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European Journal of Pharmacology 430 (2001) 41–47

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Sex differences in antinociceptive and motoric effects of cannabinoids

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Received 26 April 2001; received in revised form 24 July 2001; accepted 31 July 2001

Abstract

Cannabinoids are currently used for the treatment of excessive weight loss and nausea; however, there are very few studies that have examined cannabinoid effects in females of any species. A previous study has shown that there are sex differences in cannabinoid pharmacokinetics in rats, suggesting that there could be sex differences in cannabinoid-induced behaviors. To address this issue, Δ^9-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol (natural cannabinoids) or (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)-phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol) (CP55940, a synthetic cannabinoid) was administered i.p. to male and female Sprague-Dawley rats, who were tested on the 50 °C warm water tail withdrawal, paw pressure, catalepsy bar and spontaneous locomotor activity tests at various times post-injection. At the doses tested, all three cannabinoid agonists produced greater effects in females than males in two or more behavioral tests. This study demonstrates that there are sex differences in the behavioral effects of cannabinoids in the rat.

Keywords: Cannabinoid; Gender; Pain; Locomotor activity, Spontaneous; Catalepsy; (Rat)

1. Introduction

Cannabinoids are potentially useful for treating a variety of medical conditions (see reviews: Taylor, 1997; Fuentes et al., 1999). For example, a synthetic oral form of Δ^9-tetrahydrocannabinol, dronabinol, is currently available by prescription for the treatment of excessive weight loss in acquired immune deficiency syndrome (AIDS) patients and nausea in cancer patients undergoing chemotherapy. The apparent analgesic effects of cannabinoids are still under scrutiny. In animal models, cannabinoids have been shown to suppress pain caused by various types of acute noxious stimuli such as thermal (e.g., Buxbaum, 1972), chemical (Welburn et al., 1976) and mechanical (Smith et al., 1998); they are also effective in reducing chronic neuropathic pain (Herzberg et al., 1997) and inflammatory pain (Smith et al., 1998). Cannabinoids have been shown to produce analgesia in rodents (e.g., Martin et al., 1993), non-human primates (Vivian et al., 1998) and humans (Greenwald and Stitzer, 2000), without the untoward effects associated with the opiate analgesics, such as respiratory depression. However, cannabinoids do produce undesired side-effects such as sedation (Sanudo-Pena et al., 2000) and catalepsy (Prescott et al., 1992; Sanudo-Pena et al., 2000).

Cannabinoid-related sex differences have been demonstrated in adult rats. For example, Δ^9-tetrahydrocannabinol has been shown to be metabolized differently in males compared to females: females preferentially metabolize Δ^9-tetrahydrocannabinol to 11-hydroxy-Δ^9-tetrahydrocannabinol (a potent active metabolite), whereas males metabolize Δ^9-tetrahydrocannabinol to 11-hydroxy-Δ^9-tetrahydrocannabinol and numerous other compounds (Narimatsu et al., 1991). The motoric effects produced by cannabinoids have also been shown to be more profound in female than male rats (Cohn et al., 1972).

If cannabinoids are to be effectively instituted as novel analgesic compounds, it is important to determine whether males and females respond similarly to them. Although cannabinoid-induced antinociception has been demonstrated in female mice (Welburn et al., 1976), there are no direct comparisons between males and females of any species. The purpose of the present study was to compare the antinociceptive and motoric effects of cannabinoids in male versus female rats.

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0014-2999/01/$ - see front matter
PII: S0014-2999(01)01267-5

2. Materials and methods

2.1. Subjects

The subjects used were 212 male and 212 female gonadally intact Sprague-Dawley rats (2.5–3.5 months old). Males and females were housed in same-sex pairs within $35.0 \times 25.0 \times 17.0$-cm plastic tubs, in separate rooms under a 12:12-h light/dark cycle. Access to food (Teklad rat chow) and water were ad libitum except during testing when water was removed.

2.2. Drugs

Δ^9-Tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol and (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)-phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol) (CP55940) were obtained from the National Institute on Drug Abuse (Bethesda, MD). Drugs were prepared in a 1:1:18 emulphor/ethanol/saline solution; 1, 3, or 10 mg/kg Δ^9-tetrahydrocannabinol, 0.3, 1, 3, or 10 mg/kg 11-hydroxy-Δ^9-tetrahydrocannabinol or 0.1, 0.3, or 0.56 mg/kg CP55940 was administered i.p. in a volume of 1 ml/kg.

2.3. Apparatus

For the tail withdrawal procedure, a 2.5-l water bath (Precision Scientifics, Chicago, IL) with the temperature set at 50.0 ± 0.2 °C was used. Rats were restrained in Plexiglas tubes (IITC, Los Angeles, CA) with an opening at one end through which the tail hung freely. For the paw pressure test, an Analgesy-meter (Ugo-Basile, Varese, Italy) was used. Rats were restrained lightly with a towel and a hindpaw was placed on a small pedestal. A conical, blunt-tipped probe was lowered onto the paw by depressing a foot pedal; the probe exerted pressure that increased at a constant rate starting at 30 g and increasing 40 g/s. Catalepsy was assessed by using a bar test. Sedation was measured in a $20 \times 40 \times 23$-cm clear Plexiglas rodent cage placed within a photobeam apparatus (Opto-varimex, Columbus Instruments, Columbus, OH). Fifteen photobeams crossed the width of the cage, 2.5 cm apart and 8 cm above the cage floor.

2.4. Behavioral procedure

All rats were pretested twice on each nociceptive apparatus the day before testing to establish a baseline value for antinociception and to habituate rats to handling. On the test day, rats were injected with vehicle, Δ^9-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol, or CP55940 and tested for antinociception at 15-, 30-, 60-, 90-, 120-, 240-, 300-, 360- and 420-min post-injection. Each rat received only vehicle or one dose of one drug, as previous studies indicate that male and female rats may develop analgesic tolerance differently (e.g., Craft et al., 1999). For the tail withdrawal test, the distal 5 cm of the tail was placed in a 50 °C warm water bath and the latency for tail withdrawal was recorded to the nearest 0.1 s using a hand-held stop watch. To prevent tissue damage, the tail was removed from the water bath if no attempt was made to remove it in 30 s. Immediately following the tail withdrawal test, rats were tested in the paw pressure apparatus. Latency to withdraw or attempt to withdraw the paw was recorded in seconds. If no attempt was made to escape when 25 s (1130 g) was reached, the paw was removed to avoid tissue damage. Following the paw pressure test at 30-, 60-, 120- and 240-min post-injection only, rats were placed into the locomotor chambers and the number of photobeam breaks in 5 min was recorded. For the catalepsy test, rats were tested at one time point only (15, 30, 60, 240 or 420 min), as preliminary data showed that baseline responses increased significantly with repeated testing (data not shown). The forepaws were placed on a raised bar, and latency to remove both forepaws or climb onto the bar was recorded to the nearest second. Rats were taken off the bar after 60 s if no response was made.

2.5. Determination of estrous cyclicity

Stage of estrous cycle was determined cytologically by vaginal lavage, immediately after testing. Proestrus was identified by the predominance of nucleated epithelial cells, estrus was identified by the presence of dense sheets of cornified epithelial cells, diestrus-1 was identified by the presence of scattered, nucleated or cornified epithelial cells and leukocytes, and diestrus-2 was identified by a relative lack of any cells (Freeman, 1998).

2.6. Data analysis

To determine if there were sex differences in nociceptive and locomotor responses after vehicle administration, time course data (15–240 min) from vehicle-treated rats were analyzed with a two-way (sex, time (repeated)) ANOVA (analysis of variance). To determine if there were sex differences in catalepsy responses after vehicle administration, data from vehicle-treated rats were analyzed with a two-way (sex, time) ANOVA. To determine if there were sex differences in drug effects for each nociceptive test, time course data (15–240 min) from rats were analyzed with a three-way (sex, dose, time (repeated)) ANOVA; effects at 300- to 420-min post-injection were only examined in a subset of rats, so data at these later time points were not included in analyses. Because there was a sex difference in baseline locomotor activity, locomotor activity scores in drug-treated rats were transformed to percent of same-sex vehicle-treated rats' scores (%control): $100 \times$ (individual drug score/mean vehicle score). The %control locomotor data then were analyzed with a three-way (sex, dose, time (repeated)) ANOVA. To determine if there were sex differences in catalepsy after drug

treatment, data were analyzed with a three-way (sex, dose, time) ANOVA. Subsequently, to determine if there were differences in nociceptive or locomotor responses after drug treatment among females in various stages of the estrous cycle, data were analyzed with a two-way (dose, time (repeated)) ANOVA using estrous stage as a covariate. To determine if there were estrous stage differences in catalepsy after drug treatment, data were analyzed with a two-way (dose, time) ANOVA using estrous stage as a covariate. Significance level was $P \leq 0.05$ for all statistical tests.

3. Results

3.1. Baseline responding

There were no significant sex differences in nociceptive or catalepsy responses in vehicle-treated rats. However, females were more active than males in the spontaneous locomotor activity test ($P = 0.047$) (data not shown).

3.2. Δ^9-Tetrahydrocannabinol-induced effects

Δ^9-Tetrahydrocannabinol (1–10 mg/kg) produced dose- and time-dependent antinociception in the tail withdrawal (Fig. 1A) and paw pressure (Fig. 1B) tests in both males and females; however, Δ^9-tetrahydrocannabinol was approximately 2–3 times more potent in females than males, at the time of peak effect (Table 1). A higher dose of Δ^9-tetrahydrocannabinol, 30 mg/kg, did not produce any greater increases in tail withdrawal latency in males (data not shown). Δ^9-Tetrahydrocannabinol also produced dose- and time-dependent sedation on the locomotor activity test in both sexes (Fig. 1C), and at the doses tested, produced significantly greater sedation in females than males (Fig. 1C). Δ^9-Tetrahydrocannabinol (10 mg/kg) also produced time-dependent catalepsy in both sexes (Fig. 1D), and produced greater catalepsy in females than males.

3.3. 11-Hydroxy-Δ^9-tetrahydrocannabinol-induced effects

11-Hydroxy-Δ^9-tetrahydrocannabinol produced dose- and time-dependent antinociception in the tail withdrawal

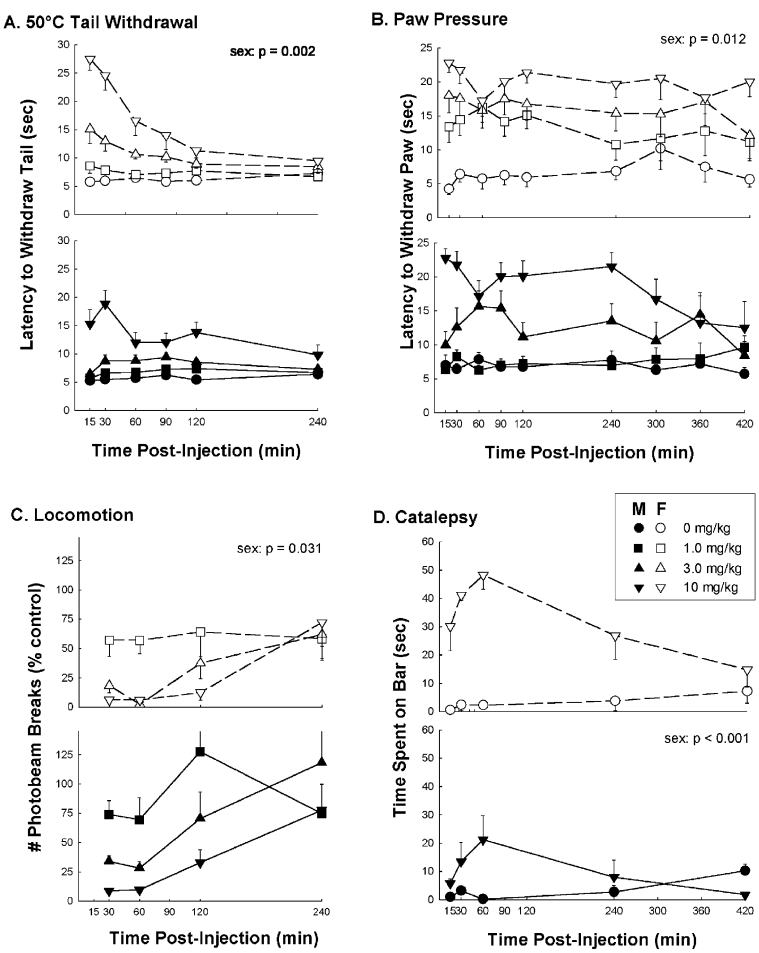

Fig. 1. Time course of i.p. Δ^9-tetrahydrocannabinol-induced behavioral effects in male (M) and female (F) rats. (A) Antinociception, tail withdrawal test ($N = 10$–17 rats/sex/dose). (B) Antinociception, paw pressure test ($N = 10$–17 rats/sex/dose). (C) Sedation, spontaneous locomotor activity test ($N = 7$–10 rats/sex/dose). (D) Catalepsy, bar test ($N = 4$–7 rats/sex/dose/time point). Means ± S.E.M are presented.

Table 1
Relative potency ratios (95% C.L.) of three cannabinoids in male compared to female rats

Groups	Test	Potency ratios[a]
Δ^9-Tetrahydrocannabinol	Tail withdrawal	1.98 (1.20, 3.61)
	Paw pressure	2.95 (1.13, 16.7)
	Sedation	1.26 (0.70, 2.37)
11-Hydroxy-Δ^9-tetrahydrocannabinol	Tail withdrawal	2.04 (1.20, 3.69)
	Paw pressure	1.13 (0.63, 2.05)
	Sedation	2.24 (0.68, 11.3)
CP55940	Tail withdrawal	1.67 (0.97, 3.47)
	Paw pressure	1.27 (0.90, 1.85)
	Sedation	1.67 (0.68, 7.53)

[a]Potency ratios were calculated with Procedure 11 (Tallarida and Murray, 1991) using data from the time of peak effect, determined visually from the figures. Potency ratios reflect how much more drug is needed in male rats compared to female rats to produce an equivalent effect.

test (Fig. 2A) and paw pressure test (Fig. 2B) in both sexes. In the tail withdrawal test, 11-hydroxy-Δ^9-tetrahydrocannabinol was approximately twice as potent in females than males at the time of peak effect (Table 1). In contrast, there was no significant sex difference in 11-hydroxy-Δ^9-tetrahydrocannabinol's antinociceptive effect on the paw pressure test. 11-Hydroxy-Δ^9-tetrahydrocannabinol also produced time-dependent sedation in both sexes (Fig. 2C), although this effect was more clearly dose-dependent in females; at the doses tested, 11-hydroxy-Δ^9-tetrahydrocannabinol produced significantly greater sedation in females than males. 11-Hydroxy-Δ^9-tetrahydrocannabinol (10 mg/kg) also produced time-dependent catalepsy in both sexes, but with no significant sex difference (Fig. 2D).

3.4. CP55940-induced effects

CP55940 produced dose- and time-dependent antinociception in the tail withdrawal and paw pressure tests in both sexes. In the tail withdrawal test, CP55940 produced a significantly greater effects in females than males (Fig. 3A). There was no sex difference in CP55940's antinociceptive effect on the paw pressure test (Fig. 3B). CP55940 also produced dose- and time-dependent sedation in both

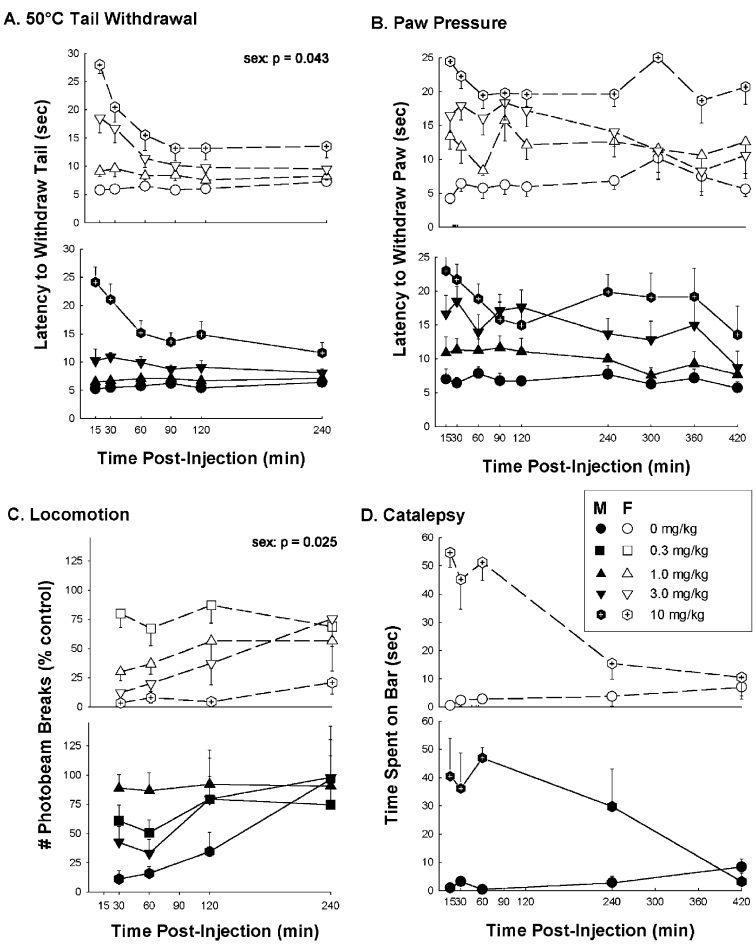

Fig. 2. Time course of i.p. 11-hydroxy-Δ^9-tetrahydrocannabinol-induced behavioral effects in male (M) and female (F) rats. Control data (0 mg/kg) are replotted from Fig. 1. (A) Antinociception, tail withdrawal test ($N = 9$–17 rats/sex/dose). (B) Antinociception, paw pressure test ($N = 9$–17 rats/sex/dose). (C) Sedation, spontaneous locomotor activity test ($N = 6$–10 rats/sex/dose). (D) Catalepsy, bar test ($N = 4$–7 rats/sex/dose/time point). Means ± S.E.M are presented.

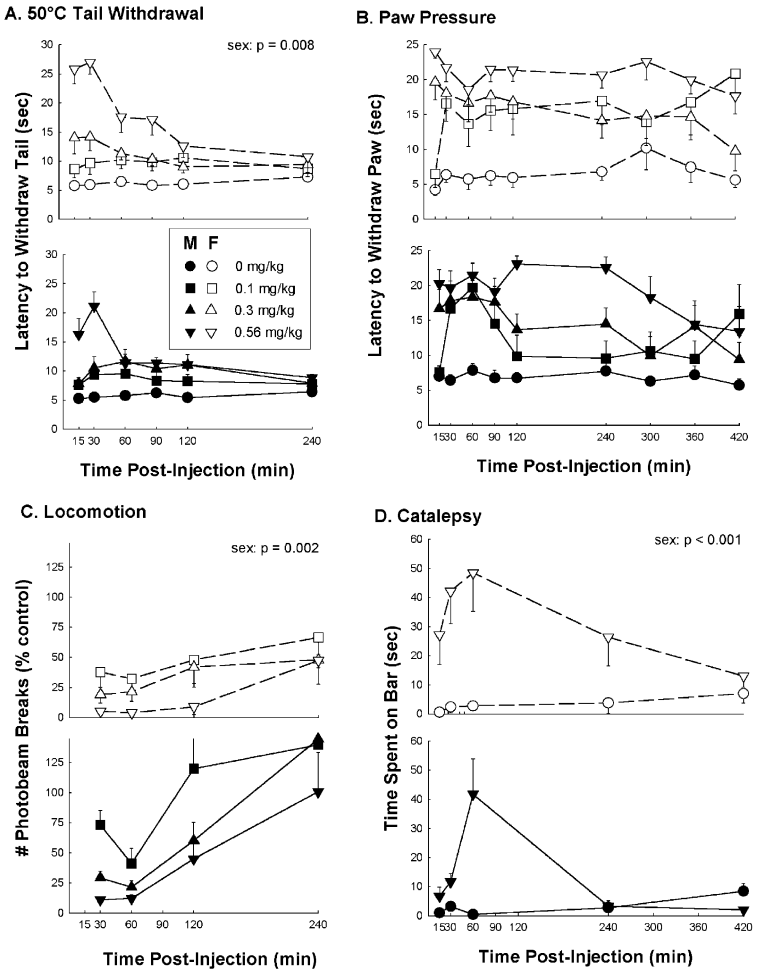

Fig. 3. Time course of i.p. CP55940-induced behavioral effects in male (M) and female (F) rats. Control data (0 mg/kg) are replotted from Fig. 1. (A) Antinociception, tail withdrawal test ($N = 8–17$ rats/sex/dose). (B) Antinociception, paw pressure test ($N = 8–17$ rats/sex/dose). (C) Sedation, spontaneous locomotor activity test ($N = 6–8$ rats/sex/dose). (D) Catalepsy, bar test ($N = 4–7$ rats/sex/dose/time point). Means ± S.E.M are presented.

sexes (Fig. 3C); at the doses tested, CP55940 produced significantly greater sedation in females than males (Fig. 3C). CP55940 (0.56 mg/kg) also produced time-dependent catalepsy in both sexes, with greater catalepsy in females than males (Fig. 3D).

3.5. Estrous cyclicity

Post hoc analysis revealed that antinociceptive and motoric effects were not significantly different between females in different stages of estrous. Ten percent of females were in proestrus, 10% in estrus, 64% in diestrus-1 and 16% in diestrus-2.

4. Discussion

This study demonstrates that there are sex differences in the antinociceptive and motoric effects of cannabinoids in rats. At the doses tested, Δ^9-tetrahydrocannabinol produced a significantly greater effect in females than males in antinociception, spontaneous locomotor activity, and catalepsy; 11-hydroxy-Δ^9-tetrahydrocannabinol produced a significantly greater effect females than males in antinociception (tail withdrawal), and spontaneous locomotor activity; and CP55940 produced a significantly greater effect in females than males in antinociception (tail withdrawal), spontaneous locomotor activity and catalepsy. These results corroborate a previous study that showed that female rats were more sensitive than males to the motoric effects of marijuana extract (Cohn et al., 1972).

In contrast to analyses of the time course of cannabinoid effect, potency ratios determined at the time of peak effect only revealed that cannabinoids were significantly more potent in females than males in only one-third of cases (Table 1). One reason for the discrepancy between time courses and potency ratio analyses is the greater statistical power of the time course analyses, which are based on multiple samples rather than behavior at a single time point. Additionally, because a given cannabinoid dose produced not only slightly greater maximal effects, but was also longer-acting in females than males, significant sex differences in cannabinoid effect were more often

observed when the entire time course was taken into account. Because different conclusions may be drawn from the two different analyses—sex differences versus no sex differences—it is clearly important to sample the entire time course of drug effect when examining individual differences.

One reason that Δ^9-tetrahydrocannabinol may produce greater effects in females than males is that systemically administered Δ^9-tetrahydrocannabinol is metabolized in the liver, and liver metabolism of Δ^9-tetrahydrocannabinol differs in male and female rats: females preferentially metabolize Δ^9-tetrahydrocannabinol to 11-hydroxy-Δ^9-tetrahydrocannabinol, whereas males metabolize Δ^9-tetrahydrocannabinol to 11-hydroxy-Δ^9-tetrahydrocannabinol and numerous other compounds (Narimatsu et al., 1991). Sex differences in the amount of 11-hydroxy-Δ^9-tetrahydrocannabinol produced could result in sex differences in the behavioral effects of Δ^9-tetrahydrocannabinol, because 11-hydroxy-Δ^9-tetrahydrocannabinol is a more potent analgesic than Δ^9-tetrahydrocannabinol when administered s.c. (Martin, 1985) or i.t. (Welch and Stevens, 1992; Welch et al., 1995). If females metabolize Δ^9-tetrahydrocannabinol predominantly to 11-hydroxy-Δ^9-tetrahydrocannabinol and males produce a variety of other metabolites besides 11-hydroxy-Δ^9-tetrahydrocannabinol that are less effective at inducing antinociception, then it might be predicted that systemic Δ^9-tetrahydrocannabinol would produce a greater effect in females than males in inducing antinociception, sedation, and catalepsy. In the present study, to determine if sex differences in metabolism could account for sex differences in Δ^9-tetrahydrocannabinol's effects, 11-hydroxy-Δ^9-tetrahydrocannabinol itself was examined in males and females. Similar to Δ^9-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol also produced greater antinociception and sedation in females than males. This result suggests that sex differences in Δ^9-tetrahydrocannabinol's effects may not be due simply to greater 11-hydroxy-Δ^9-tetrahydrocannabinol production in females than males. Sex differences in 11-hydroxy-Δ^9-tetrahydrocannabinol's effects could be explained by sex differences in metabolism of 11-hydroxy-Δ^9-tetrahydrocannabinol to other active metabolites, or sex differences in cannabinoid pharmacodynamics. A related compound, 11-hydroxy-Δ^8-tetrahydrocannabinol, is known to be metabolized to an active metabolite, 11-oxo-Δ^8-tetrahydrocannabinol (Watanabe et al., 1980), but it is not known whether females produce more of this metabolite than males. Sex differences in systemic CP55940-induced antinociception were similar to those obtained with Δ^9-tetrahydrocannabinol. Both compounds are metabolized in the liver by similar cytochrome *P*450 enzymes to similar metabolites (Thomas and Martin, 1990). Consequently, if sex differences in Δ^9-tetrahydrocannabinol-induced behavioral effects are due to sex differences in cytochrome P450 enzyme activity, it might be predicted that similar sex differences in CP55940-induced behavioral effects would be observed. To our knowledge, the behavioral effects of CP55940 metabolites have never been examined.

Another factor that could contribute to sex differences in behavioral effects of cannabinoids is sex differences in body fat. Body fat can affect how lipophilic drugs such as cannabinoids are absorbed and distributed, particularly since cannabinoids tend to sequester in fat tissue (Nahas et al., 1981). Because male rats have more fat than females in the internal body cavity (Uhley et al., 1997), it is possible that more drug is absorbed and captured by fat tissue in males compared to females when cannabinoids are administered i.p., thereby decreasing their central nervous system effects. The results of the present study support the hypothesis that the existence of sex differences in drug effect is correlated with the lipophilicity of the various cannabinoids. That is, the most consistent sex differences were observed with the most lipophilic cannabinoid, Δ^9-tetrahydrocannabinol, and the least consistent sex differences were observed with the least lipophilic cannabinoid, 11-hydroxy-Δ^9-tetrahydrocannabinol (Thomas et al., 1990).

Estrous cycle did not significantly affect behavioral responses in females. However, most of the females were in diestrus-1 at the time of testing, thus, the negative result may be due to an inadequate sample of females in other estrous stages. To better resolve this issue a future study employing controlled sampling of females in specific estrous stages must be completed.

The longer duration of antinociceptive action for cannabinoids versus a pressure stimulus as compared to a thermal stimulus was an interesting finding. At 7-h post-injection, all three cannabinoids at the highest doses tested were still producing antinociception in the paw pressure test, particularly in females. It is possible that animal response on the paw pressure test is more sensitive than responding on the tail withdrawal test to cannabinoids' motor attenuating effects, although the fact that the motoric effects of cannabinoids dissipated before the paw pressure effect argues against this hypothesis. In any case, cannabinoids appear to be particularly effective against pain induced by mechanical stimuli.

This is the first study to demonstrate sex differences in the antinociceptive effects of cannabinoids in rats. This study also corroborates a previous study demonstrating sex differences in cannabinoid-induced motoric effects. These results could have implications for the medicinal use of cannabinoids. Currently, we are determining if sex differences in cannabinoid pharmacodynamics or pharmacokinetics underlie sex differences in cannabinoid-induced behavioral effects.

Acknowledgements

The authors thank Dr. M. Morgan for loan of the paw pressure apparatus. This research was supported in part by a grant from the National Institute on Drug Abuse (DA06036) to A.H.T.

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