Exploring the Endocannabinoid System: From Circadian Rhythms to Sleep Regulation and Potential Therapeutic Insights

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The endogenous cannabinoid system (ECS) orchestrates a myriad of physiological processes, ranging from neurodevelopment and immune regulation to mood modulation and sleep-wake cycles. Comprising cannabinoid receptors (CB1 and CB2), endocannabinoid ligands, and enzymes for synthesis and degradation, the ECS governs intricate pathways crucial for maintaining homeostasis. Cannabinoids, both endogenous and exogenous, interact with this system, exerting profound effects on various aspects of human health and behavior. In recent years, substantial research has illuminated the therapeutic potential of cannabinoids, particularly cannabidiol (CBD), in managing sleep disorders. This article explores the intricate interplay between the ECS and sleep architecture, delving into the mechanisms underlying cannabinoid modulation of sleep patterns and the implications for clinical practice. Notably, it synthesizes findings from preclinical and clinical studies, shedding light on the multifaceted pharmacological actions of CBD and its role in targeting diverse pathophysiological pathways implicated in sleep disturbances. Moreover, it underscores the need for further research to establish optimal dosing regimens, long-term safety, and efficacy in diverse patient populations. By integrating CBD into comprehensive treatment strategies alongside cognitive-behavioral therapy for insomnia (CBT-I) and lifestyle modifications, this article advocates for a holistic approach to addressing the multifactorial nature of sleep disorders, thereby offering a promising avenue for enhancing the quality of life for millions worldwide.

Humans have historically used Cannabis sativa for its noted effects, such as euphoria, stress reduction, increased appetite, and potential alterations in anxiety. The isolation of the active component, Δ9-tetrahydrocannabinol (THC), occurred in 1964 [1], yet the major components of the ECS were not identified until the early 1990s. Subsequently, it became well-established that the endocannabinoid system comprises cannabinoid receptors (CBRs), endogenous ligands (like 2-arachidonoylglycerol (2-AG) and N-arachidonylethanolamine (AEA or anandamide), and enzymes responsible for synthesizing and degrading ECS [2–6].

The ECS system's ubiquitous presence in both central and peripheral locations suggest its involvement in various human physiological aspects [7]. Extensive literature links the ECS system not only to mediating feeding behavior, reward,

stress, and anxiety but also to influencing glucose metabolism, pain, immune response, neurological disorders, and depression [8–10].

The endogenous cannabinoid system (ECS) regulates various biological functions, including neurodevelopment, learning, memory, sleep, mood, motor control, appetite, and reward [11,12]. It consists of CB1 and CB2 receptors, metabotropic receptors, endocannabinoid ligands, and synthesizing/ degrading enzymes [13,14]. CB1 receptors are primarily in the CNS, while CB2 receptors are in peripheral tissues and microglia [15–18]. Activation of CB1 and CB2 receptors modulates intracellular pathways, impacting neurotransmitter release and synaptic transmission. THC, the main psychoactive constituent in cannabis, is a partial agonist of CB1 receptors [19–21]. AEA and 2-AG, the primary endocannabinoid ligands, act on both CB1 and CB2 receptors [23-29]. Alterations in ECS constituents are evident in depression, anxiety, schizophrenia, Alzheimer's disease, Parkinson's disease, borderline personality disorder, antisocial personality disorder, and posttraumatic stress disorder [22–27].

Cannabinoids as Potential Treatments for Sleep Disorders: Evidence and Implications

Chronic cannabis use has been demonstrated to disrupt circadian rhythms and diminish the duration of the deepest phase (stage N3) of non-rapid eye movement (NREM) sleep [28,29]. Cannabidiol (CBD) is believed to contribute to circadian rhythm disruption, while THC is thought to be responsible for alterations in sleep architecture [30,31]. The quality of sleep significantly impacts cannabis abstinence or relapse [32,33]. Therefore, the reduced efficacy of cannabis in promoting sleep in chronic users, as well as subsequent sleep difficulties upon cessation of cannabis use, could impede cessation efforts and increase the risk of relapse [33]. In cases of obstructive sleep apnea (OSA) in individuals tolerating continuous positive airway pressure (CPAP) treatment, cannabinoids are being explored as potential treatments [34]. Preclinical studies have suggested that combining oleamide and THC helps stabilize respiration across sleep stages and maintain autonomic stability during sleep [35]. Clinical investigations have found that the synthetic THC dronabinol lowered the apnea-hypopnea index, deemed safe for short-term obstructive sleep apnea treatment [30,34]. Patients with posttraumatic stress disorder (PTSD) experiencing nightmares were administered the synthetic endocannabinoid receptor agonist nabilone, which reduced nightmare frequency compared to a placebo [36–38]. Additionally, a single study investigating the effects of cannabidiol on REM behavior disorder reported improved symptoms [30]. Based on these findings, cannabinoids could serve as alternative treatments for various sleep disorders [39].

Exploring the Role of Peripheral Endocannabinoid System in Circadian Rhythms and Metabolism

While endocannabinoids can be measured in blood lipid extracts, the specific origin of peripheral concentrations of serum ECS remains unclear [8]. Emerging data suggests that circulating ECS may derive from various tissues housing the enzymatic machinery responsible for ECS synthesis [8], including the brain, gut, muscle, pancreas, and adipose tissue [7]. Compounds similar to ECS, such as N-acyl ethanolamines (NAEs) like oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), structurally resemble AEA but do not bind cannabinoid receptors. These lipids, produced by similar enzymatic machinery as AEA, can also be measured in circulation [8] and might produce similar physiological effects without binding C receptors [40].

The purposeful release of these ECS and NAEs into circulation as physiological signals or their role merely as markers of tissue endocannabinoid tone remains uncertain. A recent focus on the ECS system's ability to control feeding, body weight, and peripheral metabolism in obese animals has made it a target for potential anti-obesity drugs [41–44]. Notably, rimonabant, a selective CB1 receptor blocker

approved in Europe as an appetite suppressant, showed beneficial metabolic effects beyond weight loss but was withdrawn due to severe psychiatric adverse effects [45]. Despite extensive research on the ECS system, its relation to the circadian system and sleep, which significantly modulate mammalian metabolism, mood, and behavior, has been largely overlooked. Limited studies have explored circadian fluctuations in the ECS system or how the ECS system regulates circadian rhythms [46]. Early research hinted at the ECS system's role in modulating brain temperature rhythms [47], and recent studies demonstrate diurnal variations in CBRs and ligands in rat brains and liver [48,49]. However, comprehensive investigations of the 24-hour variations in ECS activity are required to unravel links between ECS, circadian disturbances, sleep regulation, and their implications on behavior and physiology.

Exploring the Role of Palmitoylethanolamide and Cannabinoids in Sleep Disorders: Mechanisms, Implications, and Challenges

Among the main commercially marketed compounds, one of the most widely used for sleep disorders is palmitoylethanolamide (PEA). Findings from literature highlighted that PEA notably reduced the time taken to fall asleep in individuals experiencing sleep latency issues. This decrease in sleep onset latency might be attributed to various physiological responses triggered by PEA [50]. An elevation in Anandamide (AEA) levels through the endocannabinoid system, alterations in inflammatory signaling, or a reduction in pain sensitivity could collectively facilitate quicker sleep [51]. Sleep disturbances have been associated with inflammation and inflammatory signaling, contributing to potential disruptions in sleep patterns [52,53]. Hence, changes in inflammation sensitivity, whether in signaling pathways or receptor activity, might influence sleep quality [54]. Nonetheless, since this trial didn't measure AEA concentrations or observe alterations in serum cytokines, these conclusions remain speculative. Supplementation with PEA improved the duration to attain full wakefulness and enhanced cognitive function upon waking [50,55]. This holds particular significance considering that sleep inertia and daytime grogginess are common side effects associated with many pharmaceutical sleep disturbance treatments [50]. The combined observations of the PEA group falling asleep quicker and reporting increased alertness and wakefulness upon waking, compared to the placebo group, suggest that future investigations on PEA and sleep should target populations facing difficulties both in falling asleep and waking up [50]. Understanding the intricate interplay between cannabinoids and sleep architecture is essential for elucidating their therapeutic potential in managing sleep disorders. Chronic cannabis use has been associated with alterations in sleep architecture, including disruptions in the REM-NREM sleep cycle and reductions in total sleep time and sleep efficiency [31]. These effects are believed to be mediated by the endocannabinoid system, which modulates neurotransmission and neuroendocrine signaling pathways involved in sleep regulation [11]. Cannabis contains over 100 different cannabinoids, each exerting distinct effects on sleep architecture and quality [56]. THC, the primary psychoactive component of cannabis, has been shown to exert biphasic effects on sleep, initially promoting sleep onset but subsequently disrupting sleep continuity and architecture [11,29]. Chronic THC use has been associated with reductions in REM sleep duration and alterations in NREM sleep stages, particularly a decrease in the duration of stage N3 sleep, also known as slow-wave sleep (SWS) [57]. Conversely, CBD, a non-intoxicating cannabinoid, has demonstrated potential therapeutic effects in ameliorating sleep disturbances associated with anxiety, chronic pain, and neurodegenerative disorders [58,59]. CBD has been shown to exert anxiolytic, analgesic, and neuroprotective properties, which may indirectly improve sleep quality by alleviating underlying conditions contributing to sleep disturbances [60,61]. The endocannabinoid system, comprising cannabinoid receptors (CB1 and CB2) and endogenous ligands such as AEA and 2-arachidonoylglycerol (2-AG), plays a pivotal role in regulating diverse physiological processes, including sleep-wake cycles [11,62].

Endocannabinoid signaling influences neurotransmitter release, synaptic plasticity, and neuroinflammatory responses, all of which contribute to the modulation of sleep patterns and homeostasis [11]. Despite the therapeutic potential of cannabinoids in managing sleep disorders, several challenges and limitations warrant consideration. The psychoactive effects of THC, including impairment of cognitive function, memory consolidation, and psychomotor performance, pose significant safety concerns, particularly in vulnerable populations such as adolescents and individuals with psychiatric disorders [63]. Moreover, the long-term effects of chronic cannabis use on sleep architecture and quality remain poorly understood, with conflicting evidence regarding its impact on sleep duration, continuity, and architecture [29]. Longitudinal studies examining the effects of chronic cannabis exposure on sleep parameters are needed to elucidate its potential risks and benefits in the context of sleep health [64].

Conclusion

Therapeutic Potential of CBD in Sleep Disorders: Mechanisms, Challenges, and Future Directions

In conclusion, cannabinoids, particularly CBD, represent a promising avenue for the management of sleep disorders, offering a novel therapeutic approach for individuals experiencing sleep disturbances [65]. The multifaceted pharmacological actions of CBD, coupled with its favorable safety profile and potential for alleviating a wide range of symptoms, position it as a promising candidate for addressing various sleep-related issues [66]. However, despite the growing body of evidence supporting the therapeutic potential of CBD in sleep disorders, further research is needed to fully elucidate its mechanisms of action and optimize its clinical utility [58,67]. CBD, a non-intoxicating component of cannabis, has garnered considerable attention for its purported therapeutic effects across a spectrum of medical conditions, including anxiety, chronic pain, epilepsy, and sleep disorders [68]. Unlike THC, CBD does not induce psychoactive effects, making it an attractive option for patients seeking symptom relief without the cognitive impairment associated with traditional cannabis use [69]. Several preclinical and clinical studies have provided insights into the potential mechanisms underlying the sleep-promoting effects of CBD [31,61,70]. CBD has been shown to modulate endocannabinoid signaling, interact with serotonin receptors, and regulate GABAergic neurotransmission, all of which play crucial roles in sleep-wake regulation and homeostasis [11,71]. By enhancing serotoninergic tone and promoting GABAergic inhibition, CBD may exert anxiolytic and sedative effects, thereby facilitating sleep onset and maintenance [72]. Moreover, CBD possesses anti-inflammatory, neuroprotective, and antioxidant properties, which may contribute to its efficacy in mitigating underlying factors contributing to sleep disturbances, such as neuroinflammation, oxidative stress, and neuronal hyperexcitability [73]. By targeting multiple pathophysiological pathways implicated in sleep disorders, CBD holds promise as a multifaceted therapeutic agent for improving sleep quality and overall well-being [74]. Clinical trials investigating the efficacy of CBD in sleep disorders have yielded promising results, albeit with some inconsistencies and methodological limitations. Studies evaluating the effects of CBD on insomnia, sleep apnea, REM behavior disorder, and other sleep-related conditions have reported improvements in subjective sleep parameters, including sleep quality, sleep latency, and sleep duration [75]. However, larger scale randomized controlled trials with standardized outcome measures and longer follow-up periods are needed to establish the safety, efficacy, and optimal dosing regimens of CBD for different sleep disorders [76]. One area of particular interest is the potential use of CBD as an adjunctive therapy for sleep disorders refractory to conventional treatment approaches. Patients with treatment-resistant insomnia, restless leg syndrome, and circadian rhythm disorders may benefit from the addition of CBD to

their therapeutic regimen, either as monotherapy or in combination with existing pharmacological interventions [65]. By targeting complementary pathways involved in sleep regulation, CBD may offer synergistic effects and enhance the overall therapeutic response in refractory cases [77]. Furthermore, CBD's favorable safety profile and low risk of adverse effects make it an attractive option for long-term use in chronic sleep disorders [78,79]. Unlike conventional sedative-hypnotic medications, which are associated with tolerance, dependence, and withdrawal symptoms, CBD exhibits minimal potential for abuse and addiction, making it a safer alternative for sustained sleep management [80,81]. Conversely a systematic review of AminiLari and colleagues examined 39 trials involving 5100 patients to assess the effectiveness of medical cannabis for impaired sleep, finding that while it may offer modest improvements in sleep quality and disturbance for chronic pain patients, it also poses risks of adverse effects such as dizziness and somnolence. In conclusion, medical cannabis shows promise for alleviating sleep issues in individuals with chronic pain, though the benefits may be limited, and caution is warranted due to potential side effects [82].

In addition to its potential as a standalone therapy, CBD may also complement other non-pharmacological approaches to sleep hygiene and behavioral interventions [83–85]. Integrative treatment strategies incorporating CBD, cognitive-behavioral therapy for insomnia (CBT-I), relaxation techniques, and lifestyle modifications could offer holistic and personalized approaches to addressing the multifactorial nature of sleep disorders [86,87]. The research on the potential implications of CBD in managing sleep disorders presents a promising avenue for clinical practice [58,88]. CBD emerges as a novel therapeutic agent with significant potential to address sleep disturbances effectively, offering a safe and well-tolerated alternative to conventional pharmacotherapy.

The therapeutic role of CBD in sleep disorders holds substantial promise for clinical applications. Its multifaceted pharmacological actions, including its interactions with endocannabinoid signaling, serotonin receptors, and GABAergic neurotransmission, suggest that CBD can play a pivotal role in modulating sleep-wake regulation and promoting sleep quality. The favorable safety profile of CBD, coupled with its minimal potential for abuse and addiction, positions it as an attractive option for long-term use in chronic sleep disorders. Moreover, CBD's ability to target multiple pathophysiological pathways implicated in sleep disturbances, such as neuroinflammation, oxidative stress, and neuronal hyperexcitability, underscores its potential as a multifaceted therapeutic agent for improving overall sleep quality and well-being. Clinical trials investigating the efficacy of CBD in sleep disorders have yielded promising results, although further research is needed to establish optimal dosing regimens, long-term safety, and efficacy in diverse patient populations. Integrating CBD into comprehensive treatment strategies, alongside cognitive-behavioral therapy for insomnia (CBT-I) and lifestyle modifications, offers a holistic approach to addressing the multifactorial nature of sleep disorders.

In summary, CBD holds immense promise as a novel therapeutic intervention for managing sleep disorders, offering clinicians and patients alike a safe, effective, and well-tolerated alternative to conventional pharmacotherapy [58]. By harnessing the therapeutic potential of CBD and advancing our understanding of its role in sleep regulation, we can improve the management of sleep disorders and enhance the quality of life for millions worldwide.

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