

# Pharmacokinetics and Pharmacodynamics of Cannabinoids

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## Abstract

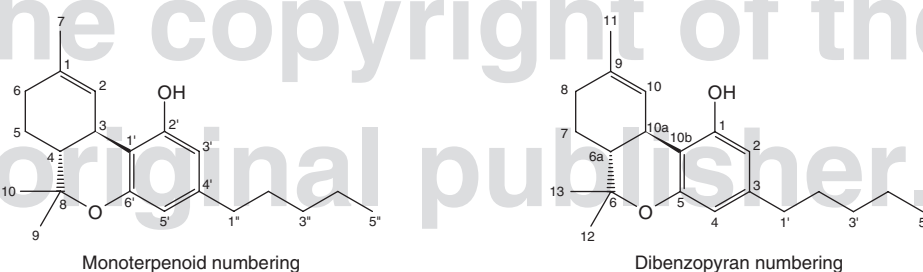
$\Delta^9$ -Tetrahydrocannabinol (THC) is the main source of the pharmacological effects caused by the consumption of cannabis, both the marijuana-like action and the medicinal benefits of the plant. However, its acid metabolite THC-COOH, the non-psychoactive cannabidiol (CBD), several cannabinoid analogues 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 to 30 minutes, and taper off within 2 to 3 hours. Following oral ingestion, psychotropic effects set in with a delay of 30 to 90 minutes, reach their maximum after 2 to 3 hours and last for about 4 to 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.



**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).

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.

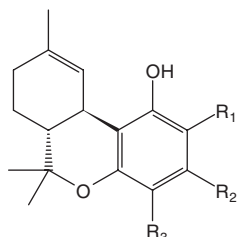
## 1. Taxonomy

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 com-

pounds, 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), cannabidiol (CBD),  $\Delta^9$ -THC,  $\Delta^8$ -THC, cannabicyclol (CBL), cannabielsoin (CBE), cannabinol (CBN), cannabiodiol (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



**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  $C_5$  side chain ( $R_2 = C_5H_{11}$ ) and its two corresponding carboxylic acids A and B with  $R_1$  or  $R_3 = COOH$  (see table I).

propyl homologue ( $C_3$  side chain) of  $\Delta^9$ -THC ( $\Delta^9$ -*trans*-tetrahydrocannabivarin);<sup>[10-12]</sup> the methyl ( $C_1$  side chain) and butyl ( $C_4$  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>

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>TM</sup> Use of tradenames is for product identification only and does not imply endorsement (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  $pK_a$  is 10.6.<sup>[18]</sup>

THC is thermolabile and photolabile.<sup>[21,22]</sup> Storage leads to a cumulative decrease in THC content

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

Cannabinoid	$R_1^a$	$R_2$	$R_3$
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabinolic acid A	COOH	$C_5H_{11}$	H
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabinolic acid B	H	$C_5H_{11}$	COOH
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabinol	H	$C_5H_{11}$	H
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabinolic acid- $C_4$	COOH or H	$C_4H_9$	H or COOH
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabinol- $C_4$	H	$C_4H_9$	H
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabivarinic acid	COOH	$C_3H_7$	H
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabivarin	H	$C_3H_7$	H
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabiorcolic acid	COOH or H	$CH_3$	H or COOH
$\Delta^9$ - <i>trans</i> -Tetrahydrocannabiorcol	H	$CH_3$	H

a See figure 2 for the basic chemical structure of  $\Delta^9$ -*trans*-tetrahydrocannabinol.

**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.

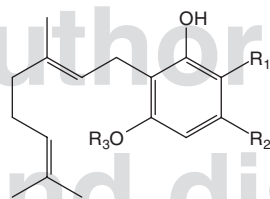
through oxidation of THC to CBN.<sup>[23,24]</sup> Within 47 weeks, the THC content of marijuana (dried leaves and flowers of *Cannabis sativa*) decreased by 7% with dark and dry storage at 5°C, and by 13% at 20°C.<sup>[24]</sup> Dronabinol rapidly degrades in acid solutions. The kinetics seem to be 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.

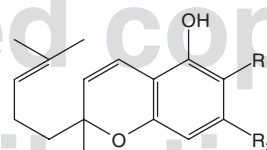
### 3. Pharmacokinetics of $\Delta^9$ -Tetrahydrocannabinol

Cannabis products are commonly either inhaled by smoking a cannabis cigarette, taken orally as dronabinol capsules or in baked foods or liquids (figure 4). Various other routes of administration



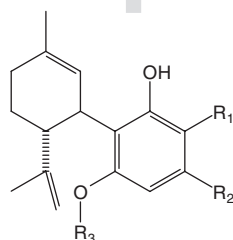
R<sub>1</sub> = H or COOH  
R<sub>2</sub> = C<sub>3</sub> or C<sub>5</sub> side chain  
R<sub>3</sub> = H or CH<sub>3</sub>

#### Cannabigerol type



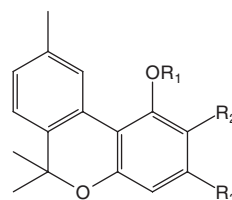
R<sub>1</sub> = H or COOH  
R<sub>2</sub> = C<sub>3</sub> or C<sub>5</sub> side chain

#### Cannabichromene type



R<sub>1</sub> = H or COOH  
R<sub>2</sub> = C<sub>1</sub>, C<sub>3</sub>, C<sub>4</sub>, or C<sub>5</sub> side chain  
R<sub>3</sub> = H or CH<sub>3</sub>

#### Cannabidiol type



R<sub>1</sub> = H or C<sub>3</sub>  
R<sub>2</sub> = H or COOH  
R<sub>3</sub> = C<sub>1</sub>, C<sub>3</sub>, C<sub>4</sub>, or C<sub>5</sub> side chain

#### Cannabinol type

**Fig. 3.** Some phytocannabinoids.

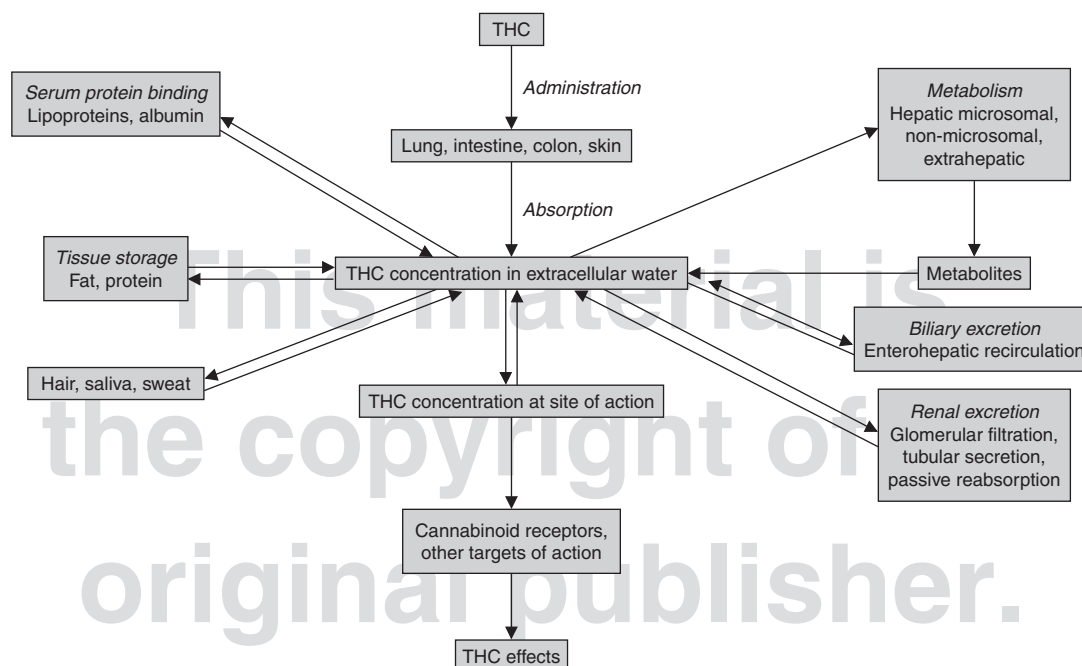


Fig. 4. Pharmacokinetic properties of  $\Delta^9$ -tetrahydrocannabinol (THC) [reproduced from Brenneisen<sup>[34]</sup> with permission].

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 to 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  $23 \pm 16\%$ <sup>[38]</sup> and  $27 \pm 10\%$ <sup>[42]</sup> for heavy users versus  $10 \pm 7\%$  and  $14 \pm 1\%$  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

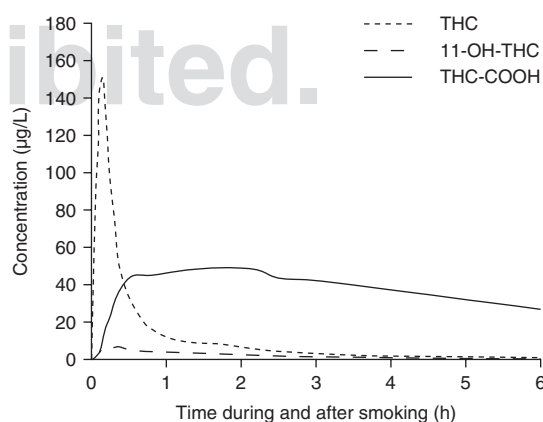


Fig. 5. Mean plasma concentrations of  $\Delta^9$ -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) of six subjects during and after smoking a cannabis cigarette containing about 34mg of THC.<sup>[35]</sup>

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

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>

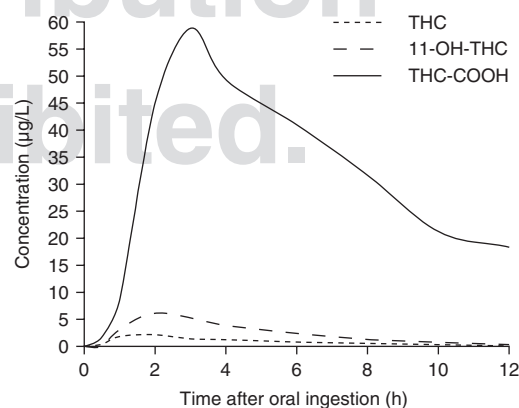
### 3.1.2 Oral Administration

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>

$\Delta^9$ -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. 95% 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



**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).

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 calculated 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 permeability 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 physicochemical 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>

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-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 104:1.<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 concentration.<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 demonstra-

ted 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  $\mu\text{g/L}$  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).

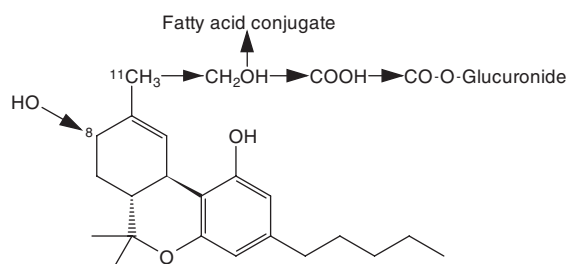


Fig. 7. Main metabolic pathways of  $\Delta^9$ -tetrahydrocannabinol.

Hydroxylation results in 11-OH-THC and further oxidation in THC-COOH, which may be 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  $11.8 \pm 3.0$  L/h ( $197 \pm 50$  ml/min) for women and  $14.9 \pm 3.7$  L/h ( $248 \pm 62$  ml/min) for men,<sup>[31]</sup> whereas others have determined higher mean clearance rates of about 36 L/h (600 ml/min) for naive THC users and about 60 L/h (1000 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>

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

Subjects	Dose (mg)	AUC ( $\mu\text{g} \cdot \text{min}/\text{L}$ )	$C_{\text{max}}$ ( $\mu\text{g}/\text{L}$ )	$t_{1/2\beta}$ (h)	Vd (L)	CL (ml/min)	References
<b>Intravenous</b>							
4 nonusers	0.5			$57 \pm 4$	$658 \pm 174$		57
5 regular users	0.5			$27 \pm 1$	$597 \pm 76$		57
6 males (drug free)	2			$19.6 \pm 4.1$	$626 \pm 296$	$605 \pm 149$	32
6 males (long-term)	2			$18.7 \pm 4.2$	$742 \pm 331$	$977 \pm 304$	32
6 males	4		$70 \pm 30$	36	$734 \pm 444$	$248 \pm 62$	31
6 females	2.2		$85 \pm 26$	29	$523 \pm 217$	$197 \pm 50$	31
11 males	5	$4330 \pm 620$	$161-316$				37 39
9 heavy users	5	$4300 \pm 1670$	$288 \pm 119$				38
9 light users	5	$6040 \pm 2.21$	$302 \pm 95$				38
5 heavy users	5	$5180 \pm 830$		>20		$980 \pm 150$	42
4 light users	5	$5460 \pm 1180$		>20		$950 \pm 200$	42
4 heavy users	5	$9908 \pm 3785$	$438 \pm 36$	$1.9 \pm 0.3$	$75 \pm 16$	$777 \pm 690$	33
4 light users	5	$7094 \pm 2248$	$386 \pm 29$	$1.6 \pm 0.5$	$74 \pm 35$	$771 \pm 287$	33
<b>Oral</b>							
6 males	20		$14.5 \pm 9.7$	25			31
6 females	15		$9.4 \pm 4.5$	25			31
11 males	20	$1020 \pm 320$	$4.4-11$				37 39
3 males	$3 \times 15$		$4-6$				46
3 males, 3 females	15		$3-5$				46
20 AIDS patients	$2 \times 2.5$		2.01 (0.58-12.48)				44
7 men, 10 women	10	$610 \pm 310$	$4.7 \pm 3.0$				41
<b>Inhalational</b>							
11 males	19	$1960 \pm 650$	$33-118$				37 39
9 heavy users	19	$2160 \pm 1030$	$98 \pm 44$				38
9 light users	19	$1420 \pm 740$	$67 \pm 38$				38
5 heavy users	10	$2450 \pm 530$					42
4 light users	10	$1420 \pm 340$					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;  **$C_{\text{max}}$**  = maximum plasma concentration;  **$t_{1/2\beta}$**  = plasma elimination half-life; **Vd** = volume of distribution.

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 average peak concentrations of 84.3  $\mu\text{g/L}$  (range 50.0–129.0  $\mu\text{g/L}$ ) for the lower dose and 162.2  $\mu\text{g/L}$  (range 76.0–267.0  $\mu\text{g/L}$ ) for the higher dose, then rapidly decreased to low concentrations of about 1–4  $\mu\text{g/L}$  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 4.4–11  $\mu\text{g/L}$  after THC 20mg,<sup>[39]</sup> 2.7–6.3  $\mu\text{g/L}$  after THC 15mg<sup>[46]</sup> and 0.58–12.48  $\mu\text{g/L}$  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  $\mu\text{g/L}$  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

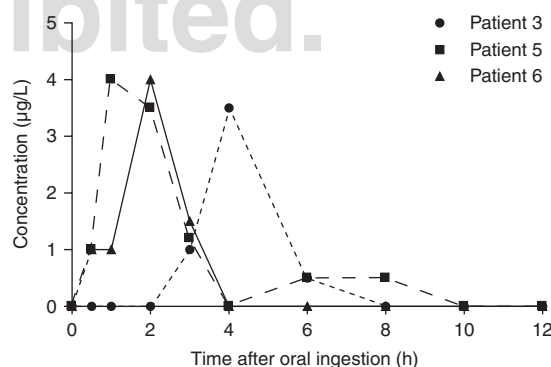


Fig. 8. Plasma concentrations of  $\Delta^9$ -tetrahydrocannabinol (THC) of three of the six cancer patients of figure 6 after ingestion of one oral dose of THC 15mg (estimated from graphs of figure 2 of Frytak et al.,<sup>[46]</sup> with permission).

**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

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 to 36 hours for THC, from 12 to 36 hours for 11-OH-THC and from 25 to 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>

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 (1992) 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 (1992), 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>

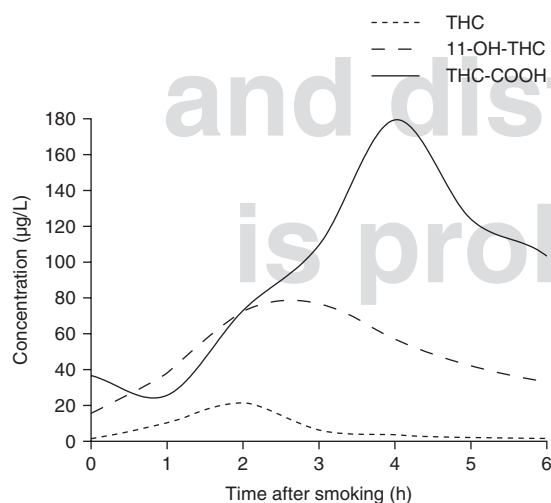
A urinary excretion half-life of THC-COOH of about 30 hours was observed with a 7-day monitoring period and of 44–60 hours with a 14-day period.<sup>[96]</sup> Other groups calculated similar average urinary excretion half-lives of about 2 days with a 12-day monitoring period<sup>[33]</sup> and of about 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 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  $77.3 \pm 29.7$   $\mu\text{g/L}$  after 3 hours and THC-COOH peaking at  $179.4 \pm 146.9$   $\mu\text{g/L}$  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 metabolites in the faeces are only present in the nonconjugated form.<sup>[31,104]</sup>



**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>

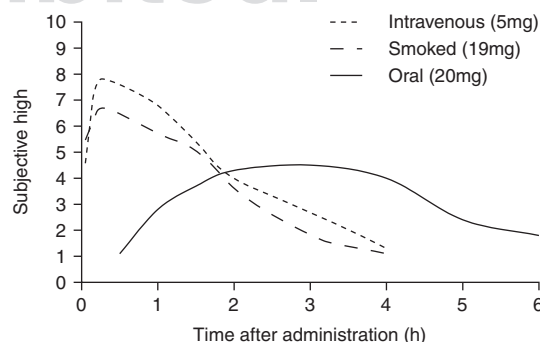
### 3.6 Time–Effect Relationship

#### 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 after 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 to 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,



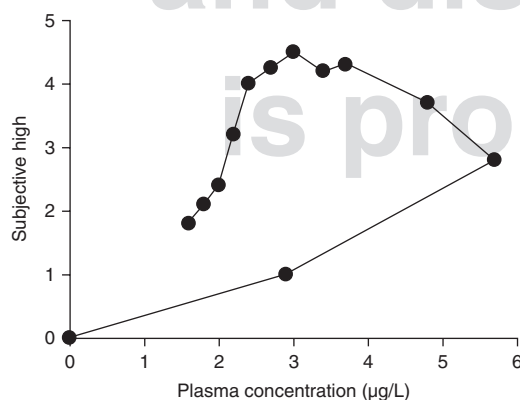
**Fig. 10.** Time course of subjective effects following three modes of administration of  $\Delta^9$ -tetrahydrocannabinol. A rating of the degree of ‘high’ was made by subjects on a 0–10 scale.<sup>[37,39]</sup>

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>

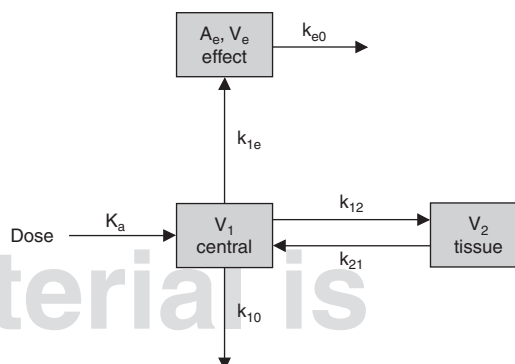
### 3.6.2 Pharmacokinetic-Pharmacodynamic Modelling

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 intravenous 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 (1984)<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 ( $A_e$ ):



**Fig. 11.** Phase plot of subjective 'high' versus plasma  $\Delta^9$ -tetrahydrocannabinol (THC) concentration from 0 to 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.

$$E = \frac{(k_{e0} \cdot A_e / k_{e1} \cdot V_1)^\gamma}{(k_{e0} \cdot A_e / k_{e1} \cdot V_1)^\gamma + C_{ss,50}}$$

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 (0.0078–0.012  $\text{min}^{-1}$ ) 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 nonpsychotropic 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 to 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 cannabinoil.<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 nonpsychotropic 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  $\Delta^8$ -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 analgesic, 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 arachidonylethanolamide (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



Fig. 13. Major endocannabinoids.

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>

#### 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>  $\Delta^9$ -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 $\Delta^9$ -Tetrahydrocannabinol

The pharmacological activity of  $\Delta^9$ -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<sub>50</sub>) 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

**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

from the effects of cannabis or single cannabinoids.<sup>[174]</sup>

#### 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 peptides. 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> Vasodilation 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 antineoplastic 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 nonpsychotropic 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> antidystonic,<sup>[238]</sup> antiemetic<sup>[239]</sup> and anti-inflamma-

tory<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.

##### 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  $\Delta^8$ -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 psychoactivity.<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  $\Delta^8$ -THC metabolite THC-COOH, is under clinical investigation for inflammation and pain.<sup>[65,249]</sup>



Fig. 14. Classical synthetic cannabinoids.

#### 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>



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

## 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% to 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 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,  $\beta$ -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 arachidonylethanolamide (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 dexamabinol 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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### References

- Loewe S. Cannabiswirkstoffe und Pharmakologie der Cannabinoide. *Archiv Experimentelle Pathologie Pharmakologie* 1950; 211: 175-93
- Dewey WL. Cannabinoid pharmacology. *Pharmacol Rev* 1986; 38 (2): 151-78
- Hollister LE. Health aspects of cannabis. *Pharmacol Rev* 1986; 38: 1-20
- Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of the active constituent of hashish. *J Am Chem Soc* 1964; 86: 1646-7
- Devane WA, Dysarz III FA, Johnson MR, et al. Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* 1988; 34 (5): 605-13
- Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992; 258 (5090): 1946-9
- Razdan RK. Structure-activity relationships in cannabinoids. *Pharmacol Rev* 1986; 38: 75-149
- Pate D. Taxonomy of cannabinoids. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 15-26
- ElSohly MA. Chemical constituents of cannabis. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 27-36
- Field BI, Arndt RR. Cannabinoid compounds in South African *Cannabis sativa* L. *J Pharm Pharmacol* 1980; 32 (1): 21-4
- Pitts JE, Neal JD, Gough TA. Some features of Cannabis plants grown in the United Kingdom from seeds of known origin. *J Pharm Pharmacol* 1992; 44 (12): 947-51
- Rowan MG, Fairbairn JW. Cannabinoid patterns in seedlings of *Cannabis sativa* L. and their use in the determination of chemical race. *J Pharm Pharmacol* 1977; 29 (8): 491-4
- Harvey DJ. Characterization of the butyl homologues of delta1-tetrahydrocannabinol, cannabinol and cannabidiol in samples of cannabis by combined gas chromatography and mass spectrometry. *J Pharm Pharmacol* 1976; 28 (4): 280-5
- Vree TB, Breimer DD, van Ginneken CA, et al. Identification in hashish of tetrahydrocannabinol, cannabidiol and cannabinol analogues with a methyl side-chain. *J Pharm Pharmacol* 1972; 24 (1): 7-12
- ElSohly MA, Ross SA, Mehmedic Z, et al. Potency trends of Δ9-THC and other cannabinoids in confiscated marijuana from 1980-1997. *J Forensic Sci* 2000; 45 (1): 24-30
- Brenneisen R. Psychotrope drogen: II. Bestimmung der Cannabinoide in *Cannabis sativa* L. und in Cannabisprodukten mittels Hochdruckflüssigkeitschromatographie (HPLC). *Pharm Acta Helv* 1984; 59: 247-59
- Baker PB, Taylor BJ, Gough TA. The tetrahydrocannabinol and tetrahydrocannabinolic acid content of cannabis products. *J Pharm Pharmacol* 1981; 33 (6): 369-72
- Garrett ER, Hunt CA. Physicochemical properties, solubility, and protein binding of Δ9-tetrahydrocannabinol. *J Pharm Sci* 1974; 63 (7): 1056-64
- Mechoulam R. Chemistry of cannabis. *Handbook Exp Pharmacol* 1981; 53: 119-34
- Thomas BF, Compton DR, Martin BR. Characterization of the lipophilicity of natural and synthetic analogs of delta 9-tetrahydrocannabinol and its relationship to pharmacological potency. *J Pharmacol Exp Ther* 1990; 255 (2): 624-30
- Johnson JR, Jennison TA, Peat MA, et al. Stability of delta 9-tetrahydrocannabinol (THC), 11-hydroxy-THC, and 11-nor-9-carboxy-THC in blood and plasma. *J Anal Toxicol* 1984; 8 (5): 202-4
- N.N. Monographs: Dronabinol capsules 2.5 / 5 or 10mg (NRF 22.7.); oily dronabinol drops 2.5% (NRF 22.8). In: *Bundesvereinigung Deutscher Apothekerverbände, editor. Neues Rezepturformularium (NRF), Loose-Leaf Collection of 2001*. Eschborn, Germany: Govi-Verlag Pharmazeutischer Verlag / Stuttgart, Germany: Deutscher Apotheker-Verlag, 2001
- Agurell S, Leander K. Stability, transfer and absorption of cannabinoid constituents of cannabis (hashish) during smoking. *Acta Pharm Suec* 1971; 8 (4): 391-402

24. Fairbairn JW, Liebmann JA, Rowan MG. The stability of cannabis and its preparations on storage. *J Pharm Pharmacol* 1976; 28: 1-7
25. Brenneisen R, Egli A, Elsohly MA, et al. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. *Int J Clin Pharmacol Ther* 1996; 34 (10): 446-52
26. Stinchcomb A, Challapalli P, Harris K, et al. Optimization of in vitro experimental conditions for measuring the percutaneous absorption of  $\Delta^9$ -THC, cannabidiol, and WIN55,212-2 [abstract]. 2001 Symposium on the Cannabinoids. Burlington (VT): International Cannabinoid Research Society, 2001; 161
27. Guy GW, Flint ME. A phase one study of sublingual Cannabis based medicinal extracts. 2000 Symposium on the Cannabinoids. Burlington (VT): International Cannabinoid Research Society; 2000, 115
28. Merritt JC, Olsen JL, Armstrong JR, et al. Topical delta 9-tetrahydrocannabinol in hypertensive glaucomas. *J Pharm Pharmacol* 1981; 33 (1): 40-1
29. Lichtman AH, Peart J, Poklis JL, et al. Pharmacological evaluation of aerosolized cannabinoids in mice. *Eur J Pharmacol* 2000; 399 (2-3): 141-9
30. Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax* 1976; 31 (6): 720-3
31. Wall ME, Sadler BM, Brine D, et al. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol, in men and women. *Clin Pharmacol Ther* 1983; 34 (3): 352-63
32. Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. *J Pharmacol Exp Ther* 1980; 215 (1): 35-44
33. Kelly P, Jones RT. Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users. *J Anal Toxicol* 1992; 16 (4): 228-35
34. Brenneisen R. Pharmacokinetik. In: Grotenhermen F, editor. Cannabis und Cannabinoide. Pharmakologie, Toxikologie und Therapeutisches Potenzial. Göttingen: Hans Huber Verlag, 2001: 87-92
35. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids: I. absorption of THC and formation of 11-OH-THC and THC-COOH during and after smoking marijuana. *J Anal Toxicol* 1992; 16 (5): 276-82
36. Chiang CW, Barnett G. Marijuana effect and delta-9-tetrahydrocannabinol plasma level. *Clin Pharmacol Ther* 1984; 36 (2): 234-8
37. Hollister LE, Gillespie HK, Ohlsson A, et al. Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? *J Clin Pharmacol* 1981; 21 (8-9 Suppl.): 171S-7S
38. Lindgren JE, Ohlsson A, Agurell S, et al. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology* 1981; 74 (3): 208-12
39. Ohlsson A, Lindgren JE, Wahlen A, et al. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin Pharmacol Ther* 1980; 28 (3): 409-16
40. Perez-Reyes M, Di Guiseppi S, Davis KH, et al. Comparison of effects of marijuana cigarettes to three different potencies. *Clin Pharmacol Ther* 1982; 31 (5): 617-24
41. Sporkert F, Pragst F, Ploner CJ, et al. Pharmacokinetic investigation of delta-9-tetrahydrocannabinol and its metabolites after single administration of 10mg Marinol in attendance of a psychiatric study with 17 volunteers. Poster at the 39th Annual International Meeting, International Association of Forensic Toxicologists; 2001 Aug 26-30; Prague, Czech Republic
42. Ohlsson A, Lindgren JE, Wahlen A, et al. Single dose kinetics of deuterium labelled  $\Delta^1$ -tetrahydrocannabinol in heavy and light cannabis users. *Biomed Mass Spectrom* 1982; 9 (1): 6-10
43. Davis KH, McDaniell JA, Cadwell LW, et al. Some smoking characteristics of marijuana cigarettes. In: Agurell S, Dewey WL, Willette RE, editors. The cannabinoids: chemical, pharmacologic and therapeutic aspects. New York: Academic Press, 1984: 245-61
44. Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses* 1997; 13 (4): 305-15
45. Law B, Mason PA, Moffat AC, et al. Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. *J Pharm Pharmacol* 1984; 36 (5): 289-94
46. Frytak S, Moertel CG, Rubin J. Metabolic studies of delta-9-tetrahydrocannabinol in cancer patients. *Cancer Treat Rep* 1984; 68 (12): 1427-31
47. Harvey DJ. Metabolism and pharmacokinetics of the cannabinoids. In: Watson RR, editor. Biochemistry and physiology of substance abuse. Vol III. Boca Raton (FL): CRC Press, 1991: 279-365
48. Lemberger L, Weiss JL, Watanabe AM, et al. Delta-9-tetrahydrocannabinol. Temporal correlation of the psychologic effects and blood levels after various routes of administration. *N Engl J Med* 1972; 286 (13): 685-8
49. Chiang CW, Barnett G, Brine D. Systemic absorption of delta 9-tetrahydrocannabinol after ophthalmic administration to the rabbit. *J Pharm Sci* 1983; 72 (2): 136-8
50. ElSohly MA, Stanford DF, Harland EC, et al. Rectal bioavailability of delta-9-tetrahydrocannabinol from the hemisuccinate ester in monkeys. *J Pharm Sci* 1991; 80 (10): 942-5
51. Notcutt W, Price M, Miller R, et al. Medicinal cannabis extracts in chronic pain: (5) cognitive function and blood cannabinoid levels. 2001 Congress on Cannabis and the Cannabinoids. Cologne: International Association for Cannabis as Medicine, 28
52. Touitou E, Fabin B, Dany S, et al. Transdermal delivery of tetrahydrocannabinol. *Int J Pharm* 1988; 43: 9-15
53. Leuschner JT, Harvey DJ, Bullingham RE, et al. Pharmacokinetics of delta 9-tetrahydrocannabinol in rabbits following single or multiple intravenous doses. *Drug Metab Dispos* 1986; 14 (2): 230-8
54. Widman M, Agurell S, Ehrnebo M, et al. Binding of (+)- and (-)- $\Delta^1$ - tetrahydrocannabinols and (-)-7-hydroxy- $\Delta^1$ -tetrahydrocannabinol to blood cells and plasma proteins in man. *J Pharm Pharmacol* 1974; 26 (11): 914-6
55. Fehr KO, Kalant H. Fate of  $^{14}C$ -delta1-THC in rat plasma after intravenous injection and smoking. *Eur J Pharmacol* 1974; 25 (1): 1-8
56. Wahlqvist M, Nilsson IM, Sandberg F, et al. Binding of delta-1-tetrahydrocannabinol to human plasma proteins. *Biochem Pharmacol* 1970; 19 (9): 2579-84
57. Lemberger L, Tamarkin NR, Axelrod J, et al. Delta-9-tetrahydrocannabinol: metabolism and disposition in long-term marijuana smokers. *Science* 1971; 173 (991): 72-4
58. Barnett G, Chiang CW, Perez-Reyes M, et al. Kinetic study of smoking marijuana. *J Pharmacokinetic Biopharm* 1982; 10 (5): 495-506

59. Brewster ME, Pop E, Foltz RL, et al. Clinical pharmacokinetics of escalating i.v. doses of dexanabinol (HU-211), a neuroprotectant agent, in normal volunteers. *Int J Clin Pharmacol Ther* 1997; 35 (9): 361-5
60. Sticht G, Käferstein H. Grundbegriffe, toxikokinetik und toxikodynamik. In: Berghaus G, Krüger HP, editors. *Cannabis im Straßenverkehr*. Stuttgart: Gustav Fischer, 1998: 1-11
61. Ryrfeldt A, Ramsay CH, Nilsson IM, et al. Whole-body autoradiography of  $\Delta^1$ -tetrahydrocannabinol and  $\Delta^1$  (6)-tetrahydrocannabinol in mouse: pharmacokinetic aspects of  $\Delta^1$ -tetrahydrocannabinol and its metabolites. *Acta Pharm Suec* 1973; 10 (1): 13-28
62. Ho BT, Fritchie GE, Kralik PM, et al. Distribution of tritiated- $\Delta^1$ -tetrahydrocannabinol in rat tissues after inhalation. *J Pharm Pharmacol* 1970; 22 (7): 538-9
63. Gill EW, Jones G. Brain levels of  $\Delta^1$ -tetrahydrocannabinol and its metabolites in mice: correlation with behaviour, and the effect of the metabolic inhibitors SKF 525A and piperonyl butoxide. *Biochem Pharmacol* 1972; 21 (16): 2237-48
64. Chiang CN, Rapaka RS. Pharmacokinetics and disposition of cannabinoids. *NIDA Res Monogr* 1987; 79: 173-88
65. Perez-Reyes M, Simmons J, Brine D, et al. Rate of penetration of  $\Delta^9$ -tetrahydrocannabinol and 11-hydroxy- $\Delta^9$ -tetrahydrocannabinol to the brain of mice. In: Nahas GG, editor. *Marihuana: chemistry, biochemistry, and cellular effects*. New York: Springer, 1976: 179-85
66. Agurell S, Nilsson IM, Ohlsson A, et al. On the metabolism of tritium-labelled, 1-tetrahydrocannabinol in the rabbit. *Biochem Pharmacol* 1970; 19 (4): 1333-9
67. Johansson E, Noren K, Sjovall J, et al. Determination of delta 1-tetrahydrocannabinol in human fat biopsies from marihuana users by gas chromatography-mass spectrometry. *Biomed Chromatogr* 1989; 3 (1): 35-8
68. Kreuz DS, Axelrod J. Delta-9-tetrahydrocannabinol: localization in body fat. *Science* 1973; 179 (71): 391-3
69. Harvey DJ, Leuschner JT, Paton WD. Gas chromatographic and mass spectrometric studies on the metabolism and pharmacokinetics of delta 1-tetrahydrocannabinol in the rabbit. *J Chromatogr* 1982; 239: 243-50
70. Haggerty GC, Deskin R, Kurtz PJ, et al. The pharmacological activity of the fatty acid conjugate 11-palmitoyloxy-delta 9-tetrahydrocannabinol. *Toxicol Appl Pharmacol* 1986; 84 (3): 599-606
71. Leighty EG, Fentiman Jr AF, Foltz RL. Long-retained metabolites of  $\Delta^9$ - and  $\Delta^8$ -tetrahydrocannabinols identified as novel fatty acid conjugates. *Res Commun Chem Pathol Pharmacol* 1976; 14 (1): 13-28
72. Blackard C, Tennes K. Human placental transfer of cannabinoids [letter]. *N Engl J Med* 1984; 311: 797
73. Abrams RM, Cook CE, Davis KH, et al. Plasma delta-9-tetrahydrocannabinol in pregnant sheep and fetus after inhalation of smoke from a marijuana cigarette. *Alcohol Drug Res* 1985-1986; 6: 361-9
74. Bailey JR, Cunny HC, Paule MG, et al. Fetal disposition of delta 9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. *Toxicol Appl Pharmacol* 1987; 90: 315-21
75. Hutchings DE, Martin BR, Gamagaris Z, et al. Plasma concentrations of delta-9-tetrahydrocannabinol in dams and fetuses following acute or multiple prenatal dosing in rats. *Life Sci* 1989; 44 (11): 697-701
76. Martin BR, Dewey WL, Harris LS, et al. 3H-delta 9-tetrahydrocannabinol distribution in pregnant dogs and their fetuses. *Res Commun Chem Pathol Pharmacol* 1977; 17: 457-70
77. Boskovic R, Klein J, Woodland C, et al. The role of the placenta in variability of fetal exposure to cocaine and cannabinoids: a twin study. *Can J Physiol Pharmacol* 2001; 79 (11): 942-5
78. Chao FC, Green DE, Forrest IS, et al. The passage of  $\Delta^1$ -tetrahydrocannabinol into the milk of lactating squirrel monkeys. *Res Commun Chem Pathol Pharmacol* 1976; 15: 303-17
79. Perez-Reyes M, Wall ME. Presence of delta 9-tetrahydrocannabinol in human milk. *N Engl J Med* 1982; 307: 819-20
80. Matsunaga T, Iwawaki Y, Watanabe K, et al. Metabolism of delta 9-tetrahydrocannabinol by cytochrome P450 isozymes purified from hepatic microsomes of monkeys. *Life Sci* 1995; 56 (23-24): 2089-95
81. Narimatsu S, Watanabe K, Matsunaga T, et al. Cytochrome P-450 isozymes involved in the oxidative metabolism of delta 9-tetrahydrocannabinol by liver microsomes of adult female rats. *Drug Metab Dispos* 1992; 20 (1): 79-83
82. Watanabe K, Matsunaga T, Yamamoto I, et al. Involvement of CYP2C in the metabolism of cannabinoids by human hepatic microsomes from an old woman. *Biol Pharm Bull* 1995; 18 (8): 1138-41
83. Alozie SO, Martin BR, Harris LS, et al. 3H-delta 9-Tetrahydrocannabinol, 3H-cannabinol and 3H-cannabidiol: penetration and regional distribution in rat brain. *Pharmacol Biochem Behav* 1980; 12 (2): 217-21
84. Borys HK, Karler R. Cannabidiol and delta 9-tetrahydrocannabinol metabolism: in vitro comparison of mouse and rat liver crude microsome preparations. *Biochem Pharmacol* 1979; 28 (9): 1553-9
85. Harvey DJ, Brown NK. Comparative in vitro metabolism of the cannabinoids. *Pharmacol Biochem Behav* 1991; 40 (3): 533-40
86. Grotenhermen F. Review of unwanted actions of cannabis and THC. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 233-48
87. Harvey DJ, Paton WDM. Examination of the metabolites of  $\Delta^1$ -tetrahydrocannabinol in mouse, liver, heart and lung by combined gas chromatography and mass spectrometry. In: Nahas GG, editor. *Marihuana: chemistry, biochemistry and cellular effects*. New York: Springer-Verlag, 1976: 93-107
88. Nakazawa K, Costa E. Metabolism of delta 9-tetrahydrocannabinol by lung and liver homogenates of rats treated with methylcholanthrene. *Nature* 1971; 234 (5323): 48-9
89. Widman M, Nordqvist M, Dollery CT, et al. Metabolism of delta 1-tetrahydrocannabinol by the isolated perfused dog lung. Comparison with in vitro liver metabolism. *J Pharm Pharmacol* 1975; 27 (11): 842-8
90. Wall ME. The in vivo and in vitro metabolism of tetrahydrocannabinol. *Ann N Y Acad Sci* 1971; 191: 23-9
91. Widman M, Halldin M, Martin B. In vitro metabolism of tetrahydrocannabinol by rhesus monkey liver and human liver. *Adv Biosci* 1978; 22-23: 101-3
92. Leighty EG. Metabolism and distribution of cannabinoids in rats after different methods of administration. *Biochem Pharmacol* 1973; 22 (13): 1613-21
93. Johansson E, Halldin MM, Agurell S, et al. Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana. *Eur J Clin Pharmacol* 1989; 37 (3): 273-7
94. Schwartz RH, Hayden GF, Riddile M. Laboratory detection of marijuana use: experience with a photometric immunoassay to measure urinary cannabinoids. *Am J Dis Child* 1985; 139 (11): 1093-6

95. Ellis Jr GM, Mann MA, Judson BA, et al. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. *Clin Pharmacol Ther* 1985; 38 (5): 572-8
96. Huestis MA, Cone EJ. Urinary excretion half-life of 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol in humans. *Ther Drug Monit* 1998; 20 (5): 570-6
97. Johansson E, Halldin MM. Urinary excretion half-life of delta 1-tetrahydrocannabinol-7-oic acid in heavy marijuana users after smoking. *J Anal Toxicol* 1989; 13 (4): 218-23
98. Halldin MM, Andersson LK, Widman M, et al. Further urinary metabolites of delta 1-tetrahydrocannabinol in man. *Arzneimittel Forschung* 1982; 32 (9): 1135-8
99. Halldin MM, Carlsson S, Kanter SL, et al. Urinary metabolites of delta 1-tetrahydrocannabinol in man. *Arzneimittel Forschung* 1982; 32 (7): 764-8
100. Williams PL, Moffat AC. Identification in human urine of delta 9-tetrahydrocannabinol-11-oic acid glucuronide: a tetrahydrocannabinol metabolite. *J Pharm Pharmacol* 1980; 32 (7): 445-8
101. Alburges ME, Peat MA. Profiles of delta 9-tetrahydrocannabinol metabolites in urine of marijuana users: preliminary observations by high performance liquid chromatography-radioimmunoassay. *J Forensic Sci* 1986; 31 (2): 695-706
102. Wall ME, Perez-Reyes M. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. *J Clin Pharmacol* 1981; 21 (8-9 Suppl.): 178S-89S
103. Manno JE, Manno BR, Kemp PM, et al. Temporal indication of marijuana use can be estimated from plasma and urine concentrations of  $\Delta^9$ -tetrahydrocannabinol, 11-hydroxy- $\Delta^9$ -tetrahydrocannabinol, and 11-nor- $\Delta^9$ -tetrahydrocannabinol-9-carboxylic acid. *J Anal Toxicol* 2001; 25 (7): 538-49
104. Mikes F, Hofmann A, Waser PG. Identification of (-)-delta 9- $\Delta^9$ -trans-tetrahydrocannabinol and two of its metabolites in rats by use of combination gas chromatography-mass spectrometry and mass fragmentography. *Biochem Pharmacol* 1971; 20 (9): 2469-76
105. Harder S, Rietbrock S. Concentration-effect relationship of delta-9-tetrahydrocannabinol and prediction of psychotropic effects after smoking marijuana. *Int J Clin Pharmacol Ther* 1997; 35 (4): 155-9
106. Robbe HWJ. Influence of marijuana on driving. Maastricht: Institut for Human Psychopharmacology, University of Limburg, 1994
107. Barnett G, Licko V, Thompson T. Behavioral pharmacokinetics of marijuana. *Psychopharmacology* 1985; 85 (1): 51-6
108. Cocchetto DM, Owens SM, Perez-Reyes M, et al. Relationship between plasma delta-9-tetrahydrocannabinol concentration and pharmacologic effects in man. *Psychopharmacology* 1981; 75 (2): 158-64
109. Nyoni EC, Sitaram BR, Taylor DA. Determination of delta 9-tetrahydrocannabinol levels in brain tissue using high-performance liquid chromatography with electrochemical detection. *J Chromatogr B Biomed Appl* 1996; 679 (1-2): 79-84
110. McIsaac W, Fritch G, Idanpaan-Heikkila J, et al. Distribution of marijuana in monkey brain and concomitant behavioural effects. *Nature* 1971; 230 (5296): 593-4
111. Ohlsson A, Widman M, Carlsson S, et al. Plasma and brain levels of delta 6-THC and seven monooxygenated metabolites correlated to the cataleptic effect in the mouse. *Acta Pharmacol Toxicol (Copenh)*; 1980; 47 (4): 308-17
112. Law B, Moffat AC. The influence of the metabolism and elimination of cannabinoids on forensic analysis and interpretation. In: Harvey DJ, editor. *Marijuana '84: Proceedings of the Oxford Symposium on Cannabis*. Oxford: IRL Press Limited, 1985: 197-204
113. McBurney LJ, Bobbie BA, Sepp LA. GC/MS and EMIT analyses for delta 9-tetrahydrocannabinol metabolites in plasma and urine of human subjects. *J Anal Toxicol* 1986; 10 (2): 56-64
114. Daldrup TH. Cannabis im Straßenverkehr. Final report commissioned by the Ministry of Economy, Technology and Traffic of North Rhine-Westphalia. Düsseldorf: University of Düsseldorf, 1996
115. Hanson V, Buonarati M, Baselt R, et al. Comparison of 3H- and 125I-radioimmunoassay and gas chromatography/mass spectrometry for the determination of  $\Delta^9$ -tetrahydrocannabinol and cannabinoids in blood and serum. *J Anal Toxicol* 1983; 7: 96-102
116. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids: II. models for the prediction of time of marijuana exposure from plasma concentrations of delta 9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (THC-COOH). *J Anal Toxicol* 1992; 16 (5): 283-90
117. Agurell S, Halldin M, Lindgren JE, et al. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* 1986; 38 (1): 21-43
118. Ohlsson A, Lindgren JE, Andersson S, et al. Single dose kinetics of cannabidiol in man. In: Agurell S, Dewey WL, Willette R, editors. *The cannabinoids: chemical, pharmacologic, and therapeutic aspects*. New York: Academic Press, 1984: 219-25
119. Agurell S, Carlsson S, Lindgren JE, et al. Interactions of delta 1-tetrahydrocannabinol with cannabidiol and cannabidiol following oral administration in man: assay of cannabidiol and cannabidiol by mass fragmentography. *Experientia* 1981; 37 (10): 1090-2
120. Consroe P, Laguna J, Allender J, et al. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav* 1991; 40 (3): 701-8
121. Harvey DJ, Mechoulam R. Metabolites of cannabidiol identified in human urine. *Xenobiotica* 1990; 20 (3): 303-20
122. Wall ME, Brine DR, Perez-Reyes M. Metabolism of cannabinoids in man. In: Braude MC, Szara S, editors. *Pharmacology of marijuana*. New York: Raven Press, 1976: 93-113
123. Lemberger L, Rubin A, Wolen R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. *Cancer Treat Rev* 1982; 9 Suppl B: 17-23
124. Rubin A, Lemberger L, Warrick P, et al. Physiologic disposition of nabilone, a cannabinol derivative, in man. *Clin Pharmacol Ther* 1977; 22 (1): 85-91
125. Sullivan HR, Kau DL, Wood PG. Pharmacokinetics of nabilone, a psychotropically active 9-ketocannabinoid, in the dog. Utilization of quantitative selected ion monitoring and deuterium labeling. *Biomed Mass Spectrom* 1978; 5 (4): 296-301
126. Sullivan HR, Hanasono GK, Miller WM, et al. Species specificity in the metabolism of nabilone: relationship between toxicity and metabolic routes. *Xenobiotica* 1987; 17 (4): 459-68
127. Bornheim LM, Grillo MP. Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of cannabidiol-hydroxyquinone as a P450 inactivator. *Chem Res Toxicol* 1998; 11 (10): 1209-16
128. Jaeger W, Benet LZ, Bornheim LM. Inhibition of cyclosporine and tetrahydrocannabinol metabolism by cannabidiol in mouse and human microsomes. *Xenobiotica* 1996; 26 (3): 275-84
129. Watanabe K, Arai M, Narimatsu S, et al. Self-catalyzed inactivation of cytochrome P-450 during microsomal metabolism of cannabidiol. *Biochem Pharmacol* 1987; 36 (20): 3371-7

130. Yamamoto I, Watanabe K, Narimatsu S, et al. Recent advances in the metabolism of cannabinoids. *Int J Biochem Cell Biol* 1995; 27 (8): 741-6
131. Bornheim LM, Kim KY, Li J, et al. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metab Dispos* 1995; 23 (8): 825-31
132. Hunt CA, Jones RT, Herning RI, et al. Evidence that cannabidiol does not significantly alter the pharmacokinetics of tetrahydrocannabinol in man. *J Pharmacokinet Biopharm* 1981; 9 (3): 245-60
133. Bornheim LM, Everhart ET, Li J, et al. Induction and genetic regulation of mouse hepatic cytochrome P450 by cannabidiol. *Biochem Pharmacol* 1994; 48 (1): 161-71
134. Watanabe K, Arai M, Narimatsu S, et al. Effect of repeated administration of 11-hydroxy-delta 8-tetrahydrocannabinol, an active metabolite of delta 8-tetrahydrocannabinol, on the hepatic microsomal drug-metabolizing enzyme system of mice. *Biochem Pharmacol* 1986; 35 (11): 1861-5
135. Costa B, Parolaro D, Colleoni M. Chronic cannabinoid, CP-55,940, administration alters biotransformation in the rat. *Eur J Pharmacol* 1996; 313 (1-2): 17-24
136. Hollister LE, Gillespie H. Interactions in man of delta-9-tetrahydrocannabinol: II. cannabiniol and cannabidiol. *Clin Pharmacol Ther* 1975; 18 (1): 80-3
137. Zuardi AW, Shirakawa I, Finkelfarb E, et al. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology* 1982; 76 (3): 245-50
138. Karniol IG, Shirakawa I, Kasinski N, et al. Cannabidiol interferes with the effects of delta 9-tetrahydrocannabinol in man. *Eur J Pharmacol* 1974; 28 (1): 172-7
139. Petitot F, Jeantaud B, Reibaud M, et al. Complex pharmacology of natural cannabinoids: evidence for partial agonist activity of  $\Delta^9$ -tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life Sci* 1998; 63 (1): PL1-6
140. De Petrocellis L, Melck D, Bisogno T, et al. Finding of the endocannabinoid signalling system in Hydra, a very primitive organism: possible role in the feeding response. *Neuroscience* 1999; 92 (1): 377-87
141. Bueb JL, Lambert DM, Tschirhart EJ. Receptor-independent effects of natural cannabinoids in rat peritoneal mast cells in vitro. *Biochim Biophys Acta* 2001; 1538 (2-3): 252-9
142. Hampson A. Cannabinoids as neuroprotectants against ischemia. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 101-10
143. Ralevic V, Kendall DA. Cannabinoids inhibit pre- and postjunctionally sympathetic neurotransmission in rat mesenteric arteries. *Eur J Pharmacol* 2002; 444 (3): 171-81
144. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sci* 1995; 56 (23-24): 2097-102
145. Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther* 1997; 74 (2): 129-80
146. Pertwee RG. Sites and mechanisms of action. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 73-88
147. Schweitzer P. Cannabinoids decrease the K<sup>+</sup> M-current in hippocampal CA1 neurons. *J Neurosci* 2000; 20: 51-8
148. Glass M, Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. *J Neurosci* 1997; 17: 5327-33
149. Galiègue S, Mary S, Marchand J, et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur J Biochem* 1995; 232: 54-61
150. Breivogel CS, Griffin G, Di Marzo V, et al. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. *Mol Pharmacol* 2001; 60 (1): 155-63
151. Di Marzo V, Breivogel CS, Tao Q, et al. Levels, metabolism, and pharmacological activity of anandamide in CB1 (1) cannabinoid receptor knockout mice: evidence for non-CB1 (1), non-CB2 (2) receptor-mediated actions of anandamide in mouse brain. *J Neurochem* 2000; 75 (6): 2434-44
152. Pertwee RG. Evidence for the presence of CB1 cannabinoid receptors on peripheral neurones and for the existence of neuronal non-CB1 cannabinoid receptors. *Life Sci* 1999; 65: 597-605
153. Recht LD, Salmons R, Rosetti R, et al. Antitumor effects of ajulemic acid (CT3), a synthetic non-psychoactive cannabinoid. *Biochem Pharmacol* 2001; 62 (6): 755-63
154. Sanchez C, de Ceballos ML, del Pulgar TG, et al. Inhibition of glioma growth in vivo by selective activation of the CB2 cannabinoid receptor. *Cancer Res* 2001; 61 (15): 5784-9
155. Giuffrida A, Beltramo M, Piomelli D. Mechanisms of endocannabinoid inactivation: biochemistry and pharmacology. *J Pharmacol Exp Ther* 2001; 298 (1): 7-14
156. Sugiura T, Kondo S, Sukagawa A, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun* 1995; 215 (1): 89-97
157. De Petrocellis L, Melck D, Bisogno T, et al. Endocannabinoids and fatty acid amides in cancer, inflammation and related disorders. *Chem Phys Lipids* 2000; 108 (1-2): 191-209
158. Di Marzo V. 'Endocannabinoids' and other fatty acid derivatives with cannabimimetic properties: biochemistry and possible physiopathological relevance. *Biochim Biophys Acta* 1998; 1392 (2-3): 153-75
159. Cravatt BF, Demarest K, Patricelli MP, et al. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc Natl Acad Sci U S A* 2001; 98 (16): 9371-6
160. Abadji V, Lin S, Gihan T, et al. (R)-Methanandamide: a chiral novel anandamide possessing higher potency and metabolic stability. *J Med Chem* 1994; 37: 1889-93
161. Pertwee RG. Pharmacology of cannabinoid receptor ligands. *Curr Med Chem* 1999; 6: 635-64
162. Walker JM, Huang SM, Strangman NM, et al. Pain modulation by release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci U S A* 1999; 96 (21): 12198-203
163. Baker D, Pryce G, Croxford JL, et al. Endocannabinoids control spasticity in a multiple sclerosis model. *FASEB J* 2001; 15 (2): 300-2
164. Siegling A, Hofmann HA, Denzer D, et al. Cannabinoid CB1 receptor upregulation in a rat model of chronic neuropathic pain. *Eur J Pharmacol* 2001; 415 (1): R5-7
165. Izzo AA, Fezza F, Capasso R, et al. Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. *Br J Pharmacol* 2001; 134 (3): 563-70
166. Di Marzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 2001; 410 (6830): 822-5

167. Darmani NA. Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB (1) receptors in the least shrew. *Pharmacol Biochem Behav* 2001; 69 (1-2): 239-49
168. Leweke FM, Giuffrida A, Wurster U, et al. Elevated endogenous cannabinoids in schizophrenia. *Neuroreport* 1999; 10 (8): 1665-9
169. Beaulieu P, Bisogno T, Punwar S, et al. Role of the endogenous cannabinoid system in the formalin test of persistent pain in the rat. *Eur J Pharmacol* 2000; 396 (2-3): 85-92
170. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 1996; 91 (11): 1585-614
171. Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press, 2002
172. Hall W, Solowij N, Lemon J. The health and psychological consequences of cannabis use. Canberra: Commonwealth Department of Human Services and Health, Monograph Series No. 25, 1994
173. House of Lords Select Committee on Science and Technology. Cannabis: the scientific and medical evidence. London: The Stationery Office, 1998
174. Joy JE, Watson SJ, Benson JA, editors. Marijuana and medicine: assessing the science base. Washington, DC: Institute of Medicine, National Academy Press, 1999
175. Kalant H, Corrigal W, Hall W, et al., editors. The health effects of cannabis. Toronto (ON): Centre for Addiction and Mental Health, 1999
176. Sulcova E, Mechoulam R, Fride E. Biphasic effects of anandamide. *Pharmacol Biochem Behav* 1998; 59 (2): 347-52
177. Thompson GR, Rosenkrantz H, Schaeppi UH, et al. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. *Toxicol Appl Pharmacol* 1973; 25 (3): 363-72
178. Bachs L, Morland H. Acute cardiovascular fatalities following cannabis use. *Forensic Sci Int* 2001; 124 (2-3): 200-3
179. Mittleman MA, Lewis RA, Maclure M, et al. Triggering myocardial infarction by marijuana. *Circulation* 2001; 103 (23): 2805-9
180. Pope HJ. Cannabis, cognition, and residual confounding. *JAMA* 2002; 287 (9): 1172-4
181. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* 2002; 287 (9): 1123-31
182. Lyketsoy CG, Garrett E, Liang KY, et al. Cannabis use and cognitive decline in persons under 65 years of age. *Am J Epidemiol* 1999; 149 (9): 794-800
183. Pope Jr HG, Gruber AJ, Hudson JI, et al. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry* 2001; 58 (10): 909-15
184. Russo E, Mathre ML, Byrne A, et al. Chronic cannabis use in the compassionate investigational new drug program: an examination of benefits and adverse effects of legal medical cannabis. *J Cannabis Ther* 2002; 2 (1): 3-57
185. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol* 1998; 20 (3): 293-306
186. Solowij N, Grenyer BFS. Long term effects of cannabis on psyche and cognition. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press, 2002: 299-312
187. Mattes RD, Shaw LM, Engelman K. Effects of cannabinoids (marijuana) on taste intensity and hedonic ratings and salivary flow of adults. *Chem Senses* 1994; 19 (2): 125-40
188. Freeman FR. Effects of marijuana on sleeping states. *JAMA* 1972; 220 (10): 1364-5
189. Lissoni P, Resentini M, Mauri R, et al. Effects of tetrahydrocannabinol on melatonin secretion in man. *Horm Metab Res* 1986; 18 (1): 77-8
190. Wachtel SR, ElSohly MA, Ross SA, et al. Comparison of the subjective effects of delta (9)-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology* 2002; 161 (4): 331-9
191. Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. *Life Sci* 1999; 65: 715-23
192. Heyser CJ, Hampson RE, Deadwyler SA. Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: alterations in short-term memory associated with changes in task specific firing of hippocampal cells. *J Pharmacol Exp Ther* 1993; 264 (1): 294-307
193. Slikker Jr W, Paule MG, Ali SF, et al. Behavioral, neurochemical and neurohistochemical effects of chronic marijuana smoke exposure in the nonhuman primate. In: Myrphy L, Bartke A, editors. Marijuana/cannabinoids: neurobiology and neurophysiology. Boca Raton (FL): CRC Press, 1992: 219-73
194. Kelly TH, Foltin RW, Emurian CS, et al. Performance-based testing for drugs of abuse: dose and time profiles of marijuana, amphetamine, alcohol, and diazepam. *J Anal Toxicol* 1993; 17 (5): 264-72
195. Perez-Reyes M. The psychologic and physiologic effects of active cannabinoids. In: Nahas G, Sutin KM, Harvey DJ, et al. Marijuana and medicine. Totowa (NJ): Humana Press, 1999: 245-52
196. Sañudo-Peña MC, Tsou K, Walker JM. Motor actions of cannabinoids in the basal ganglia output nuclei. *Life Sci* 1999; 65: 703-13
197. Pertwee R. In vivo interactions between psychotropic cannabinoids and other drugs involving central and peripheral neurochemical mediators. In: Myrphy L, Bartke A, editors. Marijuana/cannabinoids: neurobiology and neurophysiology. Boca Raton (FL): CRC Press, 1992: 165-218
198. Domino EF. Cannabinoids and the cholinergic system. In: Nahas G, Sutin KM, Harvey DJ, et al., editors. Marijuana and medicine. Totowa (NJ): Humana Press, 1999: 223-6
199. Fan P. Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion neurons. *J Neurophysiol* 1995; 73 (2): 907-10
200. Müller-Vahl KR, Kolbe H, Schneider U, et al. Movement disorders. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press, 2002: 205-14
201. Musty RE, Consroe P. Spastic disorders. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press, 2002: 195-204
202. Tashkin DP, Levisman JA, Abbasi AS, et al. Short-term effects of smoked marijuana on left ventricular function in man. *Chest* 1977; 72 (1): 20-6
203. Benowitz NL, Jones RT. Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clin Pharmacol Ther* 1975; 18 (3): 287-97
204. Formukong EA, Evans AT, Evans FJ. The inhibitory effects of cannabinoids, the active constituents of Cannabis sativa L., on human and rabbit platelet aggregation. *J Pharm Pharmacol* 1989; 41 (10): 705-9

205. O'Leary DS, Block RI, Koepfel JA, et al. Effects of smoking marijuana on brain perfusion and cognition. *Neuropsychopharmacology* 2002; 26 (6): 802-16
206. Wagner JA, Varga K, Kunos G. Cardiovascular actions of cannabinoids and their generation during shock. *J Mol Med* 1998; 76 (12): 824-36
207. Wagner JA, Jarai Z, Batkai S, et al. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB1 receptors. *Eur J Pharmacol* 2001; 423 (2-3): 203-10
208. Van Klingeren B, Ten Ham M. Antibacterial activity of  $\Delta^9$ -tetrahydrocannabinol and cannabidiol. *Antonie Van Leeuwenhoek* 1976; 42 (1-2): 9-12
209. Lancz G, Specter S, Brown HK. Suppressive effect of delta-9-tetrahydrocannabinol on herpes simplex virus infectivity in vitro. *Proc Soc Exp Biol Med* 1991; 196 (4): 401-4
210. Paté D. Glaucoma and cannabinoids. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 215-24
211. Colasanti BK. A comparison of the ocular and central effects of delta 9-tetrahydrocannabinol and cannabigerol. *J Ocul Pharmacol* 1990; 6 (4): 259-69
212. Murphy L. Hormonal system and reproduction. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 289-98
213. Tahir SK, Trogadis JE, Stevens JK, et al. Cytoskeletal organization following cannabinoid treatment in undifferentiated and differentiated PC12 cells. *Biochem Cell Biol* 1992; 70 (10-11): 1159-73
214. De Petrocellis L, Melck D, Palmisano A, et al. The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. *Proc Natl Acad Sci U S A* 1998; 95 (14): 8375-80
215. Melck D, De Petrocellis L, Orlando P, et al. Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation. *Endocrinology* 2000; 141 (1): 118-26
216. Galve-Roperh I, Sanchez C, Cortes ML, et al. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nat Med* 2000; 6 (3): 313-9
217. Cabral G. Immune system. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 279-88
218. Melamed R. Possible mechanisms in autoimmune diseases. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 111-22
219. Evans AT, Formukong EA, Evans FJ. Actions of cannabis constituents on enzymes of arachidonate metabolism: anti-inflammatory potential. *Biochem Pharmacol* 1987; 36 (12): 2035-7
220. Sofia RD, Nalepa SD, Harakal JJ, et al. Anti-edema and analgesic properties of  $\Delta^9$ -tetrahydrocannabinol (THC). *J Pharmacol Exp Ther* 1973; 186 (3): 646-55
221. Hembree III WC, Nahas GG, Zeidenberg P, et al. Changes in human spermatozoa associated with high dose marijuana smoking. *Adv Biosci* 1978; 22-23: 429-39
222. Chang MC, Berkery D, Schuel R, et al. Evidence for a cannabinoid receptor in sea urchin sperm and its role in blockade of the acrosome reaction. *Mol Reprod Dev* 1993; 36 (4): 507-16
223. Williams CM, Kirkham TC. Anandamide induces overeating: mediation by central cannabinoid (CB1) receptors. *Psychopharmacology* 1999; 143 (3): 315-7
224. Williams CM, Kirkham TC. Observational analysis of feeding induced by delta (9)-THC and anandamide. *Physiol Behav* 2002; 76 (2): 241-50
225. Shook JE, Burks TF. Psychoactive cannabinoids reduce gastrointestinal propulsion and motility in rodents. *J Pharmacol Exp Ther* 1989; 249 (2): 444-9
226. McCallum RW, Soykan I, Sridhar KR, et al. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. *Aliment Pharmacol Ther* 1999; 13 (1): 77-80
227. Coruzzi G, Adami M, Coppelli G, et al. Inhibitory effect of the cannabinoid receptor agonist WIN 55,212-2 on pentagastrin-induced gastric acid secretion in the anaesthetized rat. *Naunyn Schmiedeberg Arch Pharmacol* 1999; 360 (6): 715-8
228. Adami M, Frati P, Bertini S, et al. Gastric antisecretory role and immunohistochemical localization of cannabinoid receptors in the rat stomach. *Br J Pharmacol* 2002; 135 (7): 1598-606
229. Lemberger L, Crabtree RE, Rowe HM. 11-Hydroxy- $\Delta^9$ -tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marijuana in man. *Science* 1972; 177 (43): 62-4
230. Perez-Reyes M, Timmons M, Lipton M, et al. Intravenous injection in man of delta-9 tetrahydrocannabinol and 11-OH-delta-9-tetrahydrocannabinol. *Science* 1972; 177 (49): 633-5
231. Karler R, Turkianis SA. Different cannabinoids exhibit different pharmacological and toxicological properties. *NIDA Res Monogr* 1987; 79: 96-107
232. Burstein SH, Audette CA, Doyle SA, et al. Antagonism to the actions of platelet activating factor by a nonpsychoactive cannabinoid. *J Pharmacol Exp Ther* 1989; 251 (2): 531-5
233. Burstein SH. The cannabinoid acids: nonpsychoactive derivatives with therapeutic potential. *Pharmacol Ther* 1999; 82 (1): 87-96
234. Doyle SA, Burstein SH, Dewey WL, et al. Further studies on the antinociceptive effects of delta 6-THC-7-oic acid. *Agents Actions* 1990; 31 (1-2): 157-63
235. Burstein S, Hunter SA, Latham V, et al. A major metabolite of delta 1-tetrahydrocannabinol reduces its cataleptic effect in mice. *Experientia* 1987; 43 (4): 402-3
236. Zuairi AW, Guimarães FS, Guimarães VMC, et al. Cannabidiol: possible therapeutic application. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 359-70
237. Karler R, Turkianis SA. The cannabinoids as potential antiepileptics. *J Clin Pharmacol* 1981; 21 (8-9 Suppl.): 437S-48S
238. Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. *Int J Neurosci* 1986; 30 (4): 277-82
239. Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a nonpsychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *Neuroreport* 2002; 13 (5): 567-70
240. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral antiarthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci U S A* 2000; 97 (17): 9561-6

241. Colasanti BK, Brown RE, Craig CR. Ocular hypotension, ocular toxicity, and neurotoxicity in response to marijuana extract and cannabidiol. *Gen Pharmacol* 1984; 15 (6): 479-84
242. Baek SH, Kim YO, Kwag JS, et al. Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII): antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Arch Pharm Res* 1998; 21 (3): 353-6
243. Fride E, Barg J, Levy R, et al. Low doses of anandamides inhibit pharmacological effects of delta 9-tetrahydrocannabinol. *J Pharmacol Exp Ther* 1995; 272 (2): 699-707
244. Archer RA, Stark P, Lemberger L, Nabilone. In: Mechoulam R, editor. *Cannabinoids as therapeutic agents*. Boca Raton: CRC Press, 1986: 85-103
245. Little PJ, Compton DR, Mechoulam R, et al. Stereochemical effects of 11-OH- $\Delta^8$ -THC-dimethylheptyl in mice and dogs. *Pharmacol Biochem Behav* 1989; 32: 661-6
246. Ottani A, Giuliani D. HU 210: a potent tool for investigations of the cannabinoid system. *CNS Drug Rev* 2001; 7 (2): 131-45
247. Titishov N, Mechoulam R, Zimmerman AM. Stereospecific effects of (-)- and (+)-7-hydroxy-delta-6-tetrahydrocannabinol-dimethylheptyl on the immune system of mice. *Pharmacology* 1989; 39 (6): 337-49
248. Mechoulam R, Shohami E. HU-211: cannabinoid neuroprotective agent. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 389-400
249. Burstein S. Therapeutic potential of ajulemic acid (CT3). In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press, 2002: 381-8
250. Jain AK, Ryan JR, McMahon FG, et al. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 1981; 21 (8-9 Suppl.): 320S-6S
251. Citron ML, Herman TS, Vreeland F, et al. Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. *Cancer Treat Rep* 1985; 69: 109-12
252. Lucraft HH, Palmer MK. Randomized clinical trial of levonantradol and chlorpromazine in the prevention of radiotherapy-induced vomiting. *Clin Radiol* 1982; 33 (6): 621-2
253. Showalter VM, Compton DR, Martin BR, et al. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. *J Pharmacol Exp Ther* 1996; 278 (3): 989-99
254. Melvin LS, Milne GM, Johnson MR, et al. Structure-activity relationships for cannabinoid receptor-binding and analgesic activity: studies of bicyclic cannabinoid analogs. *Mol Pharmacol* 1993; 44 (5): 1008-15
255. Beltramo M, Stella N, Calignano A, et al. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. *Science* 1997; 277 (5329): 1094-7
256. Jaggar SI, Hasnie FS, Sellaturay S, et al. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998; 76 (1-2): 189-99
257. Terranova J-P, Storme J-J, Lafon N, et al. Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR 141716. *Psychopharmacology* 1996; 126: 165-72
258. Huestis MA, Gorelick DA, Heishman SJ, et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Arch Gen Psychiatry* 2001; 58 (4): 322-8
259. Di Marzo V, Hill MP, Bisogno T, et al. Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. *FASEB J* 2000; 14 (10): 1432-8
260. Müller-Vahl KR, Schneider U, Emrich HM. Nabilone increases choreatic movements in Huntington's disease. *Mov Disord* 1999; 14 (6): 1038-40
261. Romero J, Garcia-Palomero E, Castro JG, et al. Effects of chronic exposure to  $\Delta^9$ -tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Brain Res Mol Brain Res* 1997; 46 (1-2): 100-8
262. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci* 1976; 282: 221-39
263. Stefanis C. Biological aspects of cannabis use. *NIDA Res Monogr* 1978; 19: 149-78
264. Bass CE, Martin BR. Time course for the induction and maintenance of tolerance to Delta (9)-tetrahydrocannabinol in mice. *Drug Alcohol Depend* 2000; 60 (2): 113-9
265. Luthra YK, Esber HJ, Lariviere DM, et al. Assessment of tolerance to immunosuppressive activity of delta 9-tetrahydrocannabinol in rats. *J Immunopharmacol* 1980; 2 (2): 245-56
266. Miczek KA, Dixit BN. Behavioral and biochemical effects of chronic delta 9-tetrahydrocannabinol in rats. *Psychopharmacology (Berl)* 1980; 67 (2): 195-202
267. Smith CG, Almirez RG, Berenberg J, et al. Tolerance develops to the disruptive effects of delta 9-tetrahydrocannabinol on primate menstrual cycle. *Science* 1983; 219 (4591): 1453-5
268. Di Marzo V, Berrendero F, Bisogno T, et al. Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of  $\Delta^9$ -tetrahydrocannabinol-tolerant rats. *J Neurochem* 2000; 74 (4): 1627-35
269. Rubino T, Vigano D, Massi P, et al. Changes in the cannabinoid receptor binding, G protein coupling, and cyclic AMP cascade in the CNS of rats tolerant to and dependent on the synthetic cannabinoid compound CP55,940. *J Neurochem* 2000; 75 (5): 2080-6
270. Abood ME, Sauss C, Fan F, et al. Development of behavioral tolerance to delta 9-THC without alteration of cannabinoid receptor binding or mRNA levels in whole brain. *Pharmacol Biochem Behav* 1993; 46 (3): 575-9
271. Rubino T, Vigano D, Costa B, et al. Loss of cannabinoid-stimulated guanosine 5'-O-(3-[35S]thiotriphosphate) binding without receptor down-regulation in brain regions of anandamide-tolerant rats. *J Neurochem* 2000; 75 (6): 2478-84
272. Georgotas A, Zeidenberg P. Observations on the effects of four weeks of heavy marijuana smoking on group interaction and individual behavior. *Compr Psychiatry* 1979; 20 (5): 427-32
273. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. *Exp Clin Psychopharmacol* 1994; 2: 244-68
274. Kleiber D, Soellner R, Tossman P. *Cannabiskonsum in der Bundesrepublik Deutschland: Entwicklungstendenzen, Konsummuster und Einflussfaktoren*. Bonn: Federal Ministry of Health, 1997
275. Roques B. *Problemes posées par la dangerosité des drogues. Rapport du professeur Bernhard Roques au Secrétaire d'Etat à la Santé*. Paris, 1998

276. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol®). *J Psychoactive Drugs* 1998; 30 (2): 187-96
277. British Medical Association. Therapeutic uses of cannabis. Amsterdam: Harwood Academic Publishers, 1997
278. Grinspoon L, Bakalar JB. Marijuana, the forbidden medicine. New Haven (CT): Yale University Press, 1993
279. Grotenhermen F. Review of therapeutic effects. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press, 2002: 123-42
280. Mathre ML, editor. Cannabis in medical practice: a legal, historical and pharmacological overview of the therapeutic use of marijuana. Jefferson (NC): McFarland & Co, 1997
281. Mechoulam R, editor. Cannabinoids as therapeutic agents. Boca Raton: CRC Press, 1986
282. Dansak DA. As an antiemetic and appetite stimulant in cancer patients. In: Mathre ML, editor. Cannabis in medical practice: a legal, historical and pharmacological overview of the therapeutic use of marijuana. Jefferson (NC): McFarland & Co, 1997: 69-83
283. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J Pain Symptom Manage* 1991; 6 (6): 352-9
284. Sallan SE, Cronin C, Zelen M, et al. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 1980; 302 (3): 135-8
285. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *J Pain Symptom Manage* 1997; 14 (1): 7-14
286. Plasse TF, Gorter RW, Krasnow SH, et al. Recent clinical experience with dronabinol. *Pharmacol Biochem Behav* 1991; 40 (3): 695-700
287. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995; 10 (2): 89-97
288. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002; 20 (2): 567-73
289. Soderpalm AH, Schuster A, de Wit H. Antiemetic efficacy of smoked marijuana: subjective and behavioral effects on nausea induced by syrup of ipecac. *Pharmacol Biochem Behav* 2001; 69 (3-4): 343-50
290. Maurer M, Henn V, Dittrich A, et al. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry Neurol Sci* 1990; 240 (1): 1-4
291. Petro DJ. Marijuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics* 1980; 21 (1): 81-5
292. Killestein J, Hoogervorst EL, Reif M, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002; 58 (9): 1404-7
293. Martyn CN, Illis LS, Thom J. Nabilone in the treatment of multiple sclerosis [letter]. *Lancet* 1995; 345 (8949): 579
294. Meinck HM, Schonle PW, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *J Neurol* 1989; 236 (2): 120-2
295. Petro DJ, Ellenberger Jr C. Treatment of human spasticity with delta 9-tetrahydrocannabinol. *J Clin Pharmacol* 1981; 21 (8-9 Suppl.): 413S-6S
296. Ungerleider JT, Andysiak T, Fairbanks L, et al. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse* 1987; 7 (1): 39-50
297. Elsner F, Radbruch L, Sabatowski R. Tetrahydrocannabinol zur Therapie chronischer Schmerzen [Tetrahydrocannabinol for treatment of chronic pain]. *Schmerz* 2001; 15 (3): 200-4
298. Notcutt W, Price M, Miller R, et al. Medicinal cannabis extracts in chronic pain: (2) comparison of two patients with back pain and sciatica. 2001 Congress on Cannabis and the Cannabinoids, Cologne: International Association for Cannabis as Medicine, 25
299. Notcutt W, Price M, Miller R, et al. Medicinal cannabis extracts in chronic pain: (3) comparison of two patients with multiple sclerosis. 2001 Congress on Cannabis and the Cannabinoids. Cologne: International Association for Cannabis as Medicine, 26
300. Noyes Jr R, Brunk SF, Avery DAH, et al. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 1975; 18 (1): 84-9
301. Noyes Jr R, Brunk SF, Baram DA, et al. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol* 1975; 15 (2-3): 139-43
302. Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Ann Neurol* 1983; 13 (6): 669-71
303. Fox SH, Kellett M, Moore AP, et al. Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. *Mov Disord* 2002; 17 (1): 145-9
304. Hemming M, Yellowlees PM. Effective treatment of Tourette's syndrome with marijuana. *J Psychopharmacol* 1993; 7: 389-91
305. Müller-Vahl KR, Schneider U, Kolbe H, et al. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol [letter]. *Am J Psychiatry* 1999; 156 (3): 495
306. Müller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with  $\Delta^9$ -tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002; 35 (2): 57-61
307. Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome [letter]. *J Clin Psychopharmacol* 1998; 8: 844
308. Sieradzan KA, Fox SH, Hill M, et al. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. *Neurology* 2001; 57 (11): 2108-11
309. Hartley JP, Nogrady SG, Seaton A. Bronchodilator effect of delta-1-tetrahydrocannabinol. *Br J Clin Pharmacol* 1978; 5 (6): 523-5
310. Tashkin DP, Shapiro BJ, Frank IM. Acute effects of smoked marijuana and oral  $\Delta^9$ -tetrahydrocannabinol on specific airway conductance in asthmatic subjects. *Am Rev Respir Dis* 1974; 109 (4): 420-8
311. Crawford WJ, Merritt JC. Effects of tetrahydrocannabinol on arterial and intraocular hypertension. *Int J Clin Pharmacol Biopharm* 1979; 17 (5): 191-6
312. Hepler RS, Frank IR. Marijuana smoking and intraocular pressure [letter]. *JAMA* 1971; 217 (10): 1392
313. Hepler RS, Petrus RJ. Experiences with administration of marijuana to glaucoma patients. In: Cohen S, Stillman RC, editors. The therapeutic potential of marijuana. New York: Plenum Medical Book, 1976: 63-75

314. Merritt JC, Crawford WJ, Alexander PC, et al. Effect of marijuana on intraocular and blood pressure in glaucoma. *Ophthalmology* 1980; 87 (3): 222-8
315. Schnelle M, Grotenhermen F, Reif M, et al. Ergebnisse einer standardisierten Umfrage zur medizinischen Verwendung von Cannabisprodukten im deutschen Sprachraum, [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. *Forsch Komplementarmed [Res Complementary Med]* 1999; 36
316. Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. *Epilepsia* 2001; 42 (10): 1266-72
317. Gilson I, Busalacchi M. Marijuana for intractable hiccups [letter]. *Lancet* 1998; 351 (9098): 267
318. Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs* 1998; 30 (2): 171-7
319. Mikuriya TH. Cannabis substitution: an adjunctive therapeutic tool in the treatment of alcoholism. *Med Times* 1970; 98 (4): 187-91
320. Volicer L, Stelly M, Morris J, et al. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; 12 (9): 913-9
321. Ralevic V, Kendall DA. Cannabinoid inhibition of capsaicin-sensitive sensory neurotransmission in the rat mesenteric arterial bed. *Eur J Pharmacol* 2001; 418 (1-2): 117-25
322. Jacobsson SO, Wallin T, Fowler CJ. Inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids: relative involvement of cannabinoid and vanilloid receptors. *J Pharmacol Exp Ther* 2001; 299 (3): 951-9
323. Guzman M, Sanchez C, Galve-Roperh I. Control of the cell survival/death decision by cannabinoids. *J Mol Med* 2001; 78 (11): 613-25
324. Izzo AA, Pinto L, Borrelli F, et al. Central and peripheral cannabinoid modulation of gastrointestinal transit in physiological states or during the diarrhoea induced by croton oil. *Br J Pharmacol* 2000; 129 (8): 1627-32
325. Calignano A, Katona I, Desarnaud F, et al. Bidirectional control of airway responsiveness by endogenous cannabinoids. *Nature* 2000; 408 (6808): 96-101
326. Carley DW, Pavlovic S, Janelidze M, et al. Functional role for cannabinoids in respiratory stability during sleep. *Sleep* 2002; 25 (4): 391-8
327. Pryor GT, Husain S, Mitoma C. Acute and subacute interactions between delta-9-tetrahydrocannabinol and other drugs in the rat. *Ann N Y Acad Sci* 1976; 281: 171-89
328. Kosel BW, Aweeka FT, Benowitz NL, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *AIDS* 2002; 16 (4): 543-50
329. Zullino DF, Delessert D, Eap CB, et al. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int Clin Psychopharmacol* 2002; 17 (3): 141-3
330. Hollister LE. Interactions of marijuana and  $\Delta^9$ -THC with other drugs. In: Nahas G, Sutin KM, Harvey DJ, et al., editors. *Marijuana and medicine*. Totowa (NJ): Humana Press, 1999: 273-7
331. Sutin KM, Nahas GG. Physiological and pharmacological interactions of marijuana ( $\Delta^9$ -THC) with drugs and anesthetics. In: Nahas G, Sutin KM, Harvey DJ, et al., editors. *Marijuana and medicine*. Totowa (NJ): Humana Press, 1999: 253-71
332. Brody S, Preut R. Cannabis, tobacco, and caffeine use modify the blood pressure reactivity protection of ascorbic acid. *Pharmacol Biochem Behav* 2002; 72 (4): 811-6
333. Welch SP, Eads M. Synergistic interactions of endogenous opioids and cannabinoid systems. *Brain Res* 1999; 848 (1-2): 183-90
334. Koe BK, Milne GM, Weissman A, et al. Enhancement of brain [ $^3$ H]flunitrazepam binding and analgesic activity of synthetic cannabinimimetics. *Eur J Pharmacol* 1985; 109 (2): 201-12
335. Moss DE, Manderscheid PZ, Montgomery SP, et al. Nicotine and cannabinoids as adjuncts to neuroleptics in the treatment of Tourette syndrome and other motor disorders. *Life Sci* 1989; 44 (21): 1521-5
336. Perez-Reyes M, Burstein SH, White WR, et al. Antagonism of marijuana effects by indomethacin in humans. *Life Sci* 1991; 48 (6): 507-15
337. Green K, Kearse EC, McIntyre OL. Interaction between delta-9-tetrahydrocannabinol and indomethacin. *Ophthalmic Res* 2001; 33 (4): 217-20
338. Mechoulam R, Hanus L, Fride E. Towards cannabinoid drugs: revisited. *Prog Med Chem* 1998; 35: 199-243
339. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* 2001; 134 (4): 845-52