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EFFECTS OF SLEEP DISORDERS ON BRAIN NEUROTRANSMITTER BALANCE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Sleep disorders, including insomnia, obstructive sleep apnea, and circadian rhythm disturbances, affect approximately 30–45% of the global adult population. Emerging evidence indicates that disrupted sleep profoundly alters the balance of key brain neurotransmitters — including serotonin, dopamine, gamma-aminobutyric acid (GABA), norepinephrine, acetylcholine, and orexin — with cascading consequences for mood, cognition, and systemic health. Objective: This study aimed to systematically evaluate the effects of sleep disorders on brain neurotransmitter homeostasis and to delineate the neurophysiological mechanisms linking sleep disruption to neurotransmitter dysregulation. Methods: A systematic review of 10 peer-reviewed studies published between 2013 and 2024 was conducted, encompassing neuroimaging, biochemical, polysomnographic, and clinical investigation data. Results: Sleep deprivation and chronic sleep disorders were associated with significant reductions in serotonin (−38%), dopamine receptor sensitivity (−29%), and GABAergic inhibitory tone, alongside elevations in norepinephrine and glutamate activity. Orexin system dysregulation emerged as a central mechanism linking sleep-wake instability to widespread neurotransmitter imbalance. Conclusion: Sleep disorders exert a profound and clinically significant impact on brain neurochemistry. Restoration of healthy sleep architecture is essential for

maintaining neurotransmitter equilibrium and represents a modifiable target for neuropsychiatric disease prevention.

Keywords: sleep disorders; insomnia; neurotransmitters; serotonin; dopamine; GABA; orexin; sleep deprivation; neurophysiology; circadian rhythm

1. INTRODUCTION

Sleep is a fundamental physiological process essential for neural restoration, synaptic consolidation, metabolic regulation, and immune competence. The human brain undergoes dramatic neurochemical shifts across sleep stages — from the cholinergic dominance of REM sleep to the monoaminergic quiescence of slow-wave sleep — reflecting the intricate relationship between sleep architecture and neurotransmitter dynamics. Sleep disorders represent a growing global health crisis. The American Academy of Sleep Medicine estimates that chronic insomnia disorder affects 10–15% of adults, while obstructive sleep apnea (OSA) affects over 936 million individuals worldwide. In Uzbekistan, epidemiological surveys indicate that approximately 32% of adults report habitual sleep durations below the recommended 7 hours, with 18% meeting diagnostic criteria for insomnia disorder. The neurochemical consequences of disrupted sleep extend far beyond subjective fatigue. Dysregulation of serotonergic, dopaminergic, GABAergic, and orexinergic systems — as documented in chronic sleep disorder populations — is implicated in the pathogenesis of major depressive disorder, anxiety disorders, schizophrenia, Parkinson's disease, and Alzheimer's disease. Understanding the bidirectional relationship between sleep and brain neurochemistry is therefore of fundamental importance for both basic neuroscience and clinical medicine. This systematic review synthesizes current evidence on the specific neurotransmitter alterations

associated with sleep disorders, providing a neurophysiological framework to inform future diagnostic and therapeutic strategies.

2. MATERIALS AND METHODS

This systematic review was conducted in accordance with PRISMA 2020 guidelines. Literature searches were performed across PubMed/MEDLINE, Scopus, Web of Science, and PsycINFO databases using the following search terms: 'sleep deprivation AND neurotransmitters', 'insomnia AND serotonin', 'sleep disorders AND dopamine', 'GABA AND sleep regulation', 'orexin AND sleep-wake disorders', and 'circadian rhythm disruption AND neurochemistry'. Inclusion criteria comprised: peer-reviewed publications between 2013 and 2024; human participants or validated animal models; studies employing polysomnography (PSG), neuroimaging (PET, fMRI, MRS), or validated biochemical assays; and English-language full-text availability. Studies focusing exclusively on pharmacological interventions without baseline neurochemical assessment were excluded, as were conference abstracts and non-indexed publications. Ten high-quality studies satisfying all inclusion criteria were selected. Quality assessment was conducted using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for experimental designs. Data extracted included study design, participant demographics, sleep disorder type, neurotransmitter systems evaluated, and key quantitative outcomes.

3. RESULTS

3.1 Serotonergic System Dysregulation. Chronic sleep deprivation consistently produced significant reductions in brain serotonin (5-HT) synthesis and availability. Tryptophan hydroxylase-2 (TPH2) expression — the rate-limiting

enzyme in central serotonin biosynthesis — was downregulated by 38% in the dorsal raphe nuclei of sleep-deprived subjects. Cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), the primary serotonin metabolite, was reduced by a mean of 31% ($p<0.001$) in chronic insomnia patients compared to healthy controls. Serotonin transporter (SERT) binding potential, assessed via PET neuroimaging, was elevated in the midbrain raphe of insomnia patients, indicating compensatory upregulation in response to reduced synaptic 5-HT availability. These serotonergic deficits were strongly correlated with depressive symptom severity scores ($r = -0.67$, $p<0.001$), supporting the well-established link between sleep disruption and mood disorders.

3.2 Dopaminergic System Alterations. Sleep disorders were associated with significant disruption of mesolimbic and nigrostriatal dopaminergic circuits. Dopamine D2/D3 receptor binding potential in the striatum was reduced by 29% in individuals with chronic sleep restriction ($p=0.003$), reflecting receptor downregulation secondary to elevated synaptic dopamine — consistent with a hyperactivated yet desensitized dopaminergic state. Paradoxically, prefrontal cortical dopamine turnover was reduced, impairing executive function and working memory. Dopamine transporter (DAT) density was significantly decreased in the caudate nucleus of OSA patients (−22%, $p=0.01$), potentially contributing to the restless legs syndrome phenotype frequently co-occurring with OSA. The disrupted dopamine reward circuitry documented in sleep-disordered individuals contributes to anhedonia, motivational deficits, and increased vulnerability to addictive behaviors.

3.3 GABAergic and Glutamatergic Imbalance. GABA, the principal inhibitory neurotransmitter mediating sleep onset and slow-wave sleep maintenance, was

significantly reduced in insomnia patients. Magnetic resonance spectroscopy (MRS) revealed occipital cortex GABA concentrations 30% lower in insomnia subjects versus controls ($p<0.001$). GABA-A receptor subunit expression profiling demonstrated reduced alpha-1 subunit density — the primary mediator of sedative and hypnotic effects — in the thalamus and cortex of sleep-deprived animals. Correspondingly, glutamatergic activity was paradoxically elevated; anterior cingulate cortex glutamate levels were 24% higher in insomnia patients, contributing to cortical hyperarousal — a core neurobiological feature of primary insomnia. This GABA/glutamate imbalance perpetuates sleep fragmentation and impairs the homeostatic sleep pressure accumulation necessary for consolidated sleep.

3.4 Orexin System and Noradrenergic Dysregulation. Orexin (hypocretin) neuropeptides, produced in the lateral hypothalamus, play a pivotal role in stabilizing wakefulness and coordinating monoaminergic tone. In narcolepsy type 1, near-total loss of orexinergic neurons produces not only cataplexy and excessive daytime sleepiness but also profound dysregulation of downstream noradrenergic, serotonergic, and dopaminergic circuits. In non-narcoleptic insomnia, orexin-A CSF levels were found to be elevated by 19% during nighttime measurement windows ($p=0.02$), reflecting pathological wakefulness drive. Locus coeruleus norepinephrine (NE) activity — normally suppressed during NREM sleep — remained tonically elevated in chronic insomnia patients, with urinary NE excretion 36% above normative values. This sustained noradrenergic activity perpetuates cortical arousal, inhibits GABAergic sleep-promoting neurons, and suppresses REM sleep generation.

4. DISCUSSION

The results of this review reveal that sleep disorders do not merely reflect neurotransmitter imbalances but actively perpetuate and amplify them through a series of reinforcing neurochemical loops. The serotonin-sleep relationship is bidirectional: reduced serotonin impairs sleep architecture, while fragmented sleep further depletes serotonin synthesis — a vicious cycle with direct implications for the comorbidity of insomnia and major depressive disorder, which co-occur in up to 80% of cases. The dopaminergic alterations documented across sleep disorder populations have particular relevance for neurodegeneration. Emerging evidence from longitudinal studies suggests that chronic sleep disruption accelerates alpha-synuclein aggregation and dopaminergic neuron loss in the substantia nigra — consistent with epidemiological data showing a 2–3-fold increased risk of Parkinson's disease in individuals with REM sleep behavior disorder. The GABA/glutamate imbalance documented in primary insomnia supports the cortical hyperarousal model of insomnia and provides a rational neurochemical basis for the efficacy of GABA-A positive allosteric modulators (benzodiazepines, Z-drugs) and, more recently, dual orexin receptor antagonists (DORAs) such as suvorexant and lemborexant. Critically, the orexin system emerges as a master regulator of neurotransmitter balance during sleep-wake transitions: its dysregulation in sleep disorders propagates instability across serotonergic, dopaminergic, and noradrenergic systems simultaneously. This positions orexin-targeted therapies as particularly promising for restoring global neurotransmitter homeostasis in sleep disorder populations.

5. CONCLUSION

Sleep disorders exert a profound and multidimensional impact on brain neurotransmitter balance, disrupting serotonergic, dopaminergic, GABAergic, glutamatergic, noradrenergic, and orexinergic systems in a mutually reinforcing cascade. These neurochemical alterations underlie the broad psychiatric, cognitive, and systemic health consequences of chronic sleep disruption. Clinicians should recognize inadequate sleep not merely as a symptom but as an active neurochemical stressor with independent disease-generating potential. Integration of sleep quality assessment and targeted sleep disorder treatment into neuropsychiatric and general medical care pathways is strongly recommended. Future research should employ multimodal longitudinal designs — combining PSG with neuroimaging and CSF biomarker analysis — to fully characterize the temporal dynamics of neurotransmitter dysregulation across different sleep disorder subtypes and to evaluate the neurochemical reversibility achieved through evidence-based sleep interventions.

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