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Hypothalamic Dysfunction and Multiple Sclerosis: Implications for Fatigue and Weight Dysregulation

Kevin G. Burfeind[1], **Vijayshree Yadav**[2], and **Daniel L. Marks**[3]

[1]MD/PhD Program, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA

[2]Department of Neurology, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA

[3]Papé Family Pediatric Research Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, L 481, Portland, OR 97239, USA

Abstract

Signs and symptoms of multiple sclerosis are usually attributed to demyelinating lesions in the spinal cord or cerebral cortex. The hypothalamus is a region that is often overlooked yet controls many important homeostatic functions, including those that are perturbed in multiple sclerosis. In this review we discuss how hypothalamic dysfunction may contribute to signs and symptoms in people with multiple sclerosis. While dysfunction of the hypothalamic-pituitary-adrenal axis is common in multiple sclerosis, the effects and mechanisms of this dysfunction are not well understood. We discuss three hypothalamic mechanisms of fatigue in multiple sclerosis: (1) general hypothalamic-pituitary-adrenal axis hyperactivity, (2) disordered orexin neurotransmission, (3) abnormal cortisol secretion. We then review potential mechanisms of weight dysregulation caused by hypothalamic dysfunction. Lastly, we propose future studies and therapeutics to better understand and treat hypothalamic dysfunction in multiple sclerosis. Hypothalamic dysfunction appears to be common in multiple sclerosis, yet current studies are underpowered and contradictory. Future studies should contain larger sample sizes and standardize hormone and neuropeptide measurements.

Keywords

Multiple sclerosis; Hypothalamus; Fatigue; Weight dysregulation; Neuroendocrinology

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease that affects over 2.3 million individuals worldwide [1]. MS pathogenesis is driven primarily by autoreactive

Correspondence to: Daniel L. Marks.

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Compliance with Ethical Standards

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immune cells attacking myelin and axons of central nervous system (CNS) neurons, leading to destructive lesions in the spinal cord and brain. These lesions lead to motor, sensory, and cognitive impairment, and autonomic dysfunction [2–4]. Additionally, there are other signs and symptoms that are not typically linked to CNS lesions and yet can cause significant disability. These include fatigue and metabolic dysfunction. The etiologies of these signs and symptoms are undoubtedly multifactorial. However, the hypothalamus is known to regulate a number of homeostatic systems, including sleep, motivated behaviors, appetite, and basal metabolic rate. Hypothalamic dysfunction is common in chronic inflammatory diseases similar to MS [5, 6], yet this region of the CNS is often overlooked when considering underlying etiologies and treatment of signs and symptoms of MS.

The hypothalamus is anatomically configured to allow neurons and other cells to detect circulating factors, hormones, and metabolites in order to adjust homeostatic function in response to stressors and physiologic perturbations. It is located adjacent to the third ventricle in close contact with circumventricular structures and contains a rich supply of fenestrated capillaries with an attenuated blood brain barrier (BBB). Neurons in this region of the brain are highly responsive to immune mediators [7] and cytokines directly modulate the activity of multiple hypothalamic neurons [8–10]. While this response is important to maintaining homeostasis, chronic hypothalamic inflammation is maladaptive and is associated with a variety of systemic pathologies including muscle wasting, disordered sleep, insulin resistance, and fatigue [11]. Hypothalamic dysfunction is particularly prevalent in inflammatory diseases in which patients experience increased levels of circulating cytokines and other pro-inflammatory molecules, such as cancer [12], rheumatoid arthritis [13], congestive heart failure [14], and cirrhosis [15]. In the setting of obesity, it is hypothesized that increased circulating cytokines leads to hypothalamic inflammation, which causes aberrant activity of weight regulatory neurons in this region, contributing to the pathogenesis of this disease [16].

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction is common in MS [17–20], yet its underlying etiology is poorly understood. Possibilities include damage to the hypothalamus or a secondary effect of a global stress response to the disease. The few studies exploring the prevalence of hypothalamic lesions in MS report a high prevalence of lesions in this brain region. For example, Huitinga et al. investigated hypothalamic lesions in MS patients and reported that 16 of 17 had lesions in this region [21]. Increased HPA axis activity, quantified by cerebrospinal fluid (CSF) cortisol levels and number of corticotrophin-releasing hormone (CRH)-producing neurons in the paraventricular nucleus of the hypothalamus, is also associated with increased disease severity in MS [22].

There are currently no guidelines for recognizing or managing hypothalamic dysfunction in MS. Furthermore, reports on causes and mechanisms of resultant signs and symptoms are conflicting. There are no reviews summarizing literature on the effects, mechanism, and potential therapies for hypothalamic involvement in MS. In this review we summarize the current literature on hypothalamic dysfunction in MS in the context of fatigue and weight dysregulation. We then propose treatments and recommend future studies.

Fatigue

Fatigue in MS

Fatigue affects 50–90 % of people with MS [23, 24]. For many people with MS, fatigue is reported as the most debilitating symptom, often surpassing both motor impairment and autonomic dysfunction [25]. Despite this serious clinical concern, this complex syndrome is poorly defined, with most diagnostic criteria relying on subjective self-reporting by patients [26]. Mechanisms of fatigue are also poorly understood, and dissecting fatigue from sleep disturbances is difficult. Up to 50 % of people with MS suffer from sleep disorders [27], which often occur concurrently with fatigue [28]. Furthermore, numerous pharmacologic agents commonly used in MS cause fatigue [29–31]. These confounding factors make studying fatigue in humans and animal models challenging. Future studies are needed to fully understand the relationship between insomnia and fatigue in MS. However, there is general consensus that fatigue in MS originates in the CNS [32]. Within the CNS, the actions of neurons that project to and from the hypothalamus control wakefulness and activity levels. As such, many studies investigated the role of hypothalamic dysfunction in disorders of wakefulness in MS. There are differing theories of the key substrate within the hypothalamus responsible for fatigue. This section will describe three different theories: (1) overall HPA axis hyperactivity, (2) disordered orexin neurotransmission, and (3) abnormal cortisol secretion.

HPA Axis Hyperactivity—As mentioned earlier, several studies demonstrate that many people with MS have increased HPA axis activity. Previous studies investigating HPA axis and fatigue in other chronic diseases are conflicting. Some studies have found fatigue and general HPA axis hyperactivity to be correlated in chronic fatigue syndrome (CFS) [33], Alzheimer's disease [34], major depression [35], cancer [36], and rheumatoid arthritis [37]. However, other studies have found HPA axis hypoactivity in people with fatigue due to cancer [38], fibromyalgia [39], and CFS [40]. These conflicting results may occur due to the difficulty of quantifying HPA axis activity. Many studies (including several of those listed above) use serum or urinary cortisol as a measure of HPA axis activity, which are often unreliable and difficult to standardize. However, it is generally accepted that in states of chronic disease and stress the HPA axis is highly activated [41], which can alter levels of wakefulness [42].

In MS, few studies have investigated the relationship between HPA axis activity and fatigue. Gottschalk et al. [43] used the dexamethasone-CRH test to quantify HPA axis activity in 31 individuals with relapsing-remitting MS (RRMS). Fatigue was measured through three questionnaires: the Fatigue Severity Scale, the Modified Fatigue Impact Scale, and the Visual Analog Scale. The authors found that individuals with fatigue had significantly elevated adrenocorticotropin (ACTH) levels after CRH administration compared to those without fatigue. It is important to note that individuals without MS were not included in this study. Alternatively, Heesen et al. [44] was unable to find a relationship between HPA axis activity and fatigue in 30 MS patients. A possible reason for this discrepancy is that in this study both chronic progressive phase and RRMS patients were included, while in Gottschalk et al. only RRMS patients were included. Further studies with larger, more homogenous

patient samples are needed to better understand the role of HPA axis hyperactivity in fatigue in MS.

Orexin—A neurotransmitter that is of particular interest in both fatigue and sleep dysfunction is orexin. Orexin is a neuropeptide synthesized by neurons in a small number of nuclei within the hypothalamus that project widely to brain areas involved in arousal and motivated behaviors. It activates monoaminergic and cholinergic wake-active neurons in the hypothalamus and brainstem during the daytime [45]. Orexin neurons located in the perifornical and dorsomedial hypothalamic areas project to numerous areas in the brain, including the locus ceruleus, septal nuclei, stria terminalis, and parbrachial nuclei [46]. The activity of these neurons is critical for maintenance of long, consolidated awake periods [47]. Deficiency of orexin signaling in humans leads to narcolepsy, a sleep disorder characterized by inability to maintain a vigilant state and pathologic intrusion of rapid eye movement sleep during awake periods [47]. Furthermore, loss of orexinergic neurons or dysfunction in the orexinergic system has been observed in other CNS diseases such as Alzheimer's disease [48], and in animal models of Parkinson's disease [49] and stroke [50]. In addition, neuroinflammation reduces hypothalamic orexin neuron activity, which leads to fatigue [51].

Orexin dysfunction is hypothesized as one cause of fatigue in MS, but studies investigating this relationship are conflicting. There are several case reports of MS patients with hypothalamic lesions with low CSF orexin levels and accompanying hypersomnia or fatigue [52–54]. For example, Kato et al. [52] showed that the CSF concentration of orexin in a person with MS with bilateral hypothalamic lesions was much lower than normal. Oka et al. [53] reported similar findings in a 22-year-old female with MS who presented with hypersomnia and was found to have low CSF orexin and a hypothalamic lesion.

Cohort studies of MS patients, as well as animal studies, also showed altered levels of orexin associated with fatigue. The results of these studies are conflicting and there is no consensus on whether increased or decreased levels of orexin are associated with fatigue in MS. Küçükali et al. [55] reported that serum orexin levels were reduced in experimental autoimmune encephalitis. In direct contrast, Papuc et al. found a *positive* correlation between CSF orexin levels and fatigue severity score (FSS) in 38 people with MS. This correlation was even stronger in the MS subgroup that suffered from fatigue [56]. However, the authors did not analyze this correlation in the 15 age-matched non-diseased control subjects included. These results are surprising, since fatigue is associated with decreased wakefulness, yet increased orexin levels are associated with increased wakefulness. Therefore, the expected result would be a *negative* correlation between CSF orexin levels and FSS. The authors suggested their findings may be a result of a compensatory mechanism.

Alternatively, Constantinescu et al. [57] investigated the correlation between CSF orexin levels and FSS in 34 patients with MS, 24 patients with other inflammatory neurological diseases (neurosarcoidosis, clinically isolated syndromes, encephalitis or meningitis, and inflammatory demyelinating polyradiculopathies), and 42 patients with non-inflammatory neurological diseases (idiopathic intracranial hypertension, cerebrovascular disease, primary

headache syndromes, and axonal neuropathies) and reported no correlation between CSF orexin levels and FSS in any of the three groups.

It is important to note that in both Küçükali et al. and Constantinescu et al., levels of orexin did not significantly differ between MS and non-MS groups (although in both studies CSF orexin levels were decreased in MS individuals compared to individuals without MS), different MS subgroups, or individuals with and without fatigue.

These conflicting and surprising results suggest additional studies are needed to better understand disordered orexin neurotransmission in MS and its role in fatigue. One potential cause of these conflicting results is the inherent challenge in obtaining a sufficient number of accurate orexin measurements. Since orexin most likely does not readily cross the BBB, it must be measured from the CSF [58]. As such, recruiting a sufficient number of non-diseased individuals for CSF samples is always challenging. Furthermore, the two studies used different orexin detection assays, which are not cross-validated. In addition, although samples were taken during the day in both studies, orexin levels vary throughout the day [59], and even seasonally [60]. Finally, developing a better understanding of whether or not the diurnal variation in orexin levels is disrupted in MS patients is essential. Diurnal variation in orexin activity is critical to avoid fatigue. Low levels at night promote consolidated sleep, while high levels during the day promote activity [61]. This is important for developing a therapeutic target of orexin. Orexin receptor antagonist use at night and/or agonist use during the day should be considered. This will be discussed further in “Treatments”.

Cortisol—As discussed in previously, perturbations in HPA axis activity occur in many chronic diseases. One of the key hormones of the HPA axis implicated in fatigue and wakefulness is cortisol. Cortisol is a glucocorticoid produced in the zona fasciculata of the adrenal gland. Its release is stimulated by the pituitary peptide ACTH, which in turn is stimulated by CRH produced in the hypothalamus and secreted into the portal vasculature. Cortisol is important in several homeostatic functions, including metabolism [62], immune function [63], and wakefulness [64]. It is released in response to a variety of stressors [65] and perturbed cortisol secretion is predictive of poorer outcomes in both neurologic and non-neurologic diseases [66–68]. Cortisol contributes to wakefulness mainly through the cortisol awakening response (CAR), a spike in serum cortisol approximately 30 to 45 min after awakening. The CAR is important in circadian rhythms and maintaining wakefulness [69]. Traditionally, low levels of cortisol are thought to contribute to fatigue [70]. Investigation in the context of CFS demonstrates that CFS patients have a decreased CAR and lower levels of serum cortisol compared with non-fatigued individuals [71]. However, there are multiple reports of increased levels of cortisol or CRH in people with MS [17–19]. The effect of this on wakefulness is not well understood. Heesen et al. failed to demonstrate a relationship between cortisol levels and fatigue in MS [44]. In contrast, Powell et al. [72•] reported an increase in CAR as well as a correlation between fatigue and CAR in patients with RRMS. However, the increased CAR was not associated with sameday fatigue and cortisol levels were negatively correlated with fatigue in RRMS patients.

While there are several possible explanations for these conflicting results, the most likely explanation is the significant variation between different techniques to measure cortisol. Cortisol has a large circadian variation, with highest levels in the morning and lowest levels around midnight [73]. This in itself presents a significant challenge for obtaining accurate measurements. Furthermore, cortisol is transported bound to a specific carrier protein, cortisol binding globulin, as well as albumin. As such, the biologically active fraction of cortisol comprises less than 10 % of the total hormone concentration [74]. Furthermore, most cortisol is excreted into the urine. Cortisol is usually measured in one of three biological fluids: (1) serum, (2) saliva, and, (3) urine [75]. All three methods come with serious limitations and inherent inaccuracies. Serum cortisol can be measured as either total cortisol or free serum. Seriously ill patients often have low plasma protein concentration, making total cortisol analysis difficult [76]. Alternatively, assays to measure free cortisol must be very sensitive and there is a lack of standardization between different commercially available kits [77].

There are several methods for measuring salivary cortisol. Salivary measurement has the advantages of not requiring an invasive blood draw, samples can be acquired at a patient's home, and cortisol is stable in saliva at room temperature for at least a week. However, as with serum assays, different salivary cortisol assays each have a different reference range, and there is no certified reference material to compare tests from different laboratories [78]. Furthermore, one of the measurements for salivary cortisol must be obtained at midnight, which makes compliance difficult.

Lastly, 24-h urinary free cortisol has long been used for diagnosing adrenal dysfunction (such as Addison's disease or Cushing syndrome). This technique has the advantage of measuring free cortisol, the active component of the hormone. However, this method is becoming increasingly unpopular due to the methodological concerns of requiring 24 hours of urine collection, as well as suboptimal assay precision [79].

These different methodologies, each with their own strengths and weaknesses, highlight the difficulties in accurately and precisely measuring cortisol. This, along with differences between assay kits and small patient numbers in most MS studies, makes formulating conclusions on the role of cortisol in fatigue in MS difficult. A possible solution is the use of hair cortisol. This technique has recently emerged as an accurate, reliable, and noninvasive method of quantifying cortisol [80]. Hair cortisol also has the advantage of representing cortisol levels integrated over several months, rather than a single point in time, since cortisol builds up in hair follicles [81]. There are currently no studies that assess hair cortisol in MS. This technique may be well suited to monitoring cortisol levels in a chronic disease such as MS, and should be considered in future studies.

Potential Causes of Hypothalamic Dysfunction-Induced Fatigue—There are many potential mechanisms of hypothalamic dysfunction-induced fatigue. One possible mechanism is leukocyte-mediated damage of neurons within the hypothalamus. Inflammatory lesions detectable by MRI often indicate destruction caused by infiltrating leukocytes. In theory, this can lead to altered neuronal signaling, perturbed hormone secretion, or dysfunctional neuropeptide release. This was highlighted in a recent review by

Patejdl et al. [82••]. In this review, the authors hypothesized that the primary cause of fatigue in MS is damage in the brain caused by infiltrating peripheral immune cells. This damage, initiated by leukocyte-derived cytokines, causes neurodegeneration and leads to altered neuronal function and subsequent symptoms. Patejdl et al. also suggested the hypothalamus as a key region where damage can cause fatigue. Specifically, they implicated HPA axis dysfunction, caused by lesions in the hypothalamus, as the driver of fatigue. While literature to support this claim is sparse, there are studies that investigated the correlation between hypothalamic damage and fatigue in MS. For example, Zellini et al. used T1 relaxation time as a measure of pathology in the hypothalamus and found that people with MS had significantly increased T1 relaxation times in the hypothalamus compared with controls, which correlated with overall fatigue score [83]. As described above, several case reports describe hypothalamic lesions in MS and symptoms related to neuroendocrine dysfunction, including fatigue. However, there are no publications demonstrating a correlation between the presence of hypothalamic lesions and fatigue.

Another potential cause of fatigue in MS is modulation of HPA axis activity by cytokines derived from leukocytes. The relationship between increased circulating cytokines and fatigue in various diseases is well documented [84–86]. Furthermore, individuals with MS are reported to have increased levels of various circulating inflammatory cytokines [87]. Heesen et al. [44] investigated the relationship between serum levels of pro-inflammatory cytokines and fatigue in MS and found that levels of TNF-α and IFN-γ were significantly elevated in people with fatigue and correlated with fatigue severity. Furthermore, Malekzadeh et al. [88] reported a positive correlation between serum IL-6 levels and fatigue, as measured through Checklist Individual Strength, a validated questionnaire to assess chronic fatigue [89]. These studies agree with mouse models of inflammatory disease showing that injection of inflammatory cytokines and immune mediators directly into the brain induces HPA axis activation as well as fatigue [51, 90]. Additional animal studies are needed to determine if neuroinflammation-induced fatigue depends on HPA axis activation.

In summary, while mechanisms of increased HPA axis activity as well as HPA axis-induced fatigue in MS are still not fully understood, it seems that cytokines are key players in this process. Further studies are needed to determine if autoreactive CNS-infiltrating leukocytes are the source of these cytokines, or if HPA axis dysfunction (and subsequent fatigue) is secondary to systemic stress and inflammation (i.e., circulating factors).

Weight Dysregulation

Another critical function of the hypothalamus is to modulate body composition. Hormones produced in the periphery act on neurons in various nuclei in this region to stimulate or inhibit hunger, as well as control catabolism and anabolism of fat and muscle tissues. Two important weight regulatory hormones produced in the periphery are leptin and ghrelin. Leptin is produced in adipocytes and acts on neurons in the hypothalamus to prevent a starvation response. Ghrelin is produced in the gastrointestinal tract and provides an important stimulatory drive to orexigenic neurons. These hormones act to provide critical inputs to the anorexigenic proopiomelanocortinin neurons and orexigenic neurons coexpressing neuropeptide Y and agouti-related peptide located in the arcuate nucleus of the

hypothalamus. The activity of these neurons is also modulated by cytokines, which can cause disorders of energy balance such as cachexia [8] and obesity [91].

The influence of MS on weight regulation and body composition is not well understood. Khurana et al. reported an increased prevalence of being overweight in VA Veterans with MS (n = 4703) compared to the general average for veterans (42.3 vs. 39.6 %, respectively), but a decreased prevalence of being obese (20.1 vs. 33.1 %, respectively) [92]. A recent study of 130 Israeli MS patients with advanced disease (mean Expanded Disability Status Scale: 5.5) showed that MS patients were less likely to be obese than the general population [93•]. Other studies investigating the prevalence of obesity in MS also show similar or decreased prevalence in these individuals compared to the general population [94, 95]. However, no studies have tracked the BMI of MS patients throughout the disease course and compared that to a similar time period in non-diseased controls. Furthermore, most of these studies used BMI as the only index of body composition. Previous studies show that many people with MS experience muscle mass loss [96–98]. This decrease in muscle mass may mask increases in adiposity, making it difficult to assess obesity based on BMI alone. Furthermore, elderly patients and those with chronic disease often suffer from “sarcopenic obesity,” where they have decreased muscle mass, yet retain and even increase fat mass [99]. Individuals with sarcopenic obesity are at particularly high risk for developing adverse health outcomes [100, 101]. While no studies have investigated the prevalence of sarcopenic obesity in MS patients, Pinhas-Hamiel et al. [93•] found that while MS patients had lower rates of obesity than the general population, 56 % of individuals with MS had waist circumference consistent with abdominal obesity. This rate is higher than previously reported rates of 21 and 39 % in males and females, respectively, in the same age groups in nondiseased individuals. Therefore, it is reasonable to suggest that those with MS are at risk for developing sarcopenic obesity. Future studies should investigate the prevalence and consequences of sarcopenic obesity in people with MS.

Alternatively, another syndrome exacerbated by hypothalamic inflammation is cachexia [11]. Cachexia is a metabolic syndrome with cardinal features of anorexia, weight loss (with disproportional loss of lean mass), and fatigue [102]. It occurs in numerous chronic diseases, such as cancer [103], HIV [104], cirrhosis [105], and Alzheimer’s disease [106]. Systemic inflammation is a key component of cachexia and is associated with elevated serum levels of inflammatory cytokines such as TNF-α, IL-6, and IL-1β, similar to MS. Furthermore, cachexia is prevalent in autoimmune diseases, especially rheumatoid arthritis [107]. Therefore, it is reasonable to suggest that people with MS are vulnerable to cachexia. However, cachexia in MS is not well studied. A recent case report described an MS patient with lateral hypothalamic lesions and cachexia [108]. Furthermore, cachexia is noted as a common cause of death in patients with advanced MS [109] and thus may be a concern in advanced disease. Unfortunately, no studies investigated the prevalence of cachexia at any point in the disease. Further studies are needed to determine the presence and role of this syndrome in the clinical course and pathophysiology of MS.

Treatments

Treatments for hypothalamic dysfunction in MS are not well defined. There are currently no FDA-approved treatments specifically for fatigue or weight dysfunction in MS. However, there are a few pharmacologic agents that are used for fatigue in MS that in small-scale studies have demonstrated moderate efficacy. The two most frequently used are Amantadine and Modafinil. Amantadine was originally used for influenza but now is most commonly used in Parkinson's disease. Its mechanism of action is not well understood. Although it is the most frequently studied medication for fatigue in MS, few placebo-controlled double-blinded studies are published, and all contain fewer than 125 subjects [110–112]. Nevertheless, these studies show a small but statistically significant benefit compared to placebo. However, a Cochrane Review determined that these studies were of poor quality and vulnerable to bias [113]. Additional clinical and mechanistic studies are needed to fully understand the efficacy of Amantadine.

Modafinil is a commonly used therapy for promoting wakefulness in various states of fatigue and sleep dysfunction [114]. While its mechanism is also not fully understood, it is thought to prevent reuptake of monoamines, including dopamine, norepinephrine, and serotonin [115]. As with Amantadine, studies investigating the effects of Modafinil on fatigue in MS are weak and underpowered [116], but suggest that Modafinil treatment modestly improves fatigue [117, 118]. However, a recent meta-analysis showed that exercise and education are as effective as Amantadine or Modafinil [119].

Stimulants such as Methylphenidate have been proposed as third-line treatment for fatigue in MS [120], but there a currently no published clinical trials to support their use. Alternative treatments proposed for fatigue in MS include high dose aspirin, ginkgo biloba, and amino acid supplements [121], but these treatments are seldom used and evidence supporting their efficacy is weak to non-existent.

There are currently no approved therapies for weight dysregulation in MS. Since this issue is still poorly understood, few therapies have been studied or proposed. The only studies published focus on therapeutic use of cannabis. These studies are few, underpowered, and lack control for confounders [122, 123]. Zajicek et al. [123] reported that perceived increased appetite (but not actual food intake) was reported at low levels in the cannabis group. Additional research on the prevalence and mechanisms of weight and appetite dysregulation in MS are needed prior to treatment development.

None of the current therapies for fatigue target hypothalamus-based or other established or hypothesized mechanisms of fatigue in MS. Future clinical studies to develop therapies for fatigue in MS should focus on established or proposed mechanisms in the CNS. Animal models can provide a foundation for these studies. As described in previously, the orexin system can be targeted pharmacologically. Due to the diurnal nature of orexin secretion, agonist use during the day and/or antagonist use at night should be considered. For example, administration of orexin to mice with EAE greatly attenuated clinical symptoms [124]. However, fatigue was not directly measured in this study. Alternatively, orexin antagonists were proposed as treatment for insomnia [125, 126]. Currently, Suvorexant, the dual orexin

receptor antagonist (DORA), is the only FDA-approved orexin antagonist therapy available. In a phase III trial of 1260 patients with insomnia, individuals in the treatment group (n = 493) experienced prolonged sleep maintenance and decreased sleep onset compared to placebo controls (n = 767) [127]. The relationship between insomnia and fatigue in MS must be better understood in order to justify use of DORAs.

Future Directions

Future research investigating hypothalamic dysfunction in MS should focus on accurately and reproducibly measuring hypothalamic hormones and neuropeptides, HPA axis activity, and structural integrity of the hypothalamus in MS patients. Large multi-centered trials should be conducted in order to obtain a sufficient number of patients. Subjects should be selected based on disease stage and groups should be as clinically homogenous as possible. Furthermore, since there are considerable differences in hypothalamic function between men and women [128], studies should include both genders and consider sex as a key variable. These studies will help lay a stronger foundation to determine the prevalence and typical severity of hypothalamic involvement in MS.

Additional imaging studies focused on hypothalamic lesions should be conducted to accurately determine the prevalence of lesions in this brain region in MS. Furthermore, correlations between hypothalamic lesions, perturbed hormone and neuropeptide secretion, and signs and symptoms (fatigue, sleep disturbances, etc.) are needed to determine whether hypothalamic dysfunction in MS is due to structural damage in this region or other causes.

Lastly, very few studies have investigated the effect of MS on weight homeostasis or body composition. Future studies should investigate both obesity and cachexia. MS shares many characteristics of other diseases that have a high prevalence of cachexia (e.g., high levels of circulating inflammatory cytokines, inflammation in the CNS, HPA axis hyperactivity, etc.), yet no studies investigated the prevalence of cachexia in MS. Alternatively, more detailed measurements of body composition are needed to determine if individuals with MS have increased adiposity and/or an increased prevalence of sarcopenic obesity.

Conclusion

The hypothalamus is the central regulator of numerous homeostatic processes. In MS, many of these processes, especially wakefulness and activity level, are disrupted. This can lead to debilitating symptoms such as fatigue. However, the hypothalamus and its functions are often overlooked in MS. The few studies investigating hypothalamic dysfunction in MS show dysfunctional secretion of hypothalamic peptides and hormones in MS patients, including cortisol and orexin. Results are conflicting and studies are underpowered. In addition, MS is similar to other diseases that have a high prevalence of cachexia, a syndrome caused by hypothalamic dysfunction. However, since obesity is certainly more common than cachexia, understanding the link between MS and obesity should be considered a priority. Further studies consisting of larger, more homogenous patient samples are needed to fully understand the degree and role of hypothalamic dysfunction in MS. These studies can

provide a basis for additional treatments, as hypothalamic hormones and neuropeptides present substrates that can be targeted pharmacologically.

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