sciendo Acta Marisiensis - Seria Medica 2022;68(4):150-153 DOI: 10.2478/amma-2022-0023

REVIEW

Cannabidiol in the context of sleeping disorders-induced oxidative stress

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Sleep disorders can be the result of psychiatric or neurological conditions, such as post-traumatic stress disorders, depression, anxiety, Alzheimer's disease, Parkinson's disease. At the same time, changes in sleep, known as sleep disorders, are closely related to various metabolic dysfunctions, which in turn are the result of the generation of reactive oxygen species, or otherwise known as oxidative stress. For this reason, cannabinoid derivatives are increasingly used for this purpose. Among the most used are delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD). These agents interact with the endogenous endocannabinoid system, either by direct action on specific receptors, or by increasing the availability of endocannabinoids, modifying particular mental states (anxiety, depression). The results of the studies specified in this article provide promising evidence regarding the positive effects of CBD, which extend beyond the scope of sleep disorders, with possible applications also in the case of the accumulation of reactive oxygen species.

Keywords: cannabidiol, tetrahydrocanabinol, oxidative stress, sleep, post-traumatic stress disorder

Received 29 August 2022 / Accepted 8 September 2022

Introduction

First of all, it must be determined what sleep means and how it can be defined. Thus, from a behavioral point of view, sleep is a state in which the awareness of external stimuli is reduced to a minimum, being essential for survival, it being known that a deprivation of this state is accompanied by mood disorders, alterations of cognitive functions, disorders of the normal functioning of some organs with extension on the disruption of the processes involved in the body's homeostasis.

Physiologically, this state consists of two phases, one known as rapid eye movement (REM) and one as non-rapid eye movement (NREM). They can be distinguished by means of techniques such as electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG). In addition, a differentiation can be made between the two phases of sleep, thus REM sleep is characterized by waves with oscillations of small amplitude but with increased frequency, rapid movements of the eyeballs, hence the name paradoxical sleep, while NREM sleep is characterized by high-amplitude but low-frequency waves (slow wave sleep), and is divided into 3 other subphases [1]. At the same time, the circadian rhythm also intervenes in the regulation of sleep homeostasis, which ultimately influences the depth and duration of sleep. Thus, the influences that can interfere in the sleep balance are associated with various psychiatric and neurodegenerative pathologies [2].

The waking state is under the control of nuclei that form a system known as the ascending reticular activating system (ARAS). These nuclei are represented by locus coeruleus, from which noradrenaline (NE) is released, raphe nuclei from which serotonin (5-HT) is released, pedunculopontine tegmentum and latero-dorsal tegmentum for acetylcholine (Ach), midbrain for glutamate (Glu) and substantia nigra and ventral tegmental area for dopamine (DA). In these nuclei, other cells involved in the state of wakefulness can be mentioned, such as histaminergic cells (posterior hypothalamic area), orexin cells (lateral hypothalamus), cholinergic cells (basal forebrain), neuropeptide Y (NPY) cells (suprachiasmic nucleus), and glutamatergic cells (ventro medial prefrontal cortex) [3].

Oxidative stress and sleep deprivation

As the importance of sleep in the body's homeostasis is presented in multiple works in the literature [4,5,6], its lack, known as sleep deprivation (SD) is directly related to various conditions of a physiological nature, but also of a psychiatric nature (depression, post-traumatic stress, anxiety) [7, 8, 9, 10]. In this sense, the presence of oxidative stress in cases of SD has a special and perhaps underexploited importance. This particular state, known as oxidative stress, can be broadly defined as the inability of endogenous antioxidant systems superoxide dismutase, (SOD), catalase (CAT), glutathione peroxidase (GPx) to neutralize the overproduction of reactive oxygen and nitrogen species (ROS, RNS) [11]. Likewise, the positive effects of oxidative stress should not be excluded, as they are extensively discussed in another article [12]. Therefore, the central nervous system (CNS), due to the high content of polyunsaturated fatty acids (PUFAs) and transition metals (Fe^{2+}, Cu^{2+}), makes the brain an organ susceptible to oxidative stress [13].

Corroborated with those discussed previously, it has been observed in experimental studies that in the case of SD, the plasma level of 8-isoprostane (marker of oxida-

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tive stress) is increased. In addition, the presence of a cycle between oxidative stress and psychiatric symptoms can be discussed. Thus, the increase in the level of oxidative stress markers (such as malondialdehyde, MDA) has been correlated with the induction of anxiety, depression and memory deficit [14]. Also, in studies on people known to have depressive illness or anxiety, the level of MDA has been observed to be increased, while the activity of antioxidant systems is altered [15, 16]. This connection is based on the hypothesis that sleep has antioxidant properties, scavenging free radicals formed during the waking period [17]. At the same time, experimental studies on rats demonstrated that the activity of SOD, CAT, GPx and the level of total glutathione are decreased during periods of SD [18, 19]. It is necessary to mention that the period of SD is also important, thus in the acute phase (6 hours of SD) the level of reduced glutathione (GSH) and GPx activity are increased, but a period of 5-11 days of SD alters the redox homeostasis, with bad consequences also on cognitive function [20, 21]. These data suggest that short periods of SD increase the body's antioxidant function, while prolonged wakefulness generates chronic oxidative stress, and prevents the recovery of antioxidant mechanisms.

At the same time, SD also influences the activity of the immune system, observing an increase in the levels of IL-1, IL-6, IL-17, TNF-α and NF-κB, which have the potential to affect neuronal plasticity [22, 23, 24, 25, 26]. In the regulation of the antioxidant response, with increased expression of SOD and heme-oxygenase (HO), the MAPK pathway is involved [27].

As stated previously, sleep has positive effects on the body, and redox homeostasis is not an abstraction. Moreover, in early development, SD can affect the formation and maturation of neuronal circuits through oxidative-inflammatory mechanisms, effects that can ultimately translate into changes in psychiatric development.

Cannabidiol in sleeping disorders

Because of sleep disorders, globally there are immeasurable costs at the level of society, such as those in the health system, such an estimate was made in the United States, costs that were between 30-107 billion dollars [28] . In this paper, we want to briefly present the effects of using derivatives from the Cannabis sativa plant on sleep. Two of the most widespread constituents of the cannabis plant are represented by delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD). Regarding the location of these two compounds, THC is found in the aerial parts of the plant (especially the sugar leaves, and the buds). It should be noted that the largest amount is found in the flowers of female marijuana plants. Regarding CBD, it can be stated that it is found in the aerial parts of hemp (the flowers, stems and leaves), and various extraction methods can be applied from the raw plant material [29]. The difference between the two, apart from the structural one, lies in the observed pharmacodynamic effects. Thus, THC is characterized by a (dose-dependent) "high" effect, through its biphasic action on CB1 receptors. In contrast, CBD is devoid of psychotropic effects, acts on CB2 receptors and counteracts THC-mediated effects [30]. Also, CBD is characterized by an antagonistic activity towards G protein-coupled receptor 55 (GPR55), and an agonistic activity towards 5-HT1A receptor, α1 adrenergic receptor, and Transient Receptor Potential Ankyrin 1 (TRPA1). In higher concentrations, it also shows affinity for peroxisome proliferator-activated receptor gamma (PPAR-γ) and Transient Receptor Potential Vanilloid (TRPV1 and TRPV2) [31]. In the same note, the presence of the endocannabinoid system should be mentioned, consisting of anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which influences the activity of the sleep-wake cycle [32].

As for the therapeutic use of preparations containing THC, it is applied in the relief of some symptoms and pathologies, pain, nausea, spasm, appetite stimulation, depression, post-traumatic stress disorder (PTSD). Also, some studies support the presence of beneficial effects in the case of patients with opioid withdrawal symptoms [33].

In the case of CBD, it finds applicability in multiple neurological pathologies (epilepsy, Alzheimer's disease, Parkinson's disease), explained both by the direct mechanism of action (influence on the previously mentioned receptors) and indirectly by modulating oxidative stress. Also, other possible off-label uses of CBD are for pain relief, but also for the possible anti-aging effect [34]. Regarding veterinary use, data available in the literature referring to the use of this compound in animals are currently limited and focus on companion animals and horses. However, it is used to relieve pain associated with osteoarthritis, neuropathic pain, respiratory and cardiovascular pathologies, and epilepsy [35].

Regarding the legal status, according to the Controlled Substance Act, CBD is included in Schedule I of prohibited substances. However, hemp is legal and the Food and Drug Administration (FDA) considers that apart from Epidiolex®, no other pharmaceutical formulation is recognized. In Romania, the consumption of cannabis is not prohibited, but its possession and sale are considered illegal activities and considering that CBD is not on the list of prohibited substances, many food supplements are marketed, but without knowing the exact quantity and/or composition [36].

CBD exhibits opposite effects depending on the dose used, thus at low doses stimulatory effects are observed, while high doses are associated with sedative effects, as suggested in multiple studies. In human subjects, the use of 160 mg/day of CBD increased total sleep duration [37, 38, 39]. In cases of insomnia, which is characterized by dissatisfaction with the quantity and quality of sleep, an experimental study on rats conducted by Chagas et al., observed an increase in the percentage of sleep in the group treated with CBD compared to the control group [40].

At the same time, it is suggested that CBD influences the REM sleep period, most likely by improving the state of anxiety, with no effect on the NREM period, effects supported by the fact that CBD reduced insomnia in cases of sleep disorders related to post traumatic-stress disorder (PTSD) [41, 42]. Apart from the fact that CBD also finds applicability in neurodegenerative pathologies, such as Parkinson's disease [43, 44], these diseases are also characterized by REM sleep behavior disorder, in which the patient finds himself in a state of parasomnia, characterized by loss of muscle rigidity associated with nightmares, and CBD has been shown to reduce these symptoms [45].

Prazosin is currently used for nightmares associated with PTSD, but major interest is also being shown in CBD [46]. In an animal model of PTSD, microinjection of CBD into the central nucleus of the amygdala improved REM sleep and minimal effects on NREM [41]. As a mechanism, the anxiolytic effect mediated (by activation) of 5-HT1A receptors, but also the increase of anandamide activity following the blocking of fatty acid amide hydrolase (FAAH) is proposed [47, 48]. Also, in patients with nightmares associated with PTSD, the use of nabilone, a synthetic derivative of THC, increased the number of hours of sleep as well as its quality, and reduced the frequency of reported nightmares [49].

Last but not least, an equally often debated topic is related to the influence of pain on sleep. Thus, chronic pain is responsible for patients' inability to have restful sleep. Thus, the use of the THC/CBD combination in a 1:1 ratio was tried, where it was observed that the number of hours of sleep does not increase, but after a subjective assessment of the patients included in the study, it increases its quality [50]. In a comparative study, in patients with fibromyalgia, nabilone was found to be more effective in improving sleep quality compared to amitriptyline, with the mention that the latter was also found to be effective [51].

Conclusions

In conclusion, CBD used in high doses has beneficial effects on the quality and quantity of sleep, without any signs of intoxication being reported. In addition, the compound finds applicability in the context of neurodegenerative and neurological diseases, but this time discussed in relation to sleep-related symptomatology. It should also be noted that the THC/CBD combination improves sleep characteristics in patients with chronic pain. In this sense, more studies are needed to attest to these beneficial effects on sleep, but also the influence that CBD has on oxidative stress, associated markers and cognitive abilities, directly related to PTSD.

Acknowledgements

This work was supported by the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Research Grant number 510/19/17.01.2022.

Author's contribution

GJ – Conceptualization, Supervision, Writing – review & editing, funding acquisition
CMR – Supervision, Writing – review & editing
AP – Writing and Editing
BEŐ – Writing and Editing
AMT – Writing and Editing
MGB – Writing and Editing
RȘ – Writing and Editing

Conflicts of Interest

The authors declare no financial or other conflict of interest.

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