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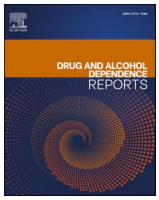

Δ^9-tetrahydrocannabinol discrimination: Effects of route of administration in mice

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HIGHLIGHTS

- We examined if route of administration altered THC's discriminative stimulus in mice.
- i.p., p.o., s.c., and aerosolized THC fully substituted for i.p. THC.
- THC's time course was similar for i.p., s.c., and p.o. routes of administration.
- Aerosolized THC had a quicker onset and shorter duration of effects.
- Multiple routes of THC administration produced THC-like psychoactive effects in mice.

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ABSTRACT

Background: Route of administration is an important pharmacokinetic variable in development of translationally relevant preclinical models. Humans primarily administer cannabis through smoking, vaping, and edibles. In contrast, preclinical research has historically utilized injected Δ^9-tetrahydrocannabinol (THC). The present study sought to examine how route of administration affected the potency and time course of THC's discriminative stimulus properties.

Methods: Adult female and male C57BL/6 mice were trained to discriminate intraperitoneal (i.p.) THC from vehicle in a drug discrimination procedure. After discrimination was acquired, a dose-effect curve was determined for i.p., oral (p.o.), subcutaneous (s.c.), and aerosolized THC. Subsequently, the time course of effects of each route of administration was determined.

Results: THC administered i.p., p.o., s.c., or via aerosolization fully substituted for i.p. THC. The potency of THC's psychoactive effects was similar for i.p., p.o., and s.c., except that THC was more potent when administered s.c. vs p.o. in females. All routes of administration had a similar potency in both sexes. The duration of THC's psychoactive effects was similar across i.p., s.c., and p.o. routes of administration, whereas aerosolized THC produced a faster onset and shorter duration of effects compared to the other routes.

Conclusion: THC administered via multiple routes of administration, including those commonly used in preclinical research (i.p. and s.c.) and more translationally relevant routes (aerosol and p.o.), produced THC-like discriminative stimulus effects in mice trained to discriminate i.p. THC. More precise predictions of THC's effects in humans may result from use of these translationally relevant routes of administration.

1. Introduction

Δ^9-Tetrahydrocannabinol (THC) is the primary psychoactive constituent in cannabis. Rodent models have played an integral part in determining the mechanisms of cannabimimetic activity, including studies on behavioral and pharmacokinetic effects of THC (Balster and Prescott, 1992; Panagis et al., 2008; Ruiz et al., 2021a; Ruiz et al., 2021b; Tanda and Goldberg, 2003). Although rodent models have contributed to many new discoveries in cannabinoid research, there are still areas for improvement in their translational relevance (e.g., Moore et al., 2022b).

Route of administration is an important pharmacokinetic variable in development of translationally relevant preclinical models. Humans primarily administer cannabis through smoking, vaping, and edibles

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(Fataar and Hammond, 2019; Meacham et al., 2018; Schauer et al., 2016; Spindle et al., 2019). In contrast, preclinical research has historically utilized injected THC or other cannabinoids in most studies, although rodent research with other routes of administration is gaining momentum (Bruijnzeel et al., 2016; Manwell et al., 2014a; Manwell et al., 2014b; Marshell et al., 2014; Moore et al., 2022b; Nguyen et al., 2016; Ruiz et al., 2021b; Wiebelhaus et al., 2012; Wiley et al., 2021b). Most behavioral studies in rodents have used intraperitoneal (i.p.) or subcutaneous (s.c.) injections of cannabinoids (Aceto et al., 1996; Brents et al., 2013; Dorr and Steinberg, 1976; Eckard et al., 2020; Gatch and Forster, 2016; Jarbe and McMillan, 1980; Marusich et al., 2022; McMahon et al., 2008; Walentiny et al., 2015; Wiley et al., 2007). Thus, first-pass metabolism (i.p.) and delayed onset of effects (i.p. and s.c.) may play a greater role in rodent models than in human users. Use of different routes of administration across species decreases translational relevance for several reasons. First-pass metabolism of THC, which occurs with i.p. dosing, produces a metabolite with psychoactivity [11-hydroxy-tetrahydrocannabinol (11-OH-THC)] (Browne and Weissman, 1981; Wiley et al., 2021a). Although aerosol exposure to THC also produces 11-OH-THC rodent brain (Ruiz et al., 2021b), i.p. injection produces much greater levels of 11-OH-THC in rodents than aerosol (Ruiz et al., 2021a). Furthermore, smoking or vaping THC heats or burns the substance, which can change its chemical composition, while degradation during storage can have similar effects (Bell and Nida, 2015; Eichler et al., 2012; Thomas et al., 2017). Thus, metabolism and changes in chemical composition during heating can affect the potency or time course of THC's pharmacological effects.

The present study sought to examine how route of administration affected the potency and time course of THC's discriminative stimulus properties in a mouse model. Drug discrimination is a behavioral model of the interoceptive effects of a drug (Barrett et al., 2005; Solinas et al., 2006). THC discrimination is a reliable and pharmacologically selective animal model of cannabinoid psychoactivity (Balster and Prescott, 1992), and has been recommended as a primary method for preclinical evaluation of cannabinoid abuse liability by U.S. federal agencies such as the FDA and DEA (Food and Drug Administration, 2010). Prior research on effects of route of administration on THC discrimination in Long Evans rats showed that i.p. and oral THC had similar potencies, while potency was lower for s.c. THC (Wiley et al., 2021b). Aerosolized THC produced the quickest onset and shortest duration of discriminative stimulus effects, while s.c. administration produced the longest lasting effects.

Although effects of route of administration on THC discrimination have been examined in rats (Wiley et al., 2021b), mice are also commonly used for THC discrimination studies (Brents et al., 2013; Grim et al., 2016; Marshell et al., 2014; Marusich et al., 2022; Marusich et al., 2018; McMahon et al., 2008; Vann et al., 2009; Wiley et al., 2015), and species differences in preclinical models of THC use are largely unexplored. Despite THC having similar binding and activation of the cannabinoid receptor 1 in rats and mice (Wiley et al., 2021a), species differences among rodents have been noted for aversive and rewarding effects of cannabinoids. Kappa opioid receptors modulate aversive properties of THC in mice (Cheng et al., 2004; Ghozland et al., 2002), but not rats (Flax et al., 2015). Furthermore, administration of the cannabinoid receptor 1 antagonist rimonabant had little effect in a place preference study in mice (Hutcheson et al., 1998), was rewarding in rats in one study (Sañudo-Peña et al., 1997), but had no effect in rats in another study (Chaperon et al., 1998). Prior research showed a species by sex interaction in effects of THC in that sex differences in THC discrimination were noted in rats, with THC being more potent in female Sprague-Dawley rats than males trained to discriminate THC from vehicle, but this sex difference was not found in C57BL/6 mice (Wiley et al., 2021a). There are also species differences in common training doses used in THC discrimination studies using i.p. dosing with lower doses used in rats (Wiley et al., 2014; Wiley et al., 2017; Wiley et al., 2021b) than in mice (Marusich et al., 2022; Marusich et al., 2018; Wiley et al., 2016). Mice also metabolize THC more quickly than rats (Borys and Karler, 1979; Harvey and Brown, 1991). No prior research has determined if there are species differences based on route of THC administration to our knowledge. Thus, the present study sought to extend existing research on how route of administration affects THC's discriminative stimulus properties.

2. Materials and methods

2.1. Subjects

Adult male and female drug- and experimentally-naïve C57BL/6 mice (24-27 g for males and 17-20 g for females at the beginning of the experiment; Envigo, Frederick, MD, USA) were individually housed upon arrival in polycarbonate cages in a temperature-controlled (20-26°C) environment with a 12 h light-dark cycle (lights on at 7 am). Mice had free access to water in the home cage, were lightly food restricted (i.e., fed about 2-3 g daily), and were fed immediately after their experimental session. Experiments complied with the Institutional Animal Care and Use Committee for RTI and with the ARRIVE guidelines. All research was conducted as humanely as possible, and followed the principles of laboratory animal care (National Research Council, 2011).

2.2. Apparatus

Standard mouse operant chambers (Coulbourn Instruments, Whitehall, PA, USA) were enclosed in light- and sound-attenuating isolation cubicles equipped with exhaust fans for ventilation and speakers for white noise. Each operant chamber contained a house light near the ceiling, two nosepoke apertures, stimulus lights above each aperture, and a food cup. A pellet dispenser delivered 20-mg food pellets (Bioserv Inc., Frenchtown, NJ, USA) into the food cup. Chamber operations (i.e., illumination of lights, generation of white noise, delivery of food pellets, and recording of responses) were controlled by a computer system (Graphic State Software, Coulbourn Instruments).

For the aerosol route of administration, THC aerosol was delivered to mouse-sized anesthesia-induction chambers (10 cm X 10 cm X 10 cm; EZ-177 Sure-Seal, E-Z-Anesthesia, Palmer, PA, USA) via a commercially available vaporizer (Model SVS-200, Scientific Vapor, Bend, OR, USA) connected to an e-vape controller (LJARI, La Jolla, CA, USA), as described previously (Wiley et al., 2021b). Airflow was constant (1 L/min), and aerosol was dispensed from an e-cigarette tank (Innokin Zenith, Element Vape, South El Monte, CA, USA) via Tygon tubing (Fisher Scientific, Pittsburgh, PA, USA). The system was configured at 10 W using a 1.6 Ω atomizer (Innokin Z-Coil 1.6 Ω, Element Vape). The atomizer was changed approximately every 5-7 days of aerosol exposure.

2.3. Chemicals

Δ^9-Tetrahydrocannabinol (National Institute on Drug Abuse, NIDA, Rockville, MD, USA) was suspended in a 7.8% polysorbate 80 (Fisher Scientific) and 92.2% saline (Patterson Vet Supply, Blythewood, SC) mixture for systemic administration. Intraperitoneal (i.p.) and subcutaneous (s.c.) injections of THC or vehicle were given at a volume of 10 ml/kg whereas the volume of oral gavage (p.o.) THC administrations was 5 ml/kg. For aerosolization, THC was mixed in 100% propylene glycol (PG) (Fisher Scientific) because this vehicle has been used in prior rodent studies with aerosolized THC (Gutierrez et al., 2022; Moore et al., 2022a; Nguyen et al., 2016; Ruiz et al., 2021b; Wiley et al., 2021b). Concentrations for aerosol administration are expressed as mg/ml in the e-cigarette tank and may not be representative of the actual amount of drug administered.

2.4. Procedure

Mice of both sexes (n=12 males and 10 females at start of study) were trained to respond on one aperture following administration of 5.6 mg/kg THC and to respond on another aperture after injection with vehicle according to a fixed ratio 10 (FR10) schedule of food reinforcement, under which 10 consecutive nose pokes into the correct (injection-appropriate) aperture resulted in delivery of a food pellet. During training, THC and vehicle were administered i.p. 30 min prior to the start of the training session. Responses on the incorrect aperture reset the ratio requirement on the correct aperture. Prior to each daily training session, mice received a single injection of THC or vehicle in a double alternation schedule (e.g., two sessions with THC pre-injection followed by two sessions with vehicle pre-injection). These single daily 15 min training sessions were held on weekdays until the mice consistently met three criteria: (1) the first completed FR10 was on the correct aperture, (2) $\geq$ 80% of the total responding occurred on the correct aperture, and (3) response rate was $\geq$ 0.1 responses/s. When these criteria had been met for the most recent THC training dose and vehicle sessions and 8 of the 10 most recent sessions, reliable discrimination had been established and testing began.

Following successful acquisition of the discrimination, stimulus substitution tests were typically conducted on Tuesdays and Fridays during 15-min test sessions, with maintenance of training continuing on intervening days. During test sessions, responses on either aperture delivered reinforcement according to a FR10 schedule of reinforcement. In order to be tested, mice must have completed the first FR10 on the injection-appropriate aperture, made at least 80% of all responses on the injection-appropriate aperture, and had a response rate $\geq$ 0.1 responses/s during the preceding day's training session. In addition, the mouse must have met these same criteria during the most recent training session with the alternate training compound (i.e., THC training dose or vehicle). After passing stimulus substitution tests for the training drug and vehicle, an initial substitution dose-effect curve was determined for i.p. THC in each sex. Subsequently, dose-effect curves were determined for p.o., aerosolized, and s.c. THC in that order. Doses were presented in ascending order for each dose-effect curve.

For the i.p., p.o. and s.c. dose-effect curves, THC was injected 30 min prior to the start of the test session. For the aerosol concentration-effect curve, exposures occurred in the aerosol chambers prior to placement in the drug discrimination chambers. Mice were exposed to each THC concentration for ten 6-s infusions, with a 12-s inter-infusion interval, except for the 600 mg/ml exposure where mice received twenty 6-s infusions (with 12-s inter-infusion interval) of 300 mg/ml THC. After the exposure session, mice were placed in their home cage to await placement in the operant chamber for the drug discrimination session. Pre-session wait time was 15 min for the aerosol concentration-effect curve and varied from 5 min to 6 h for the time course determination, which is described in the next paragraph.

After all dose-effect curves were completed, time course assessments of THC were conducted in a fixed order: i.p., p.o., s.c., aerosol. For each route of administration, a single dose/concentration of THC was assessed at different pre-session times: 10 mg/kg (i.p., s.c.), 30 mg/kg (p.o.), and 300 mg/ml (aerosol). These doses/concentrations were chosen for the time course tests because they produced full substitution (average of $\geq$ 80% THC-aperture responding) in both sexes for the given route of administration. For time course examinations, THC was administered at 5, 15, 30, 60, 120, 180, 240, 300, and 360 min pre-session, with each pretreatment evaluated during a separate session. Pretreatment times were evaluated in ascending order.

2.5. Data analysis

For each test session, mean (±SEM) percent responding on the drug aperture and rate of responding (responses/s) were calculated for the entire session. ED_{50}s (and 95% confidence limits) were calculated separately for each sex and route of administration using least-squares linear regression on the linear part of the dose-effect curves for percent drug-aperture responding, plotted against $\log_{10}$ transformation of the dose. Because mice that responded less than 10 times during a test session did not nose poke in either aperture enough times to earn a reinforcer, their aperture selection data were excluded from data analysis, but their data were included in response rate calculations. Mean substitution was used for aperture selection data in these instances to maintain equal n's across time. For each route of administration, aperture selection data and response-rate data for the dose-effect curves were analyzed using separate mixed factorial analysis of variance (ANOVA) across dose (repeated factor) and sex (between-subjects factor). Aperture selection data for 30 and 100 mg/kg i.p. THC, 100 mg/kg p.o. THC, and 100 mg/kg s.c. THC were excluded from analyses because these doses produced severe response rates suppression in most of the mice. Response rate data for 100 mg/kg i.p. THC were excluded from analyses because this dose was only tested in n=3-4 mice/sex because it produced complete suppression of responding in all mice except one, but these data were retained in graphs. For each time course, percentage of responding on the THC-associated aperture and response-rate data were analyzed using separate mixed factorial analysis of variance (ANOVA) across time (repeated factor) and sex (between-subjects factor).

Due to attrition over the course of the study, not all mice were evaluated at all time points. Data for mice that were not tested at all time points were excluded from time course analysis. Supplemental Fig.s show side-by-side comparison graphs with data for percentage of responding on the THC-associated aperture (Fig. S1) and response rates (Fig. S2) for all mice tested at any timepoint compared to graphs with data only for mice that completed tests at all time points. Significant ANOVAs were followed by Tukey post hoc tests ($\alpha = 0.05$) to determine differences between means. NCSS 11 Statistical Software (NCSS Statistical Software, Kaysville, UT, USA) was used for all analyses and GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA) was used to create Fig.s.

3. Results

3.1. Dose-effect curve data

All mice successfully acquired THC discrimination. Females met acquisition criteria considerably faster than males, with an average (± SEM) of 25 (± 2.9) and 52 (± 5.8) discrimination sessions for females and males, respectively. Fig. 1 shows the results of tests with different doses of THC delivered i.p. (panels A and B), p.o. (panels C and D), s.c (panels E and F), and as an aerosol (panels G and H) on percent of THC-aperture responding (left panels) and response rate (right panels). As expected, i.p. THC produced full, dose-dependent substitution for the 5.6 mg/kg training dose in both male and female mice [Fig. 1A; main effect of dose: $F(5,100)=60.06$, $p<0.05$]. Although the ED_{50} value for males was lower than for females (2.03-3.28 mg/kg, respectively), confidence limits were overlapping (Table 1) and the ANOVA was not significant for sex or sex X dose interaction effects. Response rates did not differ significantly across sex (Fig. 1B) and showed a biphasic effect, with slight (but statistically significant) increases at 3 mg/kg and significant decreases at 10 and 30 mg/kg, as compared to vehicle [main effect of dose: $F(6,120)=63.25$, $p<0.05$].

Systemic injection of THC p.o. (Fig. 1C) and s.c. (Fig. 1E) produced similar patterns of dose-dependent substitution for the i.p. 5.6 mg/kg THC training dose in both sexes [main effect of p.o. dose: $F(3,60)=39.87$, $p<0.05$; main effect of s.c. dose: $F(4,80)=41.67$, $p<0.05$]. ED_{50} values across sex differed slightly for these routes of administration, but like with i.p. injection, confidence limits were overlapping (Table 1) and the ANOVAs were not significant for sex or sex X dose interaction effects for either of these two routes of administration. Across i.p., p.o., and s.c. routes of administration, ED_{50} values were generally comparable for males. In females, s.c. THC was 2.9-fold more potent than p.o. THC,

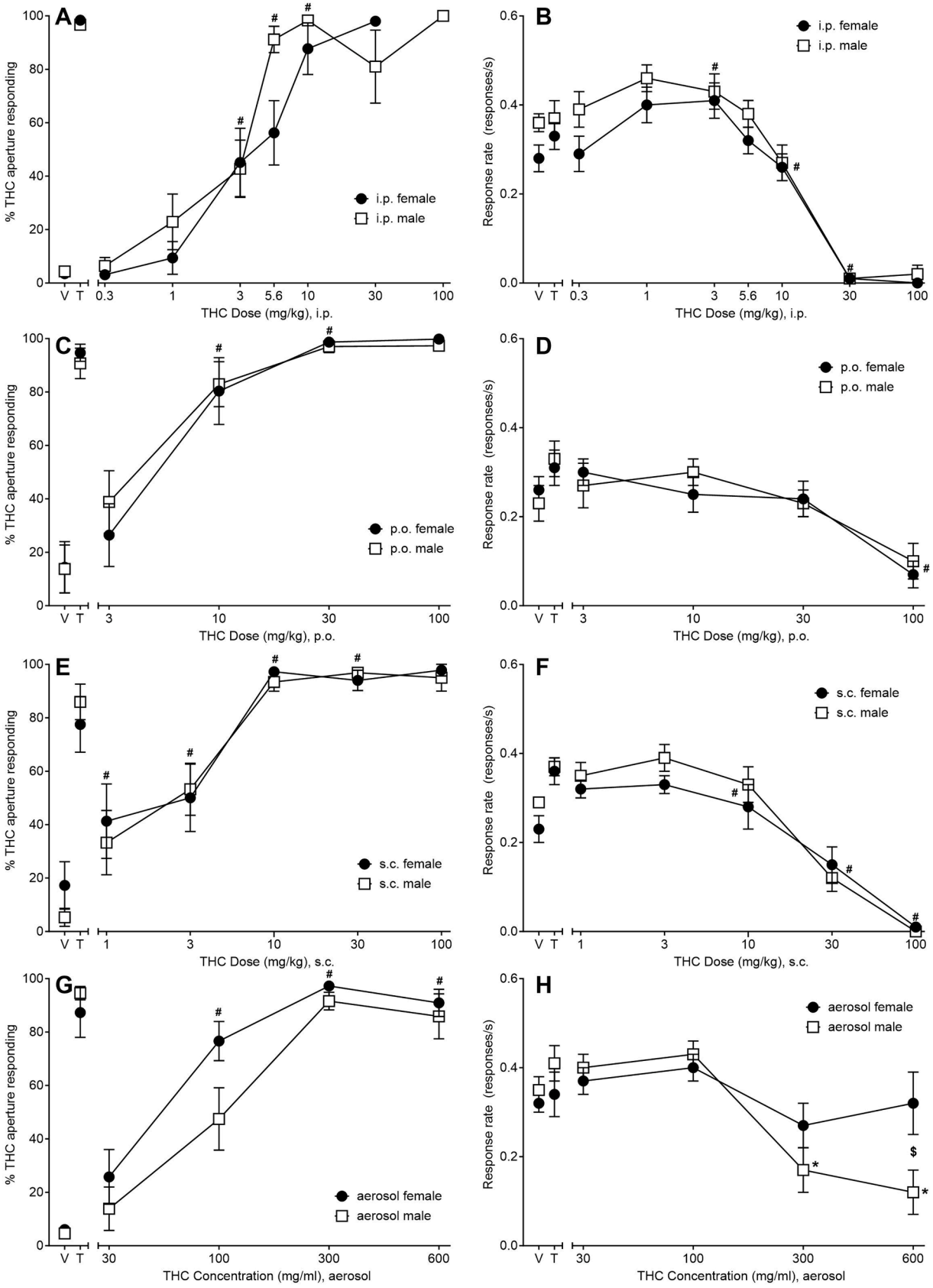

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Fig. 1. Effects of THC administered intraperitoneally (i.p.; panels A and B), via oral gavage (p.o.; panels C and D), subcutaneously (s.c.; panels E and F), or aerosolized (panels G and H) on percentage of responses that occurred on the THC-associated aperture (left panels) and response rates (right panels) in adult female (filled circles) and male (open squares) C57BL/6 mice trained to discriminate 5.6 mg/kg THC (i.p.) from vehicle in a drug discrimination procedure. Control tests with vehicle (V; administered via same route of administration as in the THC dose-effect curve) and 5.6 mg/kg THC (T; administered i.p.) were conducted prior to each dose-effect curve, with results shown at the left side of the panels. Note that the X-axis values differ across route of administration. Each point represents the mean (± SEM) of data for female (n=8-10) and male (n=7-12) mice, except for %THC aperture responding for 30 mg/kg THC in the i.p. dose-effect curve for females (n=1) and males (n=2), 100 mg/kg THC in the p.o. dose-effect curve for females (n=4), and 100 mg/kg THC in the s.c. dose-effect curve for females (n=2) and males (n=2) [i.e., in these instances, data for this variable were excluded when mouse made fewer than 10 overall responses and these doses were not included in the dose-effect ANOVAs]. In addition, only 3 female and 4 male mice were assessed with 100 mg/kg i.p. THC. For response rate data, pound sign (#) indicates a significant main effect of dose, with a significant post-hoc difference ($p<0.05$) from vehicle for the indicated dose across sexes. Asterisks (*) indicate a significant sex X dose interaction, with a significant post-hoc difference ($p<0.05$) from vehicle for the indicated dose and sex. Dollar sign ($) indicates a significant sex X dose interaction, with a significant post-hoc sex difference at the indicated dose ($p<0.05$).

Table 1
THC potency in drug discrimination across route of administration in male and female C57BL/6 mice.

Route of Administration	Males ED50 (± 95% CI)	Females ED50 (± 95% CI)
Intraperitoneal (i.p.)	2.03 mg/kg (1.57 – 2.61)	3.28 mg/kg (2.26 – 4.77)
Oral gavage (p.o.)	3.40 mg/kg (2.09 – 5.55)	5.36 mg/kg (3.65 – 7.87)
Subcutaneous (s.c.)	2.14 mg/kg (1.42 – 3.20)	1.88 mg/kg (1.05 – 3.37)
Aerosol	94.49 mg/ml (68.70 – 129.95)	39.05 mg/ml (21.50 – 70.93)

albeit linearity of the dose-effect function was not ideal for the s.c. route and complicated best fit for the linear regression curve used to calculate ED_{50}. Significant response rate decreases (compared to vehicle) were observed across sex with p.o. [Fig. 1D; main effect of dose: $F(4,80)=13.06$, $p<0.05$] and s.c. administration [Fig. 1F; main effect of dose: $F(5,88)=18.21$, $p<0.05$] at higher doses, with an increase also seen at 10 mg/kg s.c. THC (Fig. 1F).

As shown in Fig. 1G, aerosolized THC produced concentration-dependent increases in responding on the THC-associated aperture in both sexes [main effect of dose: $F(4,80)=69.56$, $p<0.05$], with 2.4-fold greater potency in females than males [Table 1; main effect of sex: $F(1,20)=9.11$, $p<0.05$]. The sex X dose interaction effect was not significant. Further, whereas aerosolized THC significantly decreased overall response rates in males (compared to vehicle), it did not significantly affect rates in females [Fig. 1H; concentration X sex interaction: $F(4,80)=3.66$, $p<0.05$].

3.2. Time course data

Fig. 2 shows the results of tests at different pre-session injection intervals with THC delivered i.p. (panels A and B), p.o. (panels C and D), s.c. (panels E and F), and as an aerosol (panels G and H) on percent of THC-aperture responding (left panels) and response rate (right panels). At the 5-min time point, aperture response choices after i.p. injection with 10 mg/kg THC were significantly different from the THC training dose value, but not significantly different from vehicle across both sexes [Fig. 2A; main effect of time: $F(10,120)=16.23$, $p<0.05$; sex X time interaction: $F(10,120)=1.30$, $p=0.24$]. At all other time points and for the THC training dose, THC-aperture responding was significantly higher for both sexes than when mice received vehicle. Response rates following i.p. injection exhibited significant increases (compared to vehicle levels) after the THC training dose (at 30 min) and at the 15-, 120-, 180-, and 300-min time points [Fig. 2B; main effect of time: $F(10,120)=2.63$, $p<0.05$; sex X time interaction: $F(10,120)=1.25$, $p=0.27$].

After p.o. administration of 30 mg/kg THC, the time of onset for THC-like discriminative stimulus effects was similar to that seen with i.p. injection of 10 mg/kg THC, with THC-aperture responding significantly different from the i.p. training dose at 5 min and significantly different from vehicle levels at time points from 15-300 min [Fig. 2C; main effect of time: $F(10,120)=19.89$, $p<0.05$; sex X time interaction: $F(10,120)=1.74$, $p=0.08$]. However, by 360 min post-injection, response selection was predominantly on the vehicle aperture for both sexes. Response rates across sex were significantly increased by the 30 mg/kg p.o. THC dose at 180 and 240 min post-injection, as compared to vehicle [Fig. 2D; main effect of time: $F(10,120)=6.41$, $p<0.05$; sex X time interaction: $F(10,120)=2.33$, $p<0.05$].

Following s.c. injection of 10 mg/kg THC, onset of THC-like discriminative stimulus effects was rapid and enduring. At 5 min post-injection, responding on the THC-associated aperture was significantly lower than responding on this aperture after the i.p. THC training dose, but by 15 min post-injection and at all subsequent time points up to 360 min post-injection, responding significantly exceeded vehicle levels and occurred predominantly on the THC-associated aperture [Fig. 2E; main effect of time: $F(10,120)=40.34$, $p<0.05$; sex X time interaction: $F(10,120)=0.74$, $p=0.69$]. Significantly increased response rates were seen following the i.p. THC training dose and at the 180-, 240- and 360-min time points for s.c. 10 mg/kg THC [Fig. 2F; main effect of time: $F(10,120)=3.11$, $p<0.05$; sex X time interaction: $F(10,120)=1.71$, $p=0.08$].

Onset of the THC-like effects of aerosolized THC was rapid, occurring prior to the first measurement timepoint at 5 min post-exposure. Responding was predominantly on the on the THC-associated aperture at 5-60 min post-exposure in both sexes and was significantly greater than responding on this aperture after vehicle administration at these timepoints [Fig. 2G; main effect of time: $F(10,70)=32.21$, $p<0.05$; sex X time interaction: $F(10,120)=0.27$, $p=0.99$]. While responding on the THC-associated aperture was still greater than vehicle level responding on this aperture at 120 min, responding on this aperture showed steep declines and was significantly different from the level observed following injection with the i.p. THC training dose. At timepoints from 180-360 min post-exposure, the cannabimimetic discriminative stimulus effects of aerosolized THC had dissipated and responding was predominantly on the vehicle-associated aperture in both sexes. Response rates were significantly reduced compared to vehicle at the 5-min timepoint for both sexes [Fig. 2H; main effect of time: $F(10,70)=9.94$, $p<0.05$; sex X time interaction: $F(10,120)=0.91$, $p=0.53$], but did not differ from response rates following vehicle at any of the other timepoints.

4. Discussion

The present study found that THC administered i.p., p.o., s.c., or via aerosolization fully substituted for i.p. THC in mice of both sexes. The potency of THC's discriminative stimulus effects was similar for i.p., p.o., and s.c. THC for both sexes, with overlapping confidence intervals across routes of administration, except that confidence intervals for p.o. and s.c. THC did not overlap for females. Additionally, each route of administration had a similar potency in both sexes. Sex differences in effects of THC were minimal in this mouse study, which is in contrast to human lab studies indicating greater subjective effects of oral or smoked THC/cannabis in women than men (Fogel et al., 2017; Matheson et al., 2020; Sholler et al., 2021). Although the dose the mice received when

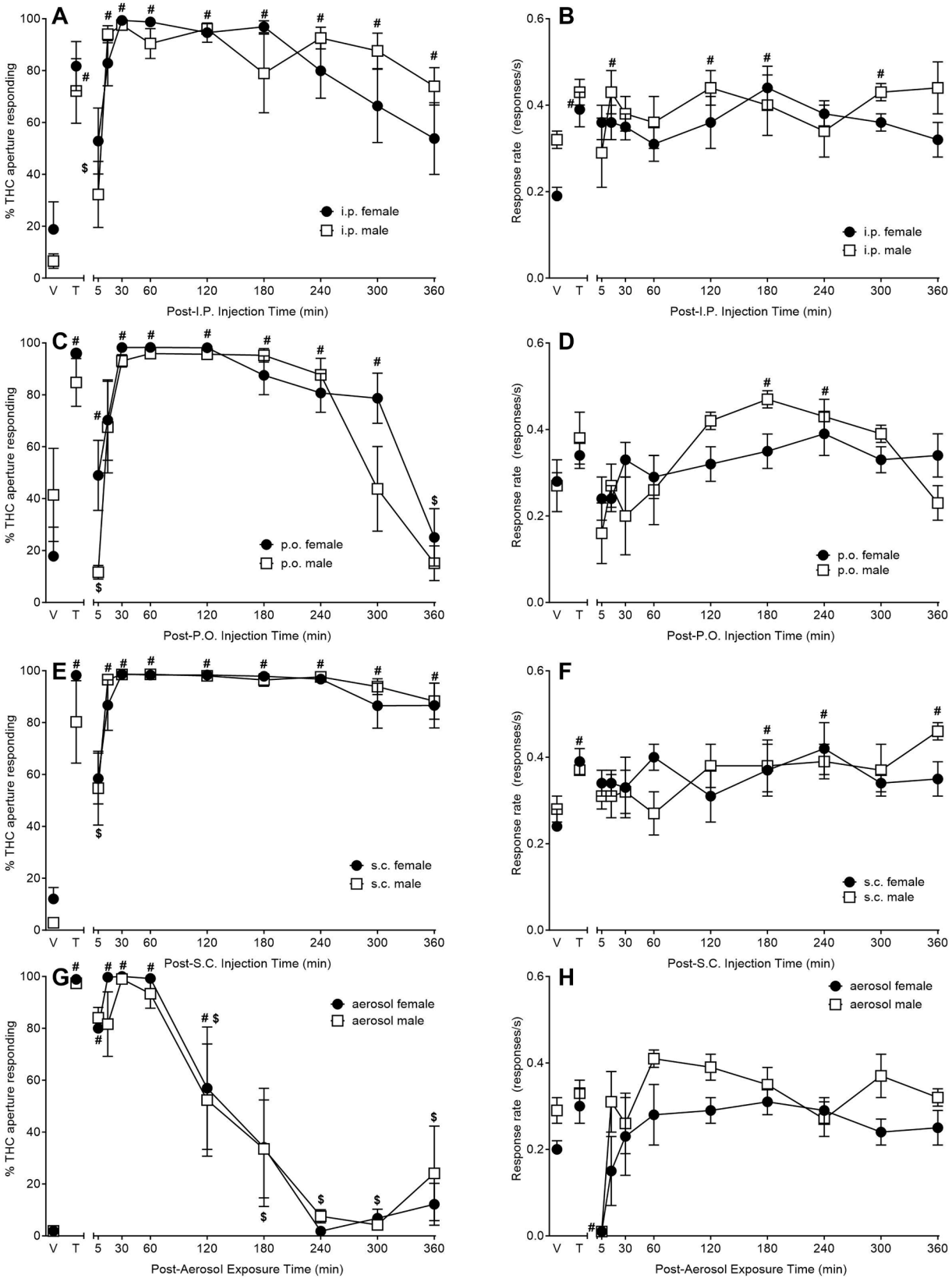

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Fig. 2. Effects of THC as a function of time on percentage of responses that occurred on the THC-associated aperture (left panels) and response rates (right panels) in adult female (filled circles) and male (open squares) C57BL/6 mice trained to discriminate 5.6 mg/kg THC (i.p.) from vehicle in a drug discrimination procedure. THC dose was 10 mg/kg for i.p. (panels A and B), 30 mg/kg for p.o. (panels C and D), and 10 mg/kg for the s.c. time courses (panels E and F). Concentration for the aerosolized THC time course was 300 mg/ml (panels G and H). Control tests with vehicle (V; administered i.p. 30 min pre-session) and 5.6 mg/kg THC (T; administered i.p. 30 min pre-session) were conducted prior to each time course, with results shown at the left side of the panels. Each point for the i.p., p.o., and s.c. time courses represents the mean (± SEM) of data for female (n=8) and male (n=6) mice, except for %THC aperture responding for 5 min i.p. for males (n=5), 5 min p.o. for males (n=3), 30 min p.o. for males (n=2), and 5 min p.o. for females (n=5). For the aerosolized THC time course, each point represents the mean (± SEM) of data for female (n=4) and male (n=5) mice, except for %THC aperture responding at 5 min for males (n=2), 30 min for males (n=4), 5 min for females (n=1), and 15 and 30 min for females (n=3). Exceptions to the typical n for % THC aperture responding resulted from exclusion of data for this variable when a mouse responded fewer than 10 overall responses. Pound signs (#) indicate a significant main effect of time, with a significant post-hoc difference ($p<0.05$) from the vehicle value for the indicated dose across sexes. Dollar signs ($) indicate a significant main effect of time, with a significant post-hoc difference ($p<0.05$) from the THC training dose value for the indicated time across sexes.

exposed to aerosolized THC is unknown, and, therefore, cannot be compared to other routes of administration, aerosolized THC produced concentration-dependent discriminative stimulus effects with similar potency in males and females.

Comparison of the time course of effects across routes of administration showed that i.p., s.c., and p.o. THC had similar time courses, producing %THC-aperture responding that was significantly different from vehicle for 15-300 (p.o.) or 15-360 min (i.p. and s.c.). While aerosolized THC had the quickest onset, with discriminative stimulus effects that were significantly different from vehicle at 5 min post exposure, the effects were short lived. %THC-aperture responding significantly differed from the i.p. THC training dose starting at 120 min following aerosol exposure. Subcutaneous THC produced the most persistent discriminative stimulus effects, producing full substitution (≥ 80% THC aperture responding) starting at 15 min, and full substitution lasted 360 min. In general, the discriminative stimulus effects of THC were surprisingly long lasting for all routes except aerosol. The rank order of duration of effects across routes was s.c. > i.p. > p.o. > aerosol. It would be interesting to determine if the duration of effects of s.c. THC lasts substantially longer than 6 h in future studies.

Comparison of the present study to a similar study conducted in Long Evans rats indicates that there are species differences in the psychoactive effects of THC. THC produced more potent discriminative stimulus effects when administered i.p. or p.o. than when administered s.c. in rats (Wiley et al., 2021b), whereas the present study in mice showed the opposite, with THC being most potent when administered s.c. In rats, THC was more potent in females than males when given i.p., but it was more potent in male than female mice when given i.p. and p.o. in the present study. However, prior studies have shown smaller sex differences in i.p. THC potency in mice (Wiley et al., 2021a). Differences in potency across route of administration and sex within species should be interpreted with caution though since most routes of administration had overlapping confidence intervals for both sexes in the present study and in the prior rat study (Wiley et al., 2021b). THC was more potent in rats (Wiley et al., 2021b) than in mice (present study) when administered i.p. or p.o., which is consistent with the use of lower training doses for THC discrimination in rats than in mice (Marusich et al., 2022; Marusich et al., 2018; Wiley et al., 2014; Wiley et al., 2017; Wiley et al., 2016; Wiley et al., 2021b).

THC also produced a quicker onset of discriminative stimulus in mice than rats, with full substitution occurring at 15 min post-exposure for mice when THC was administered via all routes except p.o. in the present study. In contrast, full substitution in rats was not achieved until 30 min post-exposure for all routes, except aerosolized THC (Wiley et al., 2021b). THC also had a longer duration of action in mice than rats for systemic routes of administration, with i.p., p.o., and s.c. THC producing full substitution for 240 min or longer in mice, whereas full substitution in rats began to subside after 120 min in rats for i.p. and p.o. THC. In contrast, aerosolized THC produced longer lasting discriminative stimulus effects in rats (Wiley et al., 2021b) than in mice in the present study. It was surprising that THC had longer lasting discriminative stimulus effects in mice than rats following most routes of administration given that in vitro studies have shown that THC is metabolized more quickly in mice than in rats (Borys and Karler, 1979; Harvey and Brown, 1991). This species difference may be due to failure of these in vitro preparations to provide adequate models for in vivo pharmacokinetics. Another potential contributing factor could be different time courses for 11-OH-THC in rats and mice since this metabolite is psychoactive and also substitutes for THC (Wiley et al., 2021a). Future studies should investigate the in vivo pharmacokinetics of THC across species as well as provide direct comparisons of the time course of 11-OH-THC in rats and mice.

Results of the present study are in accordance with past studies showing that cannabinoids continue to produce THC-like discriminative stimulus effects when administered via different routes of administration than those used for training. CP55,940, AB-CHMINACA, and AMB-FUBINACA all produced THC-like effects when administered i.p. or via aerosol in mice trained to discriminate i.p. THC from vehicle (Wiley et al., 2019). In a similar study, mice trained to discriminate i.p. THC from vehicle showed full substitution when JWH-018 and JWH-073 were administered i.p., and when JWH-018 was administered via aerosol, whereas the highest concentration of aerosolized JWH-073 tested only produced approximately 50% THC-lever responding (Marshell et al., 2014). Notably, both studies only examined effects of THC administered i.p. Thus, the present study and the similar past study in rats (Wiley et al., 2021b) are the first to demonstrate that THC substitutes for itself when administered via different routes of administration. Studies on discrimination of other drug classes administered via injection or aerosol have shown mixed effects regarding whether drugs will substitute when administered by different routes of administration. Aerosolized nicotine only partially substituted for s.c. nicotine in mice (Lefever et al., 2019), whereas i.p. toluene fully substituted for aerosolized toluene (Shelton and Slavova-Hernandez, 2009), and smoked phencyclidine fully substituted for i.p. phencyclidine (Wessinger et al., 1985).

It remains unknown if the different time courses and potencies of discriminative stimulus effects in the present study are attributable to differences in THC and/or 11-OH-THC levels in brain. Although there have been studies of THC levels in blood and brain following THC exposure in mice (Dumbraveanu et al., 2023; Torrens et al., 2020; Upadhyay et al., 2023; Wilson et al., 2002), to our knowledge there are no studies that compared multiple of the routes of administration used in the present study. Methodological differences across these studies complicate interpretation of the pharmacokinetics of THC and 11-OH-THC across routes of administration in mice.

5. Conclusion

In summary, the present study showed that THC administered via multiple routes of administration, including those commonly used in preclinical research (i.p. and s.c.) and more translationally relevant routes (aerosol and p.o.), produced THC-like discriminative stimulus effects in adult male and female C57BL/6 mice trained to discriminate i.p. THC as has been previously found for adult Long Evans rats (Wiley et al., 2021b). The study also found that the duration of discriminative stimulus effects of THC was similar across i.p., s.c., and p.o. routes of

administration, whereas aerosolized THC produced a faster onset and shorter duration of effects compared to the other routes. The interoceptive effects of THC were longer lasting and less potent in mice in the present study than in rats in a prior study (Wiley et al., 2021b), except when aerosolized THC was administered. Ultimately, this study established the utility of aerosolized and orally administered THC in studies of psychoactive effects of THC in mice. More precise predictions of THC's effects in humans may result from use of these translationally relevant routes of administration.

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Contributors

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Julie A. Marusich: Resources, Writing – original draft, Writing – review & editing, Funding acquisition. **Jenny L. Wiley:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Visualization, Funding acquisition.

Declaration of Competing Interest

none

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Supplementary materials

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