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Neurobehavioral and physiological changes in pregnant rats following REM sleep deprivation model

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ABSTRACT

Objective: Sleep is a fundamental physiological process regulated by complex interactions, with interleukins (ILs) playing a key role in linking the immune system to sleep-wake cycles. Disruptions in this balance, often involving proinflammatory cytokines like IL-1β and IL-6, contribute to various sleep and neuroinflammatory disorders.

Materials and Methods: This study investigated the effects of REM sleep deprivation (SD) using the multi-platform technique in pregnant rats for 21 days, followed by behavioral and immunological assays. Rats were subjected to 18 hours of deprivation daily but allowed 6 hours of recovery sleep.

Results: Behavioral testing showed that SD rats exhibited significantly lower locomotor activity (distance and ambulatory activity) compared to controls, indicating reduced general motor functions. However, the Elevated Plus Maze revealed no significant difference in anxiety-like behavior between the groups.

Conclusion: ELISA results demonstrated a statistically significant elevation of both IL-15 and the anti-inflammatory cytokine IL-10 in the SD group. The elevated IL-15 level is interpreted as a marker of potential nerve damage. The increase in IL-10 is suggested to be a counter-regulatory response to rising pro-inflammatory markers such as IFN-γ, which was also found to be higher, though not significantly.

Keywords: Sleep deprivation, Interleukin, Neuroinflammation

1. INTRODUCTION

Sleep is a fundamental physiological process essential for maintaining overall health and cognitive function. It is intricately regulated by complex interactions between the nervous, endocrine, and immune systems. Emerging evidence highlights the pivotal role of cytokines, particularly interleukins (ILs), in linking the immune system to sleep regulation. ILs act as molecular mediators that influence both sleep-wake cycles and neuroinflammatory responses, establishing a bidirectional relationship between immune activity and sleep [1]. Disruptions in this delicate balance, caused by chronic inflammation or immune dysregulation, are increasingly recognized as contributors to various sleep disorders and associated conditions, such as insomnia, neurodegenerative diseases, and mood disorders [2]. Understanding how ILs regulate sleep provides valuable insights into the pathophysiology of these conditions and offers potential therapeutic avenues for intervention. The interplay between sleep and neuroinflammation is orchestrated by ILs, a group of cytokines that regulate immune responses and neural activity within the central nervous system (CNS). Sleep disturbances often occur alongside neuroinflammatory disorders, creating a bidirectional relationship where neuroinflammation disrupts sleep architecture, and poor sleep exacerbates inflammatory processes [2]. ILs represent a broad family of cytokines that act as central mediators in the orchestration of both innate and adaptive inflammatory immune responses [3]. Pro-inflammatory ILs, such as IL-1β, IL-6, and TNF-α, are pivotal in mediating the body's response to stressors, including sleep loss, while anti-inflammatory cytokines like IL-10 and IL-4 serve as critical counterbalances [4, 5]. IL-6 has garnered significant attention because its elevated levels have been repeatedly linked to sleep disturbances, mood alterations, and impaired cognitive performance. The dysregulation of these IL signaling pathways is thought to reflect an underlying shift in the immune milieu, which, over time, may predispose affected individuals to a range of chronic diseases, including cardiovascular disorders, diabetes, and neurodegeneration [6]. The mechanistic basis by which sleep deprivation (SD) induces alterations in IL expression involves

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several interrelated pathways. Experimental models indicate that acute SD can enhance cellular inflammatory responses via Toll-like receptor (TLR) signaling, particularly TLR-4 activation, which leads to increased production of pro-inflammatory cytokines such as IL-6 and TNF-α from monocytes and other immune cells [6, 7]. These molecular events collectively result in an environment that is primed for inflammation, with ILs serving both as markers and mediators of the adverse physiological consequences of sleep deficiency [8]. The impact of sleep loss on IL dynamics appears to be influenced by the duration and intensity of the SD. While acute SD, whether complete or partial, has been consistently associated with transient increases in cytokine production (notably IL-6), chronic sleep impairment or fragmentation appears to result in a more sustained dysregulation of these cytokine networks [8, 9]. Among the myriads of ILs implicated in sleep-related immune alterations, IL-6 has emerged as a central player. Multiple studies have documented that acute SD leads to an elevation in circulating IL-6 levels, which in turn correlates with alterations in mood, increased perception of effort during exercise, and cognitive impairments such as diminished memory performance [3]. Evidence from studies in individuals with insomnia comorbid with depression indicates that alterations in anti-inflammatory cytokine profiles—such as reductions in IL-4, IL-5, IL-10, and IL-13—are associated with poorer cognitive performance and more severe depressive symptoms [5]. Produced by regulatory T cells (Tregs), macrophages, and dendritic cells, IL-10 suppresses the production of pro-inflammatory cytokines such as IL-6, IL-17, and TNF-α by downregulating nuclear factor kappa B (NF-κB) signaling and enhancing the expression of suppressor of cytokine signaling (SOCS) proteins [10]. Elevated levels of IL-10 are associated with reduced microglial activation, decreased oxidative stress, and stabilization of the blood-brain barrier (BBB), all of which contribute to improved sleep quality [11]. IL-17, primarily produced by Th17 cells, amplifies inflammatory responses in the CNS by recruiting additional immune cells through chemokine release, which perpetuates inflammation and disrupts sleep-regulating neural networks [12]. Additionally, IL-23, an upstream regulator of IL-17, exacerbates neuroinflammation by promoting IL-17 secretion, leading to chronic sleep disturbances often observed in autoimmune conditions such as psoriasis and rheumatoid arthritis [13]. The aim of this study was to investigate the effects of gestational sleep deprivation (GSD) throughout the entire gestational period on the inflammatory profile and behavioral responses of pregnant rats. We hypothesized that chronic sleep restriction during pregnancy would induce a pro-inflammatory state and alter anxiety-like behaviors in the maternal subjects, as reflected by changes in systemic cytokine levels and performance in behavioral paradigms.

2. MATERIALS and METHODS

Animals

This study protocol was approved by the Marmara University Local Ethics Committee for Animal Experiments (Protocol Code: 33.2024mar). A total of 12 female Wistar rats used in this study, weighing between 270 and 300 g, were provided by the Marmara University Experimental Animals Research and Implementation Center. The animals were randomly assigned to two experimental groups: (1) the Control group (n=6), which was maintained under standard laboratory conditions, and (2) the REM SD group (n=6). In the REM SD model (multi-platform technique), pregnant animals were placed on identical cylinder blocks with a height of 16 cm and a base diameter of 6.5 cm in a polyurethane pool with a water height of 15 cm and a diameter of 75 cm. The distance between the blocks in the pool, which will have a total of 10 cylindrical blocks, was 11 cm. The relevant blocks extend 1 cm above the water level. There was one empty block for each animal. Animals were able to move between the blocks. During each experimental procedure, there were at least two animals in the pool to avoid social isolation. Unlimited access to water and food was provided with a mechanism suspended from above. The animal entering the REM sleep phase lost muscle tone, fell into the water, and woke up (Figure 1). The experiment was carried out at room temperature. The water temperature was the same as room temperature. The SD protocol was initiated on gestational day 1 (G1) and continued throughout the entire pregnancy period (21 days) until parturition. For 21 days, pregnant animals were exposed to REM SD for 18 hours per day, including the dark phase (Start: 16:00, End: 10:00). They were allowed to sleep in their own cages for 6 hours (Start: 10:00, End: 16:00) [14]. All behavioral assessments and biological sample collections were conducted one month after parturition (postpartum day 30). Following the completion of the locomotor activity and elevated plus maze tests, terminal blood samples were collected via cardiac puncture during the transcardiac perfusion procedure.



Figure 1. *REM sleep deprivation setup*

Behavioral Tests

Behavioral tests were performed between 8 AM and 12 PM. Before the behavioral tests began, the animals were accustomed to the behavior laboratory for 30 minutes. The locomotor activity test was used to evaluate motor functions, and the elevated plus maze was used to evaluate anxiety behavior.

Locomotor Activity Test

The locomotor activity test allows a comprehensive examination of the locomotor activity levels of experimental animals. The activity meter (Commat Ltd., ACT 508), which is a 40x40x40 cm cage, records the locomotor activity parameters such as ambulatory, horizontal, and vertical activities of animals.

The locomotor activity test was performed 1 month after the rats gave birth. The rats were placed in the cage, and all movements were recorded for 5 minutes. The alterations of location and position were recorded in the cage's software via horizontal and vertical motion sensors inside the cage. Between tests, the cage was cleaned with 70% ethanol and allowed to dry. As a result of this test, data regarding the distance, the ambulatory activity, the ambulatory activity time, the ambulatory percentage, the stereotypic activity, the stereotypic time, the stereotypic percentage, the vertical activity, the vertical time, the horizontal activity, the resting time, and the resting percentage were obtained. Ambulatory activity represents periods when the rat is mobile [15].

Elevated Plus Maze

The elevated plus maze was performed 1 month after the rats gave birth. The maze has four arms (two open and two enclosed) as a plus shape. The rats were placed facing an open arm at the junction of the four arms of the maze. Entries and durations in each arm were recorded by a video-tracking system and an observer for 5 minutes. Between tests, the maze was cleaned with 70% ethanol and allowed to dry. As a result of this test, data regarding the open arm entries made, the open arm time, the ratio of open arm entries, the ratio of open arm time, the closed arm entries made, the closed arm time, the ratio of closed arm entries, the ratio of closed arm time, and the total entries were obtained. An increase in open arm activity reflects anti-anxiety behavior [16].

Enzyme-linked Immunosorbent Assay (ELISA)

Blood samples were collected at the end of the experimental period, immediately following the completion of the locomotor activity and elevated plus maze tests. Terminal blood samples were obtained via cardiac puncture during the transcardiac perfusion procedure under deep anesthesia. The levels of IL-6, IL-10, IL-15, IL-17, IL-23, and IFN-γ were evaluated using the ELISA technique in accordance with the kit's instructions (BT-Lab, Korea). Results for IL-17 and IL-10 were expressed in pg/ml, while IL-6, IL-15, IL-23, and IFN-γ levels were reported in ng/L. The ELISA procedure involved using 96-well plates coated with monoclonal antibodies specific to each protein. Prior to the assay, all materials were brought to room temperature for 30 minutes. Serial dilutions of the stock standard solution were prepared to generate five standards in accordance with the kit protocol. Two blank wells, five duplicate standard wells, and wells for serum samples were designated on each plate. In the first step, 50 µL of each standard and 40 µL of serum samples were added to the respective wells, followed by 10 µL of specific anti-IL-6, IL-10, IL-15, IL-17, IL-23, or IFN-γ antibodies. Next, 50 µL of Streptavidin-HRP was added to each well. Blank wells did not receive any solution at this point. The plate was covered and incubated at 37°C for 60 minutes, after which the wells were washed five times according to the recommended protocol. Then, 50 µL of substrate A solution was added, followed by 50 µL of substrate B solution to each well. The plate was covered and incubated at 37°C in the dark for 10 minutes, with the color change to blue being monitored. Afterward, 50 µL of stop solution was added, causing the blue color to turn yellow, and the absorbance was measured at 450 nm using a Multiskan™ FC Microplate Photometer (Thermo Fisher Scientific Inc.). The concentration of unknown samples was determined by constructing a calibration curve from the known concentrations of the standard solutions and applying the corresponding equation.

Statistical Analysis

All behavioral and biochemical data were expressed as mean ± standard error of the mean (SEM) and analyzed using the GraphPad Prism 6.01 software. Behavioral parameters and cytokine levels of the GSD and control rats were compared using the unpaired t-test. Additionally, a Pearson correlation analysis was performed to evaluate the potential relationship between serum cytokine levels and behavioral test parameters. For all analyses, a p-value of less than 0.05 was considered statistically significant.

3. RESULTS

Locomotor Activity Test

The distance (cm) (t=2.518, df=10; p=0.0305; n=6), the ambulatory activity (t=2.769, df=10; p=0.0198; n=6), the ambulatory activity time (ms) (t=2.770, df=10; p=0.0198; n=6), and the ambulatory % (t=2.726, df=10; p=0.0213; n=6) were higher in control rats compared to GSD rats. There was no statistically significant difference in the stereotypic activity, the stereotypic time (ms), the stereotypic (%), the vertical activity, the vertical time (ms), the horizontal activity, the resting time (ms), and the resting (percentage) between GSD and control rats (p>0.05).

Elevated Plus Maze

There was no statistically significant difference in the open arm entries made, the open arm time (sec), the ratio of open arm entries, the ratio of open arm time, the closed arm entries made, the closed arm time (sec), the ratio of closed arm entries, the ratio of closed arm time, and the total entries made between GSD and control rats (p>0.05) (Figure 2).

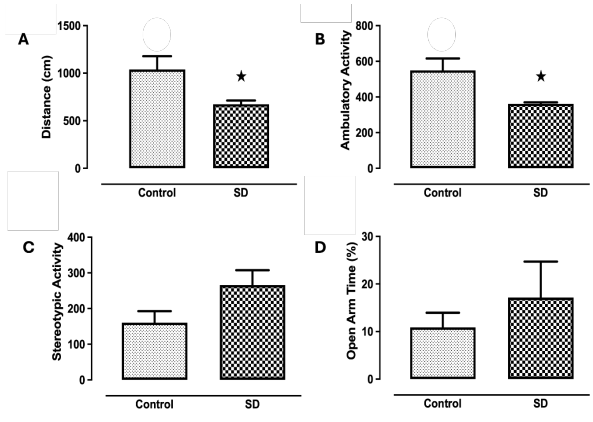


Figure 2. *Comparison of (A) the distance (cm) (LAT), (B) the ambulatory activity (LAT), (C) the stereotypic activity (LAT), and (D) the ratio of open arm time (%) (EPM) between the SD group and the control group. Data are shown as mean ± standard error of the mean (SEM). Unpaired*

*t-test, * p<0.05. LAT: Locomotor activity test, EPM: Elevated plus maze*

ELISA Results

Analysis of IL-15 level revealed a statistically significant difference between the control and SD groups. The control group exhibited a lower level of IL-15, while the SD group showed a higher level of IL-15 (p=0.0286). Although IL-17, IL-23 and IFN-g levels were lower in the control group and higher in the SD group, this difference was not statistically significant. A non-significant trend was observed for IL-6 levels to be higher in the control group compared to the SD group. A statistically significant difference was found in IL-10 levels between the control and SD groups (p=0.0286), with the control group exhibiting lower values. All values are reported in pg/mL (Figure 3).

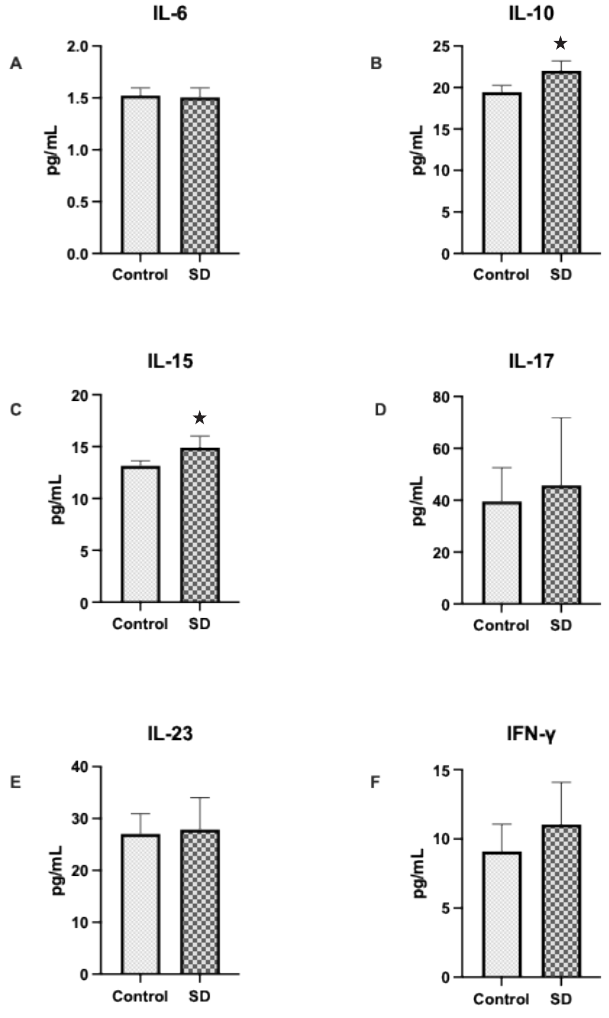


Figure 3. *Concentrations of interleukin 6 (IL-6) A, interleukin 10 (IL-10) B, interleukin 15 (IL-15) C, interleukin 17 (IL-17) D, interleukin 23 (IL-23) E, and Interferon gamma (IFN-γ) F, in control and sleep-deprived rats (SD). Data are presented in pg/mL*

4. DISCUSSION

The locomotor activity test is one of the open field tests. It allows a comprehensive examination of the locomotor activity levels of experimental animals. As a result of this test, the distance and the ambulatory activity were lower in the SD group. Ambulatory activity represents periods when the rat is mobile. These results demonstrate that SD reduced general motor functions and preserved stereotyped behavior. The elevated plus maze evaluates anxiety levels of experimental animals. An increase in open arm activity reflects anti-anxiety behavior. As a result of this test, there was no significant difference in the ratio of open arm time. This result reveals that SD has no significant anxiolytic/anxiogenic effects. Pires et al., examined the effects of sleep restriction during pregnancy on postpartum maternal behavior in rodents. Similar to our study, no significant differences were observed in the elevated plus maze test [17]. In our study, although SD led to observable changes in behavior and cytokine levels, a Pearson correlation analysis revealed no statistically significant relationship between behavioral parameters and cytokine levels ($P > 0.05$). This lack of significance might be due to the small sample size (n=6 per group) and the inherent variability in postpartum biological responses. However, the trends observed in both locomotor activity and inflammatory markers suggest a complex interaction that warrants further investigation with larger cohorts. A decade of research has provided robust evidence that both insufficient sleep (e.g., insomnia) and deviations from optimal sleep duration adversely affect inflammatory disease outcomes and contribute to all-cause mortality [18, 19]. According to a meta-analysis, no association was found between the age of the participants and the impact of sleep disturbance on inflammation [6]. Even modest SD activates inflammatory cellular and genomic markers, resulting from the up-regulation of molecular signaling that drives increased IL−6 and TNF gene transcription [20]. In the study by Shearer et al., healthy young men were subjected to an 88-hour protocol of either Total Sleep Deprivation (TSD) or Partial Sleep Deprivation (PSD), the latter involving two 2-hour nap opportunities daily. The study analyzed daily plasma IL−6 levels, revealing that IL−6 kinetics differed significantly based on the type of SD. Following four consecutive nights, IL−6 showed a continuous increase only in the TSD group, but this sustained elevation was absent in the PSD group [21]. In our study, rats were allowed to sleep 6 hours per day; this resting phase might have a potential protective effect, although our correlation analysis did not provide definitive statistical evidence for this link. In contrast, repeated sleep restriction for a period of time (12 days, 4 hours of sleep opportunity per night) increased the level of IL-6 [22]. Van Leeuwen et al., found that IL−17 showed a statistically significant increase in its mRNA expression following the sleep restriction period, and its protein levels remained significantly elevated even after the subsequent recovery sleep. IL−6 mRNA expression showed a significant elevation after sleep restriction, but its protein concentration did not reach a statistically significant increase following the recovery sleep period [23]. The modest 6-hour daily sleep opportunity allotted to the rats likely mitigated the inflammatory response, as evidenced by

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the lack of a statistically significant difference in IL−6 levels between the sleep-deprived and control groups in our study. The statistically insignificant increase observed in IL−17 protein levels in our study may be attributable to the adequate recovery sleep opportunity provided to the rats. In this study, IL-10 level was significantly increased in the SD group. However, according to one study, there was no statistically significant effect of SD on the level of IL-10 [21]. As a regulatory response to increasing pro-inflammatory cytokines (e.g., IL−12 and IFN−γ), anti-inflammatory cytokines like IL−10 are known to increase during sleep loss. In our study, the elevated IL−10 levels observed in the SD group support the conclusion that the increase in IL−10 occurred as a counter-regulatory response to the increase in IFN−γ found in our study. Lange et al., also reported that during the sleep loss phase, the ratio of IL-12/IL-10 (inflammatory/anti-inflammatory) approached 1 [24]. IL-15 is predominantly known for its activity as a proinflammatory cytokine [25]. An increase in non-rapid eye movement sleep (NREMS) was observed in rabbits following the intracerebroventricular (ICV) injection of IL-15 [26]. This finding suggests the hypothesis that an increased NREMS drive may elevate IL-15 levels. The statistically significant elevation in IL-15 levels detected in our current study provides support for this assumption. The study by Huang et al., in 2007 suggested a neuroprotective role for IL-15 signaling, based on the observed increase in motor neuron loss after facial nerve injury in knockout mice [27]. In our current investigation, however, the elevated IL-15 level is interpreted as a marker reflecting the severity of nerve damage. A previous study demonstrated an elevated serum concentration of IL-15 in IL15Rα KO (IL-15 receptor knockout) mice. Concomitantly, this increase was associated with a reduction in anxiety-like behavior, as assessed by the elevated maze test, compared to control animals [28]. We suggest that the decreased anxiety-like behavior observed in the SD group during the elevated maze test is potentially caused by the significant elevation of IL-15 levels.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Marmara University Local Ethics Committee for Animal Experiments (Approval number: 33.2024mar).

Conflict of interest: The authors declare that there is no conflict of interest.

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Author Contributions: OK: Contributed to the writing of the manuscript, statistical analysis, and animal studies, SY: Contributed to the animal study and behavioral analyses, IPE: Contributed to the performance of ELISA tests and to statistical analysis, SDY: Contributed to the writing of the manuscript and to the design and implementation of the animal sleep deprivation model. All authors read and approved the final version of the manuscript to be published.

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