Pharmacology of Cannabis

Mandakini Sadhir

University of Kentucky, m.sadhir@uky.edu

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Mandakini Sadhir*, MD
Division of Adolescent Medicine,
Department of Pediatrics, University of Kentucky,
Lexington, Kentucky, USA

Abstract
Cannabis has been used for recreational purposes around the world. It is derived from the plant cannabis sativa which has various other compounds known as cannabinoids. Most common form of cannabis used for recreational purpose is marijuana, which is prepared from dried flowering tops and leaves. The primary psychoactive component is delta 9-tetrahydrocannabinol (δ-9THC), which exerts its physiological and psychological effects through its interaction with CB1 and CB2 receptors. Smoking is the most commonly used method with onset of effects within minutes after inhalation. Oral ingestion of cannabis has varied absorption with delayed onset but longer duration of action. Urine drug screen is the most common method for detecting cannabis use. Other cannabionoids such as cannabidiol have been utilized for medicinal purpose and research is ongoing to fully understand its role in treatment of various health conditions. Synthetic cannabis has emerged as drug of abuse over recent years and poses greater challenges due to serious physiological and psychological effects and inability to be detected in standard screening tests.

Keywords: Cannabis, marijuana, cannabinoids, CB receptors, CB2 receptors, delta 9-tetrahydrocannabinol (δ-9THC), synthetic cannabinoids

Introduction
Cannabis has been used for recreational purpose around the world for many decades. Its use however has increased in recent years among adolescents and young adults. Much of this increase seems to correlate with low risk perception (1, 2). The primary psychoactive constituent of cannabis is delta 9-tetrahydrocannabinol (δ-9THC) known to have various physiological and psychological effects. Chronic use leads to dependence and behavioral disturbances (3). Multiple studies have explored effects of cannabis on various health conditions, but its medicinal use is currently limited (3, 4). Debate exits over decriminalization and legalization of
cannabis with potential to have varied consequences (5). This paper describes main cannabinoids, their mechanism of action and metabolism in humans.

**Phyto-cannabinoids**

Cannabis is derived from a female plant Cannabis sativa which contains many compounds known as phyto-cannabinoids or commonly cannabinoids. The principal cannabinoids are delta 9-tetrahydrocannabinol (δ-9THC), cannabidiol (CBD) and cannabinol (CBN) (4). THC initially isolated in 1964, is a primary psychoactive agent and has been widely studied (6, 7). Over the years, many new cannabinoid and non- cannabinoid compounds in the plant have been discovered (4). The number of cannabinoids identified since 2005 has increased from 70 to 104. Other known compounds in the plant have also increased from 400 to 650 (4). The content of THC varies in different sources and preparations of cannabis. Its content is highest in the flowering tops and subsequently declines in the leaves, stem and seeds of the plant (8). Most common form of cannabis that is used for recreational purpose is Marijuana with THC content from 0.5% to 5%. It is prepared from the dried flowering tops and leaves (6-8). Another form of cannabis is hashish with THC content 2–20% and is derived from dried cannabis resin and compressed flowers (9). The potency of cannabis products has increase significantly from approx. 3% to 12-16% or higher (percent THC weight/per dry weight of cannabis) over the past decades due to sophisticated cultivation and plant breeding techniques. The concentration of THC can also reach about 80% using butane hash oil (4). In the 1960’s and 1970’s, a cannabis product for example contained about 10 mg of THC. But, current joint made of other subspecies of cannabis may contain about 150 mg of THC. Current generation of cannabis user may be exposed to higher concentrations of THC as compared to those who used cannabis decades earlier (8).

Cannabidiol (CBD) is a non-psychoactive cannabinoid obtained from the plant. Over the years, it has drawn much attention due to its pharmacological activity and therapeutic use (10). CBD is found to have neuroprotective, analgesic, sedative, anti-emetic, anti-spasmodic, anti- anxiety and anti-inflammatory properties. Research is ongoing to understand its role in treatment of various health conditions (10, 11).

**Mechanism of action**

Cannabinoids are known to exert their physiological action through G protein coupled receptors known as CB1 and CB2. These receptors were initially identified in 1990s and have been extensively studied (12). Activation of these receptors leads to inhibition of adenyl cyclase resulting in decreased production of cAMP and changes in ion channel activity. Through these receptors, cannabinoids hyperpolarize neurons by closing voltage-dependent calcium channels and activate potassium channels (13). CB1 receptors are present in both central and peripheral nervous system. They are mostly present in region of brain associated with memory, cognition, reward, anxiety, pain perception, movement (12-14). These include cortex, hippocampus, olfactory area, basal ganglia, cerebellum and spinal cord. Few CB1 receptors are found in the brainstem and thus administration of cannabinoids is not associated with respiratory depression unlike opioids (8, 13, 14). CB1 receptor activation has also shown to modulate neurotransmitters in the brain, including glutamate, γ- amino butyric acid (GABA), opioids, dopamine, and serotonin, resulting in varied effects (8, 9). Role of serotonin receptor 5-HT2A in causing some of specific effects of THC such as memory deficits, anxiolytic-like effects, and social interaction has been reported (15). CB2 receptors are present in the cells of immune system predominantly in the spleen and macrophages and appear to play role in modulation of cytokine release and immune cell migration (14).

**Endocannabinoids**

Endocannabinoids are endogenous compounds discovered in the 1990s that interact with cannabinoid receptors and produce similar effects as cannabis (10). The two main endogenous compounds are anandamide (from the Sanskrit word ananda, meaning bliss) and 2-arachidonoylglycerol (2AG) (10). These are derivative of the fatty acid arachidonic acid.
related to the prostaglandins. Anandamide is partial agonist for both CB1 and CB2 receptors with CB1 efficacy higher than CB2. It produces similar effects to δ-9THC, but is less potent and has shorter half-life due to rapid metabolism (9, 16). 2-Arachidonoylglycerol was originally identified in intestinal tissue and is found at much higher levels than anandamide in the brain. 2-AG is thought to be the main endogenous agonist for both CB1 and CB2 receptors (16). Endocannabinoids also interact with other G protein coupled receptor and ion channels. Some of the known ion channel are vanilloid receptor-type 1 (TRPV1) activated by anandamide. Other receptors are several types of potassium channels, alpha7 nicotinic receptors and 5-HT3 receptors (10, 11). The endocannabinoid system comprised of endocannabinoids and its receptors is thought to mediate various physiological processes and are implicated in health and disease (16).

Absorption of cannabis

The tetrahydrocannabinol and other cannabinoids have varied absorption and effects depending on dose, route of administration and vehicle. Further physiological factors such as metabolism and excretion can influence drug concentrations and its subsequent effects (11). Smoking is most common and widely used method. After inhalation, THC is rapidly absorbed through lungs and reaches brain quickly with physiological and psychological effects becoming apparent within seconds to minutes (10, 17). The effects then reach a plateau that can last 2–4 h before slowly declining. While, the amount of THC absorbed is higher with inhalation, the bioavailability varies according to the depth of inhalation, puff duration and breath-hold (17). Absorption of THC is variable when ingested. When taken orally, some of the THC is degraded by liver due to first pass metabolism and converted to 11-hydroxy δ 9_Tetrahydrocannabinol (11-OH-THC). Further, 11-OH-THC is oxidized by microsomal alcohol dehydrogenase and aldehyde oxygenase to produce the non-psychoactive metabolite, THCCOOH (11). The majority of cannabinoids (80-90%) are excreted within five days as hydroxylated and carboxylated metabolites (18). The elimination of metabolites is mostly through feces (65%) and approximately 20% in urine (17). Among the major metabolites, 11-OH-THC is predominantly excreted in feces and THCCOOH is excreted in urine mainly as a glucuronic acid conjugate. This particular metabolite has been utilized for diagnostic purposes for detection of cannabis in urine (17).

Distribution

Cannabinoids are highly lipophilic and get distributed in adipose tissue, liver, lung and spleen (9). Following assimilation in blood, concentration of THC in plasma decreases due to peripheral redistribution particularly in adipose tissues. Sequestration in adipose tissue prolongs elimination half-life that can last for several days (8, 11). From the adipose tissue, THC gets slowly released into the blood stream and other body compartments including the brain. Cannabinoids also cross the placenta, entering into fetal circulation and secreted in breast milk (9).

Metabolism and elimination

THC is metabolized in the liver by microsomal hydroxylation and oxidation using enzymes of Cytochrome P 450 Complex generating more than 100 metabolites (18, 19). As a result of hydroxylation, THC generates a psychoactive compound 11-hydroxy δ 9_Tetrahydrocannabinol (11-OH-THC). Further, 11-OH-THC is oxidized by microsomal alcohol dehydrogenase and aldehyde oxygenase to produce the non-psychoactive metabolite, THCCOOH (11). The majority of cannabinoids (80-90%) are excreted within five days as hydroxylated and carboxylated metabolites (18). The elimination of metabolites is mostly through feces (65%) and approximately 20% in urine (17). Among the major metabolites, 11-OH-THC is predominantly excreted in feces and THCCOOH is excreted in urine mainly as a glucuronic acid conjugate. This particular metabolite has been utilized for diagnostic purposes for detection of cannabis in urine (17).
Detection and analysis of cannabis

Cannabinoids can be detected in urine, blood, saliva, hair and nail using various analytical techniques (20). These techniques are utilized to measure cannabinoids for research studies, drug treatment and employment related drug screening. Various chromatographic techniques such as thin layer chromatography (TLC), high performance thin layer chromatography (HPTLC), gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography-mass spectrometry (HPLC-MS) have been utilized for detection and quantitation of cannabis metabolites (17). The preferred sample for screening is urine to check for presence of urine metabolites particularly glucuronic acid conjugate of THCCOOH (20). The main techniques utilized for urine drug screening are immunoassay and gas chromatography-mass spectrometry (GC-MS). Immunoassays are the most common method for initial screening while GC-MS is used for confirmation (21, 22). The cut off limit for cannabis metabolites in immunoassay is 50ng/ml; it is 15 ng/ml for GC-MS. Detection of metabolites in urine varies depending on frequency and duration of cannabis use. It can be detected anywhere from 3 days (single use) up to 30 days or longer (long term heavy smoker) (22).

Detection of THC and its metabolites is influenced by various other factors in addition to sensitivity and specificity of assays. These factors include route of administration, amount of cannabinoids consumed and absorbed, body fat content, rate of metabolism and excretion, time of specimen collection (9, 20).

There has been growing interest in utilization of oral fluids as an alternative biological specimen for detection of drugs in forensic and clinical settings (23). Studies have shown oral fluids to be simple, non-invasive method of specimen collection with advantages of observed specimen collection, making adulteration difficult. It has shown to have stronger correlation with blood than urine concentration of cannabis metabolites and can detect recent exposure (23). It also offers ease of multiple sample collections and lower biohazard risk of specimen collection. Currently, research on oral fluids in ongoing and further evaluation is needed before implementing it a drug screening test (23).

Synthetic cannabinoids

Synthetic cannabinoids are a heterogeneous group of compounds originally synthesized for research purpose to explore endogenous cannabinoid system for possible therapeutic use (24). However, these compounds became drugs of abuse and were marketed as “designer drugs”. In the 2000s, synthetic cannabinoids were sold under brand names such as “spice” and “K2,” labeled as herbal incense. These became very popular drugs of abuse as they could not be detected by standard screening tests (25).

The synthetic cannabinoids acts on cannabinoid receptors and have greater affinity to CB1 than CB2 receptors. Both animal and in vitro studies have shown that synthetic cannabinoids are 2-100 times more potent than THC (25). Synthetic cannabinoids are metabolized in the liver via conjugation and oxidation pathways and have longer elimination half-life (24, 25). Use of synthetic cannabinoids has resulted in medical and psychiatric emergencies due to their intense physiological and psychological effects. Some of the common adverse effects include seizures, myocardial infarction, acute renal failure, anxiety, agitation, psychosis, suicidal ideation, and cognitive impairment. Long-term or residual effects are currently unknown (26, 27).

References

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