Cannabinoids Pharmacology, Abuse, and Addiction

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Marilyn A. Huestis and Michael L. Smith

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Abstract

Cannabis has a long history of therapeutic use and misuse. **Δ**-9-tetrahydrocannabinol (THC) was identified as the principle psychoactive component of cannabis in 1965. For the next two decades, cannabis research focused on THC pharmacology. Smoked or inhaled THC rapidly delivers the drug to the brain increasing its abuse liability. Once present in the brain THC hijacks important functions of the endogenous cannabinoid system modulating the release and

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D.W. Pfaff, N.D. Volkow (eds.), *Neuroscience in the 21st Century*,
DOI 10.1007/978-1-4939-3474-4_158

reuptake of a wide variety of other neurotransmitters. THC disrupts memory, executive function, attention, hormone secretion, motor initiation and movement, decision-making, mood, and others. An individual using less than daily cannabis is considered an occasional user, while one who generally consumes the drug daily is considered a frequent cannabis user. The brain adapts to continuous CB1-cannabinoid receptor stimulation by reducing the density of receptors, but this can be reversed over weeks of sustained cannabis abstinence.

One of the major public health and safety considerations at this time of increasing cannabis medicalization and legalization is the effects on brain development in cannabis smokers that initiate use prior to the age of 17 years. The connections between different areas of the brain may not develop normally in these frequent adolescent cannabis smokers, and the changes in brain development may not be reversible. Another major public concern is the increased incidence of cannabis-impaired driving. Since the 1970s the incidence of drunk driving decreased, although it remains the major killer on the roads; however, drugged driving and, in particular, cannabis-impaired driving increased. The prevalence of THC in drivers' blood or oral fluid increased 48 % between the 2007 and 2013–2014 National Roadside Surveys.

Importantly, individuals predisposed to develop schizophrenia or psychosis may have their condition exacerbated by cannabis intake and frequently may have their first schizophrenic break occur earlier following cannabis smoking. But the therapeutic potential of cannabinoids such as cannabidiol (CBD) or mixed THC and CBD plant extracts are currently being investigated to treat a wide variety of diseases. CBD has neuroprotective properties that are exploited as treatments for Davet's syndrome, treatment resistant seizures in children refractory to other available therapies. The discovery of the cannabinoid receptors, CB1 and CB2, and identification of anandamide and other endogenous cannabinoids, improved our understanding of THC effects on the brain and mechanisms of cannabis addiction. Cannabis is addictive and is the principal drug of abuse for 75 % of 12–17 year olds seeking drug treatment. It is an exciting and concerning time for cannabis research. Potential new therapies for a wide variety of disorders co-occur with increased cannabis dependence and treatment demands, and concern over the long-term effects of frequent cannabis abuse in adolescents and the increased morbidity and mortality of cannabis-impaired driving.

Keywords

Abuse • Addiction • Brain development • Brain imaging • Brain damage • Cannabidiol • Cannabinoids • Cannabinoid receptor • Cannabinoid therapy • Cannabis • Cannabis dependence • Cannabis-impaired driving • CB1 • CB2 • Chronic frequent smoker • DAWN • Driving under the influence of drugs • Endogenous cannabinoid system • fMRI • Marijuana • Neuroadaptation • Novel psychoactive substances • Oral • Occasional smoker • Pharmacodynamics • Pharmacokinetics • Pharmacology • Pharmacotherapies • Rimonabant • Sativex • Smoking • Synthetic cannabinoids • **Δ**-9-Tetrahydrocannabinol • THC • TEDS

Brief History

The complex *Cannabis sativa* plant has a long and interesting history of therapeutic use and misuse for over 4000 years. Cannabis (marijuana, hashish, and sinsemilla) is self-administered for its mood-altering properties, produces reversible psychological impairment, and can result in dependence, partial tolerance development for some effects, and an abstinence syndrome after drug cessation following chronic frequent intake. A mixture of depressant and stimulant effects is noted at low doses; cannabis acts as a central nervous system (CNS) depressant at high doses. The oldest known pharmacopeia, Pen-ts'ao Ching, describes the medicinal properties of cannabis based on an oral history dating to the Xia Dynasty (ca. 2727 BC). Indications were female weakness, rheumatism, malaria, gout, boils, constipation, and absent-mindedness. A warning stated that negative psychiatric effects may occur from excessive use. Over succeeding centuries cannabis was mentioned in texts from many countries as a medicine and drug of abuse. In 1894, the *Report of the Indian Hemp Drugs Commission* concluded that "There is no evidence of any weight regarding mental and moral injuries from moderate use of these drugs," but later cannabis was found to have no proven medicinal value and placed in Schedule I of the US Controlled Substance List. Scientists and laymen continue to debate the harmful versus beneficial effects of cannabis.

Public opinion about the medicalization and legalization of cannabis is changing again, as it continues to cycle over time, with the current perception being use of cannabis is associated with few risks. Cannabis use is legal in Uruguay, with varying enforcement around the world from practically legal to severe penalties. In the USA, medical marijuana is approved in 23 states and recreational cannabis is legal in four and the District of Columbia, with continued legislative initiatives in most states. FDA-approved synthetic oral Δ9-tetrahydrocannabinol (THC) or dronabinol increases appetite in patients suffering from AIDS wasting disease and also reduces chemotherapy-induced nausea and vomiting. Cannabis extracts containing up to 109 different cannabinoids, and terpenes and other chemicals, especially those rich in THC and/or cannabidiol (CBD) are among the most relevant cannabinoids for pharmacotherapies proposed to treat a wide variety of conditions. Perhaps the most urgent disease driving the medical marijuana movement is Dravet's syndrome that produces severe and frequent seizures in children that are intractable with other pharmacotherapies. Double blind, placebo controlled, and randomized clinical studies have not been performed to verify efficacy and safety of these different plant cannabinoid medications. A major issue with the nonregulated use of these new products is concern for acute and long-term toxicity, including brain development, impaired performance, and lack of data on the stability of CBD and other cannabinoid concentrations in the products.

With perceived low risk of use, medication development, new cannabis delivery systems including vaporizers, edibles, and vape pens, and major increases in the potency of cannabis, cannabis abuse, and dependence are increasing. The latest Treatment Episodes Data Set (TEDS) documents that cannabis is the primary drug

of abuse for 75 % of admissions for drug treatment of 12–17 year olds in the USA (TEDS 2014). The major concerns with increased licit cannabis pharmacotherapy and illicit cannabis abuse are the adverse effects on development of the adolescent brain (Pope et al. 2003) and driving under the influence of cannabis, both important public health and safety issues.

Cannabis Pharmacology

Endogenous Cannabinoid System

THC was identified as the principal psychoactive compound in the cannabis plant in 1965, expanding research focused on THC's effects and mechanisms of action (Mechoulam and Gaoni 1965). THC, like other psychoactive drugs, interacts with brain receptors to produce its effects. In 1988, the first cannabinoid receptor, CB1, was identified and cloned (Devane et al. 1988). CB1 cannabinoid receptors are primarily located on presynaptic terminals and are present in the brain in the highest density of all 7-transmembrane G-protein coupled receptors. The highest CB1 receptor densities are in the nucleus accumbens, hypothalamus, amygdala, hippocampus, cerebellum, and neocortex, although distribution is throughout the brain (Fig. 1). CB1receptor activation decreases cellular cyclic adenosine monophosphate (cAMP) concentrations and inhibits potassium, sodium, and N-and P/Q-type-calcium channels by reducing membrane potentials.

The structure of the first endogenous cannabinoid neurotransmitter, anandamide was determined shortly after characterization of the CB1 receptor (Devane et al. 1992). Anandamide, arachidonyl ethanolamide, has a chemical structure dissimilar to THC, but its three-dimensional structure allows it to bind to the same receptors. Anandamide is an unsaturated fatty acid ethanolamide, not a peptide like many other neurotransmitters, slowing its discovery. Unlike most other neurotransmitters that are stored in vesicles, the endogenous cannabinoid neurotransmitters are synthesized as needed from membrane phospholipids. They are synthesized in dendrites but transported to nerve terminals to bind to receptors on presynaptic neurons. The endogenous cannabinoids act by inhibiting the release of fast-acting neurotransmitters, principally γ-aminobutyric acid (GABA) and glutamate. The distribution of GABA and glutamate receptors allows excitation or inhibition to prevail in various conditions. Neurons regulate their excitatory (glutamate) and inhibitory (GABA) actions by releasing endocannabinoids, thus adding another layer of plasticity to neurons reacting to conventional transmitters, such as dopamine and serotonin. This natural arrangement of endocannabinoids stimulating both excitatory and inhibitory actions explains the stimulatory or inhibitory effects of THC depending on the brain region involved.

In the nucleus accumbens, THC binds to CB1 receptors next to dopamine neurons and increases the amount of dopamine released into the synapse. Dopamine binds to

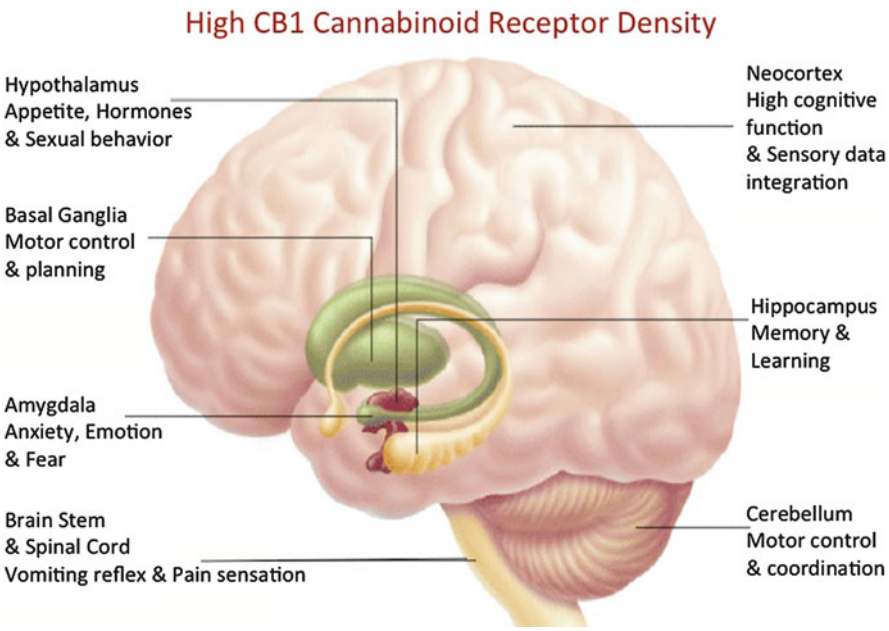

Fig. 1 Brain locations with the highest concentrations of CB1 receptors and the types of functions they control

its postsynaptic neurons producing euphoria. In the hippocampus, THC binds to CB1 receptors on glutamate terminals, inhibiting Ca^{2+} influx that suppresses glutamate release. Glutamate release and binding to postsynaptic neurons is necessary in certain types of learning and explains the detrimental effect of THC on memory. Another process disrupted by THC is the synthesis of the endocannabinoid 2-arachidonyl glycerol (2-AG) that depresses GABA inhibition, facilitating long-term potentiation at glutamate excitatory synapses. Disruption of 2-AG synthesis could lead to adverse effects that linger after THC is removed from the brain. When cannabis is taken, THC binds to CB1 receptors, hijacking normal brain functions and interfering with other neurotransmitter activities.

A second receptor, the CB2 cannabinoid receptor, is found primarily in the periphery and modulates cannabis' immune function. CB2 receptors are present in the brain in low density, and new research suggests that they play an important role in drug dependence. Another cannabinoid receptor was identified pharmacologically but to date has not been cloned or further characterized. There also are multiple other cannabinoid neurotransmitters, enzymes that synthesize and metabolize neurotransmitters, and transporters that play a critical role in THC's physiological and behavioral processes. The endogenous cannabinoid system is described in more detail in another chapter of this book.

Cannabinoid Pharmacodynamic Effects

Cannabis is self-administered for its mood-altering properties and can lead to drug dependence. CB1 cannabinoid receptor localization explains known THC effects of euphoria, hunger, modified emotions, memory loss, reaction time, sustained attention, poor movement and coordination, and impaired executive function. Other behavioral effects of cannabis include feelings of relaxation, altered time perception, lack of concentration, impaired learning, and mood changes such as panic reactions and paranoia, the intensity of which is associated with dose, mode of administration, smokers' expectations of effects, drug use environment, and user personality. Its spectrum of behavioral effects is unique, preventing classification of the drug as a stimulant, sedative, tranquilizer, or hallucinogen. The most frequent physiological effects include increased heart rate, conjunctival suffusion, dry mouth and throat, increased appetite, and vasodilation.

Figure 2 shows the complex dose–response effects of drugs. Absorption of a drug into the blood is highly dependent upon the route of administration, with smoked drug rapidly transferred from the lung into the blood, while oral administration may result in degradation in the acidic stomach environment and first pass metabolism in the liver. Maximum drug concentrations and time of maximum concentrations are

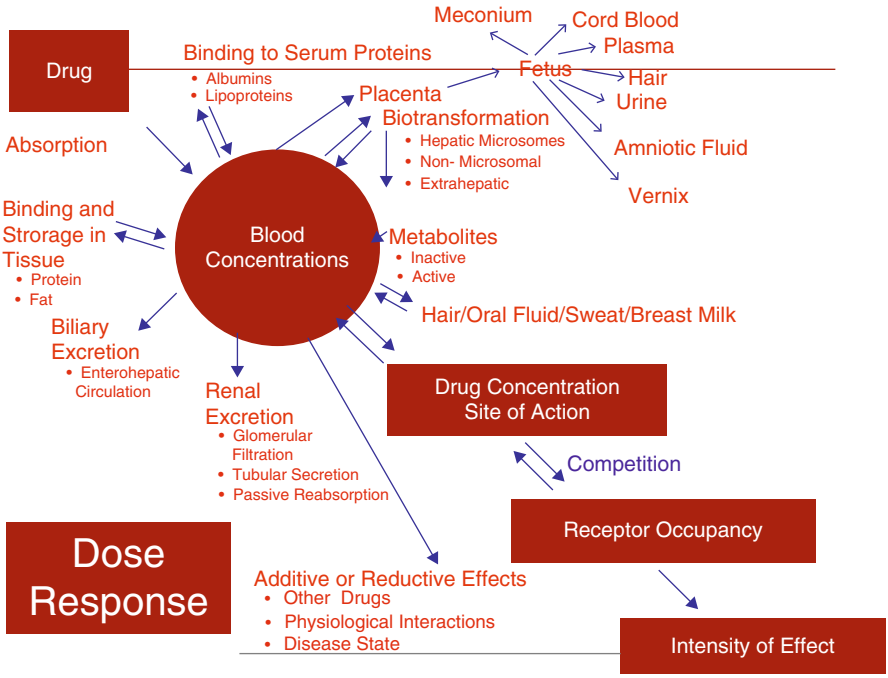

Fig. 2 Diagram of the complex interactions within the human body that produce the pharmacodynamic effects of cannabis

greatly affected by the route of drug administration. Also, the abuse liability of a drug is related to the rapidity of drug delivery to the brain; hence, smoked, inhaled, and intravenous administrations are associated with the highest abuse liability. After entry into the blood, the drug may or may not be bound to circulating proteins or lipoproteins, greatly affecting the amount of circulating free drug that can readily pass membranes and bind to its active sites. Initially, drug is distributed into the most highly perfused organs (brain, heart, lung, liver, kidney, and others) and later into adipose tissue where it may accumulate with chronic frequent exposures. Simultaneously, metabolism leads to active (e.g., 11-hydroxy-THC [11-OH-THC]) and inactive (e.g., 11-nor-9-carboxy-THC [THCCOOH]) metabolites and renal and fecal excretion through the bile begins. Free drug binds to cannabinoid receptors in the central nervous system and periphery, producing cannabis' characteristic effects; however, there may be competition at the site of action by other endogenous or exogenous ligands, including agonists and antagonists. Finally, other drugs bind to their receptors producing activity that may be additive or synergistic in effect, or may produce actions that are antagonistic to cannabis' effects, finally producing the observed effect intensity. In addition, disease state and age can affect the observed effect intensity.

Acute subjective and physiological effects are measurable after the first puff of a cannabis cigarette, generally returning to baseline within 3–6 h after exposure. THC concentration-effect curves for heart rate and subjective "high" display a counterclockwise hysteresis, documenting a delay between peak plasma concentrations and peak effects (Fig. 3). Cannabis smokers titrate their dose based on their smoking typography or manner of smoking, with peak concentrations occurring prior to the end of smoking. A counterclockwise hysteresis is generally indicative of a prominent distribution phase, perhaps due to redistribution of the drug from the vascular compartment to the drug's site of action, the brain. During absorption, there is nearly a linear increase in THC concentrations and subjective and physiological effects prior to the end of smoking at about 9 min. After this time, THC blood concentrations decrease rapidly with little change in effects during THC distribution throughout the body and rapid metabolism to active and inactive metabolites. After the initial 45–60 min distribution phase, a new linear relationship is established between concentrations and effects. The complexity of interpretation of results when a hysteresis is present is that quite different effects are observed at the same blood THC concentration. However, rarely are blood samples collected in real life situations before the end of cannabis smoking during the absorption phase, removing that concern.

Development of the first selective and orally active CB1 antagonist SR141716 (rimonabant) enabled exploration of the endogenous cannabinoid system and identification of many of its important functions. This pharmacological tool demonstrated for the first time in cannabis smokers that rimonabant blocked the psychological and physiological effects of smoked cannabis without altering THC pharmacokinetics (Huestis et al. 2001), documenting that THC's psychoactive and cardiovascular effects were modulated in humans through the CB1-cannabinoid receptor.

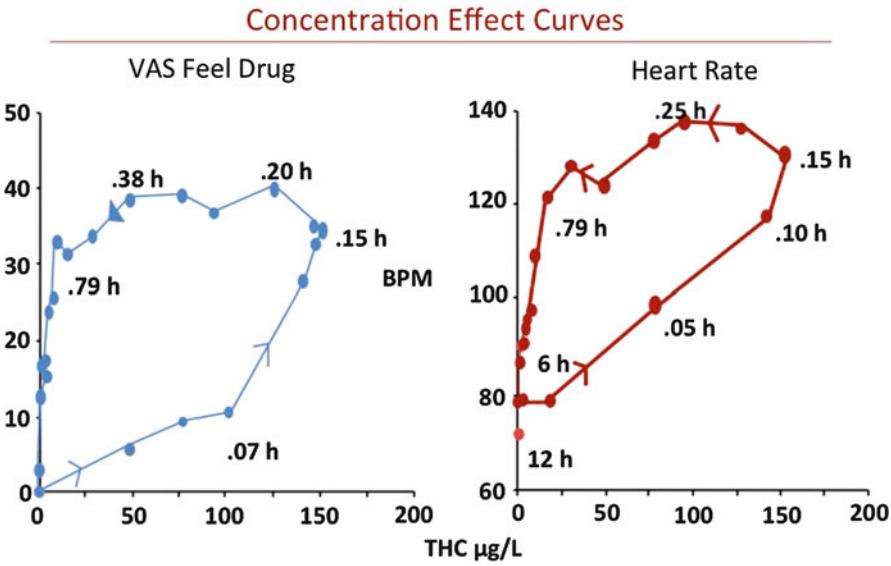

Fig. 3 Visual analog scale (*VAS*) for "How strongly do you feel the drug now?" and heart rate (beats per minute, *BPM*) measures for a subject after smoking a 3.55 % Δ9-tetrahydrocannabinol (*THC*) cigarette demonstrating a counterclockwise hysteresis for the concentration-effect curves. Following the times shown post smoking, first effects increase with plasma concentrations of THC during the absorption phase and reach a peak just prior to the end of smoking. During the distribution phase that follows, effects remain elevated as plasma concentrations decrease. (Reprinted with permission Huestis 2010)

Cannabis is the source of more positive workplace drug tests than any other drug of abuse and is the most common illicit substance detected in blood and oral fluid of nighttime drivers in the USA. The harmful effects of cannabis abuse were primarily anecdotal prior to 1980. A NIDA 1982 monograph concluded that there was insufficient evidence that cannabis use caused permanent health problems, brain damage, or led to abuse of other drugs (Relman 1982). However, in 1987 a longitudinal study linked cannabis use and development of schizophrenia (Andreasson et al. 1987). In the following years, genetics, neurochemistry, and neuroimaging findings suggested that individuals may be predisposed to develop schizophrenia, psychosis, or to become addicted after using cannabis. Brain development, including connections between different areas of the brain, may be affected in young people initiating frequent cannabis use in their teens.

Chronic frequent cannabis intake produces cognitive and psychomotor deficits for up to 4 weeks of sustained abstinence. Residual neuropsychological deficits may persist in chronic daily cannabis smokers for days to weeks after last drug exposure. On days 0, 1, 7, and 28 of sustained cannabis abstinence, a neuropsychological test battery was administered to assess general intellectual function, abstraction ability, sustained attention, verbal fluency, and ability to learn and recall new verbal and visuospatial information in 63 current heavy smokers, 45 former heavy users who

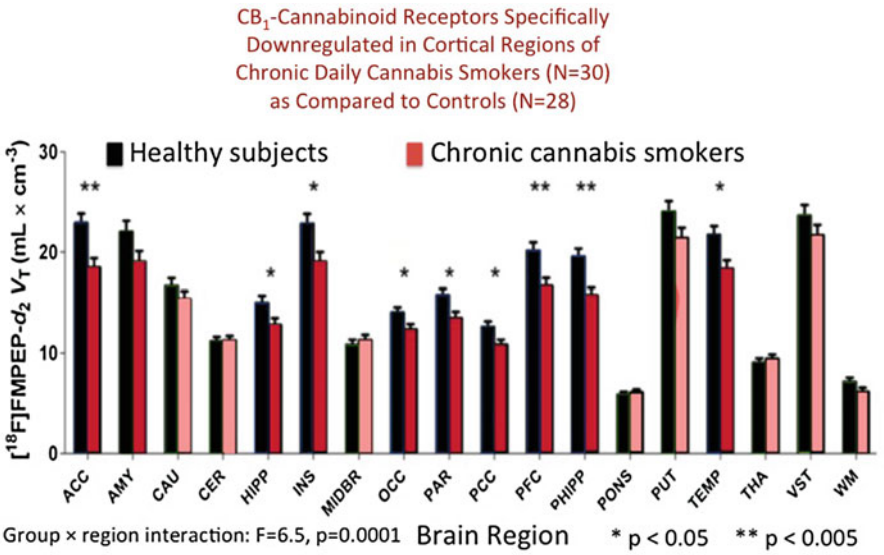

Fig. 4 VT of [18 F]FMPEP-d2 (a measure of CB1 receptor density) in cortical regions is lower at baseline in chronic daily cannabis smokers (*red bars*, n = 30) than in control subjects (*black bars*, n = 28). Values are estimated marginal means from the repeated measures analysis of variance that controls for body mass index (BMI). Values are adjusted to an average BMI of 24.8 kg m^{-2}. Error bars are s.e.m. (Abbreviations: *ACC* anterior cingulate cortex, *AMY* amygdala, *CAU* caudate nucleus, *CER* cerebellum, *HIPP* hippocampus, *INS* insula, *MIDBR* midbrain, *OCC* occipital cortex, *PAR* parietal cortex, *PCC* posterior cingulate cortex, *PFC* prefrontal cortex, *PHIPP* parahippocampal gyrus, *PUT* putamen, *TEMP* lateral temporal cortex, *THA* thalamus, *VST* ventral striatum, *WM* white matter, $^{*}P < 0.05$, $^{**}P < 0.005$, two-tailed *t* test). (Reprinted with permission Hirvonen et al. 2012)

smoked cannabis fewer than 12 times in the last 3 months, and 72 control subjects who smoked no more than 50 times in their lives (Pope et al. 2001). On days 0, 1, and 7, current heavy smokers scored significantly below control subjects on recall of word lists. By day 28 of abstinence, there were no significant differences among the groups nor were there significant associations between cumulative lifetime cannabis smoking and test scores. Others found that cognitive deficits persisted for 28 days in the heaviest cannabis smokers, but it is conceivable that with additional abstinence these individuals also would perform similarly to controls. Although the mechanism of these residual cognitive and motor deficits is uncertain, these effects might be attributable to the persistence of cannabinoids in the brain.

Significant downregulation of CB1-cannabinoid receptors in chronic frequent cannabis smokers was observed that reversed with sustained abstinence (Hirvonen et al. 2012). With positron emission tomography (PET) imaging, reversible and regionally selective downregulation of brain cannabinoid CB1 receptors occurred in 30 human subjects who chronically smoked cannabis (Fig. 4). The density of CB1 cannabinoid receptors in the brains of chronic frequent cannabis smokers was significantly lower in cortical brain regions. Downregulation correlated with years

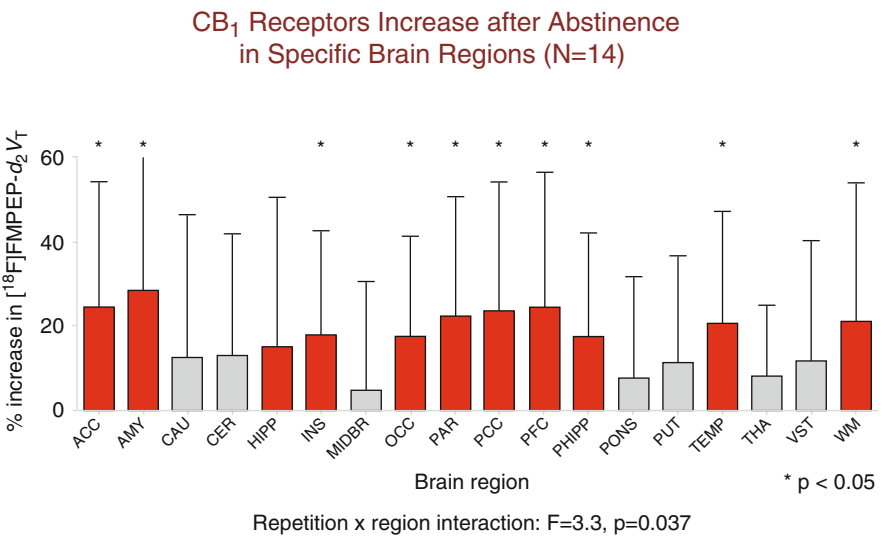

Fig. 5 VT of [18 F]FMPEP-d2 increased after abstinence in the 14 cannabis smokers who completed two PET scans before and after abstinence. Significant increases were mostly seen in regions with reduced VT at baseline. Error bars are S.D. of percent change. Abbreviations of brain regions are the same as those in Fig. 1. *$P < 0.05$, two-tailed paired samples t-test (Reprinted with permission Hirvonen et al. 2012)

of cannabis smoking. After about four weeks of continuously monitored abstinence from cannabis in a secure research unit, CB1 receptor density returned to normal levels in the 14 participants who remained in the study for 28 days (Fig. 5). This was the first direct demonstration of cortical cannabinoid CB1-receptor downregulation in the human brain as a neuroadaptation that may promote cannabis dependence.

Neuroadaptation of the brain to continuous stimulation reduced availability of CB1 cannabinoid receptors, and sustained abstinence resulted in additional neuroadaptation to increase receptor density. Residual THC blood concentrations also were measureable in some of these same individuals for as long as 30 days with a low limit of quantification (LOQ) of 0.5 μg/L (Fig. 6) (Bergamaschi et al. 2013). Furthermore, the reduced CB1 cannabinoid receptor density and residual THC concentrations were accompanied by significant psychomotor impairment in critical tracking and divided attention tasks for at least 3 weeks (Bosker et al. 2013).

Cannabinoids readily cross placental membranes and expose the developing fetus, although concentrations are lower in fetal blood and tissues than in maternal plasma and tissues. THC metabolites, 11-OH-THC and THCCOOH, cross the placenta much less efficiently, and it is probable that THCCOOH does not pass from mother to fetus by placental transfer. THC in human umbilical cord blood is three to six times lower than in maternal blood, with greater transfer to the fetus early in pregnancy. THC also concentrates into breast milk from maternal plasma due to its high lipophilicity. In utero cannabis exposure results in adverse developmental outcomes. In a 1982–2006 longitudinal study, young adults exposed in utero to

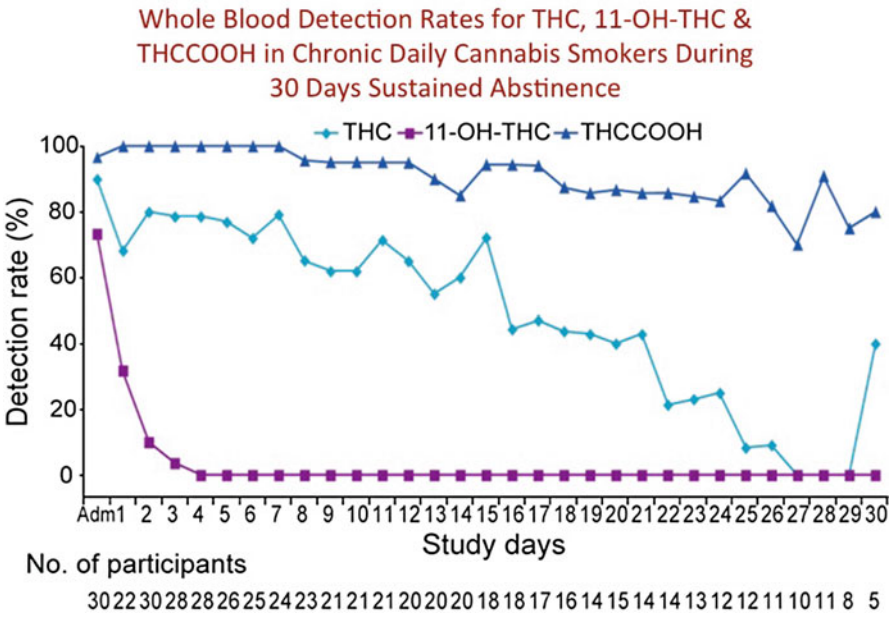

Fig. 6 Cannabinoid detection rates in chronic daily cannabis smokers on the basis of the method's limits of quantification, 0.25 μg/L for THC and THCCOOH and 0.5 μg/L for 11-OH-THC (Reprinted with permission Bergamaschi et al. 2013)

cannabis smoking had permanent deficits in executive function and sustained attention (Smith et al. 2006). fMRI activity in these now 18–22 year old subjects showed decreased activity in right frontal brain regions and increased activity in left brain regions compared to age-matched controls (Smith et al. 2010). Other fMRI studies showed that recent cannabis users had deficits in spatial working memory and compensated by "working harder," calling upon additional brain regions to solve problems. This increased brain demand during cannabis intoxication can explain the observed impairment of divided attention and executive function. Cannabinoids affect embryo implantation and may increase vulnerability to substance abuse problems later in life. Cannabis smoking causes deficits in brain function while THC is present to bind to receptors, with especially long-lasting effects in chronic frequent smokers and in those exposed at a young age when brains are still developing.

Cannabis use is increasing following the approval of medical cannabis in 23 US states and many countries and legalization of cannabis in four US states and the District of Columbia. A major concern is driving under the influence of cannabis. Cannabis, the most common illicit drug identified in motor vehicle crashes, had a higher prevalence than alcohol in drivers' blood or oral fluid specimens in the USA in the 2013–2014 National Roadside Study (Berning et al. 2015). In fact, the percentage of weekend nighttime drivers with measureable THC in their blood or oral fluid increased to 12.6 %, a 48 % increase since 2007 (Compton and Berning

2009). The incidence of THC-impaired driving significantly increased in Washington state from 19.1 % before legalization to 24.9 % after cannabis legalization (Couper and Peterson 2014). These statistics highlight an important public health and safety concern. On road, simulator and laboratory task research demonstrates that individuals who use cannabis and drive are at a higher risk of being killed in a car crash compared to drug free drivers and the risk and duration of effects increases with THC concentration in the driver's blood. A study of 3,398 drivers killed in automobile crashes in Australia found that drivers with $\geq$ 5 μg/L of THC in their blood were 6.8 times more likely to be culpable for the accident than drug free drivers (Drummer et al. 2004). Culpability statistics do not delineate the specific physiological deficit but demonstrate impairment of skills needed to safely operate a motor vehicle.

Simulator and laboratory task analyses are able to examine particular motor and attention effects, with much better control on all aspects of the experiment than is possible with on the road driving or epidemiological studies. Recent studies from the world's most advanced driving simulator found that participants with 8.2 μg/L THC in their blood demonstrated significantly increased standard deviation of lateral position, a measure of lane weaving while driving, equivalent to drivers with a 0.05 g/dL blood alcohol concentration (Hartman et al. 2015a). A THC blood concentration of 13.1 μg/L produced equivalent lateral control impairment in the same participants as a 0.08 g/dL blood alcohol concentration. Twelve occasional cannabis users showed impairment in motor control, dual task processing, motor inhibition, and cognition after smoking a cannabis cigarette with 500 μg/kg body weight and effects lasted up to 8 h (Ramaekers et al. 2009). Twelve chronic cannabis users in the same study had impaired reaction time but were able to compensate on other tasks. Motor performance impairments are thought to be mediated through CB1 receptors in the cerebellum while attention and cognition decrements involve the neocortex.

Cannabis smoke condensate yield, including potential mutagens, was more than in tobacco cigarette smoke, but generally fewer cannabis cigarettes are smoked per day than tobacco cigarettes. In a comparison of toxic components in cannabis and tobacco smoke, ammonia was present at concentrations up to 20-fold greater and hydrogen cyanide, nitrous oxide, and some aromatic amines at concentrations three to five times higher in cannabis than tobacco smoke. There also are indications that cannabis inhibits the human immune system. Some of the most reproducible findings suggest that THC inhibits the progression of responsive macrophages to full activation by limiting their capacity to respond to immunogenic signals.

Synthetic cannabinoids are one of the largest classes of novel psychoactive substances (NPS) – the emerging face of drug abuse. Synthetic cannabinoids were developed as legitimate research tools to explore the endocannabinoid system and as potential therapeutics. Synthetic cannabinoids are agonists at CB1 and CB2 cannabinoid receptors and elicit cannabimimetic effects qualitatively similar to THC but of greater magnitude and duration than cannabis' effects. Synthetic cannabinoids are synthesized in clandestine laboratories, sprayed onto dried plant materials or sold as the liquid chemical, and initially marketed as legal cannabis alternatives in Europe in

the early 2000s. They are primarily sold on the Internet, but prior to scheduling also in head shops and convenience stores labeled as "not for human consumption." As new synthetic cannabinoids are scheduled, more structurally diverse cannabimimetic compounds emerge, which may not be covered under current regulations. Synthetic cannabinoids popularity is attributed to intense psychoactive effects and lack of detectability in routine urine drug tests. Some synthetic cannabinoids metabolites also may be active and prolong the parent compound's psychoactive and physiological effects and contribute to intoxication severity. Documented serious adverse effects and limited human pharmacology data make synthetic cannabinoids intake an important public health and safety concern. Acute adverse effects generally subside within 24–48 h, with patients treated with benzodiazepines and supportive care. Synthetic cannabinoid intake may produce acute kidney injury, stroke, seizures, myocardial infarction, and death. Synthetic cannabinoids also impair driving. In DUID suspects, synthetic cannabinoids blood concentrations are low, with no clear correlation to impairment. Withdrawal symptoms similar to those following chronic frequent cannabis intake are observed in chronic synthetic cannabinoids smokers after at least 1 week of abstinence.

Cannabinoid Pharmacokinetics

The cannabis plant contains more than 100 cannabinoids including the primary psychoactive component THC and delta-9-tetrahydrocannabinolic acid, its precursor that decarboxylates with heat producing THC. THC may degrade when exposed to air, heat, or light, and acid exposure can oxidize THC to CBN that is approximately 10 % as potent. Most pharmacokinetic studies relevant to addiction for cannabis focus on THC, determining THC's time course of absorption, distribution, metabolism, and elimination. Smoking, the principal cannabis administration route provides rapid and efficient drug delivery from lungs to brain, contributing to its abuse potential. Intense pleasurable and strongly reinforcing effects are due to immediate central nervous system drug exposure. The absorption and distribution of THC following smoked cannabis is displayed in Fig. 7, where each arrow represents a single paced puff on the cannabis cigarette. Note that THC concentrations rapidly increase during smoking and peak prior to the end of smoking as users titrate their dose by adjusting their smoking topography. 11-OH-THC and THCCOOH concentrations increase more slowly, with 11-OH-THC concentrations generally less than 10 % of THC concentrations. Figure 8 displays individual plasma THC profiles after controlled paced cannabis smoking, demonstrating the large variability between individual smokers. THC percentage, the number of puffs on the cannabis cigarette, the length of inhalation, hold time in the lungs, exhalation, and time between puffs were controlled, yet participants titrated their dose to their individual level of comfort with the immediate tachycardia and subjective effects that begin to occur with the first puff on the cannabis cigarette.

Bioavailability of smoked THC is approximately 25 %, with large intra- and inter-subject variability due to many factors including their smoking topography. THC is

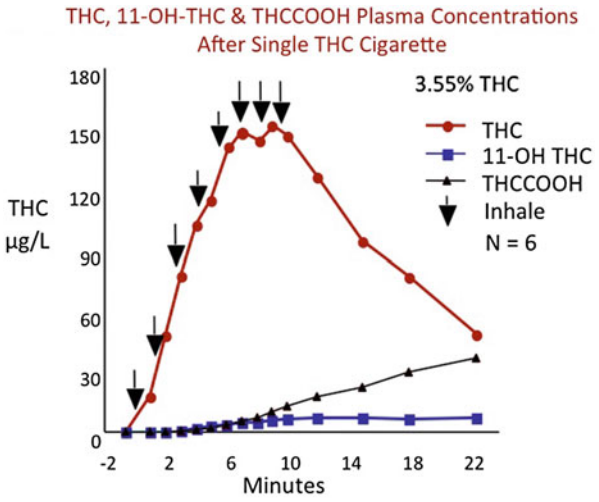

Fig. 7 Mean (N = 6) plasma concentrations of Δ9-tetrahydrocannabinol (THC, ●), 11-hydroxy-THC (11-OH-THC, ■), and 11-nor-9-carboxy-THC (THCCOOH, ♦) by gas chromatography mass spectrometry during smoking of a single 3.55 % THC cigarette. Each *arrow* represents one inhalation or puff on the cannabis cigarette (Adapted from Huestis and Smith 2005, Fig. 1)

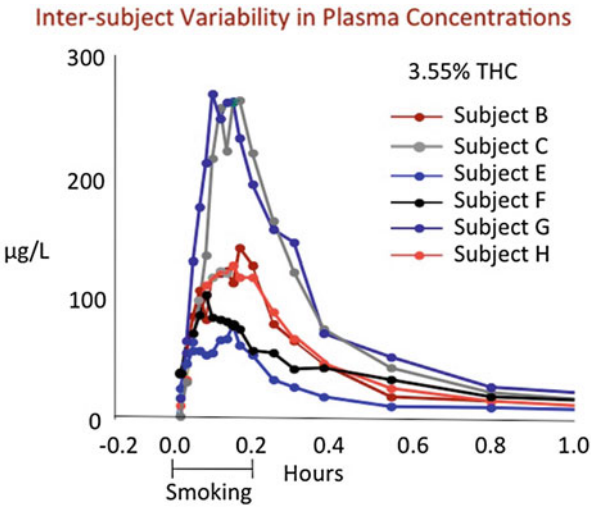

Fig. 8 Plasma THC concentrations for six subjects after smoking a single 3.55 % Δ9-tetrahydrocannabinol (THC) cigarette (Reprinted with permission Huestis et al. 1992)

metabolized to 11-OH-THC, an equipotent THC metabolite, and further oxidized to the nonpsychoactive metabolite THCCOOH. Figure 9 depicts the primary metabolism of THC to 11-OH-THC and THCCOOH. Structures for CBN and CBD also are shown since they are present in the cannabis smoke inhaled. Six subjects smoked a single marijuana cigarette receiving 16 and 30 mg THC doses, respective mean ± SD plasma THC concentrations were 7.0 ± 8.1 and 18.1 ± 12.0 µg/L following one

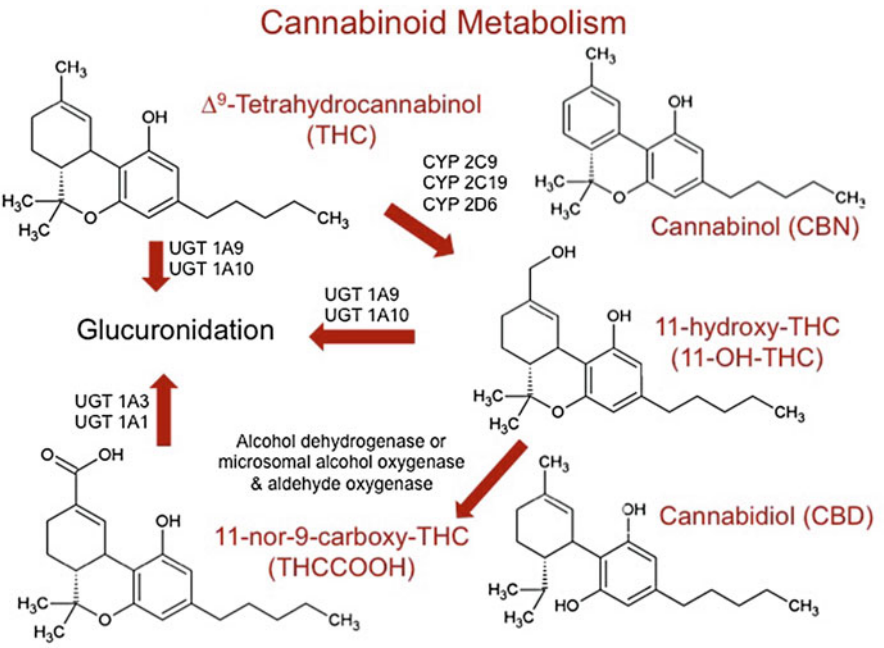

Fig. 9 Major metabolic route for Δ9-tetrahydrocannabinol (*THC*), the primary psychoactive component of cannabis, to its equipotent metabolite 11-hydroxy-THC (11-OH-THC) and its primary inactive metabolite, 11-nor-9-carboxy-THC (THCCOOH). THC, 11-OH-THC, and THCCOOH also undergo phase 2 metabolism with glucuronic acid and sulfates. Metabolic enzymes are listed next to the arrows. Structures of cannabinol (*CBN*) and cannabidiol (*CBD*) also are displayed since they are inhaled during cannabis smoking

inhalation with mean (range) maximum concentrations of 84.3 (range 50–129) and 162.2 μg/L (76–267) (Huestis et al. 1992). Plasma THCCOOH concentrations are greater than those of THC 30–45 min after smoking in occasional cannabis users, with no significant difference in metabolism between men and women. Vaporization also offers an efficient delivery system reducing side stream smoke losses and harmful by-products that do not volatilize at the lower temperatures utilized; however, the temperatures employed to vaporize cannabis are lower than those occurring during smoking, reducing the release of THC from the plant material.

Median blood concentrations of THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide in 19 cannabis users following smoking of a 6.7 % cannabis cigarette are shown in Fig. 10 (Hartman et al. 2015b). Although this recent controlled cannabinoid administration study reported blood data, much of the earlier data reported plasma concentrations. Furthermore, with the advent of liquid chromatography-tandem mass spectrometry, free and glucuronidated cannabinoids could be measured. This enabled a search for markers of recent cannabis use. Blood CBD, CBN, and THC-glucuronide were all determined to be markers of recent cannabis exposure within 4 h; however, absence of these markers in blood did not

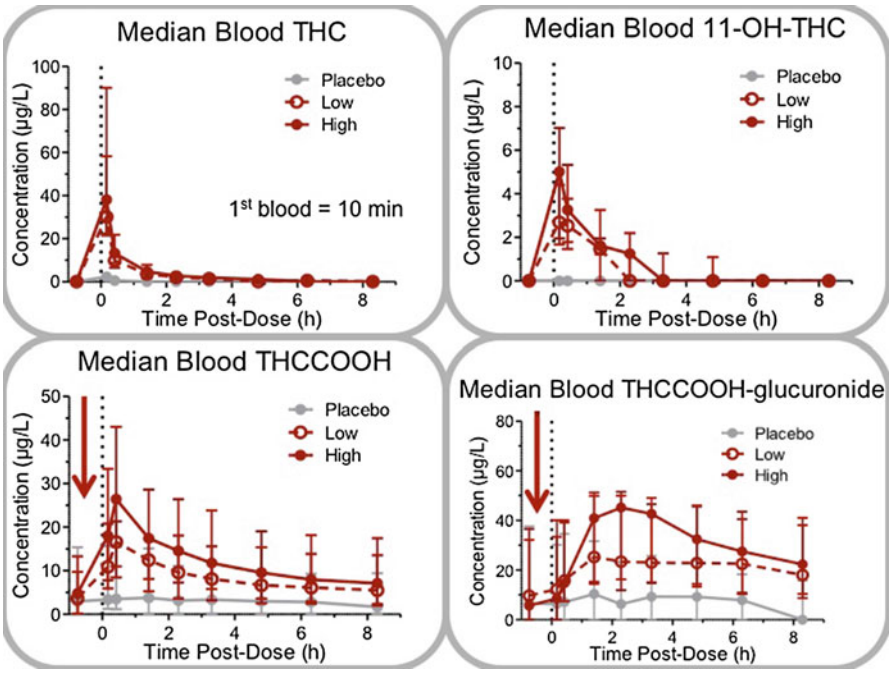

Fig. 10 Median (interquartile range) blood concentrations after cannabis vaporization of a low (2.9 %) and high (6.7 %) Δ9-tetrahydrocannabinol (THC) cannabis cigarette in 19 occasional cannabis users. Limits of quantification were 1 µg/L for THC, 11-hydroxy-THC (11-OH-THC), 11-nor-9-carboxy-THC (THCCOOH), and 5 µg/L for THCCOOH-glucuronide (THCCOOH-gluc) (Reprinted with permission Hartman et al. 2015b)

preclude recent use (Schwope et al. 2011). Additionally, the CBD content of the cannabis cigarettes smoked contained low CBD concentration; some recent cannabis formulations were engineered to contain higher CBD concentrations and may produce prolonged CBD detection in blood. Accurate determination of blood to plasma cannabinoid ratios is important for interpreting forensic blood concentration results. Cannabinoids do not distribute well into erythrocytes resulting in lower blood concentrations as seen in the THC and THC-glucuronide concentrations (Fig. 11) and THCCOOH and THCCOOH-glucuronide concentrations (Fig. 12). Previous blood:plasma ratios were determined with either fortified blood or plasma or with frozen specimens. Following controlled cannabis smoking, all blood and plasma specimens were analyzed within established stability requirements to determine the best blood:plasma ratios. Median (range) blood:plasma ratios were respectively 0.68 (0.31–1.1), 0.63 (0.38 –1.1), 0.59 (0.41–1.2), 0.84 (0.47–1.3), and 0.47 (0.24 –1.1) for THC, 11-OH-THC, THCCOOH, CBN, and THCCOOH-glucuronide (Desrosiers et al. 2014).

Absorption studies following oral THC are important since the licensed synthetic THC (dronabinol) medication is taken orally and also because abuse by the oral

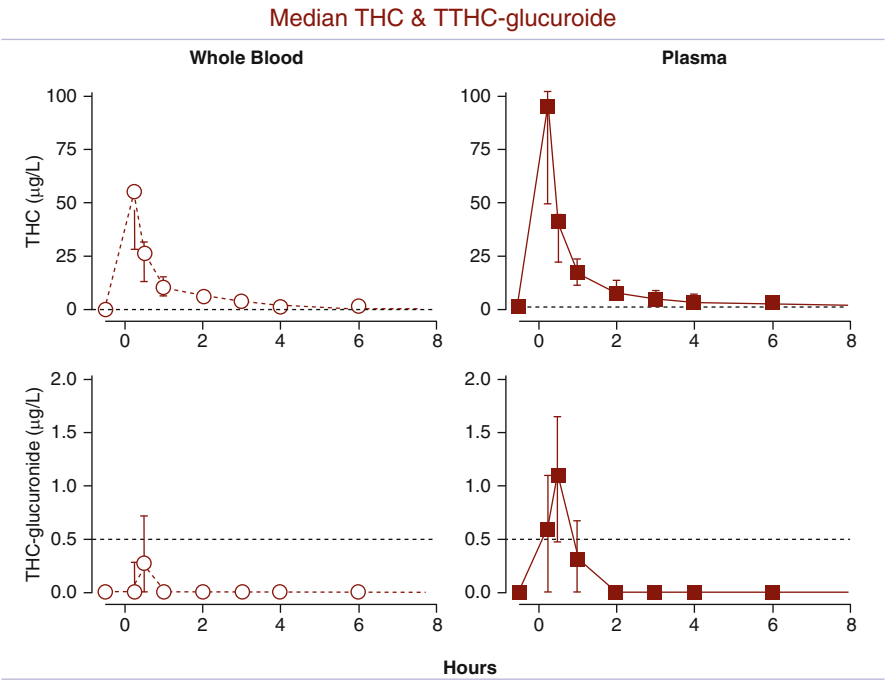

Fig. 11 Median (interquartile range) whole blood and plasma concentrations following smoking of a 6.8 % Δ9-tetrahydrocannabinol (THC) cannabis cigarette in 10 chronic frequent cannabis users. *Dotted lines* indicate limits of quantification: 1 µg/L for THC and 0.5 µg/L for THC-glucuronide (THC-gluc). (Reprinted with permission Schwope et al. 2011b)

route is common. In Colorado that legalized cannabis, edible cannabis products are frequently consumed, with many adverse events including psychosis. Bioavailability is lower compared to smoking, estimated as about 6 %. Absorption is slower when cannabinoids are ingested, with lower, delayed peak concentrations. Blood THC, 11-OH-THC, and THCCOOH concentrations following oral ingestion of 0.39 mg and 14.8 mg THC/day in hemp oil and 7.5 mg THC/day in dronabinol capsules for 5 days were low (Goodwin et al. 2006). Peak THC and 11-OH-THC concentrations were approximately equal and never exceeded 6.1 µg/L. THCCOOH concentrations were equal to or above 1.0 µg/L after 1.5–4.5 h and peaked at up to 43 µg/L. The vehicle is important for improving THC bioavailability, with sesame oil increasing absorption. The time to plasma THC Cmax after oral ingestion is about 2–4 h, compared to minutes after smoking. Furthermore, two peak THC concentrations after ingestion are possible due to enterohepatic recirculation. Unlike smoked cannabis where post dose 11-OH-THC concentrations are approximately 10 % of THC's, oral ingestion results in approximately equal blood concentrations, doubling pharmacodynamic effects due to their equivalent potency.

Chronic frequent cannabis smokers present with a different blood cannabinoid profile after oral ingestion. Six chronic cannabis smokers received 20 mg oral THC

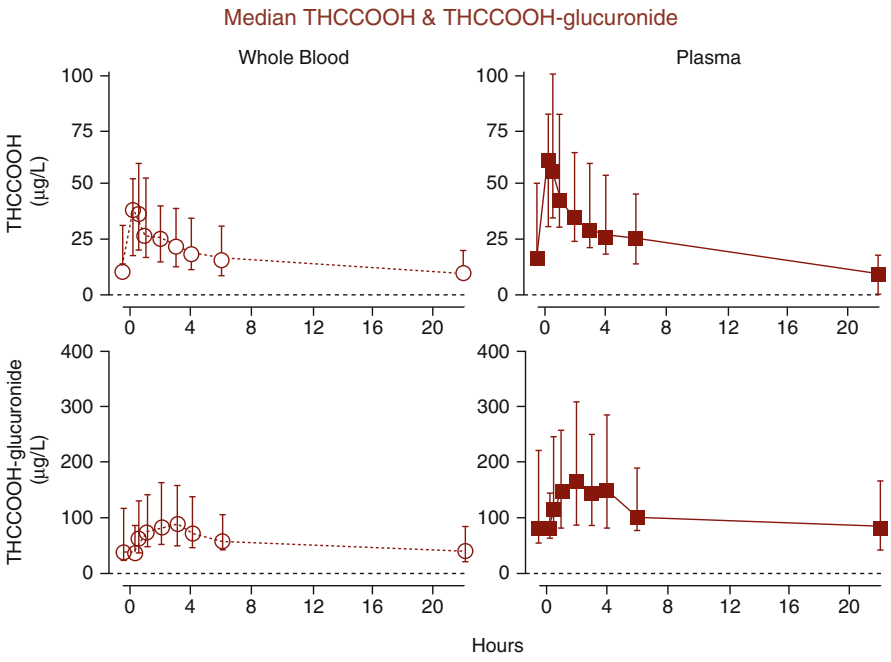

Fig. 12 Median (interquartile range) whole blood and plasma concentrations following smoking of a 6.8 % Δ9-tetrahydrocannabinol (THC) cannabis cigarette. *Dotted lines* indicate limits of quantification: 5 µg/L for 11-nor-9-carboxy-THC (THCCOOH) and THCCOOH-glucuronide (THCCOOH-gluc) (Reprinted with permission Schwope et al. 2011b)

every 4–8 h up to 120 mg THC/day over 7 days (Schwilke et al 2009). Participants had cannabinoids present at the beginning of the study and free 11-OH-THC and THCCOOH blood concentrations increased during dosing but THC concentrations did not. About 22.5 h after the last dose, mean (SEM) peak blood concentrations of free THC, 11-OH-THC, and THCCOOH were 3.8 (0.5), 3.0 (0.7), and 196.9 (39.9) µg/L.

THC concentrations decrease rapidly after smoking due to distribution into tissues, hepatic metabolism, and urinary and fecal excretion. THC is highly lipophilic and rapidly taken up by highly perfused tissues, such as lung, heart, brain, and liver. Secondarily, THC distributes into adipose tissue, with chronic frequent cannabis smokers developing large THC body burdens. Following Phase I metabolism, Phase II glucuronidation of cannabinoids occurs to produce more water-soluble metabolites and increase elimination. Terminal THC elimination half-life is about 4 days. Occasional cannabis smokers eliminate 80–90 % of a THC dose in 5 days with 65 % in feces and approximately 30 % in urine. Metabolites are primarily hydroxylated and carboxylated. Of the many acidic urinary metabolites, THCCOOH-glucuronide is primary, while 11-OH-THC predominates in feces. The percent of a smoked THC dose excreted in urine as total THCCOOH over

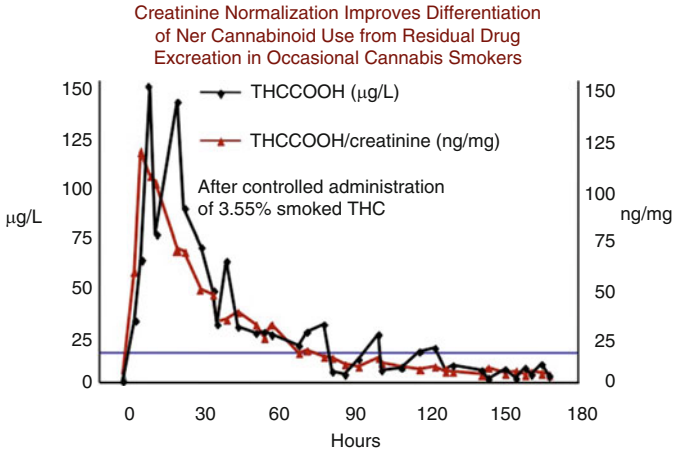

Fig. 13 Urinary excretion profile of total 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH, ◆) as measured by gas chromatography mass spectrometry (GC-MS) after hydrolysis in one subject following smoking of a single 3.55 % Δ9-tetrahydrocannabinol cigarette. The horizontal line at 15 µg/L represents the current GC-MS cutoff used in most testing programs. The urinary THCCOOH concentrations (µg/L) normalized to urine creatinine concentrations (mg/mL) are illustrated with *closed triangles* (▲) (Reprinted with permission Huestis and Cone 1998)

7 days in occasional cannabis smokers is about 0.5 %. Detection times in urine after smoking a 3.55 % THC cigarette with a 15 µg/L urine THCCOOH cutoff concentration is 2–5 days for occasional cannabis smokers but can extend to weeks in chronic daily cannabis smokers. Typical total THCCOOH (THCCOOH + THCCOOH-glucuronide) excretion profiles in less than daily cannabis smokers with and without creatinine normalization over 7 days are shown in Fig. 13. Note that individual urine void concentrations are variable based on the cannabis smoker's state of hydration, sometimes increasing or decreasing over time. Dividing the THCCOOH urine concentration by urine creatinine concentration removes much of the void-to-void variation and improving interpretation of urine cannabinoid results. In a drug treatment, workplace, or pain management setting, it is important to know if a later positive urine cannabinoid test is due to a second cannabis relapse or whether it is due to residual cannabinoid excretion from a previous cannabis intake.

Cannabinoid urinary excretion was quantified in chronic, daily cannabis smokers residing on a secure unit under 24-h/day continuous medical surveillance for up to 30 days (Lowe et al. 2009). Fourteen participants had measurable urine THC for at least 24 h after abstinence initiation, with 7 participant's urine THC-positive for more than 3 days, 5 for 3–7 days, one for 12 days, and one for 24 days. 11-OH-THC and THCCOOH were detected in urine from one chronic frequent cannabis smoker for at least 24 days. THC and 11-OH-THC in urine do not indicate recent cannabis intake, as suggested by other investigators.

Cannabis Abuse and Dependence

In 2009, the DAWN report of emergency department visits listed 376,467 due to cannabis and 213,118 for heroin. This was a large increase from previous reports. Analysis of seized cannabis showed that mean THC content of cannabis in 1993 was 3.4 % and in 2008, 8.8 %, with some hash oils containing up to 29.3 % THC. Cannabis smokers exposed to these high doses may have strong tachycardia, shifts in blood pressure, and even paranoia that end with a trip to the emergency department.

An understanding of the pharmacology of a drug is important for understanding its abuse liability or propensity for addiction. The mechanisms for addiction are complex but one important component involves receptors in the brain. As mentioned, the brain's normal function involves production of neurotransmitters that bind to cannabinoid receptors and modulate multiple transduction mechanisms that influence cell function. Following constant drug intake, the normal function of the endogenous cannabinoid system is changed, with development of dependence and/or addiction. At this point, continued drug abuse also becomes important for preventing cannabis withdrawal. Criteria for defining cannabis withdrawal are included in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V). These criteria include: cessation of heavy and prolonged cannabis use, development of three or more of the following seven symptoms within days after stopping cannabis use: (1) irritability, anger, or aggression, (2) nervousness or anxiety, (3) sleep difficulty (insomnia), (4) decreased appetite or weight loss, (5) restlessness, (6) depressed mood, (7) physical symptoms causing significant discomfort from at least one of the following: stomach pain, shakiness/tremors, sweating, fever, chills, or headache. Cannabis' abuse potential is related to its pharmacokinetics, pharmacodynamic effects, dose, and duration of use. Table 1 lists withdrawal symptoms and their prevalence for 29 chronic frequent cannabis smokers over 2 to 30 days of abstinence (Lee et al. 2014).

Contrary to common belief, marijuana or cannabis can be addictive. Addiction is the inability of an individual to consistently abstain from using a drug. Research suggests that about 1 in 11 cannabis users becomes addicted to marijuana (Anthony et al. 1994; Lopez-Quintero et al. 2011). This number increases among those who start as teens (to about 17 % or 1 in 6) and among people who use marijuana daily (to 25–50 %) (Volkow et al. 2014). Most habit-forming drugs increase the release of dopamine in the nucleus accumbens, and this is believed to be the molecular basis for addiction to cannabis. Much of the debate over whether or not cannabis is addictive subsided when animal studies showed that rodents and monkeys self-administered THC and selected compartments where THC was administered over placebo compartments, just as they did with heroin and other addictive drugs. The dose of THC was important, as animals chose THC at low doses but were averse to selecting high dose THC.

As mentioned, cannabis use can precipitate schizophrenia in some users, an adverse outcome of abuse. British investigators compared cannabis use in first episode cases of psychosis with healthy controls, specifically the use of "skunk," cannabis with high THC content. Cannabis use was similar between groups but case

Table 1 Frequency and severity of cannabis abstinence symptoms reported by 29 adult chronic cannabis smokers during 2–30 days of monitored abstinence[a]

	Symptoms	Prevalence (%) Total[b] (moderate–severe[c])	Change over time[d]		Days different from day 1[f]	Proposed DSM-5[g]
			F (P)	Direction[e]		
Likert	Feel thirsty	35.9 (2.9)	14.62 (0.0001)	↓	8, 12, 17–19, 23	
	Dry mouth/throat	25.6 (0.5)	21.54 (<0.0001)	↓	8, 11, 18, 19, 25, 29	
	Feel hungry	23.8 (3.1)	18.96 (<0.0001)	↓	4, 8, 11–16, 19, 21, 22	
	Mellow	20.3 (3.1)	23.98 (<0.0001)	↓	3–9, 11–23, 25–29	
	Increased appetite	18.0 (2.0)	0.13 (0.72)			
	Increased sexual arousal	15.2 (5.1)	0.03 (0.87)			
	Strange/vivid dreams	14.3 (4.9)	11.59 (0.0007)	↑	None	√
	Yawning	13.1 (0.4)	1.20 (0.27)			
	Fatigue/tiredness	12.3 (0.5)	0.10 (0.76)			
	Talkative	11.3 (0.0)	1.07 (0.30)			
	Feel sluggish/heavy	10.0 (0.5)	2.01 (0.16)			
	Decreased appetite	7.4 (0.5)	12.35 (0.0005)	↓	4–19, 21, 22, 25–27	√
	Muscle aches/pains	6.7 (0.2)	0.22 (0.64)			
	Sweating	4.0 (0.2)				√
	Headache	3.4 (0.4)				√
	Chills	2.5 (0.0)				√
	Stomach pain	1.6 (0.0)				√
	Shakiness/tremulousness	0.5 (0.0)				√
VAS	Craving for marijuana	48.8 (6.2)	1.13 (0.29)			
	Irritable	36.8 (2.2)	4.77 (0.03)	↓	None	√
	Restless	26.8 (2.4)	1.91 (0.17)			√
	Angry/aggressive	36.3 (1.3)	1.18 (0.28)			√
	Depressed	31.0 (0.2)	0.20 (0.66)			√

(*continued*)

Table 1 (continued)

	Symptoms	Prevalence (%) Total[b] (moderate–severe[c])	Change over time[d]		Days different from day 1[f]	Proposed DSM-5[g]
			F (P)	Direction[e]		
	Anxious	28.7 (2.2)	8.35 (0.004)	↓	None	√
	High	27.0 (0.7)	5.89 (0.016)	↓	3, 6–15, 17, 18	
	Stimulated	27.0 (0.9)	5.48 (0.020)	↓	5–7, 13, 15–19	
	Good drug effect	25.6 (1.1)	1.92 (0.17)			
	Sedated	25.4 (0.2)	2.93 (0.087)			
	Stoned	24.7 (0.4)	0.36 (0.55)			
SMHSQ	Depth of sleep		15.85 (<0.0001)	↑	4, 6, 8–12, 14–18, 20–22, 25–28	
	Frequency of waking		6.94 (0.0087)	↓	None	
	Sleep quality		0.79 (0.37)			
	Morning drowsiness		0.44 (0.51)			
	Sleep satisfaction		0.05 (0.82)			
	Early waking		3.14 (0.077)			
	Difficulty getting off to sleep		7.29 (0.0072)	↑	None	
	Hours of sleep		1.59 (0.21)			
	Sleep latency		0.51 (0.47)			

Symptoms assessed on five-point Likert scales: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe, on 100-mm visual analogue scales (VAS) anchored with "not at all" (0) at the left end and "extremely" (100) at the right end; only symptoms that had at least 5 % prevalence and/or included in the DSM-5 proposed criteria for cannabis withdrawal are shown

[a]Number of participants decreased over time

[b]Number of responses with severity ratings ≥1 (Likert or VAS)

[c]Number of responses with severity ratings ≥3 (Likert) or ≥50 (VAS)

[d]Evaluated with repeated measures mixed linear regression as difference from admission scores after adjusting for duration of stay

[e]↓ and ↑ denote significant decrease and increase over time, respectively

[f]Evaluated with post hoc analysis after the Dunnett-Hsu adjustment

[g]√ Denotes symptoms included in the proposed DSM-5 diagnostic criteria for cannabis withdrawal syndrome (www.dsm5.org)

patients were 3–5 time more likely to use "skunk" daily compared to controls (Di Forti et al. 2015). The authors examined explanations including the possibility that individuals with psychotic behaviors might self-medicate with cannabis but it appeared that use preceded the episodes not vice versa. These recent data may encourage scientists to investigate the abuse liability and long-term adverse effects of higher potency and synthetic cannabinoids.

The primary focus of preventing cannabis abuse is in adolescents and young adults, a reasonable strategy considering data suggest nonreversible brain damage from early onset chronic frequent cannabis use and data showing cannabis is the primary illicit drug of abuse for 12–17 year olds admitted for drug abuse treatment. Additionally, early prevention efforts are more effective. The 2013 *Monitoring the Future Survey* of US high school students reported that the 5-year trend shows significant increases in past-year and past-month (current) marijuana use across the three grades, 8th, 10th, and 12th as well as increases in lifetime and daily marijuana use among 10th graders (Johnston et al. 2014). These grades correspond to approximate ages 14, 16, and 18 years, respectively. From 2008 to 2013, past-month use increased from 5.8 % to 7.0 % among 8th graders, 13.8–18.0 % among 10th graders, and from 19.4 % to 22.7 % among 12th graders. Selecting 12th graders for further study, investigators found that increases and decreases over the past 20 years correlated with the youth's perception of risk, this latter increase following an increase in the number of youth believing cannabis was not harmful.

Daily use statistics also were alarming. In 2013 compared to 2008, daily use by 8th, 10th, and 12th graders was respectively 1.1 versus 0.9 %, 4.0 versus 2.7 % and 6.5 versus 5.4 %. The increase for 10th graders was significant. From the mid-1970s, the percentage of youth using cannabis daily generally decreased until the mid-1990s but then began to increase. Some analysts reported that the change in perception of harm paralleled the advent of legalization of cannabis for medicinal purposes and finally legalization for recreational use.

One aspect of addiction relevant to safety and treatment is tolerance. As with other addictive drugs, tolerance has a molecular basis. For cannabis, internalization of CB1 receptors due to repeated exposure to THC is the neuroadaptation leading to tolerance. The development of tolerance was studied following around-the-clock (every 3.5–6 h) 20 mg oral synthetic THC in daily cannabis smokers: 40 mg day 1; 100 mg days 2–4; and 120 mg days 5–7 (Gorelick et al. 2012). Systolic and diastolic blood pressure, heart rate, and symptoms of subjective intoxication (100 mm visual analogue scales) were assessed on the morning of day 1 (before oral THC) and on days 2, 4, and 6, every 30 min for 3 h after the first THC dose. Morning subjective intoxication ratings increased from days 1–2 and declined on days 4 and 6. The morning THC dose increased intoxication ratings on day 2 but had less effect on days 4 and 6, a pattern consistent with tolerance. THC lowered blood pressure and increased heart rate over 6 days. Plasma THC and 11-OH-THC increased significantly over the first 5 dosing days reaching mean C_{max} of 30 and 15 μg/L on day 5. Six days of around-the-clock, oral THC produced tolerance to subjective intoxication but not to cardiovascular effects.

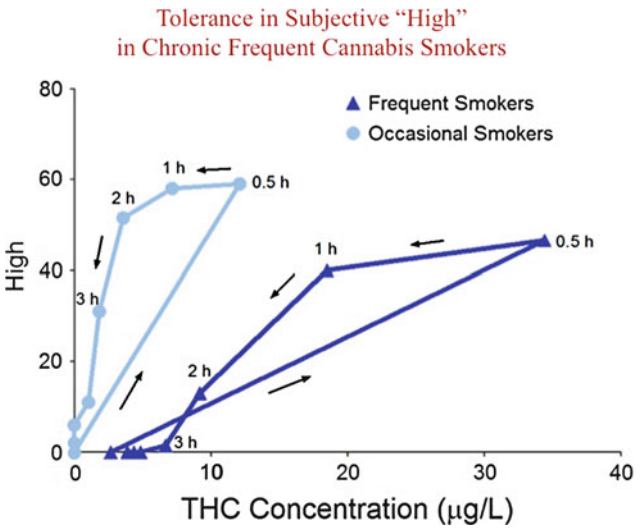

Fig. 14 Mean (standard deviation) visual analog scale (VAS) score for "High" in 14 frequent and 11 occasional cannabis smokers following controlled smoking of a 6.8 % THC (54 mg) cannabis cigarette (Reprinted with permission Desrosiers et al. 2015)

Tolerance also was demonstrated in 14 chronic frequent cannabis smokers compared to 10 occasional smokers following smoking of a 6.8 % THC cigarette (Desrosiers et al. 2015). Occasional cannabis smokers reported a greater "High" at lower THC concentrations than chronic frequent cannabis smokers at higher THC levels (Fig. 14). In addition, the counterclockwise hysteresis characteristic of THC concentration-effect relationships is shown. Tolerance can develop in a different manner to any cannabis physiological, cognitive, or subjective effect with chronic frequent exposure, but usually tolerance is partial, not complete for any effect, and tolerance is lost with short cannabis abstinences.

The combination of equal amounts of THC and CBD, another natural plant cannabinoid, in an oromucosal spray, Sativex™, is currently approved in multiple European, Canadian, and South American countries to treat spasticity due to multiple sclerosis and neurogenic pain. Others suggested that CBD modulated THC's effect; however, it was shown that equal doses of 5 or 15 mg CBD and THC did not alter THC's pharmacodynamic or pharmacokinetic effects (Karschner et al. 2011). Much more research is needed to demonstrate the effectiveness of cannabinoids, determine mechanisms of action, standardize drug composition and potency, and document in accepted FDA-approved trials the long-term effectiveness and lack of adverse outcomes of potential new medications. There is a long list of potential cannabinoids therapeutic uses, but these new medications must undergo the same developmental approval requirements of all new drugs. There is a strong movement to improve the ability to do clinical trials on cannabinoids, which currently are Schedule I substances, with all the restrictions and barriers that accompany this classification.

Outlook

We know that the endocannabinoid system appeared early in evolution and is required for brain plasticity. Future research will focus on discovering more detailed information on the endocannabinoid system, determining long-term sequelae of cannabis on this system, evaluating potential therapeutic effects of multiple cannabinoids, and developing therapies for cannabis dependence. Neurotransmitter transporters and enzymes that produce and metabolize neurotransmitters will provide new targets for pharmacotherapies to treat multiple diseases. Research on cannabinoid effects on the developing brain is important for educating the public on the dangers of use, especially prior to age 17 years. fMRI and other brain-imaging studies will provide more information on the brain's activities, in real time, while individuals are under the influence of cannabis. Advances in monitoring cannabinoids in multiple biological matrices continue to improve interpretation of cannabinoid results. For example, identifying new markers in blood may indicate recency of cannabis intake for application in driving under the influence applications. Oral fluid cannabinoids will find utility in on-site testing, treatment programs and roadside testing. New models from measurements of cannabinoids in blood and urine will assist in identifying relapse in cannabis dependence treatment. More well-controlled, double blind, and randomized studies are needed to document whether cannabinoid therapies including synthetic or cannabis plant extracts are effective at treating a wide variety of diseases.

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