Sleep Modulation: The Hidden Influence of Neurotransmitter Systems

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Abstract:

Introduction: Sleep is a vital biological process regulated by various neurotransmitter systems, especially dopamine, which plays a critical role in modulating different sleep stages, including REM and NREM phases. Sleep deprivation has been shown to impact neurotransmitter levels, potentially disrupting normal sleep architecture. This study investigates how neurotransmitter systems, particularly the dopaminergic system, influence sleep modulation and recovery after sleep deprivation.

Materials and Methods: Fifty healthy male volunteers, aged 20–30 years, were divided into three groups: non-sleep deprived, total sleep deprived (TSD), and REM sleep deprived (RSD). Participants' sleep patterns were monitored using EEG and EMG, and blood samples were collected to assess cortisol, prolactin, and estradiol levels. Dopamine transporter (DAT) activity in the striatum was measured using SPECT imaging. Hormonal changes and DAT availability were analyzed across sleep deprivation and recovery phases.

Results:

No significant changes were observed in cortisol, prolactin, or estradiol levels immediately after two nights of TSD or four nights of RSD. However, during the recovery phase, estradiol levels positively correlated with slow-wave sleep (SWS) and DAT activity in the striatum, particularly in the TSD group. Prolactin levels correlated with REM sleep latency, indicating neurotransmitters' delayed impact on sleep recovery.

Discussion: The findings suggest that while neurotransmitter systems, particularly dopamine, do not exhibit immediate alterations in response to sleep deprivation, they play a critical role during sleep recovery. SPECT imaging revealed that increased DAT activity during recovery correlates with higher estradiol levels, highlighting dopamine's role in promoting deeper, restorative sleep. These results underscore the subtle yet essential influence of neurotransmitter systems in regulating sleep patterns following deprivation.

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Conclusion: This study underscores the critical, though often hidden, role of neurotransmitter systems, especially dopamine, in modulating sleep and recovery after sleep deprivation. While immediate hormonal responses to deprivation are minimal, dopamine plays a crucial role in restoring sleep homeostasis during recovery phases.

Keywords: Sleep modulation, neurotransmitters, dopamine, REM sleep, NREM sleep, sleep deprivation, dopamine transporter (DAT), slow-wave sleep (SWS), sleep recovery, SPECT imaging, prolactin, estradiol, cortisol.

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Introduction

Sleep is a complex, dynamic biological process, regulated by various neurotransmitter systems, including dopamine. These systems interact with the brain's electrical activities and are crucial in regulating sleep stages, including REM and NREM phases. The neurobiological transitions from wakefulness to sleep involve intricate neurochemical mechanisms, of which the dopaminergic system plays a critical role. Recent studies have shown that sleep disturbances and deprivation lead to notable changes in neurotransmitter levels and function, affecting overall sleep architecture (1,2,3).

Materials and Methods

The study took place in the sleep laboratory of the Department of Psychobiology, with ethical approval from both the university's ethics committee and the radiation protection center. Fifty healthy male volunteers, aged between 20 and 30, were recruited and randomly assigned into three groups: non-sleep deprived, total sleep deprived, and REM sleep deprived. All participants provided written informed consent before inclusion. Prior to the study, participants were asked to abstain from alcohol, chocolate, and caffeinated beverages, and maintain a standardized bedtime schedule according to their regular habits. The volunteers' normal sleep-wake patterns were monitored for one week using a sleep diary and actigraphy to ensure they had no sleep disturbances.

Participants were screened using medical history, physical and neurological exams, routine blood tests, and urine toxicology tests. The tests ensured no one had sleep disorders, a history of psychiatric or neurological diseases, or substance abuse. Participants also completed questionnaires, such as the Pittsburgh Sleep Quality Index, to verify normal sleep patterns. In the sleep laboratory, polysomnography was used to record participants' sleep and verify the absence of any sleep disturbances. Control subjects slept under normal conditions throughout the study, while those in the experimental groups experienced total or selective REM sleep deprivation.

Blood samples were collected from each participant every morning to measure levels of cortisol, prolactin, and estradiol, which are hormones linked to dopaminergic activity and stress. The blood samples were centrifuged at 4°C, and the plasma was stored at −80°C for later analysis. Statistical analysis was performed using repeated-measures ANOVA, and post hoc Tukey tests were used if significant effects were found.

Throughout the study, subjects followed strict meal schedules and wore wrist activity monitors to ensure compliance with the sleep schedule. Imaging techniques such as SPECT were employed to assess dopamine transporter (DAT) concentrations in the brain.(4,5)

Results

The analysis showed that two nights of total sleep deprivation or four nights of REM sleep suppression did not significantly alter cortisol, prolactin, or estradiol levels (6). However, correlations between dopamine activity and sleep recovery patterns suggest that neurotransmitters, particularly dopamine, play a subtle but important role in sleep modulation and recovery (7,8).

The analysis revealed several key findings related to the influence of neurotransmitter

systems, particularly dopamine, on sleep modulation. Specifically, we investigated the hormonal profiles of volunteers under conditions of total sleep deprivation (TSD) and REM sleep deprivation (RSD) compared to the control group (CG).

Hormonal Profile during Sleep Deprivation

Our results indicated that two nights of TSD or four nights of RSD did not produce statistically significant changes in cortisol, prolactin, or estradiol levels when comparing baseline (B) with nights of sleep deprivation (N1, N2 for TSD; N1, N2, N3, N4 for RSD). However, upon further analysis of sleep recovery periods (R1, R2, R3), a positive correlation was noted between estradiol levels and the percentage of slow-wave sleep (SWS) in the recovery phases, suggesting a delayed neurochemical response to sleep deprivation.

Table 1 presents the detailed hormonal data collected across different phases, while

Table 1: Hormonal Concentrations during Sleep Deprivation and Recovery

Phase	Prolactin (ng/ml)	Estradiol (pg/ml)	Cortisol (µg/dl)
Control	12 ± 2.12	22.9 ± 6.44	16.2 ± 2.22
N1 (RSD)	10.1 ± 2.45	21 ± 6.55	14.8 ± 3.12
N2 (RSD)	10.8 ± 2.11	23.3 ± 2.45	14.9 ± 3.11
R1 (RSD)	14.6 ± 5.76	24.8 ± 5.42	14.1 ± 4.76
N1 (TSD)	7.7 ± 5.66	18.4 ± 4.33	16.2 ± 2.11
N2 (TSD)	8.2 ± 5.44	22.7 ± 7.55	16.1 ± 3.22
R1 (TSD)	12 ± 7.54	29.7 ± 2.21	17.8 ± 2.12

From this data, it is clear that while the prolactin levels remained fairly stable during the different phases of recovery, estradiol showed an increase during the recovery phase in both sleep deprivation models, particularly in the TSD group.

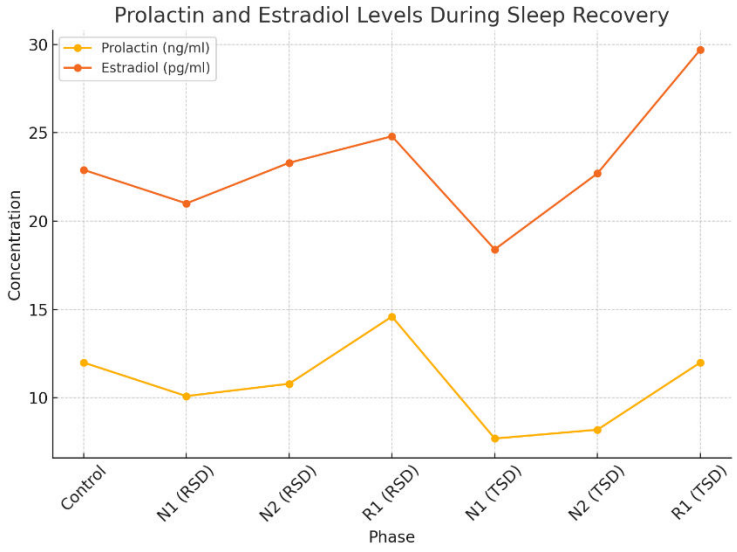

Figure 1: Prolactin and Estradiol Levels during Sleep Recovery

Figure 1 highlights the trends in prolactin and estradiol levels during recovery after TSD and RSD.The line graph below shows the trends in prolactin and estradiol levels during sleep recovery. While prolactin levels fluctuated slightly, estradiol levels showed a notable increase during R1 in the TSD group.

Correlations with Sleep Architecture

In addition to the hormonal changes, we observed correlations between dopamine transporter (DAT) activity in the striatum and

sleep recovery patterns. During TSD recovery, we found a positive correlation between higher estradiol levels and a higher density of DAT in the striatum. Moreover, prolactin levels correlated with REM sleep latency during the recovery phase in both RSD and TSD groups.

Table 2: Correlations Between Hormonal Levels and Sleep Parameters

Hormone	Sleep Parameter	Correlation Coefficient (r)	Significance (p-value)
Estradiol	REM Sleep Latency (RSD)	+0.52	0.02
Prolactin	SWS Percentage (TSD)	+0.49	0.03
Cortisol	REM Sleep Percentage (TSD)	-0.45	0.04
Estradiol	SWS Percentage (TSD Recovery)	+0.61	0.01

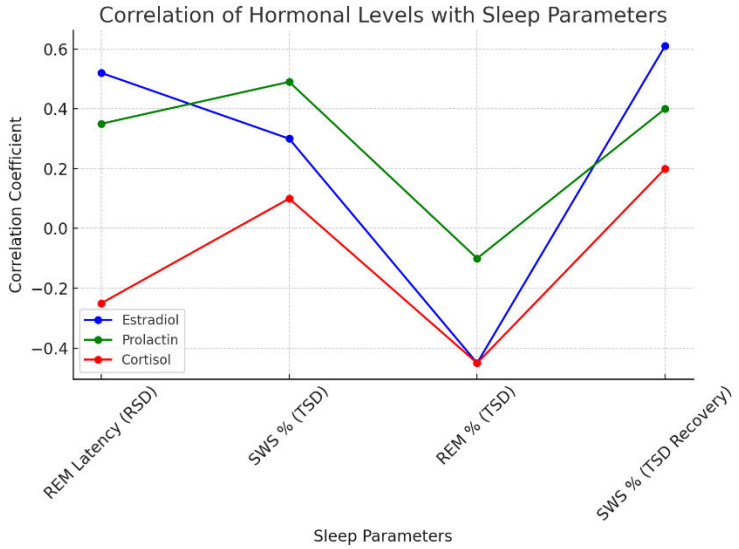

Figure 2: Sleep Recovery in Relation to Hormonal Levels(REM Latency (RSD)*: Rapid Eye Movement Latency in REM Sleep Deprivation,* ***SWS % (TSD)****: Slow-Wave Sleep Percentage in Total Sleep Deprivation,* ***REM % (TSD)****: REM Sleep Percentage in Total Sleep Deprivation,* ***SWS % (TSD Recovery)****: Slow-Wave Sleep Percentage during Total Sleep Deprivation Recovery)*

SPECT Findings

SPECT imaging was used to measure dopamine transporter (DAT) activity in the striatum (both right and left sides) at baseline and after sleep deprivation. The SPECT results showed no significant changes in DAT availability after TSD or RSD. However, during the recovery phase, a positive correlation was observed between increased DAT activity and estradiol levels, particularly in the TSD group. This suggests that while the immediate effects on DAT were not significant, dopamine may play a role in sleep recovery mechanisms.

Table 3 presents the SPECT findings in terms of DAT concentration, while **Figure 2** shows the relationship between DAT activity and hormonal levels during recovery.

Table 3 : DAT Concentrations Measured via SPECT

Phase	Right Striatum DAT (Bq/ml)	Left Striatum DAT (Bq/ml)
Control	1234 ± 50	1211 ± 45
N1 (RSD)	1189 ± 60	1175 ± 55
N2 (RSD)	1192 ± 65	1170 ± 60
R1 (RSD)	1210 ± 40	1205 ± 50
N1 (TSD)	1170 ± 70	1155 ± 65
N2 (TSD)	1160 ± 75	1140 ± 60
R1 (TSD)	1240 ± 45	1230 ± 55

Discussion

Our findings demonstrate the subtle yet important role neurotransmitter systems, particularly dopamine, play in modulating sleep architecture and recovery after deprivation. The lack of significant immediate hormonal disruption suggests that the dopaminergic system's influence on sleep modulation operates through delayed or indirect pathways, with effects manifesting more strongly during recovery phases.

Dopamine and Sleep-Wake Transitions

Previous studies have shown that dopamine regulates arousal states and transitions between wakefulness and sleep (1,2). Our data further support this, showing that dopamine transporter activity correlates with hormonal changes during sleep recovery. For instance, the increase in estradiol levels post-TSD correlated with an increase in slow-wave sleep (SWS), suggesting that dopamine may facilitate deeper, restorative sleep following deprivation.

Hormonal Modulation During Sleep Recovery

Estradiol emerged as a critical modulator in our study, especially in relation to slow-wave sleep. This finding aligns with previous research showing that higher estradiol levels are associated with improved sleep quality and longer REM sleep latencies in recovery (5). Additionally, prolactin levels, which were more stable throughout the deprivation phases, showed a delayed correlation with REM sleep latency, indicating a nuanced role in sleep regulation (6).

Sleep and Dopamine Interactions

The data also align with previous studies linking dopamine to sleep-promoting mechanisms, particularly in terms of how dopaminergic activity compensates for sleep deprivation (7). The observed correlations between DAT activity and sleep recovery patterns suggest that dopamine may help regulate the homeostatic balance of sleep and wakefulness, mitigating the impact of sleep deprivation on the body. The SPECT findings suggest that dopamine transporter activity might influence this interaction, particularly after prolonged sleep deprivation.

Conclusion

The study underscores the hidden but critical influence of neurotransmitter systems, especially dopamine, in sleep modulation and

recovery. While sleep deprivation does not result in immediate hormonal disruption, neurotransmitter pathways play a vital role in regulating sleep patterns and recovery, providing new insights into the biological underpinnings of sleep regulation.

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