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Cannabinoids in disguise: Δ^9-Tetrahydrocannabinol-like effects of tetramethylcyclopropyl ketone indoles

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ABSTRACT

Synthetic indole-derived cannabinoids have become commonly used recreational drugs and continue to be abused despite their adverse consequences. As compounds that were identified early in the epidemic (e.g., naphthoylindoles) have become legally banned, new compounds have appeared on the drug market. Two tetramethylcyclopropyl ketone indoles, UR-144 [(1-pentyl-1H-indol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone] and XLR-11 [(1-(5-fluoropentyl)-1H-indol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone], recently have been identified in confiscated products. These compounds are structurally related to a series of CB_2-selective compounds explored by Abbott Labs. The purpose of the present study was to evaluate the extent to which UR-144 and XLR-11 shared cannabinoid effects with Δ^9-tetrahydrocannabinol (Δ^9-THC). Indices of in vitro and in vivo activity at cannabinoid receptors were assessed. Similar to other psychoactive cannabinoid agonists, XLR-11 and UR-144 showed low nanomolar (<30) affinity for CB_1 and CB_2 receptors, activated these receptors as full agonists, and produced dose-dependent effects that were blocked by rimonabant in mice, including antinociception, hypothermia, catalepsy and suppression of locomotor activity. The potency of both compounds was several-fold greater than Δ^9-THC. XLR-11 and UR-144 also substituted for Δ^9-THC in a Δ^9-THC discrimination procedure in mice, effects that were attenuated by rimonabant. Analysis of urine from mice treated with the compounds revealed that both were extensively metabolized, with predominant urinary excretion as glucuronide conjugates. Together, these results demonstrate that UR-144 and XLR-11 share a pharmacological profile of in vitro and in vivo effects with Δ^9-THC and other abused indole-derived cannabinoids and would be predicted to produce Δ^9-THC-like subjective effects in humans.

1. Introduction

Originally developed for research purposes, synthetic cannabinoids began to appear as drugs of abuse in Europe and the U.S. during the mid-2000s (EMCDDA, 2009). These chemicals are synthesized in clandestine labs, sprayed on dried plant material, and packaged in foil packets with product names such as “Spice,” “K2,” “herbal incense,” or “Scooby Snax.” Usually labeled “not for human consumption,” the products are nevertheless typically smoked in order to achieve a marijuana-like intoxication, although most of the synthetic cannabinoids that have been identified from product samples are structurally distinct from the tetrahydrocannabinols contained in marijuana (Cox et al., 2012; Denooz et al., 2013; Logan et al., 2012). Further, anecdotal evidence suggest that they may be more toxic, with tachycardia, anxiety and psychoses sometimes reported (Forrester et al., 2012; Gunderson et al., 2012), as well as recently reported cases of acute kidney failure (Bhanushali et al., 2013; Center for Disease Control and Prevention, 2013). Usage also seems to have increased dramatically over the last few years. For example, in 2010, the number of calls to the American Association of Poison Control Centers regarding synthetic cannabinoids totaled 2906, with calls coming from 48 different states (Wells and Ott, 2011). This number increased to 6968 and 5202 calls in 2011 and 2012, respectively (American Association of Poison Control Centers, 2013). In comparison, approximately four times fewer calls were made to Texas Poison Control centers concerning marijuana versus synthetic cannabinoids in 2010 (Forrester et al., 2012).

To date, the most prevalent synthetic cannabinoids identified in herbal incense products can be classified into seven structural groups: naphthoylindoles (e.g., JWH-018, JWH-073, JWH-081, AM-2201), naphthylmethylindoles (JWH-185, JWH-199), naphthoylpyrroles (JWH-369, JWH-370), naphthylmethylindenes (JWH-176), phenylacetylindoles (JWH-250, RCS-4), cyclohexylphenols

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(CP47,497), and tetrahydrocannabinols (HU-210) (EMCDDA, 2009). Initials generally refer to the lab in which the chemical was originally synthesized: JWH (John W. Huffman, Clemson University, Clemson, SC; Huffman et al., 1994), AM (Alexandros Makriyannis, Northeastern University, Boston, MA; Järbe et al., 2011), CP (Pfizer, Inc., Groton, CT; Little et al., 1988), HU (Hebrew University, Jerusalem, Israel; Mechoulam et al., 1988), and RCS (unconfirmed derivation; Kavanagh et al., 2012). With the exception of novel compounds that were synthesized outside of the auspices of recognized research laboratories (e.g., RCS compounds), binding affinities for CB_1 (brain) and CB_2 (peripheral) cannabinoid receptors have been published for most compounds in all categories (Manera et al., 2008); however, extant in vivo research on synthetic cannabinoids of abuse is relatively sparse, with the majority of work on naphthoylindoles (Ginsburg et al., 2012; Hruba et al., 2012; Järbe et al., 2011; Wiebelhaus et al., 2012; Wiley et al., 1998). The results of this limited research suggest that the potency of a synthetic cannabinoid for producing cannabimimetic effects is related to its affinity for the CB_1 receptor (Wiley et al., 2012a; Wiley et al., 1998), although there are exceptions (e.g., JWH-415; Wiley et al., 2012b). In compounds with a naphthoyl substituent (e.g., JWH-018; Fig. 1), tolerance for structural diversity of the non-naphthoyl substituent has been observed, with low nanomolar (<100) CB_1 affinity and cannabimimetic activity in mice having been reported for compounds with indole, pyrrole and indene substituents (Huffman and Padgett, 2005; Wiley et al., 1998). Indole-derived cannabinoids with substitutions for the prototypic naphthoyl have been less explored (although see research on phenylacetylindoles: Wiley et al., 2012a); however, increased legal restriction has resulted in exploitation of new structural motifs from the scientific literature or *de novo* inventions. For example, XLR-11, one of the newest synthetic cannabinoids identified in products (Uchiyama et al., 2013), appears to have been developed solely for recreational use. It is a derivative of a series of 3-(tetramethylcyclopropylmethanoyl) indole compounds, which includes UR-144 (another compound identified in products; Kavanagh et al., 2013; Uchiyama et al., 2013), A-796,260, and A-834,735, but it is not listed in the scientific or patent literature along with these related compounds (Frost et al., 2010, 2008). UR-144 and XLR-11 were recently placed in Schedule I of the Controlled Substance Act (Drug Enforcement Administration, 2013). As more compounds are banned, manufacturers must find alternative compounds in an attempt to provide products that are still legal, resulting in myriad of unusual chemicals that have never been evaluated scientifically (Shanks et al., 2012; Uchiyama et al., 2013).

The purpose of the present study was to examine the in vitro and in vivo pharmacology of UR-144 and XLR-11, two 3-tetramethylcyclopropyl ketone indole-derived cannabinoids (Fig. 1) that have been identified with increasing frequency in recently confiscated products (Terrence Boos, U.S. Drug Enforcement Agency, personal communication). Emphasis was placed on assessment in assays that have been used to predict the abuse liability of cannabinoids, including binding and activation of CB_1 receptors, pharmacological equivalence with Δ^9-tetrahydrocannabinol (Δ^9-THC) in a battery of tests in mice, and Δ^9-THC drug discrimination. In addition, preliminary analysis of urinary metabolites was undertaken to aid in development of forensic markers and assessment of metabolic transformations, chemical exposures, biochemical responses, and their sequelae.

2. Methods

2.1. Subjects

Male ICR mice (25–32 g), obtained from Harlan Laboratories (Indianapolis, IN) and housed singly in polycarbonate mouse cages, were used for assessment of locomotor suppression, antinociception, hypothermia, and catalepsy. These mice had free access to food when in their home cages. Separate mice were used for testing each dose of each compound (Δ^9-THC, XLR-11, and UR-144) in this battery of procedures. Some of these mice were later re-used to evaluate rimonabant antagonism of the cannabimimetic effects of the compounds in the tetrad. Singly housed male C57/Bl6J inbred mice (20–25 g) [Jackson Laboratories, Bar Harbor, ME] were used in the drug discrimination experiments. These mice were maintained at 85–90% of free-feeding body weights by restricting daily ration of standard rodent chow. At the start of this investigation, these mice had already been trained to discriminate Δ^9-THC from vehicle and had been tested with other cannabinoid compounds as part of another (unpublished) study. All animals were maintained in a temperature-controlled (20–22 °C) environment with a 12-h light–dark cycle (lights on at 6 a.m.) and received water ad libitum. The in vivo studies reported in this manuscript

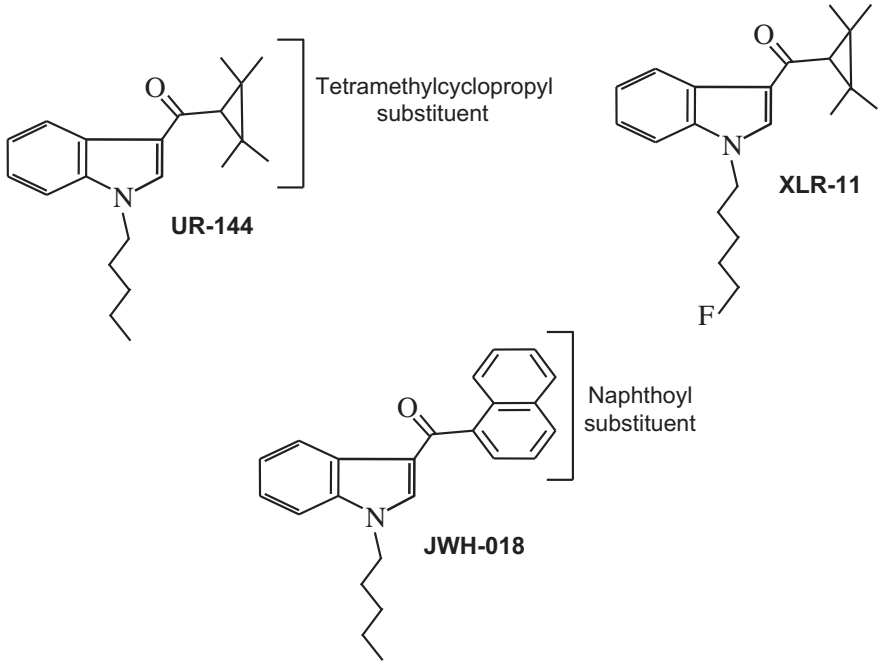

Fig. 1. Chemical structures of UR-144, XLR-11, and JWH-018.