

# Pharmacokinetics and Pharmacodynamics of Cannabinoids

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## Abstract

$\Delta^9$ -Tetrahydrocannabinol (THC) is the main source of the pharmacological effects caused by the consumption of cannabis, both the marijuana-like action and the medicinal benefits of the plant. However, its acid metabolite THC-COOH, the non-psychotropic cannabidiol (CBD), several cannabinoid analogues and newly discovered modulators of the endogenous cannabinoid system are also promising candidates for clinical research and therapeutic uses. Cannabinoids exert many effects through activation of G-protein-coupled cannabinoid receptors in the brain and peripheral tissues. Additionally, there is evidence for non-receptor-dependent mechanisms.

Natural cannabis products and single cannabinoids are usually inhaled or taken orally; the rectal route, sublingual administration, transdermal delivery, eye drops and aerosols have only been used in a few studies and are of little relevance in practice today. The pharmacokinetics of THC vary as a function of its route of administration. Pulmonary assimilation of inhaled THC causes a maximum plasma concentration within minutes, psychotropic effects start within seconds to a few minutes, reach a maximum after 15–30 minutes, and taper off within 2–3 hours. Following oral ingestion, psychotropic effects set in with a delay of 30–90 minutes, reach their maximum after 2–3 hours and last for about 4–12 hours, depending on dose and specific effect.

At doses exceeding the psychotropic threshold, ingestion of cannabis usually causes enhanced well-being and relaxation with an intensification of ordinary sensory experiences. The most important acute adverse effects caused by overdosing are anxiety and panic attacks, and with regard to somatic effects increased heart rate and changes in blood pressure. Regular use of cannabis may lead to dependency and to a mild withdrawal syndrome. The existence and the intensity of possible long-term adverse effects on psyche and cognition, immune system, fertility and pregnancy remain controversial. They are reported to be low in humans and do not preclude legitimate therapeutic use of cannabis-based drugs.

Properties of cannabis that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, sedation, improvement of mood, stimulation of appetite, antiemesis, lowering of intraocular pressure, bronchodilation, neuroprotection and induction of apoptosis in cancer cells.

The chemical structure of the first phytocannabinoids was successfully characterised in the 1930s and 1940s,<sup>[1]</sup> but it was not until 1964 that the chemical structure of  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), mainly responsible for the pharmacological effects of the cannabis plant,<sup>[2,3]</sup> had been identified and synthesised.<sup>[4]</sup> Another scientific breakthrough in cannabinoid research has been the detection of a system of specific cannabinoid receptors in mammals<sup>[5]</sup> and their endogenous ligands<sup>[6]</sup> within the past 15 years.

## 1. Taxonomy

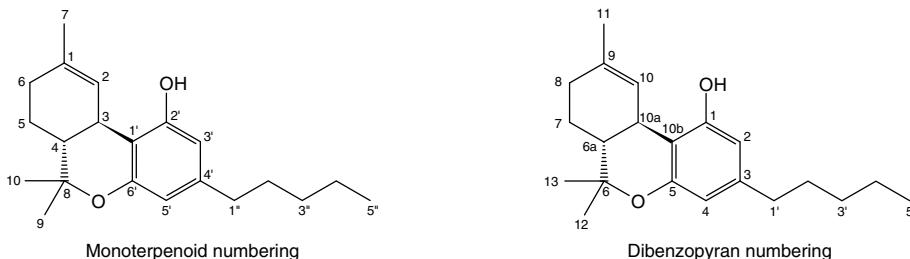
Originally, the term cannabinoid referred to the phytocannabinoids of *Cannabis sativa* L. with a typical C<sub>21</sub> structure and their transformation products,<sup>[7]</sup> but this restricted pharmacognostic definition has been discarded in favour of a broader concept based on pharmacology and synthetic chemistry.<sup>[8]</sup> Today the term cannabinoid may comprise all ligands of the cannabinoid receptor and related compounds, including endogenous ligands of the receptors and a large number of synthetic cannabinoid analogues.

The phytocannabinoids have been numbered according to the monoterpenoid system or the dibenzopyran system (figure 1); the latter system will be employed in this review. A total of 66 phytocannabinoids have been identified, most of them belonging to several subclasses or types:<sup>[9]</sup> the cannabigerol (CBG), cannabichromene (CBC), can-

nabidiol (CBD),  $\Delta^9$ -THC,  $\Delta^8$ -THC, cannabicyclol (CBL), cannabiolsoin (CBE), cannabinol (CBN), cannabidiol (CBDL) and cannabitriol (CBTL) types. A total of nine cannabinoids belong to the  $\Delta^9$ -THC group, with side chains of one, three, four and five carbons (figure 2 and table I).

The cannabinoid acids of  $\Delta^9$ -THC, CBD, CBC and CBG are the quantitatively most important cannabinoids present in the plant (see table II and figure 3). Their relative concentrations vary, and plants have been described that mainly contain one of these cannabinoids with a C<sub>5</sub> side chain or contain the propyl homologue (C<sub>3</sub> side chain) of  $\Delta^9$ -THC ( $\Delta^9$ -trans-tetrahydrocannabivarin);<sup>[10-12]</sup> the methyl (C<sub>1</sub> side chain) and butyl (C<sub>4</sub> side chain) homologues are always present in very low concentrations.<sup>[13,14]</sup>

The cannabinoid acids of THC are devoid of psychotropic effects<sup>[2]</sup> and have to be decarboxylated to the phenols to produce marijuana-like effects, e.g. by smoking the dried plant matter. The ratio of  $\Delta^9$ -THC acids to phenolic  $\Delta^9$ -THC has been reported to range between 2 : 1<sup>[11]</sup> and >20 : 1<sup>[16]</sup> in leaves and flowers of *Cannabis sativa*. In plants grown in the United Kingdom from Moroccan, Sri Lankan and Zambian seed stock, the  $\Delta^9$ -THC acids/ $\Delta^9$ -THC ratio was 17 : 1 compared with 2 : 1 in the plants from the original areas with hotter climates.<sup>[11]</sup> In cannabis resin (hashish), the THC acids/THC ratio was reported to range between 6.1 : 1 and 0.5 : 1.<sup>[17]</sup>



**Fig. 1.** Chemical structure of tetrahydrocannabinol (THC), the main cannabinoid in the cannabis plant, numbered according to the monoterpenoid system ( $\Delta^1$ -THC) and dibenzopyran system ( $\Delta^9$ -THC).

Natural  $\Delta^9$ -THC has two chiral centres at C-6a and C-10a in the *trans* configuration. Usually the acronym THC is applied to this naturally occurring (*-trans*-isomer of  $\Delta^9$ -THC, and will be used in this text as well. The generic name for  $\Delta^9$ -*trans*-tetrahydrocannabinol is dronabinol. Marinol<sup>TM1</sup> (Unimed Pharmaceuticals, Inc.) contains synthetic dronabinol, dissolved in sesame oil, as capsules of 2.5, 5 and 10mg of dronabinol.

## 2. Physicochemical Properties and Degradation of Dronabinol

THC and many of its metabolites are highly lipophilic and essentially water-insoluble.<sup>[18]</sup> Calculations of the n-octanol/water partition coefficient ( $K_{ow}$ ) of THC at neutral pH vary between 6000 using shake-flask methodology<sup>[19]</sup> and 9 440 000 by reverse-phase high-pressure liquid chromatographic estimation.<sup>[20]</sup> The wide range for aqueous solubility and  $K_{ow}$ , can be attributed to the difficulty of uniformly dissolving this essentially water-insoluble substance and accurately measuring small amounts of it. The spectrophotometric pKa is 10.6.<sup>[18]</sup>

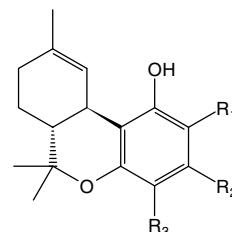
THC is thermolabile and photolabile.<sup>[21,22]</sup> Storage leads to a cumulative decrease in THC content through oxidation of THC to CBN.<sup>[23,24]</sup> Within 47 weeks, the THC content of marijuana (dried leaves and flowers of *Cannabis sativa*) decreased by 7% with dark and dry storage at 5°C, and by 13% at

20°C.<sup>[24]</sup> Dronabinol rapidly degrades in acid solutions. The kinetics seem to be first order and specifically hydrogen ion-catalysed,<sup>[18]</sup> so that significant degradation is assumed to occur in the normal stomach with a half-life of 1 hour at pH 1.<sup>[18]</sup>

Decarboxylation of the THC acids to the corresponding phenols occurs readily over time, upon heating<sup>[16,23]</sup> or under alkaline conditions. Heating for 5 minutes at a temperature of 200–210°C has been reported to be optimal for this purpose,<sup>[16]</sup> but a few seconds in burning cannabis cigarettes are equally sufficient. Slow decarboxylation of THC acid occurs at room temperature.

## 3. Pharmacokinetics of $\Delta^9$ -Tetrahydrocannabinol

Cannabis products are commonly either inhaled by smoking a cannabis cigarette, taken orally as dronabinol capsules or in baked foods or liquids



**Fig. 2.** Cannabinoids of the  $\Delta^9$ -tetrahydrocannabinol (THC) type. The most widespread cannabinoids are the phenolic  $\Delta^9$ -THCs with 21 carbon atoms and a C<sub>5</sub> side chain (R<sub>2</sub> = C<sub>5</sub>H<sub>11</sub>) and its two corresponding carboxylic acids A and B with R<sub>1</sub> or R<sub>3</sub> = COOH (see table I).

<sup>1</sup> Use of tradenames is for product identification only and does not imply endorsement.

**Table I.** Cannabinoids of the  $\Delta^9$ -trans-tetrahydrocannabinol type

Cannabinoid	R <sub>1</sub> <sup>a</sup>	R <sub>2</sub>	R <sub>3</sub>
$\Delta^9$ -trans-Tetrahydrocannabinolic acid A	COOH	C <sub>5</sub> H <sub>11</sub>	H
$\Delta^9$ -trans-Tetrahydrocannabinolic acid B	H	C <sub>5</sub> H <sub>11</sub>	COOH
$\Delta^9$ -trans-Tetrahydrocannabinol	H	C <sub>5</sub> H <sub>11</sub>	H
$\Delta^9$ -trans-Tetrahydrocannabinolic acid-C <sub>4</sub>	COOH or H	C <sub>4</sub> H <sub>9</sub>	H or COOH
$\Delta^9$ -trans-Tetrahydrocannabinol-C <sub>4</sub>	H	C <sub>4</sub> H <sub>9</sub>	H
$\Delta^9$ -trans-Tetrahydrocannabivarinic acid	COOH	C <sub>3</sub> H <sub>7</sub>	H
$\Delta^9$ -trans-Tetrahydrocannabivarin	H	C <sub>3</sub> H <sub>7</sub>	H
$\Delta^9$ -trans-Tetrahydrocannabiorcolic acid	COOH or H	CH <sub>3</sub>	H or COOH
$\Delta^9$ -trans-Tetrahydrocannabiorcol	H	CH <sub>3</sub>	H

<sup>a</sup> See figure 2 for the basic chemical structure of  $\Delta^9$ -trans-tetrahydrocannabinol.

(figure 4). Various other routes of administration and delivery forms have been tested for therapeutic purposes. The rectal route with suppositories has been applied in some patients,<sup>[25]</sup> and dermal<sup>[26]</sup> and sublingual<sup>[27]</sup> administration are under investigation. Other methods include eye drops to decrease intraocular pressure,<sup>[28]</sup> as well as aerosols and inhalation with vaporisers to avoid the harm associated with smoking.<sup>[29,30]</sup> The kinetics of cannabinoids are much the same for females and males,<sup>[31]</sup> as well as for frequent and infrequent users.<sup>[32,33]</sup>

### 3.1 Absorption

#### 3.1.1 Inhalation

THC is detectable in plasma only seconds after the first puff of a cannabis cigarette<sup>[35]</sup> with peak plasma concentrations being measured 3–10 minutes after onset of smoking (figure 5).<sup>[35–40]</sup> Systemic bioavailability generally ranges between about 10 and 35%, and regular users are more efficient (table III).<sup>[38]</sup> Bioavailability varies according to depth of inhalation, puff duration and breathhold.

A systemic bioavailability of 23 ± 16%<sup>[38]</sup> and 27 ± 10%<sup>[42]</sup> for heavy users versus 10 ± 7% and 14 ± 1% for occasional users of the drug was reported. In a study with a smoking machine, patterns of cannabis smoking were simulated with regard to puff duration and volume,<sup>[43]</sup> resulting in 16 to 19% of THC in the mainstream smoke. If the whole cigarette was smoked in one puff the percentage of THC in the mainstream increased to 69%. About 30% is assumed to be destroyed by pyrolysis. With smoking, additional THC is lost in the butt, in sidestream smoke, and by incomplete absorption in the lungs. Smoking a pipe that produces little sidestream smoke may also result in high effectiveness, with 45% of THC transferred via the mainstream smoke in one smoker tested.<sup>[23]</sup>

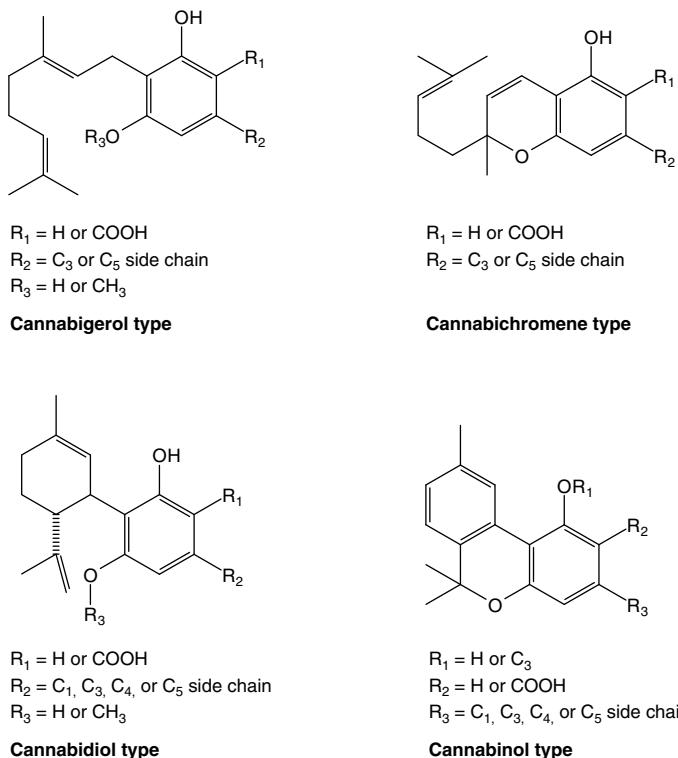
#### 3.1.2 Oral Administration

With oral use, absorption is slow and erratic, resulting in maximal plasma concentrations usually after 60–120 minutes (figure 6).<sup>[31,39,44]</sup> In several studies, maximal plasma concentrations were observed as late as 4 hours<sup>[45]</sup> and even 6 hours in some cases.<sup>[39,41,46]</sup> Several subjects showed more than one plasma peak.<sup>[37,39,41]</sup>

**Table II.** Average cannabinoid concentrations in 35 312 cannabis preparations confiscated in the US between 1980 and 1997<sup>[15]</sup>

	THC (%)	CBD (%)	CBC (%)	CBN (%)
Marijuana	3.1	0.3	0.2	0.3
Sinsemilla	8.0	0.6	0.2	0.2
Hashish	5.2	4.2	0.4	1.7
Hashish oil	15.0	2.7	1.1	4.1

**CBC** = cannabichromene; **CBD** = cannabidiol; **CBN** = cannabinol; **THC** =  $\Delta^9$ -tetrahydrocannabinol.



**Fig. 3.** Some phytocannabinoids.

$\Delta^9$ -THC is expected to be degraded by the acid of the stomach and in the gut.<sup>[18]</sup> At low pH, isomerisation to  $\Delta^8$ -THC and protonation of the oxygen in the pyran ring may occur with cleavage to substituted CBDs.<sup>[18]</sup> It has been suggested that a somewhat higher bioavailability is obtained in an oil formulation.<sup>[47]</sup> However, absorption seems to be nearly complete in different vehicles. Ninety-five percent of total radioactivity of radiolabelled THC was absorbed from the gastrointestinal tract in an oil vehicle<sup>[31]</sup> and 90–95% if taken in a cherry syrup vehicle,<sup>[48]</sup> but it is unclear from these data how much of this radioactivity belongs to unchanged THC and how much to breakdown products.

An extensive first-pass liver metabolism further reduces the oral bioavailability of THC, i.e. much of the THC is initially metabolised in the liver before it reaches the sites of action. Ingestion of THC

20mg in a chocolate cookie<sup>[39]</sup> and administration of dronabinol 10mg<sup>[41]</sup> resulted in a very low systemic bioavailability of  $6 \pm 3\%$  (range 4–12%)<sup>[39]</sup> or  $7 \pm 3\%$  (range 2–14%),<sup>[41]</sup> respectively, with a high interindividual variation.

### 3.1.3 Ophthalmic Administration

A study in rabbits with THC in light mineral oil determined a variable systemic bioavailability of 6–40% with ophthalmic administration.<sup>[49]</sup> Plasma concentrations peaked after 1 hour and remained high for several hours.

### 3.1.4 Rectal Administration

With rectal application, systemic bioavailability strongly differed depending on suppository formulations. Among formulations containing several polar esters of THC in various suppository bases, THC-hemisuccinate in Witepsol H15 showed the highest bioavailability in monkeys and was calcu-

lated to be 13.5%.<sup>[50]</sup> The rectal bioavailability of this formulation was calculated to be about as twice as high as oral bioavailability in a small clinical study.<sup>[25]</sup>

### 3.1.5 Sublingual Administration

Clinical studies are under way using a liquid cannabis extract applied under the tongue. A phase I study in six healthy volunteers receiving up to 20mg of THC was reported to result in 'relatively fast' effects.<sup>[27]</sup> In phase II studies, THC plasma concentrations of up to 14 µg/L were noted.<sup>[51]</sup>

### 3.1.6 Dermal Administration

In a study using the more stable  $\Delta^8$ -THC isomer, the permeability coefficient of THC was significantly enhanced by water and by oleic acid in propylene glycol and ethanol,<sup>[52]</sup> resulting in significant THC concentrations in the blood of rats. Studies designed to develop transdermal delivery of cannabinoids found a mean effective permeabil-

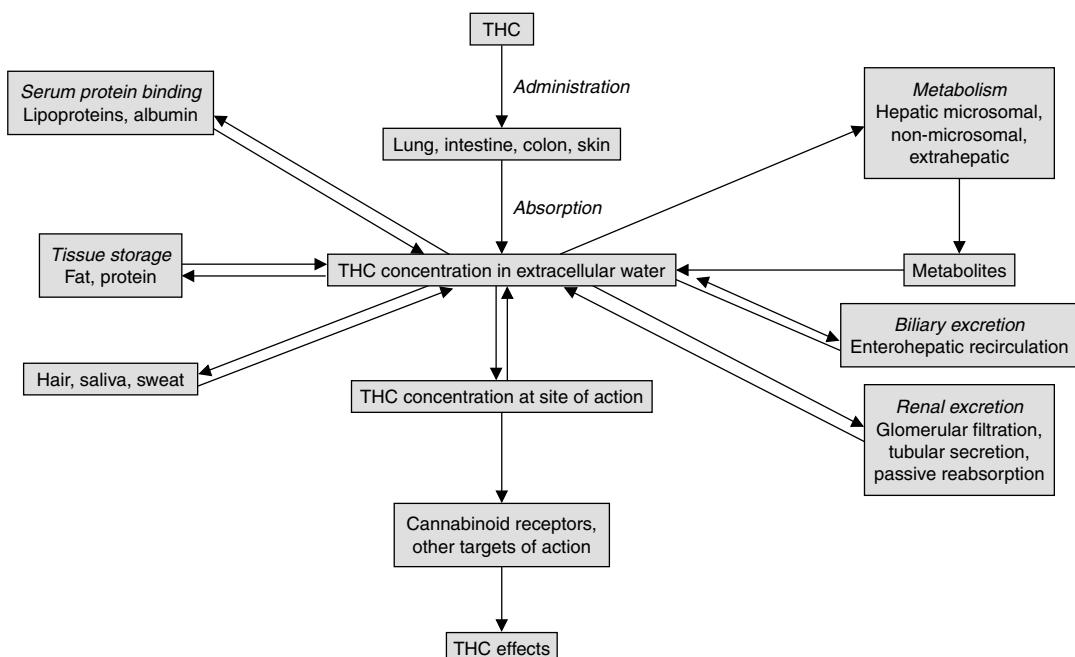
ity coefficient for  $\Delta^9$ -THC in propylene glycol of  $6.3 \times 10^{-6}$  cm/h.<sup>[26]</sup>

## 3.2 Distribution

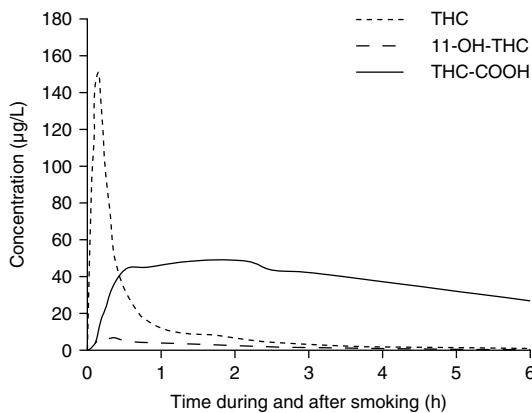
Tissue distribution of THC and its metabolites is assumed to be governed only by their physico-chemical properties, with no specific transport processes or barriers affecting the concentration of the drug in the tissues.<sup>[53]</sup>

About 90% of THC in the blood is distributed to the plasma, another 10% to red blood cells.<sup>[54]</sup> 95–99% of plasma THC is bound to plasma proteins, mainly to lipoproteins and less to albumin.<sup>[32,54–56]</sup>

The time course of plasma concentrations of cannabinoids has been described to fit to open two-compartment,<sup>[31,57]</sup> three-compartment<sup>[44,58,59]</sup> or four-compartment<sup>[32]</sup> models. Even five- and six-compartment models have been found in computer models to best fit the THC plasma course in animals.<sup>[53]</sup>



**Fig. 4.** Pharmacokinetic properties of  $\Delta^9$ -tetrahydrocannabinol (THC) [reproduced from Brenneisen<sup>[34]</sup> with permission].



**Fig. 5.** Mean plasma concentrations of  $\Delta^9$ -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) of six subjects during and after smoking a cannabis cigarette containing about 34mg of THC.<sup>[35]</sup>

The apparent (initial) volume of distribution of THC is small for a lipophilic drug, equivalent to the plasma volume of about 2.5–3L, reflecting high protein binding that complicates initial disposition. It was reported to be  $2.55 \pm 1.93$ L in drug-free users<sup>[32]</sup> and  $6.38 \pm 4.1$ L in regular users.<sup>[32]</sup> The steady-state volume of distribution has been estimated to be more than 100 times larger, in the range of about 10 L/kg.<sup>[31,32,57]</sup> These early data have been questioned because of the possible inaccuracy of the quantification methods used.

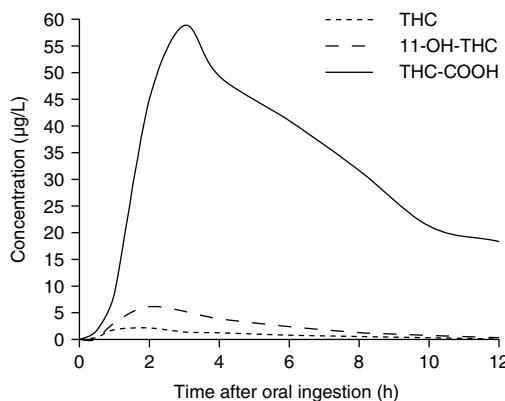
Based on pharmacokinetic data of two studies that used gas chromatography-mass spectrometry (GC-MS) for analysis of THC concentration, an average volume of distribution of 236L (or 3.4 L/kg assuming 70kg bodyweight) has been calculated.<sup>[60]</sup> Even smaller steady-state volumes of distribution of about 1 L/kg have been reported using GC-MS.<sup>[33]</sup> This volume is still about 20 times the plasma volume, since the majority of the lipophilic drug is in the tissues.

### 3.2.1 Distribution to Tissues

The lipophilicity of THC with high binding to tissue and in particular to fat causes a change of distribution pattern over time.<sup>[61]</sup> THC rapidly penetrates highly vascularised tissues, among them liver, heart, fat, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid and pituitary gland, resulting in a rapid decrease in plasma concentration.<sup>[62]</sup> Only about 1% of THC administered intravenously is found in the brain at the time of peak psychoactivity.<sup>[63]</sup> The relatively low concentration in the brain is probably due to high perfusion rate of the brain moving THC in and out of the brain rapidly.<sup>[64]</sup> Penetration of the metabolite 11-hydroxy- $\Delta^9$ -tetrahydrocannabinol (11-OH-THC) into the brain seems to be faster and higher than that of the parent compound.<sup>[63,65]</sup> Thus, it can be expected that 11-OH-

**Table III.** Systemic bioavailability of  $\Delta^9$ -tetrahydrocannabinol (THC)

Subjects	Systemic bioavailability (%)		Formulation	Reference
	average	range		
<b>Oral</b>				
11 frequent or infrequent users	6 ± 3	4–12	THC in chocolate cookie	39
6 men, 6 women	10–20		THC in sesame oil	31
7 men, 10 women	7 ± 3	2–14	THC in sesame oil	41
<b>Inhalational</b>				
9 heavy users	23 ± 6	6–56	Marijuana cigarette	38
9 light users	10 ± 7	2–22	Marijuana cigarette	38
5 heavy users	27 ± 10	16–39	Marijuana cigarette	42
4 light users	14 ± 1	13–14	Marijuana cigarette	42
11 frequent or infrequent users	18 ± 6	8–24	THC in cigarette	39
<b>Rectal</b>				
2 patients with spasticity	190–220% of oral bioavailability		Suppository with THC-hemisuccinate	25



**Fig. 6.** Mean plasma concentrations of  $\Delta^9$ -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) of six cancer patients after ingestion of one oral dose of THC 15mg (estimated from single graphs for each patient of Frytak et al.,<sup>[46]</sup> with permission). The plasma courses of THC showed considerable interindividual variation (see figure 8 for the individual courses of THC plasma concentrations of three patients).

THC will significantly contribute to the overall central effects of THC, especially with oral use.

Subsequently, intensive accumulation occurs in less vascularised tissues and finally in body fat,<sup>[66-68]</sup> the major long-term storage site, resulting in concentration ratios between fat and plasma of up to  $10^4 : 1$ .<sup>[69]</sup> The exact composition of the material accumulated in fat is unknown,<sup>[47]</sup> among them being unaltered THC and its hydroxy metabolites.<sup>[68]</sup> A substantial proportion of the deposit in fat seems to consist of fatty acid conjugates of 11-OH-THC.<sup>[70,71]</sup>

### 3.2.2 Distribution to Fetus and Breast Milk

In animals and humans, THC rapidly crosses the placenta.<sup>[72]</sup> The course of THC concentrations in fetal blood closely approximates that in the maternal blood, though fetal plasma concentrations were found to be lower than maternal concentrations in several species.<sup>[73-76]</sup> The metabolites 11-OH-THC and 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol (THC-COOH) cross the placenta much less efficiently than THC.<sup>[74,76]</sup> Following oral intake, THC plasma concentrations in the fetus are about one-tenth of the maternal plasma concentra-

tion.<sup>[75]</sup> In comparison, the fetal concentration is about one-third of the maternal plasma concentration after intravenous or inhaled THC.<sup>[73,76]</sup> Thus, oral intake may have less effect on the fetus compared with inhalation. A study with dizygotic twins demonstrated that the placenta plays a major role in the variability of fetal exposure to cannabinoids.<sup>[77]</sup>

THC passes into the breast milk. In monkeys, 0.2% of the THC ingested by the mother appeared in the milk.<sup>[78]</sup> Long-term administration leads to accumulation.<sup>[79]</sup> In a human female, the THC concentration in milk was 8.4 times higher than in plasma, in the low µg/L range.<sup>[79]</sup> Thus, a nursing infant might ingest daily THC amounts in the range of about 0.01–0.1mg from the milk of a mother who is consuming one or two cannabis cigarettes a day.

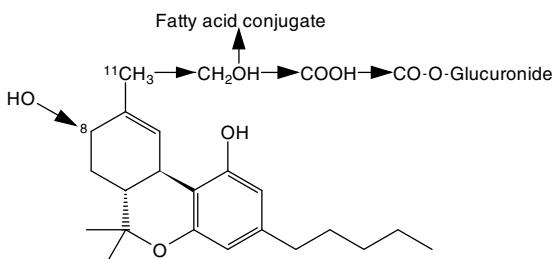
### 3.3 Metabolism

Metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation catalysed by enzymes of the cytochrome P450 (CYP) complex;<sup>[80,81]</sup> a member of the CYP2C subfamily of isoenzymes plays the major role in humans.<sup>[82]</sup> In rats, more than 80% of intravenous THC was metabolised within 5 minutes.<sup>[83]</sup>

Metabolic rates show relevant interspecies differences<sup>[84,85]</sup> that may be attributed to different profiles of CYP isoenzymes.<sup>[85]</sup> This fact may be in part responsible for some problems of interspecies extrapolation of pharmacological and toxicological effects.<sup>[86]</sup> In humans, allylic oxidation, epoxidation, aliphatic oxidation, decarboxylation and conjugation have been described.<sup>[64]</sup>

Nearly 100 metabolites have been identified for THC.<sup>[85]</sup> Besides the liver, other tissues are also able to metabolise cannabinoids but to a much lesser degree, among them the heart and the lung.<sup>[87-89]</sup>

Major metabolites are monohydroxylated compounds. In humans<sup>[90,91]</sup> and many other species,<sup>[85,87]</sup> C-11 is the major site attacked (figure 7). Hydroxylation results in 11-OH-THC and further oxidation in THC-COOH, which may be



**Fig. 7.** Main metabolic pathways of  $\Delta^9$ -tetrahydrocannabinol.

glucuronidated to 11-nor-9-carboxy-THC glucuronide. Long-chain fatty acid conjugates of 11-OH-THC are proposed to be a form in which THC may be stored within tissues.<sup>[92]</sup> The C-8 position is also attacked in humans but to a much lesser degree than C-11.<sup>[91]</sup>

Average plasma clearance rates have been reported to be  $11.8 \pm 3.0 \text{ L/h}$  ( $197 \pm 50 \text{ ml/min}$ ) for women and  $14.9 \pm 3.7 \text{ L/h}$  ( $248 \pm 62 \text{ ml/min}$ ) for men,<sup>[31]</sup> whereas others have determined higher mean clearance rates of about  $36 \text{ L/h}$  ( $600 \text{ ml/min}$ ) for naive THC users and about  $60 \text{ L/h}$  ( $1000 \text{ ml/min}$ ) for regular users (see table IV).<sup>[32]</sup> The latter values are similar to the volume of hepatic blood flow,<sup>[32,42]</sup> indicating that the limiting step of the metabolic rate is controlled by hepatic blood flow. These high clearance rates explain the high degree of first-pass metabolism and the much higher concentration of 11-OH-THC after oral administration compared with inhalation.

### 3.4 Time Course of Plasma Concentration of $\Delta^9$ -Tetrahydrocannabinol and Metabolites

Intravenous infusion of THC 5mg within 2 minutes caused average plasma concentrations at 2 minutes after the end of infusion of  $438 \mu\text{g/L}$  in frequent and of  $386 \mu\text{g/L}$  in infrequent users, that fell rapidly to an average of 25 and  $20 \mu\text{g/L}$  at 90 minutes.<sup>[33]</sup>

The course of plasma THC concentrations after inhalation resembles that after intravenous administration.<sup>[35,40]</sup> Smoking a single cannabis cigarette containing about 16 or 34mg of THC caused aver-

age peak concentrations of  $84.3 \mu\text{g/L}$  (range  $50.0\text{--}129.0 \mu\text{g/L}$ ) for the lower dose and  $162.2 \mu\text{g/L}$  (range  $76.0\text{--}267.0 \mu\text{g/L}$ ) for the higher dose, then rapidly decreased to low concentrations of about  $1\text{--}4 \mu\text{g/L}$  within 3–4 hours (figure 5).<sup>[35]</sup>

The maximal THC plasma concentration after smoking a marijuana cigarette (3.55% THC) was reported to exceed the maximal THC-COOH concentration by 3-fold and the maximal 11-OH-THC concentration by 20-fold.<sup>[35]</sup> However, THC/11-OH-THC ratios declined and reached a ratio of about 2 : 1 after 2–3 hours.<sup>[35]</sup> Peak concentrations for THC were observed 8 minutes (range 6–10 minutes) after onset of smoking, whereas 11-OH-THC peaked at 15 minutes (range 9–23 minutes) and THC-COOH at 81 minutes (range 32–133 minutes).<sup>[35]</sup>

After oral administration, the THC plasma concentration shows a flat course with peaks of  $4.4\text{--}11 \mu\text{g/L}$  after THC 20mg,<sup>[39]</sup>  $2.7\text{--}6.3 \mu\text{g/L}$  after THC 15mg<sup>[46]</sup> and  $0.58\text{--}12.48 \mu\text{g/L}$  after THC 2.5mg (figure 6).<sup>[44]</sup> Much higher amounts of 11-OH-THC are formed than with inhalational or intravenous administration.<sup>[25,31,46]</sup> In a study by Wall et al., the ratio of THC and 11-OH-THC plasma concentrations in men and women was about 2 : 1 to 1 : 1.<sup>[31]</sup> In several clinical studies,<sup>[44,46]</sup> 11-OH-THC concentrations even exceeded THC concentrations. In a study with dronabinol 2.5 mg/day, mean maximal THC concentrations were  $2.01 \mu\text{g/L}$  compared with  $4.61 \mu\text{g/L}$  for 11-OH-THC.<sup>[44]</sup> The course of THC plasma concentrations shows a high interindividual variation (figure 8).

### 3.5 Elimination

#### 3.5.1 Elimination from Plasma

About 6 hours after intravenous administration of THC a pseudoequilibrium is reached between plasma and tissues.<sup>[64]</sup> The concentration in plasma usually has dropped below  $2 \mu\text{g/L}$  at this time and then decreases more slowly with increasing time from use.<sup>[35,40]</sup>

After smoking a low dose cannabis cigarette (about 16mg of THC), the detection limit of  $0.5 \mu\text{g/L}$  of THC in plasma was reached after 7.2 hours

(range 3–12 hours), and following a high dose cigarette (about 34mg of THC) a plasma concentration of 0.5 µg/L of THC was reached within 12.5 hours (range 6–27 hours).<sup>[35]</sup> THC-COOH was detectable for a considerably longer time: for 3.5 days (range 2–7 days) after the low dose and for 6.3 days (range 3–7 days) after smoking the high dose.<sup>[35]</sup>

The major reason for the slow elimination of THC from the plasma is the slow rediffusion of THC from body fat and other tissues into the blood.<sup>[53]</sup>

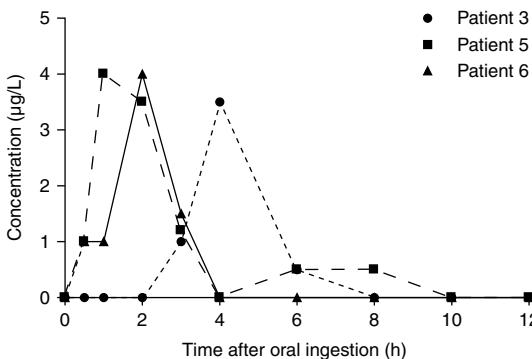
The true elimination half-life of THC from the plasma is difficult to calculate, as the equilibrium

ratio plasma/fatty tissue is reached only slowly, resulting in very low plasma concentrations that are difficult to analyse. In a study by Wall et al., the half-life of the terminal phase ( $t_{1/2\beta}$ ) ranged from 25–36 hours for THC, from 12–36 hours for 11-OH-THC and from 25–55 hours for THC-COOH after oral or intravenous administration in men and women.<sup>[31]</sup> The plasma concentration was followed for 72 hours in this study, not long enough to determine the half-life accurately. Similar elimination half-lives for THC in the range of 20–30 hours determined over similar periods have been reported by others.<sup>[32,42,57]</sup>

**Table IV.** Pharmacokinetic data for  $\Delta^9$ -tetrahydrocannabinol

Subjects	Dose (mg)	AUC (µg • min/L)	C <sub>max</sub> (µg/L)	t <sub>1/2β</sub> (h)	Vd (L)	CL (ml/min)	References
<b>Intravenous</b>							
4 nonusers	0.5			57 ± 4	658 ± 174		57
5 regular users	0.5			27 ± 1	597 ± 76		57
6 males (drug free)	2			19.6 ± 4.1	626 ± 296	605 ± 149	32
6 males (long-term)	2			18.7 ± 4.2	742 ± 331	977 ± 304	32
6 males	4		70 ± 30	36	734 ± 444	248 ± 62	31
6 females	2.2		85 ± 26	29	523 ± 217	197 ± 50	31
11 males	5	4330 ± 620	161–316				37, 39
9 heavy users	5	4300 ± 1670	288 ± 119				38
9 light users	5	6040 ± 2.21	302 ± 95				38
5 heavy users	5	5180 ± 830		>20		980 ± 150	42
4 light users	5	5460 ± 1180		>20		950 ± 200	42
4 heavy users	5	9908 ± 3785	438 ± 36	1.9 ± 0.3	75 ± 16	777 ± 690	33
4 light users	5	7094 ± 2248	386 ± 29	1.6 ± 0.5	74 ± 35	771 ± 287	33
<b>Oral</b>							
6 males	20		14.5 ± 9.7	25			31
6 females	15		9.4 ± 4.5	25			31
11 males	20	1020 ± 320	4.4–11				37, 39
3 males	3 × 15		4–6				46
3 males, 3 females	15		3–5				46
20 AIDS patients	2 × 2.5		2.01 (0.58–12.48)				44
7 men, 10 women	10	610 ± 310	4.7 ± 3.0				41
<b>Inhalational</b>							
11 males	19	1960 ± 650	33–118				37, 39
9 heavy users	19	2160 ± 1030	98 ± 44				38
9 light users	19	1420 ± 740	67 ± 38				38
5 heavy users	10	2450 ± 530					42
4 light users	10	1420 ± 340					42
6 males	15.8		84 (50–129)				35
6 males	33.8		162 (76–267)				35

AUC = area under the concentration-time curve; CL = systemic clearance; C<sub>max</sub> = maximum plasma concentration; t<sub>1/2β</sub> = plasma elimination half-life; Vd = volume of distribution.



**Fig. 8.** Plasma concentrations of  $\Delta^9$ -tetrahydrocannabinol (THC) of three of the six cancer patients of figure 6 after ingestion of one oral dose of THC 15mg (estimated from graphs of figure 2 of Frytak et al.,<sup>[46]</sup> with permission).

Longer half-lives of THC plasma elimination have been determined after higher doses and longer periods of measurement in animals<sup>[69]</sup> and humans,<sup>[93]</sup> up to 12.6 days with 4 weeks of observation.<sup>[93]</sup> However, it is unclear whether THC could always be reliably distinguished from its metabolites, thus overestimating the length of the half-life.<sup>[33]</sup> Kelly and Jones measured a  $t_{1/2\beta}$  for THC of only 117 minutes for frequent and 93 minutes for infrequent users.<sup>[33]</sup>

The elimination half-life for THC metabolites from plasma is longer than the elimination half-life of the parent molecule. In a study by Hunt and Jones,<sup>[32]</sup> the medium  $t_{1/2\beta}$  of THC for frequent users was about 19 hours and of the overall metabolites 53 hours. In the study by Kelly and Jones, the plasma elimination half-life for THC-COOH was  $5.2 \pm 0.8$  days for frequent and  $6.2 \pm 6.7$  days for infrequent cannabis users.<sup>[33]</sup>

### 3.5.2 Excretion with Urine and Faeces

THC is excreted within days and weeks, mainly as acid metabolites, about 20–35% in urine and 65–80% in faeces, less than 5% of an oral dose as unchanged drug in the faeces.<sup>[31,32]</sup> After 3 days, overall excretion rates were about 65% following oral and about 45% with intravenous administration (see table V).<sup>[31]</sup>

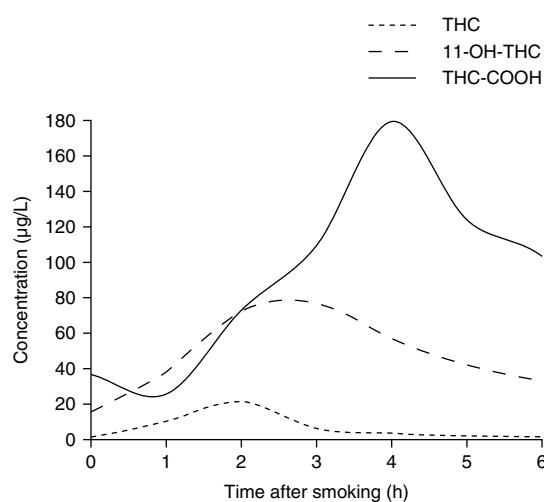
A single dose of THC may result in detectable metabolites in urine for up to 12 days,<sup>[45]</sup> usually for 3–5 days.<sup>[94]</sup> The average time to the first negative result in urine screening for THC metabolites (enzyme immunoassay with a cut-off calibration of 20 µg/L) was 8.5 days (range 3–18 days) for infrequent users and 19.1 days (range 3–46 days) for regular users.<sup>[95]</sup> Since urine excretion of metabolites does not decrease monotonously, urine screenings may fluctuate between positive and negative results for several days. The average time until the last positive result was 12.9 days (3–29 days) for light users and 31.5 days (4–77 days) for heavy users.<sup>[95]</sup>

A urinary excretion half-life of THC-COOH of about 30 hours was observed with a 7-day monitoring period and of 44–60 hours with a 14-day period.<sup>[96]</sup> Other groups calculated similar average urinary excretion half lives of about 2 days with a 12-day monitoring period<sup>[33]</sup> and of about 3 days (range 0.9–9.8 days) when THC-COOH was measured for 25 days.<sup>[97]</sup>

Mainly acids are excreted with the urine,<sup>[98,99]</sup> the main metabolite being the acid glucuronide of THC-COOH.<sup>[100]</sup> Free THC-COOH is not excreted in significant concentrations.<sup>[33,45,101]</sup> Several authors reported that the concentrations of THC and 11-OH-THC in urine were insignificant,<sup>[18,102]</sup> but a recent study found significant concentrations of

**Table V.** Mean cumulative cannabinoid excretion<sup>[31]</sup>

Subjects/route	Urine (%)		Faeces (%)		Total (%) at 72h	% of total in urine at 72h
	24h	72h	24h	72h		
Women/intravenous	11 ± 2	16 ± 3	9 ± 11	26 ± 19	42	38.1
Men/intravenous	10 ± 5	15 ± 4	14 ± 11	35 ± 11	50	30.0
Women/oral	12.5 ± 3.0	15.9 ± 3.6	9 ± 11	48 ± 6	63.9	24.9
Men/oral	10.3 ± 2.1	13.4 ± 2.0	24 ± 42	53 ± 18	66.4	20.2



**Fig. 9.** Mean urine concentrations of unchanged  $\Delta^9$ -tetrahydrocannabinol (THC) and its major metabolites 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) after smoking a cannabis cigarette containing about 27mg of THC by eight subjects with self-reported history of light marijuana use (one to three cigarettes per week or less). One subject later admitted regular use and presented with high baseline concentrations of 11-OH-THC and THC-COOH.<sup>[103]</sup>

these neutral cannabinoids by using an enzymatic hydrolysis step in the extraction protocol, with THC concentrations peaking at 21.5 µg/L (range 3.2–53.3 µg/L) 2 hours after smoking THC 27mg in a cannabis cigarette, 11-OH-THC peaking at 77.3 ± 29.7 µg/L after 3 hours and THC-COOH peaking at 179.4 ± 146.9 µg/L after 4 hours (figure 9).<sup>[103]</sup>

Renal clearance has been reported to decrease from a maximum of 1.2 L/h (20 ml/min) at approximately 100 minutes to 0.06 L/h (1 ml/min) after 4 days of THC administration.<sup>[32]</sup> The high lipophilicity of THC, resulting in high tubular reabsorption, explains the low renal excretion of the unchanged drug.<sup>[18]</sup>

Excretion is delayed by an extensive enterohepatic recirculation of metabolites.<sup>[31,102]</sup> Due to this marked enterohepatic recirculation and the high protein binding of cannabinoids, they are predominantly excreted with the faeces. In contrast to urine excretion, the acid and neutral THC metabo-

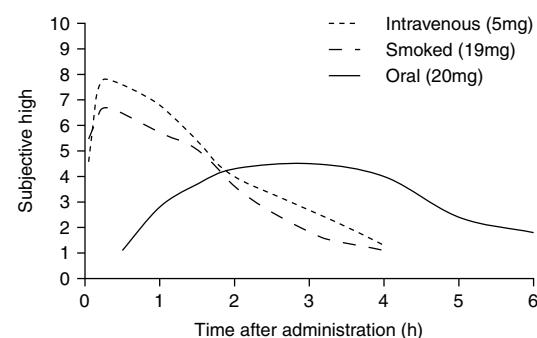
lites in the faeces are only present in the nonconjugated form.<sup>[31,104]</sup>

### 3.6 Time–Effect Relationship

#### 3.6.1 Correlation of Time and Effects

Peak ‘highs’ after intravenous and inhalational administration were noted after 20–30 minutes, and decreased to low levels after 3 hours and to baseline after 4 hours (figure 10).<sup>[36–38]</sup> Maximum increase of heart rate was noted earlier, within a few (1–5) minutes decreasing to baseline after 3 hours.<sup>[38]</sup> Conjunctival reddening was also noted within a few minutes and subsided in some participants by 3 hours after smoking.<sup>[42]</sup> Duration of maximal effects is dose dependent, and was found to be 45 minutes after THC 9mg<sup>[105]</sup> and more than 60 minutes with higher doses.<sup>[106]</sup>

Following inhalation, THC plasma concentrations have already dropped significantly before maximal psychotropic effects are achieved.<sup>[36,39]</sup> It has been proposed that the first hour represents the distribution phase<sup>[60]</sup> and that after 1 hour the central compartment has reached equilibrium with the effect compartment.<sup>[36]</sup> Hence, about 1–4 hours af-



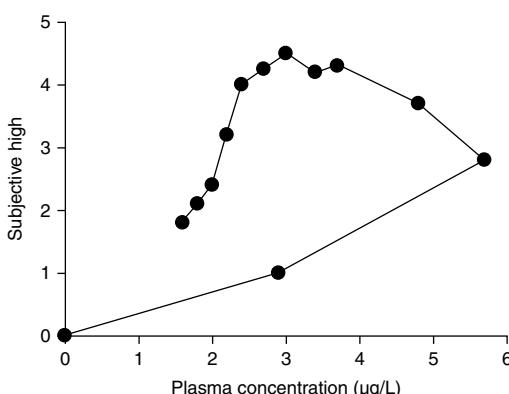
**Fig. 10.** Time course of subjective effects following three modes of administration of  $\Delta^9$ -tetrahydrocannabinol. A rating of the degree of ‘high’ was made by subjects on a 0–10 scale.<sup>[37,39]</sup>

ter smoking there is a good correlation between plasma concentration and effects.<sup>[36,107,108]</sup>

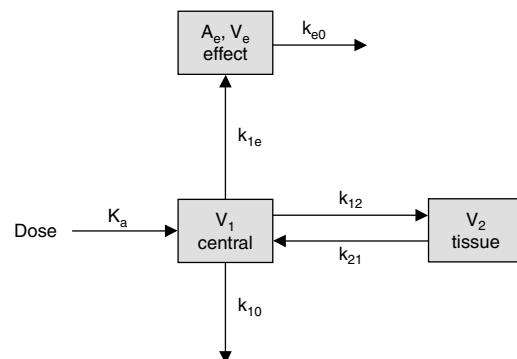
After oral use (THC 20mg in a cookie), reddening of the conjunctivae occurred within 30–60 minutes and was maximal from 60–180 minutes, gradually lessening thereafter.<sup>[39]</sup> As with inhalation, the pulse rate often returned to baseline or below even while the participants felt ‘high’.<sup>[39]</sup> Psychotropic effects after oral use set in after 30–90 minutes,<sup>[31,37]</sup> were maximal between 2 and 4 hours, and declined to low levels after 6 hours.<sup>[37]</sup> Maximal psychotropic effects were usually delayed for 1–3 hours, when plasma concentrations had already started to fall.<sup>[37]</sup>

### 3.6.2 Pharmacokinetic-Pharmacodynamic Modelling

With both inhalational and oral use, the association between THC concentrations in the plasma and subsequent psychotropic effects describes a hysteresis over time (figure 11). The intensity of THC effects depends on the concentration in the effect compartment. Although THC quickly crosses the blood-brain barrier,<sup>[109]</sup> plasma concentrations are already falling while brain concentrations are still rising.<sup>[109–111]</sup> In monkeys, an in-



**Fig. 11.** Phase plot of subjective ‘high’ versus plasma  $\Delta^9$ -tetrahydrocannabinol (THC) concentration from 0–360 minutes after oral ingestion of THC 15mg in a chocolate cookie.<sup>[37]</sup> Every solid point in the figure marks 30 minutes of time. The maximum THC plasma concentration (5.7  $\mu\text{g/L}$ ) was reached after 60 minutes, whereas the maximum subjective ‘high’ (on a 0–10 scale; see figure 10) was noted 2–4 hours after intake of the cannabinoid.



**Fig. 12.** Kinetic and dynamic model for  $\Delta^9$ -tetrahydrocannabinol (THC).<sup>[36]</sup>  $K_a$ ,  $k_{12}$ ,  $k_{21}$  and  $k_{10}$  describe THC kinetics in the empirical two-compartment model. The rate constants  $k_{1e}$  and  $k_{e0}$  characterise the effect compartment.  $A_e$  is the amount of THC in the effect compartment.  $V_e$ ,  $V_1$  and  $V_2$  are the volumes of the respective compartments.

travenous dose of radiolabelled THC resulted in peak radioactivity levels in the brain after 15–60 minutes, in accordance with the time of maximal effect after intravenous and inhalational administration in humans.<sup>[110]</sup> Chiang and Barnett<sup>[36]</sup> have proposed a kinetic and dynamic model based on an open two-compartment model (figure 12).

According to the Hill equation, there is a relationship between the intensity of the psychotropic effects (E) and the amount of THC in the effect compartment ( $A_e$ ) [equation 1]:

$$E = \frac{(k_{e0} \cdot A_e / k_{el} \cdot V_1)^\gamma}{(k_{e0} \cdot A_e / k_{el} \cdot V_1)^\gamma + C_{ss,50}}$$

The steady-state plasma concentration at 50% of the maximum psychotropic effect ( $C_{ss,50}$ ) was ascertained to be 25–29  $\mu\text{g/L}$  by using cannabis cigarettes of three different potencies.<sup>[36]</sup> The elimination rate constant from the effect compartment ( $k_{e0}$ ) was 0.03–0.04  $\text{min}^{-1}$ , and the sigmoid parameter  $\gamma$  (the degree of sigmoidicity of the effect/amount relationship) was 1.5–2.0. The transfer rate constant  $k_{21}$  from the tissue compartment was much smaller ( $0.0078\text{--}0.012 \text{ min}^{-1}$ ) than the elimination rate constant. Thus, the time course of effects must precede the time course of the THC

amount in the tissue compartment.<sup>[36]</sup> The rate constant  $k_{10}$  probably consists of a mixture of constants for metabolism and distribution between the central and deep tissue compartments.<sup>[36]</sup>

### 3.6.3 Predicting Time of Use

Several methods and models have been proposed for predicting time of administration. They are based on THC plasma concentrations<sup>[112,113]</sup> or the ratio of THC and its metabolites THC-COOH and 11-OH-THC in the plasma.<sup>[45,114-116]</sup> The higher the THC-COOH/THC ratio the longer time has passed since consumption.

In urine, THC concentrations above 2 µg/L were proposed as a marker for cannabis use within 5 hours after smoking (figure 9).<sup>[103]</sup> Others suggested that 8β,11-dihydroxy-THC showed promise as a urine marker for recent use,<sup>[113]</sup> whereas Manno et al. detected 8β,11-dihydroxy-THC only in the urine of a regular user and not in the urine of the light users in his study.<sup>[103]</sup>

## 3.7 Pharmacokinetics of Other Cannabinoids

The pharmacokinetics of other cannabinoids resemble the kinetics of THC.<sup>[117]</sup> Pharmacokinetics will be reviewed briefly for the phytocannabinoid cannabidiol, for nabilone, a synthetic ketocannabinoid that is available on prescription in several countries, and for dexanabinol, a non-psychotropic analogue of Δ<sup>8</sup>-THC under clinical investigation.

### 3.7.1 Cannabidiol

Average systemic bioavailability of inhaled CBD in a group of cannabis users was 31% (range 11–45%).<sup>[118]</sup> The plasma pattern was similar to that of THC. After oral administration of CBD 40mg, the plasma course over 6 hours was in the same range as the course after THC 20mg.<sup>[119]</sup> Daily oral doses of CBD 10 mg/kg per day for 6 weeks in patients with Huntington's disease resulted in mean weekly plasma concentrations of 5.9–11.2 µg/L.<sup>[120]</sup> In rats receiving intravenous THC and CBD (each 1 mg/kg bodyweight), brain concentrations of unchanged CBD were higher

than that of THC 5 minutes after administration.<sup>[83]</sup> The volume of distribution was about 30 L/kg, greater than for THC,<sup>[118]</sup> and the plasma clearance was similar to that of THC, ranging from 58 to 94 L/h (960–1560 ml/min).<sup>[118]</sup> An average  $t_{1/2\beta}$  of 24 hours (range 18–33 hours) during an observation period of 72 hours was determined after intravenous injection of 20mg.<sup>[118]</sup>

The metabolic pattern is similar to that of THC.<sup>[121,122]</sup> Several cyclised cannabinoids were identified, among them Δ<sup>9</sup>-THC, Δ<sup>8</sup>-THC and cannabinol.<sup>[121]</sup> The excretion rate of metabolites in urine (16% in 72 hours) is similar to that of THC,<sup>[122]</sup> whereas unlike THC a high percentage of unchanged CBD is excreted in the faeces.<sup>[122]</sup>

### 3.7.2 Nabilone

The absorption of oral nabilone (as a polyvinylpyrrolidone coprecipitate) is nearly complete,<sup>[123]</sup> with plasma concentrations peaking at 1–4 hours. Nabilone was reported to disappear from plasma relatively fast, with a half-life of about 2 hours,<sup>[123,124]</sup> and total radioactivity disappeared slowly with a half-life of 30 hours.<sup>[123]</sup> Circulating metabolites in plasma include isomeric carbinols with long half lives formed by reduction of the ketone at C-9.<sup>[124-126]</sup>

### 3.7.3 Dexanabinol

The pharmacokinetics of the synthetic non-psychotropic cannabinoid dexanabinol (HU-211) were evaluated with doses of 48, 100 and 200mg as short intravenous infusions in healthy volunteers. The plasma course was best fitted to a three-compartment model with a  $t_{1/2\beta}$  of approximately 9 hours.<sup>[59]</sup> The plasma clearance of the drug (about 102 L/h [1700 ml/min]) and the volume of distribution (about 15 L/kg) were somewhat higher than seen with THC.

### 3.7.4 Metabolic Interaction of Cannabinoids

Metabolic interaction between cannabinoids has been observed, but only cannabidiol seems to have a significant effect on THC by inhibiting hepatic microsomal THC metabolism through inactivation of the CYP oxidative system.<sup>[127-130]</sup>

Treatment of mice with high doses of CBD (120 mg/kg) resulted in changes of metabolism of THC (12 mg/kg) and modest elevation of THC blood concentrations.<sup>[131]</sup> Brain concentrations of THC increased by nearly 3-fold.<sup>[131]</sup> However, there was no or minimal effect of CBD on THC plasma concentrations in humans.<sup>[119,132]</sup> Repeated administration of THC and THC metabolites,<sup>[133,134]</sup> other cannabinoid receptor agonists<sup>[135]</sup> and even CBD<sup>[133]</sup> increased the activity of CYP by enzyme induction, thus decreasing the inactivating effect caused by CBD.

In humans, pretreatment with oral CBD 40mg resulted in a delayed, longer and only slightly reinforced action of oral THC 20mg.<sup>[136]</sup> However, simultaneous administration of CBD and THC resulted in a significant block of several THC effects, among them anxiety and other subjective alterations caused by THC<sup>[137]</sup> and tachycardia,<sup>[138]</sup> presumably due to antagonistic interaction of CBD at the CB<sub>1</sub> receptor.<sup>[139]</sup>

## 4. Pharmacodynamics

### 4.1 Mechanism of Action

The majority of phytocannabinoid effects are mediated through agonistic or antagonistic actions at specific receptors sites. Cannabinoid receptors and their endogenous ligands together constitute the 'endogenous cannabinoid system' or the 'endocannabinoid system' that is teleologically millions of years old.<sup>[140]</sup>

Some non-receptor-mediated effects of phytocannabinoids and synthetic derivatives have also been described e.g. effects on the immune system,<sup>[141]</sup> neuroprotective effects in ischaemia and hypoxia,<sup>[142]</sup> and some effects on circulation.<sup>[143]</sup> The antiemetic effects of THC are in part non-receptor-mediated, the rationale for the clinical use of THC as an antiemetic in children receiving cancer chemotherapy.<sup>[144]</sup> Due to the lower CB<sub>1</sub> receptor density in the brain of children compared with adults, they tolerated relatively high doses of Δ<sup>8</sup>-THC in a clinical study without significant adverse effects.<sup>[144]</sup> It is possible that some of these effects

are mediated by cannabinoid receptor subtypes that have not yet been identified.

#### 4.1.1 Cannabinoid Receptors

To date, two cannabinoid receptors have been identified, CB<sub>1</sub> receptors (cloned in 1990) and CB<sub>2</sub> receptors (cloned in 1993),<sup>[145]</sup> both coupled through inhibiting G proteins (G<sub>i</sub> proteins), negatively to adenylate cyclase and positively to mitogen-activated protein kinase. Activation of G<sub>i</sub> proteins causes inhibition of adenylate cyclase, thus inhibiting the conversion of AMP to cyclic AMP.

CB<sub>1</sub> receptors are also coupled to ion channels through G<sub>i/o</sub>, negatively to N-type and P/Q-type calcium channels and positively to A-type and inwardly rectifying potassium channels.<sup>[146]</sup> They may also mobilise arachidonic acid and close serotonin (5-HT<sub>3</sub>) receptor ion channels,<sup>[146]</sup> and some CB<sub>1</sub> receptors are negatively coupled to M-type potassium channels.<sup>[147]</sup> Under certain conditions, they may also activate adenylate cyclase through stimulating G proteins (G<sub>s</sub> proteins).<sup>[148]</sup>

CB<sub>1</sub> receptors are found mainly on neurons in the brain, spinal cord and peripheral nervous system, but are also present in certain peripheral organs and tissues, among them endocrine glands, leucocytes, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts.<sup>[145]</sup>

CB<sub>2</sub> receptors occur principally in immune cells, among them leucocytes, spleen and tonsils,<sup>[146]</sup> and there is markedly more mRNA for CB<sub>2</sub> than for CB<sub>1</sub> in the immune system. Levels of CB<sub>1</sub> and CB<sub>2</sub> mRNA in human leucocytes have been shown to vary with cell type (B cells > natural killer cells > monocytes > polymorphonuclear neutrophils, CD4+ and CD8+ cells).<sup>[149]</sup>

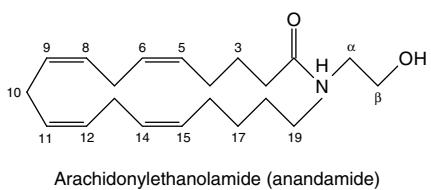
There is some evidence for the existence of one or more additional cannabinoid receptor subtypes.<sup>[150-152]</sup>

Activation of the CB<sub>1</sub> receptor produces marijuana-like effects on psyche and circulation, whereas activation of the CB<sub>2</sub> receptor does not. Hence, selective CB<sub>2</sub> receptor agonists have become an increasingly investigated target for therapeutic uses of cannabinoids, among them an-

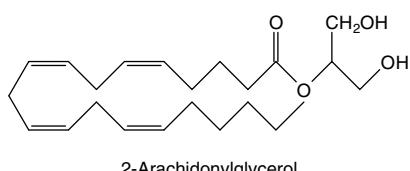
algesic, anti-inflammatory and antineoplastic actions.<sup>[153,154]</sup>

#### 4.1.2 Endocannabinoids

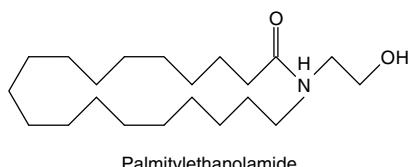
The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, endogenous cannabinoids or endocannabinoids, a family of endogenous lipids (figure 13).<sup>[6,155,156]</sup> The most important of these endocannabinoids are arachidonyl ethanolamide (anandamide) and 2-arachidonylglycerol, both of which are thought to serve as neurotransmitters or neuromodulators.<sup>[146,157]</sup> Endocannabinoids are released from cells in a stimulus-dependent manner by cleavage of membrane lipid precursors.<sup>[155]</sup> After release, they are rapidly deactivated by uptake into cells via a carrier-mediated mechanism and enzymatic hydrolysis by fatty acid amide hydrolase (FAAH).<sup>[155,158]</sup> In mice, lack of FAAH resulted in supersensitivity to anandamide and enhanced endogenous cannabinoid signalling.<sup>[159]</sup>



Arachidonyl ethanolamide (anandamide)



2-Arachidonylglycerol



Palmitylethanolamide

**Fig. 13.** Major endocannabinoids.

#### 4.1.3 Affinity for the Cannabinoid Receptor

Cannabinoids show different affinity to CB<sub>1</sub> and CB<sub>2</sub> receptors. Synthetic cannabinoids have been developed that act as highly selective agonists or antagonists at one of these receptor types.<sup>[146,160,161]</sup> Δ<sup>9</sup>-THC has approximately equal affinity for the CB<sub>1</sub> and CB<sub>2</sub> receptor, whereas anandamide has marginal selectivity for CB<sub>1</sub> receptors.<sup>[161]</sup> However, the efficacy of THC and anandamide is less at CB<sub>2</sub> than at CB<sub>1</sub> receptors. As a partial (low-efficacy) agonist, THC can behave either as an agonist or antagonist at CB<sub>2</sub> receptors.<sup>[146]</sup>

#### 4.1.4 Tonic Activity of the Endocannabinoid System

The endogenous cannabinoid system has been demonstrated to be tonically active in several conditions. Endocannabinoid levels have been demonstrated to be increased in a pain circuit of the brain (periaqueductal gray) following painful stimuli.<sup>[162]</sup> Tonic control of spasticity by the endocannabinoid system has been observed in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice, an animal model of multiple sclerosis.<sup>[163]</sup> An increase of cannabinoid receptors following nerve damage was demonstrated in a rat model of chronic neuropathic pain<sup>[164]</sup> and in a mouse model of intestinal inflammation.<sup>[165]</sup> This may increase the potency of cannabinoid agonists used for the treatment of these conditions. Tonic activity has also been demonstrated with regard to appetite control<sup>[166]</sup> and with regard to vomiting in emetic circuits of the brain.<sup>[167]</sup> Elevated endocannabinoid levels have been detected in cerebrospinal fluid of schizophrenic patients.<sup>[168]</sup> In other models, tonic or enhanced activity could not be demonstrated, e.g. in a rat model of inflammatory hyperalgesia.<sup>[169]</sup>

#### 4.2 Pharmacological Effects of Δ<sup>9</sup>-Tetrahydrocannabinol

The pharmacological activity of Δ<sup>9</sup>-THC is stereoselective, with the natural (*−*)-*trans* isomer (dronabinol) being 6–100 times more potent than the (+)-*trans* isomer depending on the assay.<sup>[2]</sup>

The activation of the cannabinoid system through THC and other phytocannabinoids, synthetic and endogenous cannabinoids causes numerous actions that have been extensively reviewed (see table VI).<sup>[2,3,170-175]</sup> Additional non-receptor-mediated effects have come into focus as well.<sup>[142]</sup> Some effects of cannabinoid receptor agonists show a biphasic behaviour in dependency on dose, e.g. low doses of anandamide stimulated phagocytosis and stimulated behavioural activities in mice, whereas high doses decreased activities and caused inhibitory effects on immune functions.<sup>[176]</sup>

#### 4.2.1 Toxicity

The median lethal dose ( $LD_{50}$ ) of oral THC in rats was 800–1900 mg/kg depending on sex and strain.<sup>[177]</sup> There were no cases of death due to toxicity following the maximum oral THC dose in dogs (up to 3000 mg/kg THC) and monkeys (up to 9000 mg/kg THC).<sup>[177]</sup> Acute fatal cases in humans

have not been substantiated. However, myocardial infarction may be triggered by THC due to effects on circulation.<sup>[178,179]</sup>

Adverse effects of medical cannabis use are within the range of effects tolerated for other medications.<sup>[173,174]</sup> It is controversial whether heavy regular consumption may impair cognition,<sup>[180,181]</sup> but this impairment seems to be minimal if it exists.<sup>[182,183]</sup> Long-term medical use of cannabis has been reported to be well tolerated without significant physical or cognitive impairment.<sup>[184]</sup> There is conflicting evidence that infants exposed to THC *in utero* experience developmental and cognitive impairment.<sup>[185]</sup> Cannabis can induce a schizophrenic psychosis in vulnerable persons, presumably without increasing the incidence of the disease.<sup>[172,186]</sup>

The harmful effects of combustion products produced by smoking cannabis have to be distinguished from the effects of cannabis or single cannabinoids.<sup>[174]</sup>

**Table VI.** Physiological effects of  $\Delta^9$ -tetrahydrocannabinol. These dose-dependent effects have been observed in clinical studies, *in vivo* or *in vitro*

Body system	Effects
Psyche and perception	Fatigue, euphoria, enhanced well-being, dysphoria, anxiety, reduction of anxiety, depersonalisation, increased sensory perception, heightened sexual experience, hallucinations, alteration of time perception, aggravation of psychotic states, sleep
Cognition and psychomotor performance	Fragmented thinking, enhanced creativity, disturbed memory, unsteady gait, ataxia, slurred speech, weakness, deterioration or amelioration of motor coordination
Nervous system	Analgesia, muscle relaxation, appetite stimulation, vomiting, antiemetic effects, neuroprotection in ischaemia and hypoxia
Body temperature	Decrease of body temperature
Cardiovascular system	Tachycardia, enhanced heart activity, increased output, increase in oxygen demand, vasodilation, orthostatic hypotension, hypertension (in horizontal position), inhibition of platelet aggregation
Eye	Reddened conjunctivae, reduced tear flow, decrease of intraocular pressure
Respiratory system	Bronchodilation
Gastrointestinal tract	Hyposalivation and dry mouth, reduced bowel movements and delayed gastric emptying
Hormonal system	Influence on luteinising hormone, follicle-stimulating hormone, testosterone, prolactin, somatotropin, thyroid-stimulating hormone, glucose metabolism, reduced sperm count and sperm motility, disturbed menstrual cycle and suppressed ovulation
Immune system	Impairment of cell-mediated and humoral immunity, immune stimulation, anti-inflammatory and antiallergic effects
Fetal development	Malformations, growth retardation, impairment of fetal and postnatal cerebral development, impairment of cognitive functions
Genetic material and cancer	Antineoplastic activity, inhibition of synthesis of DNA, RNA and proteins

#### 4.2.2 Psyche, Cognition and Behaviour

In many species the behavioural actions of low doses of THC are characterised by a unique mixture of depressant and stimulant effects in the CNS.<sup>[2]</sup>

In humans, THC intoxication is usually described as a pleasant and relaxing experience. Use in a social context may result in laughter and talkativeness. Occasionally there are unpleasant feelings such as anxiety that may escalate to panic. A sense of enhanced well-being may alternate with dysphoric phases. THC improves taste responsiveness and enhance the sensory appeal of foods.<sup>[187]</sup> It may induce sleep.<sup>[188,189]</sup> Whole cannabis preparations and THC produce similar subjective effects if administered via the same routes (oral, inhalation).<sup>[190]</sup>

Acute THC intoxication impairs learning and memory,<sup>[191-193]</sup> and adversely affects psychomotor and cognitive performance,<sup>[186]</sup> reducing the ability to drive a car and to operate machinery. Reduced reaction time also affects the response of the pupil of the eye. A brief light flash causes a decreased amplitude of constriction and a reduced velocity of constriction and dilation.<sup>[194]</sup>

The most conspicuous psychological effects of THC in humans have been divided into four groups: affective (euphoria and easy laughter), sensory (increased perception of external stimuli and of the person's own body), somatic (feeling of the body floating or sinking in the bed) and cognitive (distortion of time perception, memory lapses, difficulty in concentration).<sup>[195]</sup>

#### 4.2.3 Central Nervous System and Neurochemistry

Most effects of THC (e.g. analgesia, appetite enhancement, muscle relaxation and hormonal actions) are mediated by central cannabinoid receptors, their distribution reflecting many of the medicinal benefits and adverse effects.<sup>[146,191,196]</sup>

Cannabinoids interact with a multitude of neurotransmitters and neuromodulators,<sup>[2,197]</sup> among them acetylcholine, dopamine,  $\gamma$ -aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid pep-

tides. A number of pharmacological effects can be explained (at least in part) on the basis of such interactions. For example, tachycardia and hyposalivation with dry mouth<sup>[187,198]</sup> are mediated by effects of THC on release and turnover of acetylcholine.<sup>[198]</sup> In a rat model, cannabinoid agonists inhibited activation of serotonin 5-HT<sub>3</sub> receptors, explaining the antiemetic properties of cannabinoids by interactions with serotonin.<sup>[199]</sup> Therapeutic effects on movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutaminergic and dopaminergic transmitter systems.<sup>[200,201]</sup>

#### 4.2.4 Circulatory System

THC can induce tachycardia<sup>[195]</sup> and increase cardiac output with increased cardiac work and oxygen demand.<sup>[202]</sup> It can also produce peripheral vasodilation, orthostatic hypotension<sup>[3,203]</sup> and reduced platelet aggregation.<sup>[204]</sup> There was no change of mean global cerebral blood flow after smoking cannabis, but increases and decreases in several regions.<sup>[205]</sup> The tachycardic effect of THC is presumably based on vagal inhibition and can be attenuated by  $\beta$ -blockers.<sup>[195]</sup> Due to the development of tolerance, long-term use can lead to bradycardia.<sup>[203]</sup> The endogenous cannabinoid system seems to play a major role in the control of blood pressure. Endocannabinoids are produced by the vascular endothelium, circulating macrophages and platelets.<sup>[206]</sup> Vascular resistance in the coronaries and the brain is lowered primarily by direct activation of vascular cannabinoid CB<sub>1</sub> receptors.<sup>[207]</sup>

### 4.3 Effects on Some Other Organ Systems

#### 4.3.1 Antibacterial and Antiviral Actions

Antibacterial actions have been demonstrated for CBD, CBG and THC.<sup>[208]</sup> Incubation with THC reduced the infectious potency of herpes simplex viruses.<sup>[209]</sup>

#### 4.3.2 Eye

The evidence of cannabinoid receptors at different sites (anterior eye, retina, corneal epithelium) suggests that cannabinoids influence different

physiological functions in the human eye.<sup>[210]</sup> Vasoconstriction in the eye is observed as conjunctival reddening after THC exposure.<sup>[2]</sup> THC and some other cannabinoids decrease intraocular pressure.<sup>[210,211]</sup>

#### **4.3.3 Hormonal System and Fertility**

THC interacts with the hypothalamic-pituitary-adrenal axis, influencing numerous hormonal processes.<sup>[212]</sup> Minor changes in human hormone levels due to acute cannabis or THC ingestion usually remain in the normal range.<sup>[3]</sup> Tolerance develops to these effects, however, and even regular cannabis users demonstrate normal hormone levels.

#### **4.3.4 Genetics and Cell Metabolism**

THC can inhibit DNA, RNA, and protein synthesis, and can influence the cell cycle. However, very high doses are required to produce this effect *in vitro*.<sup>[213]</sup> Cannabinoid agonists inhibited human breast cancer cell proliferation *in vitro*,<sup>[214,215]</sup> and, directly applied at the tumour site, showed anti-neoplastic activity against malignant gliomas in rats.<sup>[216]</sup>

#### **4.3.5 Immune System**

Animal and cell experiments have demonstrated that THC exerts complex effects on cellular and humoral immunity.<sup>[217,218]</sup> It is not clear whether and to what extent these effects are of clinical relevance in humans with respect to beneficial (inflammation,<sup>[219,220]</sup> allergies, autoimmune processes<sup>[218]</sup>) and undesirable (decreased resistance towards pathogens and carcinogens) effects.<sup>[217]</sup>

#### **4.3.6 Sperm**

After several weeks of daily smoking eight to ten cannabis cigarettes, a slight decrease in sperm count was observed in humans, without impairment of their function.<sup>[221]</sup> In animal studies, high doses of cannabinoids inhibited the acrosome reaction.<sup>[222]</sup>

#### **4.3.7 Digestive Tract**

Anandamide induces overeating in rats through a CB<sub>1</sub> receptor mediated mechanism.<sup>[223]</sup> Cannabinoid-induced eating is ascribed to an increase of the incentive value of food.<sup>[224]</sup> Cannabinoid agonists inhibit gastrointestinal motility and gastric

emptying in rats.<sup>[225]</sup> In a study with humans, THC caused a significant delay in gastric emptying.<sup>[226]</sup> In addition, CB<sub>1</sub> agonists inhibited pentagastrin-induced gastric acid secretion in the rat,<sup>[227]</sup> mediated by suppression of vagal drive to the stomach through activation of CB<sub>1</sub> receptors.<sup>[228]</sup>

### **4.4 Pharmacological Activity of $\Delta^9$ -Tetrahydrocannabinol Metabolites**

#### **4.4.1 11-Hydroxy- $\Delta^9$ -Tetrahydrocannabinol**

11-OH-THC is the most important psychotropic metabolite of  $\Delta^9$ -THC, with a similar spectrum of actions and similar kinetic profiles as the parent molecule.<sup>[122,229,230]</sup> After intravenous administration in humans, 11-OH-THC was equipotent to THC in causing psychic effects and reduction in intraocular pressure.<sup>[230]</sup> In some pharmacological animal tests, 11-OH-THC was three to seven times more potent than THC.<sup>[231]</sup>

#### **4.4.2 11-Nor-9-Carboxy- $\Delta^9$ -Tetrahydrocannabinol**

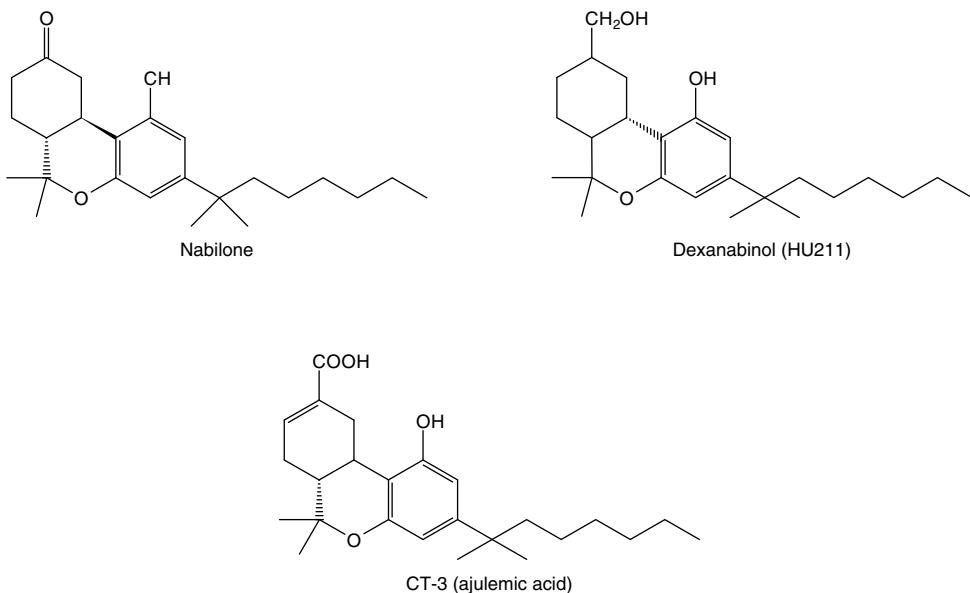
THC-COOH is the most important non-psychotropic metabolite of  $\Delta^9$ -THC. It possesses anti-inflammatory and analgesic properties by mechanisms similar to those of nonsteroidal anti-inflammatory drugs.<sup>[232-234]</sup> THC-COOH antagonises some effects (for example the cataleptic effect in mice) of the parent drug through an unknown mechanism.<sup>[235]</sup>

### **4.5 Pharmacological Effects of Other Cannabinoids**

#### **4.5.1 Phytocannabinoids**

Cannabidiol (CBD) is a nonpsychotropic cannabinoid, for which sedating,<sup>[236]</sup> antiepileptic,<sup>[237]</sup> anticonvulsant,<sup>[238]</sup> antiemetic<sup>[239]</sup> and anti-inflammatory<sup>[240]</sup> effects have been observed. It reduced intraocular pressure,<sup>[241]</sup> was neuroprotective<sup>[142]</sup> and antagonised the psychotropic and several other effects of THC.<sup>[137]</sup> Anxiolytic and antipsychotic properties might prove useful in psychiatry.<sup>[137,236]</sup>

The nonpsychotropic cannabinoids CBG and CBC show sedative effects. CBG has been observed to decrease intraocular pressure,<sup>[211]</sup> showed antitumour activity against human cancer cells<sup>[242]</sup> and has antibiotic properties.



**Fig. 14.** Classical synthetic cannabinoids.

#### 4.5.2 Endocannabinoids

Anandamide (arachidonyl-ethanolamide), an endocannabinoid, produces pharmacological effects similar to those of THC. However, there are apparently some significant differences with THC. Under certain circumstances, anandamide acts as a partial agonist at the CB<sub>1</sub> receptor,<sup>[243]</sup> and very low doses of anandamide antagonised the actions of THC. It is assumed that low doses of anandamide activated stimulating G<sub>s</sub> protein pathways and not inhibiting G<sub>i</sub> proteins, or caused an allosteric modulation of the cannabinoid receptor.<sup>[243]</sup>

#### 4.5.3 Classical Synthetic Cannabinoids

Among the classical synthetic cannabinoids that retain the phytocannabinoid ring structures and their oxygen atoms are nabilone, HU-210 and dexanabinol. Nabilone is available on prescription in several countries with a similar pharmacological profile as THC (figure 14).<sup>[244]</sup> HU-210, an analogue of Δ<sup>8</sup>-THC with a dimethylheptyl side chain, is between 80 and 800 times more active than THC,<sup>[245,246]</sup> while its enantiomer dexanabinol (HU-211) is completely devoid of psychoactiv-

ity.<sup>[247]</sup> Dexanabinol is an N-methyl-D-aspartate (NMDA) antagonist with neuroprotective properties in hypoxia and ischaemia.<sup>[248]</sup> It is under clinical investigation for the treatment of brain injuries and stroke.<sup>[248]</sup> CT-3 or ajulemic acid, a derivative of the Δ<sup>8</sup>-THC metabolite THC-COOH, is under clinical investigation for inflammation and pain.<sup>[65,249]</sup>

#### 4.5.4 Nonclassical Synthetic Cannabinoids

Levonantradol, which was under clinical investigation for the treatment of pain<sup>[250]</sup> and the adverse effects of chemotherapy<sup>[251]</sup> and radiotherapy,<sup>[252]</sup> is a nonclassical cannabinoid with a more radical change from the typical structure. Other nonclassical cannabinoids are the aminoalkylindol WIN-55,212-2, which has a 6.75-fold bias towards the CB<sub>2</sub> receptor<sup>[253]</sup> and the bicyclic cannabinoid analogue CP-55,940, a widely-used agonist for the testing of cannabinoid receptor affinity with a potency 4–25 times greater than that of THC depending on assay.<sup>[254]</sup>

#### 4.5.5 Anandamide Analogues

Several anandamide congeners have been synthesised,<sup>[160]</sup> among them (*R*)-(+)- $\alpha$ -methanandamide that possesses both a 4-fold higher affinity for the CB<sub>1</sub> receptor and a greater catabolic resistance than anandamide. Fatty acid-based compounds have been synthesised that mimic the structure of anandamide, but act as inhibitors of the catabolic amidase enzyme FAAH.<sup>[158]</sup>

AM-404 is a synthetic fatty amide that acts as a selective inhibitor of anandamide transport, thus preventing cellular reuptake of anandamide<sup>[255]</sup> and increasing circulating anandamide concentrations.<sup>[155]</sup>

#### 4.5.6 Therapeutic Potential of Antagonists

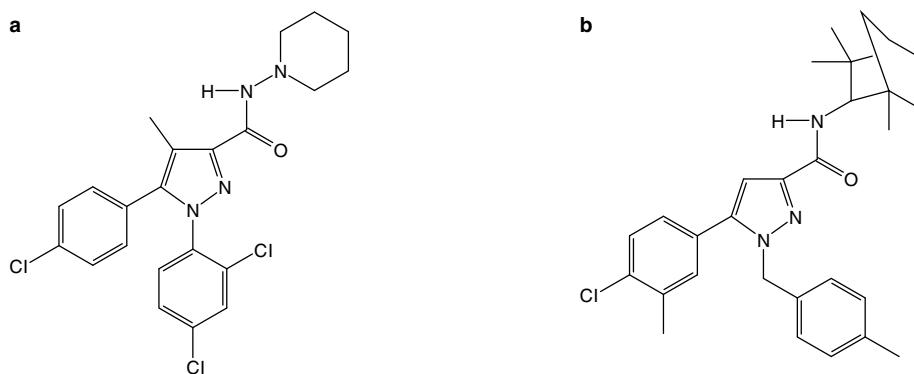
When administered by themselves, cannabinoid receptor antagonists (e.g. SR141716A; figure 15) may behave as inverse agonists in several bioassay systems and produce effects that are opposite in direction from those produced by cannabinoid receptor agonists, e.g. hyperalgesia<sup>[256]</sup> and improvement of memory.<sup>[257]</sup> Possible therapeutic potential was proposed for obesity,<sup>[258]</sup> schizophrenia,<sup>[35]</sup> in conditions with lowered blood pressure,<sup>[207]</sup> Parkinson's disease,<sup>[259]</sup> Huntington's disease<sup>[260]</sup> and to improve memory in Alzheimer's disease.<sup>[35]</sup>

## 5. Tolerance and Dependency

### 5.1 Tolerance

Tolerance develops to most of the effects of THC,<sup>[261]</sup> among them the cardiovascular, psychological and skin hypothermic effects,<sup>[262,263]</sup> analgesia,<sup>[264]</sup> immunosuppression,<sup>[265]</sup> corticosteroid release,<sup>[266]</sup> and disruption of the hypothalamo-hypophyseal axis,<sup>[267]</sup> causing alterations in endocannabinoid formation and content in the brain.<sup>[268]</sup> In a 30-day study volunteers received daily oral doses of THC 210mg and developed tolerance to cognitive and psychomotor impairment and to the psychological 'high' by the end of the study.<sup>[262]</sup> After a few days an increased heart rate was replaced by a normal, or slowed, heart rate. Tolerance also develops to orthostatic hypotension.<sup>[203]</sup>

Tolerance can mainly be attributed to pharmacodynamic changes, presumably based on receptor downregulation and/or receptor desensitisation.<sup>[268,269]</sup> Rate and duration of tolerance varies with different effects. Rats receiving THC over a period of 5 days exhibited a decreased specific binding ranging from 20–60% in different receptor sites of the brain compared with controls.<sup>[261]</sup> However, in another study no significant alteration in receptor binding was observed after chronic administration of THC, resulting in 27-fold behavioural tolerance.<sup>[270]</sup> Long-term administration of



**Fig. 15.** Cannabinoid receptor antagonists, SR 141716A (a) and SR 144528 (b).

anandamide also resulted in behavioural tolerance without receptor downregulation,<sup>[271]</sup> and it was proposed that desensitisation of the CB<sub>1</sub> receptor might account for this observation.<sup>[271]</sup> Tolerance has been observed to occur together with modified biotransformation activities with regard to mitochondrial oxygen consumption, mono-oxygenase activities and the content of liver microsomal CYP.<sup>[135]</sup> However, only a small proportion of tolerance can be attributed to changes in metabolism.<sup>[32]</sup>

### 5.2 Withdrawal and Dependency

After abrupt cessation of long-term administration of high doses of THC, withdrawal has been observed in humans.<sup>[262,272]</sup> Subjects complained of inner unrest, irritability and insomnia, and presented 'hot flashes', sweating, rhinorrhoea, loose stools, hiccups and anorexia. Withdrawal symptoms in humans are usually mild and the risk for physical and psychic dependency is low compared with opioids, tobacco, alcohol and benzodiazepines.<sup>[273-275]</sup> A review of several indicators of the abuse potential of oral dronabinol in a therapeutic context found little evidence of such a problem.<sup>[276]</sup>

## 6. Therapeutic Uses

Cannabis preparations have been employed in the treatment of numerous diseases, with marked differences in the available supporting data.<sup>[171,173,174,277]</sup> Besides phytocannabinoids, several synthetic cannabinoid derivatives that are devoid of psychotropic effects are under clinical investigation, and modulators of the endocannabinoid system (such as reuptake inhibitors and antagonists at the CB<sub>1</sub> or CB<sub>2</sub> receptor) will presumably follow.

### 6.1 Hierarchy of Therapeutic Effects

Possible indications for cannabis preparations have been extensively reviewed.<sup>[171,173,174,277-281]</sup> To do justice to the scientific evidence with regard to different indications, a hierarchy of therapeutic

effects can be devised, with established effects, relatively well-confirmed effects, less confirmed effects and a basic research stage. However the history of research into the therapeutic benefits of cannabis and cannabinoids has demonstrated that the scientific evidence for a specific indication does not necessarily reflect the actual therapeutic potential for a given disease, but sometimes obstacles to clinical research.

### 6.2 Established Effects

Dronabinol is approved for use in refractory nausea and vomiting caused by antineoplastic drugs in cancer<sup>[144,282-284]</sup> and for appetite loss in anorexia and cachexia of HIV/AIDS patients.<sup>[285-287]</sup> These effects can be regarded as established effects for THC and cannabis. THC is also effective in cancer cachexia<sup>[288]</sup> and nausea induced by syrup of ipecac.<sup>[289]</sup> Nabilone is approved for nausea and vomiting associated with cancer chemotherapy.

### 6.3 Relatively Well-Confirmed Effects

Spasticity due to spinal cord injury<sup>[25,290,291]</sup> and multiple sclerosis,<sup>[25,291-296]</sup> chronic painful conditions, especially neurogenic pain,<sup>[290,291,297-301]</sup> movement disorders (including Tourette's syndrome, dystonia and levodopa-induced dyskinesia),<sup>[200,302-308]</sup> asthma<sup>[30,309,310]</sup> and glaucoma<sup>[28,311-314]</sup> can be regarded as relatively well-confirmed effects with small placebo-controlled trials demonstrating benefits. However, results were sometimes conflicting.

### 6.4 Less Confirmed Effects

There are several indications in which mainly only case reports suggest benefits. These are allergies,<sup>[315]</sup> inflammation,<sup>[174]</sup> epilepsy,<sup>[316]</sup> intractable hiccups,<sup>[317]</sup> depression,<sup>[287]</sup> bipolar disorders,<sup>[318]</sup> anxiety disorders,<sup>[174]</sup> dependency on opioids and alcohol,<sup>[315,319]</sup> withdrawal symptoms<sup>[319]</sup> and disturbed behaviour in Alzheimer's disease.<sup>[320]</sup>

## 6.5 Basic Research Stage

Basic research shows promising possible future therapeutic indications, among them neuroprotection in hypoxia and ischaemia due to traumatic head injury, nerve gas damage and stroke.<sup>[142,248]</sup> Some immunological mechanisms of THC hint of possible benefits in basic mechanisms of T helper 1 dominated autoimmune diseases, such as multiple sclerosis, arthritis and Crohn's disease.<sup>[218]</sup> Other fields of research are disorders of blood pressure<sup>[207,321]</sup> and antineoplastic activity.<sup>[154,322]</sup> Cannabinoids seem to be able to control the cell survival/death decision.<sup>[323]</sup> Thus, cannabinoids may induce proliferation, growth arrest or apoptosis in a number of cells depending on dose.<sup>[323]</sup> Several effects observed in animal studies provide the basis for further research, among them effects against diarrhoea in mice,<sup>[324]</sup> inhibition of bronchospasms provoked by chemical irritants in rats<sup>[325]</sup> and stabilisation of respiration in sleep-related breathing disorders (e.g. apnoea).<sup>[326]</sup>

## 7. Drug Interactions

Interactions with other drugs may depend on activity on similar effector systems or metabolic interactions.<sup>[327]</sup>

Since cannabinoids are strongly bound to proteins, interactions with other protein-bound drugs may also occur. They might also interact with drugs that, such as THC, are metabolised by enzymes of the CYP complex. However, there was only a minor influence of cannabis smoking and oral dronabinol on the pharmacokinetic parameters of antiretroviral medications used in HIV infection and metabolised by CYP enzymes, and the use of cannabinoids is unlikely to affect antiretroviral efficacy.<sup>[328]</sup> Cessation of tobacco and cannabis smoking was reported to result in elevated blood concentrations of antipsychotic medication (clozapine or olanzapine) due to cessation of induction of CYP1A2 by smoke constituents.<sup>[329]</sup>

Other medicines may enhance or attenuate certain actions of THC, or certain actions of these medicines may be enhanced or attenuated by

THC.<sup>[330,331]</sup> Moreover, it is possible that certain effects are enhanced and others reduced, as is the case with phenothiazines used against the adverse effects of cancer chemotherapy. In a study by Lane et al., a combination of prochlorperazine and dronabinol was more effective in reducing unwanted effects of the antineoplastic medication than the phenothiazine alone, and the incidence of cannabinoid-induced adverse effects was decreased when dronabinol was combined with prochlorperazine, which also has antipsychotic properties.<sup>[283]</sup> Cannabis, caffeine and tobacco reduced the blood pressure reactivity protection of ascorbic acid, probably through their dopaminergic effects.<sup>[332]</sup>

Of greatest clinical relevance is reinforcement of the sedating effect of other psychotropic substances (alcohol, benzodiazepines), and the interaction with substances that act on heart and circulation (such as amphetamines, adrenaline, atropine, β-blockers, diuretics and tricyclic antidepressants).<sup>[330,331]</sup>

A number of additive effects may be desirable, such as the enhancement of muscle relaxants, bronchodilators and antiglaucoma medication,<sup>[210]</sup> the analgesic effect of opioids,<sup>[333]</sup> the antiemetic effect of the phenothiazines<sup>[283]</sup> and the antiepileptic action of benzodiazepines.<sup>[334]</sup> THC may antagonise the antipsychotic actions of neuroleptics<sup>[331]</sup> and may improve their clinical responsiveness in motor disorders.<sup>[335]</sup>

Indomethacin, (aspirin (acetylsalicylic acid) and other nonsteroidal anti-inflammatory drugs antagonise the effects of THC. Indomethacin significantly reduced subjective 'high',<sup>[336]</sup> tachycardia<sup>[336]</sup> and decrease of intraocular pressure following topical THC (eye drops).<sup>[337]</sup> These interactions reflect the fact that several THC effects are at least in part mediated by prostaglandin-mediated processes.<sup>[2,337]</sup>

## 8. Conclusions

The discovery, within the past 15 years, of a system of specific cannabinoid receptors in humans and their endogenous ligands has strongly

stimulated cannabinoid research, with about 650 articles published in Medline-listed journals in 2001 compared with about 250 in 1986. It has become apparent that the endocannabinoid system plays a major role in signal transduction in neuronal cells, and arachidonyl ethanolamide (anandamide) seems to be a central inhibitory compound in the central nervous system.<sup>[338]</sup>

Mechanisms of action of cannabinoids are complex, not only involving activation of and interaction at the cannabinoid receptor, but also activation of vanilloid receptors,<sup>[322]</sup> influence of endocannabinoid concentration,<sup>[339]</sup> antioxidant activity,<sup>[142]</sup> metabolic interaction with other compounds, and several others. There is still much to learn about the physiological role of the natural ligands for the CB receptor, about the long-term effects of cannabis use, and even some controversial findings on cannabinoid pharmacokinetics remain to be solved. However, because of the millennia-long use of cannabis for recreational, religious and medicinal purposes, which in recent decades has been accompanied by research in several disciplines, we do not expect to encounter with the medicinal use of cannabinoids the same unpleasant surprises that occasionally occur with newly designed synthetic drugs.

Many people who suffer from severe illnesses have discovered cannabis as a beneficial remedy, and surveys in Europe and North America show that increasing numbers of citizens in several countries reject criminal prosecution of patients who benefit from the drug. The psychotropic and circulatory effects of CB<sub>1</sub> receptor agonists and the stigma of cannabis as a recreational and addicting drug are still major obstacles to the legal therapeutic utilisation of the whole range of potentially beneficial effects. Properly designed and executed clinical studies are necessary to verify anecdotal experiences and the results from smaller uncontrolled studies, and to overcome uncertainties and scepticism.

Aside from phytocannabinoids and cannabis preparations, cannabinoid analogues that do not bind to the CB<sub>1</sub> receptor are attractive compounds

for clinical research, among them dexanabinol and CT-3. Additional ideas for the separation of the desired therapeutic effects from the psychotropic actions comprise the concurrent administration of THC and CBD, the design of CB<sub>1</sub> receptor agonists that do not cross the blood-brain barrier, and the development of compounds that influence endocannabinoid levels by inhibition of their membrane transport or hydrolysis. The future will show which strategies prove successful and which drugs will follow dronabinol and nabilone into the pharmacy.

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