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Perspective

Cannabidiol in sport: Ergogenic or else?

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ABSTRACT

In the sports domain, cannabis is prohibited by the World Anti-Doping Agency (WADA) across all sports in competition since 2004. The few studies on physical exercise and cannabis focused on the main compound i.e. Δ9-tetrahydrocannabinol. Cannabidiol (CBD) is another well-known phytocannabinoid present in dried or heated preparations of cannabis. Unlike Δ9-tetrahydrocannabinol, CBD is non-intoxicating but exhibits pharmacological properties that are interesting for medical use. The worldwide regulatory status of CBD is complex and this compound is still a controlled substance in many countries. Interestingly, however, the World Anti-Doping Agency removed CBD from the list of prohibited substances – in or out of competition - since 2018. This recent decision by the WADA leaves the door open for CBD use by athletes. In the present opinion article we wish to expose the different CBD properties discovered in preclinical studies that could be further tested in the sport domain to ascertain its utility. Preclinical studies suggest that CBD could be useful to athletes due to its anti-inflammatory, analgesic, anxiolytic, neuroprotective properties and its influence on the sleep-wake cycle. Unfortunately, almost no clinical data are available on CBD in the context of exercise, which makes its use in this context still premature.

1. Introduction

In the sports domain, cannabis is prohibited by the World Anti-Doping Agency (WADA) across all sports in competition since 2004 [1]. However, athletes may use it outside of competition for social, recreational or performance-enhancing purposes [2]. Δ9 Tetrahydrocannabinol (Δ9-THC) may be responsible of some adverse effects in sport performance [1] and this makes cannabis unattractive for athletes.

Cannabidiol (CBD) is another well-known phytocannabinoid present in dried or heated preparations of cannabis [3]. Unlike Δ9-THC, CBD is non-intoxicating but exhibits pharmacological properties that are interesting for medical use. Some preclinical and clinical data have shown anxiolytic, anti-inflammatory or neuroprotective effects for this compound with a relative safe adverse event profile [4]. Interestingly, the WADA removed CBD from the list of prohibited substances – in or

Abbreviations: 2-AG, 2-arachidonylglycérol; 5-HT_{1A}, Serotonin 1A receptor; Aβ, Beta amyloid; AEA, Anadamide; Δ9-THC, Delta 9-tetrahydrocannabinol; CB1, Cannabinoid receptor 1; CB2, Cannabinoid receptor 2; CBD, Cannabidiol; CTE, Chronic traumatic encephalopathy; DOMS, Delayed onset muscle soreness; FAAH, fatty acid amide hydrolase; GDNF, Glial cell line-derived neurotrophic factor; NO, Nitric oxide; NFT, Neurofibrillary tangles; NGF, Nerve growth factor; mTBI, Mild traumatic brain injury; PGE 2, Prostaglandin E2; PPARγ, Peroxisome proliferator-activated receptor γ; TRPV1, Transient receptor potential cation channel subfamily V member 1; WADA, World Anti-Doping Agency

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out of competition since 2018. This recent consideration by the WADA leaves the door open for CBD use by athletes. In the present opinion article, we wish to expose the different CBD properties discovered in preclinical and clinical studies that could be further tested in sport domain to ascertain its utility.

2. Overview of CBD

As specified previously, CBD is one of the most abundant phytocannabinoids derived from cannabis [3]. It can be extracted from the plant or synthetically produced [5]. In commerce, CBD can be found in different products such as oil solution, spray, pills, tincture, e-liquid or balm [3] and the administration route influences CBD pharmacokinetics [6]. Peak plasma concentrations and total drug exposure across time are dose-dependent [6]. Intravenous injection, smoking or inhalation allow to reach more rapidly higher maximum plasma concentrations [6].

Although CBD has a low affinity for the orthosteric binding sites of cannabinoid receptors, CB_1 and CB_2, it may modulate their activities, either by acting as a negative allosteric modulator [7], or by increasing the endogenous levels of the endocannabinoid anandamide (AEA) [8]. The endocannabinoid system is not the only target of CBD. Among other effects, it has been shown that this compound is able to activate the serotonin 5-HT_{1A} receptor [9], the vanilloid TRPV1 receptor [8], the peroxisome proliferator-activated receptor γ (PPARγ) [10].

3. Anti-inflammatory and analgesic effects

Since the 1980s' some studies have shown the anti-inflammatory and analgesic properties of CBD. First reports *in vitro* showed that CBD acts on cells and mediators involved in inflammatory and hyperalgesia processes [11,12]. Briefly, CBD modulates, directly or indirectly, receptors involved in inflammation such as CB2 [13], TRPV1 [14], PPARγ [15] or Adenosine (A2A), a receptor that can down regulate over-reactive immune cells [16]. CBD decreases different markers of inflammation as cytokines, prostaglandin E2 (PGE2), cyclooxygenases activities, nitric oxide (NO) and oxygen-derived free radical productions and reduces the edema [17,18]. CBD also exerts promising analgesic effects in different models of inflammatory and chronic pain by regulating pro-inflammatory agents and affecting targets involved in nociception, such as 5-HT_{1A} and TRPV1 receptors [9,19,20].

Therefore, athletes could benefit from this phytocannabinoid to manage pain, inflammation and the swelling processes associated with injury and CBD could become an alternative to non-steroidal anti-inflammatory drugs, opioids or corticosteroids [21].

Despite the lack of studies on the use of CBD in the management of sports injury, some data suggest its potential utility in osteoarthritis, delayed onset muscle soreness (DOMS), and overuse injury associated with neuropathic pain and concussion.

In an animal model of osteoarthritis, the intra-articular injection of CBD was able to reduce the acute phase of inflammation, by decreasing significantly rolling and adherent leucocytes and synovial hyperaemia [19]. Moreover, CBD was also able to inhibit the mechanosensitivity of joint nociceptors, reducing spontaneous pain induced by joint degeneration or inflammation, and the allodynia or hyperalgesia due to the central sensitization subsequent to neuropathic pain [19]. The anti-inflammatory effect involved CB2 and TRPV1 receptors, while analgesia seemed to be partly TRPV1 receptor-dependent [19]. Indeed, as already shown in a rat model [20], CBD is able to bind and desensitize this mediator of hyperalgesia [8]. Interestingly, TRPV1 sensitization expressed in the muscular thin-fiber afferents is also involved in DOMS which is characterized by muscle fiber damage, inflammation, oxidative stress and hyperalgesia [22]. Thus, we hypothesize that swelling, oxidative stress and inflammation during DOMS could be attenuated by CBD anti-inflammatory properties, triggering *in fine* a decrease in muscular soreness induced by strenuous exercise.

CBD use could be of particular interest in the management of overuse injuries characterized by chronic inflammation, production, persistence of reactive oxygen species [23] and, sometimes, chronic or neuropathic pain [24]. Preclinical studies suggest that CBD possesses therapeutic potential in different types of neuropathic pain by acting on TRPV1 and 5-HT_{1A} receptors involved in pain pathways [25–28]. In these studies, CBD use was able to reduce allodynia or hyperalgesia associated with neuropathic pain by acting on microglia density in the dorsal spinal cord [28]and modulating the periaqueductal grey activity [29]. Additionally, the affective dimension of pain could be reduced by CBD at the level of the rostral anterior cingulate cortex [27] and the dorsal raphe nucleus [9].

Once again, clinical studies are scarces but CBD could be a safer alternative to opioids often used in chronic pain.

4. Anxiolytic effects

Like the whole population, athletes are exposed to anxiety-provoking situation or unjustified fear [30] [31]. Thus, management of anxiety before, during and after a performance is advised in athletes to avoid anxiety disorders and performance decrease and to improve recovery [31]. For this reason, CBD could be useful due to its anxiolytic properties, which were confirmed by preclinical studies in different animal models of innate fear and anxiety-like behavior [30]. In human, CBD is able to decrease perceived anxiety before, during, and after anxiety provoking-situations [32,33]. These effects have been related to 5-HT_{1A} receptor activation and/or indirect potentiation of endocannabinoid transmission [34], and could occur in brain areas involved in anxiety, such as limbic and paralimbic brain structures [32].

Interestingly, several studies indicate that CBD improves also fear memory processes. The compound was shown to impair the acquisition of fear learning in an animal model of schizophrenia [35] and facilitate the processes of fear extinction in healthy humans [36]. These properties may be interesting for athletes subject to post traumatic stress disorder such as after sport-related musculoskeletal injury or concussion [31].

5. Neuroprotective effects

Sports-related concussion is a common injury and is considered as a type of mild traumatic brain injury (mTBI) [37]. Concussed individuals may develop acute signs and symptoms (fatigue, dizziness, headache, irritability memory impairment, concentration difficulty) that may resolve spontaneously following rest [38]. Traumatic brain injury (TBI) induces a complex cascade of events including glutamate excitotoxicity [39]. Recently, Belardo et al. [39] have shown in a rodent model of mTBI that repeated treatment with CBD oil exerts beneficial effects on behavioral dysfunctions (pain, aggressiveness, depressive-like behavior) associated with mTBI. The authors reported also that CBD was able to counteract glutamate excitotoxicity and normalize glutamate and GABA extracellular levels in the medial prefrontal cortex. These results are interesting as the management of mTBI is important and currently no adequate pharmacotherapies are available [39]. Indeed, repetitive mTBI may increase the risk to develop long-term neurological complications such as chronic traumatic encephalopathy (CTE) [40]. CTE is a neurogenerative disease characterized by progressive decline of memory and cognition, depression, suicidal behavior, poor impulse control aggressiveness, and, sometimes, dementia similar to Alzheimer disease (AD) [40]. Indeed, CTE shares some neuropathological features with AD. Neurofibrillary tangles (NFT), hyperphosphorylated tau, beta amyloid (Aβ) deposition, reactive oxidative stress, chronic neuroinflammation are generally present in both AD and CTE [41]. Interestingly, preclinical studies on AD have shown that CBD decreases Aβ-mediated cell death and neurotoxicity in cells [42] and inhibits Aβ-induced tau protein hyperphosphorylation in the mouse hippocampus [43]. CBD is also able to inhibit oxidative stress and neuroinflammation

via the stimulation of the Wnt pathway (involved in the control of neuronal homeostasis) and PPARγ activation [44]. Future preclinical studies are needed to confirm the therapeutic potential of CBD in sport-induced CTE.

6. Sleep disturbances

Already in the 1970's, some authors observed that CBD could affect sleep in humans [45]. This is not surprising as the ECS is involved in the sleep-wake cycle [46]. In murine models, studies found that CBD could be a wake-promoting agent [47] or on the contrary a sleep-inducing agent [48]. The few studies available in humans also suggest that CBD may produce opposite effects according the dose used and act mainly when the sleep – wake cycle is disturbed [45,49,50]. As in animal models, these studies suggest a biphasic effect with lower doses increasing wakefulness and higher doses causing sedating effects that facilitate sleep [51]. Bell-shaped dose-response curves for CBD are, in fact, not unusual [52]. Although the mechanisms underlying these CBD properties must still be clarified, these preliminary observations spotlight CBD as a potential tool for managing athlete sleep and sleepiness. Noteworthy, in some sports, such as Ultra endurance race, the ability to stay awake could be a performance determinant [53]. On the contrary, sleep loss due to anxiety is common in athletes and it impacts negatively cognitive and physiological functions, thus consequently decreasing sport performance [54].

7. Limits

Preclinical studies suggest that CBD could be useful to athletes due to its anti-inflammatory, analgesic, anxiolytic and neuroprotective properties and its influence on the sleep-wake cycle. Unfortunately, almost no clinical data are available on the use of CBD in the context of exercise performance. Therefore, even though CBD seems an interesting molecule with a wide range of properties potentially useful for athletes, it is still premature to advise its use in this context for several important reasons.

Firstly, only few studies are available on CBD use in adults and the recent approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) of botanical CBD as a therapeutic drug against some types of untreatable pediatric epilepsy [3] does not justify its indiscriminate use as a food supplement or for other, yet to be proven, therapeutic indications in humans.

Secondly, concerning the different properties presented in this paper and the reports mentioned, no study compared so far CBD with conventional medications or therapies already approved and used by athletes. It is possible that CBD is less effective or induces undesirable side effects compared to these medications, although it seems to be relatively safe in humans [4]. The most commonly reported side effects in clinical studies were tiredness, diarrhea, and changes in appetite/weight. Additionally, CBD could modulate other physiological processes or systems that may directly or indirectly affect negatively or positively performance, such as food intake [55], metabolism [56], and the cardiovascular [57] or musculoskeletal [58,59] systems.

Thirdly, it is important to consider dosage and administration issues. The desired effects (anxiolytic, neuroprotective, anti-inflammatory, antalgic, etc.) seem to be dose-dependent and future clinical studies will have to define the right dose and route of administration for the expected therapeutic effects, particularly as only few data are available concerning CBD pharmacokinetics [6]. Moreover, it is important to keep in mind that CBD could interact with conventional medications by affecting drug metabolizing enzymes or drug transporters [4]. Thus, at least for now, CBD should not be used along with conventional medications to avoid undesirable effects or alteration of their therapeutic effects.

Fourthly, the regulation of non-standardized CBD products currently available off-the-counter is very poor. Non-clinically approved or not sufficiently controlled preparations purported to contain CBD, which are increasingly present on the market, often report inaccurate data on the actual purity and amount of this compound, or on the concomitant presence of THC. Such products do not always contain the concentration of CBD declared on the label and may contain higher THC amounts [60], which can lead to intoxication or to a positive drug test. Additionally, chemical components present in CBD products could be unsafe. For example, approximatively 8% of vaping-associated lunge injury was subsequent to CBD tinctures [61].

Finally, as previously mentioned, the worldwide regulatory status of CBD is complex and constantly changing. While CBD is legal in many countries as a component of medications, it may be simultaneously illegal as a component of a non-approved *Cannabis* extracts containing > 0.2 % or 0.3 % THC [3]. Thus, CBD use may be either legal or illegal depending on the laws of the country where the athlete performs, even though WADA removed this compound from the list of prohibited substances.

8. Conclusions

In conclusion, preclinical studies have shown that CBD has anti-inflammatory, analgesic, anxiolytic and neuroprotective properties and influence on the sleep-wake cycle. Therefore, CBD can be considered a promising compound in the sport domain to help athletes to manage injury, anxiety, stress or sleep disorders. Nevertheless, the lack of clinical studies in this context, and the scarcity of regulation and control on CBD products, do not allow to advice athletes to use this cannabinoid correctly and safely, at least for the moment. Therefore, there is an urgent need to test CBD in appropriate clinical trials in athletes.

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Declaration of Competing Interest

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