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Δ^9-Tetrahydrocannabinol Enhancement of Lordosis Behavior in Estrogen Treated Female Rats[1]

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GORDON, J. H., B. L. BROMLEY, R. A. GORSKI AND E. ZIMMERMANN. *Δ^9-tetrahydrocannabinol enhancement of lordosis behavior in estrogen treated female rats.* PHARMAC. BIOCHEM. BEHAV. 8(5) 603–608, 1978. – Estrogen and progesterone (PROG) are both considered essential hormones for the display of sexual receptivity in the female rat. Δ^9-tetrahydrocannabinol (THC), one of the active components of marijuana, was tested in ovariectomized rats for possible estrogenic and anti-estrogenic activity using the display of lordosis behavior, one of the components of sexual receptivity, as an endpoint. Test animals were treated with THC (1.25, 2.50 or 10.00 mg/kg/day) or estradiol benzoate (EB) + THC (2.0 μg/kg/day and 10.0 mg/kg/day, respectively) followed by 500 μg PROG and tested for lordosis behavior on Day 5. The animals treated with THC alone failed to show any lordosis behavior, similar to oil and vehicle controls, while the behavioral effects of EB were not antagonized by the 10.0 mg/kg dose of THC. Thus, the estrogenic effects of THC, using the lordosis system as an end point, are at best minimal, if present at all. The effects of acute THC in EB primed rats (2.0 μg/kg/day × 3) were also tested in this study. At relatively low doses (0.5 and 1.5 mg/kg) of THC, a significant increase in the lordosis quotient (LQ; number of lordosis responses/number of mounts × 100) was noted. At a higher dose (3.0 mg/kg) of THC, a significant reduction in the LQ was noted, indicating a dose-dependent effect of THC. Following adrenalectomy, the dose-response curve for THC was shifted to the left, as a lower dose (0.15 mg/kg) of THC was now capable of enhancing the LQ, while the 0.5 and 1.5 mg doses were no longer effective (similar to the 3.0 mg/kg dose in non-adrenalectomized animals). The biphasic action of PROG on LQ was also utilized to rule out adrenal involvement in the enhanced behavior seen in the EB primed and THC treated animals. When a behaviorally effective dose of PROG was administered, 18 hr prior to PROG followed by a behavioral test, it antagonized the behavioral effects of the second dose of PROG, while a behaviorally effective dose of THC, given 18 hr prior to PROG followed by a behavior test, was ineffective in antagonizing the behavioral effects of PROG, indicating that minimal, if any, PROG is released from the adrenal following a behaviorally effective dose of THC. Thus, it appears that THC is capable of enhancing sexual receptivity of female rats by a direct action on the central nervous system.

Δ^9-tetrahydrocannabinol Marijuana Lordosis behavior Estrogen Progesterone Sex behavior

MARIJUANA and one of its principal psychoactive components, Δ^9-tetrahydrocannabinol (THC), produce a wide variety of physiological and pharmacological effects. In low doses THC produces a decrease in spontaneous activity, moderate hypothermia, ataxia, and hypersensitivity to tactile and auditory stimulation, while high doses cause a marked hypothermia, sedation and reduced reactivity to environmental stimuli [26].

Reproductive studies have reported that chronic oral administration of marijuana resin "significantly reduced fertility" in the rat [36]. In males both THC and marijuana have been reported to reduce the concentration of testosterone in the plasma of rats and man [29,52], although conflicting reports have been published [27,32]. THC has also been reported to suppress spermatogenesis, reduce the weight of the testes and the accessory reproductive organs [17], and to decrease some components of male sexual behavior [10, 13, 33]. THC has been shown to prolong the estrous cycle of adult rats [6] and to decrease the proestrous surge of LH and thus inhibit ovulation in the rat [7,39]. However, there is little information available on the effects of THC on female reproductive behavior.

The ovarian hormones estrogen and progesterone (PROG) are both considered essential for the display of reproductive behavior, or sexual receptivity, in female rodents [56]. The inhibitory effect of ovariectomy (Ovx)

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on sexual behavior is quite dramatic, and complete receptive behavior can be restored by exogenous hormone administration. While either a high dose (50 μg) or prolonged treatment (1 μg/day × 7) with estradiol benzoate (EB) alone is sufficient to facilitate normal levels of lordosis behavior, one component of sexual receptivity, in Ovx rats [14,54]. Treatment with PROG alone will not facilitate any of the behaviors associated with receptivity in the female rodent. However, there is no doubt that PROG can markedly potentiate the low levels of lordosis responding induced by a single injection of 5 μg EB [1] or three daily injections of 2 μg EB [8] when injected 4–8 hr before the behavioral test. The temporal pattern of hormone levels and behavioral receptivity in both intact and Ovx EB-PROG primed rats is consistent with an important role for PROG as well as estrogen in the control of sexual receptivity [2, 3, 23]. In addition, PROG has been shown to have a biphasic action on sexual receptivity – an initial facilitatory phase, followed by a refractory period which apparently persists until the animal is re-exposed to estrogen [30, 37, 55].

Although several drugs, treatments, or surgical manipulations have been shown to substitute for some of the actions of PROG [9, 12, 19–22, 24, 34, 35, 38, 44, 58], exposure to estrogen or an estrogenic compound is essential for the animal to show receptive behavior in response to physiological stimulus. Because of the proposed estrogenic properties and the potent central effects of THC, the following study was undertaken to ascertain what effects THC would have on female rat reproductive behavior.

GENERAL METHOD AND PROCEDURES

Simonsen Sprague-Dawley rats were used in all experiments. Animals were housed 6–8 per cage and given ad lib access to Purina rat chow and tap water, and maintained in a reversed light room (lights on from 10:00 p.m. to 11:00 a.m.). Adrenalectomy (Adx) and Ovx were performed under ether anesthesia, and at least a one week recovery period was allowed following surgery, before behavioral tests were started. Adx animals were housed in individual cages and maintained on 0.9% saline.

Tests for female sexual behavior were the same in all experiments and started at approximately 1:00 p.m. Test animals were placed in a Plexiglas arena, in a room that was illuminated with a 25 W red bulb, with two or three sexually experienced Long-Evans male rats which had been adapted to the test arena for at least 15 min. After the test animal had been mounted 15 times, a lordosis quotient (LQ) was computed for each animal by dividing the number of lordotic responses by the number of mounts and multiplying by 100.

THC was supplied as an ethanol solution by the National Institute of Drug Abuse and was injected IP in a vehicle of 20% propylene glycol and 1% Tween 80 in saline. EB and PROG were dissolved in sesame oil and injected SC.

Statistical comparisons between groups utilized Student's *t* test and means that are referred to as significantly different were at a probability of 0.05 or less [53].

EXPERIMENT 1: EFFECTS OF CHRONIC THC ON LORDOSIS BEHAVIOR

It has been proposed that THC may have estrogenic properties because of changes in vaginal histology and slower uterine weight loss following Ovx [50,51] and the reported competition of THC with estrogen for binding sites in rat uterine estrogen receptors [43], although alternative explanations for these phenomena have been suggested and opposite results reported [40]. As either estrogen or an estrogenic compound are required for the display of lordosis behavior, the following experiment was designed to test for any central estrogenic or anti-estrogenic actions of THC.

Method and Results

Ovx animals were treated daily with either THC (1.25, 2.5 or 10.0 mg/kg), EB (2.0 μg/kg), oil (0.05 ml/100 g), or a combination of EB (2.0 μg/kg) and THC (10.0 mg/kg) for four days and tested for sex behavior on Day 5, 3–5 hr after receiving 500 μg of PROG.

None of the THC treated groups (N = 12/group) displayed any lordosis behavior following the 500 μg dose of PROG on Day 5. The oil-treated group produced the identical result of no lordosis responses observed in any of the test animals. The simultaneous treatment with both EB and THC produced levels of lordosis behavior that were indistinguishable from the animals that were treated with EB only (84 ± 5, N = 6; 89 ± 7, N = 9, respectively). These data do not provide support for any central estrogenic or anti-estrogenic effects of THC in this experimental paradigm.

EXPERIMENT 2: EFFECTS OF ACUTE THC ON LORDOSIS BEHAVIOR IN EB PRIMED FEMALE RATS

A variety of centrally acting drugs can enhance the level of lordosis behavior seen in an EB primed female rat [12, 19, 20, 24, 35]. Since THC has potent central nervous system actions, the possibility of an acute enhancement or suppression of lordosis behavior in the EB primed rat was tested.

Methods and Results

Ovx rats were primed with EB (2.0 μg/kg/day) for three days and tested for sex behavior on Day 4, 3–5 hr after PROG (500 μg) or 1–2 hr after THC. The test time for THC was chosen to correspond with the profound hormonal effects noted in previous experiments [4,5].

There was a dose-dependent effect of THC on LQ, as shown in Fig. 1. At the lower doses (0.5–1.5 mg/kg) of THC a significant increase in LQ relative to oil + vehicle treated group was noted, with the 1.5 mg/kg dose producing LQ scores that were statistically indistinguishable from the PROG treated group. The 3.0 mg/kg dose of THC caused a significant decrease in LQ relative to the oil + vehicle treated group. This decrease in LQ was directly related to the ability of the animal to respond to its environment, as almost all spontaneous motor activity was absent at doses of 3.0 mg/kg.

EXPERIMENT 3: THE POSSIBLE ROLE OF ADRENAL PROG IN THE THC ENHANCEMENT OF LQ

Because of the reported release of ACTH folloiwng THC administration [4, 28, 41], the next series of experiments was designed to test for possible adrenal involvement in the enhanced lordosis response seen in the THC treated animals. Two separate experimental designs were used to test this possibility.

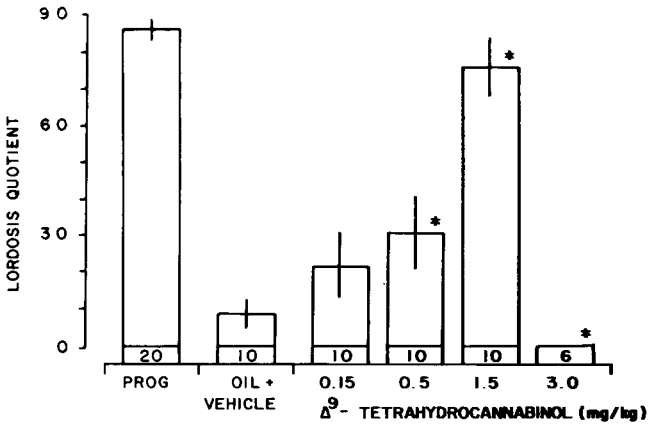

FIG. 1. All groups were Ovx, allowed a three week recovery period prior to receiving EB (2.0 μg/kg/day X 3) and tested for lordosis behavior on Day 4 following either PROG (500 μg/rat), THC vehicle, or THC. Tests were scored 3–5 hr after PROG or 1–2 hr after THC or oil and vehicle. *Significantly different from oil + vehicle group; $p<0.05$, Student's t test.

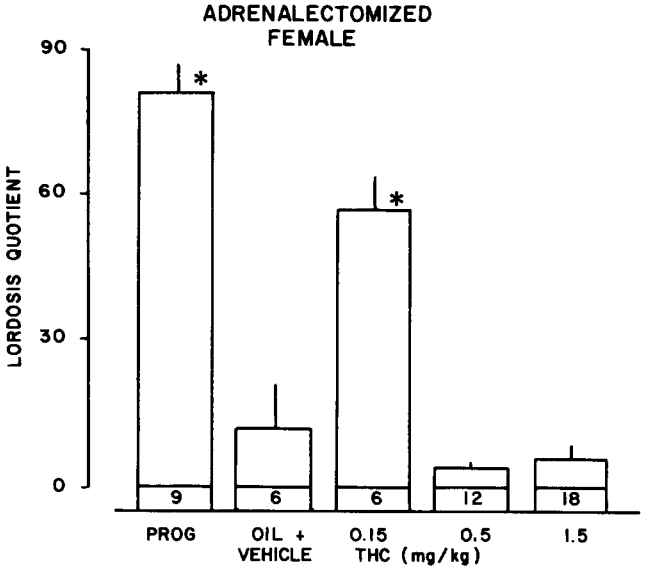

FIG. 2. Ovx animals were Adx one week prior to treatment with EB (2.0 μg/kg/day X 3) and tested for behavior on Day 4 following either PROG (500 μg/rat), vehicle or THC. Behavior tests were scored 3–5 hr following PROG or 1–2 hr following THC or oil and vehicle. *Significantly different from oil + vehicle group; $p<0.05$, Student's t test.

Experiment 3a. Methods and Results

The first experimental design was to utilize the classical approach of Adx, thus removing the possible intermediary site of action for THC. Adx Ovx rats were primed with EB (2.0 μg/kg/day) for three days and treated with either THC, PROG or oil as described in Experiment 2.

The results of this experiment are shown in Fig. 2. Adx did not alter the ability of the test animals to respond to the EB + PROG treatment with high LQ scores, as the LQ of this group was similar to the EB + PROG group reported in Fig. 1. Adx did inhibit the enhanced LQ seen following 0.5 or 1.5 mg/kg doses of THC; however, the Adx animals were capable of showing a marked response to the lower (0.15 mg/kg) dose of THC. Thus, Adx appears to have shifted the dose response curve to the left. The Adx animals also showed an increased sensitivity to the depressant effects of THC, as the lower 0.5 and 1.5 mg/kg doses were effective in decreasing the majority of the spontaneous motor activity, similar to the 3.0 mg/kg dose in the non-Adx group in Experiment 2 (Fig. 1).

Experiment 3b. Methods and Results

The second experimental design utilized the biphasic action of PROG; thus, by administering PROG at 30 hr the animals will be behaviorally refractory to a second dose of PROG at 48 hr. Ovx animals were treated with 4.0 μg of EB at 0 hr, followed at 30 hr with either oil, THC, or PROG. At 48 hr all groups received 500 μg of PROG and were tested for lordosis behavior at 52–54 hr (4–6 hr following the 500 μg dose of PROG).

Animals which received oil at 30 hr displayed high levels of lordosis following the PROG at 48 hr (Table 1). Similar high levels of lordosis were seen in animals that received either a low dose of PROG (10 μg) or the 1.5 mg/kg dose of THC at 30 hr, while animals that received 25–150 μg PROG at 30 hr displayed a reduced level of lordosis following the 500 μg dose of PROG at 48 hr. The behavioral refractoriness to PROG is well known [30, 37, 53], and can be readily noted in the groups that received 25–150 μg PROG 18 hr prior to the 500 μg dose of PROG for the sex behavior test. These data thus suggest that only minimal amounts of PROG, if any, are released from the adrenal glands following a behaviorally effective dose of THC.

DISCUSSION

The lack of lordosis behavior following 4 days of THC treatment would rule out any central estrogenic effects of THC for the doses used in this study. These doses (1.25–10.0 mg/kg) were effective in producing the reported peripheral "estrogenic" effects; i.e., alterations in vaginal histology and a slower uterine weight loss following Ovx [50,51]. The administration of cannabis extract has been reported to cause a cessation of vaginal cycles and the appearance of a diestrus-type smear, as well as reduction in the estrogen-induced accumulation of glycogen and water [16]. The differences in experimental design, route of administration, dose and form of drug (i.e., resin or extract of marijuana, or synthetic THC) preclude any definitive explanation for these experimental discrepancies at this time. However, our data in this study indicate that THC has no estrogenic or anti-estrogenic effects within the central nervous system (Experiment 1), as measured by the animals' ability to display lordosis behavior following chronic treatment.

However, THC may act as an estrogenic substance in the periphery, as differences in the rates of receptor replenishment following an anti-estrogen (CI-628) have been reported between uterus and brain [31]. In addition, the peripheral tissues, particularly the vaginal epithelium, are more sensitive to estrogen replacement than the lordosis system [15]. The peripheral estrogenic effects of THC are

TABLE 1

LACK OF BEHAVIORAL REFRACTORINESS TO PROGESTERONE FOLLOWING THC

Group	Treatment 0 hr	Treatment 30 hr	Treatment 48 hr	Lordosis Quotient 52–54 hr
1	EB* (4.0 μg/rat)	Oil	PROG (500 μg/rat)	76 ± 8† (6)
2	EB* (4.0 μg/rat)	PROG (10 μg/rat)	PROG (500 μg/rat)	85 ± 7 (6)
3	EB* (4.0 μg/rat)	PROG (25 μg/rat)	PROG (500 μg/rat)	46 ± 11‡ (8)
4	EB* (4.0 μg/rat)	PROG (75 μg/rat)	PROG (500 μg/rat)	38 ± 12‡ (8)
5	EB* (4.0 μg/rat)	PROG (150 μg/rat)	PROG (500 μg/rat)	11 ± 5‡ (8)
6	EB* (4.0 μg/rat)	THC (1.5 mg/kg)	PROG (500 μg/rat)	72 ± 6 (8)

*EB (estradiol benzoate) and PROG (progesterone) were administered SC in 0.1 ml of sesame oil. THC (Δ^9-tetrahydrocannabinol) was administered IP in a volume of 0.2 ml/100 g body wt. of a saline vehicle which contained 1% Tween 80 and 20% propylene glycol.

†Values are the mean ± SE for (N) animals.

‡Significant ($p<0.05$) reduction from group 1, Student's t test.

minimal at best [43, 50, 51], thus, these systems could respond to the estrogenic effects of THC prior to or without the induction of lordosis behavior.

High levels of lordosis behavior are seen in EB treated Ovx rats when a number of centrally active drugs are substituted for PROG. These drugs include norepinephrine (NE) agonists [12,19], and dopamine (DA) and 5-hydroxytryptamine (5-HT) antagonists [19, 20, 24, 35, 58], and now THC. The effects of THC on NE are complex, with both increases, at low doses, and decreases, at high doses, in NE turnover reported, as well as decreases in DA turnover [42]. Also, both increases [48] and decreases [25] in the level of 5-HT have been reported. THC has also been reported to block a 5-HT stimulated release of prolactin [5], the audiogenic stress induced depletion of 5-HT [11], and to increase the toxicity of cyproheptadine, a 5-HT antagonist [49].

Because the actions of THC on the catecholamines and 5-HT are complex, it is hard to suggest the mechanisms by which THC is causing the enhanced lordosis behavior in the EB primed rat. However, the antagonism of 5-HT appears to be the most consistent action of THC [5, 11, 49], and could be a possible explanation for the enhanced LQ, as 5-HT antagonists have been reported to increase the LQ of EB primed rats [20, 24, 35, 58]. The decreased DA turnover could also account for the enhanced LQ, as similar decreases in DA turnover have been reported to increase LQ [21,38]. The increased norepinephrine turnover [42] and the increased sensitivity to tactile and auditory stimulation [26] could also play a role in the enhanced LQ. Even the depressant effects of THC cannot be ruled out at this time as a possible mechanism for the enhanced LQ, as the cortical application of KCl (to cause a spreading depression) has been reported to enhance lordosis behavior [9, 34, 44].

The present experimental results do rule out adrenal steroids as a possible mechanism for the THC enhancement of LQ seen in the EB treated animals. Following Adx the experimental animals are much more sensitive to the depressant effects of THC. The dose response curve appeared to be shifted to the left, as a dose of THC that was ineffective in the intact animal (0.15 mg/kg) was capable of enhancing the lordosis behavior of the Adx animals, while higher doses (0.5 and 1.5 mg/kg) were much more effective in depressing the animal's spontaneous motor activity and reactivity to environmental stimuli. This observation of the enhanced sensitivity to the depressant effects of THC is supported in part by the reports that adrenal steroid therapy can antagonize the anesthetic effects of barbiturates [47], and that the anesthetic action of steroid hormones can be enhanced by Adx [45,46].

An intermediary role of adrenal steroids is also questioned by the results of Experiment 3b. In rats PROG exerts a biphasic action on ovarian function [18,57], and a similar biphasic action on sexual receptivity has been

reported [30, 37, 55]. Rats that received a behaviorally effective dose of PROG (150 μg/rat) 18 hr prior to a second dose of PROG (500 μg/rat) were incapable of showing an enhanced LQ (Table 1), while a behaviorally ineffective dose of PROG (10 μg/rat) at 30 hr had no effect on the level of lordosis displayed following the 500 μg dose of PROG at 48 hr. The THC treatment produced the opposite effects, as a behaviorally effective dose of THC (1.5 mg/kg) at 30 hr had no effect on the LQ following the 500 μg dose of PROG at 48 hr. Thus, it would appear that adrenal PROG, or similar-acting adrenal steroids [22], are not involved in the enhanced LQ seen in the THC treated rats.

The enhanced lordosis behavior seen in the THC treated rats is at least partially, if not totally, due to one or more of the reported alterations in biogenic amine function. Which of the proposed alterations in amine function are involved, and whether these alterations are direct or indirect effects of the THC, remain the topics for future study.

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