similar residual learning deficits have been reported after chronic ethanol treatment. However, it is noteworthy that 3 months of treatment with ethanol had no significant residual effects on learning behavior in the rat (D. W. Walker, personal communication); at least 5 months was necessary (Walker and Freund 1971, 1973; Bond and DiGiusto 1976; Fehr et al. 1976).

The mechanisms by which cannabis treatment produces long-term learning impairment are still unknown, but certain hypotheses can probably be ruled out. For example, it is unlikely that the residual effects of the drug are due to nonspecific sedative effects of intoxication, as proposed for certain residual effects of chronic ethanol or pentobarbital treatment (Snell and Harris 1980). Observation of our cannabis-treated rats in their home cages revealed that they were never ataxic or sedated by the cannabis and were usually more active than controls, especially after the first 2 weeks of chronic treatment. Other investigators have reported a similar hyperactivity in intoxicated rats that received even larger oral doses of cannabis for at least 2 weeks (Rosenkrantz et al. 1975).

Another explanation which can probably be excluded is that the impaired maze learning was an indirect consequence of growth impairment in the cannabis-treated group. Growth was slowed by only 5%–10%, and only for the first 5 weeks of treatment. After food restriction was started, body weight was the same in the two groups for the duration of the experiment and was, in any case, not sufficient to result in malnutrition. Rats held at constant body weight of the order used here are generally healthier and live longer than rats left on unrestricted diet (LeBlanc 1972).

There are at least three ways in which the present results might be explained. First, it is possible that the cannabis treatment produced a residual fear of novelty or a fear of open spaces. This might explain why a higher proportion of cannabis-treated animals were reluctant to leave the center platform of the eight-arm maze on day 1 of testing. It may also account for the lower rate of arm entry on the eight-arm maze, possibly reflecting a greater degree of hesitancy or vigilance in subjects of the cannabis group. However, this type of explanation cannot account for all of the observed learning deficits, since on the 12-arm maze, rats in the vehicle and cannabis groups did not differ on these measures, but still exhibited very different learning abilities.

A second possibility is that long-term cannabis treatment produced a type of perseverative behavior, resulting in reduced ability of the animal to withhold incorrect responses. Because there was a trend, even though not statistically significant, for cannabis-treated subjects to make more perseverative errors than control rats on the eight-arm radial maze, this type of explanation cannot be ruled out. However, the negligible difference between the groups on the 12-arm radial maze suggests that the residual effect of the drug on perseverative responding cannot fully explain the observed disruption of learning.

A third possibility is that the chronic drug treatment reduced the rat's ability to make use of spatial cues. Although the procedures used in the present experiments did not permit a direct test of this idea, it seems likely that such an impaired

utilization of spatial cues, along with a tendency toward increased perseveration and vigilance, combined to produce the learning impairment on the radial-arm maze.

Whatever interpretation is advanced to explain the present data, it seems possible that long-term cannabis administration produces a variety of behavioral changes that are similar to those produced by hippocampal damage. As in the case of the Hebb-Williams maze (Fehr et al. 1976), the impairment of radial-arm maze performance produced by cannabis is similar, though on a smaller scale, to the effects of hippocampal lesions (Kimble 1978; Olton et al. 1978). The companion paper (Stiglick and Kalant 1982) demonstrates that this similarity may be extended to a differential reinforcement of low-rate responding (DRL) schedule and to open field activity.

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