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Systematic Review/Meta-Analysis on the Role of CB1R Regulation in Sleep-Wake Cycle in Rats

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 May 2024 and was last updated on 06 May 2024.

INTRODUCTION

Review question / Objective (1) Subjects: In vivo studies that record the sleep-wake cycle of experimental animals under controlled environments (e.g., light-dark cycles). There is no restriction on the breed of rats; (2) Intervention: Studies using CB1R agonists or antagonists, at any dosage and through any administration route; (3) Control Group: Studies using saline or solvent as controls, with other conditions remaining consistent; (4) Outcome Indicators: W time, NREM sleep time, REM sleep time, sleep latency, as well as duration and frequency of each sleep stage after drug administration; (5) Study Design: Randomized controlled animal experiments, regardless of whether blinding or allocation concealment is reported.

Condition being studied Sleep is a fundamental aspect of health, essential for regulating metabolism, mood, performance, memory

consolidation, learning, and appetite. Chronic sleep deprivation has been associated with various adverse health effects, including diabetes, obesity, hypertension, and cardiovascular diseases. Additionally, research has linked chronic sleep deprivation to increased pain sensitivity, resulting in a higher incidence of postoperative pain and an increased risk of chronic pain. Therefore, improving sleep quality is a consistent priority for clinical decision-makers and healthcare providers. Sleep and wakefulness (W) represent two distinct functional states of the brain. The sleep-wake cycle is classified into W, non-rapid eye movement (NREM) sleep, also known as slow-wave sleep, and rapid eye movement (REM) sleep, also known as paradoxical sleep. The regulation and maintenance of these states are influenced by circadian rhythm and external environmental changes.

Research on the pharmacological effects of the cannabinoid system on the circadian sleep cycle is currently gaining momentum. Cannabinoids encompass natural, endogenous, and synthetic

cannabinoids. Their primary mechanism of action involves activating the G-protein-coupled receptors cannabinoid type-1 (CB1R) and cannabinoid type-2 (CB2R). CB1R is predominantly expressed in the central nervous system, with a wide distribution across the basal ganglia, cerebral cortex, cerebellum, olfactory bulb, and hippocampus. Alternatively, CB2R is mainly located in the peripheral immune system, such as the spleen, bones, and skin. Multiple studies have demonstrated the significant role CB1R plays in regulating the sleep-wake cycle. For example, Pérez-Morales et al. showed that injecting an endogenous CB1R agonist, 2-arachidonoylglycerol (2-AG), into the lateral hypothalamus of Wistar rats increased the frequency of REM sleep, extended the average duration of NREM sleep, and prolonged total sleep time. The CB1R antagonist AM-251 reversed these effects when administered alongside 2-AG. Similarly, Bogáthy et al. found that intraperitoneal injection of AM-251 in Wistar rats lengthened W but shortened both NREM and REM sleep, without significantly altering sleep latency. Murillo-Rodríguez et al. showed that injecting CB1R antagonist SR141716A into sleep-deprived rats heightened their alertness and reduced sleep recovery following prolonged W.

Nevertheless, studies on CB1R regulation in rodents have yielded conflicting results. Some experiments suggest a minor effect of CB1R on NREM sleep, while others find no significant impact on sleep duration in rats. To address this, this study compiled related research from Chinese and English databases to comprehensively investigate and report the effects of CB1R regulation on the sleep-wake cycle in rats following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This approach aims to offer novel insights and evidence-based guidance for the clinical treatment of sleep disorders, as well as the comorbidity of sleep deprivation and pain.

METHODS

Participant or population Subjects: In vivo studies that record the sleep-wake cycle of experimental animals under controlled environments (e.g., light-dark cycles). There is no restriction on the breed of rats.

Intervention Intervention: Studies using CB1R agonists or antagonists, at any dosage and through any administration route.

Comparator Control Group: Studies using saline or solvent as controls, with other conditions remaining consistent.

Study designs to be included Study Design: Randomized controlled animal experiments, regardless of whether blinding or allocation concealment is reported.

Eligibility criteria Exclusion Criteria (1) Non-Chinese or non-English literature; (2) Studies involving CB1R knockout experiments; (3) Studies that involve simultaneous use of CB1R agonists and antagonists in animals; (4) Studies utilizing modulators that act indirectly on CB1R; (5) Studies with inconsistent outcome measures or incomplete data; (6) Purely descriptive studies, personal experiences, conference materials, or similar; (7) If the same study data is published more than once, only the most recent publication is included.

Information sources Primary computer-based searches were conducted in four English databases, namely, Cochrane Library, PubMed, Web of Science, and Embase, alongside four Chinese databases, including the Chinese Biomedicine Literature Database (CBM), China National Knowledge Infrastructure, WanFang Data, and VIP. Additionally, supplementary searches were performed on academic platforms such as Google Scholar, Baidu Scholar, and Muchong.com, along with backward tracking of references from the included studies. The search period spanned from the inception of the databases to November 2023, with the supplementary search extending to January 2024.

Main outcome(s) Outcome Indicators: W time, NREM sleep time, REM sleep time, sleep latency, as well as duration and frequency of each sleep stage after drug administration.

Quality assessment / Risk of bias analysis The quality of the included studies was evaluated using the SYRCLE's Risk of Bias tool for animal studies. This tool contains ten items and assesses various bias types, including selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding of researchers), detection bias (random outcome assessment, blinding of assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other sources of bias. This tool is suitable for assessing bias in animal intervention studies. In this study, the evaluation results were categorized as "low risk," "uncertain risk," or "high risk." Two trained evaluators independently conducted this

assessment, cross-checking for accuracy. In cases of disagreement, a third party was consulted for resolution.

Strategy of data synthesis The study employed RevMan 5.3 software from Cochrane to conduct meta-analyses on the extracted outcome measures. The standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for continuous data to measure effect sizes. Data presented in graphical form were extracted using the Engauge Digitizer software. If studies presented the sleep-wake cycle in percentages (%), the data was converted to time (min) using Excel. When the number of rats in the experimental group was not specified, the minimum reported number was used to reduce weighting. All meta-analysis results were displayed as forest plots. Heterogeneity among studies was assessed (with a significance level of $\alpha = 0.1$), using the I^2 statistic. If $P \leq 0.1$ and $I^2 > 50\%$, significant heterogeneity was assumed, prompting the use of a random-effects model. If $P > 0.1$ and $I^2 < 10$, Beggs Test was employed to detect publication bias. The significance level for the meta-analysis was set to $\alpha = 0.05$, with P-values below this threshold indicating statistically significant differences.

Subgroup analysis Because of the limited number of studies, a subgroup analysis of the dose-response relationship of CB1R modulators was not feasible.

Sensitivity analysis Sensitivity analysis was conducted by removing one study at a time to assess its impact on the overall effect, revealing stable outcomes.

Country(ies) involved China.

Keywords CB1R Regulation; sleep-wake cycle; Systematic Review.

Contributions of each author

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