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Peripheral and Central Mechanisms of Fatigue in Inflammatory and Noninflammatory Rheumatic Diseases

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Abstract Fatigue is a common symptom in a large number of medical and psychological disorders, including many rheumatologic illnesses. A frequent question for health care providers is related to whether reported fatigue is "in the mind" or "in the body"—that is, central or peripheral. If fatigue occurs at rest without any exertion, this suggests psychological or central origins. If patients relate their fatigue mostly to physical activities, including exercise, their symptoms can be considered peripheral. However, most syndromes of fatigue seem to depend on both peripheral and central mechanisms. Sometimes, muscle biopsy with histochemistry may be necessary for the appropriate tissue diagnosis, whereas serological tests generally provide little reliable information about the origin of muscle fatigue. Muscle function and peripheral fatigue can be quantified by contractile force and action potential measurements, whereas validated questionnaires are frequently used for assessment of mental fatigue. Fatigue is a hallmark of many rheumatologic conditions, including fibromyalgia, myalgic encephalitis/chronic fatigue syndrome, rheumatoid arthritis, systemic lupus, Sjogren's syndrome, and ankylosing spondylitis. Whereas many studies have focused on disease activity as a correlate to these patients' fatigue, it has become apparent that other factors, including negative affect and pain, are some of the most powerful predictors for fatigue. Conversely, sleep problems, including insomnia, seem to be less important for fatigue. There are several effective treatment strategies available for fatigued patients with rheumatologic disorders, including pharmacological and nonpharmacological therapies.

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Introduction

Fatigue is a common symptom in the general population, with up to 50 % of individuals reporting fatigue in large surveys [1, 2]. Fatiguing syndromes can be separated into central fatigue, which is defined as difficulty initiating or sustaining voluntary activities [3], and peripheral fatigue, which is caused by neuromuscular factors. Central fatigue represents a failure to complete physical and mental tasks that require self-motivation and internal cues, in the absence of demonstrable cognitive failure or motor weakness [4]. Furthermore, any voluntary activity depends on applied effort, which is controlled by motivational input and perceived demand via feedback from motor, sensory, and cognitive systems. Hence, any dissociation between the level of internal input (motivational and affective) and perceived effort results in the sense of fatigue. Assuming that pathological central fatigue is an amplified sense of physiological fatigue induced by a mismatch between actual and perceived effort, clinical studies of fatigue disorders have provided clues regarding the neural substrates of this feeling. In particular, brain lesions in the pathways of arousal and attention, such as the reticular and limbic systems and the basal ganglia, often result in pathological fatigue [3]. Fatigue itself can also be the primary symptom of a disease—as in myalgic encephalitis/chronic fatigue syndrome (ME/CFS), which might therefore be an excellent model for studying the mechanisms underlying fatigue symptoms.

Typically, self-reported fatigue is transient, self-limiting, and explained by prevailing circumstances. However, a small minority of individuals experiences persistent and debilitating

fatigue. When fatigue cannot be explained by a medical condition, such as depression, cancer, infections, or inflammatory disorders, it may represent ME/CFS. This often disabling syndrome is characterized by profound fatigue lasting at least 6 months and accompanied by numerous psychological and somatic symptoms [5]. ME/CFS is a clinical diagnosis without distinguishing physical or routine laboratory findings. Infectious-, immunological-, neuroendocrine-, sleep-, psychiatric-, and malignancy-related mechanisms have been investigated; however, a unifying etiology for ME/CFS has yet to emerge. It seems likely that ME/CFS is a heterogeneous illness representing a common pathway for different pathophysiological abnormalities that manifest with similar symptoms. Recent studies found biochemical and genetic abnormalities in ME/CFS patients, such as a decreased concentration of serum acetyl-L-carnitine [6], a serotonin-transporter gene promoter polymorphism [7], and autoantibodies against the muscarinic cholinergic receptor [8]. Regardless of the pathogenesis, patients with ME/CFS have substantially impaired function that often results in significant morbidity [9–11].

Similarly, patients with a variety of rheumatologic disorders often complain of disabling fatigue, which cannot be explained by disease activity of their underlying medical conditions. Thus, overlap of fatiguing syndromes with rheumatologic conditions needs to be strongly considered.

Epidemiology and Public Health Impact of Chronic Fatigue Including ME/CFS

Epidemiological studies have estimated the prevalence of ME/CFS in the US at 0.4 %, and this rate appears to have remained relatively stable over 10 years of follow-up [12, 13]. Thus, over 1.3 million individuals in the U.S. alone have ME/CFS, and their quality of life is comparable to that of patients with congestive heart failure (CHF) [14]. Unfortunately, recovery of ME/CFS becomes uncommon after >3 years of illness [15]. ME/CFS often co-occurs with other conditions, such as fibromyalgia (FM), irritable bowel syndrome (IBS), and temporomandibular disorder (TMD) [16, 17] but has been best studied in relation to FM, a syndrome of widespread pain, tenderness, and somatic symptoms [18]. Interestingly, 20 %–70 % of FM patients appear to meet criteria for ME/CFS [19, 20], and conversely, 35 %–70 % of those with ME/CFS–like illnesses have concurrent FM [21]. In general, many ME/CFS patients continue to experience severe symptoms despite treatments, and there are no therapies to date that can effectively prevent disease occurrence or progression. Despite rapid advances in our understanding of ME/CFS, we still lack a unifying construct about some of the most important pathogenetic mechanisms of this illness. While much of the recent attention has been directed to infections as a pathway to ME/CFS [22], less attention has focused on abnormal peripheral input from muscle receptors as a relevant mechanism for ME/CFS fatigue, as well as pain. It is possible that specific peripheral fatigue and pain pathways have become sensitized in ME/CFS patients by yet unknown mechanisms (infections, physical and/or psychological stressors) [23–25] and that continuous input from these pathways is necessary to maintain the chronic fatigue state, as well as pain.

Fatigue Definition and Fatigue Pathways

Fatigue is a complex phenomenon and one of the most common experiences in sickness and in health [26, 27]. It has been studied in people with various medical diagnoses—for example, hypertension, myocardial infarction, chronic heart failure, cancer, multiple sclerosis, depression, and rheumatoid arthritis (RA) [28]. In contrast to weakness associated with primary muscle disorders such as inflammatory and noninflammatory myopathies, fatigue has been conceptualized as a central nervous system phenomenon, because rest does not seem to significantly improve symptoms [29]. In general, fatigue has been defined as a subjective, unpleasant symptom that incorporates total body feelings ranging from tiredness to exhaustion, creating an unrelenting overall condition that interferes with individuals' ability to function in their normal capacity. Although it is often difficult for patients to distinguish “fatigue” from “tiredness” and “task failure,” multiple assessment tools can be used to capture specific fatigue dimensions.

Poor Correlation of Disease Activity With Chronic Fatigue

Chronic fatigue, often worsened by physical or mental exertion, is one of the most important symptoms of ME/CFS. However, profound fatigue is an important characteristic not only of ME/CFS, but frequently also of congestive heart failure (CHF) [29], RA [30], and systemic lupus (SLE) [31]. All these syndromes are associated with reduced exercise capacity, autonomic nervous system (ANS) dysfunction, progression over time, and poor prognosis [32]. Traditionally, explanations for fatigue experienced by CHF patients have focused on reduced cardiac output. However, cardiac function of these patients correlates only poorly with reported fatigue levels. In addition, similar to ME/CFS, the type of exercise performed seems to influence whether individuals with CHF will experience profound fatigue; that is, low incremental exercise testing is more likely to lead to fatigue [33], whereas rapidly increasing exercise levels more frequently results in breathlessness, even

if the workload is standardized. Metabolic abnormalities in skeletal muscles with early acidosis and the presence of other metabolites during exercise appear to be responsible for enhanced fatigue in CHF [34].

Autonomic Abnormalities in ME/CFS

A characteristic of chronic fatigue disorders, including ME/CFS, RA, and SLE, is persistent activation of the sympathetic nervous system [35], as shown by organ-specific catecholamine spillover [36–38], muscle sympathetic nerve activation [39], and plasma catecholamine levels [40]. Sympathetic activation during exercise is also increased in these patients, as compared with normal controls [41]. Tests of autonomic function suggest that patients with ME/CFS also have reduced vagal and sympathetic responsiveness to standardized laboratory stimuli (paced breathing, standing up) and after a walking test [42, 43] and that these alterations are inversely related to their overall fitness [44]. Similarly, after undergoing standardized mental stressors, fatigued patients also demonstrate reduced autonomic responsiveness (increase in sympathetic drive and reduction of vagal modulation) [45]. These findings emphasize the diminished cardiac response to exercise in patients with ME/CFS [46], which may contribute to their physical fatigue and inactive life style [47]. Similar reductions in cardiac autonomic responsiveness can be detected in other illnesses, such as arterial hypertension or myocardial infarction [48]. Generally, most patients with unexplained chronic fatigue seem to present with resting sympathetic hyperactivity and reduced vagal modulation [49].

Exercise and Fatigue

Patients with ME/CFS who are unable to remain active become increasingly deconditioned, and their ability to tolerate exercise stress is impaired, as compared with normal individuals. Indeed, some studies suggest that ME/CFS patients may have more difficulty than normal controls in recovering from physical stressors, as measured by increased allostatic load [50]. Importantly, exercise limitations of ME/CFS patients do not seem to be related to abnormal central hemodynamic or pulmonary function, and deficits in voluntary contraction can be normalized by electrical muscle stimulation, indicating failure of central motor control, rather than alterations in muscle membranes [51]. Overall, muscle fatigue in many chronic fatigue states is most likely caused by a variety of peripheral and central factors [52], including a combination of disuse, impaired blood flow, and catabolic myopathy.

Pain and Fatigue in ME/CFS

In addition to debilitating fatigue, the majority of patients with ME/CFS experience chronic pain [53, 54]. These pain complaints show great overlap with FM, but also with IBS and TMD, where most patients report varying levels of fatigue and pain. Over the last 10 years, increasing evidence for central sensitization of pain pathways in ME/CFS has been accumulated, providing mechanistic explanations for increased pain sensitivity in this disorder [53]. Central sensitization is defined as increased central neuronal responsiveness to nociceptive and nonnociceptive stimuli, resulting in hyperalgesia and allodynia, associated with chronic widespread pain [55]. Several investigations have shown that peripheral impulse input appears to be necessary for maintaining the sensitized state in many chronic pain conditions [56–60]. Such peripheral impulse input can be related to muscle metabolites [61], which may also be relevant for ME/CFS patients, who show not only chronic fatigue, but also hyperalgesia and allodynia [62]. Hyperalgesia and allodynia, characterized by quantitative sensory testing, are consistent with sensitization of peripheral and central pain pathways [63••]. Importantly, sensitization of other sensory pathways besides pain has also been reported, including sight, sound, and smell [64•, 65].

Brain Abnormalities in Fatigue Disorders

Previous research has demonstrated significant associations between mental fatigue and brain changes detectable by magnetic resonance brain imaging [66, 67]. For example, in ME/CFS patients, frontal, cingulate, parietal, and cerebellar brain regions have all demonstrated abnormal activity, as compared with normal controls [68–70]. Overall, it appears that mental fatigue has widespread effects on attention, working memory, and executive control.

Reduced Brain Volume

Although fatigue is a common feeling that interferes with physical and mental activities, its underlying neuronal mechanisms remain unclear. It is reported by more than 20 % of people seen in primary care settings [71]. Voxel-based morphometry demonstrated that ME/CFS patients had reduced gray-matter volume in bilateral prefrontal cortices. Furthermore, the volume reduction in the right prefrontal cortex correlated with the severity of the fatigue of the subjects. These results are consistent with previous reports of abnormal acetyl-L-carnitine uptake within the same brain regions of patients with ME/CFS. Thus, the prefrontal cortex might be

an important area of the neural system involved in the processing of fatigue

Similarly, cerebral volumes were significantly smaller in patients with rheumatological illnesses including SLE, as compared with healthy volunteers, and this atrophy was related to disease duration [72, 73]. SLE patients with cognitive impairment had significantly more cerebral atrophy when compared with SLE patients without cognitive changes [74]. Importantly, cerebral volume loss was not associated with total corticosteroid dose or the presence of antiphospholipid antibodies.

In contrast, magnetic resonance brain imaging of patients with RA suggests that this chronic illness is associated with changes in the subcortical gray matter, rather than with cortical gray matter atrophy [75•]. The observed atrophy of basal ganglia in RA may play an important role for these patients' pain processing and response to aversive stimuli.

Fatigue in Inflammatory Rheumatologic Disorders

Rheumatoid Arthritis

Fatigue is a common symptom in RA and is considered highly relevant by most patients [76–85]. Significant fatigue is reported by up to 80 % of RA patients and is often associated with disease activity [86–89]. Similar to several other illnesses, including FM and ME/CFS, RA-related fatigue is strongly affected by pain and depression [82–87, 89, 90], as well as other psychosocial factors, including health beliefs, illness perceptions, and poor social support [79]. In multivariate regression analysis, depression was the most important factor associated with fatigue, followed by physical and psychological dysfunction [78]. There was, however, no association between level of fatigue and age or disease duration, indicating that age-related changes and disease duration are less important for RA fatigue. Other comorbidities, including cardiovascular and respiratory diseases, were not directly related to fatigue in RA. RA-related fatigue was significantly reduced in several large, randomized controlled trials after use of the tumor necrosis factor (TNF) inhibitors etanercept and adalimumab, suggesting involvement of cytokines in its pathogenesis [91]. However, despite decreasing inflammation of RA patients, the disease-modifying antirheumatic drugs leflunomide and methotrexate were unable to improve their fatigue levels [92].

Reports of fatigue are extremely common in the general population and the clinic [2, 93], and 38 % of individuals report "substantial fatigue" [1]. Although often associated with inflammation, some of the most important predictors of fatigue include depression, pain, and psychosocial factors [78, 79]. Fatigue in RA seems to peak in the early afternoon [94], improve with disease treatment, and be absent in most patients in remission [95]. However, over 60 % of the variance in fatigue in RA can be explained by demographic, psychosocial, and disease-related factors [86]. Specifically, sleep quality, physical activity, number of comorbidities, functional status, and duration of disease predicted most of RA patients' fatigue, but the single most important variable seems to be pain. Most RA patients consider disease activity as the primary cause of their fatigue (64 %), and 26 % attribute their fatigue to disturbed sleep [85].

Systemic Lupus Erythematosus

Fatigue is a very common symptom in SLE and has been reported by up to 80 % of patients at some time during their illness [96, 97]. Fifty-three percent of SLE patients report fatigue as their most disabling symptom [98]. Several conditions associated with fatigue are frequently comorbid with SLE, including FM and depression [99, 100]. Although perceived as severe, levels of fatigue do not seem to correlate significantly with any laboratory measure. However, a significant correlation seems to exist between fatigue and physicians' rating of disease activity and depression, which can account for 21 % of the variance in fatigue scores [101]. Overall, the cause of SLE-related fatigue seems to be multifactorial, and this symptom is included in several indices of SLE disease activity [102].

Besides disease activity [103, 104], several other factors seem to play important roles in SLE-related fatigue, including anxiety disorders [105], poor sleep patterns [105], and low levels of aerobic fitness [106], all of which may vary between and within patients over time. The relationship between fatigue and disease activity, however, is controversial [101, 103, 104, 107], because many patients with quiescent SLE continue to experience pronounced fatigue. Nearly two thirds of SLE patients report poor sleep quality, which correlates not only with their levels of fatigue, but also with their anxiety and depression, suggesting that these disorders contribute to poor sleep in at least some SLE patients [108]. Additionally, several medications, including corticosteroids, are thought to worsen sleep quality. The American College of Rheumatology includes anxiety and mood disorder as part of the neuropsychiatric syndromes associated with SLE [109]. Anxiety and depression seem to occur in up to 33 % of SLE patients [110], although it is often difficult to determine whether mood disorders are a primary manifestation of neuropsychiatric SLE or the result of the stressors associated with this chronic illness.

Fatigue also seems to be associated with dysfunction in SLE, as indicted by the correlation of fatigue scores with several components of the SF-36 [108]. It appears that reduced functional status associated with SLE is a major factor contributing to fatigue in this disease, as shown by prospective studies over 2 years [101]. Additional factors contributing to decreased functioning and fatigue may be

deconditioning or the progressive loss of aerobic fitness and muscular power in individuals who become inactive.

Sjogren's Syndrome

Sjögren's syndrome (SS) is a chronic autoimmune rheumatic illness characterized by lymphocytic infiltration of exocrine glands, xerostomia and keratoconjunctivitis sicca, as well as extraglandular systemic manifestations often involving the lungs, kidneys, blood vessels, and muscles. The syndrome may occur alone (primary SS) or in association with other autoimmune diseases such as RA or SLE (secondary SS) [111, 112]. Besides dryness of the mucous membranes, severe fatigue is one of the most frequently reported symptoms of SS [113]. The incidence of fatigue in SS is high (57 %) and often linked to dysfunction of the ANS [114] and frequent comorbidities like FM [115]. Similar to RA and SLE, multiple factors have been associated with fatigue in SS, including disease activity, pain, depression, and sleep disturbance—in particular, insomnia [85, 116]. The precise cause of fatigue in SS remains unclear, but its severity is comparable to that of SLE.

Ankylosing Spondylitis

In several population studies, patients with AS significantly more often reported moderate to severe fatigue than did the general population [117, 118]. Importantly, self-reported health measures predicted about half of the variation of these patients' fatigue, whereas clinical measures did not significantly contribute to this variation [117, 119]. However, moderate associations of fatigue levels with inflammatory markers have been reported in patients with AS [120].

Fatigue Comparisons Between FM, RA, and AS

Fatigue is an important symptom for most FM patients and seems to contribute as much to these patients' dysfunction as pain itself [121, 122]. It also is among the most common symptoms of RA and is a major complaint in AS [123]. Fragmented sleep was found to correlate positively with levels of fatigue in RA patients [85, 124, 125], FM [122, 126], and AS [127] and has also been associated with increased pain in these patients [128]. Direct comparisons between patients with FM, RA, and AS have demonstrated more fatigue and pain in FM patients, as compared with the other patient groups. The reported levels of fatigue were similar between RA and AS patients, and positive correlations between fatigue intensity and sleep problems, as well as pain intensity, were observed in all patient groups [129]. These findings suggest that improvements of fatigue intensity and insomnia may reduce pain in patients with these rheumatic disorders.

However, not all studies have demonstrated differences in fatigue between FM and other rheumatologic illnesses such as RA and SLE. One study of FM, SLE, and RA patients who completed the revised FM Impact Questionnaire (FIQR) and/or the disease-unspecific revised Symptom Impact Questionnaire (SIQR) [130] indicated that the combination of two SIQR questions ("tenderness to touch" and "difficulty sitting for 45 minutes") plus pain in four locations (lower back, neck, hands, and arms) identified the correct diagnosis in 97 % of patients. However, no difference in fatigue levels could be detected between FM, RA, and SLE patients. These discrepancies between study results may be related to differences in disease severity between patient groups.

Fatigue Treatments

Treatment of fatigue in rheumatologic disorders is difficult because its pathogenesis is only partially understood. Moreover, effective treatments of fatigue in patients with these illnesses often need to address commonly encountered comorbidities, including mood and sleep disorders.

Pharmacological Interventions

Although most FM patients complain of pain and stiffness as their most relevant symptoms, chronic fatigue frequently limits their mental and physical functioning [131]. During several large randomized placebo-controlled clinical trials with duloxetine, milnacipran [132], pregabalin [133], or sodium oxybate [134], many patients with FM responded with significant reductions not only of pain, but also of fatigue, which was sustained during at least 3 months of therapy.

Little evidence is available for the effectiveness of pharmacological therapy for SLE-related fatigue. Because many patients with SLE have been found to have low levels of dehydroepiandrosterone (DHEA), one study investigated the ability of this drug in improving fatigue and reduced well-being of these patients [135]. This study was conducted in patients with quiescent SLE to avoid other confounding factors. Although both placebo and daily oral administration of 200-mg DHEA improved fatigue scores, there was no significant difference of DHEA over placebo. Similar findings have been reported with DHEA treatment of fatigue in patients with SS [136].

Evidence from several large randomized placebo-controlled studies has shown that treatment of AS patients with TNF-α inhibitors significantly reduced not only their joint inflammation and pain, but also fatigue [137, 138•]. In addition, TNF-α inhibitors seem to improve the sleep abnormalities of AS patients [139]. At this time, however, it is unknown what the specific contributions of joint inflammation and sleep abnormalities are to AS fatigue.

Nonpharmacological Interventions

Exercise

Reduced physical fitness is often associated with high fatigue levels in many patients with rheumatologic disorders, including RA or SLE, and may be linked to lack of physical activity [103, 106]. Several studies investigated the effect of graded exercise on fatigue and physical inactivity in such disorders [140–145]. Most patients were found to be deconditioned but responded well to interventions designed to improve their aerobic capacity, suggesting that lack of physical activity may have contributed to their symptoms [142, 144, 145]. At this time, however, follow-up studies are lacking regarding the long-term benefits of exercise on fatigue.

Many FM patients are aerobically unfit, have poor muscle strength, and demonstrate limited flexibility. However, graded aerobic exercise over several months seems to result in significant improvements of fatigue, depression, and self-reported cognitive symptoms [146, 147]. Similarly, when patients with ME/CFS were enrolled into graded aerobic exercise training programs over 4 weeks, they reported significant improvements in fatigue and depression, as compared with control groups, indicating that most patients benefited from physical activity [148]. Generally, ME/CFS patients who complete aerobic training seem to experience significant improvements in outcomes, as compared with baseline.

Psychosocial/Behavioral Treatments

Psychosocial factors seem to play an important role for fatigue of rheumatologic conditions, including SLE and RA. Several studies have targeted improvements of SLE patients' understanding, beliefs, coping styles, and social support [149•, 150–153]. Some studies used self-management and counseling interventions to improve fatigue of these patients [141, 154, 155], whereas other studies utilized telecounseling and educational tools. Most studies demonstrated significantly decreased fatigue scores after these interventions [154, 155]. Among these studies, self-management interventions were successful in enhancing self-efficacy and coping skills while reducing fatigue levels, although this reduction was not statistically significant [156]. Similarly, stress management programs, including biofeedback and cognitive treatment, significantly reduced fatigue more than did usual care [157]. However, this improvement could not be maintained over a 9-month follow-up. Overall, most chronically fatigued patients seem to respond to pharmacological and nonpharmacological interventions with significant reductions of fatigue, as compared with control groups.

A meta-analysis of cognitive behavioral therapy (CBT) trials of FM patients showed that this treatment effectively reduced depressed mood and improved self-efficacy for pain [158]. There was, however, no evidence for effectiveness of CBT for FM pain, fatigue, sleep disturbances, or health-related quality of life. In contrast, CBT was effective in reducing the symptoms of fatigue in ME/CFS patients as compared with usual care and may be even more effective as compared with other psychological therapies [159]. Overall, there is only limited evidence available for CBT efficacy for fatigue in FM, as well as ME/CFS.

Conclusions

Fatigue often is a disabling symptom associated with many rheumatologic conditions, including RA, SLE, AS, ME/CFS, and FM. Evaluation and management of fatigue in patients with such disorders is complicated by frequent comorbidities with mood and sleep disorders. Most rheumatologic patients' fatigue seems to depend on both peripheral and central mechanisms and is often associated with deconditioning. Increasing evidence appears to indicate that fatigue in rheumatologic disorders is only partially correlated with disease activity. Mood as well as sleep disorders need to be considered as important contributors to chronic fatigue. Although many rheumatologic patients report reductions of clinical fatigue with treatment of their inflammatory conditions, their responses are often incomplete, despite the use of powerful therapeutic agents. Thus, additional pharmacologic and/or nonpharmacologic therapies with antidepressants, anxiolytics, hypnotics, aerobic exercise, and CBT are frequently required. Overall, the treatment of fatigue in patients with rheumatologic conditions is often complex but can reduce this disabling symptom and improve patients' function.

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