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Pharmacokinetics and Metabolism of Δ^1-Tetrahydrocannabinol and Other Cannabinoids with Emphasis on Man*

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I. Introduction

THIS review will summarize the pharmacokinetic properties of Δ^1-tetrahydrocannabinol (Δ^1-THC, 1, fig. 1) mainly in man, since only limited information is available in experimental animals. We will also review the metabolites of Δ^1-THC, with particular emphasis on those metabolites which have either psychotomimetic properties similar to Δ^1-THC or which are eliminated in man.

Metabolic transformations have mainly been elucidated in various in vitro systems and in experimental animals. Only recently, more extensive information on the metabolism of Δ^1-THC in man has become available.

The pharmacokinetics of the isomer of Δ^1-THC, viz. Δ^6-THC (2), will be dealt with very briefly, because it only represents a minute constituent of marihuana. Two other major cannabinoids (fig. 1), cannabinol (CBN, 3) and cannabidiol (CBD, 4), will also only be briefly reviewed, because available data for these compounds is somewhat limited. We will review only more significant and recent results, since an extensive survey of all published material in the area would be too voluminous. Thus, much of the early literature not directly related to pharmacokinetics and metabolism is referred to in review articles and in proceedings of symposia.

Unfortunately, two almost equally popular numbering systems are in use today. The biogenetically based monoterpene system (Δ^1-THC) is used in this survey since it is applicable to both Δ^1-THC, CBD, and CBN. The dibenzopyran (Δ^9-THC) system which is also shown cannot be used for CBD but has lately been adopted by Chemical Abstracts. The use of these two systems has caused even more confusion when dealing with the metabolites.

The chemistry of cannabinoids has been reviewed re-

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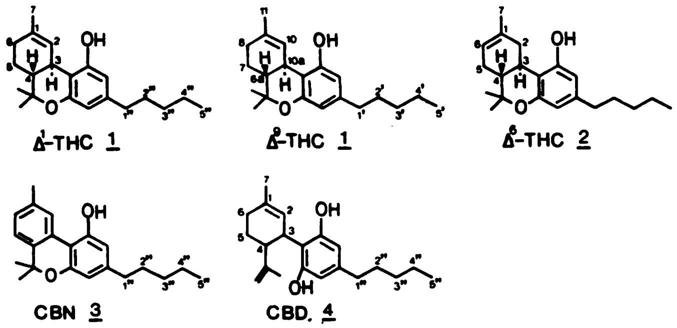


FIG. 1. Structural formulas of Δ^1-THC and the monoterpene numbering (Δ^1-*THC*) and dibenzopyran (Δ^9) numbering systems. The structural formulas and numbering systems of two other major cannabinoids, viz. cannabinol (*CBN*) and cannabidiol (*CBD*) are also shown. The structure of a minor component of cannabis, Δ^6-*THC* (Δ^8-THC dibenzopyran system) is included.

cently by Mechoulam (72) and Harvey (42). Of more than 60 cannabinoids—the term cannabinoid is used for the typical C_{21}-compounds (e.g., 1, 4) and their transformation products—only Δ^1-THC has profound psychoactive properties. CBN i.v. shows about $^1/_{10}$ the potency of Δ^1-THC in man, whereas CBD is devoid of psychotomimetic properties (50, 87). Δ^6-THC is about equipotent (52) with Δ^1-THC itself but is usually present in very small amounts compared to Δ^1-THC, CBD, and CBN. The latter three compounds occur in marihuana-type cannabis preparations in concentrations usually around 1 to 2% (72).

II. Pharmacokinetics of Δ^1-THC

A. Chemical Aspects of Δ^1-THC

The cannabinoids (1 to 4) and many of their metabolites are highly lipid soluble compounds. Δ^1-THC can be dissolved in aqueous solution only in the range of a few μg/ml or less depending upon conditions (31). The octanol/water partition ratio of Δ^1-THC at neutral pH is in the order of 6000 (72). Thus, Δ^1-THC is a resinous, essentially water-insoluble oil with a pK_a value of 10.6 (31). In contrast to almost all other psychotropic agents, it lacks a nitrogen. Δ^1-THC in aqueous solutions readily binds to glass surfaces, but this can be prevented by the use of silylated glassware (31). Δ^1-THC also rapidly diffuses into plastic containers and membranes, especially those containing plasticizers. It is a photolabile compound, susceptible to heat, acid, and oxidation by oxygen and can be partly oxidized to CBN (72). However Δ^1-THC handled correctly is a stable compound and can be stored for months at −20°C at low concentrations, dissolved in ethanol.

Natural (−)-Δ^1-THC (and CBD) has two chiral centers at C-3 and C-4 in the *trans*-configuration. This asymmetry is obviously a problem when nonlabeled, and even more so when labeled, (−)-Δ^1-THC has to be synthesized as the pure drug. Several stereospecific syntheses have been described using optically active monoterpenes as starting materials (39, 42, 72). One convenient scheme to obtain Δ^1-THC involves the use of (±)-p-mentha-2,8-dien-1-ol and olivetol (5-pentyl-resorcinol) in a one step synthesis. Also (+)-Δ^1-THC (unnatural series), CBD, and CBN have been synthesized (72).

Appropriately modified procedures have been used to allow the introduction of deuterium, tritium, or carbon-14 labels in the cannabinoid molecule. The use of a tracer in metabolic studies has been essential since the metabolic transformation products occur in large numbers but in small amounts. The early pharmacokinetic studies were also carried out with radiolabeled Δ^1-THC, since no alternative analytical methods were available at the time (63). A ^{14}C label can be introduced either into the benzene ring, into the side chain, or into the 7-position, but all procedures are comparatively tedious (42). Tritium or deuterium can more easily be introduced into the olivetol side chain by reduction of an unsaturated bond or a ketone intermediate. Such syntheses have been described by Pitt *et al.* (89) and Ohlsson *et al.* (82), while other methods have recently been reviewed by Harvey (42).

B. Influence of Route of Administration

Smoking. Cannabis preparations, particularly of the marihuana type, are usually smoked, which from the pharmacokinetic analysis point of view introduces numerous uncontrollable factors. One factor concerns the composition of the drug itself: Δ^1-THC is present in a concentration range from about 0.3% to more than 3% (in hashish up to 10%). It may occur as such, but in crude materials Δ^1-THC is usually present as monocarboxylic acids (1 with a single carboxyl group in either position in the benzene ring). Δ^1-THC is also mixed in the preparation with other cannabinoids, mainly CBD and CBN, which probably influence the pharmacokinetics of Δ^1-THC to a limited extent, as discussed later in this review. In some studies, pure Δ^1-THC has been mixed with placebo marihuana cigarettes, but in most pharmacokinetic and other studies, the Δ^1-THC content has been calculated as the sum of Δ^1-THC and the corresponding acids. The latter readily decarboxylate on heating to yield Δ^1-THC (39, 72). Although we know of no direct comparison, our results might suggest that Δ^1-THC plasma levels are in the same range, independent of whether pure Δ^1-THC or Δ^1-THC in the form of crude marihuana is smoked (2).

Thus, not only the dose of Δ^1-THC smoked is important, but also the time used for smoking. In our studies, we asked the subjects to smoke the marihuana cigarette during a period of 3 to 5 min, which is faster than the usual practice, but advantageous for kinetic analysis (2, 7). Other groups have used 10, 15, or 20 min, which is similar to actual practice, but causes the dose to be delivered over those periods of time in approximately 20 fractions (2). Furthermore, the puff duration, volume inhaled, and the holding of the breath after inhalation are of importance for the transfer of Δ^1-THC (24, 86). However, the humidity of the cigarette (humidification is frequently used to decrease harshness upon smoking) or type of cigarette paper used appear to have no influence on the percentage of transfer of Δ^1-THC (86). In addition to these confounding factors, one has to add the smokers' individual preferences in selecting their own level of intoxication.

A number of years ago, we found that about 20% of the Δ^1-THC present in a marihuana cigarette (45% with a pipe) was transferred via the main stream smoke when a group of cannabis users smoked in their usual fashion (4). We have found (5) that there is no obvious difference in the amount of Δ^1-THC transferred, whether the cigarette is smoked as a tobacco or a marihuana cigarette, with deep inhalations (5). The latter may, however, be important for the amount of Δ^1-THC absorbed by the lung (5). CBD and CBN were also transferred to a similar degree as Δ^1-THC (4).

Davis *et al.* (24) have recently published a detailed study of the smoking characteristics of marihuana cigarettes under smoking-machine conditions which simulate puff duration and puff volume of many marihuana smokers. Under these conditions, they found that 16 to 19% of the Δ^1-THC in the marihuana cigarette was found in the main stream smoke condensate. When the whole cigarette was consumed in a single puff, yielding little side stream smoke, 69% of the Δ^1-THC was recovered in the main stream smoke. One might then assume that about 30% of the Δ^1-THC (less of CBN) was destroyed by pyrolysis. A computer-based smoking dynamic system has also been developed that permits a more detailed evaluation of the smoking behavior (55).

The effect of smoking on the cannabinoids and other compounds present in cannabis preparations has recently been reviewed by Harvey (42). Apart from quantitative decarboxylation of cannabinoid acids, the ratios of cannabinoids in the smoke and in the crude drug seem to be similar, but numerous pyrolytic products are formed (4, 42). In many respects, tobacco and marihuana smoke are quite similar, apart from nicotine being obviously present in tobacco while Δ^1-THC, CBD, and CBN are present in the marihuana smoke condensate (42).

Other routes of administration. Cannabis preparations are sometimes ingested p.o., in which case the acid of the stomach can be expected to degrade Δ^1-THC. Several competing reactions occur at low pH. One is the isomerization of Δ^1-THC to the thermodynamically more stable Δ^6-THC (31). In addition to isomerization, the oxygen in the pyran ring is also protonated, causing ring cleavage to substituted CBDs (31, 42).

Δ^1-THC (5 mg), CBD, and CBN (20 mg) can also be given safely and reproducibly by the i.v. route in man if administered as a solution in 2 ml of ethanol into the injection port of a rapidly flowing i.v. solution of saline over a period of 2 min (83). In most animal experiments, i.v. formulations consist of emulsions of Δ^1-THC in Tween 80 or albumin (90).

Systemic absorption of Δ^1-THC in the rabbit after ophthalmic administration is slow and variable (19) but may be substantial. Similarly, we have found that i.p. administration of Δ^1-THC in the rat yields slowly increasing and not readily reproducible plasma levels.

C. *Measurement of Cannabinoids and Biological Fluids*

Most of the analytical development during the past decade has focused on Δ^1-THC, the important pharmacologically active constituent of marihuana (33, 42, 49). The development of the highly sensitive analytical methods needed to measure the blood or plasma levels of Δ^1-THC has, however, been somewhat disappointing. There are several reasons for this. Foremost is the high potency of Δ^1-THC. In man, doses above 10 μg of Δ^1-THC per kg consumed from smoking marihuana (calculated as absorbed Δ^1-THC) are sufficient to cause a "high."

Another complicating factor is the difficulty in separating ng amounts of Δ^1-THC from endogenous lipids. Consequently, only highly sensitive and selective assay methods are applicable, such as electron capture-gas chromatography (EC-GC), high-performance liquid chromatography (HPLC) with sensitive detectors or post-column derivatization, radioimmunoassays (RIA), combined with purification steps, or gas chromatography-mass spectrometry (GC-MS). Methods to adequately measure urinary metabolites for forensic analysis are also difficult and outside the scope of this review.

Clean-up methods [wet columns, derivatization, thin-layer chromatography (TLC)] are necessary to achieve partial purification of the Δ^1-THC in the blood plasma from interfering lipids and metabolites prior to assay. Thus, Garrett and Hunt (32) found that an EC-GC method to assay Δ^1-THC in dog plasma had a sensitivity of 0.5 to 1 ng/ml in the fasted dog, whereas the sensitivity decreased 10-fold in the nonfasted animal. The sensitivity of analytical methods for Δ^1-THC seems also to vary with species. For instance, Harvey developed a very sensitive method using a double-focusing mass spectrometer tuned to a metastable ion in the spectrum of Δ^1-THC for quantitating the cannabinoid in rabbit plasma (down to 5 pg/ml). The sensitivity in human plasma was, unfortunately, much less (42). EC-GC procedures using pentafluorobenzoate seem not to be sufficiently sensitive to measure Δ^1-THC levels in man, except for the first hour or two after smoking (32). Also, neither currently available HPLC, nor TLC methods are adequate (42).

Three methods seem to be in regular use to measure Δ^1-THC in human blood plasma. One is based upon our original GC-MS method, in which deuterated Δ^1-THC is added to the plasma sample as internal standard (3). A clean-up is achieved using a Sephadex LH-20 column, and a TMS-derivative provides increased sensitivity (down to 0.05 to 0.3 ng/ml) in the GC-MS assay (78). A similar GC-MS procedure employing chemical ionization is used by Foltz et al. (27). Cross-reactivity with other cannabinoids and their metabolites is a major drawback of RIAs. However, several groups have developed reasonably specific assays for both Δ^1-THC and its major metabolite 7-hydroxy-Δ^1-THC in human blood plasma (22, 49). The limit of sensitivity appears to be around 2 ng of Δ^1-THC per ml in human blood plasma. CBD and CBN can be measured with high sensitivity (0.1 to 0.3 ng/ml) using GC-MS essentially as described above for Δ^1-THC (1). For more extensive discussions on the analysis of cannabinoids in body fluids, we refer to recent reviews (42, 49).

D. Plasma Levels of Δ^1-THC in Man after Smoking, p.o., and i.v. Administration

Lemberger et al. were the first to study the blood levels of Δ^1-THC in man (63). They showed that radiolabeled THC given i.v. disappeared faster from the blood plasma of chronic marihuana smokers (half-life, 28 h) than from the plasma of nonusers (half-life, 57 h). There were no differences in the volume of distribution. The analytical techniques used in this study have, however, been questioned (23). Lemberger et al. also discovered that a metabolite of Δ^1-THC, 7-hydroxy-Δ^1-THC (11-hydroxy-Δ^9-THC), was quickly formed in man and present in blood, urine, and feces (63). Since the metabolite is psychoactive, this finding raised the question of whether Δ^1-THC was active per se or only (or partly) after metabolic transformation to 7-hydroxy-Δ^1-THC. Lemberger et al. also studied the temporal correlation between the peak plasma levels of radiolabeled Δ^1-THC and its metabolites and the psychological "high" (64). The discovery that the psychological effects of both p.o.-administered and inhaled Δ^1-THC were temporally correlated with plasma levels of the metabolite was taken as support for a hypothesis that the metabolite, indeed, is the active compound. This "active metabolite hypothesis" is discussed later in this review.

With availability of adequate RIA and GC-MS assay methods for Δ^1-THC in blood plasma, knowledge about the pharmacokinetics of Δ^1-THC in man has increased rapidly during the last few years.

Fig. 2 A shows the average plasma levels of Δ^1-THC after i.v. administration of 5.0 mg of Δ^1-THC during a 2-min injection period. The Δ^1-THC concentrations were followed for 4 h using a GC-MS procedure (83). Δ^1-THC levels were about 200 ng/ml at 3 min postinfusion and declined rapidly to about 15 ng/ml at 1 h and about 3 ng/ml at 4 h. In this study, the psychological "high" had essentially disappeared by 3 h (83).

From a pharmacokinetic point of view, it is advantageous to assess the kinetics of Δ^1-THC after i.v. administration compared to smoking. The latter route delivers Δ^1-THC in approximately 15 to 25 fractions or "puffs" at irregular intervals over 5 to 20 min. It is obviously difficult to obtain enough representative plasma samples during the actual smoking of Δ^1-THC, although plasma levels probably fluctuate less than one would expect (10; fig. 6). Further, since the plasma levels drop so rapidly, the influence of the first 20 min is large on the total area under the plasma curve (AUC) used to determine the systemic availability after smoking. Hence, errors in determining Δ^1-THC in the early plasma samples will influence certain kinetic parameters significantly.

Smoking a marihuana cigarette containing 19.0 mg of Δ^1-THC over a period of 5 to 7 min in order to achieve each individual subject's desired "high" yielded the plasma levels shown in fig. 2 B. Essentially, the smoking curve is parallel to the i.v. curve at about half the concentration. It should be noted that the average amount of Δ^1-THC smoked (amount of Δ^1-THC originally in the cigarette less the amount remaining in the butt) was 13.0 mg with a range of 11.6 to 15.6 mg. The curves in fig. 2, A and B, are average plasma curves. The interindividual variation is less after i.v. administration than after smoking. The curves in fig. 2, A and B, would suggest a biphasic disappearance of Δ^1-THC, but this does not include a final elimination phase.

Administration of 20 mg of Δ^1-THC p.o. in a chocolate cookie was also studied in the same subjects (83). The average plasma curve (fig. 2 C) indicates a slow increase in Δ^1-THC levels to 6 ng/ml at 1 h followed by a steady decline. The mean curve, however, is typical of few subjects; Δ^1-THC seems to be slowly and unreliably absorbed from the gut after p.o. administration, as studied in the present formulation. Some subjects showed two plasma peaks; some did not show maximum plasma concentrations until 4 to 6 h after administration, but most subjects had plasma peaks between 1 and 2 h. The low plasma levels are not due to a poor absorption of Δ^1-THC or its possible breakdown products (see section II A) as 90% of the total radioactivity was absorbed after the p.o. administration of radiolabeled Δ^1-THC (64).

In order to study the terminal half-life of Δ^1-THC, it is necessary to follow the plasma levels for 48 h or more after administration. Fig. 3 A show the average plasma levels over 48 h in a group of heavy and in a group of light marihuana users after smoking 10.0 mg of Δ^1-THC-d_3 (84). The deuterium-labeled analogue was used, since heavy users may have difficulties in abstaining from the drug for 48 to 72 h. The results after i.v. administration of 5.0 mg of Δ^1-THC-d_3 are shown in fig. 3 B. There is little difference between the two groups, although, as in a previous larger study (66), there was a trend for heavy users to obtain lower plasma levels of Δ^1-THC than light users. Part of this difference could be explained by a higher average body-weight in heavy users.

It is also clear from fig. 3, A and B, that heavy users achieved higher plasma levels of Δ^1-THC than light users smoking the same amount. This can be attributed to a more efficient smoking technique (83, 84). From fig. 3, it is evident that Δ^1-THC levels are in the 0.1 to 1 ng/ml range 6 h after smoking 10 mg of Δ^1-THC. It also appears that there is little difference (between heavy and light users) in the terminal half-life of Δ^1-THC.

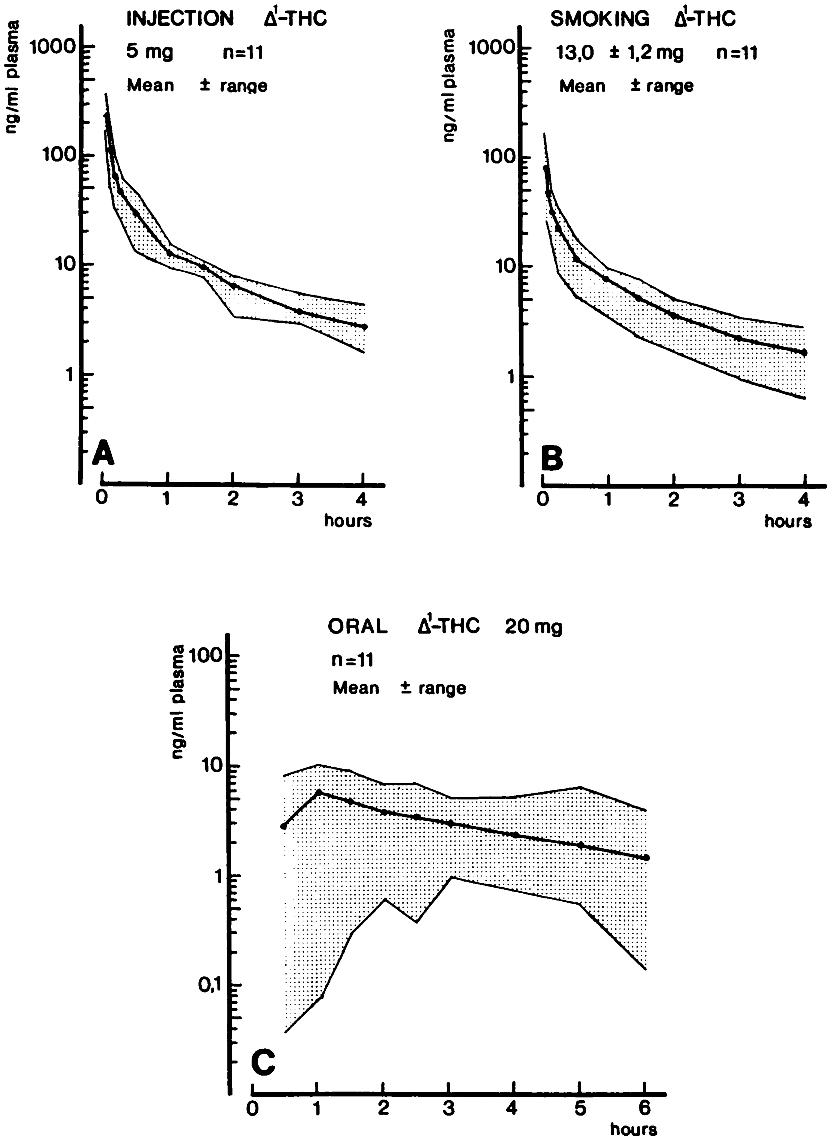


FIG. 2. Average ($n = 11$) plasma Δ^1-THC concentrations during 4 h after administration of 5.0 mg i.v. (*A*), and 13.0 mg (mean value, range 11.6 to 15.6 mg) by smoking (*B*), in a group of cannabis users. *C*, mean plasma level and range after administration of 20 mg of Δ^1-THC in a chocolate cookie. Redrawn from ref. 83.

The kinetics of Δ^1-THC in man have also been investigated in men and women by Wall *et al.* (99). Fig. 4 shows average plasma levels after 2.2 mg of Δ^1-THC by slow infusion and 15 mg p.o. in women. In general, the results of this study suggested no obvious kinetic differences between men and women. The plasma Δ^1-THC levels after i.v. dosing are clearly higher in this study (99) than in ours (83, 84) or observed at 6 h by Hunt and Jones (54). Whether this is due to differences in analytical techniques (GC-MS *versus* tritium label), in the formulation used for the i.v. administration (ethanol solution *versus* microsuspension in albumin), or something else is not clear, although we suspect it is the formulation. Studies in rats (26), where plasma levels of Δ^1-THC were compared after i.v. infusion of radiolabeled Δ^1-THC dissolved either in polyethylene glycol or premixed in plasma, suggest that higher Δ^1-THC concentrations may be caused by the protein formulation. The plasma levels (fig. 5) after p.o. dosing using an oil formulation are in the same range as ours (83). The disposition of Δ^1-THC in man has also been studied by Hunt and Jones (54). The plasma levels of Δ^1-THC they recorded during approximately 30 h after a 2-min infusion of a 2-mg ^{14}C-Δ^1-THC dose agree very closely with our findings that Δ^1-THC levels decreased to less than 1 ng/ml 3 h after dosing (84).

Plasma Δ^1-THC levels during the smoking process have probably been best studied by Barnett *et al.*, although information is quite limited (10). Their six subjects, who were male or female smokers, were asked to smoke one marihuana cigarette containing about 9 mg of Δ^1-THC at their usual pace (average, 10- to 11-min smoking time). Two h later, they were asked to smoke a second cigarette. The plasma Δ^1-THC concentrations *versus* time are shown in fig. 6 and indicate that smoking is most intense during the first few minutes. All subjects

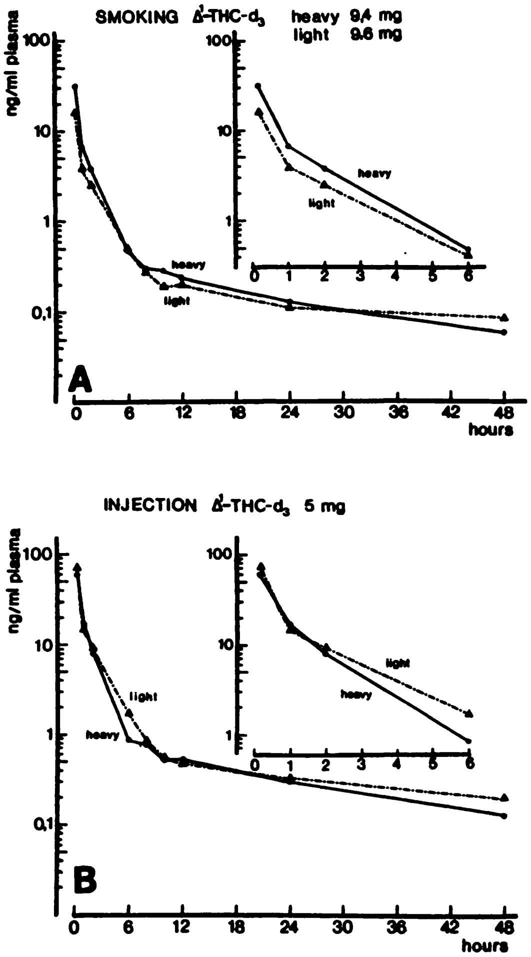


FIG. 3. *A*, mean plasma levels of Δ^1-THC-d_3 during 48 h after smoking marihuana placebo cigarettes spiked with 10 mg of Δ^1-THC-d_3. The average dose (range, 8.6 to 9.8 mg) is indicated in the figure. One group of heavy ($n = 5$) and one group of light ($n = 4$) users were investigated. The *insert* shows the average plasma concentrations during the first 6 h. *B*, average plasma levels in the same subjects after 5.0 mg of Δ^1-THC-d_3 i.v. during 2 min. Note that the first mean plasma concentration is at 10 min (*insert*). Redrawn from ref. 84.

reached maximum Δ^1-THC plasma levels before the end of smoking (10). However, the authors could not fully rule out that the time to maximum concentrations might have been an artifact of the blood sampling.

There is very little dose-response information with respect to Δ^1-THC or marihuana. However, Perez-Reyes and coworkers carried out a study that covered the dose range of 9.7 to 16.0 mg of Δ^1-THC by smoking (86). Although the subjects were asked to smoke until their usual "high," it was found that the higher potency of the marihuana, the more Δ^1-THC was smoked. They further found a direct correlation between the peak plasma Δ^1-THC level and the Δ^1-THC content of the cigarette, whereas the relation of the AUC was less straight forward. The relation of dose to pharmacological response ("high") was also reasonable (86).

E. Pharmacokinetic Parameters in Man

Plasma Δ^1-THC levels in man decay in a fashion which can be interpreted using 3-, 4-, or 5-compartment models (10, 25, 54). Although the use of compartmental models is controversial, in our experience the terminal half-life is long in both heavy and light users (half-life > 20 h) (84). Hunt and Jones also found a similar average half-life in man, about 19 h (range, 13.8 to 26.0 h), independent of whether the subjects were relatively moderate users or exposed to heavy p.o. Δ^1-THC doses for about 2 weeks (54). Similarly, Lemberger et al. found a half-life for Δ^1-THC in chronic users of 28 h, whereas it was found to be longer (half-life = 57 h) in naive users (63). Wall *et al.* likewise suggested a terminal half-life of 25 to 36 h for both men and women (99).

In fig. 7, we show the slow elimination of Δ^1-THC in a very heavy marihuana smoker after discontinuation of the drug. To control for interference from illicit use of marihuana after discontinuation, the subject received Δ^1-THC-d_2 before abstinence. The steady, parallel decline of both curves from day 1 to day 8 after discontinuation

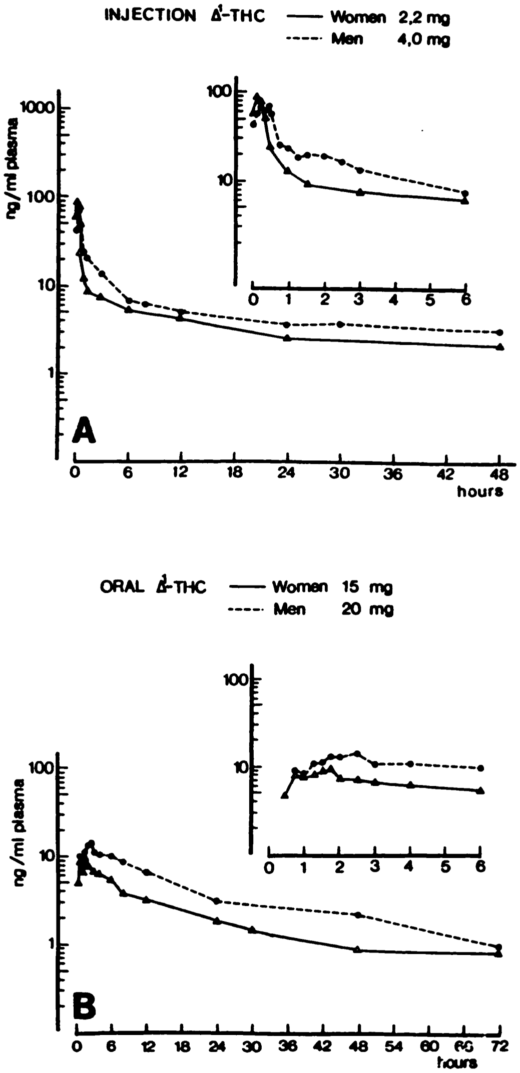


FIG. 4. Observed plasma concentrations of Δ^1-THC in a group of women ($n = 6$) administered 2.2 and men ($n = 6$) administered 4.0 mg by slow i.v. infusion (20 to 30 min) (*A*) and 15 mg (women) and 20 mg (men) in sesame oil by the p.o. route (*B*). Redrawn from ref. 99.

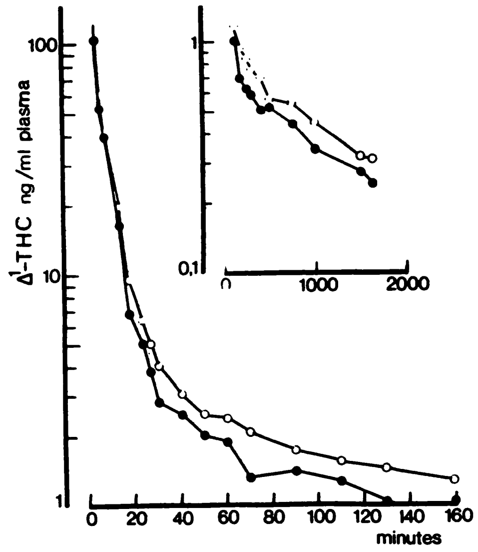


FIG. 5. Semilogarithmic plot of average Δ^1-THC plasma levels following a 2-min infusion of 2 mg of ^{14}C-Δ^1-THC in six subjects before (○) and after (●) chronic (2 weeks) p.o. Δ^1-THC administration. Redrawn from ref. 54.

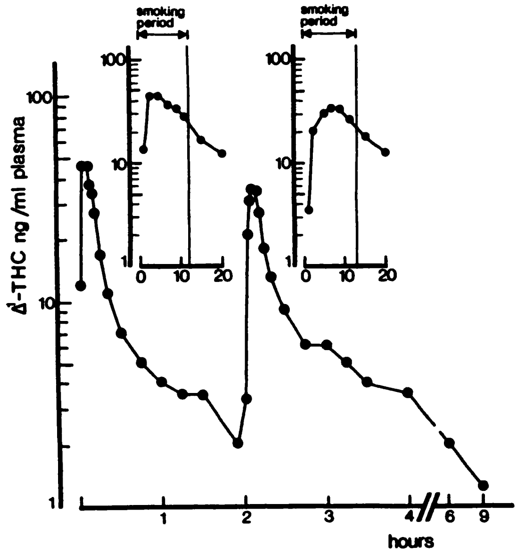


FIG. 6. Average plasma Δ^1-THC concentrations *versus* time after smoking two cigarettes, each containing about 9 mg of Δ^1-THC, 2 h apart. *Insert* shows the levels during smoking periods. Redrawn from ref. 10.

suggests a terminal half-life of 20 h with possibly a tendency to become longer (2).

Thus, the terminal half-life of Δ^1-THC is in the order of 20 to 30 h and is in the same range as many psychotropic drugs such as amitriptyline, imipramine, haloperidol, and nitrazepam. Little is known about interindividual differences in half-lives. We feel, however, that the present estimates of half-life for Δ^1-THC are based on somewhat uncertain data and should be strengthened by more long-term elimination studies using more precise assay methods.

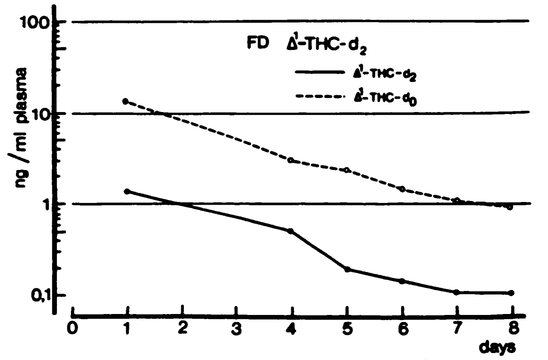


FIG. 7. Plasma levels of Δ^1-THC-d_0 (○) and Δ^1-THC-d_2 (●) in one heavy marihuana smoker who on day 0 discontinued his use of marihuana. Before discontinuation, he smoked also 40 mg of Δ^1-THC-d_2. Plasma samples were taken as indicated.

TABLE 1
Systemic availability of Δ^1-THC in man

Subjects	Route	Systemic availability (%)		Formulation	Ref.
		Average	Range		
Mixed group	Smoking	18	8–24	Marihuana	83
	p.o.	6	4–12	In chocolate cookie	
Heavy users	Smoking	23	6–56	Marihuana	66
Light	Smoking	10	2–22		
Heavy users	Smoking	27	16–39	Placebo + -THC	84
Light users	Smoking	14	13–14		
Moderate users	p.o.	10–20		Oil solution	99

The systemic availability ("bioavailability") of Δ^1-THC has been assessed by comparing the area under plasma concentration *versus* time curve (AUCs) after i.v. and p.o. administration or smoking. During smoking, the bioavailability of Δ^1-THC is limited by pyrolysis, loss through side stream smoke, inefficient absorption in the lung and, possibly, to a small extent by metabolism in the lung before entering the systemic circulation (36, 102). After p.o. administration, the availability of Δ^1-THC is limited by the sensitivity of Δ^1-THC to acidic gastric juice (see section II A) and also by presystemic elimination in gut and liver, the "first pass elimination." In table 1, we have recorded the systemic availability of Δ^1-THC, as evident from published data. We have assumed that Δ^1-THC kinetics are not dose dependent.

Thus, partly depending upon the experience of the user, the systemic availability of smoked Δ^1-THC is usually in the range of 10 to 25%. The lowest systemic availability we have recorded of smoked Δ^1-THC is 2% and the highest, 56%. Fig. 8 illustrates individual values of areas under the plasma concentrations *versus* 0- to 240-min time curves after smoking and i.v. administration of Δ^1-THC in heavy and light users of mariuana. The interindividual variation is considerable after both smoking and i.v. infusion of Δ^1-THC, and there is considerable overlap between the two groups (66). Hardly

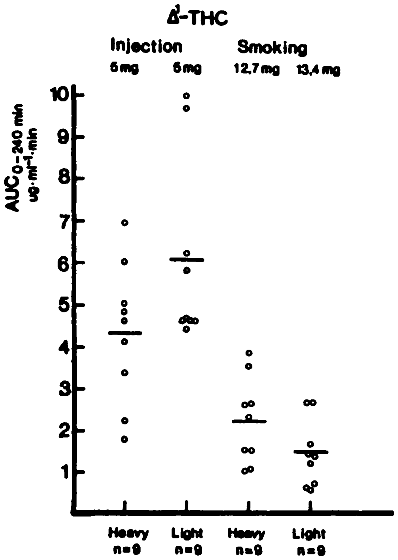


FIG. 8. Individual values of *AUC* during 240 min after administration of Δ^1-THC by smoking (average dose shown) or the i.v. (5-mg dose) route to one group of light ($n = 9$) and one group of heavy ($n = 9$) marihuana smokers. The mean AUC values are indicated by *horizontal lines*. Based on data from Lindgren et al. (66).

any data on intraindividual differences are available, but our scanty information would indicate consistency in the same individual. Furthermore, the study of Barnett *et al.* (10) provides some evidence for this assumption.

The volume of distribution of Δ^1-THC in man has been estimated by several authors to be about 10 L/kg, typical of a lipophilic drug (54, 84, 99). As such, it also shows a high plasma clearance value of 760 to 1190 ml/min in one study (84) and about 800 ml/min in another (54), close to the hepatic plasma flow of about 800 ml/min.

Limited information is available on the protein binding of Δ^1-THC and its blood/plasma distribution ratio (32, 42, 100), as conventional techniques are not readily applicable (32). In vitro experiments suggest that only 10 to 20% of Δ^1-THC in blood is bound to the red blood cells (32, 100). The remainder exists in plasma, at least 97% bound to proteins. It would appear that Δ^1-THC is mainly bound to lipoproteins, but the metabolite 7-hydroxy-Δ^1-THC is also bound to albumin (100).

F. Tolerance to Δ^1-THC—Functional Tolerance or Induced Metabolism?

Development of tolerance to both pharmacological and psychological effects of Δ^1-THC after prolonged administration is well established in both man and animals (88b, 54, 51). Two hypotheses have been suggested: (*a*) functional tolerance due to adaptation to drug concentrations or (*b*) dispositional tolerance as a result of either increased metabolism or other pharmacokinetic changes. Indeed, the early study of Lemberger *et al.* suggested that the half-life of Δ^1-THC in chronic users was clearly shorter than in nonusers, although these results have not been collaborated by later studies (63). Interpretation of the effects of an induction of metabolism is not simple, as one could also postulate that a more rapid formation of the psychoactive metabolite 7-hydroxy-Δ^1-THC could lead to an increased sensitivity rather than tolerance, provided that the further metabolism of 7-hydroxy-Δ^1-THC was less facilitated.

Hunt and Jones studied the influence of prolonged p.o. Δ^1-THC administration on the pharmacokinetics and metabolism of Δ^1-THC in man (54). They evaluated possible changes based on plasma levels of unchanged ^{14}C-Δ^1-THC after i.v. administration before and after a 2-week Δ^1-THC administration (fig. 5). Minor changes, such as an increase in plasma clearance, were caused by the previous exposure to Δ^1-THC, but the volume of distribution and most other pharmacokinetic parameters were unchanged. Consequently, they concluded that the development of tolerance to the cardiovascular and psychological effects of Δ^1-THC could not be explained by changes in drug disposition. This is also evident from fig. 5. Whether the amount of exposure was enough to cause pronounced tolerance is, however, not clear.

In two studies, we compared differences in some pharmacokinetic parameters between heavy and light cannabis users (66, 84). As discussed elsewhere, the definition of "heavy user" may be crucial—our group of heavy users could be considered as moderate (at least one marihuana cigarette per day) to heavy (10 or more per day) users. In both the study (84) shown in fig. 3 and another larger study (66) of similar design, we found limited differences in plasma levels and rate of disappearance of a Δ^1-THC i.v. dose between the two groups, although there was a nonsignificant tendency for heavy users to have lower plasma levels. The average Δ^1-THC plasma levels after smoking were, in both studies, about twice as high in heavy as in light users. This difference is probably explained by the more efficient smoking of the experienced users. Although one has to remember that there are several types of effects and mechanisms towards which tolerance can develop, such as "high," tachycardia (β-adrenergic mediation), and anticholinergic effects, it is likely that the tolerance which develops is mainly functional. There are, however, indications that very frequent marihuana smoking is needed to develop tolerance (65, 88b).

G. Relations between Plasma Levels and Effects

As early as 1972, Galanter *et al.* found indications in a group of marihuana users (after smoking radiolabeled Δ^1-THC during a period of 10 min) that the plasma levels of Δ^1-THC peaked within 15 min, accompanied by a parallel increase in pulse rate (30). Both plasma Δ^1-THC concentration and pulse rate declined rapidly, whereas the subjective "high" increased more slowly but was maintained longer. In another study, Borg *et al.* found a significant dose-response effect, both on pulse rate and impaired performance, from increasing doses of smoked Δ^1-THC (14b). Since then, many investigators, using appropriate assay methods for Δ^1-THC and occasionally also for the metabolite 7-hydroxy-Δ^1-THC, have tried to correlate plasma levels of Δ^1-THC with subjective psychological effects ("high"), pulse rate, memory, and performance tests.

In one extensive study, we attempted to correlate plasma concentrations of Δ^1-THC with self-rating of degree of intoxication, with pulse rate and with conjunctival injection after i.v., p.o., and smoke administration of Δ^1-THC (53). Before taking each blood sample from the 11 subjects, they rated their "high" on a scale from 0 to 10. Fig. 9 shows the relations between plasma Δ^1-THC concentration and "high" after i.v. administration of Δ^1-THC. There is a relation, although modest, between Δ^1-THC level and intoxication. After p.o. administration, the correlation was slightly better ($r = 0.42$), and after smoking, still somewhat better ($r = 0.53$). Equally obvious, however, was the large number of subjects experiencing only a little "high" in spite of high Δ^1-THC levels, while other subjects experienced a pronounced "high" at very low Δ^1-THC levels (53). This partial lack of correlation can be understood from fig. 10 A, where both average Δ^1-THC levels and average degree of "high" are plotted over time. After i.v. administration, the peak Δ^1-THC levels are obviously reached in the first plasma samples, but the peak "high" is not reached until 15 min after injection. Plasma Δ^1-THC levels also decline more rapidly than the psychological effects. Since it was observed that some subjects experienced only a little "high" in spite of high Δ^1-THC plasma levels during the initial distribution phase—when the drug might still not have been able to efficiently pass the blood-brain barrier—we attempted to evaluate correlations between Δ^1-THC plasma levels and "high" at different times and after different routes of administration. Correlations were slightly better for smoking from 10 to 120 min after administration but were not highly significant for any time period or any route (53).

The relation between the degree on "high" and the recorded plasma concentration (about 250 assessments) for all routes of administration is shown in table 2. The individual variability is considerable.

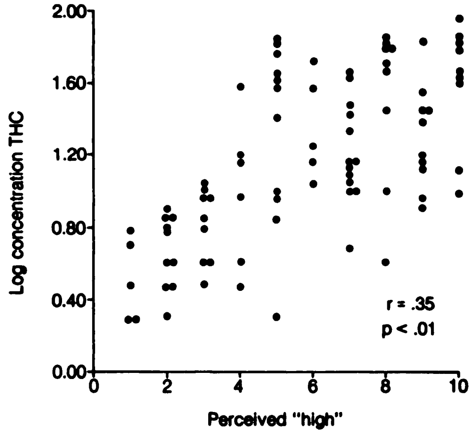


FIG. 9. Relation between log concentration of plasma Δ^1-THC and "high" after i.v. administration of 5.0 mg of Δ^1-THC. From ref. 53.

TABLE 2

Relationship between plasma Δ^1-THC concentration (ng/ml) and reported "high" after i.v. administration, p.o. administration, and smoking (from ref. 53)

Degree of "high"*	i.v. and smoked range (ng/ml)	p.o. range (ng/ml)
0	2–190	tr†–6
1	2–6	tr–6
2	2–317	tr–6
3	3–240	tr–8
4	2–251	2–10
5	2–250	1–8
6	3–210	4–6
7	4–112	2–4
8	4–215	2–3
9	7–196	2
10	5–160	

* Global self-reporting scale (0–10).

† tr, trace.

In fig. 10 C, we have shown the time course of the "highs" after all three modes of administration. The time courses after i.v. administration and smoking are quite similar, just as the plasma curves in the same subjects (fig. 2, A and B) after these routes of administration are similar. The time course of "high" after p.o. administration of 20 mg of Δ^1-THC (fig. 10 B) peaks decidedly later and at a lower maximum. However, considering the low average peak level of Δ^1-THC in these subjects (6 ng/ml; fig. 10 B), the magnitude of the "high" is still remarkable. As discussed later in this section, this can be partially attributed to the psychoactive effects of increased production of the active metabolite 7-hydroxy-Δ^1-THC after p.o. administration of Δ^1-THC. Thus, this study showed that, although there is a moderate correlation between plasma Δ^1-THC values and "high," there is also a wide variation in individual values (53). A clear-cut relationship between plasma concentrations of Δ^1-THC and degree of intoxication (evaluated by subjective "high"), as has been shown for alcohol, could not be demonstrated.

Conjunctival injection in relation to plasma Δ^1-THC concentration has also been assessed (53). It was found to be maximal 10 min after both smoking and i.v. administration and, thereafter, it decreased. After p.o. administration, the maximum conjunctival injection coincided with the Δ^1-THC plasma peak (fig. 2 C). The effect was variable but, in general, the reddening of the conjunctivae was present as long as plasma Δ^1-THC levels were above 5 ng/ml.

Another highly reliable sign of cannabis effect is the increase in pulse rate. After a 5-mg i.v. dose of Δ^1-THC, increases of 25 to 100 beats (average, +40 beats/min) at a Δ^1-THC plasma level of about 100 ng/ml were recorded (53). After smoking about 13 mg of Δ^1-THC, the maximum average increase in pulse rate was 34 at plasma levels of about 45 ng/ml. The pulse rate response occurs

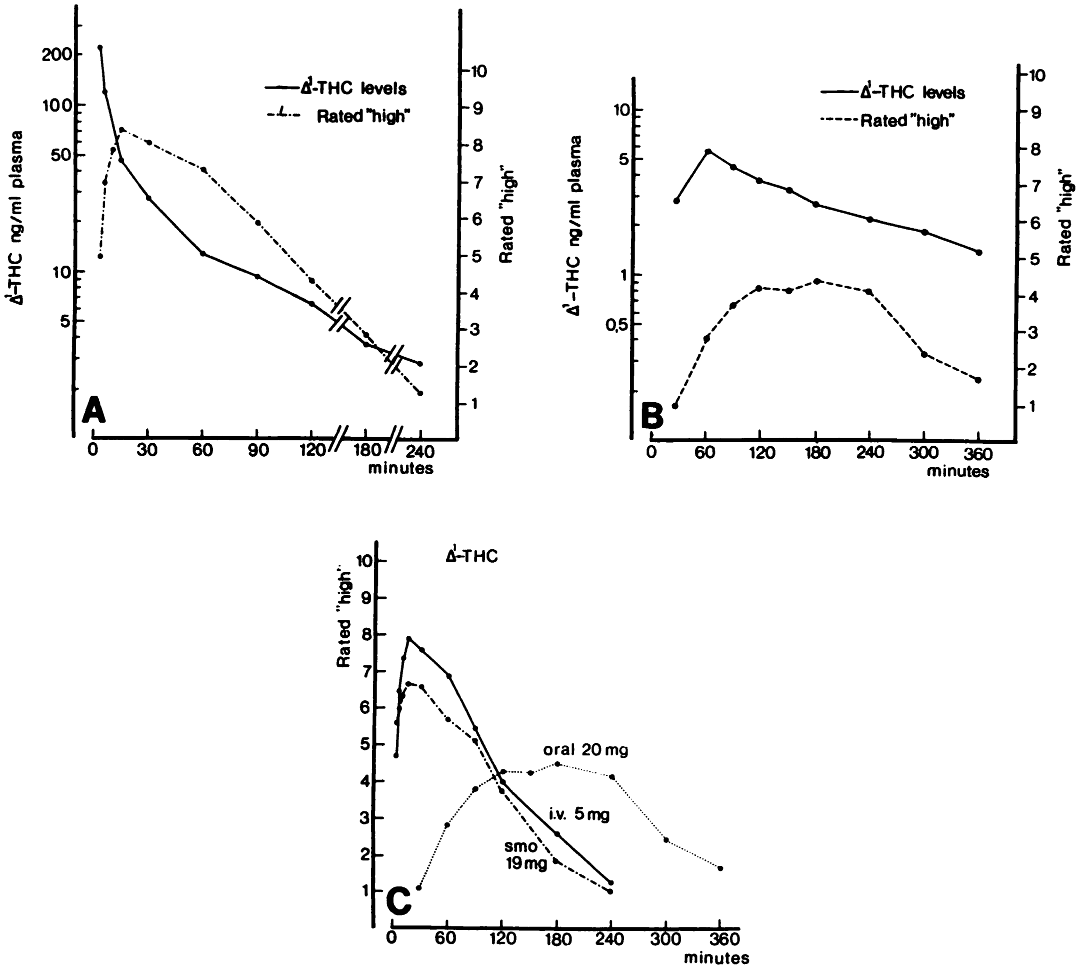


FIG. 10. Time course of average "high" *versus* plasma Δ^1-THC levels after i.v. administration (*A*) and after p.o. administration (*B*). *C*, time course of "high" ratings after three routes (i.v., smoking, p.o.) of administration of Δ^1-THC. Redrawn from ref. 53.

more rapidly than the psychological effect, but it also returns more quickly to the baseline (53).

The relationship between plasma Δ^1-THC levels after marihuana smoking and pharmacological effects (tachycardia and "high") in man has also been studied by Cocchetto et al. (21). Using hysteresis' plots, they found that both heart rate and subjective "high" were present in a "deep compartment" relative to the plasma compartment. Their finding that the time course of tachycardia as well as "high" both lagged behind the plasma concentration peak of Δ^1-THC is congruent with the findings from our group (53, 66), Wall and Perez-Reyes (98), Galanter et al. (30), and others. Cocchetto et al. (21) also suggested that plasma Δ^1-THC concentrations are poor predictors of simultaneous psychological and physiological effects. This is also in agreement with our previous study (53). Incidentally, Domino et al. have combined data from several of our studies and formulated an interesting mode. Based on certain assumptions, these workers suggested that the time course for an average subjective marihuana high might be predicted from plasma Δ^1-THC levels (25).

Miller et al. have explored more deeply the relationships in man between Δ^1-THC plasma concentrations and various effects (73). They also investigated relations to factors in the Linear Mood Scale. Although certain mood factors in the scale such as disturbed/weird and sensitive/aware correlated better with kinetic parameters than others, they concluded that a global subjective "high" rating was still the most reliable index. They also found the temporal dissociation between "high" and plasma concentrations noted by others (21, 30, 53).

The effects of Δ^6-THC seem, in general, to be very similar to those of Δ^1-THC (6). Assessment of performance by critical flicker fusion (CFF) or reaction time indicated that the lowest performance levels were obtained well after the peak in plasma level. The effect on heart rate was better correlated with plasma Δ^6-THC levels. The effect on heart rate appears to be independent of the psychological effects, since heart rate acceleration can be blocked by i.v. propranolol without altering the "high" (6).

The conclusion from a number of studies in man on relations between pharmacokinetic parameters of Δ^1-THC and psychological ("high") or physiological (pulse rate) effects is quite clear. There is a reasonable correlation between plasma Δ^1-THC level and effects on pulse rate and the even greater dissociation for the subjective "high." The mechanism for this is not understood. The lag time between peak plasma level and peak "high" cannot readily be explained by the slow formation of an active metabolite. The reason for the lag is not known, but one possible explanation—not well supported by experimental results—is that the lag could be due to a somewhat slow penetration of Δ^1-THC into the brain (85). Such a delaying process could be further influenced by the time required to start the biochemical events or, speculatively, to penetrate to the receptor, or displace a possible endogenous ligand in order to yield the desired psychological "high." Other theoretically possible explanations for the limited relations between pharmacokinetic and pharmacodynamic parameters are the presence of a bell-shaped dose-response curve or the possibility that the "high" is a net result of two counteracting dose-response curves with different shapes. Neither of these two latter explanations has any experimental support at present.

Active metabolite theory. The discovery of the active metabolite 7-hydroxy-Δ^1-THC, has led to the suggestion that rate of onset of activity following Δ^1-THC could, to a great extent, depend on its slow transformation to the active metabolite. The delay in onset of "high" and other effects could then theoretically be accounted for by the comparatively slow formation of the active compound, 7-hydroxy-Δ^1-THC (64). This hypothesis, however, does not seem plausible, since the marihuana-like psychological "high" appears at about the same "slow" rate after i.v. dose of both Δ^1-THC and 7-hydroxy-Δ^1-THC in man. The latter compound does not provide an "instant high" but has a pharmacological profile identical to Δ^1-THC itself (62, 88a).

Other experiments in man have shown that, after both i.v. administration of Δ^1-THC (99) and smoking (98), the levels of 7-hydroxy-Δ^1-THC are so low (about ⅒ of Δ^1-THC) that it would seem unlikely that the metabolite could make an important contribution to the effects of Δ^1-THC per se. Other findings, using sensitive methods, suggest, however, that, after equal i.v. doses of Δ^1-THC and 7-hydroxy-Δ^1-THC in man, the plasma levels of Δ^1-THC are about 3 times higher than those of the metabolite (98). The same 3-fold difference in plasma levels from similar doses has also been obtained in animal experiments (91). Further experiments have shown that the comparative brain levels of the isomeric 7-hydroxy-Δ^6-THC were about 3 times higher than those of Δ^1-THC (85). Thus, plasma levels of 7-hydroxy-Δ^1-THC in man ⅒ of the levels of Δ^1-THC, by extrapolation, would indicate an amount of 7-hydroxy-Δ^1-THC about ⅓ that of Δ^1-THC in the body. Further, the two compounds are about equipotent in man (88a). To summarize, present evidence indicates that it is unlikely that 7-hydroxy-Δ^1-THC contributes considerably to the effects of Δ^1-THC after *smoking* or *i.v.* injection.

After p.o. administration of Δ^1-THC to man, however, plasma levels of 7-hydroxy-Δ^1-THC are almost equal to those of Δ^1-THC (98, 99) at all sampling time periods from 1 to 6 h after administration. Based upon the relative plasma/brain levels of Δ^1-THC and 7-hydroxy-Δ^1-THC, as discussed above, one would assume that the total amount of the metabolite 7-hydroxy-Δ^1-THC in the body would be at least twice the amount of Δ^1-THC itself after p.o. administration of Δ^1-THC. It is known that, per mg administered i.v., 7-hydroxy-Δ^1-THC is equally potent in producing a "high" as Δ^1-THC (88a). One might then speculate that, after *p.o.* dosing of Δ^1-THC, the metabolite 7-hydroxy-Δ^1-THC contributes more than Δ^1-THC per se to the psychological "high."

As discussed later (section V C), 7-hydroxy-Δ^1-THC is the only metabolite that is active enough and abundant enough in man to be able to contribute to the effects of Δ^1-THC. It is true that there is a better correlation in man between the occurrence of more polar metabolites, such as Δ^1-THC-7-oic acid (24), and psychological "high" (98). Since this acid, and presumably all other polar metabolites, is inactive (98), this covariation between effect and total plasma metabolite levels seems fortuitous.

Our present views on the "active metabolite theory" may be summarized as follows. In man it is unlikely that any active metabolite, such as 7-hydroxy-Δ^1-THC, contributes in an important way to the effects of Δ^1-THC after *smoking* or *i.v.* administration. After *p.o.* administration, however, we assume that 7-hydroxy-Δ^1-THC contributes at least as much as Δ^1-THC itself.

III. Pharmacokinetics and Distribution of Δ^1-THC in Animals

The pharmacokinetics of Δ^1-THC has been studied in detail only in the dog by Garrett and Hunt (32). They estimated a terminal half-life of approximately 8 days. Harvey (42) found a terminal half-life in the rabbit of 2 to 4 days. In both these studies, the plasma Δ^1-THC levels were followed for more than 1 week. The plasma levels in other studies where Δ^1-THC has been administered to animals have usually been quite short, and the rapid decline mainly reflects uptake by the tissues. Hunt and Jones calculated that about 70% of a Δ^1-THC dose administered i.v. to an animal would be taken up by the tissues and that some 30% would be metabolized (54). After 6 h, the rate-limiting step for elimination of unmetabolized Δ^1-THC is the return to plasma of Δ^1-THC sequestered in tissues. This assumption is supported by the results in the rat of Kreuz and Axelrod (60), who found a half-life of 5 days for Δ^1-THC when determined from Δ^1-THC present in fat. If the terminal half-life is controlled by the return from tissues, one would expect that the half-life would be, as generally found in human studies (section II E), quite insensitive to changes in metabolic clearance due to induction or inhibition of Δ^1-THC metabolizing enzymes. The amount of fat in the body in man may, however, theoretically make a difference in half-life between lean and obese individuals, although this has not been tested (21).

The distribution of Δ^1-THC and its metabolites has been studied quite extensively in mice and other animals. Whole-body autoradiography of Δ^1-THC, combined with analysis of Δ^1-THC and its metabolites present in the tissues, showed that the distribution pattern in mice changes with time (91). Earlier studies in rabbits revealed similar changes with high levels of Δ^1-THC found in kidneys and lungs 2 h after an i.v. administration (102). After 3 days, however, spleen and body fat showed the highest levels of Δ^1-THC. High, sustained fat levels of Δ^1-THC have also been found by others (42). Long-chain fatty acid conjugates of Δ^1-THC metabolites may possibly be retained in the tissues (61).

The nature of the material in the tissues has been partly identified in the mouse (91). Surprisingly enough, the brain contained very low concentrations of both Δ^1-THC and metabolites. 7-Hydroxy-Δ^1-THC was produced rapidly, and the brain concentrations of this metabolite after i.v. administration of Δ^1-THC remained parallel with Δ^1-THC at about half the concentration of Δ^1-THC itself. Furthermore, in the lung, heart, kidney, and spleen, the concentration of Δ^1-THC were higher than those of 7-hydroxy-Δ^1-THC. In the liver, the situation was reversed, with the 7-hydroxy metabolite levels being higher than the Δ^1-THC levels throughout the 5-min to 96-h analyses. The levels of more polar metabolites were consistently higher (3 to 10 times) than those of Δ^1-THC itself, particularly in spleen and liver, but less so in brain. The blood levels of 7-hydroxy-Δ^1-THC remained at about 1/10 of those of Δ^1-THC.

Low levels of Δ^1-THC in the brain have been reported in three other studies (42, 57, 85) in amounts which correspond at most to 1% of the administered dose at peak concentration. If we assume that a similar distribution exists in man, one would expect that a pronounced "high" in man will be caused by the presence of as little as 10 μg of Δ^1-THC in the brain, immediately after smoking a marihuana cigarette.

The concentration of radiolabel in the brain from ^{14}C-labeled Δ^1-THC was distributed in the caudate nucleus, putamen, thalamus, pons, hippocampus, and the frontal and parietal cortex, but there was no dramatic uptake at any particular site (42). The patterns of distribution for Δ^1-THC, CBN, and CBD were similar (9) in the brain.

The route of administration and the formulation of Δ^1-THC are important for its absorption and distribution (94).

IV. Pharmacokinetics of CBD and CBN in Man

CBD is one of the major constituents in most cannabis preparations but has no pyschotomimetic effect in man (50). The compound, however, has anticonvulsant activity in animals and possibly also in man, as reviewed elsewhere (95). We recently studied the pharmacokinetics of CBD in a group of young marihuana smokers (80). The CBD plasma levels during 72 h after 20 mg i.v. and 18.8 to 19.4 mg by smoking are shown in fig. 11. We used results from three different studies for the comparison shown in fig. 12, but it is evident that the plasma patterns for Δ^1-THC, CBD, and CBN are quite similar. Systemic availability of smoked CBD ranged from 11 to 45% in five subjects with an average value of 31%. A high plasma clearance (960 to 1560 ml/min), equal to that of Δ^1-THC (see section II E), was calculated. A terminal half-life might not have been reached at 72 h, but the available data indicated half-lives for CBD of 18 to 33 h (mean, 24 h) after i.v. administration and 27 to 35 h (mean, 31 h) after smoking. The distribution volume was estimated to be about 30 L/kg, greater than for Δ^1-THC, which seems to be congruent with animal experiments (9).

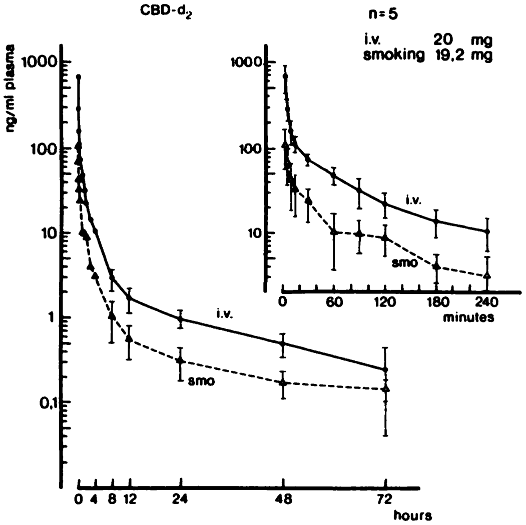


FIG. 11. Mean plasma curve (±SD) of CBD-d$_2$ after i.v. administration and smoking in five marihuana users. The *insert* shows the concentrations during the first 4 h after administration.

Wall et al. have also studied the subjective effects of i.v. CBD as well as plasma levels of unchanged CBD and metabolites (97, 98). They also found that CBD disappeared rapidly and that polar metabolites were quickly formed in large amounts, a pattern similar to Δ^1-THC.

These investigators also studied the psychoactive effects of CBN after i.v. infusion of 18 mg of CBN (97). In these volunteers, CBN induced a definite "high" in agreement with earlier reports indicating an activity about 1/10 of that of Δ^1-THC (87). CBN p.o., however, seems not to cause any "high" (50). The plasma levels of CBN in man were similar to those of CBD, and there was rapid formation of metabolites.

Plasma CBN levels found during a 4-h period following the administration of 20 mg of CBN by the i.v. route and 19 mg by smoking, respectively (79), are shown in fig. 12. Taking into account the 4-fold higher dose of i.v.

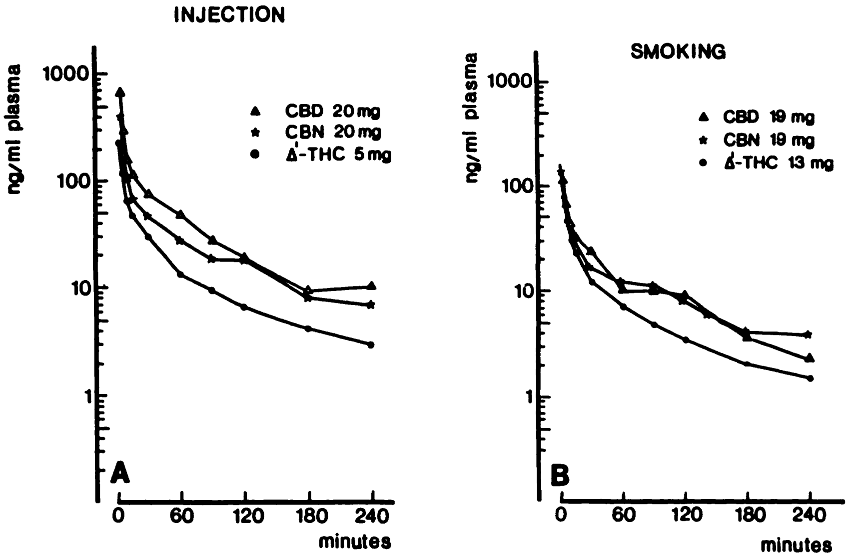


FIG. 12. *A*, average plasma levels after *i.v. administration* of 5 mg of Δ¹-THC (from ref. 83), 20 mg of CBD (81), and 20 mg of CBN (79). *B*, mean plasma levels after the same subjects *smoked* an average amount of 13 mg of Δ¹-THC ($n = 11$), 19 mg of CBD ($n = 5$), and 19 mg of CBN ($n = 7$).

CBN compared to Δ¹-THC, the similarity to Δ¹-THC is striking. The interindividual variations in plasma levels of CBN, particularly after smoking, were greater than for CBD and Δ¹-THC. Furthermore, the range in systemic availability of smoked CBN is perhaps greater (8 to 65%; mean value, 38%) than for Δ¹-THC. The plasma levels of unchanged cannabinoids during 6 h after p.o. administration of 20 mg of Δ¹-THC and 40 mg of CBD or CBN are in the same range (1).

To be able to compare more adequately the kinetics of CBD, CBN, and Δ¹-THC, cross-over studies in a sufficiently large group of subjects are necessary. However, the available information suggests that both plasma levels and terminal half-lives are rather similar after both i.v. and smoked administration of similar doses. The volumes of distribution for CBN and CBD as well as systemic availability may be somewhat greater than for Δ¹-THC.

V. Metabolism of Δ¹-THC

It has taken more than a decade of metabolic studies to progress from the early identification of 7-hydroxy-Δ¹-THC as the primary Δ¹-THC metabolite (72, 39, 42) to the elucidation of the chemical structures of the urinary metabolites of Δ¹-THC in man. Some of the reasons for this slow development are: the high potency of Δ¹-THC (a single mg absorbed is enough to produce psychoactive effects in man); the very diverse metabolism of cannabinoids (approximately 80 metabolites of Δ¹-THC are known today); the difficulties in the separation and the isolation of the metabolites; and perhaps also problems in obtaining necessary legal and ethics committee approvals for the appropriate human studies. Studies on the metabolism of Δ¹-THC have been carried out in the mouse, rat, guinea-pig, rabbit, dog, monkey, and man using both in vitro and in vivo methods. In this summary, the material has been separated into primary metabolites and metabolites eliminated in feces and urine.

A. Isolation and Identification of Metabolites

The isolation of primary metabolites of Δ¹-THC from metabolic studies using human liver (38) is, in principle, similar to the techniques used to isolate urinary metabolites with the modifications necessary due to the ubiquitous presence of carboxylic functions in urinary Δ¹-THC metabolites (34, 35). Fig. 13 shows the procedures for isolation of acidic metabolites of Δ¹-THC from the urine of man. Although these procedures are indeed tedious, they have allowed the isolation of a large number of metabolites in a reasonably pure form, the structures of which have been determined unequivocally by nuclear magnetic resonance (NMR) analysis (75, 76). Certain of these structural assignments have later been confirmed by synthesis.

Wall et al (97) have isolated metabolites using somewhat different methods. Extensive isolation schemes have been utilized by Kanter and Hollister for the separation and identification of urinary metabolites of Δ¹-THC (58, 59). Finally, Harvey and Paton have used limited isolation procedures and relied heavily on combined GC-MS for the structural assignments (47). Mass spectrometry is particularly useful, and Binder et al. could predict the position of side chain hydroxylation from mass spectrometry (MS) data (14a). The mass spectrometric fragmentations of cannabinoids and the mechanisms have been extensively investigated by Harvey (47, 40, 41, 48) and by Binder (13, 14a), using derivatization techniques. A wealth of information of the structural assignment, particularly based on MS data, is available in the subsequently quoted papers.

Gudzinowicz et al. have in their extensive review of

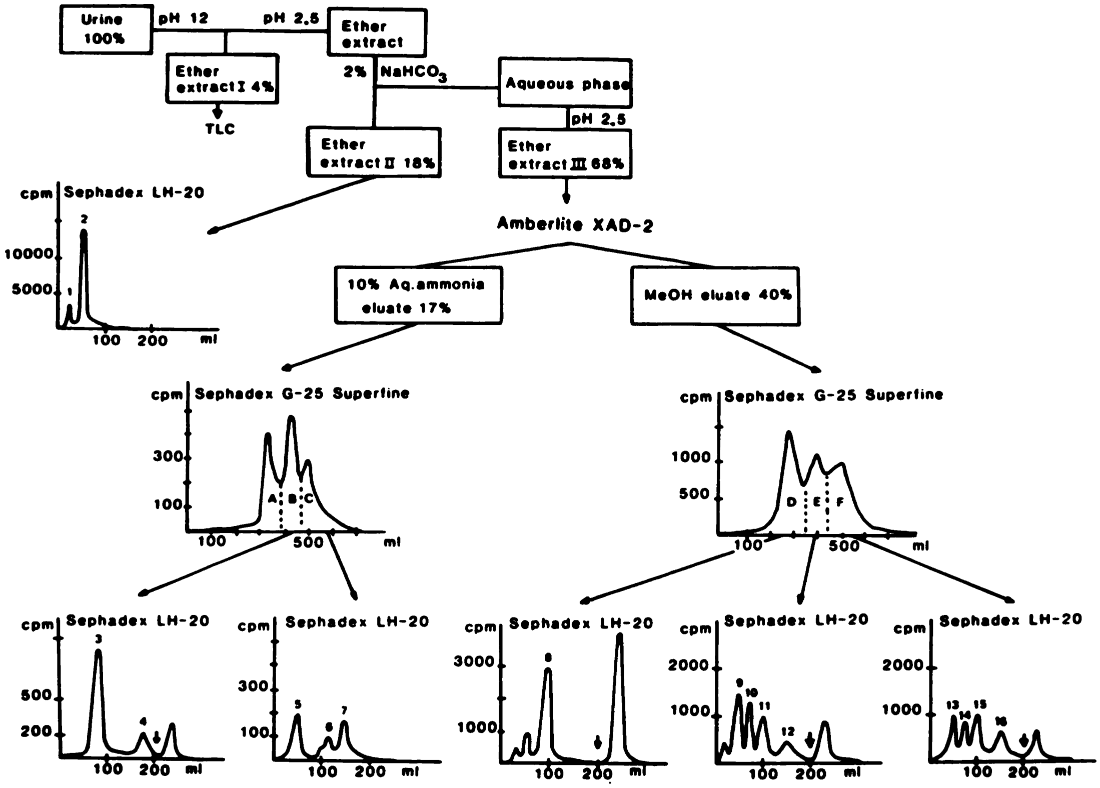


FIG. 13. Scheme for isolation of acidic metabolites in human urine (34, 35).

assay and metabolism of cannabinoids cited numerous experimental procedures (33).

B. Primary Metabolites

The experimental procedures in metabolic studies have obviously differed, depending upon the goals of the various investigations. Thus, in addition to conventional in vivo studies, certain in vitro metabolic techniques have been used mainly for two purposes: (*a*) to allow the formation of sufficient metabolites or using large amounts of "10,000 × *g* supernatant" from human or animal liver to enable a partial purification or actual isolation for the identification of the chemical structures of primary metabolites, or (*b*) to study enzymes, mechanisms, and interactions in the biotransformation of cannabinoids under more optimal conditions.

The compounds designated as "primary metabolites" have, in general, been isolated from in vitro experiments and have undergone one or two metabolic reactions, usually equivalent to the introduction of two hydroxyl groups. Excreted metabolites, particularly those in urine, have often undergone several metabolic reactions, although many exceptions are known; e.g., Δ^1-THC is eliminated in the urine to a small extent as the ether glucuronide (75, 37).

All the early isolated and structurally identified metabolites of Δ^1-THC (and also of CBD and CBN) were obtained from in vitro studies using liver preparations. The reason for this is that the major in vitro metabolites are only mono- or dihydroxylated compounds, and, since they are present in comparatively large amounts, they are more readily recognized.

7-Hydroxy-Δ^1-THC (5)was the first metabolite to be isolated, and its structure was proven by NMR and MS in 1970 by Nilsson et al. (74) and Wall et al. (96). The analogous hydroxylation of Δ^6-THC to 7-hydroxy-Δ^6-THC was shown by Burstein et al. (16) and Foltz et al. (28). The structure of 7-hydroxy-Δ^1-THC (5) is found in table 3. Approximately 80 metabolites of Δ^1-THC are now known, but table 3 only shows the structures of mono- and dioxygenated compounds, the structures of urinary metabolites identified in man, and some unusual metabolites (42). The conversion of Δ^1-THC to hydroxylated species is known to be microsomal and requires NADPH and molecular oxygen. The reaction is inhibited by carbon monoxide, indicating the involvement of cytochrome P-450 (15). Hydroxylation in the 7-position is the major initial reaction in all species except the dog. The unnatural isomer (+)-Δ^1-THC is also metabolized in the mouse in the same ways as (−)-Δ^1-THC, with (+)-7-hydroxy-Δ^1-THC being the major metabolite (56). This experiment invalidated the speculation that the apparent inactivity of (+)-Δ^1-THC in behavioral tests might be due to a lack of bioactivation. It was quickly found that (−)-7-hydroxy-Δ^1-THC was about equipotent with (−)-Δ^1-THC, even in man (96, 88a, 98, 62). This finding greatly stimulated further studies on the metabolism of Δ^1-THC and on the psychoactivity of Δ^1-THC metabolites.

Hydroxylations occur most readily in positions allylic to the double bond, as evidenced by the facile formation of 7-hydroxy-Δ^1-THC and also of the 6α- (6) and 6β-hydroxy (7) compounds (table 3). The two epimers are usually formed in roughly equal amounts; otherwise, the α-epimer dominates. Both the 6α- and the 6β-hydroxy groups can be further oxidized (43, 18, 57) to the ketone, Δ^1-THC-6-one (21). So far, no metabolite carrying a hydroxyl group in the allylic 3-position has been found. This may, however, be a position which is not readily accessible to metabolic reactions.

All major cannabinoids carry a pentyl side-chain which can be attacked by metabolizing enzymes. The first side-chain-hydroxylated metabolites, the 1″- and 3″-hydroxy metabolites, were discovered by Maynard et al. in the Δ^6-THC series as minor products of a dog liver supernatant (71). Since then, we and others (45, 102, 46) have found four side-chain-monohydroxylated compounds in the Δ^1-THC-series: 1″-hydroxy- (8); 2″-hydroxy- (9); 3″-hydroxy- (10); and 4″-hydroxy-Δ^1-THC (11, table 3).

5″-Hydroxy-Δ^1-THC has not yet been identified, neither as a monooxygenated metabolite nor as a further hydroxylated species. The identification of Δ^1-THC-5″,7-dioic acid as a metabolite of Δ^1-THC in rabbit (76) also indicates that the 5″-position of Δ^1-THC is prone to be metabolized. As discussed later, considerable species and tissue variations occur with respect to side-chain hydroxylation but, in general, it seems to be a minor pathway where 3″- and 4″-position oxygenation is favored. The occurrence of major urinary metabolites in man (section V E) with a shortened side-chain can be taken as circumstantial evidence that side-chain hydroxylations may be an initial or early reaction in the formation of these metabolites.

The stereochemistry (R and S) of the introduction of the hydroxyl group in the side-chain is not known. Harvey et al. have, however, observed by GC of the trimethylsilyl derivates that 1″-hydroxy-Δ^1-THC was present as diastereoisomers in unequal quantities in the livers of Δ^1-THC-treated guinea-pigs (46).

A number of dihydroxylated Δ^1-THC metabolites are shown in table 3. In essence, all the possibilities suggested by the monooxygenated metabolites are encountered: hydroxylation of the 7-position combined with hydroxylation of 6α- or 6β- or 1″- to 4″-positions in the side-chain; 6β-hydroxylation combined with side-chain hydroxylation; or two side-chain hydroxylations in the same metabolite. Only one example (20, table 3) of trioxygenated Δ^1-THC metabolites is shown, but several other metabolites of this type have been identified, representing the same pattern of hydroxylation as in compounds 12 to 19. The occurrence of a keto function, as in Δ^1-THC-6-one (21), in combination with a hydroxy or a carboxy group is quite common.

The presence of the allylic double bond would indicate the possibility of an epoxydation, and the expected product 1α,2α-epoxyhexahydrocannabinol (22), or its 7-hydroxy derivative, has been identified in rabbit (12), dog (45), and man (38). Δ^1-THC and other cannabinoids are rapidly oxidized by the hepatic mixed-function oxidases. Other tissues, such as intestines (*cf.* 42) and lung (102, 36), also have some capacity for metabolic activity. Of considerable interest is the finding in the dog (102), rat, and guinea-pig (36) that biotransformation of Δ^1-THC in lung tissues showed a quite different quantitative pattern from the liver. Dog liver (102) predominantly formed 6α- and 6β-hydroxylated Δ^1-THC metabolites, whereas the lung produced 3″- and 4″-hydroxy-Δ^1-THC. The perfused lungs of rats and guinea-pigs (36) converted Δ^1-THC mainly to 4″-hydroxy-Δ^1-THC, whereas the livers gave 7-hydroxy-Δ^1-THC as the major product.

Species differences of a quantitative nature can also be found. In the mouse, 6α-hydroxylation is dominant over β-hydroxylation (42), whereas in man and guinea-pig, the reverse is true. Side-chain hydroxylation occurs widely in many species but is less important in man. Thus, one has to be aware of species and tissue differences in metabolism, but on the whole, these are usually of minor importance.

Primary metabolites found in man. Primary metabolites of Δ^1-THC in man have been isolated as products of 10,000 × *g* supernatant of induced (antiepileptic drug treatment) and noninduced human livers (38). The metabolic patterns were similar in the livers, with 7-hydroxy-Δ^1-THC as the most abundant metabolite. They all formed compounds oxygenated in the 6-position, but side-chain oxygenation was most pronounced in the induced liver. Trace amounts of an epoxide were formed. Table 4 shows the relative proportions of mono- and dihydroxylated metabolites.

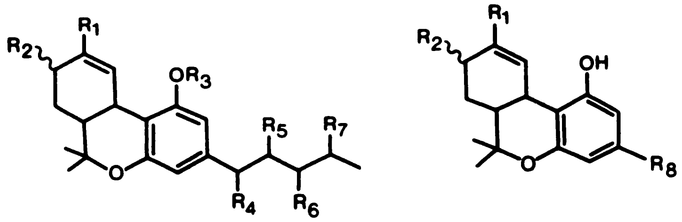
The results in table 4 are based on quite limited material, but they indicate only quantitative differences in the metabolism of Δ^1-THC (38). Hydroxylation in the 7-position of Δ^1-THC is by far the dominating metabolic reaction.

Wall and his group (97, 98, 96) and Lemberger et al. (63) have investigated the occurrence of primary metabolites in plasma after p.o. and i.v. administration of radiolabeled Δ^1-THC in man. Following i.v. infusion (98), the levels of 7-hydroxy-Δ^1-THC and 6β-hydroxy-Δ^1-THC in plasma are quite similar and at about 1/10 of the level of Δ^1-THC itself. The amounts of 6α-hydroxy-Δ^1-THC and 6,7-dihydroxy-Δ^1-THC are less than ½ of the 6β-hydroxy compound. Other more polar metabolites occur much more abundantly. After p.o. administration, the amount of 7-hydroxy-Δ^1-THC in plasma is about equal to that of Δ^1-THC itself (98). The relative proportion of dihydroxylated Δ^1-THC is also increased after p.o. ingestion of Δ^1-THC.

The findings of both the in vivo and in vitro experiments in man are congruent. Hydroxylation to 7-hydroxy-Δ^1-THC is the major initial metabolic reaction

TABLE 3

Chemical structures of some Δ^1-THC metabolites. The metabolites with the previs H have been identified as metabolites in humans. Structures 24 to 43 have been isolated as urinary excretion products



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Ref.
H 5 7-OH-Δ^1-THC	CH_2OH	H	H	H	H	H	H	C_5H_{11}	38, 74, 96, 97
H 6 6α-OH-Δ^1-THC	CH_3	α-OH							20, 38, 97, 102
H 7 6β-OH-Δ^1-THC	CH_3	β-OH							38, 45, 97, 102
8 1″-OH-Δ^1-THC	CH_3			OH					45, 46
H 9 2″-OH-Δ^1-THC	CH_3				OH				38, 45, 46
10 3″-OH-Δ^1-THC	CH_3					OH			36, 45, 102
11 4″-OH-Δ^1-THC	CH_3						OH		13, 36, 102
H 12 6α,7-diOH-Δ^1-THC	CH_2OH	α-OH							12, 38, 45, 46, 97
H 13 6β,7-diOH-Δ^1-THC	CH_2OH	β-OH							38, 45
14 1″,7-diOH-Δ^1-THC	CH_2OH			OH					46
H 15 2″,7-diOH-Δ^1-THC	CH_2OH				OH				38, 45, 46
H 16 3″,7-diOH-Δ^1-THC	CH_2OH					OH			38, 45, 46
H 17 4″,7-diOH-Δ^1-THC	CH_2OH						OH		13, 38
18 1″,6β-diOH-Δ^1-THC	CH_3	β-OH		OH					46
19 1″,3″-diOH-Δ^1-THC	CH_3			OH		OH			46
20 1″,6α,7-triOH-Δ^1-THC	CH_2OH	α-OH		OH					46
H 21 Δ^1-THC-6-one	CH_3	═0							18, 38, 57
22 Epoxyhexahydrocannabinol (EHHC)*	CH_3								12, 102
23 7-oxo-Δ^1-THC	CHO								11
H 24 Δ^1-THC-7-oic acid	COOH								11, 45, 46, 58, 76, 97, 98
H 25 Δ^1-THC-3″-oic acid	CH_3							C_2H_4COOH	35, 45, 46, 76
H 26 1″-OH-Δ^1-THC-7″-oic acid	COOH			OH					35, 46
H 27 2″-OH-Δ^1-THC-7″-oic acid	COOH				OH				35, 45, 46, 75
H 28 3″-OH-Δ^1-THC-7″-oic acid	COOH					OH			35, 45, 46, 75
H 29 4″-OH-Δ^1-THC-7″-oic acid	COOH						OH		35, 45, 46, 75
H 30 3″,4″,5″-trisnor-2″-OH-Δ^1-THC-7-oic acid	COOH							C_2H_4OH	35, 76
H 31 7-OH-Δ^1-THC-2″-oic acid	CH_2OH							CH_2COOH	35
H 32 6β-OH-Δ^1-THC-2″-oic acid	CH_3	β-OH						CH_2COOH	35, 76
H 33 7-OH-Δ^1-THC-3″-oic acid	CH_2OH							C_2H_4COOH	35, 75
H 34 6β-OH-Δ^1-THC-3″-oic acid	CH_3	β-OH						C_2H_4COOH	35, 76
H 35 6α-OH-Δ^1-THC-4″-oic acid	CH_3	α-OH						C_3H_6COOH	35
H 36 2″,3″-dehydro-6α-OH-Δ^1-THC-4″-oic acid	CH_3	α-OH						C_3H_4COOH	35
H 37 Δ^1-THC-1″,7-dioic acid	COOH							COOH	34, 76
H 38 Δ^1-THC-2″,7-dioic acid	COOH							CH_2COOH	34
H 39 Δ^1-THC-3″,7-dioic acid	COOH							C_2H_4COOH	34, 76
H 40 Δ^1-THC-4″,7-dioic acid	COOH							C_3H_6COOH	34
H 41 1″,2″-dehydro-Δ^1-THC-3″,7-dioic acid	COOH							C_2H_2COOH	34, 76
H 42 Δ^1-THC-glucuronic acid	CH_3		gluc†						37, 75
H 43 Δ^1-THC-7-oic acid glucuronide	COO	gluc†							59, 103

* Epoxy group in C-1 and C-2 position.

† Glucuronide.

TABLE 4

Approximate relative proportion and structures of metabolites formed (in vitro) by human livers (from ref. 38)

Metabolite	Structure	Noninduced	Induced
7-Hydroxy-Δ^1-THC	5	100	100
6α-Hydroxy-Δ^1-THC	6	2	2
6β-Hydroxy-Δ^1-THC	7	7	4
$2''$-Hydroxy-Δ^1-THC	9	1	
Δ^1-THC-6-one	21	1	7
6α,7-Dihydroxy-Δ^1-THC	12	1	27
6β,7-Dihydroxy-Δ^1-THC	13	1	47
$2''$,7-Dihydroxy-Δ^1-THC	15		7
$3''$,7-Dihydroxy-Δ^1-THC	16	Trace	2
$4'$,7-Dihydroxy-Δ^1-THC	17		1
7-Hydroxy-EHHC*		Trace	1

* Structure 22 with an additional hydroxyl group in 7-position.

with Δ^1-THC and, as discussed under section II G, this probably contributes considerably to the effects of Δ^1-THC per se, but only after *p.o.* administration. 6β-Hydroxylation is favored over 6α-hydroxylation. Other routes, such as epoxydation and side-chain hydroxylation at C-$2''$, C-$3''$, and C-$4''$, appear to be quite minor routes in man. However, about ½ of the amount of metabolites excreted in the urine of man (table 3) has a modified side-chain.

C. Psychoactivity of Metabolites

A number of metabolites of Δ^1-THC have been tested for psychoactivity and other pharmacological effects in man. After i.v. administration of Δ^1-THC in man, the metabolite 7-hydroxy-Δ^1-THC was found to be about equipotent to Δ^1-THC in producing marihuana-like symptoms and increased pulse rate (88a). Furthermore, Lemberger et al. found that both Δ^1-THC and 7-hydroxy-Δ^1-THC had a similar pharmacological profile and a similar disposition in man (62). Perez-Reyes and coworkers found that 6β-hydroxy-Δ^1-THC had a similar effect to Δ^1-THC but was clearly less potent (88a). These workers also showed that 6α-hydroxy-Δ^1-THC was essentially inactive in man. Δ^1-THC-7-oic acid is also without effect in man (98).

These results in man are in general agreement with results in animals. The validity of animal models (behavioral responses in mice, rats, dogs, monkeys, and cataleptic effects in the mouse) as indicators of psychotomimetic effects in man is by no means clear (39, 85, 72). However, animal experiments in the Δ^1-THC series suggest that 7-hydroxy-Δ^1-THC is more or less equipotent with Δ^1-THC, while 6α-hydroxy-Δ^1-THC is about ⅙ and 6β-hydroxy-Δ^1-THC is about ⅓ as potent (88a).

The activity of side-chain-hydroxylated compounds has been more extensively studied in the Δ^6-THC series (85, 77). On the basis of behavioral tests in the rhesus monkey, it was concluded that monohydroxylation at the $3''$-, $4''$-, or $5''$-position yielded metabolites which were at least as potent as Δ^6-THC, whereas $2''$-hydroxylation decreased the activity and $1''$-hydroxylation essentially abolished the activity (77).

In the mouse cataleptic test, Δ^6-THC, 7-hydroxy-Δ^6-THC, $3''$-hydroxy-Δ^6-THC, and $1\alpha,2\alpha$-epoxyhexahydrocannabinol were equipotent with Δ^6-THC (85). $5''$-Hydroxy-, $4''$-hydroxy-, $2''$-hydroxy-, and $1''$-hydroxy-Δ^6-THC were less active. It was also found in this study that structural factors rather than distribution to the brain were important in determining the cataleptic/psychoactive effects, although all monohydroxylated compounds reached the brain more quickly and to a larger extent than Δ^6-THC.

Martin et al. (68) have recently reviewed the pharmacological activity of Δ^6-THC metabolites and concluded that $3''$-hydroxy-Δ^1-THC is more potent (2 to 3 times) than Δ^1-THC. Hydroxylation in the $3''$- or 7-position retained or enhanced the activity of Δ^1-THC, but the combination $3''$-, 7-dihydroxy-Δ^1-THC clearly reduced the activity.

D. Routes and Rates of Excretion

If one makes a rough estimate of the elimination of Δ^1-THC in man, one finds that about ⅔ of the dose is excreted in feces and about ⅓ in the urine, all as metabolites (34, 35, 98). The elimination is quite slow, with about 50% of the dose being excreted in 4 to 5 days. A similar slow elimination rate is found in the dog, rabbit, and rat. Studies on the fate of Δ^1-THC in various animals appear to be roughly similar: viz. rapid disappearance of Δ^1-THC after i.v. administration; rapid formation of high levels of metabolites; sequestration of Δ^1-THC into various tissues; hepatic recycling of metabolites; and preferential elimination of metabolites (usually more than ⅔) via feces (26, 39). Neither Δ^1-THC nor CBD is excreted in the urine in unmetabolized form, but traces of CBN may occur (97, 98). Some Δ^1-THC may be excreted in feces (98), presumably as a hydrolysis product after elimination as the glucuronide in the bile (37, 103). More of the metabolites are excreted in the urine of rabbits (8) than of rats and mice (91, 92). The slow elimination in man indicates that the metabolites are also retained in the body and that enterohepatic circulation of Δ^1-THC metabolites is important (47, 97, 98). The conjugated fraction of metabolites in feces is small in contrast to urine, which may be the result of gastrointestinal hydrolysis of metabolites eliminated as conjugates. Free 7-hydroxy-Δ^1-THC seems to be the major fecal constituent in man, together with Δ^1-THC-7-oic acid (97, 98).

E. Metabolites in Urine and Feces

The first two urinary metabolites to be identified were metabolites 26 and 27 (table 3). They were tentatively identified by Burstein et al. as urinary metabolites of Δ^1-THC in rabbits (17). These two compounds possess a carboxyl function at the 7-position and additional hydroxyl groups at the $1''$- and $2''$-positions in the side-chain. Since oxidation at C-7 was previously established as a major route of metabolism, the finding that this position was further oxidized to a carboxyl group in urinary metabolites was to be expected. Indeed, most of the over 30 acidic metabolites so far isolated carry a carboxylic function in this position.

The further transformation of 7-hydroxy-Δ^1-THC (5) would presumably occur via the aldehyde 7-oxo-Δ^1-THC (23), a metabolite which was identified in small amounts as an incubation product of Δ^1-THC with rat liver microsomes (11).

Δ^1-THC-7-oic acid (24) has been identified as a metabolite in the guinea-pig, mouse, rabbit, rat, and man (97, 98, 42). Some of the acid is found in free form, but most of it is apparently conjugated as an ester glucuronide and perhaps also as the ether glucuronide (98, 103). The acid 24 is also referred to as 11-nor-Δ^9-THC-9-COOH, 11-carboxy-Δ^9-THC (98), or Δ^9-THC-11-oic acid (42).

A series of unsubstituted monocarboxylic acids (e.g., 25), carrying the carboxylic function in positions 1″ to 4″ in the side-chain, have been identified in the guinea-pig (46). The major acid (25), containing a 3-carboxy group, has also been identified in the mouse, rabbit, rat, and man.

It has also been assumed that shortening of the side-chain may be due to β-oxidation (46), and the occurrence of metabolite 41 may indirectly support this. On the other hand, Wall and Perez-Reyes have shown that Δ^1-THC-7-oic acid, administered i.v., is essentially eliminated without further metabolism, except for possible conjugation (98). Thus, acids may be eliminated efficiently.

The structures of 19 urinary metabolites of Δ^1-THC in the rabbit were established by Nordqvist et al. (75, 76). This represents only about 20% of the metabolites of Δ^1-THC present in the rabbit urine. The main compound isolated was 4″-, 5″-bisnor-Δ^1-THC-7,-3″-dioic acid (39) which was later found to be a main metabolite of Δ^1-THC in urine of man (34). Allylic hydroxylation at C-7 was found to be a major metabolic route, followed by oxidation of C-1″ and C-3″. Only two monocarboxylic acids were identified (24, 25). Two other isolated structures are shown as metabolites 28 and 29. Later, a large number of acidic metabolites were identified by Harvey et al., after extraction of tissues from animals administered Δ^1-THC (46). A number of urinary Δ^1-THC metabolites are also shown in table 3. The diversity encountered among the primary metabolites of Δ^1-THC is also amply illustrated for urinary metabolites, the only difference being further oxidation to acids and, sometimes, shortening of the side-chain. Several urinary glucuronides have been identified so far; e.g., the glucuronide of Δ^1-THC itself (37, 75) and the ester glucuronide of Δ^1-THC-7-oic acid (76, 98, 59, 103, 37). A further and unusual glucuronide, the 4′-C-glucuronide of Δ^6-THC, has been identified as a metabolic product of Δ^6-THC in vitro (65). Moreover, the glucuronides of 7-hydroxy-Δ^1-THC and 5″-hydroxy-Δ^1-THC have been identified in in vitro experiments (72). Most of the conjugates (ester-type glucuronides) are readily hydrolyzed by chemical (34, 35), and less readily by enzymatic, means (34, 35, 98). At present, it seems to be unclear how much of the acid 24 that exists is in conjugated or unconjugated form. As is the case for the β-glucuronide of furosemide, which is unstable at urinary pH and readily transformed to isomeric glucuronides resistant to β-glucuronidase (93), we expect the ester glucuronide of Δ^1-THC-7-oic acid to be unstable.

Metabolites excreted in man. All metabolites of Δ^1-THC identified in the urine of man or animals are of acidic nature. Fecal excretion is the major excretion route for Δ^1-THC metabolites in man, approximately 35% being eliminated by this route within 72 h. About 15% are excreted in the urine during this same period of time (98, 34, 35). The metabolites in feces are diverse with both neural, acidic, and acidic polar compounds present (98). The elimination of metabolites in man is slow, and recent data based upon RIA methods suggest that urinary Δ^1-THC metabolites may be eliminated for several weeks after the cessation of marihuana use (23).

The major metabolites in feces are 7-hydroxy-Δ^1-THC and Δ^1-THC-7-oic acid (98).

The metabolite pattern in urine is more complex, and fig. 14 shows the structures of Δ^1-THC and 18 nonconjugated metabolites isolated from human urine after p.o. administration of Δ^1-THC (34, 35). All compounds except 24 are oxidized in the side-chain. It appears likely that most of these acids were at least partly eliminated as ester glucuronides, since the original urine sample was subjected to mild base treatment to hydrolyze ester glucuronides.

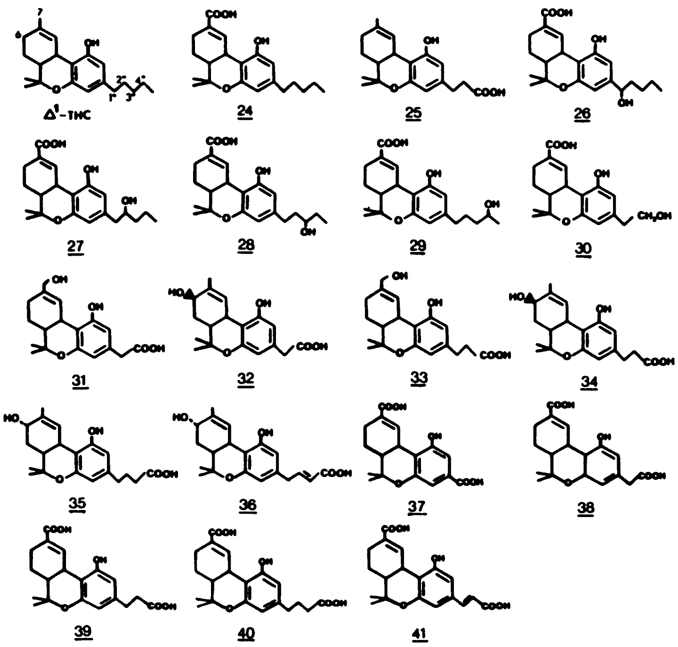


FIG. 14. Structures of Δ^1-THC metabolites isolated from human urine. The compound numbering system is the same as in table 3.

About ⅔ of the metabolites (34, 35) in human urine were identified and, in addition to the compounds shown in fig. 14, the ether glucuronide of Δ^1-THC (35) was also identified (table 3, 42, R_3 = glucuronate). Δ^1-THC-7-oic acid (24) was the most abundant metabolite (27% of the urinary metabolites), followed by the diacid 39 (8%), the 4″-hydroxy acid 29 (5%), and the acids 41, 31, 30, 32, 33, and 27 in decreasing abundance from 3 to 1% of the total amount of urinary metabolites. The remainder (fig. 14) are present within the range of 1% to trace amounts (34, 35).

The consistent occurrence of side-chain oxidation in all metabolites except 24 indicates that side-chain hydroxylation may channel the further metabolism to a compound excreted via the kidneys.

VI. Metabolism of CBD and CBN

Since Δ^1-THC is the main psychoactive principle of cannabis, metabolic and other studies have heavily focused on this compound. CBD and CBN are two other major cannabinoids and, as discussed elsewhere, there is conflicting evidence whether they interfere with the actions or kinetics of Δ^1-THC (1, 39, 72).

CBD was readily converted to a number of metabolites (table 5). 7-Hydroxy-CBD was by far the main metabolite in the rat liver, followed by 6α- and 6β-hydroxy-CBD (70). Hydroxylation was also found in all positions of the side-chain. A large number of dihydroxylated CBD-metabolites were also identified (67). The monohydroxylated metabolites and some dihydroxylated metabolites are shown in table 5, together with the major urinary CBD acid in man. The metabolite pattern is similar to that of Δ^1-THC (table 3). Almost 90% of the dioxygenated material was present as 7-hydroxylated metabolites. Side-chain hydroxylation occurred mainly at C-4″ and to a lesser degree at C-3″. The metabolism of CBD in vivo in the mouse (69) is unusually diverse, with metabolites showing a simple glucuronidation of CBD (44, R_3 = glucuronate), CBD-7-oic acid (56), partial loss of side-chain (57), and more complex metabolites.

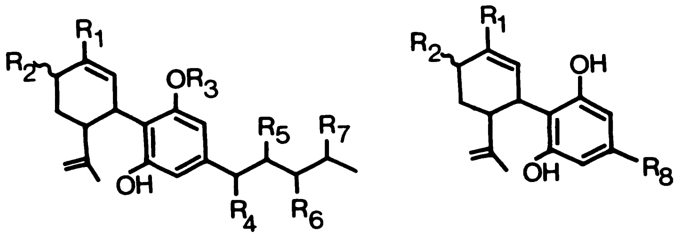
In man, CBD seems to be metabolized in a similar way as in animals, although the information is limited (97). Monohydroxylated CBD metabolites are quickly formed, primarily 7-hydroxy-CBD. One major metabolite in both plasma and urine is CBD-7-oic acid, but the amount of more polar metabolites formed seems larger than for Δ^1-THC. After i.v. administration, some CBD is eliminated in the urine in the conjugated form. Free CBD, in large amounts, is excreted in the feces. The excretion rate of metabolites in human urine is similar (16% in 72 h) to that of Δ^1-THC in man (97).

The metabolic patterns for CBN are less diverse, since one more ring is aromatic in nature. The major metabolite is 7-hydroxy-CBN (101); otherwise, all positions in the side-chain are available for metabolic oxidation (table 6), which can lead to numerous but expected end products, analogous with Δ^1-THC and CBD (101, 44, 104, 29, 106, 105). Monohydroxylated metabolites have also been identified as esters of long chain fatty acids (104).

CBN is metabolized in man (97) to large amounts of monohydroxy-CBN, as revealed by analysis of feces after i.v. administration. The level in plasma of 7-hydroxy-CBN is about $\frac{1}{10}$ of the CBN concentration. Dihydroxy-CBN, CBN-7-oic acid, and more polar metabolites are

TABLE 5

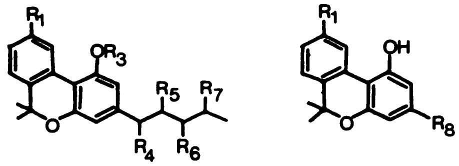
Structures of some metabolites of CBD



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Ref.
44 CBD	CH_3	H	H	H	H	H	H	C_5H_{11}	
45 7-OH-CBD	CH_2OH								46, 70
46 6α-	CH_3	α-OH							46, 70
47 6β-	CH_3	β-OH							46, 70
48 1″-	CH_3			OH					46, 70
49 2″-	CH_3				OH				70
50 3″-	CH_3					OH			46, 70
51 4″-	CH_3						OH		46, 70
52 5″-	CH_3							$C_4H_8CH_2OH$	46, 70
53 6,7-diOH-CBD	CH_2OH	OH							46, 67
54 3″,7-diOH-CBD	CH_2OH					OH			46, 67
55 4″,7-diOH-CBD	CH_2OH						OH		46, 67
56 CBD-7-oic acid	COOH								97
57 CBD-3″-oic acid	CH_3							C_2H_4COOH	68

TABLE 6

Structures of some CBD metabolites



Compound	R_1	R_3	R_4	R_5	R_6	R_7	R_8	Ref.
58 CBN	CH_3	H	H	H	H	H	C_5H_{11}	
59 7-OH-CBN	CH_2OH							101, 46, 92
60 1″-OH-CBN	CH_3		OH					44, 106, 46
61 2″-OH-CBN	CH_3			OH				44, 106
62 3″-OH-CBN	CH_3				OH			106, 46, 97
63 4″-OH-CBN	CH_3					OH		44, 46
64 5″-OH-CBN	CH_3						$C_4H_8CH_2OH$	44, 106
65 2″-7-diOH-CBN	CH_2OH			OH				29
66 CBN-7-oic-acid	COOH							97, 44
67 CBN-1″-oic acid	CH_3						COOH	44, 105
68 CBN-3″-oic acid	CH_3						C_2H_4COOH	44

also formed. Only about 8% of the CBN dose was found to be excreted in urine within 72 h, whereas 35% was excreted in the feces over this same time period.

VII. Conclusions

Plasma Δ^1-THC profiles were found to be similar after i.v. injection and smoking of Δ^1-THC. Immediately after smoking 10 to 20 mg of Δ^1-THC, as a marihuana cigarette, plasma Δ^1-THC levels of about 100 ng/ml were estimated; at 1 h, they were in the range of 10 ng/ml; at 4 h, about 1 ng/ml; and about 0.1 ng/ml at 24 to 72 h, indicating a slow terminal elimination. Most investigators estimate the terminal half-life of Δ^1-THC to be in the range of 20 to 36 h.

The systemic availability of smoked Δ^1-THC (comparison of AUC for smoked *versus* i.v. Δ^1-THC) was higher (23 ± 16%) in a group of heavy marihuana users compared to a group of light users (10 ± 7%). The variation in availability was 10-fold within each group. Administration of Δ^1-THC p.o. yields slow and erratic absorption (systemic availability, 6 ± 3%).

The average plasma clearance values are high (950 ml/min) for both heavy and light users and approach total hepatic blood flow. Other studies suggest limited variation in pharmacokinetic parameters between heavy and light users, indicating that the development of tolerance to behavioral and pharmacological effects in THC users is most likely functional and not dispositional.

Δ^1-THC is initially metabolized in man in a way similar to that in most animals, i.e., by preferential allylic oxidation to 7-hydroxy-Δ^1-THC. In addition, 6β-hydroxylation is favored over 6α-hydroxylation, whereas side-chain hydroxylation and epoxydation appear to be marginal pathways in man. Side-chain hydroxylation may preferentially lead to elimination via urine. 7-Hydroxy-Δ^1-THC will probably only contribute to a small degree to the effects of Δ^1-THC per se when smoked, whereas it could be approximately equal in effect to Δ^1-THC after p.o. administration.

Δ^1-THC-7-oic acid (as the ester glucuronide) is the major urinary Δ^1-THC metabolite in man. Almost all other identified urinary Δ^1-THC metabolites (10 to 15% of dose in 48 h) show a side-chain containing either a hydroxyl group or a carboxylic function.

The relations of plasma Δ^1-THC levels to psychological and physiological effects of Δ^1-THC are complex. A temporal dissociation between plasma concentrations and effects is evident and may possibly be explained by a somewhat slow penetration of the blood-brain barrier, slow distribution within the brain, and a lag-time in biochemical reactions.

The pharmacokinetics and metabolism of CBD and CBN in man and animals follow the pattern similar to that of Δ^1-THC.

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