IJHSR
ijhighschoolresearch.org
REVIEW ARTICLE

Orexin Dysfunction, Chronic Stress, and the Neurobiology of Burnout Syndrome

Ariana Das

Shiv Nadar School Gurgaon, The Vilas, Akashneem Marg, DLF-phase 2, Gurgaon, Haryana, 122022, Delhi; arianadas2009@gmail.com

ABSTRACT: Burnout syndrome is something commonly diagnosed in individuals who have experienced prolonged stress. These individuals often express symptoms such as fatigue, sleep disruption, and emotional dysregulation, which suggests a potential psychiatric syndrome or clinical endophenotype overlapping with features of narcolepsy and depression. Recent research and studies suggest that the orexin (hypocretin) system, which is also a key regulator of arousal and stress, may be a causal factor in the conditions' etiology. In this review, we will focus on how exactly orexin dysfunction affects stress, arousal, and overall emotional regulation, drawing on findings from neuroimaging, animal models, and molecular studies. This review explores burnout as a neurobiological condition, proposing the orexin system's dysfunction as a potential biomarker. Through bridging research across neuroscience, psychiatry, and occupational health, it aims to inform more objective diagnostics and targeted interventions.

KEYWORDS: Biology, Chronic Stress, Stress Neurobiology, Burnout Syndrome, Orexin Dysfunction, Neuroendocrine Stress Response.

Introduction

In clinical psychology, burnout is increasingly recognized as a diagnosable mental disorder, particularly among patients seeking psychological treatment due to severe functional impairment at work.[1] Clinical definitions of burnout often align with the International Classification of Diseases (ICD-10) criteria for work-related neurasthenia, which include persistent and distressing fatigue following mental or minimal physical effort, along with at least four additional symptoms such as insomnia, cognitive impairments, somatic pain, palpitations, and heightened sensitivity to sound or light.[1,2] This clinical framing underscores the debilitating nature of burnout beyond ordinary workplace stress.[1] While stressful events are often well remembered, chronic exposure to aversive experiences has been shown to impair cognitive function significantly.[3] Prolonged stress disrupts the acquisition, storage, and retrieval of novel information, particularly in tasks requiring hippocampal involvement.[3] This is largely due to chronic stress impairing long-term potentiation (LTP) in the hippocampus, a key mechanism for encoding new information, thereby weakening the brain's ability to form and retain memories.[3] As a result, chronic stress profoundly affects spatial learning and other forms of hippocampus-dependent cognition.[3]

Orexin (hypocretin) refers to a pair of neuropeptides, orexin-A and orexin-B, produced in the hypothalamus, which act via two G-coupled receptors (OX1R and OX2R) to regulate wakefulness and broader homeostatic processes, including stress, metabolism, and reward.[4] Given orexin's central role in modulating arousal, energy expenditure, and sympathetic activity, concisely shown in Figure 1,[4] orexins are increasingly implicated in the body's response to chronic stress, an adaptive process that, when prolonged, contributes to the development of occupational burnout.[5] Chronic stress refers to a sustained physiological and psychological response to persistent or repeated stressors, real or perceived, that challenge an individual's ability to maintain homeostasis over time.[6] Unlike acute stress, which is adaptive and time-limited, chronic stress arises when stressors persist without resolution, resulting in prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis, altered neurotransmitter function, and systemic wear-and-tear, often termed "allostatic load".[5,7] On the other hand, occupational burnout is characterized by stress-related symptoms in otherwise healthy, high-performing individuals who have not experienced any major adverse life events.[8]

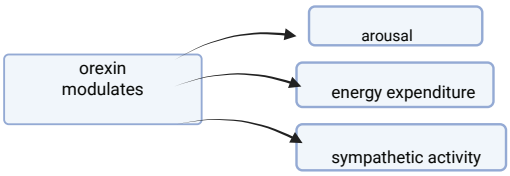

Figure 1: Simplified schematic illustrating the major physiological domains modulated by the orexin system, including arousal, energy expenditure, and sympathetic activity.[4]

Yet, the precise neurological link between chronic stress and emotional dysregulation remains unclear, prompting investigation into whether orexin system dysfunction may bridge this gap. Orexin neurons, particularly those in the perifornical and dorsomedial hypothalamus, are implicated in stress and arousal regulation, projecting widely to regions like the locus coeruleus, amygdala, etc.[9] Under repeated restraint stress, both heightened and diminished orexin activity have been observed, with reductions in CSF orexin A levels and neuronal activation following HPA axis habituation.[9] Orexin-deficient mice exhibit blunted stress responses in behavioral paradigms, further suggesting the neuropeptide's role in mediating stress-related behaviors.[10] Given orexin's role in coordinating arousal and emotion, its dysregulation may contribute to affective disturbances seen in

DOI: 10.36838/IJHSR89.103

occupational burnout.[11] Chronic emotional stress appears to disrupt emotion-regulation networks, limiting homeostatic recovery and increasing vulnerability to depression.[8] However, gaps remain in fully understanding orexin's function under repeated stress exposure.[9]

This review aims to investigate whether dysregulation in the orexin system underlies the emotional and physiological symptoms associated with occupational burnout. By synthesizing data from neuroimaging, molecular studies, and animal models, it examines how orexin contributes to stress modulation, arousal, and emotional regulation. In doing so, it proposes orexin dysfunction as a potential neurobiological marker of burnout. Understanding this link can help shift burnout diagnostics beyond subjective criteria and potentially contribute to the development of targeted, neurobiologically grounded interventions in occupational mental health.

I- Occupational Stress and Its Neurobiological Consequences:

Occupational stress is a widespread global issue with high personal and economic costs, with work-related depression alone estimated at €617 billion annually in the European Union (EU). Surveys report high prevalence worldwide, for instance, 32.4% of Japanese workers and nearly 28% of Chilean employees experience significant stress or anxiety,[12] further highlighting its immediate impact across a variety of settings. When such stress becomes chronic, it often culminates in burnout. Burnout, recognized by the World Health Organization (WHO) as a consequence of chronic workplace stress, is defined by three key factors: exhaustion, cynicism, and reduced efficacy.[13] Since Freudengraber's original concept in 1974,[14] Maslach and Jackson's framework has remained foundational in characterizing the syndrome, emphasizing emotional exhaustion, depersonalization, and diminished accomplishment.[15] However, more significantly, research has indicated an overlap with anxiety and depression, complicating the overall diagnosis.[15] This section explores the neurobiological impact of long-term occupational stress, focusing on the Hypothalamic-Pituitary-Adrenal axis (HPA axis) dysregulation and brain changes linked to emotional and cognitive symptoms.

The HPA axis is a key component of the gut-brain axis, which mediates the body's primary hormonal response through Corticotropin-Releasing Hormone (CRH), Adrenocorticotropic Hormone (ACTH), and cortisol, which operate via a negative feedback loop.[16] Normally, during slow-wave sleep, cortisol release is suppressed by reduced CRH and increased growth hormone (GH) secretion. However, chronic stress leads to abnormal activation of the HPA axis and sympathetic nervous system (SNS), disrupting the normal diurnal rhythm of GH, CRH, AND ACTH release.[17] Chronic Stress, particularly from early life experiences, can cause dysregulation of this system, disrupting cortisol regulation and impairing emotional and cognitive functioning.[18] Figure 2 shows how the orexin system interacts directly with the HPA axis. This dysregulation involves two cortisol receptors, MR and GR, where the mineralocorticoid receptor (MR) maintains baseline activity and the glucocorticoid receptor (GR) responds to acute or chronic stressors, especially in stress-sensitive regions such as the hippocampus and amygdala,[18,19] which considering orexin's dense expression in these interconnected brain regions,[20] could go on to suggest disruption of orexin signaling, as well as impairing emotional regulation and arousal control, which are core features implicated in burnout[1]. Understanding how prolonged occupational stress alters this neuroendocrine system is key to explaining burnout's neurobiology. Chronic HPA axis activation may not only disrupt cortisol regulation[19] but also interfere with orexin-linked circuits, which are essential for attention, emotional stability, and overall wakefulness, offering a pathway from sustained stress to emotional and cognitive fatigue[21].

Thus, chronic occupational stress disrupts the HPA axis and orexin-linked circuits, creating a biological pathway through which prolonged workplace strain translates into emotional exhaustion, cognitive fatigue, and vulnerability to burnout.

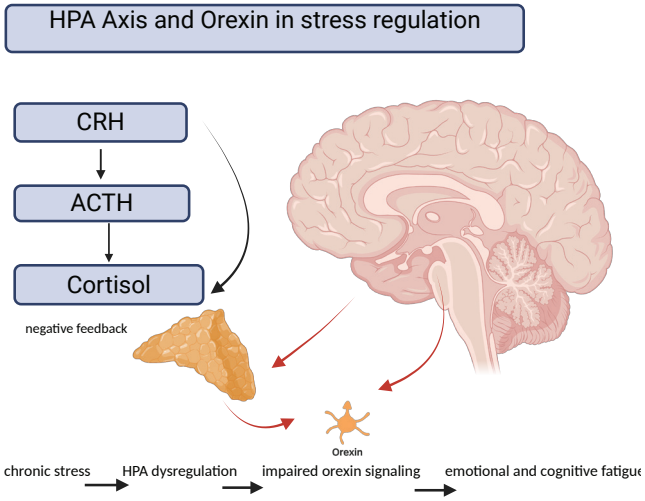

Figure 2: This shows the interaction between the HPA axis and orexin in stress regulation. Chronic stress leads to HPA axis dysregulation, which in turn disrupts orexin signaling in stress-sensitive brain regions, which contributes to emotional and cognitive fatigue.

Widespread exposure to stress is especially concerning due to its detrimental impacts on different aspects of your body/brain. Let's explore some of those impacts on systems like the brain, the immune system, the gastrointestinal system, etc.[22] Research over the past 50 years underscores stress-induced alterations in the nervous system, particularly affecting monoamine pathways.[23] Chronic stress causes structural and functional brain changes, such as hippocampal atrophy, reduced brain mass, impaired cognition and memory, as shown by Figure 3.[22,24,25] These effects depend on stress intensity and duration, with the overall outcome being reduced cognitive performance; conversely, stress reduction reliably improves cognition.[22,26]

Stress also suppresses immune function, decreasing cytotoxic T-lymphocytes and natural killer cell activity, thereby increasing susceptibility to malignant growth, genetic instability, and tumour progression.[27] While in the gastrointestinal system, stress disrupts appetite regulation via circuits involving the ventral tegmental area(VTA) and amygdala through N-methyl-D-aspartate (NMDA) receptors.[28] Nutrition and

stress are bidirectionally linked; diet influences stress responses, while stress impairs GI function.[22,29]

Together, these findings illustrate that while chronic stress can arise from many sources, occupational stress represents a particularly persistent form. Its impact is not merely psychosocial but also deeply biological, reshaping neurological, immune, and gastrointestinal systems in a way that converges with some of the core symptoms of burnout.

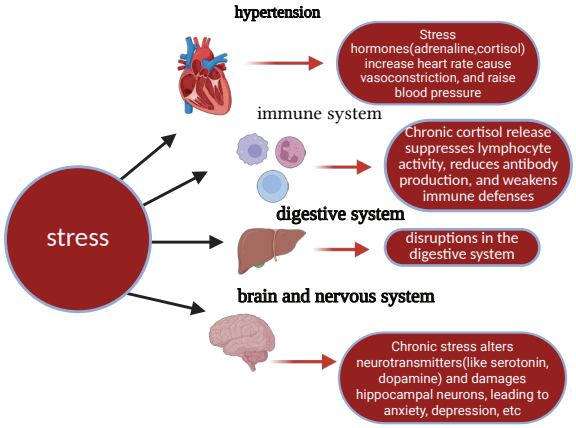

Figure 3: Stress impacts the immune system, digestive system, central nervous system, and cardiovascular system.

II- The Role of the Orexin System in Sleep, Mood, and Arousal:

The discovery of orexin-A and orexin-B, which are also known as hypocretin-1 and hypocretin-2, was first reported by Takeshi Sakurai through the process of orphan receptor cloning, marking it as a pivotal advancement in neurobiological research.[30] These neuropeptides are primarily synthesized by a specific population of neurons in the lateral hypothalamus (LH) and are structurally similar.[31] Following their identification, orexins were found to be widely distributed throughout both the central and peripheral nervous systems, suggesting their involvement in a broad range of physiological functions.[11,31]

Originally identified for their role in promoting feeding behavior, evidenced by increased food intake following central administration in rats and upregulation during fasting, orexins (both A and B) were later found to play a critical role in sleep-wake regulation.[21] The subsequent discovery that orexin deficiency leads to narcolepsy in humans and other mammals marked a turning point in understanding their function, particularly in sustaining prolonged wakefulness.[32]

ICV administration studies further reinforced this role showing that infusion of orexin A or B during the light period significantly increased wake time while suppressing both REM and non-REM sleep, thereby underscoring their wake-promoting function.[4,33] Conversely, sleep fragmentation and narcoleptic phenotypes observed in orexin knockout mice, receptor knockout models, and orexin neuron-ablated transgenic rats highlight the indispensable contribution of the system to sustaining sleep-wake states as already highlighted.[34,35]

Mechanistically, orexin neurons exert their effects through dense projections to monoaminergic populations in the brainstem and hypothalamus, including the locus coeruleus, dorsal raphe, and tuberomammillary nucleus, all of which express orexin receptors and are activated by orexin signalling. Orexins activate noradrenaline, serotonin, and histamine neurons in the brain, directly connecting them to the arousal network, which in turn helps the body stay awake.[4]

Aside from controlling wakefulness and arousal, orexins are also linked to emotions and stress. Orexin neurons get strong inputs from brain regions like the amygdala and BNST, which are integral for processing fear and emotion.[32] This allows them to influence stress hormones and body responses. In fact, overactive orexin signaling has been connected to panic disorder in both humans and animals.[36] The lateral hypothalamus (LH), where many orexin neurons are found, is often described as a 'defense area' because it helps drive stronger heart activity and stress reactions in threatening situations.[32]

Taken together, these findings illustrate how orexin systems bridge arousal, emotion, and stress physiology. This integration makes them especially vulnerable to long-term occupational stress, where chronic hyperactivation could produce a dual pattern of exhaustion and hyperarousal[37] closely resembling the dysregulated states seen in narcolepsy, depression, and ultimately, burnout syndrome.

III- Linking Orexin Deficiency to Narcolepsy and Depressive States:

Ironically, orexin neuropeptides, now recognized for their crucial role in regulating mood, arousal, and stress, were first discovered not in sleep research but in studies on appetite control and obesity, only later revealing their striking links to disorders such as narcolepsy and depression.[38]

Narcolepsy is a sleep disorder characterized by a fundamental disturbance in the regulation of sleep-wake cycles, with patients exhibiting a marked depletion of orexin-producing neurons and undetectable cerebrospinal fluid orexin concentrations.[39] The disorder affects roughly 1 in 2,000 individuals in the United States, highlighting how clinically significant this disorder is.[40,41] Extensive research demonstrates that orexin deficiency underlies narcolepsy, which manifests as an inability to sustain wakefulness, pathological intrusions of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep into waking periods, and unstable transitions between sleep and wake states.[42,43] Early evidence for this link emerged from animal studies, as prepro-orexin knockout mice and dogs with OX2R receptor mutations displayed narcoleptic phenotypes strikingly similar to those observed in humans.[44] Postmortem analyses of narcoleptic patients further confirmed these findings, revealing an 80-100% reduction of orexin-expressing neurons in the hypothalamus and undetectable peptide levels in projection areas.[45]

Importantly, beyond sleep regulation, orexin dysfunction has also been implicated in mood disorders such as depression, where altered orexin signaling may contribute to impaired arousal, circadian misalignment, and heightened vulnerability to emotional dysregulation.[43] Experimental models reinforce this link, where in zebrafish, ablation of orexin neurons increased sleep time and sleep-wake transitions, showing orexin's role in stabilizing behavioral state shifts to external inputs.[41,46]

DOI: 10.36838/IJHSR89.103

Parallel evidence comes from narcolepsy research, where it was first identified that canine narcolepsy was an autosomal recessive mutation, later pinpointed to a defective hypocretin-2 gene.[38] In humans, narcolepsy was instead traced to profound neuronal loss, with post-mortem analysis revealing a 93% reduction in hypocretin neurons compared to controls.[45,47] Notably, systemic administration of hypocretin in narcoleptic dogs produced an immediate increase in activity, calling attention to the therapeutic promise of restoring orexin signalling.[38]

Together, these findings suggest that orexin deficiency represents a unifying neurobiological mechanism underlying both narcolepsy and depressive states, suggesting that long-term occupational stress may trigger persistent orexin dysfunction underlying burnout syndrome, positioning the orexin system as a key target for diagnostics and interventions in burnout.

IV- Orexin Dysfunction Under Stress: Insights from Human and Animal Studies:

Orexins play an integral role in enabling the brain to adaptively respond to stressful stimuli, shifting the organism from a basal state to a reactive one.[48] Evidence for which comes from animal models, where orexin-deficient mice display markedly reduced stress-related behaviour, such as diminished activity in the resident intruder paradigm, therefore underscoring the importance of orexin signaling in stress regulation.[9] A functional dichotomy exists within orexin neurons, with those in the perifornical and dorsomedial hypothalamus driving stress and arousal.[9,49] Orexin's projections to the amygdala, Bed Nucleus of the Stria Terminalis (BNST), and Paraventricular Nucleus (PVN), where CRH neurons initiate the HPA axis, further link orexin to stress regulation.[9,50] Figure 4 depicts a model in which chronic occupational stress disrupts orexin signalling via mediators such as CRH and cortisol, leading to monoaminergic dysfunction and contributing to depression like symptoms, narcolepsy like symptoms, and burnout syndrome.

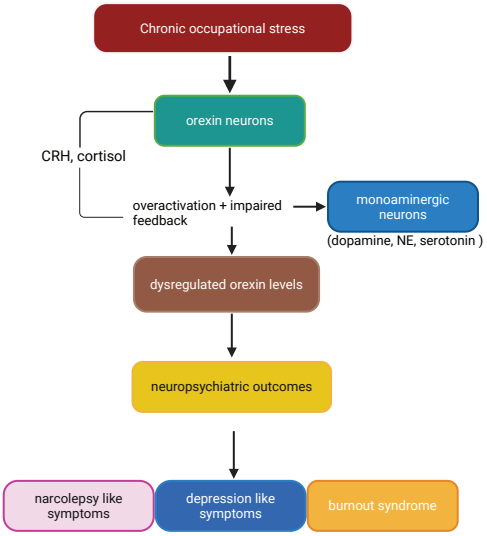

Figure 4: Proposed model of orexin dysfunction in stress-related disorders. Chronic occupational stress may lead to reduced orexin activity, disrupting the regulation of arousal, sleep-wake balance, and mood. This dysregulation overlaps with mechanisms observed in narcolepsy and depression, suggesting a potential neurobiological basis for burnout syndrome.

To further ground this link between chronic stress, HPA dysregulation, and orexin pathways, both human and neuroimaging studies and animal stress models provide converging experimental evidence

This study utilized a learned helplessness paradigm to test how orexin neurons shape stress-coping behavior. After repeated inescapable stress, mice were split into two groups: stress susceptible and stress resilient groups. Resilient mice showed higher c-fos activation in orexinergic neurons compared to susceptible ones, suggesting orexin activity supports adaptive coping. Using chemogenetic activation via Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) of orexin neurons in the lateral hypothalamus significantly increased active coping, reducing escape failures and latency. DREADDS are engineered G-protein-coupled receptors that allow researchers to selectively activate or inhibit specific neurons using otherwise inert synthetic ligands. This chemogenetic approach enables precise, cell-type-specific control of neuronal activity in freely moving animals, making it possible to directly link the activity of defined neural circuits, such as orexin neurons, to behavior and stress coping responses.[78] Conversely, reduced orexin activity was linked to helplessness-like behavior. Optogenetic experiments further confirmed that direct stimulation of orexin projections to the nucleus accumbens (NAc) and ventral tegmental area (VTA) boosted stress resilience. Behavioral assays (escape test, forced swim test) consistently showed that higher orexin activity correlates with quicker recovery and greater persistence under stress. Overall, these findings demonstrate that orexin neurons act as modulators of stress resilience, with dysfunction of orexin leading to vulnerability to depression like states[51].

Neuroimaging studies of patients with prolonged workplace stress, diagnosed with adjustment disorder but not depression, show reduced gray matter volumes in the Anterior Cingulate Cortex(ACC), Dorsolateral Prefrontal Cortex(dIPFC), and basal ganglia, regions central to stress regulation and motivation.[52] Basal ganglia volume loss correlated with perceived stress, and patients showed blunted cortisol/ACTH responses to CRH stimulation, pointing to HPA axis dysregulation specific to occupational stress.[53] These structural and endocrine changes overlap with circuits regulated by orexin, supporting its role as a pathway linking occupational stress to burnout.[54]

Rodent models of chronic unpredictable stress (CUS) show how prolonged stress reshapes brain circuits in ways relevant to occupational burnout. Repeated exposure to variable stressors produces classic signs of glucocorticoid overload, including adrenal enlargement, weight changes, and elevated corticosterone.[52] In the hippocampus and hypothalamus, neurons rich in stress hormone receptors become especially vulnerable: CUS reduces inhibitory signalling, heightens excitatory drive, and triggers dendritic retraction, cell loss, and cognitive impairments.[55,56] These maladaptive changes disrupt both cognition and emotion. Since orexin neurons are tightly connected with these stress-sensitive regions, such alterations likely extend to orexin signalling, helping explain how chronic stress can drive the fatigue, low motivation, and emotional instability central to burnout.

Altogether, evidence from both animal stress models, human neuroimaging, and behavioral experiments converges on a common mechanism: chronic stress disrupts HPA regulation, alters stress-sensitive brain circuits, and weakens orexin signalling. This chain of dysfunction links prolonged occupational stress to narcolepsy, like disturbances, depressive symptoms, and motivational decline, supporting the view that orexin dysregulation provides a unifying neurobiological substrate for burnout syndrome.

V- Burnout and Orexin: A Common Neurobiological Framework:

Although burnout is widely recognized as a pressing occupational health issue, its biological underpinnings remain poorly defined.[2] Unlike depression or anxiety, burnout has no precise diagnostic category, making it difficult for clinicians to differentiate it from mild stress-related conditions.[57] National classification systems vary considerably: for example, Dutch guidelines equate burnout with neurasthenia, whereas the Swedish framework labels it as "exhaustion disorder", a category not strictly limited to work-related causes. International frameworks further complicate this matter. In the ICD-10, burnout is described as a "state of vital exhaustion," while the DMS does not include it as a formal disorder.[1,2] This absence of standardized recognition impedes access to treatment, workplace accommodations, etc. Defining burnout through clearer biological markers would help significantly to move it beyond its status as a vague occupational label.

Clinically, burnout manifests through a constellation of persistent fatigue, insomnia, cognitive decline, and somatic complaints such as palpitations and gastrointestinal issues.[1] Chronic stress is a key driver of burnout and also significantly impacts various systems such as the immune, cardiovascular, and digestive systems.[58] Mental impairments are also prominent: patients experiencing burnout often struggle with forgetfulness, poor attention, indecisiveness, and deficits in working memory, which subsequently lead to reduced executive control and impaired job performance.[59,60] Emotionally, stress diminishes the ability to regulate affect, producing instability, heightened reactivity, and feelings of being overwhelmed.[1,61] These physical, cognitive, and emotional disruptions strongly resemble patterns observed in disorders where orexin dysfunction plays a key role.

The orexin system offers a compelling framework to explain these parallels. Orexin neurons integrate diverse signals related to circadian phase, arousal, and motivation, as we have learned previously, interacting with neurotransmitter systems including dopamine, serotonin, and histamine.[62] When disrupted, orexin signaling has been linked to psychiatric conditions such as depression and anxiety.[9] Stress studies show that orexin activity can be destabilized: in rats, sleep deprivation increases orexin mRNA expression, while recovery suppresses it, and prenatal stress blunts orexin response to starvation.[9,63,64] Dysregulated orexin function has also been implicated in anorexia nervosa and stress- induced hyperactivity.[65,66] Crucially, burnout patients often display a trajectory from stress-related hyperactivity to long-term passivity and impaired motivation.[1,67] This profession mirrors orexin's role in mediated arousal, stress responses, and sustained drive, making dysfunction in the system further plausible as a neurobiological substrate for burnout. Figure 5 shows how the two pathways converge in an overlapping manner and the similarities they share.

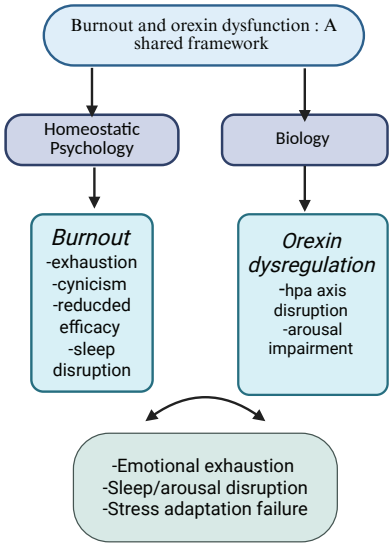

Figure 5: A flowchart showing burnout (homeostatic psychology) and orexin dysfunction (biology) as parallel pathways that converge on shared outcomes.

While narcolepsy is marked by near-total orexin neuron loss, not only producing daytime sleepiness, cognitive dysfunction, and emotional dysregulation,[68] chronic stress exerts a subtler but equally disruptive effect through HPA-orexin interactions. Normally, deep sleep suppresses HPA activity, but chronic stress, on the other hand, elevates CRH, ACTH, and cortisol.[69,70] Orexin neurons amplify this stress response: OX_2R signalling directly stimulates ACTH release, while antagonism blunts HPA activation,[71] establishing a feed-forward loop in which stress and orexin sustain one another.[72] Dysregulated orexin then destabilizes sleep-wake architecture and circadian rhythm,[73] disrupts sympathetic tone and metabolic balance,[74] and reduces emotional resilience.[75] Beyond sleep, orexin drives motivation and energy homeostasis,[41,76] indicating that dysfunction impairs not only arousal but also sustained goal-directed behavior.

Together, the literature positions orexin dysfunction as the mechanistic link between HPA dysregulation, disturbed sleep, and energy depletion. Thus, providing a plausible neurological substrate for the overlapping symptoms of narcolepsy, depression, and burnout.

■ Conclusion

Burnout has long been viewed primarily as a psychosocial phenomenon, defined by emotional exhaustion, depersonalisation, and reduced productivity. Yet emerging evidence demonstrates that prolonged stress leaves measurable biological traces, particularly within a brain's regulatory system. Chronic activation of stress pathways can disrupt not only the HPA axis but also the functional connectivity of networks involved in emotion regulation. Importantly, these disturbances interact with the orexin system, which is a central hub for

DOI: 10.36838/IJHSR89.103

arousal, wakefulness, and motivation. Suppression of the orexin system under sustained stress mirrors symptoms observed in conditions such as depression, narcolepsy, fatigue, emotional instability, and many more. Suggesting that burnout may reflect underlying neurobiological changes rather than solely psychological strain.

This review has explored how orexin may sit at the intersection of stress, mood, and cognition. Its dense projections into stress-responsive regions such as the amygdala and the hippocampus position it well to influence both emotional regulation and adaptive responses to stressors. While the dysfunction of this system offers a compelling biological framework for understanding features of burnout, it is important to emphasise that orexin is likely only one component of a broader, multifactorial process. Other components may also play a crucial role, such as inflammatory pathways, neurotransmitter changes, genetic vulnerabilities, and environmental factors. Current evidence, therefore, supports orexin's overall involvement, but not its exclusivity.

The possibility of using orexin-related measures as biomarkers is intriguing, particularly given advancements in cerebrospinal fluid sampling and neuroimaging. However, several limitations remain prevalent. Orexin levels often fluctuate with sleep, circadian rhythms, metabolic state, and psychiatric conditions, often making specificity a challenge. Additionally, ethical considerations also arise: invasive sampling, potential stigmatisation of workers, and the risk of employers missing the biological data gathered. Furthermore, while pharmacological manipulation of the orexin system, such as through orexin antagonists, shows promise in treating insomnia and anxiety, translating these interventions directly to burnout would require testing and careful regulation.

Altogether, while the orexin system provides a promising avenue for understanding the biological underpinnings of burnout, the current evidence base serves only as a preliminary. Future research should prioritize longitudinal designs and tracking of orexin activity over time, additionally examining how its suppression develops relative tosymptoms onset, and test whether restoringitst signalling meaningfully improves outcomes.

To summarize, burnout should not be viewed only through the lens of workplace psychology, nor should it be prematurely defined as a disorder rooted solely in orexin dysfunction. Instead, that evidence suggests that burnout may involve measurable neurobiological changes, with orexin presenting as one potential, not definitive, pathway. Recognizing both the promise and limitations of this model will support more balanced, ethical, and scientifically grounded progress towards early recognition and clinical recognition.

Acknowledgments

I want to express my deepest gratitude to the Indigo research team and my mentor, Dr. Jorge Avila. His constant feedback and support consistently helped me improve my writing. Figures were made with the help of Biorender. I attest that the writing, graphics, and ideas of this paper are entirely my own.

References

1. van Dam, A. A Clinical Perspective on Burnout: Diagnosis, Classification, and Treatment of Clinical Burnout. *Eur. J. Work Organ. Psychol.* **2021**, *30* (5), 732–741. https://doi.org/10.1080/1359432X.2021.1948400.
2. *ICD-10 Version:2010*. https://icd.who.int/browse10/2010/en#/VI (accessed 2025-08-16).
3. Joëls, M.; Karst, H.; Alfarez, D.; Heine, V. M.; Qin, Y.; Riel, E. V.; Verkuyl, M.; Lucassen, P. J.; Krugers, H. J. Effects of Chronic Stress on Structure and Cell Function in Rat Hippocampus and Hypothalamus. *Stress* **2004**, *7* (4), 221–231. https://doi.org/10.1080/10253890500070005.
4. Inutsuka, A.; Yamanaka, A. The Physiological Role of Orexin/Hypocretin Neurons in the Regulation of Sleep/Wakefulness and Neuroendocrine Functions. *Front. Endocrinol.* **2013**, *4*. https://doi.org/10.3389/fendo.2013.00018.
5. Valencia-Florez, K. B.; Sánchez-Castillo, H.; Vázquez, P.; Zárate, P.; Paz, D. B. Stress, a Brief Update. *Int. J. Psychol. Res.* **2023**, *16* (2), 105–121. https://doi.org/10.21500/20112084.5815.
6. Chu, B.; Marwaha, K.; Sanvictores, T.; Awosika, A. O.; Ayers, D. Physiology, Stress Reaction. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2025.
7. Koolhaas, J. M.; Bartolomucci, A.; Buwalda, B.; de Boer, S. F.; Flügge, G.; Korte, S. M.; Meerlo, P.; Murison, R.; Olivier, B.; Palanza, P.; Richter-Levin, G.; Sgoifo, A.; Steimer, T.; Stiedl, O.; van Dijk, G.; Wöhr, M.; Fuchs, E. Stress Revisited: A Critical Evaluation of the Stress Concept. *Neurosci. Biobehav. Rev.* **2011**, *35* (5), 1291–1301. https://doi.org/10.1016/j.neubiorev.2011.02.003.
8. Golkar, A.; Johansson, E.; Kasahara, M.; Osika, W.; Perski, A.; Savic, I. The Influence of Work-Related Chronic Stress on the Regulation of Emotion and on Functional Connectivity in the Brain. *PLOS ONE* **2014**, *9* (9), e104550. https://doi.org/10.1371/journal.pone.0104550.
9. Grafe, L. A.; Bhatnagar, S. Orexins and Stress. *Front. Neuroendocrinol.* **2018**, *51*, 132–145. https://doi.org/10.1016/j.yfrne.2018.06.003.
10. Johnson, P. L.; Molosh, A.; Truitt, W. A.; Fitz, S. D.; Shekhar, A. OREXIN, STRESS AND ANXIETY/PANIC STATES. *Prog. Brain Res.* **2012**, *198*, 133–161. https://doi.org/10.1016/B978-0-444-59489-1.00009-4.
11. Wang, C.; Wang, Q.; Ji, B.; Pan, Y.; Xu, C.; Cheng, B.; Bai, B.; Chen, J. The Orexin/Receptor System: Molecular Mechanism and Therapeutic Potential for Neurological Diseases. *Front. Mol. Neurosci.* **2018**, *11*. https://doi.org/10.3389/fnmol.2018.00220.
12. *Workplace stress 'a collective challenge' as work-life boundaries become blurred – UN | UN News*. https://news.un.org/en/story/2016/04/527952 (accessed 2025-08-24).
13. *Burnout is an "occupational phenomenon": International Classification of Diseases*. https://www.who.int/news/item/28-05-2019-burnout-an-occupational-phenomenon-international-classification-of-diseases (accessed 2025-08-18).
14. (PDF) Herbert J. Freudenberger and the Making of Burnout as a Psychopathological Syndrome. *ResearchGate* **2025**.
15. (PDF) The Measurement of Experienced Burnout. *ResearchGate* **2025**. https://doi.org/10.1002/job.4030020205.
16. Misiak, B.; Łoniewski, I.; Marlicz, W.; Frydecka, D.; Szulc, A.; Rudzki, L.; Samochowiec, J. The HPA Axis Dysregulation in Severe Mental Illness: Can We Shift the Blame to Gut Microbiota? *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2020**, *102*, 109951. https://doi.org/10.1016/j.pnpbp.2020.109951.
17. Standard_v_9.2_hpa_axis.Pdf. https://www.pointinstitute.org/wp-content/uploads/2012/10/standard_v_9.2_hpa_axis.pdf (accessed 2025-08-04).

18. Miller, G. E.; Chen, E.; Zhou, E. S. If It Goes up, Must It Come down? Chronic Stress and the Hypothalamic-Pituitary-Adrenocortical Axis in Humans. *Psychol. Bull.* **2007**, *133* (1), 25–45. https://doi.org/10.1037/0033-2909.133.1.25.
19. Juruena, M. F.; Bourne, M.; Young, A. H.; Cleare, A. J. Hypothalamic-Pituitary-Adrenal Axis Dysfunction by Early Life Stress. *Neurosci. Lett.* **2021**, *759*, 136037. https://doi.org/10.1016/j.neulet.2021.136037.
20. Peyron, C.; Kilduff, T. S. Mapping the Hypocretin/Orexin Neuronal System: An Unexpectedly Productive Journey. *J. Neurosci.* **2017**, 37 (9), 2268–2272. https://doi.org/10.1523/JNEUROSCI.1708-16.2016.
21. Sakurai, T. The Role of Orexin in Motivated Behaviors. *Nat. Rev. Neurosci.* **2014**, *15* (11), 719–731. https://doi.org/10.1038/nrn3837.
22. Yaribeygi, H.; Panahi, Y.; Sahraei, H.; Johnston, T. P.; Sahebkar, A. The Impact of Stress on Body Function: A Review. *EXCLI J.* **2017**, *16*, 1057–1072. https://doi.org/10.17179/excli2017-480.
23. Research, I. of M. (US) C. on M. N.; Marriott, B. M. Stress and Monoamine Neurons in the Brain. In *Food Components to Enhance Performance: An Evaluation of Potential Performance-Enhancing Food Components for Operational Rations*; National Academies Press (US), 1994.
24. Lupien, S. J.; McEwen, B. S.; Gunnar, M. R.; Heim, C. Effects of Stress throughout the Lifespan on the Brain, Behavior and Cognition. *Nat. Rev. Neurosci.* **2009**, *10* (6), 434–445. https://doi.org/10.1038/nrn2639.
25. McEwen, B. S. Stress and Hippocampal Plasticity. *Annu. Rev. Neurosci.* **1999**, *22*, 105–122. https://doi.org/10.1146/annurev.neuro.22.1.105.
26. Sandi, C. Stress and Cognition. *Wiley Interdiscip. Rev. Cogn. Sci.* **2013**, *4* (3), 245–261. https://doi.org/10.1002/wcs.1222.
27. Reiche, E. M. V.; Nunes, S. O. V.; Morimoto, H. K. Stress, Depression, the Immune System, and Cancer. *Lancet Oncol.* **2004**, *5* (10), 617–625. https://doi.org/10.1016/S1470-2045(04)01597-9.
28. *(PDF) Effects of systemic and intra-accumbal memantine administration on the impacts of plantar electrical shock in male NMRI mice*. https://www.researchgate.net/publication/266391538_Effects_of_systemic_and_intra-accumbal_memantine_administration_on_the_impacts_of_plantar_electrical_shock_in_male_NMRI_mice (accessed 2025-08-24).
29. *II. Stress and intestinal barrier function | American Journal of Physiology-Gastrointestinal and Liver Physiology | American Physiological Society*. https://journals.physiology.org/doi/full/10.1152/ajpgi.2001.280.1.G7 (accessed 2025-08-24).
30. 武桜井. オレキシンの発見. 日本薬理学雑誌 **2007**, *130* (1), 19–22. https://doi.org/10.1254/fpj.130.19.
31. *The Hypocretin/Orexin System*. https://doi.org/10.1177/014107680209500503.
32. Soya, S.; Sakurai, T. Evolution of Orexin Neuropeptide System: Structure and Function. *Front. Neurosci.* **2020**, *14*. https://doi.org/10.3389/fnins.2020.00691.
33. *Hypocretin/Orexin Overexpression Induces An Insomnia-Like Phenotype in Zebrafish - PMC*. https://pmc.ncbi.nlm.nih.gov/articles/PMC6675014/ (accessed 2025-08-25).
34. Willie, J. T.; Chemelli, R. M.; Sinton, C. M.; Tokita, S.; Williams, S. C.; Kisanuki, Y. Y.; Marcus, J. N.; Lee, C.; Elmquist, J. K.; Kohlmeier, K. A.; Leonard, C. S.; Richardson, J. A.; Hammer, R. E.; Yanagisawa, M. Distinct Narcolepsy Syndromes in Orexin Receptor-2 and Orexin Null Mice: Molecular Genetic Dissection of Non-REM and REM Sleep Regulatory Processes. *Neuron* **2003**, *38* (5), 715–730. https://doi.org/10.1016/s0896-6273(03)00330-1.
35. Beuckmann, C. T.; Sinton, C. M.; Williams, S. C.; Richardson, J. A.; Hammer, R. E.; Sakurai, T.; Yanagisawa, M. Expression of a Poly-Glutamine-Ataxin-3 Transgene in Orexin Neurons Induces Narcolepsy–Cataplexy in the Rat. *J. Neurosci.* **2004**, *24* (18), 4469–4477. https://doi.org/10.1523/JNEUROSCI.5560-03.2004.
36. *A key role for orexin in panic anxiety - PubMed*. https://pubmed.ncbi.nlm.nih.gov/20037593/ (accessed 2025-08-25).
37. Mariotti, A. The Effects of Chronic Stress on Health: New Insights into the Molecular Mechanisms of Brain–Body Communication. *Future Sci. OA* **2015**, *1* (3), FSO23. https://doi.org/10.4155/fso.15.21.
38. Siegel, J. M.; Moore, R.; Thannickal, T.; Nienhuis, R. A Brief History of Hypocretin/Orexin and Narcolepsy. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **2001**, *25* (5 Suppl), S14. https://doi.org/10.1016/S0893-133X(01)00317-7.
39. A, I.; A, Y. The Physiological Role of Orexin/Hypocretin Neurons in the Regulation of Sleep/Wakefulness and Neuroendocrine Functions. *Front. Endocrinol.* **2013**, *4*. https://doi.org/10.3389/fendo.2013.00018.
40. Mignot, E. Genetic and Familial Aspects of Narcolepsy. *Neurology* **1998**, *50* (2 Suppl 1), S16-22. https://doi.org/10.1212/wnl.50.2_suppl_1.s16.
41. Tsujino, N.; Sakurai, T. Role of Orexin in Modulating Arousal, Feeding, and Motivation. *Front. Behav. Neurosci.* **2013**, *7*. https://doi.org/10.3389/fnbeh.2013.00028.
42. Eggermann, E.; Serafin, M.; Bayer, L.; Machard, D.; Saint-Mleux, B.; Jones, B. E.; Mühlethaler, M. Orexins/Hypocretins Excite Basal Forebrain Cholinergic Neurones. *Neuroscience* **2001**, *108* (2), 177–181. https://doi.org/10.1016/s0306-4522(01)00512-7.
43. Tsujino, N.; Sakurai, T. Role of Orexin in Modulating Arousal, Feeding, and Motivation. *Front. Behav. Neurosci.* **2013**, *7*. https://doi.org/10.3389/fnbeh.2013.00028.
44. Chemelli, R. M.; Willie, J. T.; Sinton, C. M.; Elmquist, J. K.; Scammell, T.; Lee, C.; Richardson, J. A.; Williams, S. C.; Xiong, Y.; Kisanuki, Y.; Fitch, T. E.; Nakazato, M.; Hammer, R. E.; Saper, C. B.; Yanagisawa, M. Narcolepsy in Orexin Knockout Mice: Molecular Genetics of Sleep Regulation. *Cell* **1999**, *98* (4), 437–451. https://doi.org/10.1016/s0092-8674(00)81973-x.
45. Thannickal, T. C.; Moore, R. Y.; Nienhuis, R.; Ramanathan, L.; Gulyani, S.; Aldrich, M.; Cornford, M.; Siegel, J. M. Reduced Number of Hypocretin Neurons in Human Narcolepsy. *Neuron* **2000**, *27* (3), 469–474. https://doi.org/10.1016/s0896-6273(00)00058-1.
46. *Genetic ablation of hypocretin neurons alters behavioral state transitions in zebrafish - PubMed*. https://pubmed.ncbi.nlm.nih.gov/22973020/ (accessed 2025-08-25).
47. Siegel, J. M.; Moore, R.; Thannickal, T.; Nienhuis, R. A Brief History of Hypocretin/Orexin and Narcolepsy. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **2001**, *25* (5 Suppl), S14–S20. https://doi.org/10.1016/S0893-133X(01)00317-7.
48. Berridge, C. W.; España, R. A. Hypocretins: Waking, Arousal, or Action? *Neuron* **2005**, *46* (5), 696–698. https://doi.org/10.1016/j.neuron.2005.05.016.
49. Harris, G. C.; Aston-Jones, G. Arousal and Reward: A Dichotomy in Orexin Function. *Trends Neurosci.* **2006**, *29* (10), 571–577. https://doi.org/10.1016/j.tins.2006.08.002.
50. Winsky-Sommerer, R.; Yamanaka, A.; Diano, S.; Borok, E.; Roberts, A. J.; Sakurai, T.; Kilduff, T. S.; Horvath, T. L.; de Lecea, L. Interaction between the Corticotropin-Releasing Factor System and Hypocretins (Orexins): A Novel Circuit Mediating Stress Response. *J. Neurosci. Off. J. Soc. Neurosci.* **2004**, *24* (50), 11439–11448. https://doi.org/10.1523/JNEUROSCI.3459-04.2004.
51. (PDF) Orexinergic Neurons Modulate Stress Coping Responses in Mice. *ResearchGate* **2025**. https://doi.org/10.3389/fnmol.2023.1140672.

DOI: 10.36838/IJHSR89.103

52. Munhoz, C. D.; Lepsch, L. B.; Kawamoto, E. M.; Malta, M. B.; Lima, L. de S.; Werneck Avellar, M. C.; Sapolsky, R. M.; Scavone, C. Chronic Unpredictable Stress Exacerbates Lipopolysaccharide-Induced Activation of Nuclear Factor-κB in the Frontal Cortex and Hippocampus via Glucocorticoid Secretion. *J. Neurosci.* **2006**, *26* (14), 3813–3820. https://doi.org/10.1523/JNEUROSCI.4398-05.2006.
53. Lindholm, L. H.; Carlberg, B.; Samuelsson, O. Should Beta Blockers Remain First Choice in the Treatment of Primary Hypertension? A Meta-Analysis. *Lancet Lond. Engl.* **2005**, *366* (9496), 1545–1553. https://doi.org/10.1016/S0140-6736(05)67573-3.
54. Blix, E.; Perski, A.; Berglund, H.; Savic, I. Long-Term Occupational Stress Is Associated with Regional Reductions in Brain Tissue Volumes. *PLoS ONE* **2013**, *8* (6), e64065. https://doi.org/10.1371/journal.pone.0064065.
55. Herman, J. P.; Nawreen, N.; Smail, M. A.; Cotella, E. M. Brain Mechanisms of HPA Axis Regulation: Neurocircuitry and Feedback in Context Richard Kvetnansky Lecture. *Stress* **2020**, *23* (6), 617–632. https://doi.org/10.1080/10253890.2020.1859475.
56. Kim, E. J.; Pellman, B.; Kim, J. J. Stress Effects on the Hippocampus: A Critical Review. *Learn. Mem.* **2015**, *22* (9), 411–416. https://doi.org/10.1101/lm.037291.114.
57. Parent-Thirion, A. Burnout in the Workplace : A Review of Data and Policy Responses in the European Union.
58. Camiña, P. Why Zebras Don't Get Ulcers. Robert Sapolsky. *Why Don't Zebras Get Ulcers?*
59. *(PDF) Job burnout and cognitive functioning: A systematic review.* https://www.researchgate.net/publication/262008721_Job_burnout_and_cognitive_functioning_A_systematic_review (accessed 2025-08-24).
60. *(PDF) Work engagement: An emerging concept in occupational health psychology.* https://www.researchgate.net/publication/46704321_Work_engagement_An_emerging_concept_in_occupational_health_psychology (accessed 2025-08-24).
61. *Cognitive emotion regulation fails the stress test - PubMed.* https://pubmed.ncbi.nlm.nih.gov/23980142/ (accessed 2025-08-26).
62. Knez, R.; Stevanovic, D.; Fernell, E.; Gillberg, C. Orexin/Hypocretin System Dysfunction in ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations). *Neuropsychiatr. Dis. Treat.* **2022**, *18*, 2683–2702. https://doi.org/10.2147/NDT.S358373.
63. Martins, P. J. F.; Marques, M. S.; Tufik, S.; D'Almeida, V. Orexin Activation Precedes Increased NPY Expression, Hyperphagia, and Metabolic Changes in Response to Sleep Deprivation. *Am. J. Physiol. Endocrinol. Metab.* **2010**, *298* (3), E726-734. https://doi.org/10.1152/ajpendo.00660.2009.
64. Boersma, G. J.; Liang, N.-C.; Lee, R. S.; Albertz, J. D.; Kastelein, A.; Moody, L. A.; Aryal, S.; Moran, T. H.; Tamashiro, K. L. Failure to Upregulate Agrp and Orexin in Response to Activity Based Anorexia in Weight Loss Vulnerable Rats Characterized by Passive Stress Coping and Prenatal Stress Experience. *Psychoneuroendocrinology* **2016**, *67*, 171–181. https://doi.org/10.1016/j.psyneuen.2016.02.002.
65. Baranowska, B.; Baranowska-Bik, A.; Bik, W.; Martynska, L. The Role of Leptin and Orexins in the Dysfunction of Hypothalamo-Pituitary-Gonadal Regulation and in the Mechanism of Hyperactivity in Patients with Anorexia Nervosa. *Neuro Endocrinol. Lett.* **2008**, *29* (1), 37–40.
66. Grafe, L. A.; Eacret, D.; Luz, S.; Gotter, A. L.; Renger, J. J.; Winrow, C. J.; Bhatnagar, S. Orexin 2 Receptor Regulation of the Hypothalamic-Pituitary-Adrenal (HPA) Response to Acute and Repeated Stress. *Neuroscience* **2017**, *348*, 313–323. https://doi.org/10.1016/j.neuroscience.2017.02.038.
67. *Burnout and impaired cognitive performance: Review of evidence, underlying processes and future directions | Request PDF*. https://www.researchgate.net/publication/273736982_Burnout_and_impaired_cognitive_performance_Review_of_evidenceunderlying_processes_and_future_directions (accessed 2025-08-24).
68. *Hypocretin (Orexin) Receptor 1 - an overview | ScienceDirect Topics*. https://www.sciencedirect.com/topics/neuroscience/hypocretin-orexin-receptor-1?utm_source=chatgpt.com (accessed 2025-09-07).
69. *HPA Axis and Sleep - Endotext - NCBI Bookshelf*. https://www.ncbi.nlm.nih.gov/books/NBK279071/ (accessed 2025-09-07).
70. Bezerra, M. L. de S.; Rodrigues, R. N. D.; Souza, R. O. The Hypothalamic-Pituitary-Adrenal Axis and the Central Monoaminergic Systems: A Pathophysiological Link to Insomnia with Clinical Implications. *Sleep Sci. São Paulo Braz.* **2022**, *15* (1), 128–135. https://doi.org/10.5935/1984-0063.20220032.
71. Grafe, L. A.; Eacret, D.; Luz, S.; Gotter, A. L.; Renger, J. J.; Winrow, C. J.; Bhatnagar, S. Orexin 2 Receptor Regulation of the Hypothalamic-Pituitary-Adrenal (HPA) Response to Acute and Repeated Stress. *Neuroscience* **2017**, *348*, 313–323. https://doi.org/10.1016/j.neuroscience.2017.02.038.
72. Jászberényi, M.; Thurzó, B.; Bagosi, Z.; Vécsei, L.; Tanaka, M. The Orexin/Hypocretin System, the Peptidergic Regulator of Vigilance, Orchestrates Adaptation to Stress. *Biomedicines* **2024**, *12* (2), 448. https://doi.org/10.3390/biomedicines12020448.
73. Mogavero, M. P.; Godos, J.; Grosso, G.; Caraci, F.; Ferri, R. Rethinking the Role of Orexin in the Regulation of REM Sleep and Appetite. *Nutrients* **2023**, *15* (17), 3679. https://doi.org/10.3390/nu15173679.
74. Bouâouda, H.; Jha, P. K. Orexin and MCH Neurons: Regulators of Sleep and Metabolism. *Front. Neurosci.* **2023**, *17*. https://doi.org/10.3389/fnins.2023.1230428.
75. Hirotsu, C.; Tufik, S.; Andersen, M. L. Interactions between Sleep, Stress, and Metabolism: From Physiological to Pathological Conditions. *Sleep Sci.* **2015**, *8* (3), 143–152. https://doi.org/10.1016/j.slsci.2015.09.002.
76. Chatterjee, O.; Gopalakrishnan, L.; Pullimamidi, D.; Raj, C.; Yelamanchi, S.; Gangadharappa, B. S.; Nair, B.; Mahadevan, A.; Raju, R.; Keshava Prasad, T. S. A Molecular Network Map of Orexin-Orexin Receptor Signaling System. *J. Cell Commun. Signal.* **2023**, *17* (1), 217–227. https://doi.org/10.1007/s12079-022-00700-3.
77. Leonard, C. S.; Kukkonen, J. P. Orexin/Hypocretin Receptor Signalling: A Functional Perspective. *Br. J. Pharmacol.* **2014**, *171* (2), 294–313. https://doi.org/10.1111/bph.12296
78. Roth, B. L. DREADDs for Neuroscientists. *Neuron* **2016**, *89* (4), 683–694. https://doi.org/10.1016/j.neuron.2016.01.040.

Author

Ariana Das is a tenth-grade student with a strong passion for biology and scientific discovery. She enjoys exploring new concepts through independent research and is particularly interested in understanding how science shapes everyday life. Driven, curious, and enthusiastic, Ariana hopes to continue developing her skills as a young researcher and contributing meaningfully to the scientific community.