

Minireviews

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome—Metabolic Disease or Disturbed Homeostasis due to Focal Inflammation in the Hypothalamus?

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ABSTRACT

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disease characterized by debilitating fatigue, lasting for at least 6 months, with associated malaise, headaches, sleep disturbance, and cognitive impairment, which severely impacts quality of life. A significant percentage of ME/CFS patients remain undiagnosed, mainly due to the complexity of the disease and the lack of reliable objective biomarkers. ME/CFS patients display decreased metabolism and the severity of symptoms appears to be directly correlated to the degree of metabolic reduction that may be unique to each individual patient. However, the precise pathogenesis is still unknown, preventing the development of effective treatments. The ME/CFS phenotype has been

associated with abnormalities in energy metabolism, which are apparently due to mitochondrial dysfunction in the absence of mitochondrial diseases, resulting in reduced oxidative metabolism. Such mitochondria may be further contributing to the ME/CFS symptomatology by extracellular secretion of mitochondrial DNA, which could act as an innate pathogen and create an autoinflammatory state in the hypothalamus. We propose that stimulation of hypothalamic mast cells by environmental, neuroimmune, pathogenic and stress triggers activates microglia, leading to focal inflammation in the brain and disturbed homeostasis. This process could be targeted for the development of novel effective treatments.

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is defined by the original diagnostic criteria (Fukuda et al., 1994) and by the Canadian Consensus Criteria (Carruthers et al., 2003; Carruthers, 2007), followed by an international consensus (Carruthers et al., 2011) and newer clinical diagnostic criteria developed by a National Institutes of Health Pathways to Prevention Workshop (Haney et al., 2015) and the Institute of Medicine (Germain et al., 2017). ME/CFS has also been known by other names (Unger et al.,

2016), most recently as systemic exertion intolerance disease (Monro and Puri, 2018).

ME/CFS is a complex disease that involves the muscular, nervous, hormonal, and immune systems (Natelson, 2001; Georgiades et al., 2003; Brurberg et al., 2014; Brigden et al., 2017; Scheibenbogen et al., 2017). As the name implies, ME/CFS is characterized by debilitating fatigue lasting for at least 6 months, with severe impairment of daily functioning and associated symptoms, such as sleep disturbances, muscle aches, flu-like malaise, gastrointestinal symptoms, orthostatic intolerance, chronic or intermittent pain, as well as cognitive impairment reflected as memory and concentration difficulties (Natelson et al., 2007; Holgate et al., 2011; Yancey and Thomas, 2012; Ganiats, 2015; Komaroff, 2015; Scheibenbogen et al., 2017).

The intensity of symptoms appears to be significantly affected by exertion (Rowe et al., 2016). Anxiety and increased vulnerability to stress are also common in ME/CFS patients,

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ABBREVIATIONS: acetyl-CoA, acetyl-coenzyme A; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; FMS, fibromyalgia syndrome; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MetS, metabolic syndrome; mtDNA, mitochondrial DNA; SP, substance P; TCA, tricarboxylic acid; TNF, tumor necrosis factor.

including children affected by the disease (Smith et al., 2003; Crawley et al., 2009). Abnormal hypothalamic-pituitary-adrenal (HPA) axis activity has been observed in many patients (Cleare et al., 2001), thus suggesting an association between ME/CFS and disturbed neuro-endocrine mechanisms. Interestingly, ME/CFS patients are more likely to have migraine headaches than normal controls (Ravindran et al., 2011). ME/CFS is often comorbid with disorders (Table 1) that are characterized by central nervous system dysfunction (Martínez-Martínez et al., 2014), and which are also negatively affected by stress (Theoharides and Cochrane, 2004; Theoharides, 2013): Gulf War illness (Gwini et al., 2016), pelvic pain syndrome/interstitial cystitis (Whitmore and Theoharides, 2011), fibromyalgia syndrome (FMS) (Theoharides et al., 2015c), and mastocytosis (Theoharides et al., 2015d) or mast cell activation syndrome (Akin, 2014; Petra et al., 2015). However, there are distinct differences between these other diseases, such as between ME/CFS and FMS (Abbi and Natelson, 2013; Pejovic et al., 2015).

ME/CFS is estimated to affect as many as 2.5 million people in the United States, which corresponds to about 1% of the total U.S. population (Vincent et al., 2012; Ganiats, 2015; Komaroff, 2015). Other studies (Jason et al., 2009), including those conducted in Minnesota (Vincent et al., 2012), as well as in the United Kingdom (Nacul et al., 2011; Collin et al., 2017), Norway (Bakken et al., 2014), and Italy (Capelli et al., 2015), report a lower incidence. Women are apparently more susceptible than men, with an estimated ratio of 4:1 (Germain et al., 2017). The disease predominantly affects adults, even though symptoms may appear in childhood and adolescence (Jason et al., 2006; Nijhof et al., 2011; Crawley, 2014). Unfortunately, a significant number of suspected ME/CFS patients remain undiagnosed (Jason et al., 2006), mainly due to the complexity of the disease and the lack of reliable diagnostic biomarkers (Klimas et al., 2012). Multisystem diseases such as ME/CFS are often very timely and expensive to diagnose, and most patients go through years of searching and agony, as well as significant financial expenditures and impairment of their quality of life (Germain et al., 2017). The economic health burden for ME/CFS in the United States was estimated to be \$24 billion in 2018 (Jason et al., 2008). This makes imperative the need for the development of objective diagnostic biomarkers that will not only assist in the critical identification of patients with ME/CFS, but will also provide essential information on the pathophysiological mechanisms involved.

TABLE 1
Conditions often comorbid with ME/CFS

Condition
Chronic inflammatory response syndrome
Fibromyalgia syndrome
Ehlers-Danlos syndrome
Gulf War illness
Interstitial cystitis/bladder pain syndrome
Irritable bowel syndrome
Mast cell activation syndrome
Multiple chemical sensitivity syndrome
Post-Lyme syndrome
Postural orthostatic tachycardia syndrome
Post-traumatic stress disorder
Restless leg syndrome

A number of mechanisms and molecules (Table 2) have been implicated in the pathogenesis of ME/CFS (Gerwyn and Maes, 2017). Autoimmune (Sotzny et al., 2018) and metabolic (Tomas and Newton, 2018) pathways appear to play key roles in the pathophysiology of ME/CFS (Theoharides et al., 2004b; Maes et al., 2012b; Booth et al., 2012). Neuroimmune and neuroendocrine processes might also be involved, but are still largely unknown (Dietert and Dietert, 2008; Bower, 2012). Clinical and subclinical viral infections have been suspected, but never confirmed, as a possible risk factor for the development of ME/CFS (Frémont et al., 2009; Katz et al., 2009). The involvement of neuroinflammation of the brain has recently been suggested without any specific pathogenetic mechanism (Glassford, 2017; Morris et al., 2018; Tomas and Newton, 2018). Here, we give an overview of the current understanding of the associations between ME/CFS and metabolic disease, and propose that focal inflammation in the hypothalamus due to local activation of mast cells and microglia may alter homeostasis and provide a target for novel treatment approaches.

Metabolic Irregularities

ME/CFS has been found to involve irregularities in metabolism, energy, amino acids, nucleotides, nitrogen, hormones, and oxidative stress (Armstrong et al., 2014; Germain et al., 2017). In particular, it has been proposed that the severe and prolonged fatigue experienced by ME/CFS patients may be a consequence of abnormalities in bioenergetic function (Tomas et al., 2017). Much evidence suggests that the pathophysiology of ME/CFS is highly associated with alterations in normal energy metabolic processes (Fluge et al., 2016) and abnormalities in cellular bioenergetics (Hornig et al., 2015; Fluge et al., 2016; Tomas et al., 2017). There is also evidence to suggest that patients with ME/CFS might be at an increased risk for developing metabolic syndrome-associated diseases, such as diabetes, cardiovascular disease, and thyroid disease (Maloney et al., 2009).

Apparently, systemic exertion intolerance in repeated cardiopulmonary exercise tests was demonstrated in ME/CFS patients compared with healthy controls, suggesting insufficient metabolic adaptation to incremental exercise (Keller et al., 2014; Vermeulen and Vermeulen van Eck, 2014). It should be noted that the Vermeulen and Vermeulen van Eck (2014) study

TABLE 2
Dysregulated molecules that may contribute to the pathogenesis of ME/CFS

Dysregulated Molecules that May Contribute to ME/CFS Pathogenesis
Cachexins
Calcineurin
Heavy metals
Herbicides
Inflammatory cytokines
Leptin
Melatonin
MicroRNAs
Mitochondrial enzymes
Neuroendocrine disruptors
Neuropeptides
Neurotransmitters
Reactive oxygen species
Toxins (mycotoxins, <i>Borrelia</i> toxins)
Uncoupling protein 2
Xenobiotics

included controls that were not matched to ME/CFS in terms of fitness, while the Keller et al. (2014) study had no controls. McCully and coworkers (McCully and Natelson, 1999; McCully et al., 2004) published a number of papers showing that when matched for aerobic fitness, cardiorespiratory responses to exercise in patients with ME/CFS only and ME/CFS plus FMS were not different from those in sedentary healthy controls (Cook et al., 2006).

Such intolerance, if real, may involve a switch to anaerobic glycolysis, i.e., a reduction in oxidative metabolism and an increase in lactate production (Murrough et al., 2010; Shungu et al., 2012), which constitute the most common metabolic alterations observed in patients with ME/CFS. These characteristics have mainly been attributed to deconditioning, a state characterized by loss of muscle tone and power from prolonged lack of use (Bains, 2008). However, even though increased lactate production was originally noted, possibly related to the reduction of postexercise oxygen delivery (McCully et al., 2004), the same effect could not be substantiated, suggesting a possible decrease in oxygen delivery perhaps due to reduced blood flow (McCully and Natelson, 1999). In particular, there was elevated ventricular lactate, but no significant difference in high-energy phosphatase metabolites in patients with ME/CFS compared with patients with major depressive disorder or healthy volunteers (Shungu et al., 2012). In some cases, alterations in glucose utilization and lactate production were evident only after physical exercise of ME/CFS patients (Fluge et al., 2016). ME/CFS plasma and serum metabolomics point in the direction of a hypometabolic state (Fluge et al., 2016; Naviaux et al., 2016; Germain et al., 2017; Nagy-Szakal et al., 2018).

ME/CFS Association with Metabolic Disease

Metabolic syndrome (MetS) is a disorder characterized by an imbalance between energy expenditure and storage, and is diagnosed by the simultaneous presence of three of the following five conditions: 1) central type (or abdominal), 2) obesity, 3) increased blood pressure and elevated fasting glucose levels, 4) high levels of serum triglycerides, and 5) decreased high-density lipid cholesterol levels (Mottillo et al., 2010; Kaur, 2014). MetS is also linked to insulin resistance, a condition that can lead to hyperglycemia and the development of type 2 diabetes mellitus despite normal insulin secretion by pancreatic β -cells and hyperinsulinemia (Petersen and Shulman, 2006). In addition, high blood pressure and high cholesterol levels are closely linked to increased oxidative stress and endothelial dysfunction, thus enhancing the proinflammatory nature of microvascular atherosclerotic disease (Li et al., 2007). In other words, subjects with MetS are at an increased risk of developing cardiovascular disease and type 2 diabetes mellitus (Isomaa et al., 2001; Dekker et al., 2005; Petersen and Shulman, 2006).

Approximately half of patients with ME/CFS also appear to have a previously undiagnosed medical condition, most often diabetes, cardiovascular disease, and thyroid diseases (Maloney et al., 2009). Few studies have investigated the possible associations between MetS and ME/CFS (Maloney et al., 2009; Naviaux et al., 2016; Germain et al., 2017; Bozzini et al., 2018). It was first suggested that patients with ME/CFS were twice as likely to have MetS compared with controls, after adjusting for body mass index, waist circumference, triglycerides, and glucose levels (Maloney et al., 2009). MetS components

in the ME/CFS group were significantly correlated with worse fatigue, but not with worse physical or mental functioning, contrary to previous observations (Tsai et al., 2008; Maloney et al., 2009). A correlation of MetS with fatigue has also been observed in patients with FMS, a condition clinically similar to ME/CFS in which muscle pain and fatigue are the main symptoms; specifically, MetS components (low-density lipoprotein cholesterol, as well as urinary norepinephrine/epinephrine and norepinephrine/cortisol ratios), were significantly higher in women with FMS compared with healthy controls (Loevinger et al., 2007).

Some studies have reported abnormal findings concerning the cardiovascular system—but one study was in patients with small hearts (Azevedo et al., 2007; Miwa and Fujita, 2009) and the other was in adolescents (Wyller et al., 2008)—and autonomic nervous system dysfunction (Meeus et al., 2013). Low blood pressure was noted in certain ambulatory cases of patients with ME/CFS (Newton et al., 2009; Wyller et al., 2011; Frith et al., 2012). However, when patients with ME/CFS were matched to healthy controls by maximal oxygen consumption there were no differences in cardiovascular parameters (Cook et al., 2006).

Dysautonomia including postural orthostatic tachycardia syndrome may be present in many patients with ME/CFS (Hollingsworth et al., 2010) and could also explain other ME/CFS symptoms, such as fatigue, vertigo, decreased concentration, tremors, and nausea (Bozzini et al., 2018). Interestingly, the low systolic blood pressure observed in ME/CFS patients is usually accompanied by exaggerated diurnal variation, which is inversely correlated with increasing fatigue (Davis et al., 2000; Newton et al., 2009).

Overall, it appears that metabolic disease components show significant correlations with the fatigue in ME/CFS patients and not with the disease itself. For example, blood pressure, as well as insulin resistance, are probably secondary to fatigue, and most probably reflect the lack of physical activity and prolonged lack of muscle use in ME/CFS patients. This makes sense if one considers that low blood pressure could give rise to fatigue through brain or muscle hypoperfusion (Newton et al., 2009), and that insulin sensitivity is highly dependent on the oxidative capacity of the muscle (Cantó and Auwerx, 2009).

Metabolomics, small-molecule metabolite profiling (Daviss, 2005), has provided relevant information that could distinguish ME/CFS patients (Naviaux et al., 2016). Several studies have performed metabolite analysis of various biologic fluids [urine, blood, serum, and cerebrospinal fluid (CSF)] from ME/CFS patients (Georgiades et al., 2003; Jones et al., 2005; Niblett et al., 2007; Suárez et al., 2010; Armstrong et al., 2012, 2015; Hornig et al., 2016). However, despite confirming disturbances in energy, amino acid, nucleotide, nitrogen, hormone, and oxidative stress metabolomics, these studies have not been able to determine a distinct, reproducible metabolic profile for ME/CFS (Germain et al., 2017). Nevertheless, one study identified nine biochemical disturbances that were common to both male and female patients with ME/CFS, but not healthy controls (Naviaux et al., 2016). Overall, there were marked decreases in sphingolipid, glycosphingolipid, phospholipid, purine, microbiome aromatic amino acid, and branch chain amino acid metabolites, as well as in flavine adenine nucleotide and lathosterol, which identified the hypometabolic profile for ME/CFS. These changes correlated with disease severity and had an apparent diagnostic accuracy that exceeded 90%

(Naviaux et al., 2016). Interestingly, the metabolic abnormalities found in ME/CFS patients were opposite (i.e., decreased instead of being increased) to those observed in MetS, suggesting that ME/CFS patients could be more resistant to hypertension, dyslipidaemia, obesity, and insulin resistance even though the previously studies discussed had reported an increased association between ME/CFS and MetS.

Another study that used targeted plasma metabolomics reported a similar trend of hypometabolic state in ME/CFS patients (Germain et al., 2017). Even though the metabolite compounds were not all identical to the ones studied by Naviaux et al. (2016), both studies agreed on the presence of disturbances in lipid and fatty acid metabolism (Germain et al., 2017). These findings are also in agreement with reported deficiencies in urea and tricarboxylic acid (TCA) cycles (ornithine/citrulline and pyruvate/isocitrate ratios), which ultimately result in reduced levels of ATP production in patients with ME/CFS (Yamano et al., 2016). Other studies revealed that ME/CFS patients have reduced substrates that enter oxidation downstream from pyruvate dehydrogenase, such as glutamine, glutamate, and phenylalanine, thus suggesting impaired pyruvate catabolism, which ultimately results in increased utilization of acetyl-coenzyme A (acetyl-CoA)-producing amino acids as alternative substrates for fueling aerobic metabolism via the TCA cycle (Armstrong et al., 2012, 2015; Fluge et al., 2016). Reduced concentrations of amino acids that maintain TCA cycle capacity were detected in patients with ME/CFS (Fluge et al., 2016), suggesting impaired fueling of the TCA cycle by pyruvate. This finding is in line with the results of other studies where TCA cycle intermediates were also found to be reduced in both urine (Niblett et al., 2007) and plasma (Yamano et al., 2016) samples from ME/CFS patients.

Mitochondrial Dysfunction

Overall, the ME/CFS phenotype has been associated with mitochondrial dysfunction, AMP-activated protein kinase impairment, oxidative stress, and skeletal muscle cell acidosis (Kennedy et al., 2005; Myhill et al., 2009; Brown et al., 2015; Tomas et al., 2017). The main ME/CFS symptoms, such as fatigue, exercise intolerance, and myalgia, are also shared by patients diagnosed with primary mitochondrial disorders (Filler et al., 2014; Gorman et al., 2015). However, unlike the mitochondrial dysfunction observed in mitochondrial disorders, which is known to be caused by mutations in either nuclear or mitochondrial DNA (mtDNA) (Tomas et al., 2017), these mutations in patients with ME/CFS are extremely rare (Billing-Ross et al., 2016; Schoeman et al., 2017). In addition, certain mitochondrial enzymes have been found to discriminate between mitochondrial disorders and ME/CFS. Notably, respiratory chain complex I, III, and IV activity (Smits et al., 2011) appears to be significantly higher in ME/CFS patients. Instead, the ATP production rate was found to be within the normal range in ME/CFS patients, but significantly decreased in approximately three-quarters of the patients with mitochondrial disease, and was therefore regarded as the most reliable discrimination test (Smits et al., 2011).

Muscle biopsies from ME/CFS patients have shown mitochondrial degeneration, atrophy of type II fibers and fusion of mitochondrial cristae, decreased mitochondrial membrane permeability, severe deletions in mtDNA genes that are

involved in cellular energy processes, as well as oxidative damage from increased production of free radicals (Myhill et al., 2009; Morris and Maes, 2013). Mitochondrial dysfunction has also been observed in peripheral mononuclear blood cells of ME/CFS patients, even though it has not yet been elucidated if they constitute the cause of the disease (Myhill et al., 2009, 2013; Tomas et al., 2017). Notably, a significant correlation has been observed between the extent of mitochondrial dysfunction and the degree of ME/CFS severity, thus suggesting that mitochondrial dysfunction might be a contributing factor in ME/CFS pathology, at least in a subset of patients (Myhill et al., 2009; Booth et al., 2012). However, it is difficult to assess mitochondrial dysfunction, which is usually done by measuring the levels of lactate and pyruvate in the serum; it is best done by serial serum sampling from an arm after a brief period of exercise.

When limited amounts of oxygen are available, as is usually the case with intense exercise, anaerobic glycolysis (otherwise called the lactic acid system) provides an effective means of energy production. During this process, glucose is catabolized via the glycolytic pathway, resulting in pyruvate being converted to lactate by lactate dehydrogenase. This process lasts 10–30 seconds during maximal effort and produces about 5% of the glucose energy potential in the form of ATP molecules (two molecules of ATP for every molecule of glucose). ATP synthesis can be estimated by measuring the anaerobic threshold, i.e., the rate of oxygen consumption at work when blood lactic acid begins to accumulate and the maximal work rate (Morris and Maes, 2014). The anaerobic threshold indicates a switch during which ATP synthesis stops being produced by mitochondria and occurs via the anaerobic route (Morris and Maes, 2012), whereas anaerobic threshold and recovery time following exercise depend on lactate production and clearance rates (Fluge et al., 2016). When aerobic conditions are normal, pyruvate is transported into mitochondria and converted to acetyl-CoA by either pyruvate dehydrogenase or via degradation of fatty acids and ketogenic amino acids. In either case, acetyl-CoA is further oxidized in the TCA cycle, producing some ATP, and the electron transport chain (respiratory chain), which generates ATP from ADP by oxidative phosphorylation. Acetyl-CoA thereby serves to fuel mitochondrial respiration and ATP production by oxidative phosphorylation (Fluge et al., 2016) for essential tissue functions (Myhill et al., 2009).

Reduced ATP production is associated with increased levels of reactive oxygen species, which may ultimately lead to mitochondrial damage and the hypometabolic profile of ME/CFS (Armstrong et al., 2015; Naviaux et al., 2016). Severely reduced or impaired mitochondrial oxidative phosphorylation in ME/CFS patients is highly correlated with significantly increased intracellular lactate levels, even in the recovery phase of mild exercise where ATP synthesis is extremely low (Vermeulen et al., 2010; Morris and Maes, 2014).

Among the factors that may contribute to mitochondrial dysfunction, the most prominent ones appear to be increased levels of proinflammatory cytokines, such as interleukin (IL)-1 β and tumor necrosis factor (TNF), which directly inhibit mitochondrial respiration by increasing mitochondrial membrane permeability, ultimately leading to membrane depolarization and increased production of reactive oxygen species (Morris and Maes, 2013). However, even though TNF is elevated in the serum of patients with FMS (Theoharides et al., 2010), it was not consistently elevated in ME/CFS

(Brenu et al., 2011) but was apparently associated only with increased IL-4 (Hanson et al., 2001). There was also no significant difference in serum cytokine levels overnight (Nakamura et al., 2010) or postexercise (Nakamura et al., 2013). There is some evidence of a stronger correlation of cytokine alterations early in the course of illness rather than to severity (Hornig et al., 2015). It has been proposed that cytokine coexpression networks may be more predictive of ME/CFS phenotype (Klimas et al., 2012; Hornig et al., 2016), but looking for such biomarkers in the periphery would not reflect inflammation in the brain. One study reported that out of 27 cytokines studied in CSF from ME/CFS patients, only IL-10 was significantly reduced (Peterson et al., 2015). Another paper using network analysis of CSF cytokine levels reported an inverse relationship with IL-1 receptor antagonist only in classic, but not in atypical, ME/CFS (Hornig et al., 2017).

Certain microRNAs may turn out to be distinct or differentially expressed in ME/CFS. Recently, microRNAs have been implicated in the hypothalamic control of energy homeostasis (Najam et al., 2018). However, the available studies in patients with ME/CFS did not report any consistent pattern whether pre- or postexercise in plasma, (Brenu et al., 2014) natural killer cells (Petty et al., 2016), or CD8⁺ cells (Brenu et al., 2012). One recent important study showed exercise-induced changes in CSF fluid from patients with ME/CFS and Gulf War illness, and sedentary controls found 12 diminished microRNAs after exercise (Baraniuk and Shivapurkar, 2017, 2018).

Focal Inflammation in the Diencephalon and Dysfunctional HPA Axis

Neuroinflammation (Nakatomi et al., 2014; Glassford, 2017; Morris et al., 2018; Tomas and Newton, 2018) and immune dysfunction (Morris et al., 2014; Nijs et al., 2014; Trivedi et al., 2018) have been suggested as being involved in the pathogenesis of ME/CFS, but serum levels of proinflammatory cytokines have not been confirmed as will be discussed subsequently. Considerable evidence indicates that ME/CFS is characterized by dysfunction of the HPA axis (Theoharides et al., 2010;

Morris et al., 2017), and symptoms are known to worsen due to stress (Smith et al., 2003; Theoharides and Cochrane, 2004; Crawley et al., 2009; Theoharides, 2013). Stress can also worsen or precipitate obesity and cardiovascular events (Theoharides et al., 2008, 2011; Sismanopoulos et al., 2013; Alevizos et al., 2014) through local inflammation (Libby et al., 2002; Matusik et al., 2012).

Corticotropin-releasing hormone (CRH) is secreted from the hypothalamus under stress and stimulates the HPA axis via activation of two main types of G protein-coupled receptors, CRHR-1 and CRHR-2 (Chrousos, 1995). CRH secreted under acute stress has been implicated in the pathophysiology of neuroinflammatory disorders and myocardial infarction (Jiang et al., 1996; Krantz et al., 2000; O'Kane et al., 2006; Slominski, 2009).

We propose that stimulation of hypothalamic mast cells by environment, neural, immune pathogenic (Lyme, mycotoxins), or stress triggers (CRH and somatostatin) activates microglia leading to focal inflammation and disturbed homeostasis (Fig. 1). Mast cell and/or microglia triggers may derive from the nasal cavity, or may reach the brain area through a disrupted blood-brain barrier or through the lymphatics. Stimulated mast cells could secrete molecules that can alter homeostasis directly (via secretion of CRH and urocortin) or activate microglia (via secretion of histamine, tryptase, and mtDNA). Microglia then release more inflammatory molecules (IL-1 β , IL-6, and CCL2) that further disrupt homeostasis, cause mitochondrial dysfunction, and contribute to fatigue both centrally and peripherally. In fact, activated microglia molecules have been reported to contribute to the pathophysiology of sleep disorders (Nadjar et al., 2017). The involvement of more than one trigger can lead to a significantly heightened response and lower the triggering threshold of both mast cells and microglia, leading to chronic symptoms.

Mast cells are unique tissue immune cells involved in allergic reactions (Theoharides et al., 2015d); however, they also act as sensors of environmental and psychologic stress (Theoharides, 2017). Even though we invoke stimulation of mast cells in the hypothalamus, it does not necessarily mean

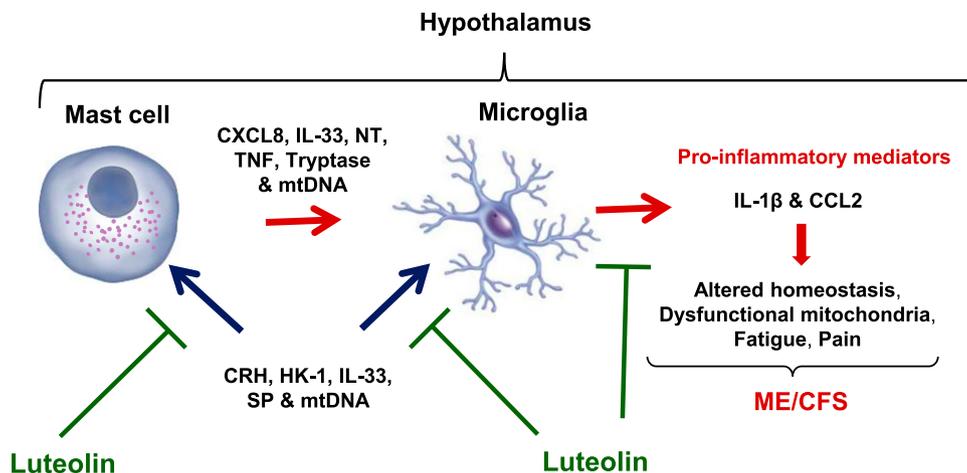


Fig. 1. Diagrammatic representation of the proposed mast cell/microglia interactions in the hypothalamus contributing to the pathogenesis of ME/CFS, which could serve as targets for treatment. Hypothalamic mast cells are stimulated by stress-associated triggers such as CRH, HK-1, and SP, along with mtDNA and IL-33; some derive from the nasal cavity, while others may reach the area through a disrupted blood-brain barrier or through lymphatics. Stimulated mast cells then secrete molecules such as CXCL8, neurotensin (NT), TNF, tryptase, and mtDNA (CXCL), which activate microglia to secrete more inflammatory molecules (especially, IL-1 β , IL-6, and CXCL8) that further disrupt homeostasis, causing mitochondrial dysfunction and contributing to symptoms of ME/CFS. Luteolin could inhibit these processes at different steps, as shown.

that mast cells should necessarily be stimulated outside the central nervous system. Nevertheless, there have been reports of an association between ME/CFS and acute rhinitis, including significantly higher TNF and CXCL8 levels in nasal lavage fluid (Repka-Ramirez et al., 2002). In addition, chronic rhinosinusitis symptoms were significantly higher in patients with ME/CFS (Chester, 2003), apparently due to nonallergic rhinitis (Baraniuk and Ho Le, 2007). It is well known that both allergic and perennial rhinitis involve activation of mast cells (Bachert et al., 2018). More recently, it was reported that the incidence of ME/CFS was higher in patients with a history of atopy (Yang et al., 2015). Moreover, circulating blood mast cell precursors were found to be higher in ME/CFS patients (Nguyen et al., 2017).

Mast cells are located perivascularly in the hypothalamus, thalamus, and third ventricle (Edvinsson et al., 1977; Pang et al., 1996). CRH could stimulate mast cells in the hypothalamus since the CRHR-1 gene is expressed on human cultured mast cells, activation of which induces production of vascular endothelial growth factor (Cao et al., 2005), which could increase permeability of the blood-brain barrier (Theoharides, 1990; Esposito et al., 2002; Theoharides and Konstantinidou, 2007) leading to inflammation of the brain (Theoharides et al., 2004a). Moreover, CRH is synthesized by mast cells (Kempuraj et al., 2004), implying it could have autocrine effects. Interestingly, even somatostatin stimulates mast cells (Theoharides et al., 1990). Mast cells are also found in the pineal, pituitary, and thyroid glands (Theoharides, 2017), further extending their contribution to the symptoms of ME/CFS, such as sleep disturbances, dysfunctional HPA axis, and fatigue due to thyroid dysfunction. Mast cells are well known for their role in allergic reactions (Beaven, 2009), but mast cells are now considered important in innate and acquired immunity (Galli et al., 2008), antigen presentation (Gong et al., 2010), and inflammation (Theoharides et al., 2012).

Mast cells can be stimulated by neurons, hormones, and environmental, neuroimmune, pathogenic, and stress triggers (Table 3) (Theoharides et al., 2015d; Theoharides, 2017). Reactive oxygen species can also stimulate mast cells (Swindle and Metcalfe, 2007; Robuffo et al., 2017; Toniato et al., 2017). Mast cells also secrete leptin, which could contribute to cachexia and fatigue (Taldeman et al., 2009). Mast cells secrete as many as 100 different mediators (Table 4) (Theoharides and Kalogeromitros, 2006; Wernersson and Pejler, 2014; Mukai et al., 2018), often selectively without degranulation (Theoharides et al., 2007) and utilizing different secretory pathways (Xu et al., 2018). Mast cells can also secrete danger signals (Theoharides, 2016), including many chemokines and cytokines (Conti et al., 2017; Mukai et al., 2018), especially mtDNA (Zhang et al., 2012), which could act as an innate pathogen (Zhang et al., 2011), leading to a localized brain autoinflammatory response (Collins et al., 2004; Marques et al., 2012; Sun et al., 2013; Theoharides et al., 2013). Extracellular mtDNA could either be secreted directly in the diencephalon or could reach the brain through lymphatics (Louveau et al., 2015). We had reported that mtDNA is increased in the serum of children with autism spectrum disorder (Zhang et al., 2010). Mast cell-derived mediators can then stimulate microglia (Patel et al., 2016; Zhang et al., 2016) to secrete additional proinflammatory and homeostasis-disrupting molecules (Table 5), contributing to fatigue and neuropsychiatric symptoms (Theoharides et al., 2016). It is interesting that peptide Y was found to be elevated in plasma

TABLE 3
Mast cell triggers

Mast Cell Trigger
Stimulating degranulation
Acetylcholine
Adenosine
Complement fragments: C3 α , C4 α , C5 α
Drugs: local anesthetics, lactam antibiotics, neuromuscular junction blockers, vancomycin
Eosinophil granule proteins
IgE
IgG ₁
IgG ₄
Lysophosphatidylserine
Histamine
Serotonin
Lysophosphatidic acid
Peptides: adrenomedullin, CGRP, endorphin, endothelin, hemokinin-1, leptin, mastoparan, neurotensin, NGF, PTH, somatostatin, SP, thrombin, VIP
Tryptase
Stimulating selective release of mediators without degranulation
ATP
<i>Borrelia burgdorferi</i> (Lyme disease)
CRH
Heavy metals: aluminum, cadmium, mercury
Herbicides: atrazine, glyphosate
IL-33
Mycotoxins
LPS
SCF
Viruses

CGRP, calcitonin-gene related peptide; LPS, lipopolysaccharide; NGF, nerve growth factor; PTH, parathyroid hormone; SCF, stem cell factor; VIP, vasoactive intestinal polypeptide.

of patients with ME/CFS and correlated significantly with stress (Fletcher et al., 2010), since this peptide is known to stimulate mast cells (Mousli and Landry, 1994).

An important part of this process is that a combination of triggers is likely to play a more important pathogenetic role than individual ones. For instance, we reported that the combination of CRH and neurotensin has a synergistic action in stimulating vascular endothelial growth factor secretion without tryptase from human mast cells (Donelan et al., 2006), as well as in inducing the expression of each other's receptors on human mast cells (Alysandratos et al., 2012). More recently, we showed that the combination of substance P (SP) and IL-33 has synergistic action in stimulating TNF secretion without tryptase from human cultured mast cells (Taracanova et al., 2017).

CRH is often released together with another peptide, neurotensin, which is vasoactive (Leeman and Carraway, 1982) and has also been implicated in inflammation (Mustain et al., 2011) and neurologic diseases (Cáceda et al., 2006). Neurotensin is increased in the skin following acute stress (Theoharides et al., 1998) and increases vascular permeability, an effect synergistic with CRH (Crompton et al., 2003; Donelan et al., 2006).

Mast cells are also stimulated by the peptide SP (Church et al., 1991; Theoharides et al., 2010; Taracanova et al., 2017), initially characterized by Leeman and colleagues (Chang and Leeman, 1970; Carraway and Leeman, 1973) and shown to participate in inflammatory processes (Höckfelt et al., 2001; O'Connor et al., 2004; Douglas and Leeman, 2011; Mashaghi et al., 2016). IL-33 is a member of the IL-1 family of cytokines and has emerged as an early warning sign (dubbed alarmin) (Moulin et al., 2007) in autoimmune or inflammatory process

TABLE 4
Mast cell mediators

Mediator	Pathophysiologic Effect
Prestored	
Biogenic amines	
Dopamine	Neurotransmission
Histamine	Vasodilation, angiogenesis, mitogenesis, pain
5-Hydroxytryptamine (5-HT, serotonin)	Vasoconstriction, pain
Polyamines	
Spermidine, spermine	Secretory granule stability, inhibition of secretion
Chemokines	
IL-8 (CXCL8), MCP-1 (CCL2), MCP-3 (CCL7), MCP-4, RANTES (CCL5), Eotaxin (CCL11)	Chemoattraction and tissue infiltration of leukocytes
Cytokines	
IL-4, IL-5, IL-6, IL-15, IL-17, IL-31, IL-33, TNF	Immune cell maturation, inflammation
Enzymes	
Arylsulfatases A	Lipid/proteoglycan hydrolysis
Beta-hexosaminidase	Degradation processes
Beta-glucuronidase	Degradation processes
Beta-glucosaminidase	Degradation processes
Beta-D-galactosidases	Degradation processes
Carboxypeptidase A	Peptide processing
Cathepsins B,C, D, E, L	Degradation processes
Chymase	Tissue damage, pain, angiotensin II synthesis
Grnzyme B	Inflammation and preapoptotic effects
Kinogenasesn	Synthesis of vasodilatory kinins, pain
Phospholipases	Arachidonic acid generation
Renin	Angiotensin II generation
Trypsin, pain	Tissue damage, activation of PAR, inflammation, pain
Metalloproteinases (CPA3, MMP9, ADAMTSS)	Tissue damage, modification of cytokines/chemokines
Growth factors	
b-FGF	Neovascularization
NGF	Nerve growth, mast cell activation
SCF mast cell growth and activation	Mast cell growth and activation
TGF β	Anti-inflammatory, profibrotic
VEGF	Neovascularization, vasodilation
Peptides	
ACTH	Neovascularization
Angiogenin	Neovascularization
Angiopoietin	Inflammation, mast cell stimulus, vasodilation
Corticotropin-releasing hormone	Analgesia
Endorphins	Sepsis
Endothelin	Inflammation, mast cell stimulus, pain, vasodilation
Hemokinin-1	Inflammation, mast cell stimulus, pain, vasodilation
Kinins (bradykinin)	Food intake regulator
Leptin	Biologic clock regulator
Melatonin	Inflammation, mast cell stimulus, vasodilation
Neurotensin	Osteoclast differentiation and activation
RANKL	Mast cell stimulant, antisecretory
Somatostatin	Inflammation, mast cell stimulus, pain
Substance P	Inflammation, vasodilation
Urocortin	Vasodilation, mast cell activation
Vasoactive intestinal peptide	
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory
Heparin	Angiogenesis, nerve growth factor stabilization
Hyaluronic acid	Connective tissue, nerve growth factor stabilization
Serglycin	Storage of granule proteases
De novo synthesized	
Chemokines	
CCL2, CXCL8, MIP-1 α , MCP-1	
Cytokines	
IL-1, 2, 3, 4, 5, 6, 8, 9, 10, 13, 16, and 18	Inflammation, leukocyte migration, pain
IFN- α , IFN- β , IFN- γ ; MIF; TGF β ; TNF	Inflammation, leukocyte proliferation/activation
Growth factors	
SCF, β -FGF, neurotrophin 3, NGF, PDGF, TGF β , VEGF	Growth of a variety of cells
Nitric oxide	Vasodilation
Phospholipid metabolites	
Leukotriene B ₄	Leukocyte chemotaxis
Leukotriene C ₄	Vasoconstriction, pain
Platelet activating factor	Platelet activation, vasodilation
Prostaglandin D ₂	Bronchoconstriction, pain

IFN, interferon; MIF, macrophage inflammatory factor; MIP, macrophage inflammatory protein; NGF, nerve growth factor; PAR, protease activated receptors; PDGF, platelet-derived growth factor; RANKL, receptor activator of nuclear factor kappa-B ligand; SCF, stem cell factor; TGF β , transforming growth factor β ; VEGF, vascular endothelial growth factor.

TABLE 5
Microglia mediators

Cytokine	Chemokine
IL-1 β	CCL2
IL-6	CXCL8 (IL-8)
TNF	CCL5 (MCP-1)

(Saluja et al., 2015; Theoharides et al., 2015a; Theoharides, 2016). IL-33 is secreted by fibroblasts and endothelial cells (Liew et al., 2010), and also from mast cells (Tung et al., 2014). IL-33 augments the effect of IgE on secretion of histamine from mast cells and basophils (Moulin et al., 2007; Silver et al., 2010).

Substance P stimulated secretion of vascular endothelial growth factor, an action augmented by IL-33 (Theoharides et al., 2010). We recently showed that stimulation of human mast cells by SP given together with IL-33 markedly increases secretion and gene expression of the proinflammatory cytokine, TNF (Taracanova et al., 2017) and of IL-1 β (unpublished results). Interestingly, chronic rhinosinusitis, which is quite common in patients with ME/CFS as discussed previously, has been associated with high levels of nasal IL-33 (Ozturan et al., 2017), which could reach the hypothalamus through the cribriform plexus.

Does Any Treatment Modality Work?

There are currently no Food and Drug Administration approved drugs for the treatment of ME/CFS and the available psychological, physical, and pharmacological interventions do not appear to be effective (Bains, 2008; Pae et al., 2009; Morris and Maes, 2014; Collatz et al., 2016; Loades et al., 2016; Brigden et al., 2017; Castro-Marrero et al., 2017). Mitochondria appear as one appealing drug target for the treatment of ME/CFS, but other papers reported no apparent alteration in ATP production (Shungu et al., 2012). Chemokines and cytokines have been proposed as targets for neuroinflammatory disorders (Pranzatelli, 2018), but they have not been tried in ME/CFS.

The peroxisome proliferator-activated receptor agonist bezafibrate improves mitochondrial function by stimulating mitochondrial biogenesis and increasing the oxidative phosphorylation efficiency in a number of studies (Wang et al., 2010; Johri et al., 2012; Valero, 2014). It has also been suggested that since fatigue is associated with hypotension in ME/CFS patients, increasing blood pressure might present an effective therapeutic approach to this symptom. Even though previous studies using the mineralocorticoid fludrocortisone failed to show any improvement (Peterson et al., 1998; Rowe et al., 2016), use of the agonist midodrine to increase blood pressure has produced some improvement in relation to fatigue (Naschitz et al., 2004). Interestingly, angiotensin II inhibitors have been shown to increase mitochondrial membrane potential, improve mitochondrial function, and stimulate mitochondrial biogenesis (de Cavanagh et al., 2011; Morris and Maes, 2014). Indeed, blockade of angiotensin II has been shown to prevent the onset of type 2 diabetes mellitus in mice by increasing fat oxidation, decreasing muscle triglycerides, and improving glucose tolerance (Mitsuishi et al., 2009). The angiotensin receptor blocker telmisartan improves mitochondrial dysfunction by enhancing mitochondrial biogenesis and

protecting vascular and endothelial cell damage (Takeuchi et al., 2013; Kurokawa et al., 2015). Similarly, the angiotensin receptor blocker losartan has been shown to improve mitochondrial respiratory chain function and coenzyme Q10 content in hypertensive animals (Sumbalová et al., 2010). However, given the blood pressure lowering effects of these agents, it is unlikely they will be useful in ME/CFS, except maybe in select patients.

Several natural compounds may have a beneficial effect on mitochondrial function. Magnesium ions play critical roles in energy metabolism and in maintaining normal muscle function by being a positively active regulator of glycolysis and of all enzymatic reactions involving phosphate group transfer from ATP (Dominguez et al., 2006; Morris and Maes, 2014). Several studies have demonstrated that magnesium ion supplements significantly increase muscle strength and maintain optimal physical activity performance in humans (Brilla and Haley, 1992; Newhouse and Finstad, 2000; Kass and Poeira, 2015; Zhang et al., 2017). In experimental animals, this improvement in exercise performance seems to occur via enhancing glucose availability in the brain and muscle, and via reducing/delaying lactate accumulation (Zhang et al., 2017). Magnesium sulfate may also improve mitochondrial respiratory function and prevent nitrous oxide production in the brain (Xu et al., 2002; Yang et al., 2007).

Coenzyme Q10 deficiency has been reported in patients with ME/CFS (Maes et al., 2009, 2012a,b; Filler et al., 2014). However, administration of coenzyme Q10 to patients with ME/CFS has failed to show any benefit (Campagnolo et al., 2017).

Naturally occurring flavonoids have potent antioxidant, anti-inflammatory, and neuroprotective actions (Middleton et al., 2000; Guo et al., 2009; Xiao et al., 2011) and are generally considered safe (Kawanishi et al., 2005; Harwood et al., 2007; Theoharides et al., 2014). The flavonoid genistein attenuates muscle fatigue in humans by downregulating oxidative stress and enhancing antioxidant enzyme activity (Ding and Liu, 2011). The flavonoids epigallocatechin, naringin, and curcumin can ameliorate ME/CFS symptoms in experimental models (Gupta et al., 2009; Sachdeva et al., 2009, 2011; Vij et al., 2009). Other reports have documented similar chronic fatigue attenuating effects for the *Astragalus* flavonoids (Kuo et al., 2009) and olive extract (Gupta et al., 2010). The isoflavones genistein and daidzein have been shown to reverse the effects of polyinosinic:polycytidylic acid on mouse locomotor activity and brain inflammatory mediator expression in a mouse model of fatigue (Vasiadi et al., 2014). Quercetin appears to increase exercise tolerance by attenuating oxidative stress in mouse brain, while at the same time conferring antioxidant and anti-inflammatory actions (Kempuraj et al., 2005; Davis et al., 2009; Ishisaka et al., 2011).

Luteolin suppresses adipocyte activation of macrophages and inflammation (Ando et al., 2009; Dequ et al., 2011), while it increases insulin sensitivity of the endothelium (Dequ et al., 2011). Luteolin also inhibits mast cells (Asadi et al., 2010; Weng et al., 2015; Patel and Theoharides, 2017) and microglia (Jang et al., 2008; Patel et al., 2016). In this context, it is interesting that luteolin improved symptoms of autism spectrum disorder (Taliou et al., 2013; Tsilioni et al., 2015), post-Lyme syndrome (Theoharides and Stewart, 2016), and brain fog (Theoharides et al., 2015b) in open-label trials. We recently showed that tetramethoxyluteolin is more potent than luteolin in its ability to inhibit human cultured microglia (Patel et al., 2016) and mast cells (Patel and Theoharides, 2017).

Intranasal administration of select flavonoids may reduce inflammation in the hypothalamus and correct the central pathogenesis of ME/CFS. For instance, intranasal administration of microvesicle-entrapped curcumin was shown to inhibit inflammation of the brain in a mouse model (Sun et al., 2010).

Conclusions

Overall, the ME/CFS phenotype has been associated with apparent abnormalities in the metabolic profile, possibly due to local inflammation in the hypothalamus. Novel treatment approaches are required to address the central pathogenic processes. Compounds that could inhibit inflammation in the brain such as tetramethoxyluteolin or the anti-inflammatory cytokine IL-37 (Dinarello et al., 2016; Mastrangelo et al., 2018) may be potential treatment options.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Hatziagelaki, Adamaki, Tsilioni, Dimitriadis, Theoharides.

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