

The Role of Endocannabinoid System in Sleep Deprivation-Induced Psychosis-Like Symptoms through Hampering Prepulse Inhibition; A Hypothesis

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Abstract

The interaction between endocannabinoid (eCB) system with in key brain structures such as hippocampus, amygdala and prefrontal cortex and sleep deprivation (SD)-induced psychosis has been less studied. The present hypothesis revolves around the question whether altered chemical dynamics within the eCB system with the resultant impact on cannabinoid receptors in key cortical hubs would impact SD-induced psychosis-like symptoms. Having this investigated research is expected to pave the path towards identifying newer drug targets namely for schizophrenia.

Keywords: endocannabinoid system; sleep deprivation; animal models; psychosis-like symptoms; drug development

The hypothesis

With today's competitive life, sleep deprivation (SD) has been turned to a constantly-growing issue leaving negative impact on overall health at personal and societal levels(1). Overwhelming stress, poor sleep hygiene habits, shift works, psycho-behavioral or medical problems, dysregulated endocrine system, the use of stimulant medications and substance abuse are among the factors which have collectively contributed to the increasing prevalence of sleep insufficiency worldwide(2, 3).

When becomes a chronic issue, the clinical consequences of untreated sleep disorders are substantial wherein hypertension, ischemic heart disease, heart failure, cerebrovascular accidents, obesity, psychiatric conditions and cognitive predicaments become underway(4). Some recent studies have proposed acute SD as an experimental animal model for psychosis(5). The state of total SD has been documented to result in perceptual disturbances such as hallucinations and illusions, thought disorder, delusions, and fear-related symptoms

in human(5). Additionally, SD is known to cause psychosis-like reduction in prepulse inhibition (PPI) in a rat model(6).

Recently, longitudinal and postmortem studies have shown that the endocannabinoid (eCB) system might be involved in neuropsychiatric disorders like schizophrenia(7). On the other hand, cannabis consumption may induce a psychotic state in normal individuals and worsen psychotic symptoms of schizophrenia patients(8). The endocannabinoid (eCB) system is known to be involved in psychoactive effects of cannabis. This system contributes to a variety of physiological processes such as appetite, pain perception, mood regulation, and cognition(9). As for appetite for instance, we know rats which undergo SD tend to have an increased food intake and this might be in some ways related to the effect of SD left on the eCB system(10).

The eCB system hosts endogenous cannabinoids such as anandamide (N-arachidonylethanolamide, (AEA), 2-arachidonoylglycerol (2-AG) and its structural analogue 2-oleoylglycerol (2-OG). It also nests the enzymes that synthesize and degrade endocannabinoids, including fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL) as well as CB1 and CB2(11). Recent findings propose that dysregulation in the eCB system may underpin the pathophysiology of schizophrenia(8). As such, therapeutic approaches in schizophrenia may at least partly depend on modulating eCB dynamics. For instance, cannabinoid drugs impair PPI in an animal model of schizophrenia(12, 13).

Continuous exposure to tetrahydrocannabinol (THC) has been shown to upregulate the eCB system, leading to long-lasting neurobiological changes in various regions of the brain(14). Also after sleep restriction, increase in endocannabinoid level is amplified(15) and levels of the eCB system compound 2-oleoylglycerol (2-OG) increased(16). By acting on cannabinoid receptors, THC also influences the release of neurotransmitters involved in the pathophysiology of schizophrenia, including dopamine and glutamate(17). As a result, heavy consumption of cannabis most often has harmful effects on an individual's health and can lead to the development of psychosis and schizophrenic-like symptoms(18, 19). The above hypothesized interplay is depicted in Figure 1.

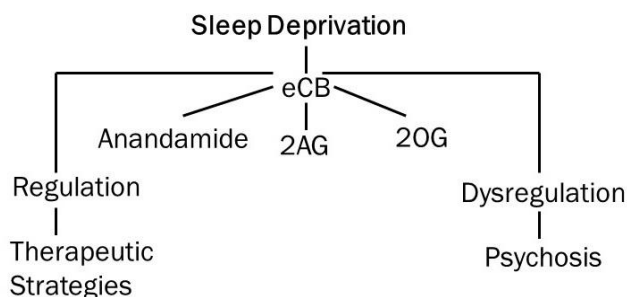


Figure 1. The hypothesized interplay between eCB system and its dysregulation in relation with sleep deprivation and psychosis. eCB: endocannabinoid system, 2AG: 2-arachidonoylglycerol, 2OG: 2-oleoylglycerol

Despite the above, the interaction between SD, psychosis, and eCB system has not been sufficiently studied yet. It is worth to investigate the mechanisms through which SD induces

psychosis-like symptoms. The question whether total and paradoxical SD impair the PPI in rats and how eCB system is involved in such impairment needs to be spotlighted in future studies. To this aim, we hypothesize that measuring circulating levels of 2-AG, 2-OG and AEA, FAAH, MAGL and CB1 in the hippocampus, amygdala and PFC using real-time PCR and HPLC would potentially provide a clue. Research may be pursued by blocking the eCB system systemically after SD using eCB receptors antagonists to identify if SD still hampers the PPI. Continued research would also need to investigate if antipsychotic and cognitive enhancing drugs, such as cannabidiol and modafinil reverse the effects of SD upon PPI impairments.

Conclusion

What already known is that SD per se is considered as a validated model for schizophrenia(5, 6). Meanwhile, what is yet to be explored is that how eCB system is involved in the process of psychosis-like behaviors induced by SD and what the mostly involved neurobiochemical elements are within the system. Having this addressed, the outcome may potentially provide novel insights into the eCB neurobiochemical dynamics implicated in the pathogenesis of schizophrenia. While other potential culprits such as genetic predisposition play key parts in the pathogenesis of schizophrenia, there are still much to be addressed with regards to the neurobiochemical interplay between sleep loss, schizophrenia and eCB system.

The present paper hypothesizes that eCB system might be critically involved in regulating the effects of SD on impairing PPI and the subsequent psychosis-like symptoms. The identification of eCB molecular pathways implicated in the deleterious psychiatric effects of SD in an animal model could potentially yield new targets for the development of more effective drugs.

Conflict of Interest

Authors declared no conflict of interest upon preparation of the resent work.

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