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Biochemical Mechanisms of Sleep Regulation

Anih, David Chinonso, Yakubu, Ojochenemi Ejeh, Arowora, Adebisi Kayode, Abah, Moses Adondua and Ugwuoke Kenneth Chinekwu

Department of Biochemistry, Faculty of Biosciences, Federal University Wukari, Taraba State, Nigeria

ABSTRACT

Sleep is a highly orchestrated neurophysiological process governed by intricate biochemical pathways involving neurotransmitters and hormones that modulate sleep architecture and circadian rhythmicity. This review presents a comprehensive synthesis of current molecular insights into the regulatory mechanisms of sleep, with a particular focus on the roles of γ-aminobutyric acid (GABA), serotonin, adenosine, acetylcholine, and norepinephrine in sleep stage modulation. It further explores the circadian and homeostatic functions of hormones, including melatonin, cortisol, orexins, leptin, and ghrelin, highlighting their integrative roles in linking neural circuitry with systemic physiological states. The article delineates how disruptions in these pathways underpin major sleep disorders, such as insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, and circadian rhythm sleep-wake disorders, through mechanisms ranging from GABAergic deficits and HPA axis hyperactivation to orexin deficiency and clock gene dysregulation. By bridging neurochemical theory with clinical pathology, the review underscores the translational potential of targeting neuroendocrine circuits for therapeutic intervention. The findings advocate for the advancement of personalized sleep medicine through molecular diagnostics and emphasize the importance of circadian coherence in neurodegenerative and metabolic disease management. Collectively, this work consolidates multidisciplinary evidence into a cohesive framework, contributing to the evolving paradigm of sleep biology and its clinical relevance.

KEYWORDS

Sleep regulation, neurotransmitters, hormones, circadian rhythm, GABA, melatonin, adenosine, orexin, sleep disorders

INTRODUCTION

Sleep is a fundamental, evolutionarily conserved biological process essential for sustaining neurocognitive performance, metabolic balance, and immune function. Globally, the burden of sleep-related disorders continues to rise, with profound consequences on mental health, cardiovascular integrity, and productivity. Over the past two decades, substantial progress has been made in elucidating the neurochemical basis of sleep, particularly the roles of neurotransmitters and hormones in orchestrating the sleep-wake cycle. Studies have established that γ-aminobutyric acid (GABA), serotonin, adenosine, acetylcholine, and norepinephrine mediate neural excitability and transitions between sleep stages[1-5], while melatonin, cortisol, orexins, leptin, and ghrelin coordinate systemic signals with circadian cues[6-9]. Despite these insights, a comprehensive synthesis that bridges neurochemical mechanisms with the pathophysiology of sleep disorders remains limited. Previous reviews have often examined neurotransmitters or hormones in isolation, without integrating their dynamic interactions or exploring emerging therapeutic targets

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based on recent molecular findings. This review aims to address this gap by presenting an updated, integrative overview of the biochemical regulation of sleep, with a focus on neurotransmitters and hormones, and their relevance to sleep disorders. By consolidating current molecular evidence, this article seeks to inform future research directions and therapeutic approaches in sleep medicine.

NEUROTRANSMITTERS IN SLEEP REGULATION

Neurotransmitters are central to the neurobiological orchestration of sleep. Their synthesis, release, receptor binding, and degradation influence neuronal excitability, synaptic communication, and the homeostatic regulation of sleep cycles.

GABA

Principal inhibitory neurotransmitter: The GABA (γ-aminobutyric acid) is the chief inhibitory neurotransmitter in the CNS, playing a dominant role in sleep induction and maintenance by inhibiting arousal-promoting neurons in the hypothalamus and brainstem. The GABA is synthesized from glutamate through the catalytic action of the enzyme Glutamic Acid Decarboxylase (GAD), as illustrated in Fig. 1. This conversion is a critical biochemical pathway that governs the balance between excitatory and inhibitory signaling in the brain. By reducing glutamate levels and increasing GABA availability, this reaction facilitates the inhibition of wake-promoting neurons and supports the initiation and maintenance of sleep. The Ventrolateral Preoptic Nucleus (VLPO) releases GABA to inhibit wake-promoting centers such as the tuberomammillary nucleus, locus coeruleus, and raphe nuclei[10]. Melatonin enhances the effect of GABA by increasing the expression and sensitivity of $GABA_A$ receptors, particularly in the hypothalamus[11]. Sleep-promoting pharmacological agents, including benzodiazepines, zolpidem, and barbiturates, act as positive allosteric modulators of $GABA_A$ receptors, further validating the centrality of GABAergic transmission in sleep[12].

Upon release, GABA binds to $GABA_A$ receptors, leading to the influx of chloride ions (Cl^-) into the postsynaptic neuron. This causes neuronal hyperpolarization, reducing neuronal excitability and facilitating sleep induction, especially during non-REM sleep. Figure 2 outlines this mechanistic pathway, visually demonstrating how GABAergic neurotransmission leads to CNS inhibition and ultimately supports sleep regulation[12].

Serotonin

A multifaceted modulator: Serotonin (5-HT), derived from the amino acid tryptophan, is synthesized primarily in the raphe nuclei and influences both sleep initiation and circadian rhythm synchronization. It plays dual roles: While certain serotonergic pathways promote sleep onset, others may promote

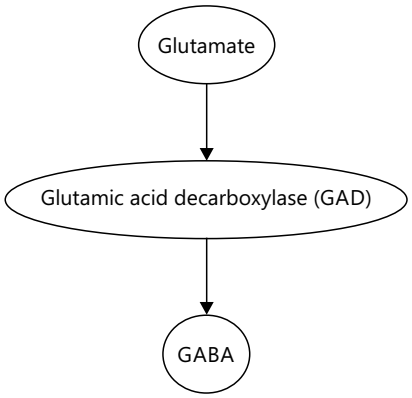

Fig. 1: Biosynthesis of GABA from glutamate via glutamic acid decarboxylase (GAD)
Glutamate, an excitatory neurotransmitter, is enzymatically converted into Gamma-Aminobutyric Acid (GABA), the primary inhibitory neurotransmitter involved in sleep regulation[10]

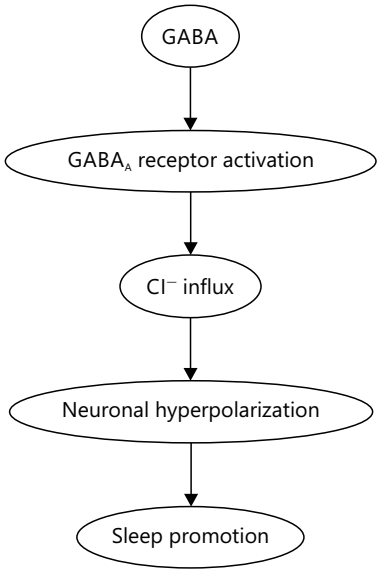

Fig. 2: Mechanism of GABA

A receptor-mediated inhibitor: GABA binding triggers Cl^- influx, leading to neuronal hyperpolarization and sleep promotion[12]

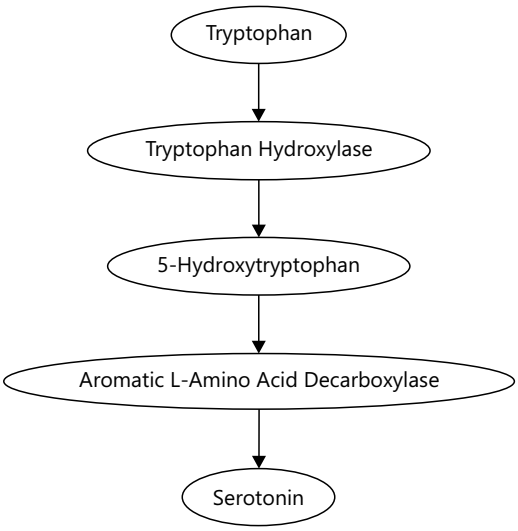

Fig. 3: Biosynthesis of serotonin

Biosynthesis of serotonin from tryptophan through the intermediate 5-hydroxytryptophan, catalyzed by tryptophan hydroxylase and Aromatic L-amino acid decarboxylase[15]

wakefulness depending on receptor subtype and regional activity. Additionally, serotonin is the precursor for melatonin synthesis in the pineal gland[13]. The SSRIs and other serotonergic agents significantly affect REM sleep patterns, sometimes reducing REM duration and altering sleep continuity[14].

The essential amino acid tryptophan is first converted by tryptophan hydroxylase into 5-hydroxytryptophan (5-HTP). Then, Aromatic L-amino acid decarboxylase (AADC) catalyzes the decarboxylation of 5-HTP to produce serotonin (5-hydroxytryptamine, 5-HT). Figure 3 visually represents this biosynthetic pathway, emphasizing the enzymatic steps that are essential for serotonin production and its regulatory role in sleep-wake cycles[15].

Adenosine

A homeostatic sleep factor: Adenosine accumulates during prolonged wakefulness as a byproduct of ATP metabolism and acts as a powerful homeostatic sleep inducer. It binds to A1 and A2A receptors in

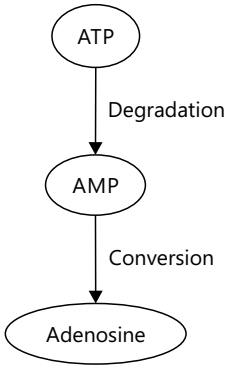

Fig. 4: Biochemical breakdown of ATP to adenosine

A process integral to sleep homeostasis. During periods of prolonged wakefulness, intracellular ATP is hydrolyzed to AMP, which is further converted to adenosine. Accumulating extracellular adenosine binds to A1 receptors in the brain, particularly in the basal forebrain, to inhibit wake-promoting neurons and promote sleep onset[15]

sleep-related regions such as the basal forebrain and inhibits wake-promoting neurotransmission. Studies have shown that the infusion of adenosine or A2A receptor agonists promotes NREM sleep, whereas A1 receptor knockout mice exhibit reduced sleep pressure[15,16]. Caffeine, a competitive antagonist of adenosine receptors, delays sleep onset and reduces total sleep time, highlighting adenosine's critical sleep-promoting role[17].

During prolonged neuronal activity or metabolic demand, ATP (Adenosine Triphosphate) is hydrolyzed to AMP (Adenosine monophosphate), which is subsequently converted into adenosine. As adenosine accumulates extracellularly, it binds to A1 receptors, especially in the basal forebrain, inhibiting wake-promoting neurons and promoting sleep onset. As illustrated in Fig. 4, adenosine is generated through the stepwise breakdown of ATP, first into AMP and subsequently into adenosine. This accumulation occurs progressively during sustained wakefulness and plays a crucial role in promoting sleep by inhibiting wake-active neurons via A1 receptors, particularly in the basal forebrain. The figure highlights the biochemical cascade from cellular energy depletion to extracellular adenosine build-up, emphasizing its homeostatic role in sleep regulation. This process has been well documented in both animal and human studies, supporting adenosine as a key sleep-inducing factor[15,17].

Adenosine binds to A1 receptors in the brain, particularly in areas like the basal forebrain. Activation of these receptors leads to the inhibition of wake-promoting neurons, reducing arousal and leading to sleep induction. This mechanism plays a key role in regulating sleep pressure during extended periods of wakefulness. Beyond its accumulation, adenosine exerts its sleep-promoting effects through targeted neuromodulation. As depicted in Fig. 5, adenosine binds to A1 receptors located in key arousal-related brain regions, such as the basal forebrain. This receptor activation inhibits wake-promoting neurons, reducing cortical arousal and promoting the transition to sleep[15,17]. The figure complements the metabolic pathway outlined in Fig. 4 by illustrating the downstream neurophysiological effects of adenosine that underpin its homeostatic role in sleep regulation.

Acetylcholine

Regulator of REM sleep: Acetylcholine is synthesized in cholinergic neurons of the basal forebrain and pontine tegmentum. It is primarily associated with cortical arousal and REM sleep, where it facilitates desynchronized EEG activity and muscle atonia. The REM-on neurons in the Laterodorsally and Pedunculopontine Tegmental Nuclei (LDT/PPT) release acetylcholine during REM sleep episodes[18]. Anticholinergic drugs tend to suppress REM sleep, and cholinesterase inhibitors such as donepezil can increase REM density, demonstrating acetylcholine's critical role in sleep architecture[19].

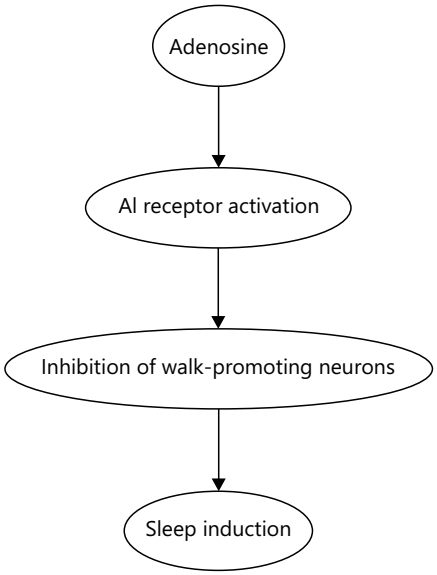

Fig. 5: Mechanism of sleep induction mediated by adenosine

This diagram illustrates how extracellular adenosine Activates A1 receptors, leading to inhibition of wake-promoting neurons in regions such as the basal forebrain and cortex. This neural suppression contributes to increased sleep pressure and facilitates sleep onset[15,17]

Norepinephrine

Modulator of arousal: Norepinephrine, secreted by the locus coeruleus, promotes wakefulness and vigilance. Its activity is highest during wakefulness, decreases during NREM sleep, and becomes nearly silent during REM sleep. However, recent studies suggest that phasic norepinephrine bursts during sleep might contribute to memory consolidation and synaptic homeostasis without fully awakening the brain, implying a nuanced role beyond simple arousal[20,21]. Dysregulation of noradrenergic tone is implicated in insomnia, PTSD, and other disorders involving disrupted sleep-wake transitions.

HORMONAL REGULATION OF SLEEP

Hormones act as systemic modulators of sleep by linking central neural circuits with peripheral physiological states. Their circadian patterns of secretion, influenced largely by light-dark cycles and metabolic cues, help regulate sleep timing, duration, and quality.

Melatonin

Circadian pacemaker: Melatonin, synthesized from serotonin in the pineal gland, is a central regulator of circadian rhythms. Its production is triggered by darkness and inhibited by light through input from the Suprachiasmatic Nucleus (SCN), which transmits light information from the retina via the retinohy pothalamic tract[22]. The enzyme Hydroxyindole-O-methyltransferase (HIOMT) catalyzes the final step in melatonin synthesis. Once secreted, melatonin binds to MT1 and MT2 receptors in the SCN to induce sleepiness and synchronize the circadian clock[23]. The biochemical pathway underlying this conversion of serotonin into melatonin is illustrated in Fig. 6, which highlights the roles of N-acetyltransferase (NAT) and Hydroxyindole-O-methyltransferase (HIOMT) in this essential circadian regulatory mechanism[22-24]. Studies have shown that exogenous melatonin supplementation can improve sleep onset latency in individuals with delayed sleep-wake phase disorder and in elderly populations with reduced endogenous production[24].

In the pineal gland, serotonin is first acetylated by N-acetyltransferase (NAT) to form N-acetyl serotonin. This intermediate is then methylated by Hydroxyindole-O-methyltransferase (HIOMT), producing melatonin. The secretion of melatonin is strongly regulated by the light-dark cycle and plays a critical role in promoting sleep[22-24].

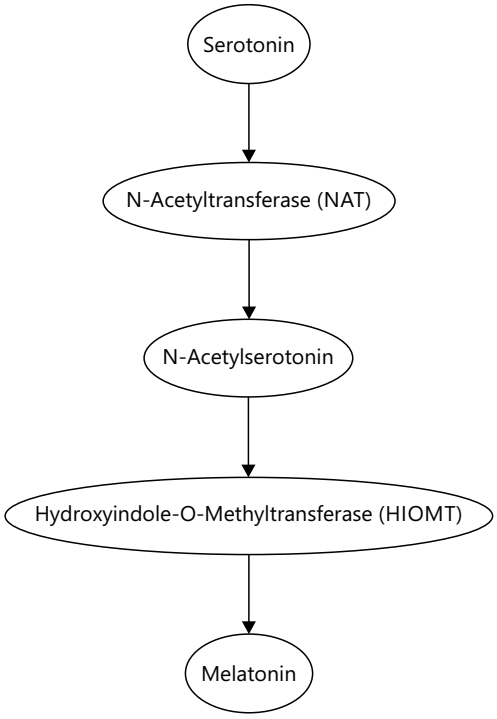

Fig. 6: Biosynthetic pathway of melatonin from serotonin
Involving the enzymes N-acetyltransferase (NAT) and Hydroxyindole-O-methyltransferase (HIOMT)[22-24]

Cortisol

Arousal hormone: Cortisol is secreted by the adrenal cortex in a circadian pattern regulated by the Hypothalamic-pituitary-adrenal (HPA) axis. It peaks in the early morning hours, promoting alertness and energy mobilization, and gradually declines throughout the day. Stress-induced HPA axis activation elevates nocturnal cortisol levels, which are associated with sleep fragmentation and reduced slow-wave sleep[25,26]. Figure 7 illustrates this hormonal cascade, beginning with the hypothalamus releasing Corticotropin-releasing Hormone (CRH), which stimulates the anterior pituitary to release Adrenocorticotropic Hormone (ACTH), ultimately leading to cortisol secretion by the adrenal cortex[7,26,27]. This dysregulation is frequently implicated in insomnia and mood disorders, where hyperactivity of the HPA axis perpetuates a cycle of poor sleep and heightened arousal[7,25,27].

Orexins (Hypocretins)

Integrators of wakefulness: Orexin-A and Orexin-B, neuropeptides synthesized in the lateral hypothalamus, are essential for sustaining wakefulness and preventing inappropriate transitions into REM sleep. These peptides activate monoaminergic and cholinergic arousal systems and stabilize sleep-wake transitions[28]. Figure 8 illustrates this neurochemical cascade, where orexin neurons enhance the activity of downstream arousal circuits, ultimately promoting and maintaining wakefulness[28-30]. Orexin deficiency is strongly implicated in narcolepsy, highlighting its vital role in sleep-wake regulation[28,29]. Deficiency in orexin neurons, due to autoimmune or genetic factors, is the primary cause of narcolepsy type 1[29]. Orexin receptor antagonists, such as suvorexant, have been developed as novel therapeutics for insomnia, demonstrating the translational potential of targeting this system[30].

Leptin and Ghrelin

Metabolic hormones influencing sleep: Leptin, produced by adipose tissue, promotes satiety and has been shown to enhance sleep, possibly by inhibiting orexin neurons[31]. Ghrelin, secreted by the stomach, stimulates hunger and may antagonize leptin's effects on sleep. Sleep deprivation leads to decreased leptin and increased ghrelin levels, contributing to increased appetite and weight gain[32]. These hormones are dysregulated in obesity-related sleep disorders such as obstructive sleep apnea (OSA), further linking metabolic and sleep homeostasis[33].

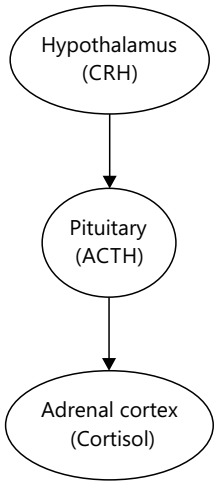

Fig. 7: Hormonal cascade of the HPA axis

A central component of the body's stress-response system. The hypothalamus secretes Corticotropin-releasing Hormone (CRH), which stimulates the anterior pituitary to release Adrenocorticotropic Hormone (ACTH). The ACTH then acts on the adrenal cortex, prompting the secretion of cortisol. This feedback system plays a pivotal role in stress regulation, circadian rhythm, and sleep-wake modulation[7,26,27]

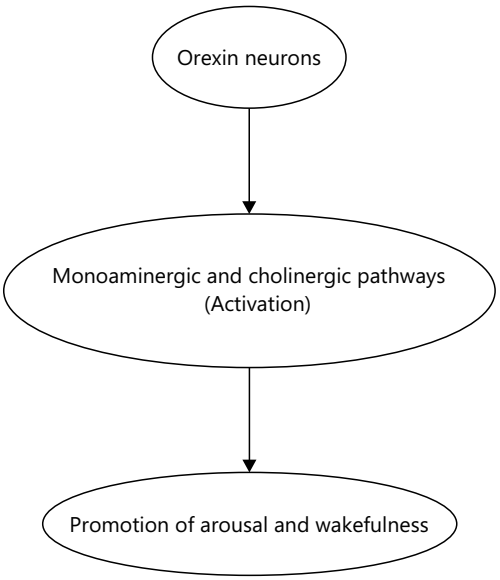

Fig. 8: Orexin-driven promotion of arousal and wakefulness

Orexin neurons located in the lateral hypothalamus activate monoaminergic (e.g., noradrenergic, serotonergic, dopaminergic) and cholinergic pathways, which collectively stimulate the brain's arousal centers. This mechanism sustains wakefulness and prevents premature transitions to sleep states[28-30]

BIOCHEMICAL DYSREGULATION IN SLEEP DISORDERS

Sleep disorders often arise from disruptions in neurotransmitter and hormonal systems. Understanding these molecular pathologies is essential for the development of targeted therapies.

Insomnia

GABA and cortisol imbalance: Insomnia, the most prevalent sleep disorder, is often associated with hyperarousal due to reduced GABAergic inhibition and excessive HPA axis activation. Neuroimaging studies have shown decreased GABA levels in the anterior cingulate cortex of insomniacs[34]. Concurrently, elevated nocturnal cortisol impairs sleep initiation and maintenance. Pharmacological interventions such as benzodiazepines, zolpidem, and eszopiclone target $GABA_A$ receptors to restore inhibitory tone and promote sleep[35]. Cognitive-behavioral Therapy for insomnia (CBT-I) has also been shown to reduce cortisol levels and improve sleep quality[36].

Narcolepsy

Orexin deficiency: Narcolepsy Type 1 is characterized by excessive daytime sleepiness, cataplexy, and disturbed nocturnal sleep. The underlying cause is a loss of orexin-producing neurons, often due to autoimmune mechanisms triggered by HLA-DQB1*06:02 positivity and possibly viral infections[37,38]. Current treatments include modafinil, sodium oxybate, and orexin receptor agonists in development, such as danavorexton, which aim to restore orexin signaling[39].

Sleep apnea and circadian hormonal disruption: The OSA is associated with intermittent hypoxia, fragmented sleep, and altered secretion of circadian hormones. Melatonin levels are often reduced in OSA patients, while the normal cortisol rhythm becomes blunted, potentially exacerbating cardiovascular and metabolic complications[40]. The CPAP therapy has been shown to restore hormonal rhythms, reduce oxidative stress, and improve cognitive performance in patients with moderate to severe OSA[41].

Restless leg syndrome (RLS) and dopaminergic dysregulation: The RLS is a sensorimotor disorder linked to dysfunction in the dopaminergic system and iron deficiency. Iron is a necessary cofactor for tyrosine hydroxylase, the enzyme that catalyzes dopamine synthesis. The MRI studies have shown reduced iron concentrations in the substantia nigra of RLS patients[42].

Although primarily dopaminergic, RLS may also reflect broader circadian misalignments. Dopamine agonists like pramipexole and ropinirole are effective in reducing RLS symptoms, although long-term use can lead to augmentation, necessitating careful clinical management[43].

Circadian rhythm sleep-wake disorders and clock gene disruption: Circadian Rhythm Sleep-Wake Disorders (CRSWDs) result from desynchronization between endogenous biological rhythms and environmental time cues. At the molecular level, these disorders are often linked to disruptions in the expression or function of core clock genes such as CLOCK, BMAL1, PER, and CRY, which regulate rhythmic transcriptional cycles across the central nervous system and peripheral tissues. Dysregulation of these genes impairs the sleep-wake cycle, leading to conditions like delayed sleep phase disorder, shift work disorder, and non-24 hrs sleep-wake rhythm disorder[44]. Emphasized that clock gene integrity is critical to maintaining circadian coherence, as these genetic networks influence melatonin secretion, core body temperature rhythms, and hormonal oscillations[44]. The CRSWDs have been associated with increased risk of mood disturbances, metabolic disorders, and reduced cognitive performance. Therapeutic approaches such as light therapy, melatonin administration, and sleep scheduling have been shown to improve entrainment by targeting the circadian system[44].

Neurodegenerative sleep disorders and circadian clock impairment: In neurodegenerative diseases such as Alzheimer's and Parkinson's, sleep disturbances are strongly linked to circadian rhythm dysfunction. Degeneration of the Suprachiasmatic nucleus (SCN), the central pacemaker, along with reduced expression of circadian genes, leads to fragmented sleep patterns, blunted melatonin rhythms, and dysregulated hormonal outputs. Yakubu *et al*.[44] highlighted the role of circadian disruption in exacerbating both sleep and cognitive symptoms in these diseases, suggesting that neurodegeneration itself may impair molecular timekeeping[44]. In Alzheimer's, diminished melatonin secretion and SCN atrophy correlate with increased nocturnal activity and daytime sleepiness. In Parkinson's, circadian phase shifts and REM sleep behavior disorder reflect dopaminergic degeneration affecting circadian synchrony. Circadian-based interventions, such as timed light exposure and melatonin therapy, can improve sleep architecture and may potentially slow cognitive decline when administered early[44].

CONCLUSION

Sleep regulation is governed by a complex interplay of neurochemical systems, with key roles played by GABA, serotonin, adenosine, melatonin, and orexins. Disruptions in these pathways contribute to the pathophysiology of various sleep disorders. Integrating molecular insights with established

neurobiological frameworks supports the advancement of targeted, precision-based therapies. Continued interdisciplinary research is essential to unravel the intricate mechanisms of sleep and to enhance clinical outcomes in associated neuropsychiatric and metabolic conditions.

SIGNIFICANCE STATEMENT

Sleep disorders affect millions worldwide, yet the underlying biochemical mechanisms governing sleep regulation remain incompletely understood, hindering the development of targeted therapies. This review elucidates the complex interplay between neurotransmitters (e.g., GABA, serotonin, adenosine) and hormones (e.g., melatonin, cortisol, orexins) in modulating sleep stages, circadian rhythms, and the pathophysiology of common sleep disorders. By integrating molecular, neurochemical, and hormonal evidence, the article provides a cohesive framework that advances understanding of sleep biology. These insights not only inform therapeutic strategies for insomnia, narcolepsy, and sleep apnea but also support the growing field of personalized sleep medicine. Furthermore, the findings have broader implications for managing neuropsychiatric and metabolic conditions, emphasizing the interdisciplinary relevance of sleep research in public health and clinical practice.

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