Review Article

Orexinergic and Hypothalamic Dysfunction in Chronic Fatigue Syndrome: A Mechanistic Framework for Biomarker Discovery and Targeted Therapies

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Chronic fatigue syndrome (CFS) is a debilitating disorder characterized by persistent fatigue, post-exertional malaise, and sleep disturbances, with no definitive diagnostic test. Emerging research suggests a critical role for hypothalamic and orexinergic dysfunction in the pathophysiology of CFS/ME, contributing to impaired sleep-wake regulation, autonomic instability, and metabolic disturbances. This review synthesizes evidence from neuroimaging, endocrine studies, and immunological analyses, highlighting alterations in orexin levels, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and inflammatory cytokine profiles as potential biomarkers. Neuroimaging findings indicate reduced hypothalamic volume and altered functional connectivity, correlating with disease severity. Further, immune-mediated neuroinflammation may disrupt orexinergic signaling, exacerbating fatigue and cognitive dysfunction. The identification of reliable biomarkers—such as cerebrospinal fluid orexin concentrations, neuroimaging markers, and inflammatory profiles—could enhance diagnostic accuracy and refine personalized treatment strategies. Future research should focus on longitudinal studies, pharmacological modulation of orexin receptors, and advanced neuroimaging techniques to elucidate causal mechanisms. Integrating wearable health technologies, cognitive behavioral therapy, and metabolic interventions may improve early detection and disease management. Addressing the public health burden of CFS/ME requires increased research investment, clinical education, and advocacy to improve patient outcomes and reduce diagnostic uncertainty. This review underscores the need for an integrative,

precision medicine approach to unravel the complexities of CFS/ME and advance targeted interventions.

1. Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) or systemic exertion intolerance disease (SEID), is a complex disorder with distinctive and debilitating symptoms. Diagnosis is based on three primary criteria: a significant and persistent reduction in the ability to engage in pre-illness activity levels for more than six months, accompanied by profound fatigue that is not lifelong, not relieved by rest, and not attributable to excessive exertion; post-exertional malaise (PEM); and unrefreshing sleep. Additionally, at least one of the following must be present: cognitive impairment or orthostatic intolerance. These diagnostic criteria underscore the multifaceted nature of CFS/ME, necessitating careful clinical evaluation to ensure accurate diagnosis[1].

Although CFS diagnosis is primarily based on clinical manifestations, some patients exhibit abnormal laboratory and imaging findings. Frequently observed alterations include dysregulations in the thyroid and adrenal axes[2][3][4][5][6], abnormal proinflammatory cytokine profiles[7][8][9], and, less commonly, changes in 24-hour urinary cortisol excretion[6][10]. These abnormalities reflect an intricate pathophysiology, likely driven by an altered inflammatory response that underlies symptom expression. Neuroimaging studies have also identified notable structural and functional brain changes, including reduced cortical volume[6][11][12][13][14], altered hypothalamic connectivity, and modifications in other brain regions, particularly in younger cohorts[15][16][17][18].

Differential diagnosis of CFS is often complex due to the lack of definitive laboratory or imaging tests, leading to frequent misdiagnosis with other rheumatologic, psychiatric, endocrine, and multisystem disorders. The etiology of CFS is linked to a complex interplay of genetic, infectious, and immune dysfunctions, though these mechanisms remain poorly understood. This complexity further complicates diagnostic precision for both primary care physicians and specialists, emphasizing the need for more reliable diagnostic tools and criteria[19][20].

The therapeutic management of CFS is as challenging as its diagnosis. Current therapeutic consensus recommends two primary interventions: graded exercise therapy (GET) and cognitive behavioral therapy (CBT). While both are considered safe, their effectiveness remains limited. Alternative

approaches, such as anti-inflammatory diets supplemented with antioxidants, have demonstrated some benefits, though no pharmacological treatment has yet achieved "gold standard" status. Antidepressants and neurostimulants, including selective serotonin reuptake inhibitors (SSRIs), methylphenidate, modafinil, and caffeine, have been used with mixed results. CFS remains a complex condition with unclear etiology, challenging diagnostic criteria, and limited treatment options, potentially affecting a larger population than previously recognized[21][22][23].

The social cost of CFS is substantial. Some studies estimate that individual medical expenses may exceed $8,000 USD per year, while productivity losses associated with the condition could reach up to $24 billion USD annually. Beyond its profound impact on patients' quality of life, the lack of societal understanding and acceptance often leads to stigmatization, which can exacerbate symptoms. Despite these challenges, further research is needed to accurately determine the full social and economic burden of CFS[1][24][25][26].

There is substantial evidence implicating hypothalamic-pituitary-adrenal (HPA) axis dysfunction in the pathophysiology of CFS[23][27][28][29]. The orexinergic system plays a determinant role in hypothalamic function, regulating the sleep-wake cycle, arousal, appetite, chronic pain, stress-induced disorders, and inflammatory responses. All these elements are dysregulated in CFS, suggesting a potential involvement of the orexinergic system in CFS-associated hypothalamic dysfunction[30][31][32][33]. This hypothesis could have significant implications for the diagnosis and treatment of CFS, as well as contribute to a better understanding of its etiopathogenesis.

This study aims to thoroughly compile evidence on the role of the orexinergic system in hypothalamic dysfunction associated with CFS. To achieve this, we will conduct a comprehensive literature review, focusing on key publications that demonstrate the direct or indirect influence of the orexinergic system on CFS etiology and clinical manifestations. The gathered information will be analyzed qualitatively and interpreted within an integrative clinical framework to assess its diagnostic and therapeutic potential, with an emphasis on precision and translational medicine.

2. The Hypothalamus and Homeostatic Regulation

2.1. Overview of Hypothalamic Anatomy and Key Nuclei

The hypothalamus, a small but complex structure within the diencephalon, maintains homeostasis by integrating autonomic and endocrine stimuli, directly influencing behavioral responses. The

hypothalamus is involved in a diverse range of functions, including energy balance, thermoregulation, circadian rhythm regulation, stress response, and emotional processing. These functions are mediated through extensive connections with the limbic system, brainstem, and pituitary gland[34][35].

From an anatomical perspective, the hypothalamus is located beneath the thalamus, at the base of the brain, surrounding the third cerebral ventricle. It can be divided into three main regions: anterior (preoptic), tuberal (middle), and posterior (mammillary). Additionally, it can be further classified into medial and lateral zones, each containing distinct functional nuclei[35].

The regulation of the sleep-wake cycle is a complex physiological process that originates in the suprachiasmatic nucleus (SCN) and is further modulated by the ventrolateral preoptic nucleus (VLPO) and the lateral hypothalamic area (LH). The SCN functions as a circadian pacemaker, synchronizing biological rhythms according to the light-dark cycle. This is achieved through direct input from the retina via the retinohypothalamic tract. Also, the SCN regulates the production and release of melatonin by the pineal gland, influencing sleep timing and circadian rhythm stability[36][37].

Sleep induction is modulated by the VLPO, which inhibits neurons of the ascending reticular system (ARS) located in the brainstem and hypothalamus. This nucleus releases gamma-aminobutyric acid (GABA) and galanin, suppressing the activity of the tuberomammillary nucleus (TMN), locus coeruleus (LC), and dorsal raphe nucleus (DRN)—all components of the ARS, a key monoaminergic center involved in wakefulness regulation[34][38].

Finally, the LH is responsible for wakefulness and maintaining arousal, primarily through the action of orexinergic neurons, which stabilize wakefulness and prevent sleep fragmentation. The projections of orexin-producing neurons reach the ARS, stimulating monoamine production and further regulating arousal, motivation, and metabolic activity. Consequently, orexin deficiency is strongly associated with narcolepsy, and in the most severe cases, with cataplexy[39][40][41].

2.2. Regulatory Roles in Sleep-Wake Cycles and Energy Balance

The energy balance regulated by the hypothalamus controls caloric intake, expenditure, and storage through the integration of circulating hormonal signals and neural circuits. Several hypothalamic regions, including the arcuate nucleus (ARC), ventromedial hypothalamus (VMH), dorsomedial hypothalamus (DMH), and LH, play key roles in the regulation of appetite, satiety, and metabolic activity.

ARC area contains two distinct neuronal populations: a) orexigenic, Agouti-related peptide (AgRP) and neuropeptide Y (NPY) neurons, which stimulate appetite by inhibiting satiety signals; b) anorexigenic, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons, which suppress appetite and enhance energy expenditure. The hormones leptin, insulin, and ghrelin are regulated through integrated signaling within the ARC, influencing energy homeostasis[42][43].

The area of VMH functions as the satiety center. Lesions in this nucleus lead to hyperphagia and severe obesity, as the VMH plays a critical role in modulating glucose metabolism and energy storage. Additionally, it exerts a sympathetic effect, influencing autonomic and metabolic regulation[44][45].

Again, LH plays a role in this regulatory circuit by stimulating appetite through the activation of orexinergic and melanin-concentrating hormone (MCH) neurons. Additionally, LH neurons interact with the dopaminergic system via the mesolimbic pathway, reinforcing reward-driven feeding behavior and motivation for food intake[46].

There is a fundamental interaction between sleep regulation and energy balance through the integration of the previously mentioned control centers. Chronic sleep deprivation leads to increased ghrelin levels and reduced leptin levels, resulting in increased appetite and weight gain. Moreover, sleep loss disrupts HPA axis function, leading to elevated cortisol secretion and increased plasmatic cortisol levels. This alteration further contributes to fat storage and insulin resistance, exacerbating metabolic dysfunction[47].

Since orexinergic neurons regulate both wakefulness and energy balance, a strong link is proposed between sleep regulation and metabolic homeostasis. Consequently, dysfunction of the orexinergic system is associated with sleep disorders and metabolic diseases, highlighting its central role in maintaining physiological equilibrium[48][49].

3. Orexinergic Signaling: Biology and Function

3.1. Structure and Distribution of Orexin Peptides

Orexin peptides, orexin-A (OXA) and orexin-B (OXB), also called hypocretins-1 and -2, are synthesized from prepro-orexin, a protein encoded by the HCRT gene. OXA consists of 33 amino acids

and contains two intramolecular disulfide bonds, enhancing its stability, while OXB is composed of 28 amino acids with a linear structure[49].

Orexinergic neurons are exclusively located in the LH but project widely to the cortex, brainstem, and limbic system. Their projections to the ARS regulate wakefulness, while connections with the PVN, ARC, and VMH influence metabolic control. Involvement in emotional processing and reward occurs through projections to the amygdala and nucleus accumbens (NAc). Additionally, orexinergic neurons modulate monoaminergic activity via connections with the LC, DRN, and TMN[48][39][40].

3.2. Downstream Signaling Pathways

Both orexin receptors are G-protein-coupled receptors (GPCRs). OX1R primarily activates Gq/11 proteins, whereas OX2R can signal through both Gq/11 and Gi/o pathways, allowing for diverse intracellular signaling mechanisms[49]. Therefore, both receptors can activate the phospholipase C (PLC) pathway, leading to an increase in intracellular calcium levels and the subsequent activation of protein kinase C (PKC)[50]. The adenylate cyclase (AC) pathway is inhibited by OX2R activation of Gi/o, leading to a reduction in cyclic adenosine monophosphate (cAMP) levels and modulating neurotransmitter release[51]. The mitogen-activated protein kinase (MAPK) pathway is activated by both orexins, regulating gene expression, promoting neuroprotection, and enhancing synaptic plasticity[52].

3.3. Physiological Roles of Orexin in Arousal, Feeding, and Metabolism

Physiologically, orexins stabilize wakefulness by activating monoaminergic and cholinergic systems in the LC, DRN, and TMN. This prevents sleep fragmentation and enhances cognitive alertness. As previously mentioned, orexin deficiency leads to narcolepsy and cataplexy[49][53]. Simultaneously, orexins stimulate appetite by activating orexigenic neurons (AgRP/NPY) in the ARC and inhibiting anorexigenic neurons (POMC/CART). They also interact with the dopaminergic system (NAc), reinforcing food-seeking behavior[54]. Finally, orexins increase basal energy expenditure by modulating sympathetic activity and glucose metabolism in the VMH. They promote lipidic β-oxidation, thermogenesis, and insulin sensitivity[55].

3.4. Orexin's Influence on the Autonomic Nervous System and Stress Response

As previously mentioned, orexins regulate sympathetic and parasympathetic activity through their connections with the ARS. Increased orexinergic activity enhances sympathetic output, facilitating cardiovascular and metabolic adaptation[56]. Orexins also activate the HPA axis by stimulating corticotropin-releasing neurons in the PVN, leading to cortisol release. This response normally enhances alertness, wakefulness, and adaptive energy mobilization, but when dysregulated, it contributes to chronic stress and anxiety-related disorders[57].

4. Hypothalamic Dysfunction in Chronic Fatigue Syndrome: Evidence and Insights

4.1. Neuroimaging Findings and Structural Alterations in CFS

Neuroimaging studies in CFS patients show reduced cortical volume in the frontal and temporal lobes, sometimes with gray matter hypodensity in the prefrontal cortex, correlating with cognitive impairment and fatigue severity[6][58].

In the hypothalamus, volume loss suggests HPA axis dysregulation, contributing to neuroendocrine dysfunction and the persistence of fatigue or post-exertional malaise[59].

Reduced fractional anisotropy (FA) in the inferior frontoparietal fasciculus and corpus callosum indicates white matter integrity loss, affecting attention, executive function, and pain processing[60]. Altered functional connectivity in the default mode network (DMN) suggests impaired cognitive control and autonomic regulation, possibly explaining post-exertional malaise[61].

4.2. Neuroendocrine Abnormalities: HPA Axis and Beyond

CFS is associated with hypoactivity of the HPA axis, leading to blunted cortisol responses and impaired stress adaptation[28]. Reduced CRH secretion from the PVN contributes to fatigue, immune dysfunction, and autonomic dysregulation[29]. Dysfunction in the autonomic nervous system results in reduced catecholamine levels, affecting vascular tone, blood pressure regulation, and postural control, commonly seen in orthostatic intolerance and postural orthostatic tachycardia syndrome (POTS)[62]. Other neuroendocrine pathways are also disrupted. Some studies suggest alterations in the

thyroid axis, particularly low T3 syndrome without primary hypothyroidism[63]. Patients with fibromyalgia exhibit changes in the growth hormone (GH) axis, including altered insulin-like growth factor-1 (IGF-1) levels, which may affect muscle recovery and energy metabolism. However, these changes are not significant in CFS/ME patients[64]. Finally, imbalances in ghrelin and leptin regulation, with increased ghrelin and decreased leptin, may contribute to appetite dysregulation and fatigue[65].

4.3. Relationship between Fatigue, Sleep Disturbances, and Orexin Signaling

Sleep-wake disturbances and circadian rhythm alterations are commonly reported in CFS and other conditions affecting hypothalamic function. Patients often exhibit delayed sleep onset, fragmented sleep, and non-restorative sleep, which contribute to daytime fatigue and cognitive impairment[66]. Circadian rhythmicity changes in CFS include altered melatonin secretion patterns and dysregulated core body temperature rhythms, indicating a desynchronization of the SCN, the central circadian pacemaker[67]. Moreover, HPA axis dysfunction and orexinergic dysregulation may exacerbate sleep fragmentation and excessive daytime sleepiness[68]. Neuroimaging and polysomnographic studies suggest reduced slow-wave sleep (SWS) and disrupted REM sleep architecture, further supporting the hypothesis that CFS involves impairments in sleep homeostasis and circadian regulation[69].

5. The Orexinergic Dysregulation in Chronic Fatigue Syndrome

5.1. Unifying Hypotheses Linking Orexin to CFS Pathophysiology

Dysfunction of the orexinergic system has been implicated in several neurodegenerative diseases and may contribute to symptoms such as fatigue and sleep disturbances[70][71]. In patients with hypersomnolence, systemic exertion intolerance disease (SEID) is a common comorbidity, potentially linked to orexinergic dysfunction[72]. Hypothalamic involvement, including altered orexin levels, has been observed in conditions like multiple sclerosis and systemic lupus erythematosus, suggesting a potential role in fatigue and excessive daytime sleepiness[73][74]. Furthermore, orexinergic dysfunction could lead to impaired energy regulation and autonomic instability, both of which are observed in patients with ME/CFS/SEID[75]. The orexinergic system's involvement in autonomic regulation suggests that its dysfunction may contribute to the characteristic symptoms of these syndromes, including fatigue and exercise intolerance.

The ESSENCE study explores orexin/hypocretin system dysfunction in neurodevelopmental disorders (NDDs) such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), suggesting a potential role in arousal, wakefulness, sleep regulation, motor control, emotional processing, and cognition. While orexin dysfunction has been implicated in psychiatric and neurological disorders, including narcolepsy and metabolic dysregulation, its role in CFS remains uncertain and unverified. The study emphasizes the need for systematic research to clarify orexin's involvement in neurodevelopmental symptoms and its potential therapeutic implications[76].

While orexin is involved in sleep regulation and metabolic processes, studies directly assessing its role in CFS are currently nonexistent. Disruptions in orexin signaling have been implicated in excessive daytime sleepiness, fragmented sleep, and metabolic dysregulation[49]. Despite chronic fatigue syndrome being characterized by persistent fatigue and unrefreshing sleep, literature evidence linking orexinergic system dysfunction to CFS is lacking. However, research on narcolepsy and other sleep disorders has demonstrated that orexin deficiency leads to excessive fatigue and disrupted sleep architecture, suggesting a potential but unproven connection[76].

Orexins strongly stimulate monoaminergic systems, including the LC noradrenergic, DRN serotonergic, and tuberomammillary histaminergic pathways, promoting wakefulness and alertness[77]. They also enhance dopaminergic activity in the ventral tegmental area (VTA), influencing motivation and reward processing. In contrast, orexins inhibit GABAergic neurons in the preoptic hypothalamus, reducing sleep drive and stabilizing wake states[49].

Beyond sleep, orexinergic modulation extends to cholinergic networks, particularly in the pedunculopontine and laterodorsal tegmental nuclei, which regulate REM sleep and cortical activation. These interactions highlight orexin's role as a central integrator of arousal, motivation, and energy balance, reinforcing its relevance in sleep disorders and metabolic dysfunction[77].

The interplay between the orexinergic system and inflammatory processes also warrants attention. CFS is often associated with immune dysregulation and elevated levels of pro-inflammatory cytokines[75]. The orexin system interacts with inflammatory pathways, suggesting that inflammation may further disrupt orexin signaling, creating a vicious cycle of fatigue and immune activation[78]. Also, orexins participate in modulating the HPA axis, with OX2R activation specifically regulating HPA axis responses to acute and repeated stress[32][79].

6. Integrative Models of Hypothalamic and Orexinergic Dysregulation in Chronic Fatigue Syndrome

6.1. Potential Feedback Loops: Stress, Immune Dysregulation, and Neuroinflammation

Research indicates that alterations in orexin levels may correlate with the severity of fatigue and sleep disturbances, both commonly reported in CFS[80]. Additionally, dysfunction of the HPA axis, which is closely linked to orexin signaling, has been observed in CFS patients, manifesting as hypocortisolism and impaired stress responses[28][29]. This dysregulation may contribute to the chronic fatigue and cognitive impairments characteristic of the syndrome[23][27]. Inflammatory processes, including elevated cytokine levels, may further disrupt orexin signaling, suggesting a complex interplay between neuroinflammation and orexinergic dysfunction in CFS[75][81]. Elevated pro-inflammatory cytokines can impair orexin neuron activity, creating a vicious cycle where inflammation suppresses orexin function, leading to worsened fatigue and immune hyperactivation[82]. The integration of orexin signaling with hypothalamic function and immune responses provides a compelling framework for understanding the multifaceted nature of CFS/ME, highlighting potential therapeutic targets within the orexin system[70][78].

CFS may involve self-perpetuating feedback loops linking stress, immune dysregulation, and neuroinflammation, contributing to persistent fatigue and autonomic dysfunction. Stressors can activate the HPA axis, leading to increased cortisol production, which may initially seem adaptive but can become maladaptive with chronic exposure, potentially resulting in hypocortisolism and altered immune responses[5][27]. This dysregulation can exacerbate inflammation, as evidenced by elevated pro-inflammatory cytokines such as IL-6 and TNF-α, which are frequently observed in CFS patients[75][80]. Blunted cortisol responses and hypoactivity of corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) may lead to reduced cortisol output, further impairing immune regulation and prolonging immune activation[9][29]. Chronic inflammation can, in turn, disrupt orexinergic signaling, exacerbating fatigue and impairing wakefulness regulation[83][84].

Neuroinflammation, driven by immune dysregulation, may further impair hypothalamic function, disrupting the balance of neuropeptides like orexin, which are crucial for regulating energy homeostasis and sleep-wake cycles[85][86]. The resulting orexin deficiency can lead to increased

fatigue and cognitive dysfunction, creating another vicious cycle where fatigue exacerbates stress responses, further impairing immune function and promoting neuroinflammation[78][80]. Moreover, neuroinflammation may reinforce this cycle by sensitizing microglia and astrocytes, increasing the release of pro-inflammatory mediators that suppress orexin neuron activity in the LH[87]. This process could lead to worsened sleep disturbances, autonomic dysfunction, and cognitive impairment, creating a self-sustaining loop of immune activation and neuroendocrine dysregulation[88]. Understanding these interconnected pathways is essential for developing targeted interventions that address the underlying mechanisms of CFS/ME.

6.2. Incorporation of Metabolic and Sleep-Wake Mechanisms

Abnormal orexin levels have been associated with sleep disturbances and metabolic dysfunctions commonly observed in CFS patients[80][89]. Poor sleep quality correlates with increased pro-inflammatory cytokines, which may exacerbate fatigue and cognitive impairments[80]. Dysregulation of the HPA axis can contribute to chronic stress, further disrupting sleep patterns and metabolic homeostasis[90]. The interaction between these systems suggests that addressing both metabolic and sleep-wake mechanisms may be essential for developing effective interventions for CFS/ME[91].

Impaired glucose metabolism and lipid oxidation have been observed in CFS, suggesting an imbalance in energy homeostasis[92]. Orexins, which stimulate sympathetic nervous system activity and modulate insulin sensitivity, may be compromised in CFS, potentially contributing to mitochondrial dysfunction and reduced ATP production[93]. This could explain persistent fatigue and exercise intolerance, hallmark symptoms of CFS.

Disruptions in circadian rhythms may further exacerbate metabolic and sleep disturbances. The SCN, which regulates sleep-wake cycles and hormone secretion, interacts with orexin neurons to synchronize arousal states[94]. Altered melatonin secretion and dysregulated HPA axis activity may lead to fragmented sleep and unrefreshing rest, worsening fatigue and impairing daytime function[95].

Finally, the abnormal network of interactions between orexin signaling, sleep disturbances, and metabolic dysregulation highlights the complexity of CFS/ME, indicating that therapeutic strategies should target these interconnected pathways to alleviate symptoms and improve patient outcomes[78][96].

7. Clinical Implications and Therapeutic Perspectives

7.1. Biomarkers of Hypothalamic and Orexinergic Dysfunction

Identifying reliable biomarkers of hypothalamic and orexinergic dysfunction is essential for understanding their role in CFS and related disorders. Several potential biomarkers have been explored via CSF analysis, neuroimaging studies, and endocrine markers. Dysfunctions in this system have been linked to various neurodegenerative diseases and conditions characterized by fatigue[70][71]. Research suggests that alterations in orexin levels may serve as potential biomarkers for hypothalamic dysfunction, with CSF orexin concentrations correlating with sleep disturbances and cognitive impairments in CFS/ME patients[29]. Additionally, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, characterized by hypocortisolism and altered cortisol rhythms, is frequently observed in CFS patients and may serve as a biomarker for disease severity[27][28].

Neuroimaging studies indicate reduced hypothalamic volume and altered functional connectivity in CFS, particularly in the hypothalamus and brainstem regions that regulate orexinergic pathways[97]. MRI and PET scans assessing hypothalamic integrity could serve as potential biomarkers for CFS-related orexin dysfunction. Additionally, voxel-based morphometry has revealed alterations in gray and white matter volumes in brain regions linked to energy regulation and sleep[15][16]. While some studies suggest that neuroinflammatory markers, such as increased levels of pro-inflammatory cytokines, may be associated with hypothalamic dysfunction, their reliability as biomarkers for CFS/ME remains inconclusive[75][98]. Integrating neuroimaging techniques with biomarker analysis could provide a comprehensive understanding of disease mechanisms and improve diagnostic accuracy.

CSF orexin-A concentrations have been investigated as a biomarker for narcolepsy, but findings in CFS remain inconsistent. While some studies report normal orexin levels, others suggest subtle alterations that may reflect dysregulated wakefulness regulation[92][93]. Since orexin neurons regulate the HPA axis, abnormalities in cortisol secretion may indicate hypothalamic dysfunction. Many CFS patients exhibit blunted cortisol responses and altered diurnal rhythms, suggesting impaired HPA regulation[28]. Chronic inflammation and immune dysregulation may also suppress orexinergic activity. Poor sleep quality in CFS patients correlates with elevated levels of circulating pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, suggesting that sleep disturbances

may exacerbate immune dysregulation[80]. Also, increased levels of IFN-γ, IL-10, and IL-5 have been reported[9]. However, further research is needed, as no systematic study has established a consistent baseline difference in the CFS cytokine profile[8].

Beyond neuroimaging and molecular biomarkers, behavioral and physiological indicators provide further insights into hypothalamic and orexinergic dysfunction in CFS/ME. Altered sleep patterns, including fragmented sleep architecture and non-restorative sleep, are common in CFS/ME and have been linked to disruptions in orexin signaling[99]. Additionally, autonomic nervous system dysfunction, which is regulated in part by the hypothalamus, has been observed in CFS/ME patients, manifesting as abnormal heart rate variability and blood pressure regulation[90]. These findings suggest that a multifactorial approach, incorporating hormonal, neuroimaging, and physiological markers, may enhance our understanding of CFS/ME pathophysiology.

Advancements in technology, such as wearable devices and mobile health applications, offer promising tools for real-time symptom monitoring and biomarker assessment. These technologies enable continuous tracking of sleep patterns, activity levels, and physiological responses, allowing for more precise evaluation of hypothalamic and orexinergic dysfunction[100]. As digital health solutions become more sophisticated, they may facilitate earlier identification of biomarkers and improve disease characterization.

Biomarkers of hypothalamic and orexinergic dysfunction in CFS/ME, including altered orexin levels, HPA axis dysregulation, neuroimaging findings, and inflammatory cytokine profiles, hold promise for improving diagnostic accuracy and advancing our understanding of disease mechanisms. Future research should focus on refining these biomarkers, integrating novel imaging techniques and digital monitoring tools, and exploring the complex interplay between hypothalamic function, orexin signaling, and systemic inflammation in CFS/ME.

7.2. Pharmacological Modulation of Orexin Receptors

Pharmacological modulation of orexin receptors represents a promising approach for managing symptoms of CFS/ME. The orexinergic system, which regulates wakefulness, energy metabolism, and stress responses, has been implicated in the pathophysiology of these conditions.

Orexin receptor antagonists, such as daridorexant and lemborexant, have shown potential in improving sleep quality and reducing fatigue in patients with insomnia, a common comorbidity in

CFS/ME[101][102]. These dual orexin receptor antagonists (DO-RAs) block orexin signaling, promoting sleep without the adverse effects typically associated with traditional sedatives[103].

Another class of drugs, wakefulness-promoting agents like modafinil, has been investigated for its potential benefits in CFS/ME. Modafinil enhances orexin signaling, potentially improving alertness and reducing fatigue[85]. Studies suggest that modafinil stimulates specific hypothalamic circuits, promoting adaptive stress responses and alleviating cognitive impairments associated with CFS/ME[104]. Thus, orexin modulation via modafinil may offer a dual benefit: enhancing wakefulness while addressing orexinergic dysfunction observed in CFS/ME[85].

In clinical practice, improvements in fatigue symptoms, metabolic function, and motivation, along with a reduced frequency of post-exertional malaise, have been reported with low-dose modafinil (100 mg) combined with non-pharmacological interventions, including Cognitive Behavioral Therapy (CBT), an anti-inflammatory diet, gradual exercise, and antioxidant therapy[6][104][105].

By contrast, the interaction between orexin receptors and inflammatory cytokines adds complexity to CFS/ME management. Research suggests that orexin signaling may exert anti-inflammatory effects, indicating that targeting the orexin system could help mitigate the neuroinflammation commonly observed in these conditions[78][106]. This underscores the potential of personalized medicine approaches that integrate pharmacological orexin modulation with immune regulation in CFS/ME patients.

Therefore, orexin receptor modulation, particularly through orexin receptor antagonists and wakefulness-promoting agents like modafinil, presents a promising strategy for managing the multifaceted symptoms of CFS and ME. Further research is needed to optimize these interventions and evaluate their long-term efficacy and safety in diverse patient populations.

7.3. Behavioral and Lifestyle Interventions Targeting Sleep and Energy Balance

Behavioral and lifestyle interventions targeting sleep and energy balance are essential for managing CFS/ME. These strategies can significantly enhance quality of life by addressing sleep disturbances and energy regulation.

One effective approach is CBT, which has been shown to promote healthier lifestyle habits. Macovei et al.[107] found that CBT effectively reduces fatigue in patients with rheumatic disorders, suggesting its potential applicability to CFS/ME. Furthermore, lifestyle modifications, such as regular physical

activity, can improve energy levels and sleep quality. Rozich et al.[108] highlights that recreational exercise reduces fatigue and improves clinical outcomes in patients with inflammatory bowel disease, indicating a broader role for physical activity in fatigue-related conditions.

Sleep hygiene practices are also critical in CFS/ME management. Establishing a consistent sleep schedule and creating a restful sleep environment can help alleviate fatigue symptoms. Wendt et al. [109] emphasize that sleep disturbances are closely linked to daytime fatigue, and addressing these issues through behavioral interventions can lead to significant health improvements. Moreover, the Energy Envelope Theory suggests that pacing activities to stay within individual energy limits may help prevent post-exertional malaise and enhance energy management[110].

Nutrition also plays a crucial role in energy balance and overall well-being. A balanced diet can help stabilize energy levels and improve sleep quality. Integrating dietary interventions with physical activity and sleep hygiene provides a comprehensive approach to CFS/ME management. For instance, the SYNCHRONIZE study protocol evaluates the effectiveness of a multidisciplinary intervention incorporating nutritional guidance, chronobiology, and physical exercise in patients with fibromyalgia and CFS[111].

As previously discussed, behavioral and lifestyle interventions focusing on sleep hygiene, physical activity, and nutrition are fundamental to CFS and ME management. These strategies not only improve sleep quality and energy balance but also enhance overall quality of life. Future research should further investigate their efficacy across diverse populations to establish standardized treatment protocols.

7.4. Personalized Medicine Approaches

Personalized medicine approaches for CFS/ME are increasingly recognized as essential for effective management and treatment. Integrating biomarkers, genetic factors, and individualized therapeutic strategies may enhance patient outcomes.

For instance, Milrad et al.[80] emphasize the importance of identifying neuroendocrine and mood-related indicators to optimize interventions such as CBT for sleep disturbances, which are prevalent in CFS patients. Similarly, Fluge et al.[112] highlight metabolic profiling as a promising avenue, identifying impaired pyruvate dehydrogenase function in CFS, which could guide targeted metabolic interventions.

Furthermore, HPA axis dysfunction is well-documented in CFS, suggesting that personalized treatments could focus on restoring hormonal balance[28][29]. Also, the orexinergic system's role in sleep-wake regulation presents another target for personalized therapies. Research suggests that orexin receptor antagonists may offer novel treatment options for CFS-related sleep disturbances[101].

Overall, a personalized medicine approach that integrates metabolic, neuroendocrine, and orexinergic factors could significantly improve CFS/ME management, tailoring interventions to individual patient profiles and enhancing treatment efficacy[91][113].

8. Future Directions in Research

8.1. Advanced Neuroimaging Techniques for Hypothalamic Assessment

Advanced neuroimaging techniques are increasingly pivotal in assessing hypothalamic function, particularly in CFS/ME. Methods such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) enable the visualization of brain structures and connectivity, providing insights into the hypothalamus's role in energy regulation and sleep-wake cycles[114].

Research suggests that altered hypothalamic activity can significantly impact orexin production, which is essential for maintaining wakefulness and energy balance. For instance, studies on narcolepsy have shown that the loss of hypocretin-producing neurons in the hypothalamus correlates with sleep disturbances, underscoring its role in sleep regulation[115]. Moreover, advanced neuroimaging may help identify structural changes in the hypothalamus associated with neuroinflammatory processes, which are often observed in CFS/ME. However, direct evidence linking neuroinflammation in CFS/ME to hypothalamic imaging findings remains limited[116].

The integration of machine learning with neuroimaging data further enhances the ability to analyze complex brain activity and structural patterns, potentially leading to personalized treatment strategies[117][118]. This approach may help identify neurobiological markers associated with hypothalamic dysfunction, paving the way for targeted interventions tailored to the unique needs of CFS/ME patients[119].

Summarizing, advanced neuroimaging techniques provide valuable insights into hypothalamic function and its role in CFS and ME. By elucidating the neurobiological underpinnings of these

conditions, neuroimaging can inform personalized medicine approaches, ultimately improving patient outcomes.

8.2. Longitudinal Studies and Large-Scale Cohorts

These studies are essential for understanding the pathophysiology of CFS/ME. These studies provide critical insights into the temporal dynamics of hypothalamic dysfunction, neuroinflammation, and orexinergic system involvement in these conditions.

For instance, Byrne et al.[120] emphasizes the need for replicating findings on hypothalamic volumes and their association with fatigue severity and illness duration in larger longitudinal cohorts. Such research can clarify how chronic stress and inflammation affect hypothalamic function over time, potentially guiding the development of targeted interventions.

Moreover, longitudinal studies can help identify biomarkers correlated with symptom severity and disease progression. Corbitt et al.[75] highlights the importance of cytokine profiles in understanding immune dysregulation in CFS/ME, suggesting that longitudinal designs could clarify the relationship between cytokine levels and clinical outcomes. Similarly, Finkelmeyer et al.[16] demonstrate how neuroimaging studies tracking brain changes over time can reveal structural and functional alterations associated with fatigue and cognitive dysfunction.

The integration of neuroimaging techniques with longitudinal data further enhances our understanding of the neurobiological underpinnings of CFS/ME. For example, studies utilizing voxel-based morphometry to assess gray and white matter changes in CFS patients over time provide valuable insights into disease progression and its impact on brain structure[16].

At present, longitudinal studies and large-scale cohorts are essential for advancing knowledge of CFS, identifying biomarkers, and guiding the development of effective therapeutic strategies.

8.3. Translational Opportunities and Novel Therapeutic Targets

Translational research in CFS/ME increasingly focuses on novel therapeutic targets, particularly those related to sleep and energy regulation. The orexinergic system, which plays a crucial role in sleep-wake cycles and energy balance, has emerged as a promising target for pharmacological interventions. Ghanemi and Hu[121] highlight that orexin receptors are key players in sleep-wake disorder

treatments, suggesting that targeting this system could lead to effective therapies for CFS/ME patients experiencing fatigue and sleep disturbances.

Moreover, the integration of behavioral and lifestyle interventions, such as Cognitive Behavioral Therapy for Insomnia (CBT-I), offers additional opportunities to improve sleep quality and overall health in CFS/ME populations. Smyth[122] reports that such interventions significantly enhance sleep outcomes and reduce fatigue, thereby improving quality of life. The potential for personalized interventions that combine pharmacological and behavioral strategies is particularly noteworthy, as they address the unique needs of each patient[123].

Furthermore, advancements in technology, such as mobile health applications and wearable devices, provide innovative platforms for monitoring sleep patterns and implementing interventions. These tools enable real-time feedback and personalized treatment adjustments, improving adherence and effectiveness[100]. The integration of such technologies with traditional therapeutic approaches represents a significant advancement in CFS/ME management.

The exploration of novel therapeutic targets, particularly within the orexinergic system, alongside behavioral interventions and technological advancements, presents substantial translational opportunities for improving CFS/ME outcomes. Continued research in these areas is essential for developing effective, personalized treatment strategies that address the multifaceted nature of these conditions[124][125].

9. Discussion

9.1. Summary of Key Findings

The present review outlines how hypothalamic and orexinergic dysfunction may underlie crucial facets of CFS/ME, including sleep disturbances, metabolic dysregulation, and autonomic instability. Specifically, evidence suggests that (1) neuroimaging abnormalities (e.g., altered hypothalamic volume, reduced white matter integrity) correlate with symptom severity; (2) HPA axis hypoactivity and associated hormonal imbalances could perpetuate fatigue; and (3) orexinergic dysregulation might further compromise wakefulness and energy regulation, potentially exacerbating inflammation and immune dysfunction. These interlinked processes reinforce the complexity of CFS/ME, highlighting a multifactorial etiology that demands integrated diagnostic and therapeutic frameworks[28][29].

9.2. Critical Appraisal and Mechanistic Implications

A major strength of the reviewed literature is its broad scope, addressing immune function, neuroendocrine pathways, and the neural underpinnings of fatigue[70][75]. Yet critical appraisal reveals ongoing challenges:

1. Heterogeneity of Criteria and Cohorts. Multiple diagnostic criteria are employed across studies (e.g., Fukuda, Canadian Consensus), creating patient samples with varied clinical profiles. This heterogeneity can obscure robust biomarker discovery and confound comparisons between investigations[20].
2. Limited Direct Evidence of Orexin Alterations in CFS/ME. Although preclinical and clinical findings link orexin deficiency to narcolepsy, fragmented sleep, and metabolic disruption, few studies directly measure orexin levels in CFS/ME cohorts. The prevailing assumption of orexinergic involvement remains more inferential than conclusive[49][76].
3. Sample Size and Power. Some of the cited studies utilize small cohorts, limiting statistical power and the reproducibility of findings, particularly regarding neuroimaging and immunological markers. Larger cohorts would bolster the reliability of associations between hypothalamic or orexinergic dysfunction and specific clinical outcomes[120].

Despite these limitations, an emerging mechanistic framework posits that hypothalamic disruption—via HPA axis dysregulation and deficient orexin signaling—can initiate or perpetuate a cycle of chronic inflammation, reduced stress resilience, and disordered sleep-wake regulation[75][80]. This cycle may be amplified by compromised metabolic pathways, such as impaired glucose utilization or mitochondrial dysfunction, thereby intensifying post-exertional malaise and autonomic dysregulation[92][126].

9.3. Limitations of the Current Evidence Base

The synthesis presented also highlights methodological and conceptual challenges that constrain definitive conclusions:

- Inconsistent Biomarker Profiles. While cytokine imbalances and cortisol abnormalities are frequently reported, no single biomarker consistently distinguishes CFS/ME from other fatigue-related or inflammatory conditions[8][9].

- Temporal or Causal Relationships. Most studies are cross-sectional, making it difficult to determine whether hypothalamic or orexin changes precede, follow, or parallel disease progression. Longitudinal designs are needed to establish causal inferences[16][120].
- Comorbidities and Confounders. Many patients experience overlapping conditions (e.g., depression, fibromyalgia), which can distort neuroendocrine or immunologic readouts and confound interpretations of hypothalamic function[64].

9.4. Research Opportunities Perspectives

Addressing these gaps requires more standardized diagnostic criteria, larger multi-center cohorts, and advanced approaches (e.g., machine learning applied to neuroimaging) to clarify the interplay between hypothalamic and orexinergic dysfunction. Longitudinal studies tracking shifts in HPA hormones, orexin levels, and inflammatory markers could identify prognostic indicators and reveal windows for therapeutic intervention[75][114]. Additionally, controlled trials of orexin receptor modulators, in combination with behavioral approaches (e.g., CBT, pacing), hold promise for improving both daytime function and sleep quality in CFS/ME[101][102].

10. Conclusion

Mounting evidence supports a unifying model in which hypothalamic and orexinergic dysfunction contribute to the core features of CFS/ME. Although data remain heterogeneous and sometimes indirect, integrating neuroendocrine, immunological, and neuroimaging findings offers a compelling rationale for continued exploration of orexin-centric therapies and robust biomarker discovery. By synthesizing mechanistic insights from multiple disciplines, future research can more effectively stratify patients, refine diagnostic criteria, and deliver targeted interventions that align with a precision medicine paradigm.

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