WHO Expert Committee on Drug Dependence Pre-Review

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Isomers of THC

Section 2: Pharmacology

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

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Contents

1. General Pharmacology

Tetrahydrocannabinol (THC) isomers included in the pharmacology pre-review are listed below, along with their more common names in bold type. For ease of presentation, the common name specified below has been used in each pharmacology section.

- 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol **[$\Delta^{6a(10a)}$-THC]**
- (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol **[$\Delta^{6a(7)}$-THC]**
- (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol **[Δ^{7}-THC]**
- (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol **[Δ^{8}-THC]**
- 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol **[Δ^{10}-THC]**
- (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol **[$\Delta^{9(11)}$-THC]**

1.1 Routes of administration and dosage

While several isomers were administered to humans in the context of early experimental studies on cannabis and its constituents, none of the six of the THC isomers are regularly administered to humans currently. However, tetrahydrocannabinol isomers are lipophilic and would be expected to be readily absorbed and distributed to the brain and other organs following many routes of administration, including intraperitoneal (i.p.), oral (p.o.), intramuscular (i.m.), intravenous (i.v.), and inhalation. The limited direct information available on THC isomers suggests that Δ^{8}-THC, $\Delta^{9(11)}$-THC, and $\Delta^{6a(10a)}$-THC are absorbed and distributed to the brain after systemic administration, as indicated by their ability to induce cannabimimetic behavioral effects. Based upon the extant research, Δ^{8}-THC and $\Delta^{9(11)}$-THC each produced overt Δ^{9}-THC-like pharmacological effects following i.v. administration (mice),[1] i.m. injection (rhesus monkeys),[2, 3] and i.p. injection (rats)[2, 4] whereas Δ^{10}-THC (i.m.) did not produce cannabimimetic effects (pigeons).[5] In humans, Δ^{8}-THC was active orally, following i.v. injection,[6] and when inhaled via smoking.[7] $\Delta^{6a(10a)}$-THC also produced Δ^{9}-THC-like effects when smoked.[8] None of the other isomers have been tested in humans. Additional details of the study designs and endpoints are provided in Section 8 of this pre-review.

1.2 Pharmacokinetics

Data on the specific pharmacokinetic profile of the six listed isomers are sparse (except Δ^8-THC metabolism); however, the core tetrahydrocannabinol structure present in these isomers suggests common biotransformational processes. Initial metabolism of the tetrahydrocannabinols following parenteral injection or oral administration occurs primarily in the liver and is catalyzed by cytochrome P-450 (CYP) enzymes.[9] Tetrahydrocannabinols are extensively metabolized, resulting in numerous metabolites.[9] Because the profile of these enzymes varies across species and among individuals, variations in the ratio of these metabolites have been noted.[10]

The isomer that has received the greatest amount of research attention is Δ^8-THC. Hydroxylation of the C-11 site to form 11-hydroxy-Δ^8-tetrahydrocannabinol (11-OH-Δ^8-THC) is the initial step of biotransformation of Δ^8-THC in most species, including humans.[10, 11] This major metabolite is psychoactive and exhibits stereoselectivity resembling that of the parent compound: whereas (-)-11-OH-Δ^8-THC (i.m.) fully substitutes for Δ^9-THC in pigeons trained to discriminate Δ^9-THC from vehicle, (+)-11-OH-Δ^8-THC failed to do so.[12] In an earlier human study, 11-OH-Δ^8-THC (i.v.) was also reported to produce psychological and physiological effects resembling those of Δ^9-THC in a small sample of men.[7] Although hydroxylation of Δ^8-THC at C-11 to form 11-OH-Δ^8-THC is most common, hydroxylation may also occur at C-7, resulting in formation of 7α-OH-THC and 7β-OH-THC in rodents[10] and 7β-OH-THC in human hepatic microsomes.[13] The primary CYP isoenzymes that catalyze the hydroxylation reaction are CYP2C9 and CYP3A4.[13] A secondary metabolite, 11-nor-9-carboxy-Δ^8-tetrahydrocannabinol (11-COOH-Δ^8-THC or Δ^8-THC-COOH), is formed through oxidation of 11-OH-Δ^8-THC.[14] Δ^8-THC-COOH lacks cannabimimetic effect in mice.[14]

Specific data are also available on a second isomer, $\Delta^{9(11)}$-THC. Because of its double bond at the C-11 site, $\Delta^{9(11)}$-THC has a more diverse profile of metabolites than Δ^9- and Δ^8-THC.[10] In rats and mice, initial metabolites with the largest relative concentrations are 8α-OH-THC, 8β-OH-THC, and 11-dihydroxy-hexahydrocannabinol.[10]

1.3 Pharmacodynamics

Exogenously administered cannabinoids produce their characteristic effects through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions.[15] Within this endocannabinoid system, two cannabinoid receptors, CB_1 and CB_2, have been identified.[16, 17] While CB_1 receptors are widespread and abundant in the brain and periphery, CB_2 receptors are confined primarily to the periphery,[18] although recent evidence

suggests that CB_2 receptors may be present in the brain under certain conditions.[19] Psychoactive cannabinoids bind to and activate CB_1 receptors in the brain in a manner resembling activation by their endogenous ligands (e.g., anandamide and 2-arachidonoylglycerol). For example, research has shown that the discriminative stimulus effects of Δ^9-THC in animals were reversed by pre-injection with rimonabant, a selective CB_1 receptor antagonist, but not by injection with SR144528, selective CB_2 receptor antagonist.[20] Antagonists of other major neurotransmitter systems (e.g., dopamine, acetylcholine, norepinephrine, mu opioid) also did not alter the discriminative stimulus effects of Δ^9-THC in rats.[21] In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64% Δ^9-THC,[22] suggesting that the antagonism results from preclinical Δ^9-THC discrimination experiments are translational.

Most studies with the six listed isomers were completed in animals and humans prior to 1990 (see Section 8 of this report). Discovery of the endocannabinoid system did not occur until 1992[23] and synthesis of the first selective CB_1 receptor antagonist (SR141716A, rimonabant) was not reported until 1994.[24] Hence, effective tools for determination of the most probable mechanism underlying any abuse- or dependence-related pharmacological effects of the six listed THC isomers were not available until after publication of the studies in which these effects were reported. Non-cannabinoid mechanisms have not been explored.

2. Dependence Potential

2.1 Animal Studies

None of the THC isomers have been assessed for dependence potential in animals.

2.2 Human Studies

None of the THC isomers have been assessed for dependence potential in humans.

3. Abuse Potential

3.1 Animal Studies

Only a limited number of studies have reported successful acquisition of cannabinoid i.v. self-administration in rats, with WIN55,212-2 (a synthetic aminoalkylindole cannabinoid) being the predominant training drug.[25-27] To date, successful acquisition of reliable i.v. Δ^9-THC self-administration has been reported in squirrel monkeys only in a single lab.[28, 29] None of the six THC isomers were evaluated in this model. Hence, preclinical assessment of abuse liability of these isomers has concentrated on determination of their pharmacological similarity to Δ^9-THC, particularly substitution for Δ^9-THC in animals trained to discriminate this drug from vehicle.

Of the six THC isomers reviewed here, three have been tested for substitution in Δ^9-THC-trained animals. $\Delta^{9(11)}$-THC produced full dose-dependent substitution for Δ^9-THC in male rats trained to discriminate 3 mg/kg Δ^9-THC (i.p.) from vehicle, with approximately 3-fold less potency than Δ^9-THC (ED_{50} = 3.2 mg/kg i.p. for $\Delta^{9(11)}$-THC vs. 1 mg/kg i.p. for Δ^9-THC).[2] Similar results were reported with $\Delta^{9(11)}$-THC when it was tested earlier in a Δ^9-THC discrimination procedure using a water maze apparatus.[30] $\Delta^{9(11)}$-THC (i.m.) also fully substituted with less potency than Δ^9-THC in male rhesus monkeys trained in Δ^9-THC discrimination,[2] albeit it was less efficacious in this species at producing typical high dose cannabinoid effects such as ptosis, sedation and ataxia.[31] In contrast, an earlier study reported that $\Delta^{9(11)}$-THC did not substitute for Δ^9-THC in rats up to a dose of 30 mg/kg.[1] In male mice, $\Delta^{9(11)}$-THC (i.v.) effected a tetrad of characteristic Δ^9-THC-like effects, including suppression of locomotor activity, hypothermia, antinociception, and ring immobility.[1, 31] Again, in this species, it was several-fold less potent than Δ^9-THC for each dependent measure.

A second isomer that has been tested in Δ^9-THC discrimination is Δ^8-THC. In male mice, Δ^8-THC (i.v.) showed pharmacological similarity to Δ^9-THC by inducing the characteristic tetrad of cannabinoid effects.[1] Δ^8-THC also produced full substitution for Δ^9-THC in male rats (i.p.)[4, 30] and rhesus monkeys (i.m.)[3] trained to discriminate Δ^9-THC from vehicle. In rats, Δ^8-THC was trained as a discriminative stimulus in a t-maze discrimination procedure where it and Δ^9-THC cross-substituted with each other.[4, 32] In all studies cited above, Δ^8-THC showed less potency than Δ^9-THC. Further, the Δ^9-THC-like discriminative stimulus effects of Δ^8-THC were stereoselective, as (+)Δ^8-THC (i.p.) failed to substitute for Δ^9-THC in male rats.[33]

In contrast with Δ^8-THC and $\Delta^{9(11)}$-THC, Δ^{10}-THC (i.m.) failed to substitute for Δ^9-THC in male pigeons.[5] Reports of evaluation of the other 3 isomers ($\Delta^{6a(10a)}$-THC, Δ^7-THC, and $\Delta^{6a(7)}$-THC) in drug discrimination assays were not found, although the 1R and 1S stereoisomers of an acetate analog of $\Delta^{6a(10a)}$-THC (i.m.) fully

and dose-dependently substituted for Δ^9-THC in pigeons with less potency than Δ^9-THC.[5] While Mechoulam et al.[34] reported that Δ^7-THC is inactive in animals, a later study showed that its C-9 epimers are stereoselective with the quasi-axial methyl epimer acting as a weakly active cannabinoid in the tetrad tests in mice and the quasi-equatorial methyl epimer showing only slightly diminished activity in these tests as compared with Δ^9-THC.[35]

3.2 Human Studies

Systematic investigation of THC isomers in humans has not been undertaken. The scant available knowledge of the abuse potential of THC isomers rests primarily on early observational studies in which their subjective or physiological effects in human volunteers were compared to those reported following Δ^9-THC administration. Of the six THC isomers included in this pre-review, Δ^8-THC and $\Delta^{6a(10a)}$-THC have been assessed in humans. Both isomers produced similar subjective effects in humans when administered orally, i.v., and/or when smoked.[6-8, 36]

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