Pharmacology, Biochemistry and Behavior xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Cross-substitution of Δ^9-tetrahydrocannabinol and JWH-018 in drug discrimination in rats

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ARTICLE INFO

Article history:
Received 19 February 2014
Received in revised form 7 May 2014
Accepted 22 May 2014
Available online xxxx

Keywords:
Discriminative stimulus
Indole cannabinoids
JWH-018
JWH-073
JWH-210
Synthetic cannabinoids
Δ^9-tetrahydrocannabinol

ABSTRACT

Synthetic indole-derived cannabinoids, originally developed to probe cannabinoid CB_1 and CB_2 receptors, have become widely abused for their marijuana-like intoxicating properties. The present study examined the effects of indole-derived cannabinoids in rats trained to discriminate Δ^9-tetrahydrocannabinol (Δ^9-THC) from vehicle. In addition, the effects of Δ^9-THC in rats trained to discriminate JWH-018 from vehicle were assessed. Adult male Sprague–Dawley rats were trained to discriminate 3 mg/kg Δ^9-THC or 0.3 mg/kg JWH-018 from vehicle. JWH-018, JWH-073, and JWH-210 fully substituted in Δ^9-THC-trained rats and Δ^9-THC substituted in JWH-018-trained rats. In contrast, JWH-320, an indole-derived cannabinoid without affinity for CB_1 receptors, failed to substitute for Δ^9-THC. Pre-treatment with 1 mg/kg rimonabant significantly reduced responding on the JWH-018-associated lever in JWH-018-trained rats. These results support the conclusion that the interoceptive effects of Δ^9-THC and synthetic indole-derived cannabinoids show a large degree of overlap, which is predictive of their use for their marijuana-like intoxicating properties. Characterization of the extent of pharmacological differences among structural classes of cannabinoids, and determination of their mechanisms remain important goals.

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1. Introduction

Synthetic indole-derived cannabinoids were originally developed as research tools to probe cannabinoid CB_1 and CB_2 receptors (Aung et al., 2000; Huffman, 2000; Huffman et al., 1994; Wiley et al., 2011). Over the past decade, however, some of these compounds have been synthesized illicitly, sprayed on plant material, marketed in brightly colored packages labeled "not for human consumption," and, despite this warning, regularly smoked for their marijuana-like intoxicating properties (Vardakou et al., 2010). Abuse of synthetic indole-derived cannabinoids has rapidly increased to the point of becoming a substantial international social and public health issue, which continues to be fueled by the steady influx of new compounds available for online purchase as the "old" compounds are banned (Tofighi and Lee, 2012; Uchiyama et al., 2013; Winstock and Barratt, 2013). Because initial structure–activity relationship studies focused primarily on binding data (reviewed in Huffman, 1999; Huffman and Padgett, 2005; Manera et al., 2008), the preclinical in vivo pharmacology of most synthetic indole-derived cannabinoids remained poorly characterized, although there are a few early studies including in vivo pharmacology (Wiley et al., 1995a, 1998).

As abuse of indole-derived synthetic cannabinoids has become more widespread, additional studies examining their in vivo effects have appeared in the scientific literature (Brents et al., 2013; Seely et al., 2012; Wiebelhaus et al., 2012; Wiley et al., 2012). Several studies have utilized Δ^9-tetrahydrocannabinol (Δ^9-THC) discrimination, a pharmacologically selective animal model of marijuana intoxication (Balster and Prescott, 1992), as a way to evaluate the abuse liability of these compounds. In rats, the prototypic bicyclic and aminoalkylindole synthetic cannabinoids, CP55,940 and WIN55,212-2, respectively, dose-dependently substitute and cross-substitute for Δ^9-THC (Compton et al., 1992; Gold et al., 1992; Perio et al., 1996; Wiley et al., 1995b). Compounds with alkyl group (butyl to hexyl) substitution for the morpholinoethyl group of WIN55,212-2 also dose-dependently substituted in CP55,940-trained rats at potencies consistent with their CB_1 affinity, whereas the heptyl compound did not substitute, nor did it bind to CB_1 receptors (Wiley et al., 1998). Later studies showed that indole-derived cannabinoids JWH-018, JWH-073, AM-2233, and AM-5983 also substituted for Δ^9-THC in rats and/or rhesus monkeys (Brents et al., 2013; Ginsburg et al., 2012; Järbe et al., 2010, 2011; Marusich et al., 2013), with rimonabant reversal suggesting CB_1 mediation of their Δ^9-THC-like effects (Ginsburg et al., 2012; Järbe et al., 2011). In Δ^9-THC-trained mice, two phenylacetylindoles (JWH-204 and JWH-205) and two tetramethylcyclopropyl ketone indoles (UR-144 and XLR-11) with high affinity ($K_i < 30$ nM) for the CB_1 receptor substituted, whereas another phenylacetylindole (JWH-202) with low affinity ($K_i > 1500$ nM) did not (Vann et al., 2009; Wiley et al., 2013). In the present study, rats were trained to discriminate Δ^9-THC from vehicle. Subsequently, JWH-018, JWH-073, JWH-210, and JWH-320 were

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http://dx.doi.org/10.1016/j.pbb.2014.05.016
0091-3057/© 2014 Published by Elsevier Inc.

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evaluated (see Fig. 1 for chemical structures). JWH-018 was chosen as a test compound because it was the first synthetic cannabinoid to be identified in a confiscated product (hence, it is considered to be the prototypic abused indole-derived cannabinoid). For this reason, it was also chosen as the training drug for a separate discrimination described in more detail below. JWH-073 is structurally similar to JWH-018 and was also a compound found in early abused products. JWH-210 was chosen as a test compound because of the presence of a manipulation in the naphthoyl component of the template JWH-018 structure (see Fig. 1). While compounds with substitution of the complete naphthoyl component have been assessed in drug discrimination (e.g., tetramethylcyclopropyl ketones and phenylacetylindoles), compounds with methyl additions to the naphthoyl have not been tested in this procedure, although they have appeared in confiscated products. JWH-320 was tested as a negative control for the procedure. Although it is structurally similar to other indoles that have been abused, it does not bind to the CB_1 receptor. In addition, a novel discrimination (JWH-018) was trained in a separate group of rats. Following demonstration of acquisition of the JWH-018 discrimination and training drug dose–effect curve, cross-substitution tests with Δ^9-THC were undertaken to determine the overlap of traditional and synthetic cannabinoids, and CB_1 receptor mediation was evaluated by assessment of antagonism of JWH-018's discriminative stimulus effects by the CB_1 receptor antagonist/inverse agonist, rimonabant.

2. Materials and methods

2.1. Subjects

Adult male drug naïve and experimentally naïve Sprague–Dawley rats (total n = 16) (Harlan Laboratories, Dublin, VA, USA) were individually housed upon arrival in polycarbonate cages with hardwood bedding in a temperature-controlled (20–22 °C) environment with a 12 h light–dark cycle (lights on at 6 am). Rats were maintained at 85–90% of free-feeding body weights by restricting their daily ration of rodent chow (Purina® Certified 5002 Rodent Chow, Barnes Supply, Durham, NC, USA). Water was available ad libitum in their home cages. All experiments were carried out in accordance with guidelines published in the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011), and were approved by the Institutional Animal Care and Use Committee at RTI. All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternatives to in vivo techniques, if available.

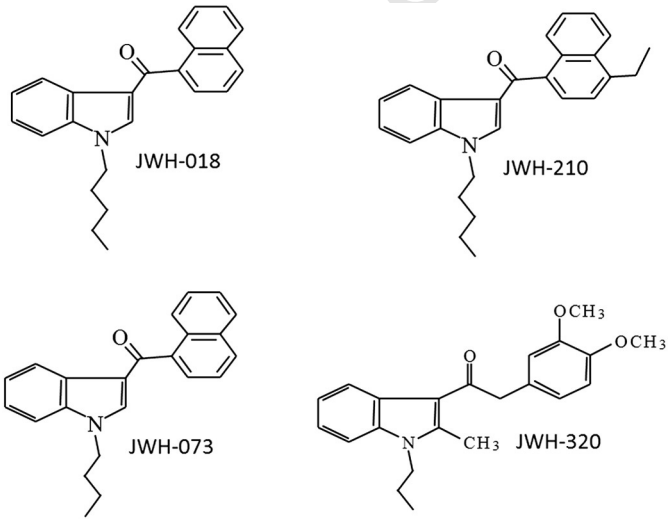

Fig. 1. Chemical structures of JWH-018, JWH-073, JWH-210, and JWH-320.

2.2. Apparatus

Standard rat operant chambers (Habitest Modular System, Coulbourn Instruments, Whitehall, PA, USA) were enclosed in light- and sound-attenuating isolation cubicles equipped with exhaust fans. Each operant chamber contained a house light near the ceiling, 2 retractable levers, a stimulus light panel above each lever, and a food cup with a light located between the levers. A pellet dispenser, located outside of the chamber, delivered 45 mg pellets (Bioserv Inc., Frenchtown, NJ, USA) into the food cup accompanied by illumination of the food cup light. During sessions, ~80 dB of white noise was delivered via a speaker located inside the isolation cubicle. Illumination of lights, delivery of food pellets, and recording of lever presses were controlled by a computer-based system (Coulbourn Instruments, Graphic State Software, v 3.03).

2.3. Procedure

Rats were randomly assigned to two groups (n = 8/group), and were trained to press one lever following administration of a cannabinoid (3 mg/kg Δ^9-THC or 0.3 mg/kg JWH-018, respectively) and to press another lever after injection with vehicle (7.8% Polysorbate 80 and 92.2% sterile saline). On the first training session rats were exposed to the operant chamber for 60 min during which a pellet was dispensed after an average of 60 s. On days 2 and 3 rats were exposed to a 60 min session during which one lever was extended for the duration of the session with the stimulus light above that lever illuminated, and lever presses were reinforced on a fixed ratio 1 (FR 1) schedule of food reinforcement. The opposite lever was extended on the second day of lever training. The fixed ratio requirement was gradually increased from FR 1 to FR 10 across the next 22 sessions which were 15 min in duration. The side of the chamber with the active lever alternated daily. Prior to sessions 26–37 injections of either vehicle or drug (3.0 mg/kg Δ^9-THC or 0.3 mg/kg JWH-018) were administered, and only the appropriate lever was extended. Rats were then assigned a drug lever and vehicle lever for the remainder of the study (i.e., vehicle = left, drug = right). Responding on the assigned lever after the appropriate injection resulted in reinforcement.

Baseline sessions then began with lever pressing on the correct lever reinforced on an FR 10, and each response on the incorrect lever reset the response requirement on the correct lever. The position of the drug lever was counterbalanced among the group of rats. The daily injections for each rat were administered in a double alternation sequence of training drug and vehicle (e.g., drug, drug, vehicle, vehicle). Rats were injected and returned to their home cages until the start of the experimental session. Training occurred during 15-min sessions conducted five days a week (Monday–Friday) until the rats had met three criteria during eight of ten consecutive sessions: (1) the first completed FR-10 was on the correct lever; (2) the percentage of correct-lever responding was ≥80% for the entire session; and (3) the response rate was ≥0.2 responses/s.

Following successful acquisition of the discrimination, stimulus substitution tests with test compounds were typically conducted on Tuesdays and Fridays during 15-min test sessions. Training continued on Mondays, Wednesdays, and Thursdays. During test sessions, responses on either lever delivered reinforcement according to a FR-10 schedule. In order to be tested, rats must have completed the first FR on the injection-appropriate lever, made at least 80% of all responses on the injection-appropriate lever, and had a response rate of ≥0.2 responses/s during the preceding day's training session.

A dose–effect determination with the training drug (Δ^9-THC or JWH-018) was performed first in each rat. Subsequently, the Δ^9-THC-trained group was tested with JWH-018, JWH-210, JWH-073, and JWH-320. One test session for each dose of each drug was conducted. Doses of each compound were administered in ascending order. After completion of the dose–effect curve with the training drug, the JWH-

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Please cite this article as: Wiley JL, et al, Cross-substitution of Δ^9-tetrahydrocannabinol and JWH-018 in drug discrimination in rats, Pharmacol Biochem Behav (2014), http://dx.doi.org/10.1016/j.pbb.2014.05.016

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