Pharmacology Biochemistry & Behavior, Vol. 4, pp. 249–254.

Chronic Administration of Delta-9-tetrahydrocannabinol to Pregnant Rats: Studies of Pup Behavior and Placental Transfer[1]

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(Received 24 January 1975)

VARDARIS, R. M., D. J. WEISZ, A. FAZEL AND A. RAWITCH. *Chronic administration of delta-9-tetrahydrocannabinol to pregnant rats: studies of pup behavior and placental transfer*[1] PHARMAC. BIOCHEM. BEHAV. 4(3) 249–254, 1976. – Tritiated delta-9-tetrahydrocannabinol was administered orally to female rats throughout pregnancy at a dose level of 2 mg/kg/day. Chemical analysis of rat pup tissues indicated an average drug level near 20 ng/gm was attained via placental transfer. Although there was no teratogenicity, the pups showed both transient and relatively permanent behavioral effects. A deficit in acquisition of a passive avoidance response at 21 days of age was observed. This effect was not apparent during retraining and testing at 90 days of age. Rats whose dams had received the drug forced control animals to back out of a push tube in 67% of the tests at 21 days of age and 94% of the tests at 90 days of age.

Delta-9-tetrahydrocannabinol Placental transfer Passive avoidance Push-tube competition

PLACENTAL transfer of cannabinoids has been demonstrated in a number of experiments [1, 7, 8, 16, 17, 18, 19, 20]. Most of the studies have been concerned with effects of cannabis on reproductive success in rodents.

In one of the few reported attempts to determine behavioral effects of placentally-transferred cannabis, Uyeno [20] injected 30, 60 and 120 mg/kg Δ-9-tetrahydrocannabinol (THC, the major psychoactive constituent of marihuana) subcutaneously and used a split-litter cross-fostering technique [21] to isolate drug effects on maternal behavior from congenital factors. The drug was administered only on the 10th, 11th and 12th days of pregnancy – the period of major neuronal differentiation in the brain [20]. In Uyeno's studies [20] THC produced significantly more abnormal pregnancies than did the vehicle (ethanol) with many of the pups being stillborn or stunted. THC had no observable effect, however, on spontaneous activity levels of 16 day old pups or on Y maze-learning of 20 day old pups.

Using a more complex maze (Lashley III), Gianutsos and Abbatiello [8] were able to demonstrate a learning deficit in pups of cannabis-treated dams. The animals were injected subcutaneously with 250 mg of a cannabis resin extract on Days 8–11 of pregnancy. In contrast to the results of Uyeno, there was little evidence of stunting.

It is possible that more significant behavioral effects would appear in the pups if the drug were administered daily to the dams throughout the entire gestation period. Furthermore it would be of interest to examine the effects of a much lower drug dose than has commonly been used in placental transfer experiments. A relatively low dose would minimize possible complications from stunting and neuroanatomical malformations.

The present study was designed to examine further the behavior of offspring of pregnant rats given THC throughout gestation. A dose of 2 mg/kg was used because it was found to be the minimum effective dose for changed social behavior in adult male rats (Vardaris, Letostak, and Sheehan, in preparation). Radioisotopic procedures permitted quantitative determinations of THC and its major

[1] This research was supported by NIMH Grant R01–MH20558 and NIDA Grant 5 R01–DA00105 to the first author as well as NIAMDD Grant AM14553 to the last author who is a recipient of Research Career Development Award AM70473.

metabolites in the pup tissues. Two techniques for measuring social behavior (open field and push-tube tasks) and one inhibitory learning situation (passive avoidance) were employed to test possible behavioral effects in the pups. In part, these tasks were chosen because the effects of THC on similar tasks have been studied using adult rats. Drew, Miller, and Wikler [4] reported that THC reduced open field ambulation, rearing, and sniffing in male rats during certain post injection intervals. Masur, Martz, and Carlini [14] found that 2.5 mg/kg THC reduced defecation, grooming, and rearing in an open field. Vardaris *et al.* (in preparation) found a decrease in aggressive behavior in the open field following administration of THC.

Competitive tasks, represented in the present study by the push-tube, have been studied by Masur, *et al.* [13]. They found that THC increased winning behavior on one food competition task but decreased it on another. The push-tube, which is not a food competition task, was used in the present study to eliminate possible food motivational effects of THC. Manning, *et al.* [12] have suggested that poorer performance by rats given THC on appetitive tasks may be due to a reduction in the effectiveness of food reinforcement. Vardaris, *et al.* (in preparation) found a decrease in winning on the push-tube task following THC administration with adult male rats. Miller, Drew and Joyce [15] reported no effect of 5 and 15 mg/kg doses of THC on either acquisition or retention of a 1 trial passive avoidance response. However it was felt that passive avoidance would be useful in the present study, as rat pups require multiple trials to learn the task thus affording more opportunity for drug effects to be observed.

METHOD

Animals

Sixteen sperm-positive Sprague-Dawley rats were obtained from the Holtzman Company. They arrived in our laboratory on the second day of gestation and were immediately placed in individual nesting cages. Throughout the period of the experiment there was free access to food, water, and nest materials. Eight of the animals were randomly assigned to the drug group for administration of THC and the remaining 8 served in the placebo group for administration of the PVP vehicle. Seven of the drug animals and 5 of the placebo group gave birth. Litter size was equated by culling from some and adding to others if necessary such that each litter contained 3 male pups and 3 female pups. The remaining 22 culled animals were used for biochemical analyses. These procedures resulted in 10 litters useable for behavioral studies – 5 THC and 5 Placebo. All pups and dams were weighed daily throughout the experiment. The dams and pups were quartered in a continuously illuminated room which was maintained at 72 ± 2°C.

Drugs

In order to facilitate the detection of small amounts of the drug, a tritiated cannabinoid (^{3}H-(-)-trans-delta-9-tetrahydrocannabinol), was used. Stock material was obtained through the National Institutes of Health from the Chemistry and Life Sciences Division of Research Triangle Institute. Its stated assay was 95% with a specific activity of 10 μC/mg. The diluent, non-radioactive delta-9-THC (97% assay in ethanol under nitrogen), was supplied by the National Institutes of Health (NIDA). The drug was administered daily in the form of an aqueous suspension in the presence of polyvinylpyrrolidone (PVP) [6]. The working suspension was adjusted with distilled water to contain 1.34 mg ^{3}H-delta-9-THC and 40.2 mg polyvinylpyrrolidone per ml. The average volume for a stomach intubation was 0.5 ml, corresponding to a dose of 2 mg/kg body weight. All drug solutions and suspensions were stored in the dark at 4°C.

Extraction of THC and Its Metabolites

The pups of both the control and THC litters, culled at random, were sacrificed and frozen within 24 hr of parturition and within 24 hr of the last intubation. Several representative pups from each litter were combined and the whole specimens homogenized in 50–100 ml of 0.9% saline with a Waring Blender (several short bursts were employed to give a uniform homogenate). Aliquots of the homogenates (20–25 ml) were extracted 3 times with equal volumes of petroleum ether and then 3 times with equal volumes of ethyl ether. The petroleum ether and ethyl ether extracts were individually pooled, taken to dryness under nitrogen and redissolved in 3 ml of an ethanol:ethyl ether (50:50) mixture. One ml aliquots of these samples were mixed with 10 ml of Bray's solution and counted on a Packard Tri-Carb Liquid Scintillation Counter for periods of from 5 min to 30 min, depending on the specific activity of the sample. Quenching corrections were derived from counting selected samples before and after the addition of known quantities of C^{14} labeled standard.

Behavioral Apparatus

The passive avoidance chamber consisted of a 37.5 x 16.5 x 16.0 cm wood box having a floor of grid bars spaced 0.45 cm apart. A partition with a 7.5 x 7.5 cm opening and a sliding door divided the box into 2 equal compartments. One compartment was painted white and the other was painted black. A 25 W incandescent lamp located 25 cm above the box illuminated the white side. The black side was covered to keep it dark. Shock from a matched impedance source [2] could be delivered to the grids on the black side of the apparatus via a Foringer Model 1155 grid scrambler.

The push-tube consisted of clear plastic tubing 3.5 cm in dia. and 30.5 cm in length. Additionally there were 2 start tubes 3.5 cm in dia. and 12.0 cm long. A white circular arena having a wood floor 61 cm in dia. and a cardboard wall 29 cm high was used for the open field tests. Illumination was provided by a 40 W incandescent lamp located 47 cm above the floor of the arena.

Procedure

Oral doses of drug and placebo were administered once daily, beginning on the third day of pregnancy and ending on the day of parturition. A standard ball-tipped feeding needle was used.

As one pup died following the culling procedures, only 29 animals from each treatment group were used for testing. At 18 days of age, the pups were placed individually in the open field arena for 5 min. This procedure was repeated 24 hr later for each animal, the purpose being to accustom the animals to the novel environment and maximize social behavior on subsequent tests by reducing exploratory tendencies.

On Day 20, the pups were tested for possible effects of prenatal treatment on social behavior. There were 29 pairs of pups. One member of each pair belonged to the THC group and the other was from the Placebo group. Each pair was placed in the open field arena for 5 min. During this period the behavior of each pup was recorded at 10 sec intervals on an ethogram or behavior-inventory checklist. The ethogram was a modified version of that devised by Grant and MacIntosh [9] for use with adult rodents. For a given 5 min test, the behavior of one member of a pair was recorded by one observer while the behavior of the other member was recorded by a second observer. The assignment of observers to either a drug or placebo animal was determined by a random schedule.

Eighteen rats were randomly selected from each of the treatment groups and tested for competitiveness in a push tube on Day 21. The methods employed for the tests were similar to those used in a parallel experiment with male adult rats (Vardaris, *et al.*, in preparation). The THC and Placebo groups contained equal numbers of males and females. Animals always were tested against members of the same sex. Briefly, one THC pup and one Placebo animal were trapped in start tubes and placed at opposite ends of the dominance tube facing each other. They were held by the tail to prevent premature entry into the main tube. The animals were released simultaneously with the start of a timer which was stopped when one of them was forced completely out of the main tube. On the rare occasions when only one animal entered the main tube, the trial was restarted. Push-tube tests were conducted (10 sec intertrial interval) until one member of the pair had evicted the other member twice. The maximum number of trials was 3.

On the same day passive avoidance training was given to 20 THC and 20 Placebo rats which were randomly selected from the pool of experimental animals. A training trial involved placement of the animal in the white compartment facing away from the door. After 10 sec the sliding door was opened, starting a timer. Immediately upon crossing to the black side, 10 of the animals chosen at random from each treatment group received a 1 sec 150 VAC (approximately 2.5 mA) scrambled footshock and the timer was stopped. The remaining 10 received no shock and were removed from the black compartment immediately after the timer was stopped. These trials were repeated with a 15 sec intertrial interval until a criterion cross-through latency of 180 sec was achieved. The maximum number of trials was 5. Non-shock animals were given 5 trials to obtain an index of spontaneous crossing behavior. At 90 days of age the dominance tube and passive avoidance tests were repeated. For passive avoidance there was 1 training trial followed 24 hr later by 1 retention test trial.

RESULTS

Biochemical Results

Small quantities of THC and its metabolites were transferred across the placenta. This resulted in an average equilibrium level of THC and its metabolites of 21.4 ng/gm (S.D. = ± 2.3) of tissue in 6 independent experimental groups (Table 1). It is interesting to note that the majority of the counts occurred, in all cases, in the more polar ethyl ether extracts. This suggests extensive metabolism of the THC to more polar derivatives, either before or after placental transfer. While counting levels were quite low, the samples were counted for sufficient time periods to obtain statistically reliable data. Four control groups (no drug administered) showed counting levels essentially within the average deviation of the background count.

The average rat pup in the drug group of this study contained an equilibrium total amount of 553 ng of THC and its metabolites at birth. An assessment of the distribution of label in the various newborn tissues was not attempted here due to the small quantities of both drug and tissue involved but would be of substantial interest.

Behavioral Results

Examination of the litters revealed no overt teratogenicity attributable to THC. There was only 1 abnormal pregnancy: a THC litter containing 3 stillborn pups and 7 healthy pups. The average litter size for THC-treated dams was 11.7 compared to 8.4 for control litters.

Body weight data for dams and pups in each treatment group were analyzed statistically to determine any drug effects. Because of small sample size the Mann-Whitney U statistic was used. No consistent weight differences between experimental and control pups were observed. The weights of dams given THC during pregnancy were, however, somewhat lower than those of the control animals, although the effect was not statistically significant. This slight difference disappeared after delivery when the THC intubations were discontinued. It was concluded from these data and from observation of the animals that THC did not have an obvious adverse effect on the general health of the animals.

The mean frequencies of 12 postures and behaviors, recorded during the open-field test, were analyzed by t tests of the differences between means for the THC and Placebo groups. The differences were consistently small in relation to the standard error and none were statistically significant. It was concluded that the prenatal treatments did not affect spontaneous social behavior in a consistent manner, given the conditions of the current experiment.

However, there was an appreciable effect of prenatal treatment on the tube behavior of the pups. For the first push-tube test (Day 21) two thirds, or 12, of the winners were drug animals. A Binomial Test revealed that the probability of an effect of that magnitude or greater occurring by chance is .238 (2-tailed test). At 90 days of age 16 of the 17 winners (one THC pup died in the interim) were in the drug group. The 2-tailed probability of obtaining such a value, or one larger, is .002.

Win latencies were analyzed to determine whether there was a relationship between strength of winning behavior in the push-tube and time required to evict an opponent. Although there was a slight tendency for the THC group to have shorter latencies (Median = 28.75 sec) than the Placebo group (Median = 34.40 sec) at 21 days of age, this difference was not statistically significant (U = 27.0). Because there was only one winning animal in the Placebo groups at 90 days of age, statistical comparisons of the win latencies were not feasible.

Table 2 contains the mean cross-through latencies on each passive avoidance training trial for all 4 treatment groups. In this table, long latencies are associated with passive avoidance, or hesitancy in crossing, while short latencies indicate relatively less passive avoidance, i.e., readiness to cross. Trial 1 latencies reflect only initial response tendencies existing prior to experience with the black compartment in which footshock might occur.

TABLE 1

RADIOACTIVITY IN WHOLE BODY TISSUES OF LITTERS BORN TO MOTHERS GIVEN THC

Litter	A		B		C		D		E		F	
Number of Pups	6.0		4.0		4.0		3.0		2.0		3.0	
Total weight (g)	42.5		29.4		30.7		23.6		14.8		14.0	
Volume of Homogenate (ml)	106.0		103.0		81.0		73.0		50.0		58.0	
Volume extracted	25.0		25.0		20.0		20.0		20.0		20.0	
Final volume of extract (ml)	3.0		3.0		3.0		3.0		3.0		3.0	
Volume counted (ml)	1.0		1.0		1.0		1.0		1.0		1.0	
Tissue weight counted (g)	3.34		2.38		2.53		2.16		1.97		1.61	
Extractions	P.E.	E.E.	P.E.	E.E.	P.E.	E.E.	P.E.	E.E.	P.E.	E.E.	P.E.	E.E.
Net CPM per sample	16.4	72.2	6.8	43.8	15.4	46.8	8.0	39.4	12.0	28.2	10.8	22.8
DPM per g*	235.0	951.0	59.0	796.0	286.0	800.0	87.0	791.0	286.0	618.0	316.0	613.0
Nanograms of THC related material per g of tissue	4.69	18.9	2.67	15.8	5.72	16.0	3.55	15.7	5.73	12.3	6.28	12.2
Total ng THC per g tissue	23.6		18.47		21.78		19.25		18.03		18.48	

*Calculated from established counting efficiency and spiking experiments as described in the text.

TABLE 2

MEAN CROSS-THROUGH LATENCIES (SEC) FOR PASSIVE AVOIDANCE TRAINING

	Shock					No Shock				
	Trial					Trial				
	1	2	3	4	5	1	2	3	4	5
THC	5.4	26.7	115.8	158.9	169.5	7.0	3.3	16.2	11.8	19.9
Placebo (PVP)	4.1	90.8	134.5	165.3	180.0	3.0	3.6	3.2	2.0	2.4

It may be seen that, except for Trial 1, latencies of the THC-shock group are consistently lower than those of the Placebo-shock group. The 2 no-shock groups have uniformly low latencies, with the values for THC being somewhat larger.

The results of passive avoidance training at 21 days of age were subjected to analysis of variance. Using a 2 x 2 factorial analysis of variance (Drug vs. Placebo and Shock vs. No Shock) a significant drug effect on Trial 1 cross-through latencies was found $F(1,36) = 5.825$, $p<0.05$). This treatment tended to produce longer initial latencies for the THC group than for the Placebo group. It was concluded that the THC animals showed some hesitancy in crossing to the black side at the beginning of the first trial.

An identical analysis was used for cross-through latencies on the second trial. There were reliable effects of Drug $F(1,36) = 5.01$, $p<0.05$) and Shock $F(1,36) = 14.81$, $p<0.001$) reflecting the facts that the reinforcing stimulus of footshock had produced passive avoidance and that the drug treatment was associated with shorter latencies than those of the placebo control group. Newman-Keuls procedures were used to test simple effects in the significant Drug x Shock interaction $F(1,36) = 4.92$, $p<0.05$). It was found that the group given placebo and footshock had reliably longer latencies than the nonshock placebo group. However latencies of the THC group given footshock did not differ significantly from either of the non-shock groups. The drug-footshock group had reliably shorter latencies than the placebo-footshock group. From these results it was concluded that the drug-footshock group showed little or no evidence of passive avoidance on the second trial.

On the third trial, however, 40% of the THC-shock animals met the learning criterion of 180 sec, while the value for trials 4 and 5 was 90%. The THC-shock group required an average of 2.9 trials to achieve the learning criterion, whereas the Placebo-Shock group had a mean of 2.0. These results indicate that the Drug animals were relatively slower in acquisition of the passive avoidance behavior but that they were capable of learning to withhold the response with sufficient training.

At 90 days of age there was no evidence of a passive avoidance deficit for the drug group. In a 10 min retention test the median latency for the drug group given footshock (571.5 sec) was not greatly different from that of the placebo group (600 sec). A Mann-Whitney U statistic was

used to test the effect of the drug, as the large number of criterion scores resulted in a skewed distribution. No significant difference was obtained ($U = 49$, $p > 0.05$). Similarly, there was no observable effect on cross-through latencies of the group not given reinforcement.

DISCUSSION

The results of the present experiment suggest that administration of THC to pregnant rats is associated with a transient passive avoidance deficit and an apparently permanent enhancement of competitiveness in their offspring. Our dosage was substantially lower than that used in previous investigations of placental transfer and resulted in an equilibrium level of only 21.4 ng/gm THC and its metabolites in neonatal tissues. It may be concluded that 2 of the 3 behavioral assessments in the current investigation were comparatively sensitive to the experimental treatments.

No signs of teratogenesis or stunting in the THC and PVP pups were observed. There were no reliable weight differences between the 2 groups of pups and no statistically significant differences between the THC and PVP dams throughout the testing period. The above findings suggest that there were no gross *in utero* and/or neonatal nutritional effects of the THC.

The fact that more of the THC pups won in the push-tube tests at 90 days of age than at 21 days is of some interest. It is generally recognized that competitiveness is a maturational process [5], tending to be stronger in adults than in the young. In the context of the present investigation it seems likely that there was less effect on competitiveness in 21 day weanling rats, because relatively little motivation to compete was present. Stronger effects might be expected at 90 days of age when competitiveness is more fully developed.

The results for open field and push-tube behavior are in contrast to the findings of Vardaris *et al.* (in preparation). In that experiment chronic administration of 1.2–2.4 mg/kg THC reduced the frequency of aggressive behavior patterns in the open field and depressed winning behavior in push-tube tests. This discrepancy in the results of the 2 studies suggests that direct oral administration of THC may affect behavior through different neuropharmacological mechanisms than does presence of the drug in the uterine environment.

Most of the prior work on the effects of THC on open field behavior has involved tests of individual animals rather than pairs of rats. Therefore, comparisons of prior findings with the present results are somewhat equivocal. Although the drug has been reported to reduce exploratory behavior and emotionality in the open field [4,14], there was no consistent effect on open field behavior in the present investigation. It is possible that presence of another pup and prior adaptation to the open field tended to depress emotionality and exploratory behavior such that no differential treatment effects could be observed. In addition, it may be noted that the behavior repetoire of weanling rats is considerably restricted relative to that of adults. By far the most common pup behavior for both the drug and placebo groups was freezing or simply standing quietly.

Prior research dealing with effects of THC on food competition in the dominance tube has yielded mixed results [13]. Hunger motivation was not used for the competitive task in the present experiment because it is known that stress from food deprivation may elicit aggressive behavior in THC treated rats [3] and also that the drug affects food intake in these animals [12]. Methodology is an important variable in the effects of THC on competitive behavior [13] and therefore the results of the current study may not be very comparable to prior findings with hunger motivated tasks. It may be mentioned however that the enhanced competitiveness observed in the THC animals from the current study is, in a general way, consistent with the findings for food competition in a straight runway, but inconsistent with the results of food competition in a Y-maze [13].

The prior evidence concerning effects of THC on passive avoidance behavior in adult rats suggests that the drug has little or no effect [15]. Relatively large doses of the drug were used, however, and could have affected motor performance rather than learning or memory. Such effects would be difficult to establish in a 1-trial inhibitory task. In the present study the THC pups executed the cross-through response more readily than did the placebo animals, suggesting that there was probably no gross effect of the experimental treatments on motor function. As rat pups require multiple training trials to acquire a passive avoidance tendency, it was possible to demonstrate that the initial deficit was overcome with additional training. A number of differences in procedure, age of animals, dosage and route of administration could account for the differences between the findings of Miller *et al.* [15] and those of the present investigation.

In general the observed learning deficit is consistent with the results of Gianutsos and Abbatiello [8] who studied complex maze learning in pups of dams treated with cannabis on Days 8–11 of gestation. The considerable differences between that task and passive avoidance make it difficult to draw general conclusions about effects on learning.

The failure of Uyeno [20] to find an effect on Y-maze learning, even with very large doses of THC given to the dams, could be due to the times during pregnancy when the drug was administered (Days 10–12) or to the use of the split-litter cross fostering technique which could have reduced the drug's effects on critical early maternal behavior.

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