PRINT ISSN 1119-8362
Electronic ISSN 2659-1499

Full-text Available Online at
https://www.ajol.info/index.php/jasem
https://www.bioline.org.br/ja

J. Appl. Sci. Environ. Manage.
Vol. 29 (4) 1217-1227 April 2025

Sleep, Neuroendocrine Disorders, And the Bidirectional Relationship between the Hypothalamic-Pituitary-Adrenal Axis: A Mini-Review

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ABSTRACT: This review explores the intricate and bidirectional relationships between the hypothalamic-pituitary-adrenal (HPA) axis, sleep architecture and regulation, and the manifestation of various neuroendocrine disorders. The HPA axis, a critical component of the stress response system, exhibits diurnal rhythmicity and is profoundly influenced by sleep. Conversely, HPA axis activity significantly impacts sleep quality, duration, and consolidation. Disruptions in either the HPA axis or sleep can lead to or exacerbate a range of neuroendocrine disorders, including depression, anxiety disorders, Cushing's syndrome, Addison's disease, and sleep disorders themselves (e.g., insomnia, sleep apnea). This review examines the physiological mechanisms underlying these interactions, focusing on the roles of key hormones like cortisol, corticotropin-releasing hormone (CRH), and adrenocorticotropic hormone (ACTH). Furthermore, it discusses the clinical implications of these interrelationships, including diagnostic considerations and potential therapeutic strategies that target the HPA axis and sleep pathways to improve outcomes in individuals with neuroendocrine disorders. A thorough understanding of this complex interplay is crucial for developing effective interventions and personalized treatment approaches.

DOI: https://dx.doi.org/10.4314/jasem.v29i4.25

Cite this Article as: UDI, O. A (2025). Sleep, Neuroendocrine Disorders, And the Bidirectional Relationship between the Hypothalamic-Pituitary-Adrenal (Hpa) Axis: A Mini-Review. *J. Appl. Sci. Environ. Manage.* 29 (4) 1217-1227

Dates: Received: 27 February 2025; Revised: 26 March 2025; Accepted: 10 April 2025; Published: 30 April 2025

Keywords: Sleep Apnea; Cushing's syndrome; Addison's disease; Stress Response; Hypothalamic-Pituitary-Adrenal

The human body has an intricate system for responding to stress and maintaining homeostasis, known as the Hypothalamic-Pituitary-Adrenal (HPA) axis (Mbiydzenyuy and Qulu, 2024). The HPA axis is a complex network of interactions between the hypothalamus, pituitary gland, and adrenal glands, which work together to release hormones in response to stress (Mueller *et al*., 2022; Esegbue *et al.*, 2019). When the body experiences stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which then triggers the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH then signals the adrenal glands to produce cortisol, the primary stress hormone, which helps the body respond to stress by increasing energy, alertness, and immune function. Once the stressor is removed, the levels of CRH, ACTH, and cortisol decrease, and the body returns to a state of homeostasis (Hinds and Sanchez, 2022; Milleniari, 2023). Sleep architecture is another critical aspect of human health, consisting of distinct stages that cycle throughout the night. These stages include wakefulness, rapid eye movement (REM) sleep, and non-REM sleep, which is further divided into three stages. Each stage serves a particular function in the restorative process of sleep, with non-REM sleep being essential for physical recovery and REM sleep playing a crucial role in cognitive functions such as memory

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consolidation. The importance of sleep for overall health cannot be overstated, as it affects various aspects, including memory, mood, immune function, and cardiovascular health (Chokroverty, 2017; Baranwal *et al*., 2022). Neuroendocrine disorders refer to conditions that affect the complex interactions between the nervous and endocrine systems. These disorders can result in hormonal imbalances, which can have significant impacts on various bodily functions, including growth, metabolism, and stress response. Neuroendocrine disorders can arise from genetic or environmental factors, with some being more prevalent than others. Common examples of neuroendocrine disorders include diabetes, acromegaly, and Cushing's disease, all of which can have profound effects on an individual's overall health and quality of life (Bala *et al.*, 2021; Kivimäki *et al*., 2023).

Significance of Interplay: The hypothalamic-pituitary-adrenal (HPA) axis, sleep, and neuroendocrine function are intricately intertwined in a complex, bidirectional relationship. The HPA axis, as the body's primary stress response system, influences both sleep architecture and the release of various hormones, including cortisol (Dressle *et al*., 2022). Conversely, sleep disturbances, whether chronic insomnia or shift work-related disruptions, can significantly impact HPA axis activity, often leading to elevated cortisol levels. Furthermore, neuroendocrine hormones, such as growth hormone and melatonin, which are regulated by both the HPA axis and sleep, play a vital role in modulating sleep cycles and HPA axis responsivity (Smith and Mong, 2019). This complex dance highlights a system where dysfunction in one area can cascade and disrupt the others. Grasping this complex interaction is essential for deciphering the underlying mechanisms of various disorders and formulating effective treatment approaches. For example, chronic stress and disrupted sleep, often leading to HPA axis dysregulation, are implicated in conditions ranging from depression and anxiety to metabolic syndrome and autoimmune diseases. By recognizing the bidirectional influences between these systems, clinicians can adopt a more holistic approach, targeting multiple aspects of the system for more effective interventions. Treating insomnia, managing stress levels, and optimizing neuroendocrine function could all contribute to improving HPA axis regulation and ultimately alleviating symptoms of associated disorders. A comprehensive understanding at the systems level offers insights for creating focused therapies that recognize and tackle the complex nature of these interrelated systems, giving hope for innovative and more efficient treatments.

MATERIALS AND METHOD

The search strategy involved leveraging the PubMed and Web of Science databases. Studies were selected if they explored the connection between sleep patterns and HPA axis function in individuals, regardless of whether they had diagnosed neuroendocrine disorders. The exclusion criteria included studies that focused exclusively on pharmacological treatments without analyzing the underlying neuroendocrine mechanisms, animal studies, and articles published in languages other than English. The chosen articles were subsequently evaluated for their methodological soundness, sample size, and the clarity of their results, emphasizing the examination of bidirectional connections between sleep architecture and HPA axis activity within different neuroendocrine disorders. The insights obtained from these studies were then integrated to offer a succinct overview of the existing knowledge regarding this intricate relationship. The primary objective is to analyze existing literature to address key questions regarding how these neuroendocrine imbalances affect: (1) sleep latency and efficiency, (2) the duration and proportion of different sleep stages, (3) the presence and severity of sleep-disordered breathing, and (4) the overall subjective sleep quality reported by affected individuals.

The Hypothalamic-Pituitary-Adrenal (HPA) Axis: The hypothalamus, a small but vital region located deep within the brain, serves as the control center for the HPA axis (Udi, 2025; Heck and Handa, 2019). Think of it as the conductor of an orchestra, orchestrating the hormonal responses to a diverse array of inputs. It constantly monitors internal and external cues, including stress signals (like encountering a dangerous situation or experiencing emotional distress), inflammatory responses (like fighting off an infection), and circadian signals (related to the daily light-dark cycle). When the hypothalamus detects a stressor or receives specific circadian signals, it initiates the HPA axis cascade. This cascade begins with the release of corticotropin-releasing hormone (CRH), a neuropeptide that acts as the primary messenger within the HPA axis. CRH is secreted from the hypothalamus and travels a short distance to the anterior pituitary gland, a pea-sized gland situated just below the hypothalamus. Upon reaching the anterior pituitary, CRH binds to specific receptors, stimulating the synthesis and release of adrenocorticotropic hormone (ACTH). ACTH is a peptide hormone that enters the bloodstream and embarks on a journey to its target organ: the adrenal cortex. The adrenal glands are two small, triangular-shaped glands located on top of the kidneys (Paloka *et al*., 2022). Each adrenal gland has two distinct

regions: the inner medulla (responsible for adrenaline production) and the outer cortex. It is the adrenal cortex that receives the ACTH signal. When ACTH reaches the adrenal cortex, it binds to receptors on the cells of the cortex, triggering a complex enzymatic process that leads to the synthesis and release of cortisol. Cortisol, often referred to as the "stress hormone," is a glucocorticoid hormone with widespread effects throughout the body. It plays a crucial role in regulating glucose metabolism, suppressing the immune system, assisting in fat, protein and carbohydrate metabolism, and increasing alertness. Its release is essential for mobilizing energy reserves to cope with stress, manage blood sugar levels, and modulate the immune response. For example, during a stressful situation like public speaking, cortisol helps provide the energy needed to perform and focuses attention on the task at hand (Das *et al.*, 2024; Goel *et al*., 2023; Heck and Handa, 2019; Vashishth *et al*., 2024).

The synthesis of cortisol within the adrenal cortex is a meticulous and multi-stepped process. It begins with cholesterol as the precursor molecule. Cholesterol is converted into cortisol through a series of enzymatic reactions, each catalyzed by a specific enzyme. These enzymes are located within the mitochondria and endoplasmic reticulum of the adrenal cortex cells. Because cholesterol is the initiating element in this process, sufficient availability of it is essential for the body to manage stress well. To prevent excessive cortisol production and maintain hormonal equilibrium, the HPA axis operates under a tightly controlled negative feedback mechanism (Androulakis 2021). As cortisol levels rise in the bloodstream, they act as inhibitors, signaling back to both the hypothalamus and the pituitary gland. High cortisol levels suppress the release of CRH from the hypothalamus, reducing the drive for ACTH production. Simultaneously, cortisol inhibits the pituitary gland's responsiveness to CRH, further dampening ACTH release (Al-Suhaimi *et al.*, 2022). This negative feedback loop ensures that cortisol levels do not spiral out of control, preventing potential damage to the body. This intricate control mechanism is akin to a thermostat, maintaining cortisol levels within a healthy range. Beyond its role in stress response, the HPA axis is also deeply intertwined with the circadian rhythm. The circadian rhythm is an internal biological clock that regulates numerous physiological processes, including the sleep-wake cycle, hormone secretion, body temperature, and metabolism, over a roughly 24-hour period. The suprachiasmatic nucleus (SCN) in the hypothalamus is considered the master pacemaker of the circadian clock. The SCN receives light information from the retina and synchronizes the body's internal rhythms with the external environment. Cortisol secretion exhibits a distinct circadian pattern. Typically, cortisol levels are highest in the morning, peaking shortly after waking. This morning surge in cortisol promotes alertness, enhances cognitive function, and prepares the body for the demands of the day. As the day progresses, cortisol levels gradually decline, reaching their lowest point around midnight, promoting relaxation and facilitating sleep. This circadian regulation of cortisol ensures that the body's stress response system is primed for the predictable challenges of daily activities (Agorastos, 2020; Luo, *et al*., 2021).

Disruption of the circadian rhythm through factors such as shift work, frequent travel across time zones (jet lag), irregular sleep schedules, or exposure to artificial light at night can severely impact HPA axis function. Such disruptions can lead to alterations in cortisol secretion patterns, potentially resulting in chronically elevated cortisol levels, impaired stress response, metabolic dysregulation, sleep disturbances, mood disorders, and a weakened immune system. For example, individuals working night shifts often experience chronic stress, sleep problems, and increased risk of metabolic diseases due to the misalignment of their circadian rhythm and their work schedule (Cingi *et al*., 2018; Steinach and Gunga, 2020).

HPA Axis and Stress Response: The hypothalamic-pituitary-adrenal (HPA) axis is a crucial neuroendocrine system that orchestrates the body's response to stress, both acute and chronic (Kinlein and Karatsoreos, 2020). When faced with a stressor, the hypothalamus releases corticotropin-releasing hormone (CRH), which triggers the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH then travels through the bloodstream to the adrenal glands, stimulating them to produce cortisol, the primary stress hormone. This cortisol surge mobilizes energy reserves by increasing glucose levels, suppressing non-essential functions like digestion, and enhancing cardiovascular tone to prepare the body for "fight or flight." This acute response is adaptive, enabling us to effectively deal with immediate threats. However, prolonged activation of the HPA axis in response to chronic stressors can have detrimental consequences on various physiological systems. Constant exposure to elevated cortisol levels can suppress the immune system, making individuals more susceptible to infections and autoimmune disorders. Metabolically, chronic stress can lead to insulin resistance, weight gain, and an increased risk of type 2 diabetes and

cardiovascular disease (Al-Suhaimi, *et al*., 2022). Furthermore, prolonged HPA axis activation can significantly impact the brain, leading to neuronal damage in areas like the hippocampus (crucial for memory) and contributing to anxiety, depression, and cognitive impairments (Sharan and Vellapandian, 2024). The delicate balance of the HPA axis is thus essential for maintaining health, and chronic disruption can pave the way for a cascade of negative health outcomes.

HPA Axis Dysfunction: Dysfunction within the HPA axis can manifest in various ways, with significant consequences for overall health, including profound effects on sleep. Cushing's syndrome, characterized by hypercortisolism (excess cortisol), can stem from various causes, such as pituitary tumors or prolonged use of corticosteroid medications. Its symptoms include weight gain, particularly in the trunk and face, high blood pressure, muscle weakness, and cognitive impairments (Reincke and Fleseriu, 2023). Insomnia, fragmented sleep, and decreased slow-wave sleep are frequently caused by the high cortisol levels in Cushing's syndrome, which also interfere with the regular sleep-wake cycle (Dressle *et al*., 2022). On the other hand, injury to the adrenal glands causes Addison's disease, which is caused by hypocortisolism (insufficient cortisol). Fatigue, weakness in the muscles, weight loss, low blood pressure, and darkening of the skin are some of the symptoms. Due to the absence of cortisol, Addison's disease patients may have severe daytime drowsiness, trouble falling and staying asleep, and even the possibility of developing sleep apnea. Other illnesses including chronic stress and trauma can also cause disruption of the HPA axis, in addition to these particular disorders. Chronic HPA axis activation brought on by extended stress can contribute to anxiety, sadness, and disturbed sleep patterns, which are frequently characterized by trouble falling asleep and frequent awakenings (Kalmbach *et al.*, 2018). Similarly, HPA axis reactivity can be permanently changed by trauma, especially early-life trauma, increasing the likelihood of stress-related diseases and sleep difficulties in later life (Blake *et al.*, 2018). For people with HPA axis dysfunction, creating focused interventions to enhance sleep quality and general well-being requires an understanding of the complex link between the HPA axis and sleep.

Sleep Architecture and Regulation

Stages of Sleep: Sleep is not a monolithic state, but rather a cyclical journey through distinct stages, each characterized by unique physiological and neurological changes. These stages can be broadly categorized into Non-Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep. The three stages of NREM sleep are NREM 1, NREM 2, and NREM 3. Theta waves predominate during NREM 1, the slower brainwave activity that occurs during the transition between awake and sleep. Muscles relax, and breathing and heart rate start to decrease. NREM 2 is a deeper sleep stage where theta waves continue, interspersed with sleep spindles and K-complexes, which protect the brain from being aroused by external stimuli. Heart rate and body temperature further decrease. Lastly, the largest and slowest brainwaves, known as delta waves, are what define NREM 3, sometimes referred to as deep sleep or slow-wave sleep. The immune system, muscle growth, and physical healing all depend on this stage, which is also the most difficult to awaken. Brain activity is greatly decreased, and breathing and heart rate are at their slowest (Andrillon, 2023; Avidan 2022; Satapathy *et al*., 2021; Prerau *et al*., 2017).

After progressing through NREM sleep, the cycle shifts into REM sleep. In stark contrast to the slow, synchronized brain activity of NREM 3, REM sleep is characterized by rapid, desynchronized brainwave activity resembling wakefulness. Rapid eye movements take place under closed eyelids, as the term implies. Blood pressure rises as breathing and heart rate become erratic and rapid. Ironically, the muscles are effectively paralyzed, preventing the body from enacting dreams, even while the brain is very active. Emotional processing, memory consolidation, and vivid dreams are all closely linked to this stage. The whole sleep cycle, from NREM 1 to REM, usually lasts between 90 and 120 minutes. It is repeated multiple times during the night, and the amount of time spent in each stage changes as the night goes on (Koob and Colrain, 2020; Prerau *et al*., 2017).

Regulation of Sleep-Wake Cycle: An intricate web of internal and external variables carefully controls the sleep-wake cycle, a basic biological function. The hypothalamic small cluster of neurons known as the suprachiasmatic nucleus (SCN) is at the center of this regulation. Sleep is regulated by circadian rhythms, which are about 24-hour cycles produced by the SCN, which serves as the body's master clock (Pandi-Perumal *et al.*, 2022). These rhythms are entrained, or synchronized, to the outside world, mostly via light exposure that is recognized by the eyes, rather than being fixed. Hormones and neurotransmitters are also important in regulating wakefulness and sleep patterns. The pineal gland produces the hormone melatonin, which is sometimes called the "sleep hormone" because it increases in the evening and encourages drowsiness (Samanta, 2022). Adenosine,

a neurotransmitter that accumulates throughout the day as a byproduct of cellular activity, also contributes to sleep pressure, making us feel tired and eventually leading to sleep. The interplay between these and other neurochemicals fine-tunes our sleep-wake cycle to ensure we are aware and effective during the day and restful during the night.

Ultimately, the control of the sleep-wake cycle is greatly influenced by outside variables. An important synchronizer that suppresses melatonin production and promotes wakefulness is light exposure, as was previously indicated. Likewise, temperature has an impact on sleep; in general, a cooler setting promotes the onset and maintenance of sleep. Exercise, mealtimes, and social interactions are a few other outside factors that can have an indirect impact on the SCN and help regulate the sleep-wake cycle overall. Unbalances in the circadian rhythm and sleep disorders can arise from disruptions to these external cues, such as shift work or jet lag (Foster, 2020).

Sleep Disorders: Stress, poor sleep hygiene, or underlying medical conditions are often the triggers for insomnia, which is characterized by difficulty falling or staying asleep and can be classified into acute and chronic forms. Sleep disorders are a serious public health concern that include a variety of conditions that interfere with normal sleep patterns. Long-term sleeplessness can cause the hypothalamic-pituitary-adrenal (HPA) axis to become dysregulated, which raises cortisol levels and intensifies the stress response. Obstructive and central apnea is two types of sleep apnea, a disorder characterized by breathing pauses during sleep (Chokroverty, 2017).

The intermittent hypoxia associated with sleep apnea can activate the HPA axis, contributing to increased blood pressure and cardiovascular risk. Narcolepsy, a neurological disorder characterized by excessive daytime sleepiness and cataplexy, is thought to be caused by a deficiency in hypocretin, a neurotransmitter that also influences hormonal regulation. Sufferers experience hormonal changes linked to sleep irregularities. Restless legs syndrome (RLS), characterized by an irresistible urge to move the legs, particularly at night, can significantly disrupt sleep and lead to distress, some studies have suggested a relationship between the systems. Finally, Parasomnias, such as sleepwalking and night terrors, involve abnormal behaviors during sleep and may arise from disruptions in neuroendocrine function, although the precise mechanisms are still unclear (Mansukhani, 2017; Wilson *et al*., 2018; Wang *et al*., 2021).

Neuroendocrine Disorders

Specific Disorders and Their Hormonal Imbalances: Thyroid disorders, both hyperthyroidism and hypothyroidism, can significantly disrupt sleep patterns and influence the hypothalamic-pituitary-adrenal (HPA) axis, a key regulator of the stress response. Hyperthyroidism, characterized by an overactive thyroid gland, often leads to insomnia, difficulty falling asleep, and frequent awakenings due to increased metabolic activity and anxiety (Yiallouris *et al.*, 2024). This state of heightened arousal can also chronically activate the HPA axis, potentially leading to elevated cortisol levels, which further exacerbate sleep disturbances and may contribute to long-term health consequences. Conversely, hypothyroidism, caused by an underactive thyroid gland, can manifest as excessive daytime sleepiness and increased sleep duration. While individuals might sleep longer, the quality of sleep is often poor, with complaints of feeling unrefreshed. Though the processes are less understood than in hyperthyroidism, hypothyroidism can also indirectly impact the HPA axis and result in changes to the generation and control of cortisol. Thus, maintaining a balanced HPA axis and reestablishing good sleep patterns depend on properly controlling thyroid function. The hypothalamic-pituitary-adrenal (HPA) axis, a critical modulator of stress response and circadian rhythms, and sleep architecture can be profoundly affected by growth hormone (GH) problems (Knezevic *et al.*, 2023). Sleep habits are frequently disturbed by acromegaly, which is defined by high growth hormone production in adults. Reduced slow-wave sleep (SWS) and rapid eye movement (REM) sleep are among the changes in sleep stages that have been documented in studies. These changes may result in daytime weariness and cognitive impairment (Lafrenière *et al.*, 2023; Wood *et al*., 2021; Diep *et al*., 2020). Moreover, acromegaly may contribute to elevated cortisol secretion and exacerbate sleep difficulties by dysregulating the HPA axis. On the other hand, GH insufficiency, whether in childhood or maturity, can similarly affect HPA axis activity and sleep. Sleep architecture changes, such as decreased SWS and increased fragmentation, have been associated with GH insufficiency. It has a complicated effect on the HPA axis; some research indicates disruption of the diurnal cortisol rhythm, while others imply lower cortisol levels and a compromised stress response (Wood *et al*., 2021; Diep *et al.*, 2020). It is essential to comprehend the complex interactions among sleep, GH problems, and HPA axis function in order to design tailored treatments that will enhance patient outcomes.

Sleep and the hypothalamic-pituitary-adrenal (HPA) axis, a crucial component for the stress response, are both greatly impacted by reproductive hormone abnormalities. Women with PCOS, a condition marked by hormonal imbalances, frequently experience disturbed sleep patterns and changed HPA axis activity, which may exacerbate anxiety and metabolic problems. Similarly, insomnia and hot flashes are often linked to menopause, which is characterized by a decrease in estrogen and progesterone. These symptoms both affect the quality of sleep and activate the HPA axis (Hantsoo *et al*., 2023). Last but not least, hypogonadism, which affects both men and women and involves a decrease in the synthesis of sex hormones, can also change hormone-mediated signaling pathways that affect sleep regulation and disturb sleep patterns. Developing focused therapies to enhance sleep and general health in people with these reproductive hormonal disorders requires an understanding of these connections.

Sleep and the hypothalamic-pituitary-adrenal (HPA) axis can be severely disrupted by a range of less frequent but no less serious illnesses, which extend beyond the well-known adrenal disorders of Cushing's syndrome and Addison's disease. The genetic condition known as congenital adrenal hyperplasia (CAH), which affects the adrenal glands' capacity to produce cortisol, might result in excessive androgen production. This can then impact the architecture of sleep, perhaps causing disruptions (Hughes *et al.*, 2019). The HPA axis may be directly impacted by the changed hormonal milieu in CAH, which is caused by both excess androgens and insufficient cortisol. This can result in dysregulation and interfere with the regular diurnal cortisol rhythm, which is essential for sleep-wake cycles.

Similarly, sleep can be severely disrupted by pheochromocytoma, a rare tumor of the adrenal medulla that results in an excess of catecholamines such as noradrenaline and adrenaline. These "fight-or-flight" hormones can cause anxiety, insomnia, and night sweats, which can disrupt sleep and make it difficult to have periods of rest.

Furthermore, the chronic overstimulation caused by pheochromocytoma can profoundly influence the HPA axis, potentially causing significant alterations in cortisol levels and influencing the body's stress response system, further exacerbating sleep disturbances. Understanding the particular processes by which these adrenal diseases affect sleep and the HPA axis is critical for designing tailored therapeutic approaches to enhance patient outcomes.

The Role of Hormones in Sleep Regulation: Hormones play a critical role in regulating sleep, acting as key messengers that orchestrate the complex processes involved in sleep initiation, maintenance, and architecture. Melatonin, often dubbed the "sleep hormone," is central to this process. Released by the pineal gland in response to darkness, melatonin promotes sleepiness and helps to regulate the sleep-wake cycle, facilitating both the onset and maintenance of sleep. The stress hormone cortisol, on the other hand, has a clear circadian rhythm; it usually peaks in the morning to encourage alertness and progressively decreases throughout the day to aid in the onset of sleep. The sleep-wake cycle can be greatly impacted by disturbances in the cortisol rhythm, which can lead to insomnia and other sleep problems. Thyroid hormones can have a significant impact on the structure and general quality of sleep. Both hyperthyroidism and hypothyroidism can interfere with sleep cycles, resulting in diminished slow-wave sleep, trouble falling asleep, and frequent awakenings. In addition to these major actors, other hormones that regulate hunger, such as ghrelin and leptin, also affect sleep. The complex relationship between hormonal regulation and the sleep-wake cycle is highlighted by the fact that imbalances in these hormones can impact the length and quality of sleep. (Camberos-Barraza *et al*., 2024).

The Interplay: HPA Axis, Sleep, and Neuroendocrine Disorders

Bidirectional Relationships: The bidirectional interaction between sleep and the hypothalamic-pituitary-adrenal (HPA) axis is complex, meaning that each can have a significant impact on the other. Insomnia and other sleep problems can be further exacerbated by dysfunction in the HPA axis, which is typified by persistent activation or suppression. For example, disturbed sleep start and maintenance can result in fragmented and non-restorative sleep due to increased cortisol levels, which are a sign of chronic stress and hyperactivity of the HPA axis. On the other hand, sleep disorders themselves can have a devastating effect on the activity of the HPA axis. Over time, chronic sleep deprivation or irregular sleep patterns may contribute to HPA axis hyperactivity by dysregulating cortisol secretion, which can result in increased levels in the evening when they should be decreasing. Additionally, sleep architecture and HPA axis function are frequently disrupted by neuroendocrine disorders like Addison's disease (cortisol deficiency) and Cushing's syndrome (excess cortisol). This leads to a vicious cycle in which hormone imbalances worsen sleep issues, which in turn causes poor sleep to further disrupt hormonal regulation. Given the interdependence of

these systems, this complex interaction emphasizes the necessity of a comprehensive strategy for treating sleep issues or HPA axis dysfunction (Mueller *et al*., 2022; Hinds and Sanchez, 2022).

Mechanisms of Interaction: The intricate interplay between neurological and systemic processes hinges on several key mechanisms. Neurotransmitter pathways, such as those utilizing GABA, glutamate, and serotonin, serve as critical communication networks. Disruptions in these pathways, whether through imbalances in neurotransmitter release, receptor sensitivity, or reuptake mechanisms, can have profound effects far beyond localized brain function. Furthermore, inflammatory processes play a significant role in this interaction. Chronic or dysregulated inflammation, both within the brain (neuroinflammation) and systemically, can alter neurotransmitter function and contribute to neurodegeneration, impacting cognitive and behavioral outcomes. Finally, genetic factors introduce an element of predisposition, influencing individual vulnerability to these interactions. Variations in genes related to neurotransmitter synthesis, inflammatory pathways, and immune function can collectively determine the susceptibility to neurological disorders influenced by systemic processes and vice versa (Konstantinou *et al*., 2022; Firdaus and Li, 2024). Understanding these multifaceted mechanisms is crucial for developing targeted therapeutic interventions.

Clinical Manifestations: When several illnesses coexist in one patient, the clinical signs of endocrine disorders can become quite complicated. For instance, sleeplessness may also be present in a patient with Cushing's syndrome, which is defined by extended exposure to elevated cortisol levels. The excess cortisol can disrupt the normal sleep-wake cycle, exacerbating pre-existing sleep difficulties or even inducing new ones (Dressle *et al.*, 2022).

Managing these patients poses significant challenges, as attributing specific symptoms to a single underlying cause becomes difficult. The complex interplay between conditions like Cushing's syndrome and insomnia necessitates a holistic approach to diagnosis and treatment. Clinicians must carefully differentiate between the symptoms stemming from each condition and consider the potential impact of one on the other. This often requires a combination of biochemical testing, imaging studies, and thorough patient history, followed by a tailored treatment plan that addresses both the root causes and the symptomatic burden of each condition.

Therapeutic and Diagnostic Methods

Diagnostic Tools: Diagnostic instruments are essential for assessing a range of medical disorders, especially those involving sleep and hormone abnormalities. The quality of sleep is evaluated using a variety of techniques, such as actigraphy, polysomnography, and sleep diaries. By recording heart rate, breathing, oxygen levels, and brain waves, polysomnography is a thorough examination that offers extensive insights into the structure and disruptions of sleep. Actigraphy, on the other hand, involves wearing a wrist device that tracks movement, thus offering a more accessible way to gauge sleep patterns over an extended period. Sleep diaries, kept by individuals over time, serve as a subjective tool to document sleep habits, contributing valuable qualitative data to the assessment process. In addition to sleep assessments, hormonal testing is critical for identifying endocrine disruptions. Cortisol level tests, such as the ACTH stimulation test, assess how well the adrenal glands are working and can assist diagnose diseases like Addison's disease or Cushing's syndrome. Thyroid hormones are essential for controlling metabolism and energy expenditure, and thyroid function tests measure their levels in the body. These hormone tests can provide a clearer picture of an individual's health status, directing treatment procedures and lifestyle improvements (Hussain *et al*., 2022; Baker *et al*., 2018). Additionally, imaging methods are crucial to the diagnosis procedure, especially when looking at hormone issues. By seeing the pituitary and adrenal glands via magnetic resonance imaging (MRI), medical professionals can spot any abnormalities or possible malignancies that might be affecting hormone production. Clinicians can create more focused and efficient interventions by integrating the findings of imaging examinations, hormonal testing, and sleep evaluations to gain a thorough picture of a patient's health.

Therapeutic Interventions: Addressing the multifaceted challenges of perimenopause requires a comprehensive approach that often incorporates both pharmacological and non-pharmacological therapeutic interventions. Pharmacological treatments frequently involve Hormone Replacement Therapy (HRT) to alleviate hormonal imbalances and associated symptoms like hot flashes and mood changes. Furthermore, medications targeting sleep disorders, such as hypnotics for short-term relief or antidepressants, which can improve sleep quality and address underlying mood disturbances, may be prescribed (Palagini *et al.*, 2024). In some cases, medications to modulate the Hypothalamic-Pituitary-Adrenal (HPA) axis, the body's stress response

system, might be considered to regulate cortisol levels and reduce anxiety. Complementing these pharmacological options are non-pharmacological interventions, including Cognitive Behavioral Therapy for Insomnia (CBT-I), a structured program to improve sleep habits and address negative thoughts surrounding sleep (Kristiansen *et al.*, 2024). Light therapy can be beneficial for regulating circadian rhythms and improving mood, particularly during the darker months. Moreover, stress management techniques, such as mindfulness and meditation, coupled with lifestyle modifications like dietary adjustments and regular exercise, play a crucial role in managing symptoms and promoting overall well-being during this transitional phase.

Personalized Medicine: A paradigm change in healthcare is represented by personalized medicine, which moves away from a "one-size-fits-all" approach to therapy and toward methods that are specifically customized for each patient. This novel method makes use of a patient's distinct traits, including their lifestyle, genetic composition, and coexisting medical disorders (comorbidities), to identify the best preventative, diagnostic, and treatment measures. In order to maximize therapy results, reduce side effects, and ultimately enhance patient well-being, customized medicine seeks to understand the unique biological and environmental elements driving disease in each individual. In addition to avoiding treatments that are unlikely to be beneficial or may even be harmful, this enables doctors to make well-informed decisions regarding which drugs or therapies are most likely to be successful for a certain patient (Kristiansen *et al.*, 2024; Andrew *et al.*, 2017).

Future Directions and Research Gaps: For future studies to completely clarify the intricate interactions between the conditions under investigation, a number of important open questions must be addressed. More precisely, there are still many unanswered questions regarding the exact mechanisms underlying the relationships that have been discovered, necessitating the investigation of numerous biological pathways and environmental factors. Finding possible therapeutic targets is another important direction for further research, with an emphasis on cutting-edge therapies that might alter particular neurotransmitter receptors or reduce inflammatory pathways linked to these interactions. Last but not least, longitudinal research is essential. To appropriately evaluate the long-term effects of these interactions and to ascertain how well putative therapies work to mitigate adverse outcomes, it is imperative to track patient cohorts over longer periods of time. Such long-term information will be crucial for creating thorough and individualized treatment plans.

Conclusion: To sum up, this review has brought to light the complex interactions among the neuroendocrine system, sleep regulation, and the hypothalamic-pituitary-adrenal (HPA) axis. The main conclusions point to a complicated reciprocal interaction in which disturbances in one area might have a substantial effect on the others, resulting in a series of physiological and psychological repercussions. Taking these results into account, a number of clinical practice implications become apparent. In order to diagnose and treat patients who may have a combination of sleep, neuroendocrine, and HPA axis issues, this study suggests using a more thorough and integrated approach. This entails meticulous evaluation of neuroendocrine aspects that may be influencing the clinical picture, as well as comprehensive screening for sleep difficulties in patients with established HPA axis dysfunction and vice versa. Lastly, it is critical to stress the significance of a patient-centered approach. In addition to treating specific symptoms, effective care must take into account the complex relationships between these systems, lifestyle choices, stress levels, and mental health in order to maximize patient outcomes and enhance quality of life in general.

Declaration of Conflict of Interest: There is no conflict of interest.

Data Availability: Data are available upon request from the corresponding author.

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