The Potential Ergogenic Effects of CBD and How the ECS Combats Performance Deficits from Overtraining

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Abstract: *Athletes seeking continuous improvements and frequently training at high intensities are limited by their ability to recover. The limiting factors for optimal recovery are often pain, stress, and inflammation and thus, many recovery supplements have been developed to attenuate an excess in these three parameters. Cannabidiol (CBD) is one of the most popular novel supplements that has been advertised for its ergogenic benefits. CBD induces many of its effects through the endocannabinoid system (ECS). The ECS has only recently emerged as an important regulator of homeostasis. Therefore, there is a limited number, if any, of research studies validating the ergogenic effects of CBD in relation to the ECS. This review summarizes the mechanisms of the ECS and how CBD may potentially serve as an effective ergogenic aid through its interactions with the ECS and other body systems. It has been found that athletes may potentially benefit from the anti-inflammatory, antioxidant, pain and stress relieving effects of CBD. The main drawback of CBD supplementation is that a very high dose is required for its benefits. Useful topics of future research include proving or disproving CBD's ergogenic efficacy in vivo.*

Introduction

For athletes trying to make consistent gains, being able to train with greater intensity and frequency is limited by their rate of recovery. Intense exercise intended to break down muscle spikes acute and localized inflammation in the damaged tissue. During rest, the body responds to this localized inflammation and overcompensates the breakdown, eliciting gains in muscle mass and performance over time. However, without proper recovery, one can become overtrained, and as a result, may experience chronic inflammation which is linked to a variety of health complications [(Smith, 2004)]. An athlete who fails to recover within 72 hours of training is categorized to be in the overtrained state [(Kenttä & Hassmén, 1998)]. In this state, despite high effort in training, the returns are maladaptive and come with a variety of side effects including poor performance, fatigue, soreness, and immune system deficits [(Kenttä & Hassmén, 1998)]. Many different recovery agents have been introduced to the athletic/fitness industry in the last few decades to combat overtraining and chronic inflammation.

One study looked at the effects of curcumin on exercise-induced inflammation. This study demonstrated that mice that were supplemented with curcumin displayed reduced increases in creatine kinase and inflammatory cytokines in their blood compared to mice who were not supplemented with curcumin after muscle-damaging exercise [(Davis et al., 2007)]. Increases in blood levels of creatine kinase and inflammatory cytokines are biomarkers of muscle damage and so this study

demonstrated that the supplementation of curcumin protects muscles from exercise-induced damage and speeds up the recovery process. Curcumin is able to enhance the recovery process primarily because of its anti-inflammatory properties which are induced through its association with transcription factors, growth regulators, and cellular signaling molecules [(Davis et al., 2007)]. In comparison to anti-inflammatory drugs, natural anti-inflammatories like curcumin are advantageous because they combat excessive exercise-induced inflammation and performance deficits usually without the side effects of synthetic drugs. One reason curcumin is so advantageous is that it selectively inhibits COX-2, as opposed to the entire prostaglandin pathway [(Goel et al., 2001)]. Many NSAIDs, like Aspirin, cannot selectively target COX-2, and therefore are linked to gastrointestinal distress and kidney damage. These side effects would be highly detrimental to athletic performance. Other NSAIDs that are COX-2 selective still have their drawbacks, like Vioxx, which was taken off the market because it increased the risk of cardiovascular malfunctions. Yet, controlling inflammation is essential for optimizing the health and recovery of an athlete. It appears that natural anti-inflammatories with COX-2 selectivity are superior anti-inflammatory ergogenic aids. There are numerous other natural anti-inflammatories that have proven to modestly improve athletic performance by combating excessive post-exercise pain and inflammation, such as omega-3 fatty acid and tart cherry concentrate [(Jouris et al., 2011; Levers et al., 2015)].

The natural anti-inflammatory supplement that has recently become very popular as an exercise recovery agent is cannabidiol. Cannabidiol, abbreviated to "CBD", is an exogenous phytocannabinoid found in the cannabis plant. Today, CBD comes in many different forms including vapes, tinctures, edibles, capsules, and creams. The therapeutic roles of CBD are long-established, with CBD supplementation treating patients with anxiety, glaucoma, chronic pain, nausea, and epilepsy [(Devinsky et al., 2014)]. CBD has been marketed by thousands of athletes on social media who claim that supplementation has helped them recover faster and train harder (example: @herbstrong on Instagram). Yet, many of these claims lack scientific evidence and are solely based on testimonies. Since CBD in the context of exercise recovery is relatively new, there is limited research available directly validating or disproving CBD as an effective ergogenic aid. However, rational inferences can be made to theoretically prove or disprove CBD's ability to serve as an ergogenic aid by examining how CBD interacts with the various body systems, particularly the endocannabinoid system (ECS). This review will outline the general mechanisms of the ECS, how CBD interacts with this system, and how CBD in conjunction with the endocannabinoid system can potentially improve athletic performance.

The Endocannabinoid System

The body's primary goal is maintaining homeostasis, and it is no doubt that all of the major body systems work together to maintain a constant state of equilibrium. It has only recently been discovered that the ECS plays a critical role in maintaining homeostasis. The ECS is responsible for modulating an extensive network of vital functions such as the nervous, endocrine, immune, and cardiovascular systems, as well as metabolism, appetite, mood, stress, and pain [(Pagotto et al., 2006)]. Although there are limited studies directly verifying that the manipulation of the ECS results in ergogenic effects, numerous studies have outlined how

the ECS affects specific endogenous targets: many of which are linked to improving athletic performance. This is true especially in the context of inflammation and pain since the ECS is highly present in the neuraxis [(Guindon & Hohmann, 2012)].

The ECS consists of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes involved in the synthesis/degradation of cannabinoids. The biological effects of some exogenous cannabinoids (such as tetrahydrocannabinol: THC) and endogenous cannabinoids (naturally produced in the body) are mediated by their actions on the cannabinoid receptors. Some exogenous phytocannabinoids, like CBD, influence the body's endogenous cannabinoids, instead of directly interacting with the cannabinoid receptors [(Leweke et al., 2012)]. The most well-studied cannabinoid receptors are CB1 and CB2, while the most well-studied endocannabinoids are anandamide (N-arachidonoyl ethanolamine, abbreviated to AEA) and 2-arachidonoyl glycerol (2-AG).

Endocannabinoid Synthesis/Degradation

Unlike other neurotransmitters, such as acetylcholine, endocannabinoids cannot be stored due to their high lipophilicity. Instead, endocannabinoids are synthesized "on-demand": precisely regulated by a system of synthesis, release, uptake, and degradation [(Pagotto et al., 2006)]. Both AEA and 2-AG are derived from arachidonic acid. AEA, like other N-acylethanolamines, is primarily synthesized by the transacylation/ phosphodiesterase pathway which involves the enzyme NAT (N-acyltransferase) and the hydrolysis of NAPE (N-arachidonoyl phosphatidyl ethanol) [(Wang & Ueda, 2009)]. For 2-AG synthesis, the cleavage of arachidonic acid from the phospholipid membrane by phospholipase C (PLC) yields diacylglycerol (DAG): a precursor of 2-AG [(Wang & Ueda, 2009)]. The hydrolysis of DAG by diacylglycerol lipase (DAGL) yields 2-AG. Both the synthesis of AEA and 2-AG are calcium and PLC dependent, and thus increasing intracellular calcium concentration or PLC activity promotes the synthesis of these endocannabinoids [(Guindon & Hohmann, 2012)].

Fatty-acid amide hydrolase (FAAH) is the primary enzyme responsible for the degradation of AEA. FAAH hydrolyzes AEA back into arachidonic acid and ethanolamine [(Bari et al., 2006)]. Monoacylglycerol lipase (MGL) is the primary enzyme responsible for the degradation of 2-AG. MGL hydrolyzes 2-AG back into arachidonic acid and glycerol [(Bari et al., 2006)]. Both of these enzymes are very efficient and are the chief limiting factors to ECS-mediated signaling.

Cannabinoid Receptors

Although other cannabinoid receptors exist, CB1 and CB2 are the major receptors of the ECS. CB1 and CB2 are both members of the seven-transmembrane-spanning G protein-coupled receptor family [(Pagotto et al., 2006)]. CB1 is most abundant in the brain and is also found in the peripheral organs such as the thyroid gland, adrenal gland, adipose tissue, liver, and gastrointestinal tract. On the other hand, CB2 is most present in the immune system. The binding and activation of these cannabinoid receptors by either endogenous or exogenous cannabinoids can yield a wide spectrum of effects. Due to its non-planar conformation, CBD has practically no affinity for cannabinoid receptors, unlike THC, whose planar conformation allows it to bind directly to cannabinoid receptors [(Burstein, 2015)]. CBD exerts its effects on the ECS through other mechanisms which will be discussed later in this review.

Pain

The activation of cannabinoid receptors by cannabinoid ligands in the nervous system can produce anti-nociceptive effects by inhibiting excitatory neurotransmitter release and the subsequent depolarization. This was verified by the administration of cannabinoid receptor agonists rescuing inflammatory nociception induced by capsaicin and injectable carrageenan in rats [(Guindon & Hohmann, 2012)]. A similar effect can be produced by drugs that inhibit the enzymatic degradation of endocannabinoids (i.e. pharmacological blockade of FAAH and MGL), which allow the endocannabinoids to accumulate and activate more cannabinoid receptors.

It has been postulated that endocannabinoids act as retrograde messengers in the central nervous system (CNS): postsynaptic endocannabinoids travel to presynaptic sites and inhibit neurotransmitter release (either GABA (gamma-aminobutyric acid) or glutamate) through the activation of CB1 receptors [(Kreitzer & Regehr, 2002)]. Inhibiting the release of GABA would have an overall excitatory effect since GABA is an inhibitory neurotransmitter while inhibiting the release of glutamate would have an overall inhibitory effect since glutamate is an excitatory neurotransmitter. The former occasion has been termed "depolarization-induced suppression of inhibition" (DSI) while the latter occasion has been termed "depolarization-induced suppression of excitation" (DSE) [(Kreitzer & Regehr, 2002)]. Whether the ECS initiates DSI or DSE depends on which would be most beneficial in the specific circumstances.

As mentioned in the example with capsaicin and injectable carrageenan above, the ECS can relieve pain. In this case, the ECS induces inhibitory effects on the nervous system through DSE. This is because the application of capsaicin and injectable carrageenan causes pain, and as a mediator of homeostasis, the ECS would logically decrease the number of excitatory neurotransmitters (glutamate) released. However, the activation of the ECS requires the stimulus to exceed a certain threshold [(Lutz et al., 2015)]. In some sense, the ECS is a "buffer" for neuronal activity: allowing for some level of acute stimuli, but mitigating the stimulus when neuronal excitation becomes prolonged or excessive [(Lutz et al., 2015)]. Repeated exposure to a stressful stimulus causes the ECS to become sensitized for that particular stress. This means that in the future, a lower threshold of stimulation is needed before the ECS is activated [(Patel & Hillard, 2008)]. After sensitization, the ECS can more efficiently mediate habituation to stress by either upregulating the production of endocannabinoids (especially 2-AG levels in the cortical brain regions) or adaptively blunting their enzymatic degradation [(Patel & Hillard, 2008)].

In the murine model, three consecutive days of 5 - 40 mg/kg/day orally-administered CBD was shown to avert the hyperalgesia effects of injectable carrageenan [(Burstein, 2015)]. CBD can enhance the neuro-modulatory function of the ECS as a pain-reliever through a similar mechanism of action to FAAH-antagonistic drugs. CBD decreases the rate of AEA degradation by inhibiting the actions of FAAH and therefore increases AEA levels. This allows for facilitated inhibition of excitatory neurotransmitter release (DSE) [(Leweke et al., 2012)]. This suggests that CBD can be used in athletics to mediate pain: CBD can be administered before intense training sessions so that athletes can "push harder" without feeling as much pain caused by metabolic stress or underlying conditions such as arthritis (25

mg/kg/day dose of CBD decreases TNF-alpha production from collagen-induced arthritis in rats) [(Crowe et al., 2014)]. CBD would also help mediate post-workout muscle soreness after intense exercise, allowing for repeated bouts of intense training.

Stress

The nervous and endocrine systems are commonly paired, working together to regulate homeostasis as one "super system". It is evident that the ECS serves as both a medium of exchange and regulator for the nervous and endocrine systems and so changes to the nervous system would subsequently lead to changes in the endocrine system. The ECS sensitization that occurs in coordination with the nervous system generally decreases the activity of the hypothalamus-pituitary-adrenal (HPA) axis. This leads to the inhibition of the release of corticotropin-releasing hormone (CRH) from the hypothalamus [(Riebe & Wotjak, 2011)]. Reduction in excessive CRH would lead to beneficial downstream effects (i.e. lower cortisol). In addition, inhibiting the release of CRH is also important in terminating the release of corticosterone once a stressful stimulus ends [(Crowe et al., 2014)]. The mediation of stress and cortisol is critical for recovery and muscle growth since chronically elevated cortisol levels can lead to muscle catabolism, fatigue, and weakness [(Wray et al., 2002)]. These stress-stabilizing effects of the ECS have also been shown to elevate mood and prevent stress-eating [(Pagotto et al., 2006)].

Like AEA and 2-AG, CBD can stabilize hormonal stress-responses [(Zuardi et al., 1993)]. Further, CBD has shown the potential to promote positive mood which would help to relieve emotional and mental stress common among competitive athletes. The anti-depressant effects of CBD can be attributed to a 5-HT1a receptor-dependent mechanism: CBD improves serotonin and glutamate cortical signaling in the prefrontal cortex by interacting with the 5-HT1a receptor [(Linge et al., 2016)]. As the 5-HT1a receptor is also the receptor for serotonin, this proves CBD's ability to interact directly with ligand receptors outside of the endocannabinoid system [(Peters et al., 2007)].

CBD can also attenuate physical stresses such as oxidative stress. Intense exercise increases oxidative stress due to the production of reactive oxygen species (ROS) [(Davis et al., 2007)]. The accumulation of ROS can result in cell damage, which can be rescued by antioxidants. CBD is resorcinol, a type of antioxidant phenol, and is capable of scavenging these free radicals, aiding in exercise recovery [(Peters et al., 2007)].

Inflammation

The effects of the ECS on neurons and hormones are primarily through the CB1 receptors, which are more widely dispersed than the CB2 receptors. However, the selective location of CB2 receptors in the immune system allows it to attenuate inflammation through immune cells such as mast cells and phagocytes [(Pagotto et al., 2006)]. The activation of CB2 receptors in these immune cells suppresses the release of pro-inflammatory cytokines and chemokines by disrupting their adenylate cyclase/cAMP pathway [(Crowe et al., 2014)]. Consequently, drugs that inhibit the actions of FAAH and MGL are also anti-inflammatory because they allow for the accumulation of endocannabinoids in the immune tissues.

The anti-inflammatory effects of CBD are very useful for athletes training with high

intensity and frequency because CBD can reduce inflammation through multiple different pathways. First, the surge in AEA levels from CBD supplementation will help activate more CB2 receptors in immune cells and blunt the release of proinflammatory cytokines such as IL-6 and TNF-alpha [(Leweke et al., 2012)]. Secondly, CBD can enhance the downregulation of the A2A adenosine receptor in over-reactive immune cells, protecting nearby tissues of exercise-damaged muscle tissue from chronic collateral inflammatory damage [(Crowe et al., 2014)]. Thirdly, CBD, like other cannabinoids can shift the downstream products of arachidonic acid from pro-inflammatory to anti-inflammatory products. Arachidonic acid, as stated before, can be used to generate the endocannabinoids AEA and 2-AG. However, arachidonic acid is also a preliminary reactant of the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. CBD has shown to promote anti-inflammatory products of the COX and LOX pathways such as lipoxin A4 and 15d-PGJ2 [(Burstein, 2015)].

Limitations of CBD

Despite the multitude of benefits that CBD offers an athlete, there are still significant limitations that should be considered. One might be the social and legal ramifications of promoting CBD. The FDA states that CBD and hemp products are legal in the USA at this time as long as they contain less than .3% THC. But, because of its shared origin to the psychoactive drug, THC, CBD has faced constant negative social perception and still lies in a legal grey area in many countries.

The overarching drawback of CBD is the high dose needed to acquire its benefits. In the murine models mentioned above, very high doses were used: ranging from 5 to 40 mg/kg/day of CBD. Although there are significant physiological differences between rodents and humans, this roughly equates to a 70 kg human consuming between 350 and 2800 mg of CBD per day. In actuality, doses of up to 1500 mg/day have been used safely in humans when researching the therapeutic roles of CBD [(Machado Bergamaschi et al., 2011)]. For a study that found CBD was beneficial for psychosis patients, doses of up to 800 mg/day for several days were used [(Leweke et al., 2012)]. The average tincture bottle of CBD oil advertised by athletes on social media contains somewhere between 250 and 1000 mg of CBD, with a few going up to 5000 mg (herbstrongco.com). The 1000 mg CBD tincture on the herbstrongco.com website costs $65.00 and is representative of the market value of CBD today. The recommended serving size of the CBD oils popularly sold online ranges from about 10 to 200 mg/day. The upper end of this recommendation is barely comparable to the efficacious doses used in research studies where CBD has shown to help with pain, stress, and inflammation. This is perhaps why so many people who try CBD do not feel much benefit from using it. A modest dose of 200 mg of CBD per day would cost an athlete upwards of 100 dollars per week.

Another potential limitation of CBD is the possibility of developing a dependence on CBD. It is a reasonable possibility that using CBD chronically, or using any substance for that matter, can lead to dependency because the body becomes accustomed to its presence. Extended use of CBD could potentially be detrimental to the endogenous mechanisms of attenuating pain, stress, and inflammation. Also, relating to the risk of dependency, is the possibility of addiction. Even though THC and CBD have drastically different effects on the body, the possibility for potentially undiscovered similar effects among phytocannabinoids, in general, must be considered. THC has been shown to

possibly lead to increased risk of consuming illicit drugs in vulnerable individuals [chronic treatment with THC]. Like many illicit drugs, CBD does affect mental and emotional states as shown by its ability to interact with the serotonin receptor, 5HT1a.

Conclusions and Future Research

In theory, CBD exhibits high potential as an ergogenic supplement, attenuating excess pain, stress, and inflammation in a variety of models and seems like a viable alternative to NSAIDs. However, it seems that relatively high doses are needed for its beneficial effects. A valuable topic of research would be directly validating or invalidating the ergogenic effects of CBD as compared to other natural anti-inflammatories such as tart cherry, vitamin C, and curcumin. If CBD proves its efficacy in enhancing exercise recovery in vivo, the exact ergogenic effects of CBD on the various other body systems should be studied since this review has only superficially covered the potential athletic enhancements in the nervous and endocrine systems. This could also potentially uncover other risks associated with CBD supplementation.

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