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⁹-Tetrahydrocannabinol-Like Discriminative Stimulus Effects of Compounds Commonly Found in K2/Spice

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Abstract

A number of cannabinoid compounds are being sold in the form of incense as “legal” alternatives to marijuana. The purpose of these experiments was to determine whether the most common of these compounds have discriminative stimulus effects similar to ⁹-tetrahydrocannabinol, the main active component in marijuana. Locomotor depressant effects of JWH-018, JWH-073, JWH-200, JWH-203, JWH-250, AM-2201 and CP 47,497-C8-homolog were tested in mice. The compounds were then tested for substitution in rats trained to discriminate ⁹-tetrahydrocannabinol (3 mg/kg, i.p.). The time course of the peak dose of each compound was also tested. Each of the synthetic cannabinoids dose-dependently decreased locomotor activity for one to two hours. Each of the compounds fully substituted for the discriminative stimulus effects of ⁹-tetrahydrocannabinol, mostly at doses that produced only marginal amounts of rate suppression. JWH-250 and CP 47,497-C8-homolog suppressed response rates at doses that fully substituted for ⁹-THC. The time courses varied markedly between compounds. Most of the compounds had a shorter onset than ⁹-THC, and three lasted substantially longer (JWH-073, JWH-250 and CP 47,497-C8-homolog). Several of the most commonly used synthetic cannabinoids produce behavioral effects comparable to those of ⁹-tetrahydrocannabinol, which suggests that these compounds may share the psychoactive effects of marijuana responsible for abuse liability. The extremely long time course of the discriminative stimulus effects and adverse effects of CP 47,497-C8-homolog suggest that CP 47,497-C8-homolog may be associated with increased hazards in humans.

Keywords

cannabinoids; drug discrimination; locomotor activity; abuse liability; mouse; rat

Introduction

A number of synthetic cannabinoid compounds are being sold in the form of incense as a quasi-legal alternative to marijuana using names such as ‘K2’ or ‘Spice’ (Fattore and Fratta, 2011; Lindigkeit et al., 2009). Use of these compounds seems to be increasing, for example, JWH-018 and JWH-073 were found in 4.5% of recent blood samples of US athletes

(Heltsley et al., 2012), and a variety of synthetic cannabinoids including AM-2201 and JWH-018 have been detected in blood samples of people ticketed for driving under the influence (Musshoff et al., 2013). Clinical case studies indicate that these substances produce cannabis-like effects, and can produce dependence following repeated administration and elicit withdrawal signs upon cessation of use in humans (Gunderson et al., 2012; Zimmermann et al.). There is at least one possible case of seizures after consumption of large doses of synthetic cannabinoids obtained over the internet (Tofighi and Lee, 2012).

In January 2012, the Drug Enforcement Agency temporarily scheduled four synthetic cannabinoids that were deemed of particular concern, JWH-073, JWH-018, JWH-200 and CP 47,497 (Office of Forensic Sciences, 2010). Other synthetic cannabinoids have since become more visible, and some of the synthetic cannabinoids most commonly found in seized samples of herbal incense include JWH-018, JWH-073, JWH-200, JWH-250, CP 47,497 and AM-2201 (Denooz et al., 2012; Logan et al., 2012).

An increasing number of studies have examined the pharmacology of JWH-018 and JWH-073, but little work has been conducted with JWH-200, JWH-250, CP 47,497 or AM-2201. Compounds of this structural class are known to produce effects at cannabinoid CB1 receptors, despite having structures different from Δ^9 -tetrahydrocannabinol (Δ^9 -THC). JWH-018, JWH-073 and CP 47,497-C8-homolog bind to cannabinoid CB1 receptors, inhibit neurotransmission in hippocampal neurons and facilitate cannabinoid CB1 receptor internalization (Atwood et al., 2010, 2011; Brents et al., 2012; Showalter et al., 1996). In addition, JWH-018 and JWH-073 bind to human cannabinoid CB2 receptors and act as agonists (Rajasekaran et al., 2013). Since these compounds share their mechanism of action with Δ^9 -THC, a major active component of marijuana, it is not surprising that JWH-018 and JWH-073 fully substituted for the discriminative stimulus effects of Δ^9 -THC in rhesus monkeys (Ginsburg et al., 2012) and that monkeys developed cross-tolerance to JWH-018 and JWH-073 following repeated administration of Δ^9 -THC (Hruba et al., 2012). In addition, JWH-018 and JWH-073 substituted for the discriminative stimulus effects of Δ^9 -THC in rats (Järbe et al., 2011; Wiley and Lefever, 2014) and mice (Brents et al., 2013; Marshall et al., 2014), and suppressed locomotor activity in mice (Wiley et al., 1998).

The purpose of the present study was to assess the potential abuse liability of several of the most commonly found synthetic cannabinoids, JWH-018, JWH-073, JWH-200, JWH-203, JWH-250, AM-2201 and CP 47,497-C8-homolog. The locomotor depressant effects of these compounds were tested to find behaviorally active dose ranges and time courses of these compounds. Subsequently, the compounds were tested in the drug discrimination assay, which is a useful animal model for detecting compounds that share subjective effects of known drugs of abuse (Balster, 1991), and is predictive of abuse liability (Horton et al., 2013). Rats were trained to discriminate Δ^9 -THC from vehicle, and the dose effect and time course of these synthetic cannabinoids were assessed.

Methods

Subjects

Male Swiss–Webster mice were obtained from Harlan (Indianapolis, IN) at approximately 8 weeks of age and tested at approximately 10 weeks of age. Mice were group housed in cages on a 12:12-h light/dark cycle and were allowed free access to food and water. Male Sprague–Dawley rats were obtained from Harlan–Sprague Dawley (Indianapolis, IN). All rats were housed individually and were maintained on a 12:12 light/dark cycle (lights on at 07:00 h). Body weights were maintained at 320–350 g by limiting food to 15 g/day, which included the food received during operant sessions. Water was readily available. All housing and procedures were in accordance with Guidelines for the Care and Use of Laboratory Animals (National Research Council 2011) and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

Locomotor Activity

The study was conducted using 40 Digiscan (model RXYZCM, Omnitech Electronics, Columbus, OH) locomotor activity testing chambers (40.5 × 40.5 × 30.5 cm) housed in sets of two, within sound-attenuating chambers. A panel of infrared beams (16 beams) and corresponding photodetectors was located in the horizontal direction along the sides of each activity chamber. A 7.5-W incandescent light above each chamber provided dim illumination and fans provided an 80-dB ambient noise level within the chamber.

Separate groups of 8 mice were injected with either vehicle (ethanol/Cremophor EL/0.9% saline 1:1:18) or a cannabinoid: ⁹-THC (1, 3, 10 or 30 mg/kg), JWH-018 (0.03, 0.1, 0.3 or 1 mg/kg), JWH-073 (0.3, 1, 3 or 10 mg/kg), JWH-200 (0.3, 1, 3 or 10 mg/kg), JWH-203 (0.3, 1, 3 or 10 mg/kg), JWH-250 (1, 3, 10 or 30 mg/kg), AM-2201 (0.1, 0.3, 1, or 3 mg/kg), CP 47,497-C8-homolog (0.3, 1, 3 or 10 mg/kg), immediately prior to locomotor activity testing. In all studies, horizontal activity (interruption of photocell beams) was measured for 8 h within 10-min periods, beginning at 08.00 h (1 h after lights on). Behavioral observations were recorded on each mouse at 30, 120 and 480 minutes following the highest dose tested.

Discrimination Procedures

Standard behavior-testing chambers (Coulbourn Instruments, Allentown, PA) were connected to IBM-PC compatible computers via LVB interfaces (Med Associates, East Fairfield, VT). The computers were programmed in Med-PC for Windows, version IV (Med Associates, East Fairfield, VT) for the operation of the chambers and collection of data.

Using a two-lever choice methodology, a pool of rats previously trained to discriminate ⁹-THC (3 mg/kg) from vehicle (ethanol/Cremophor EL/0.9% saline 1:1:18) were tested. Rats received an injection of either saline or drug and were subsequently placed in the behavior-testing chambers, where food (45 mg food pellets; Bio-Serve, Frenchtown, NJ) was available as a reinforcer for every ten responses on a designated injection-appropriate lever. The pretreatment time was 30 min. Each training session lasted a maximum of 10 min, and the rats could earn up to 20 food pellets. The rats received approximately 60 of these

sessions before they were used in tests for substitution of the experimental compounds. Rats were used in testing once they had achieved 9 of 10 sessions at 85% injection-appropriate responding for both the first reinforcer and total session. The training sessions occurred on separate days in a double alternating fashion (drug-drug-vehicle-vehicle-drug; etc.) until the training phase was complete, after which substitution tests were introduced into the training schedule such that at least one vehicle and one drug session occurred between each test (drug-vehicle-test-vehicle-drug-test-drug; etc.). The substitution tests occurred only if the rats had achieved 85% injection-appropriate responding on the two prior training sessions.

During test sessions, both levers were active, such that 10 consecutive responses on either lever led to reinforcement. For dose-effect experiments, data were collected until the first reinforcer was obtained, or for a maximum of 20 min. Each compound was tested in groups of six rats, except ⁹-THC (n=13) and JWH-073 (n=7). A repeated-measures design was used, such that each rat was tested at all doses of a given drug. Intraperitoneal injections (1 ml/kg) of vehicle, ⁹-THC (0.1 – 3 mg/kg), JWH-018 (0.05 – 0.5 mg/kg), JWH-073 (0.1 – 10 mg/kg), JWH-200 (0.1 – 5 mg/kg), JWH-203 (0.5 – 10 mg/kg), JWH-250 (0.25 – 5 mg/kg), CP 47,497-C8-homolog (0.1 – 2.5 mg/kg) occurred 30 min prior to the start of the test session. AM-2201 (0.05 – 0.5 mg/kg) was administered 20 min prior to the start of the test session. Doses were tested in no particular order.

For time course experiments, a repeated-measures design was used, such that each rat was tested at several time points following a single administration of the test compound. The rats were injected with the test compound and placed in the test chambers 5 min after administration. Data were collected until the first reinforcer was obtained, or for a maximum of 5 min, and the rats were immediately removed from the chambers. Testing was repeated at 15, 30, 60, and 120 min after administration. If necessary, testing was continued at 4, 8, 24, and 48 hr after administration until THC-appropriate responding had decreased to below 30–40%.

Drugs

⁹-Tetrahydrocannabinol, JWH-018 (1-naphthalenyl(1-pentyl-1H-indol-3-yl)methanone), JWH-073 (1-butyl-1H-indol-yl)-1-naphthalenyl-methanone), JWH-200 ([1-[2-(morpholinyl)ethyl]-1H-indol-3-yl]-1-naphthalenyl-methanone), JWH-203 (2-(2-chlorophenyl)-1-(1-phenyl)-1H-indol-3-yl)-ethanone), JWH-250 (2-(2-methoxyphenyl)-1-(1-pentyl-1H-indol-3-yl)ethanone, AM-2201 ([1-(5-fluoropentyl)-1 H-indole-3-yl] (naphthalene-1-yl)methanone) and $\pm$ -CP 47,497-C8-homolog (rel-[(1S,3R)-3-hydroxycyclohexyl]-5-(2-methylnonan-2-yl)phenol) were provided by the National Institute on Drug Abuse Drug Supply Program. All drugs were dissolved in ethanol/Cremophor EL/0.9% saline (1:1:18) and were administered i.p. in a volume of 1 ml/kg.

Data Analysis

Drug discrimination data are expressed as the mean percentage of drug-appropriate responses occurring in each test period. Rates of responding were expressed as a function of the number of responses made divided by the time to the first reinforcer. Graphs for percent drug-appropriate responding and response rate were plotted as a function of dose of test

compound (log scale). Percent drug-appropriate responding was shown only if at least 3 rats completed the first fixed ratio, whereas all rats are shown for the response rate data. Full substitution was defined as 80% drug-appropriate responding and not statistically different from the training drug.

The potencies of JWH-018, JWH-073, JWH-200, JWH-203, JWH-250, AM-2201 and CP 47,497-C8-homolog were calculated by fitting straight lines to the dose-response data for each compound by means of TableCurve 2D (Jandel Scientific, San Rafael, CA). Straight lines were fitted to the linear portion of dose-effect curves, including not more than one dose producing <20% of the maximal effect and not more than one dose producing >80% of the maximal effect. Other doses were excluded from the analyses. Differences among ED50 values were tested by one-way ANOVA followed by Tukey's test to compare individual means. Response-rate data were analyzed by one-way repeated measures analysis of variance. Effects of individual doses were compared to the vehicle control value using a priori contrasts. The criterion for significance was set a priori at $p < 0.05$.

Locomotor activity data were expressed as the mean number of photocell counts in the horizontal plane (ambulation counts) during each 10-min period of testing. A 30-min period, beginning when maximal depression of locomotor activity first appeared as a function of dose, was used for analysis of dose-response data and calculation of ED50 values. TableCurve 2D was used to estimate the maximal depression under each cannabinoid. The ED50 values were then calculated by estimating the dose producing 50% of the maximal depression from the descending linear portion of the dose response curve. A two-way repeated-measures analysis of variance (dose $\times$ time) was conducted on horizontal activity counts/10 min interval. A one-way analysis of variance was conducted on horizontal activity counts for the 30-min period of maximal effect, and planned comparisons were conducted for each dose against saline control using single degree-of-freedom F tests. Correlations between ED50 values of the cannabinoids in the discrimination and locomotor activity assays were performed by least squares regression analysis using Excel 2007.

Results

Locomotor Activity

Figure 1 shows average horizontal activity counts in 10-min bins as a function of time and dose of each test compound. Because there was little or no change in locomotor activity after the first 4 h, only the first 4 h are shown in the figure. Table 1 shows the ED50 values. Each compound produced decreases in locomotor activity as dose increased. The 2-way analysis of variance performed on data for each compound yielded a significant main effect of Treatment, as well as a Treatment $\times$ Time Period interaction (all p s < 0.01). Treatment with 9 -THC resulted in time- and dose-dependent depression of locomotor activity. Depressant effects were seen following 3 to 30 mg/kg from 10 to 40 min [$F(6,57)=4.85$, $p < .001$], and from 90 to 120 min [$F(6,57)=3.34$, $p < .001$]. The apparent stimulant effect from 30–60 minutes following 0.3, 1, and 3 mg/kg 9 -THC was not statistically significant. No unusual effects were observed during the observation periods.

JWH-018 produced time- and dose-dependent depression of locomotor activity following 0.3 and 1 mg/kg. Depressant effects of 0.3 and 1 mg/kg occurred within 20 to 30 minutes following injection and lasted 130 to 140 minutes, with peak effect between 70 to 100 min [$F(4,35)=6.32$, $p=.001$]. Treatment with JWH-073 resulted in time- and dose-dependent depression of locomotor activity following 3 and 10 mg/kg. Depressant effects of 3 and 10 mg/kg occurred within 10 to 20 minutes following injection and lasted 120 to 130 minutes, with peak effect between 10 to 40 min [$F(4,35)=9.50$, $p<.001$].

JWH-200 produced time- and dose-dependent depression of locomotor activity following 3 and 10 mg/kg. Depressant effects of 3 and 10 mg/kg occurred within 10 minutes following injection and lasted 90 to 110 minutes [$F(4,35)=9.94$, $p<.001$]. Treatment with JWH-203 resulted in time-dependent depression of locomotor activity following 10 mg/kg. Depressant effects of 10 mg/kg occurred within 10 minutes following injection and lasted 90 minutes [$F(4,35)=9.53$, $p<.001$]. JWH-250 produced time- and dose-dependent depression of locomotor activity following 10 and 30 mg/kg. Depressant effects of 10 and 30 mg/kg occurred within 10 minutes following injection and lasted 90 minutes [$F(5,42)=8.6$, $p<.001$].

Treatment with AM-2201 resulted in time- and dose-dependent depression of locomotor activity following 1 and 3 mg/kg. Depressant effects of 1 and 3 mg/kg occurred within 10 minutes following injection and lasted 70 to 110 minutes [$F(4,35)=35.28$, $p<.001$]. Treatment with CP 47,497-C8-homolog resulted in time- and dose-dependent depression of locomotor activity following 1 to 10 mg/kg. Depressant effects of 1 to 10 mg/kg occurred within 10 to 30 minutes following injection and lasted 120 minutes, with maximal suppression at 30 to 60 min [$F(4,35)=21.01$, $p<.001$].

Discrimination

JWH-018, JWH-073, JWH-200, JWH-203, JWH-250, AM-2201 and CP 47,497-C8-homolog each produced dose-dependent full substitution for the discriminative stimulus effects produced by 3 mg/kg of Δ^9 -THC (Fig. 2). ED50 values are shown in Table 1. The cannabinoids were less potent in the locomotor activity assay than in the discrimination assay, but there was no correlation between potencies of the cannabinoids in the discrimination and locomotor activity assays [$r^2=0.33$, $p=0.14$]. JWH-018, JWH-200, JWH-203, JWH-250, and AM-2201 failed to alter response rates at the doses tested. JWH-073 increased response rate following 1 mg/kg, and decreased response rate following 10 mg/kg [$F(5,30)=7.16$, $p<.001$]. Four of seven rats failed to complete the first fixed ratio when tested following 10 mg/kg JWH-073. CP 47,497-C8-homolog [$F(5,25)=3.91$, $p=.009$] decreased response rate at the highest dose tested (2.5 mg/kg).

Δ^9 -THC produced full substitution (>80%) by 30 min after administration, which lasted 4 h (Fig. 3). The discriminative stimulus effects of Δ^9 -THC were gone at 8 h after administration. JWH-018 produced full substitution for the discriminative stimulus effects of Δ^9 -THC at 15 and 60 min after administration, with effects gradually diminishing at 2 and 4 h after administration. JWH-073 produced full substitution at 30 and 60 min after administration, with its effects diminishing from 2 to 8 h. Little or no substitution was seen for Δ^9 -THC at 24 hr after administration. JWH-200 showed a more rapid onset, producing

60% drug-appropriate responding at 5 min after administration. Full substitution was observed from 30 to 60 min, and drug-appropriate responding diminished over the next 7 h.

JWH-203 was relatively short-acting, producing full substitution for the discriminative stimulus effects of Δ^9 -THC at 30 min after administration, whereas drug-appropriate responding decreased to 5% by 2 h after administration (Fig. 3). JWH-250 produced full substitution within 5 min, but the full substitution lasted for 2 h before drug-appropriate responding dropped to approximately 50% at 2 and 4 h after administration. Effects of JWH-250 were at 10% drug-appropriate responding at 24 h after administration. AM-2201 also produced full substitution within 5 min after administration, and drug-appropriate responding diminished over the 8 h of testing. CP 47,497-C8-homolog had a relatively slow onset, producing 40% drug-appropriate responding at 15 min after administration, 80% at 30 and 60 min, and 100% at 2 to 8 h, dropping to 80% drug-appropriate responding at 24 h, and its effects had dissipated at 48 h after administration.

Discussion

Synthetic cannabinoids found in gray-market compounds were found to be behaviorally active. All seven compounds (JWH-018, JWH-073, JWH-200, JWH-203, JWH-250, AM-2201 and CP 47,497-C8-homolog) dose-dependently decreased locomotor activity. The degree of effect and time courses of these compounds were similar to those of Δ^9 -THC, which agrees with an earlier report that JWH-018 suppressed locomotor activity in mice (Wiley et al., 1998).

In rats trained to discriminate Δ^9 -THC, all seven cannabinoids produced dose-dependent increases in drug-appropriate responding, indicating that they all share discriminative stimulus effects with Δ^9 -THC. This finding agrees with earlier reports that JWH-018 and JWH-073 substitute for Δ^9 -THC in rodents (Brents et al., 2013; Ginsburg et al., 2011; Jarbe, 2011; Marshall et al., 2014; Wiley and Lefever, 2014). In addition, JWH-018 has been trained as a discriminative stimulus in monkeys, and Δ^9 -THC and JWH-073 fully substitute (Rodriguez and McMahon, 2014). The discriminative stimulus effects of JWH-018 appear to be mediated by cannabinoid receptors because the cannabinoid antagonist, rimonabant, blocked the discriminative stimulus effects of JWH-018, and non-cannabinoid sedatives ketamine (NMDA receptor blocker) and midazolam (benzodiazepine) failed to substitute (Rodriguez and McMahon, 2014).

The synthetic cannabinoids produced a wide range of time courses for the discriminative stimulus effects, which may account for the varying reports of recreational users. Some users recording their experiences on websites such as Erowid.com or Bluelight.ru indicated that “Spice” was very short-acting, while others reported very long-acting effects. Of course, there is no way of knowing precisely what compounds such recreational users have taken, nor the dose; further, users often report concurrent use of other psychoactive compounds including caffeine, nicotine, antidepressants, etc. However, one case report of self-experimentation with “Spice Diamond” indicated that it had noticeable effects more than 24 h after administration (Auwärter et al., 2009). Chemical analysis revealed the presence of the two stereoisomers of a compound similar in structure to CP-47,497, with the addition of

an additional carbon on the side chain. These findings indicate that compounds structurally related to CP47,497 can produce very long-acting behavioral effects humans.

In prior work with psychostimulants (e.g., Carroll et al., 2009; Gatch et al., 2013), and to a somewhat lesser extent with serotonergic hallucinogens (Gatch et al., 2011), mouse locomotor activity has been a useful predictor of dose range and pretreatment time for drug discrimination studies in rats. In these studies, doses at which locomotor activity was suppressed also predicted doses at which rate suppression will be observed in the drug discrimination assay. This was not the case for the cannabinoids tested in the present study. There was no relationship between the time course of the locomotor depressant effects in mice and the time course of the discriminative stimulus effects. All of the test compounds produced a rapid onset of near complete suppression of locomotor activity in mice lasting 2 to 3 h; whereas the discriminative stimulus effects took anywhere from 5 min to 2 h to appear and the peak effects lasted less than 30 min (JWH-203) to more than 8 h (CP 47,497-C8-homolog).

It is not clear why the locomotor depressant effects were uniform in onset and duration, whereas the time courses of the discriminative stimulus effects varied widely. Even though the ED50 values for discrimination were less than or equal to the ED50 values for locomotor activity, there was no relationship between magnitude or potency of the compounds in depressing locomotor activity and potency of discriminative stimulus effects or incidence of rate-depression in the discrimination assay (Table 3). For example, the ED50 values of the locomotor stimulant and discriminative stimulus effects were very similar for CP 47,497-C8-homolog, which substantially suppressed operant responding. However, the potencies for the locomotor stimulant and discriminative stimulus effects for JWH-018 were also quite similar, but JWH-018 showed no rate decreasing effects. Further, JWH-073 suppressed operant responding, but its potency was 6-fold less for its locomotor depressant effects than its discriminative stimulus effects.

It is likely that the suppression of operant behavior reflects decreased motivation rather than merely suppression of the ability to move intentionally. However, this does not account for the wide range in time courses for the discriminative stimulus effects, especially since response rate did not vary significantly during the time course studies (data not shown). It is also possible that the locomotor activity and the discriminative stimulus effects are mediated by different mechanisms; however, changes in both locomotor activity and drug discrimination induced by cannabinoids are blocked by the cannabinoid antagonist rimonabant (Craft et al., 2013; Katsidoni et al, 2013; Rodriguez and McMahon, 2014). Finally, there may be a species difference in the pharmacokinetics of these cannabinoids between mice and rats, such that metabolism may take place at different rates. Unfortunately, little has been published on the metabolism of these compounds, especially regarding species differences.

Taken together, these findings indicate these seven synthetic cannabinoids (JWH-018, JWH-073, JWH-200, JWH-203, JWH-250, AM-2201 and CP 47,497-C8-homolog) are indeed behaviorally active, produce similar discriminative stimulus effects as Δ^9 -THC, and therefore may have similar abuse liability as Δ^9 -THC. One study has examined the effects of

JWH-018 on conditioned place preference (Hyatt and Fantegrossi, 2014). JWH-018 produced a conditioned aversion in naïve mice, but produced a conditioned preference at low doses in mice previously exposed to Δ^9 -THC. Further conditioned place preference and self-administration studies will be necessary to test whether the remainder of these compounds are reinforcing and will maintain drug seeking in animal models. Surveys of recreational users would be useful to find whether these compounds produce different effects in naïve versus marijuana-experience human users.

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Figure 1. Time course of locomotor stimulant effects

Average horizontal activity (Ambulation counts) as a function of time (10 min bins) and dose. Only data from the first four hours are shown. Data are from independent groups of 8 mice per dose. * indicates depressant effects ($p < 0.05$) against vehicle control.

Figure 2. Substitution for the discriminative stimulus effects of ⁹-THC: Dose effect

Upper panels, Percentage of total responses made on the drug-appropriate lever. Lower panels, Rate of responding in responses per second (r/s). Figure 2A shows data for ⁹-THC, JWH-018, JWH-073, and JWH-200. Figure 2B shows data for JWH-203, JWH-250, AM-2201 and CP 47,497-C8-homolog. All of the cannabinoids fully substituted for the discriminative stimulus effects of ⁹-THC (>80% drug-appropriate responding). ⁹-THC n=13 rats; JWH-073 n=7 rats; otherwise n=6 except where shown. * indicates rate different ($p < 0.05$) from vehicle control.

Figure 3. Time course of the discriminative stimulus effects of synthetic cannabinoids
 Percentage of total responses made on the drug-appropriate lever as a function of time. Each panel shows the effects of the peak dose of compound. JWH-073 n=8, AM-2201 n=8, CP 47,497-C8-homolog n=9; otherwise n=6 except where shown.

Table 1

ED50 values (mg/kg) for discriminative stimulus effects of cannabinoids in THC-trained rats. Data are mean $\pm$ standard error.

Drug	Drug Discrimination	Locomotor Activity
THC	0.56 $\pm$ 0.07	6.91 $\pm$ 0.15
JWH-018	0.18 $\pm$ 0.12	0.20 $\pm$ 0.13
JWH-073	0.88 $\pm$ 0.18	5.01 $\pm$ 0.12
JWH-200	1.16 $\pm$ 0.14	3.31 $\pm$ 0.10
JWH-203	1.50 $\pm$ 0.14	8.13 $\pm$ 0.16
JWH-250	1.00 $\pm$ 0.15	12.17 $\pm$ 0.16
AM-2201	0.11 $\pm$ 0.17	1.04 $\pm$ 0.08
CP 47,497-C8-homolog	0.83 $\pm$ 0.11	1.13 $\pm$ 0.11