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Structure-Activity Relationships in Man of Cannabis Constituents, and Homologs and Metabolites of Δ^9-Tetrahydrocannabinol[1]

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Abstract. Clinical studies of a variety of cannabis constituents and THC isomers, homologs and metabolites have elucidated some structure-activity relationships. The fundamental structure of THC is required for pharmacological activity, but potency may be altered greatly among different double-bond isomers, by changing length of side-chain or by metabolic hydroxylations. No material has been found in nature, either in cannabis itself or in the metabolites of THC, which differs qualitatively from THC.

Key Words
Cannabis
Clinical pharmacology
Structure-activity relationships
Tetrahydrocannabinol

The more one studies cannabis chemically, the more complicated it becomes. At present one might estimate that at least 50 compounds with potential pharmacological activity have been isolated from various strains of the plant. Similar complexity is beginning to develop in regard to metabolites of Δ^9-tetrahydrocannabinol (THC), presumed to be the major active material of cannabis. Several metabolites have now been positively identified and many others remain to be.

As both cannabis and THC have a biphasic clinical effect, with initial stimulation and elation followed by sleepiness and tranquility, it has been suggested that this course may be dependent upon the formation of successive metabolites with pharmacological actions differing from the parent compound. A great deal of the lore of cannabis use is that different types produce different clinical effects. Thus, it seemed worthwhile to study various constituents of marihuana and homologs or metabolites of THC to determine their differences in activity both qualitatively and quantitatively. This paper will summarize our studies to date.

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Experimental Studies

Δ^9-THC Compared with Synhexyl (Pyrahexal)

It had long been suspected that THC was the major active component of cannabis, based largely on animal studies (*Adams*, 1942; *Loewe*, 1946). The structure of THC then thought to occur in cannabis was what would now be known as Δ^{6a}-THC (fig. 1). Further chemical studies during the past 10 years have definitely established that the structure of THC is the levo-Δ^9-*trans* double-bond isomer (*Gaoni and Mechoulam*, 1964; *Mechoulam*, 1970).

This material was synthesized and became available for clinical testing in 1967. It proved to be highly active, with oral doses of 10–30 mg in man producing strong clinical effects identical to those of cannabis, either as marihuana or hashish (*Isbell et al.*, 1967). When we obtained the same chemical from a different source in 1968, we decided to explore a somewhat higher range of doses (30–70 mg orally) and to compare it with synhexyl. The latter compound, essentially Δ^{6a}-THC with a hexyl rather than an amyl side-chain (fig. 1) had been extensively used clinically in the late 1940s and early 1950s (*Himmelsbach*, 1944; *Parker and Wrigley*, 1950; *Thompson and Proctor*, 1953). We were able to describe extensively the clinical syndromes from these two compounds, including their time course, as well as some physiological, psychological and biochemical effects. Both THC isomers produced clinical syndromes identical to what had been described from eating hashish but an estimated potency ratio of 3:1 for Δ^9-THC over synhexyl. Another major difference was that synhexyl was

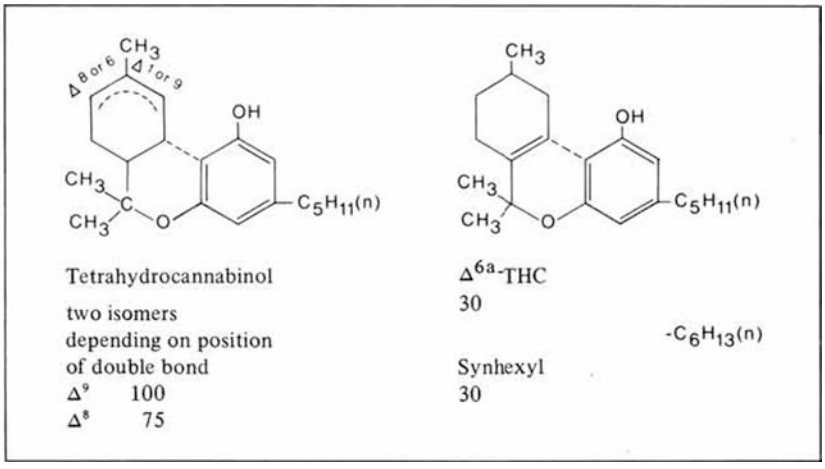

Fig. 1. Double-bond isomers and side-chain homolog of tetrahydrocannabinol. Relative potencies from clinical testing shown by figures (Δ^9-THC based at 100).

slower in onset and of longer duration than THC, suggesting slower metabolism. This study indicated that the position of the double-bond in the unsaturated alicyclic ring and/or the length of the aliphatic side-chain might alter the potency of the compound but would not markedly alter its pharmacological actions (*Hollister et al.*, 1968).

Δ^9-THC, Δ^{6a}-THC and Synhexyl Compared by Smoking

We were able to pursue the matter further when we were able to obtain some Δ^{6a}-THC, the material which for many years had been considered the active component of cannabis. Because only small quantities were available, we decided to test the material when smoked after addition to a tobacco cigarette. Although the smoking of even a regular cigarette in the manner used by marihuana smokers was adequate to produce a transient high, the effects from the three cigarettes containing the active materials were distinctly different. All showed clear resemblance to the effects obtained from marihuana, the Δ^9-THC smoke being considered to be three to six times as potent as the other two (*Hollister,* 1970). A previous study of smoked Δ^{6a}-THC, using doses almost twice as large as we had used, failed to reveal activity for this compound (*Isbell et al.*, 1967). The source of our material was different, which might have accounted for the different results. In any case, it was somewhat reassuring that the material so long considered to be the active component of hashish was indeed active. From this study, it appeared that the position of the double-bond in ring structures resembling Δ^9-THC was more important in determining potency than was a minor lengthening of the side-chain.

Activity of Cannabinol and Cannabidiol

Besides Δ^9-THC, the two most abundant cannabinoids in cannabis are cannabidiol (CBD) and cannabinol (CBN) (fig. 2). Both these materials, as well as cannabichromene, cannabigerol and cannabicyclol, were found to be inactive in monkeys and did not alter the response of these animals to doses of Δ^9-THC given concurrently (*Mechoulam et al.*, 1970). CBN in doses up to 180 mg/kg had no effect on key-pecking of pigeons trained in an operant schedule (*Frankenheim et al.*, 1971). Although earlier studies had suggested possible activity for these compounds, their activity in man had not been tested. It seemed worth doing, if for no other reason than to verify the predictability of animal testing.

We gave oral doses of each compound beginning with a 20 mg dose of Δ^9-THC that shows definite but moderate effects in man. Doses were raised progressively until at least one subject received a maximum dose of 400 mg of CBN and another, 100 mg of CBD. The latter compound was given intravenously as well, doses ranging from 5 mg (usually a very potent i.v. dose of Δ^9-THC) to 30 mg. All doses were without any discernible effects. At the largest oral doses given, it was possible to demonstrate that both CBN and CBD were excreted

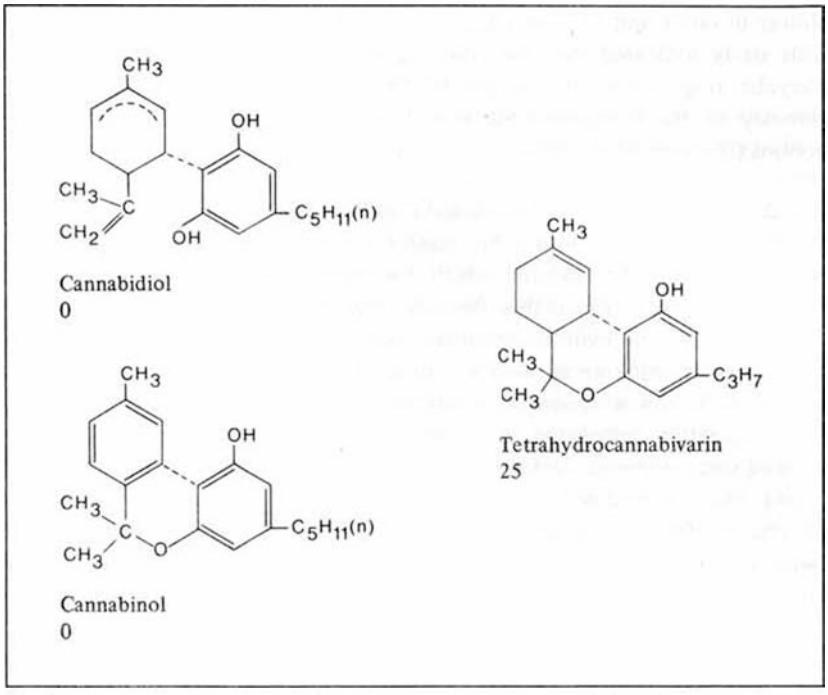

Fig. 2. Various marihuana constituents; only tetrahydrocannabivarin has fundamental THC structure. Same relative potencies as in figure 1.

partially unchanged in urine (*Hollister*, 1973). Thus, the old idea that these cannabinoids lacked pharmacological activity was confirmed in man. The question of whether or not they can interact with Δ^9-THC is still unresolved.

Δ^9-THC and Δ^8-THC

Δ^8-THC is a minor constituent of most varieties of marihuana (fig. 1). Animal studies have revealed similar pharmacological effects and similar metabolism of the two isomers (*Christensen et al.*, 1971; *Frankenheim et al.*, 1971; *Wall*, 1971). We made a direct comparison of these two isomers in man using oral doses of 20 and 40 mg of Δ^8-THC and 20 mg of Δ^9-THC. The spectrum of clinical effects was similar with both isomers but the Δ^8-THC was considered to be only three-quarters as potent as the Δ^9-THC. A range of doses of Δ^9-THC of 1–6 mg intravenously produced a wide spectrum of cannabis-like effects. The estimated ratio of potency for intravenous doses was exactly the same as for the oral doses (*Hollister and Gillespie*, 1973). This reference describes the technique we have used for intravenous administration of these compounds.

11-Hydroxy-Δ^9-THC and 11-Hydroxy-Δ^8-THC

The 11-hydroxy metabolite of Δ^9-THC has been described by a number of investigators as both a major metabolite and an active one (*Nilsson et al.*, 1970; *Wall et al.*, 1970) Similar identification has been made of an 11-hydroxy metabolite of Δ^8-THC (*Ben-Zvi et al.*, 1970). Preliminary testing of these metabolites in rats, mice and monkeys have revealed that it has actions quite similar to those of the parent compounds. Recently, these same compounds have been studied in man (fig. 3).

We gave 11-hydroxy-Δ^9-THC intravenously to four subjects who received six doses ranging from 3.5 to 5 mg. Each dose produced a profound effect which had its onset within the period of injection of the drug (that is, usually within 2 min) and which rapidly reached a point of peak intensity. Subjects frequently described it as a 'rush'. Pulse rate was markedly increased, conjunctivae were reddened, and other typical chemical effects of THC were observed. Peak effects, which began soon after injection, often lasted 90 min and residual effects were present for a few hours.

In two subjects a direct comparison was made with Δ^9-THC given in the same 5 mg doses intravenously. Although the onset of first signs of drug effect were virtually the same (a matter of great interest in regard to the idea that only the hydroxy compound may be active), the intensity of onset was considerably less. The same was true of the intensity of the total experience, which was rated

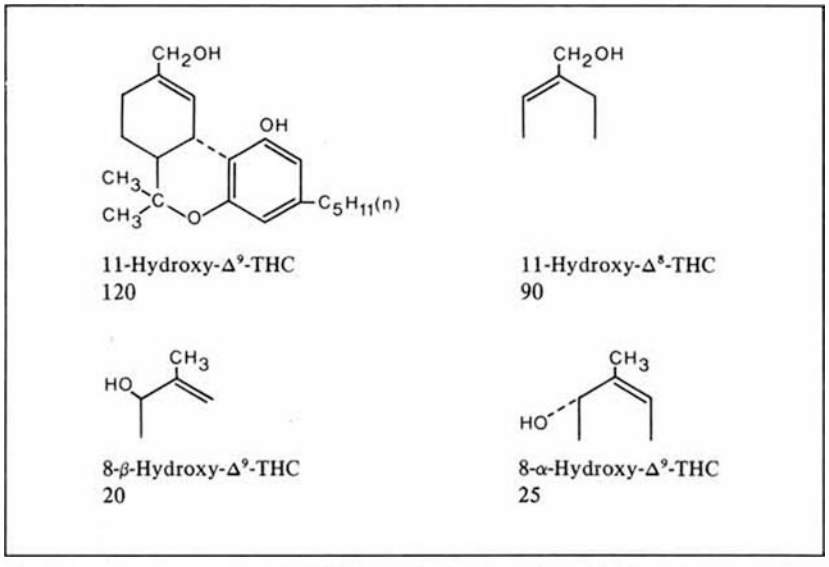

Fig. 3. Various metabolites of THC. Same relative potencies as in figure 1.

as perhaps 20 % less intense than that of the 11-hydroxy metabolite. The duration of effects was also less with the parent compound, but qualitatively the syndrome produced by each was identical.

11-Hydroxy-Δ^8-THC was given intravenously to four subjects who received seven doses ranging from 1 to 8 mg. The 1 mg dose had minimal effect, but a 2 or 3 mg dose produced a moderate effect. Qualitatively, the effects of this metabolite were identical to those of 11-hydroxy-Δ^9-THC, Δ^8-THC or Δ^9-THC. A direct comparison was made in one subject with the same dose of 5 mg of Δ^8-THC. Just as was the case with Δ^9-THC, the 11-hydroxy metabolite had no faster onset of action, but it reached a peak much faster and was generally somewhat more severe and longer in duration.

From these studies, we concluded that the 11-hydroxy metabolites were about 20 % more potent than their parent compounds and that between them the same ratio of potency held as for their parent compounds, that is, 11-hydroxy-Δ^8-THC was about three-quarters as potent as 11-hydroxy-Δ^9-THC.

These results are somewhat different from those reported by others for Δ^9-THC and its 11-hydroxy metabolite (*Perez-Reyes et al.*, 1972). They found the compounds to be equally potent but with a somewhat longer duration of action for Δ^9-THC. Judging by the development of tachycardia, the intensity of onset of the 11-hydroxy metabolite was greater, just as we found. Another study of 11-hydroxy-Δ^9-THC gave 1 mg intravenous doses to three subjects. The material was also found to be quite potent, to mimic the actions of Δ^9-THC and to have a very abrupt onset of action. Its metabolic disposition, as judged by radioactivity in plasma, was similar to that of THC (*Lemberger et al.*, 1972).

8-α-Hydroxy-THC and 8-β-Hydroxy-THC

Hydroxylation may occur on the ring at the 8-position as well, creating epimers, the 8-α- and 8-β-hydroxy metabolites (*Wall*, 1971). These have had little pharmacological study in any species (fig. 3).

We have given the 8-α-hydroxy metabolite intravenously to three subjects using five doses ranging from 2 to 14 mg. The compound had definite activity resembling that of Δ^9-THC, but even with the 14 mg dose, the whole syndrome was comparatively mild, perhaps what might have been obtained with 4 mg of Δ^9-THC. The 8-β-hydroxy metabolite was given intravenously to three subjects using eight doses ranging from 1 to 20 mg. Although doses as large as 10 mg were reported by one subject to be without effect, another obtained a clear THC effect with the same dose. A dose of 20 mg produced a clinical response comparable to that of 4 mg of Δ^9-THC.

Thus, it appears that placement of the hydroxyl group at the 8-position also creates an active metabolite, but that it is much less potent than when hydroxylation is at the 11-position. On the basis of present evidence one would judge that the 8-β-hydroxy metabolite is two-thirds as potent as the 8-α-metabolite.

Tetrahydrocannabivarin

Propyl side-chain homologs of Δ^9-THC have been isolated from a number of different species of marihuana by a number of investigators (*Gill*, 1971; *Merkus*, 1971; *De Zeeuw et al.*, 1972; *Fetterman and Turner*, 1972). Although it is rarely the major constituent, in some cannabis variants it may represent 20–30 % of the cannabinoids present (fig. 2). It seemed worthwhile to ascertain whether this material was either quantitatively or qualitatively different from Δ^9-THC.

We gave six subjects intravenous doses of 7 mg of the material. One subject experienced no detectable effects, but the remainder had mild to moderate effects similar in most respects to those they had obtained from Δ^9-THC. One would estimate the potency of this compound to be 25 % that of Δ^9-THC. Thus, it appears that shortening the side-chain reduces potency but does not appreciably alter the qualitative effects of the material.

Discussion

These studies of various cannabis constituents and homologs and isomers of THC indicate that so long as the fundamental structure of THC obtains, placement of the double-bond, changing the length of the side-chain, or producing hydroxy metabolites at the 8- or 11-positions does not alter qualitatively the actions of THC, but may vastly change potency. Changing the double-bond position from Δ^9 to Δ^8 decreases the potency of THC by 25 %, while placing the double-bond at the 6a-position decreases potency by about 70 % (fig. 1). Increasing the length of the side-chain by one carbon does not have much effect on potency (fig. 1) but decreasing by two carbons reduces potency by 75 % (fig. 2). Making hydroxy metabolites at the 11-position increases potency by about 20 %, while hydroxylation at the 8-position decreases potency by 75 % (fig. 3). When the structural constraints of THC are not fulfilled, all activity appears to be lost (fig. 2).

Thus, for the present we must conclude that no THC-like compound has been found in cannabis which is either more active than THC or qualitatively different, and that only compounds which resemble THC strongly have activity at all. The metabolism of THC produces a more potent 11-hydroxy metabolite, but the issue is still unsettled as to whether the parent compound must be hydroxylated to this metabolite in order to possess its characteristic pharmacological activity.

It is quite possible that other structural modifications of THC could change its activity considerably. A synthetic analog of THC developed many years ago appeared to be considerably different from THC (*Hardman et al.*, 1971). This compound is essentially Δ^{6a}-THC with a heptyl side-chain with methyl groups at the 1′ and 2′ positions, referred to as dimethyl-heptyl tetrahydrocannabinol

(DMHP). Recent studies in man indicate that even small doses have major cardiovascular effects but little if any psychological effects (*Lemberger et al.*, in press). Thus, the whole story on structure-activity relationships is far from complete. It is conceivable that one might be able to produce THC analogs that would separate various of its diverse pharmacological actions from each other.

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