

The endocannabinoid system, cannabis, and cannabidiol: Implications in urology and men's health

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Abstract

Background: The endocannabinoid system is a neuromodulatory system responsible for partial regulation of cognitive and emotional processes in the human central nervous system such as behavior, mood disorders, and neurologic disorders such as epilepsy. The endocannabinoid system is also prevalent throughout the peripheral nervous system and human body and its receptors and signaling pathways are present and active in areas including the male and female reproductive tracts and organ systems such as the urologic and gastrointestinal system.

Summary: The purpose of this article is to provide the reader with a brief background on the endocannabinoid system and to discuss the implications of the endocannabinoid system in urology as it applies to the male reproductive system, risk of urologic malignancy, and impact on the lower urinary tract, voiding, and urologic pain. It also summarizes and discusses the epidemiology and research on cannabis and cannabidiol products.

Key message: The endocannabinoid system affects the urologic and reproductive systems. Cannabis products and inhibitors targeting endocannabinoid pathways are being studied for their potential use as treatments for lower urinary tract symptoms and other urologic symptoms. Cannabis use adversely affects spermatogenesis and semen parameters and may be a risk factor for testicular germ cell tumors, however, it may be useful as a potential treatment for urologic symptoms. Cannabidiol products are popular in the consumer marketplace but there is still a paucity of scientific data on their potential medicinal use.

Keywords: Cannabidiol; Cannabis; Endocannabinoid system; Lower urinary tract symptoms; Men's health; Testicular cancer; Urology

1. The endocannabinoid system

The endocannabinoid system is a central and peripheral neuromodulatory system. It is characterized by 2 cannabinoid receptors, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2).^[1-3] CB1 receptor is highly expressed in the brain and peripheral tissues such as in adipocytes, circulating immune cells, skeletal muscle, exocrine pancreas, liver, and gastrointestinal tract.^[1] CB2 is present in the spleen, thymus, pancreas, and peripheral immune cells including mast cells and peripheral blood leukocytes. There are thought to be fewer CB2 receptors in the central nervous system in comparison to CB1 receptors.^[3]

Both the CB1 and CB2 receptors are G-protein coupled receptors. Their endogenous ligands are arachidonate-derived molecules, N-arachidylethanolamine (AEA) and 2-arachidonylglycerol (2AG), respectively.^[1,4] AEA and 2AG are endogenous lipids that engage the CB1 and CB2 receptors and have been shown to modulate neurologic activity and human behavior in a

mechanism similar to that of the main psychoactive component of the plant *Cannabis sativa*, delta-9-tetrahydrocannabinol (THC). Termination of signaling occurs via reuptake and enzyme hydrolysis primarily by fatty acid amide hydrolase (FAAH) and monacylglyceride lipase.^[5] Table 1 lists the key elements of the endocannabinoid system.

The endocannabinoid system regulates distinctive physiologic processes in the human body. It is implicated in stress response pathways, pain, obesity, mood, the sleep-wake cycle, hunger, and has other functional activities in organ systems including the cardiovascular, gastrointestinal, skeletal muscle, hepatic, reproductive, and urologic systems. Early theories about the role of the endocannabinoid system in human physiology came from observation of the effects of consumption of *Cannabis sativa*, commonly called cannabis or marijuana, in humans. *C. sativa* is in the hemp family, *Cannabaceae*, and is one of the oldest crops in the world.^[6] It is an herbaceous plant that has been used as a source of food and as a nonfood material predominately as a fiber for textiles and other products. People in many cultures have been consuming cannabis for medicinal and/or religious purposes. The medical use of cannabis is dated to approximately 5000 years ago. Early pharmacopeias suggest it was prescribed for fatigue, malaria, rheumatism, and eczema.^[7] In modern times, cannabis was introduced as an analgesic, anti-inflammatory, anti-convulsant, and anti-emetic in 19th century England.^[8] Eventually restrictions on the plant use occurred in western European countries and US in the 1930s.^[9]

Cannabis contains a variety of active phytochemicals including alkaloids, flavonoids, terpenoids, and cannabinoids.^[9,10] Over 100 cannabinoids have been identified, the most potent and

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Table 1
Key elements of the endocannabinoid system and cannabis terms.

Category Name	Description
Receptors	
Cannabinoid receptor 1 (CB1)	The two main cannabinoid receptors in the endocannabinoid system. Characterized as G-protein coupled receptors. Present in the central nervous system, bladder, kidney, seminal vesicle, corpus cavernosum, testis, endometrium, ovary
Cannabinoid receptor 2 (CB2)	
G protein-coupled receptor 55 (GPR55)	Thought to be the third main receptor of the endocannabinoid system. Its role is still being elucidated
Ligands	
Anandamide (AEA)	The two main endogenous endocannabinoid system ligands
2-Arachidonylglycerol (2AG)	
Enzymes	
Fatty acid amide hydrolase (FAAH)	FAAH is the primary catabolic enzyme of AEA
Monoacylglyceride lipase (MAG)	MAG is the primary catabolic enzyme of 2AG
N-acylphosphatidylethanolamine hydrolase	NAPE-PLD synthesizes AEA
phospholipase D (NAPE-PLD)	
Cannabis terms	
Delta-9-tetrahydrocannabinol (THC)	THC is the main psychoactive cannabidiol in <i>Cannabis sativa</i> , commonly called "cannabis" or "marijuana"
Cannabinoid	Cannabinoid is a term that represents > 100 phytoactive components of <i>Cannabis sativa</i>
Cannabidiol (CBD)	Commonly called CBD, this is the main non-psychoactive cannabinoid component found in <i>Cannabis sativa</i> that may have medicinal properties

psychoactive component being THC. Cannabis consumption commonly occurs via smoking, inhalation, and ingestion. The psychoactive effects of THC are largely mediated by activation of the CB1 receptor by THC.^[11] Early epidemiological studies have also shown that users of cannabis reported less depressive mood states and more positive affects as compared to nonusers.^[12] In the human brain, CB1 receptors (and to a lesser extent CB2 receptors) and enzymes are widely scattered throughout areas in the cerebral cortex including the prefrontal cortex, amygdala, hippocampus, hypothalamus, and forebrain.^[13] A genetic CB1 receptor knockout model resulted in expression of a phenotype with similarity to the symptom profile of symptomatic severe depression such as depressive-like behavior, anxiety, impaired motivation, reward salience, and altered cognitive and neurovegetative functioning. Other studies have demonstrated that there may be an increased neuroendocrine response to chronic stress in other CB receptor knockout model studies.^[14,15]

In contrast, cannabidiol is a nonpsychoactive phytocannabinoid component of cannabis. Cannabidiol has a weak affinity for CB1 and CB2 receptors.^[16,17] Its mechanism of action is likely multifold as it acts on a variety of systems including the serotonergic, opioid, and cannabinoid systems. Within the cannabinoid system, it likely acts via negative allosteric modulation.^[18,19] The potential effect of cannabidiol on numerous pathways may explain its current use and potentially broad application on numerous functions and symptoms.

2. Implications in urology

While role of the endocannabinoid system is still being fully elucidated there is some information about the endocannabinoid and the human urologic and reproductive systems. Moreover, we are learning about the potential risks and possible benefits of the use of cannabis and combined cannabinoid products on the urologic system. Clinical implications in urology include cannabis use as a risk factor in men's health as it has been shown to have adverse effects on reproductive function (eg, testicle and seminal vesicle function). Conversely THC and/or cannabidiol products may be beneficial for the treatment of some lower urinary tract symptoms including irritative voiding

symptoms and urogenital pain.^[20,21] The role of the endocannabinoid in the kidney is also of important urologic consideration but activity in the kidney may be linked to energy and homeostatic pathways active in diabetes and obesity which will not be covered in this article.^[22] For the remainder of this article we outline what is known about the endocannabinoid system in urology and the effects of cannabis on the male reproductive system and the risk of urologic malignancies as well as the possible treatment of lower urinary tract voiding symptoms and urogenital pain with cannabis/cannabidiol products.

3. Male reproductive system and urologic malignancies

The endocannabinoid system plays an important role in the male reproductive system. Receptors and ligands are present in the human testis, seminal vesicles, corpus cavernosum, and spermatozoa. Early research revealed CB1 receptor presence in the frog and rodent testis that was later confirmed in the human testis and human spermatozoa.^[23-27] Data suggests that endocannabinoid system components may help modulate sperm function in relationship to fertilization ability. In the seminal vesicles, it is postulated that the endocannabinoid system may control seminal vesicle secretory function as the main proteins including CB1, CB2, FAAH1, FAAH2, and G protein-coupled receptor 55 are all expressed in the epithelial layer of the human seminal vesicle. G protein-coupled receptor 55 has been characterized as a third main endocannabinoid family receptor however its mechanism of action is still poorly understood.^[23] CB1 and CB2 receptors have also been identified in the smooth muscle of the corpus cavernosum. Gratzke et al.^[25] demonstrated the presence of CB1 and CB2 in the human corpus cavernosum however they were unable to determine whether AEA could increase the ejaculatory threshold.^[28] Finally, there may be multiple effects of CB1 receptor activation on neurotransmitter release including dopamine and serotonin that may correlate to sexual response and behavior.^[29,30]

For the clinician, it is important to be aware of the potential deleterious effects of cannabis use on male fertility and the risk urologic malignancies such as testicle cancer. The legal status of

cannabis for both medical and recreational purposes varies across the US and it is thought that approximately 10% of regular users may develop a cannabis use disorder.^[31] Young men are more likely to use cannabis and the highest past-year prevalence has been shown to be approximately 33% in adults 18–25 years old. It has also been shown that men are almost twice as likely to use cannabis over the past month, 11.3% versus 6.7%.^[31,32] Cannabis can be addictive although relative to other substances, cannabis use disorder makes up a much small portion of global burden of disease. For example, of “two million total disability adjusted life-years lost to substance use disorders (not including tobacco),” individual substance use disorders were 47% for alcohol, 24.3% for opioids, and 5.5% for cannabis.^[32,33]

Cannabis use has been shown to be associated with adverse effects on male reproductive function. First, cannabis use may affect spermatogenesis. As abovementioned, the endocannabinoid system is present in the male reproductive tract and both in vitro and in vivo studies suggest that cannabis use may reduce spermatogenesis and damage sperm functions such motility and capacitation. A 2015 study of 1215 Danish males who had used cannabis in the past 3 months showed that use weekly or more frequent than weekly use resulted in a 28% lower sperm concentration and 29% lower total sperm count in comparison to non-users (95% confidence interval [CI] –48 to –1 and –46 to –1, respectively).^[34] A systematic review by Payne et al.^[35] found the strongest evidence of adverse effects of cannabis use on semen parameters. Men who reported using cannabis demonstrated alterations in sperm count and concentration, morphology, motility and energy metabolism, and fertilization capacity. A prospective study of 1700 men in the United Kingdom showed that men using cannabis were more likely to have abnormal sperm morphology in comparison to case matched controls.^[36] The mechanism of action of cannabis on semen parameters and fertilization capacity suggest that cannabis use inhibits sperm capacitation and activation due to high AEA levels. Cannabis use may also affect hormone levels. Cannabis use in men has not been shown to alter follicle-stimulating hormone levels in the majority of studies however studies on the potential effects of cannabis on testosterone are variable. In many animals and a few human studies, evidence suggests that there is a reduction in testosterone levels between never and chronic marijuana users however the majority of human studies do not show a significant effect of cannabis use on testosterone in comparison to the animal studies.^[36,37]

In another recent systematic review, cannabis use and urologic cancer risk are discussed. Four studies suggest that cannabis consumption may be an independent risk factor for the development of testicular germ cell tumors (TGCT). Three case-controlled studies and the meta-analysis of these studies demonstrated that men with TGCTs were more likely to be current or frequent marijuana users compared to controls. Of the largest case-controlled study, men with a TGCT were more likely to be current marijuana smokers at the referenced date compared with controls (odds ratio [OR] 1.7; 95% CI 1.1–2.5) (369 men aged 18–44 years in comparison to 979 age-matched controls without a history of TGCT).^[38,39] In the meta-analysis by Gurney et al.,^[40] results demonstrated that current, chronic, and frequent cannabis use was associated with the development of a TGCT when compared to never use. Nonseminoma development in those men using cannabis at least weekly demonstrated 2.5 times greater odds of development of a nonseminoma TGCT compared to never users (OR 2.59, 95% CI 1.60–4.19). The authors do note that these data are from 3 studies conducted in the US in the 1990s.

The relationship between bladder cancer and cannabis use has also been reported in a small case-controlled study. This study demonstrated that of 52 patients with transitional cell carcinoma, 46 (88.5%) reported a history of habitual marijuana use. However, both cancer patients and controls had high rates of concurrent tobacco use.^[41] In the data from the California Men’s Health Study, an inverse association between cannabis use and bladder cancer development was demonstrated. Eighty-nine men (0.3%) developed bladder cancer in comparison to 190 (0.4%) men who did not report cannabis use ($p < 0.001$) from the records of 84,170 participants. This study also showed a high prevalence of cannabis use in men with 34,000 (41%) cohort members reporting cannabis use, 47,092 (57%) reporting tobacco use, 22,500 (27%) reporting using both, and 23,467 (29%) using neither.^[42] In conclusion cannabis use has been shown to adversely affect numerous parameters related to spermatogenesis and sperm function and there is some data that suggests an increased risk of testicular germ cell tumors in cannabis smokers in comparison to never users.

4. Lower urinary tract and voiding

Cannabis use may also affect the urinary bladder and may improve voiding dysfunction. As aforementioned, the CB1 receptor is widely expressed throughout the central nervous system and various peripheral tissues including the urinary bladder. An early study by Bakali et al.^[43] examined the expression and distribution of CB1 and CB2 receptors in the human and rat bladder. The investigators demonstrated immunoreactivity for CB1 receptors in the bladder as well as the presence of transient receptor potential vanilloid type 1 (TRPV1), FAAH, and N-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D. TRPV1 is a well-characterized receptor in the rat and human bladder and FAAH degrades anandamide and N-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D synthesizes endocannabinoids.^[43,44] CB2 immunostaining has also been observed in the detrusor muscle of the rat bladder and is present in both the smooth muscle and the urothelium of the human bladder.^[43] The implications of this suggest that cannabis and/or THC bind to CB1 and CB2 receptors resulting in analgesic properties likely related to attenuation of nerve growth factor and subsequent inhibition of adenylyl cyclase as shown in models of hyperalgesia.^[45]

Two studies of THC and/or THC/cannabidiol cannabis products performed in patients with multiple sclerosis have shown benefit in improving urologic pain and irritative voiding symptom scores. In a small open-label study of a combined extract of THC and cannabidiol for 8 weeks followed by THC alone, urinary urgency, number and volume of incontinence episodes, and nocturia significantly decreased following treatment ($p < 0.05$) as did patient-reported pain levels, spasticity, and improvement in sleep quality in 21 patients with advanced multiple sclerosis.^[46] A larger randomized study of 630 patients with multiple sclerosis and neurogenic detrusor overactivity was also performed. This clinical study demonstrated a marked improvement in urinary incontinence episodes in patients with multiple sclerosis who took oral THC containing cannabis. The clinical study demonstrated that patients randomized to oral cannabis extract containing THC demonstrated improved episodes in urge incontinence.^[47] While more studies need to be done these studies suggest that there may be a potential role for cannabis and/or THC in the treatment of bladder symptoms.

There are a number of hypotheses on how THC and cannabidiols may work in the bladder and lower urinary tract. One hypothesis is that exogenous use (eg, cannabis and/or THC or a combined THC/cannabidiol product) or an increase in endogenous endocannabinoids may bind CB1 and CB2 receptors resulting in relaxation of the detrusor muscle during the filling phase. Another hypothesis is based on the activation of TRPV1, a receptor that is well characterized in the rat and human bladder. It is postulated that activation of TRPV1 may contribute to the development of overactive bladder symptoms and that cannabinoids may improve these symptoms.^[43,44,48]

FAAHs are an example of new agents that are being tested for their potential in treating lower urinary tract symptoms. AEA and 2AG are metabolized by FAAH and monoacylglycerol lipase respectively and inhibitors that may prevent their degradation may enhance the effectiveness of endogenous endocannabinoids thereby improving lower urinary tract symptoms.^[49] There has been one study of a FAAH inhibitor, ASP3652, in the treatment of adult male patients with chronic prostatitis/chronic pelvic pain syndrome.^[50] Total 229 patients were randomized to various doses of ASP3652 or placebo for 12 weeks and results demonstrated no difference in reduction of the primary endpoint of the National Institutes of Health Chronic Prostatitis Symptom Index in the treatment groups versus the control groups and the placebo group had similar results to the treatment groups.^[50]

Other areas of related cannabis research include a recent study investigating the impact of cannabis use on biomarkers of lower urinary tract function. Nedumaran et al.^[51] evaluated the differences in urine peptides in users and noncannabis users and found 19 of 1337 differences in protein alterations in cannabis users. Up-regulated proteins in cannabis users included some related to lipid metabolism, immune responses, inflammatory activity, and antigen binding. Proteins that were down-regulated in cannabis users were some that modulated intestinal and renal absorption, RNA and iron metabolism, neuronal differentiation, and tumor-related processes. While this study only provides exploratory proteomic knowledge that is not yet relateable to physiologic and pathophysiologic processes it clearly demonstrates that there are differences in proteins and signaling pathways that may be affected by use of cannabis and cannabinoid products.

5. Cannabidiol

It is also important for the clinician to understand some of the differences in cannabis use, THC containing products, and cannabidiol-only products in humans. Cannabidiol is one of more than 100 cannabinoids identified in the cannabis plant and it is nonpsychoactive. As aforementioned, cannabidiol does not strongly bind to CB1 or CB2 receptors like THC but may function in different ways; it is hypothesized to be a negative allosteric modulator, a potential antagonist at the GP555 receptor, and/or may modulate numerous neurotransmission pathways such as the serotonin and opioid systems. Thus, the potential for cannabidiol to be a treatment for clinical conditions with pain, mood, and anxiety-related elements is a reasonable hypothesis. Cannabidiol products are most commonly cultivated from the hemp plant and are specified to contain less than 0.3% THC in US market however there are currently hundreds of cannabidiol products available to consumers in a variety of including dietary supplements, hemp oils, topical products, and food items for both humans and pet consumption.^[52]

The safety of cannabidiol appears to be adequate and a recent phase I dose escalation study of a cannabidiol oral solution (the FDA approved cannabidiol, Epidiolex[®]), tested ascending doses of cannabidiol from 1500 mg up to 600 mg cannabidiol (n=6) per group versus placebo. The results demonstrated that cannabidiol was generally well tolerated and adverse events included increased incidence of mild to moderate diarrhea and headache in subjects taking cannabidiol versus placebo. Time to maximum plasma concentration was approximately 4–5 h and the pharmacokinetic profile based on this study suggests twice-daily dosing.^[53] It has been previously shown that cannabidiol is extensively metabolized by cytochrome P450 2C19 and CYP3A4. It has also been shown to inhibit the CYP2C family of isozymes and several UDP-glucuronosyltransferase isoforms.^[53] Despite this there are still few studies that look at potential interactions between cannabidiol with other drugs and food products and even fewer studies testing cannabidiol alone and not in combination with THC.^[53,54] Finally, the regulation of CBD products in the US is still under debate and there are safety issues related to manufacturing and potential adulteration that already exist in industries such as the pharmaceutical and dietary supplement industries regardless of its current regulatory status. This and the possibility of adulteration presence of synthetic cannabinoids are of concern in many cannabis, THC, and combination cannabidiol products.

6. Conclusions

There are many potential considerations and areas of exploration with regard to the role of the endocannabinoid system and the urologic and reproductive systems. THC containing, mixed cannabidiol products, and new FAAH inhibitors are being studied for their potential use as treatments for lower urinary tract symptoms. Cannabis use has been shown to adversely affect spermatogenesis and semen parameters and may be a risk factor for testicular germ cell tumors. Differences in THC and cannabidiol products are important for the clinician and while cannabidiol appears to be safe and well tolerated there remains a paucity of research. For the practicing urologist and clinicians treating young men and men's health it is at minimum, important to begin to understand the implications of the endocannabinoid system on the urologic and reproductive systems and consider risks, safety, and potential benefit of cannabinoid-based products.

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Statement of ethics

None.

Conflicts of interest

No conflict of interest has been declared by the author.

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Author contributions

Capodice, Jillian L: Project development, data collection, manuscript writing and editing
Kaplan, Steven A: Project development, manuscript editing.

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