

# Fatigue in chronic disease

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## A B S T R A C T

Fatigue is an extremely common complaint among patients with chronic disease. However, because of the subjective nature of fatigue, and the lack of effective therapeutics with which to treat fatigue, this symptom is often ignored by clinicians, who instead focus on hard, objective disease end-points. Recently, the symptom of fatigue has received greater attention as part of overall health-related quality of life assessments in patients with chronic disease. Furthermore, new methods are being developed to help quantify fatigue, and are being utilized more frequently in the clinical setting. Moreover, studies in patients and using animal models of disease have provided some insight into changes within the brain which appear to be linked to the genesis of central fatigue. This review focuses on fatigue in chronic disease and outlines possible mechanisms which may give rise to central fatigue in chronic disease. Moreover, methods for measuring fatigue and an approach to the fatigued patient are discussed. Hopefully, a broader understanding of this distressing symptom will lead to the development of specific therapies for treating fatigue in these patients.

## INTRODUCTION

Fatigue is a common symptom experienced by virtually everyone during the course of their lives. However, given its subjective nature, fatigue is a difficult entity to characterize and define. Fatigue encompasses complex interactions between biological, psychosocial and behavioural processes, and has been defined medically as 'that state, following a period of mental or bodily activity, characterized by a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness, sleepiness or irritability' [1]. Fatigue may be acute and self-limited or chronic and debilitating in nature. In addition, it may or may not be relieved by rest.

Fatigue is often separated arbitrarily into being central or peripheral in origin, although the two types can co-exist [2,3]. Peripheral fatigue results from neuromuscular

dysfunction outside the central nervous system (CNS) and relates to impaired neurotransmission in peripheral nerves and/or defects in muscular contraction [2]. Central fatigue implies alterations or abnormalities in neurotransmitter pathways within the CNS, and often co-exists with psychological complaints, which can include depression and anxiety [3–6]. In general, central fatigue appears to be the most relevant in patients with chronic disease, although the absolute contribution of peripheral and central fatigue to overall fatigue in patients may vary significantly between different diseases.

### Prevalence of chronic fatigue

Fatigue can be categorized as acute or chronic, and although these are arbitrary definitions they are none the less useful for examining fatigue in patient populations. Acute fatigue is usually self-limited, caused by an

**Key words:** anxiety, corticotropin-releasing hormone, cytokines, depression, fatigue, hypothalamic–pituitary–adrenal axis, inflammation, mood disorder, neurotransmitter.

**Abbreviations:** ACTH, adrenocorticotropic hormone (corticotropin); CNS, central nervous system; CRH, corticotropin-releasing hormone; 5-HT, 5-hydroxytryptamine; IL-1 $\beta$ , interleukin-1 $\beta$ ; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

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identifiable insult, occurs in healthy individuals, and is relieved by appropriate rest [7]. Chronic fatigue, however, often accompanies medical illness, lasts typically longer than 6 months, often has multiple or unknown causes, usually is poorly relieved by rest, and typically is not related to exertion [7]. Chronic fatigue is a common complaint within the general population. Specifically, the prevalence of fatigue lasting longer than 6 months among patients attending primary care practice has been reported as being between 10 and 20% [8,9]. This proportion drops to 1–3% in community-based surveys [10,11]. Thus in present-day society, significant, prolonged fatigue commonly occurs in the absence of chronic medical illness.

### Methods of measuring fatigue

Fatigue is a non-specific and highly subjective symptom which is difficult to define, making the measurement and study of fatigue extremely challenging. However, given the major significance of fatigue in the clinical setting, attempts have recently been made to measure fatigue in a relevant and reproducible fashion. These fatigue measurement scales typically involve the development and application of a series of questions in the form of self-assessment questionnaires which attempt to measure a patient's perception and severity of fatigue [3,6,12–14]. Ideally, the results from these questionnaires should be reproducible, reliable and generally applicable. Furthermore, they need to be validated for the study population being examined, and the results compared with those from normal or healthy control populations. A number of these questionnaires have been developed and are being increasingly utilized in the clinical setting [3,6,12–14].

To date, most assessments of fatigue severity have involved the utilization of *subjective* fatigue scales or questionnaires, as outlined above. However, more *objective* measurements of fatigue would conceptually appear to be desirable, but have received limited attention in the clinical setting. One research group has developed an 'Actometer' motion-sensing device in an effort to document physical activity in patients and correlate this activity with the patient's subjective complaint of fatigue [15]. This matchbox-sized device is attached to a patient's ankle and measures the number of limb movements during 5 min intervals for prolonged recording periods. The resulting data are processed by a personal computer. Interestingly, in patients with chronic fatigue syndrome, the complaint of fatigue determined by questionnaire correlates closely with diminished activity, as documented by the Actometer; however, in patients with multiple sclerosis (MS), fatigue and activity level do not correlate [15]. These findings suggest that there may be some limitations in using the Actometer type of activity-measuring devices for the determination of subjective

complaints of fatigue in patients with chronic disease, but this approach warrants further study.

Another way to potentially measure fatigue, or 'fatigueability', in patients with chronic disease could involve a determination of exercise tolerance using some form of exercise test. Cycle ergometers or treadmills could be used and the time to volitional fatigue measured. However, this type of assessment would be problematic in patients with chronic diseases associated with joint or muscle pathology, or with anaemia. Furthermore, similar potential problems with subjective fatigue versus objective activity measurements would need to be considered, as outlined above.

### FATIGUE IN CHRONIC DISEASE

Chronic fatigue is a ubiquitous complaint among patients with chronic disease. However, because of the subjective nature of fatigue and the lack of specific therapies available to treat fatigue, it is a symptom often overlooked or ignored by clinicians. Despite this, fatigue is often rated by patients with chronic disease as one of the key factors leading to a decrease in their quality of life. The importance of fatigue, and its impact on a patient's quality of life, has been increasingly recognized and studied for a number of chronic diseases, including MS [16,17], systemic lupus erythematosus (SLE) [18,19], chronic viral and cholestatic liver diseases [20,21] and rheumatoid arthritis (RA) [22,23], and in patients infected with HIV [24]. Patients with these chronic diseases consistently identify fatigue as one of the most problematic and challenging aspects of their disease.

Fatigue in chronic disease may be both central and/or peripheral in origin. Peripheral fatigue is observed in chronic diseases associated with muscle wasting and inflammation or joint abnormalities, as often occurs in RA and SLE. However, chronic disease is most commonly associated with central fatigue. Central fatigue generally correlates poorly with traditional markers of disease [18–23] and frequently co-exists with other psychological complaints, such as anxiety and depression [18,19,21–25]. As an example, fatigue occurs in up to 68% of patients with the chronic cholestatic liver disease primary biliary cirrhosis and, although it correlates strongly with self-rated depression, it does not correlate with serum biochemical measurements of disease severity or the degree of hepatic fibrosis/inflammation [21]. Similar findings have been reported in patients with MS, SLE and RA [18,19,22–25]. It is not known whether fatigue in a given disease is a consequence of simply being chronically ill, or whether it represents a specific complication of that disease. The poor correlation between fatigue and traditional markers of disease severity appear to support the latter.

## THEORIES TO EXPLAIN THE GENESIS OF CENTRAL FATIGUE IN CHRONIC DISEASE

Despite the recognition for centuries that fatigue is an integral component of chronic disease, the aetiology of fatigue in this setting is poorly understood. However, it is becoming increasingly recognized that fatigue in chronic disease appears to be mainly of central origin. A number of potential causes of central fatigue have been suggested [26], and these will be discussed below as they pertain to fatigue in chronic disease.

### Corticotropin-releasing hormone (CRH) and chronic stress

It is difficult to precisely define the term stress, but it may be considered as 'the condition where coping with various actual or perceived stimuli alters the homeostatic state of the organism' [27,28]. Patients with chronic disease can be expected to experience a high degree of stress, involving variable inputs from social (loss of social position, social support), psychological (disease labelling, depression, anxiety, coping patterns) and physical (disease activity, pain, inflammation) issues. The principal CNS components of the stress response include CRH and the sympathetic nervous system [28]. CRH has been best characterized as the main central regulator of activation of the hypothalamic–pituitary–adrenal axis, stimulating release of adrenocorticotrophic hormone (ACTH; corticotropin) from the anterior pituitary via hypothalamic projections to the median eminence [29]. However, CRH-containing nerve fibres also project from hypothalamic nuclei to brainstem autonomic nuclei and to numerous other brain areas [30]. Furthermore, CRH has been localized within a number of brain areas, including limbic and autonomic structures, suggesting a direct role for CRH in co-ordinating behavioural responses [30]. Specifically, CRH has been shown to modulate behavioural changes that occur during stressful conditions [31]. When infused centrally in rodents, CRH induces behavioural activation [32]. The recognition of the role of CRH in behavioural activation has led to the hypothesis that defective central CRH release may give rise to behavioural depression and thus fatigue (reviewed in [33]). Studies in chronic fatigue syndrome consistently suggest an impairment of central CRH synthesis and release at the level of the hypothalamus in these patients [33,34]. Although similar studies have been performed for only a few chronic disease states, these also appear to suggest the presence of abnormal central CRH pathways. Patients with SLE, RA and MS exhibit attenuated ACTH/cortisol responses during insulin-induced hypoglycaemia [35–37]. Since hypothalamic CRH release constitutes the main driving force for ACTH release during this stressor, these results are consistent with defective central CRH release in these patients. Furthermore, alterations in the hypothalamic–

pituitary–adrenal axis have been documented in patients with the chronic cholestatic liver disease primary biliary cirrhosis, as indicated by enhanced ACTH secretion in response to exogenous CRH administration, suggesting the presence of an up-regulation of pituitary CRH receptors in these patients due to chronically diminished central CRH release [38].

Chronic stress has a profound impact upon central CRH synthesis and release. However, different types of chronic stress appear to have differential effects upon central CRH. Rodents exposed to chronic physical and/or psychological stress paradigms in general exhibit increased hypothalamic CRH expression. Specifically, exposure of rats to a number of chronic stressors, including physical (e.g. repeated daily intraperitoneal injections of hypertonic saline [39]; recurrent electric shocks to the foot [40]) and psychological (e.g. recurrent mild unpredictable stresses [41]) stressors have been shown to exhibit increased central CRH levels and mRNA expression.

However, a different central CRH response to that observed in rats in response to chronic physical or psychological stress appears to occur in rats in which a chronic inflammatory response has been induced; namely, a reduction in central CRH synthesis and release has been documented in rats undergoing chronic inflammatory stress (reviewed in [27]). Specifically, in animal models of immune-mediated arthritis (adjuvant-induced arthritis in the rat [42]), SLE (MRL *lpr/lpr* mouse [27]), MS (experimental allergic encephalomyelitis in the rat [43]) and cholestatic liver disease (bile duct ligation in the rat [44]), similar patterns of defective central CRH expression and release have been observed; namely, a reduction in hypothalamic CRH expression. Moreover, rats with experimental cholestatic liver injury demonstrate behaviour that is consistent with defective central CRH release [45]. Interestingly, the defect in hypothalamic CRH release is paralleled in all of these animal models by an increase in hypothalamic arginine vasopressin expression [27,42–44]. Arginine vasopressin (with CRH) is a co-stimulator of ACTH release from the pituitary gland, and appears to take on a more significant role as an ACTH secretagogue under conditions associated with decreased hypothalamic CRH levels [39]. Since in human correlates of these chronic diseases central fatigue is a consistent finding, and since central CRH release induces behavioural activation in rodents, one can speculate that fatigue in these chronic inflammatory diseases may be due, at least in part, to defective central CRH release. The data derived from these different animal models suggest that chronic stress induced by different mechanisms produces differential alterations within the CNS. Furthermore, in animals, chronic inflammatory stress appears to correlate most strikingly with the development of low central CRH levels. Therefore fatigue could potentially be induced in patients

as a result of a similar defect in central CRH release, and this warrants further study.

### **Cytokines and immune activation**

The complaint of fatigue often accompanies acute and chronic inflammatory illness and infection. During the inflammatory process the acute-phase response is coordinated through the release of a number of cytokines that have been implicated in the genesis of non-specific symptoms of illness, including fatigue [46]. Specifically, elevated circulating levels of the cytokines interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-6 have been documented in a number of chronic diseases, including RA, SLE, MS and chronic liver disease [47–50]. Moreover, infusion of IL-1 $\beta$  into rodents produces a number of ‘sickness behaviours’, including lethargy [51], apparently via central mechanisms [51,52]. The mechanism(s) whereby elevations in cytokine levels outside the CNS may induce alterations in behaviour are unclear, but may involve direct interactions between the cytokine and the blood–brain-barrier cells, penetration into the brain through areas devoid of a blood–brain barrier, or stimulation of vagal afferents (reviewed in [53,54]). In addition, rodents with experimental cholestatic liver disease exhibit enhanced sensitivity to the lethargy-inducing effects of centrally infused IL-1 $\beta$ , suggesting that liver disease and possibly other chronic inflammatory conditions increase central sensitivity to the behavioural depressant effects of cytokines such as IL-1 $\beta$  [55]. IL-1 $\beta$  activates the hypothalamic–pituitary–adrenal axis through a mechanism involving hypothalamic release of CRH [56]. However, patients with RA fail to increase cortisol secretion following surgery, despite high circulating IL-1 $\beta$  levels, suggesting that a defect exists in the hypothalamic response to IL-1 $\beta$  in these patients [57]. In addition, rats with experimental cholestatic liver disease exhibit defective stimulation of ACTH release after the peripheral administration of IL-1 $\beta$ , consistent with abnormal hypothalamic CRH responsiveness to this cytokine in these animals [58].

IL-6 has recently received attention as another potential circulating cytokine mediator of fatigue [59,60]. Infusion of IL-6 into humans results in fever, anorexia and fatigue [61]. Moreover, circulating IL-6 levels are often elevated in chronic inflammatory diseases, such as SLE, RA, MS and chronic liver disease [47–50], and serum levels of IL-6 appear to correlate with fatigue in patients with chronic liver disease [62]. Given that circulating IL-6 levels are increased in animal models of these diseases [63–66], and that peripheral IL-6 can induce alterations in neurotransmitter (i.e. serotonergic) and neurohormone (i.e. CRH) systems within the CNS [67,68], these data suggest a potential role for IL-6 in the genesis of central fatigue.

Interferon is a pro-inflammatory cytokine that is released as part of the immune response. In addition,

interferons have been used therapeutically to treat a number of diseases, and interferon therapy is associated with a number of adverse effects, including fatigue [69]. This observation suggests that endogenous interferon production during chronic inflammation may contribute, directly or indirectly, to the genesis of fatigue in patients with chronic disease where there is accompanying activation of the immune system.

### **Central neurotransmitter pathways**

The possibility exists that fatigue in chronic disease may be due to altered central neurotransmission. The two neurotransmitter systems most commonly implicated in fatigue states are the serotonergic [5-hydroxytryptamine (5-HT)] and noradrenaline (norepinephrine) pathways [26]. Furthermore, these two neurotransmitter systems are intimately entwined in the control of central CRH release [70,71]. Serotonergic neurons project from the dorsal raphe nucleus in the midbrain to synapse with CRH-containing neurons in the paraventricular nucleus of the hypothalamus [72], and stress-induced activation of CRH neurons within the paraventricular nucleus involves activation of these serotonergic pathways [73]. Altered central serotonergic neurotransmission has been implicated in the genesis of central fatigue. Specifically, studies in patients with chronic fatigue syndrome suggest increased sensitivity to 5-HT-mediated hypothalamic activation, implying the existence of defective central serotonergic neurotransmission in these patients [74]. Moreover, medications that augment central serotonergic neurotransmission have been used with some success to treat fatigue in patients with fatigue associated with fibromyalgia [75], although they appear to be less useful in treating fatigue in patients with chronic fatigue syndrome [76]. Alternatively, enhanced central serotonergic neurotransmission has also been implicated in the genesis of fatigue. In rats exposed to prolonged exercise paradigms to exhaustion, central 5-HT levels are increased [77]. In addition, administration of a 5-HT re-uptake inhibitor to healthy control subjects reduced their capacity to exercise to exhaustion [78]. Obviously, the precise role of 5-HT in fatigue states needs to be studied further.

Although serotonergic neurotransmission has not been closely examined in patients with chronic disease, defective central serotonergic pathways have been documented in rats with experimental cholestatic liver disease complicated by lethargy [79]. Interestingly, treatment of these rats with a 5-HT<sub>1A</sub> receptor agonist resulted in an amelioration of the lethargy associated with this experimental liver disease [79]. Treatment with the 5-HT<sub>3</sub> receptor antagonist ondansetron of a patient infected with hepatitis C and complaining of fatigue and pruritus has recently been reported [80]. Ondansetron treatment resulted in an amelioration of both her fatigue and her pruritus, implicating enhanced activation of 5-HT<sub>3</sub> re-

ceptors in the itch and fatigue associated with chronic hepatitis C infection. However, the results of this case report need to be interpreted with some caution. Ondansetron therapy improved pruritus in this patient, which may have had a direct impact upon her complaint of fatigue. Furthermore, ondansetron has antidepressant properties, which could also have impacted upon her fatigue [81]. In any event, examination of abnormalities in central serotonergic neurotransmission appears to be of specific interest in the understanding and treatment of fatigue in chronic liver disease and other chronic diseases.

There is also pharmacological evidence for an interaction of CRH and noradrenaline in mediating behavioural responses to stress (reviewed in [71]). Thus defective central noradrenaline release could contribute to the genesis of fatigue, possibly by inhibition of central CRH. This theory has not been examined to date either clinically or experimentally.

Substance P is one other central neurotransmitter that has received recent attention as potentially being involved in fatigue states. Substance P is localized within the hypothalamus, and elevated levels of substance P have been documented in the cerebrospinal fluid of patients with fibromyalgia, a condition strongly associated with fatigue [82]. Moreover, elevated hypothalamic substance P levels have been documented in rats with adjuvant-induced arthritis, an animal model of RA [83]. Given that substance P inhibits the central release of CRH [84], increased hypothalamic levels of substance P may contribute to the genesis of fatigue via this mechanism.

### Disorders of mood

The complaint of fatigue in chronic disease correlates strongly with abnormalities in mood, most typically depression and anxiety [18,19,21–25]. This strong correlation appears to transcend specific causes of chronic disease, as it is found with similar frequency in virtually every chronic disease where it has been sought. Interestingly, this close association between fatigue and mood disorder has been recognized for years in patients with chronic fatigue syndrome [85,86]. Given that the neuroendocrine and neurotransmitter systems presumed to be involved in the induction of fatigue and mood disorders have many common links, this observation should not be surprising. Although the close association between fatigue and mood disorder may be due, in part, to overlapping symptoms, including fatigue, sleep disturbance, psychomotor change, cognitive impairment and mood changes, it appears that this correlation does in fact exist [18,19,21–25]. In addition, in animal models of SLE and cholestatic liver disease, the development of changes in central CRH levels parallels the development of animal correlates of depression (i.e. anhedonia or loss of interest in pleasurable activities, and anxiety [87,88]). These findings strongly suggest a link between mood disorder and fatigue in chronic disease based on defects in common

central pathways in these disorders. Furthermore, these findings suggest that treatments effective for depression may be useful in treating fatigue associated with chronic disease.

### APPROACH TO THE FATIGUED PATIENT

The first line of approach to any patient with fatigue complicating chronic disease is the exclusion of common treatable causes. These would include hypothyroidism, electrolyte imbalance, anaemia, renal failure, diabetes or side-effects of medication (e.g. anti-histamines). Furthermore, potential causes of peripheral fatigue should be identified and treated accordingly, using such modalities as analgesia, rest, massage, etc.

Therapeutic intervention in patients with central fatigue is more difficult and involves a multifaceted approach. Firstly patients need to be counselled about tailoring daily activities according to their energy levels [89,90]. Restructuring priorities of daily living can avoid unnecessary stress which may exacerbate fatigue [89,90]. Moreover, a reasonable balance between rest and activity needs to be emphasized. Excessive rest increases subjective fatigue in cancer patients [91]. A graded aerobic exercise programme should be recommended if the patient is physically capable, as this has been shown to be beneficial in patients with chronic fatigue syndrome [92]. Secondly, patients need to be assessed for co-existent mood disorder, especially depression. If clinical depression is identified then a trial of antidepressant therapy may be warranted.

Although there are currently no specific therapies available for treating central fatigue in the setting of chronic disease, non-pharmacological tools may be of potential use. Cognitive behaviour therapy is based on a patient's thoughts and beliefs about their illness (cognition) and the way they cope with it (behaviour) [93]. The aim of this approach is to identify the cognitions and behaviours in a given patient that may be contributing to their disease-related disability, in this case fatigue [93]. Cognitions and behaviours identified to be contributing to fatigue can then be modified using self-help techniques. This form of therapy has been used with some success in treating fatigue in patients with chronic fatigue syndrome [93,94]. Moreover, cognitive behaviour therapy has been used in patients with RA, and resulted in a lessening of fatigue [95]. The use of cognitive behaviour therapy in treating fatigue associated with other chronic diseases should be explored.

The concept of sleep hygiene needs to be addressed in the fatigued patient with chronic disease. Complaints of disturbed sleep are very common in patients with chronic disease (reviewed in [96]). Specifically, subjective assessments of sleep disturbance are frequently abnormal in patients with chronic diseases such as MS, SLE, RA and

primary biliary cirrhosis [21,97–99]. Moreover, subjective complaints of sleep disturbance often correlate significantly with depressive symptoms, mainly due to illness intrusiveness [100]. Interestingly, objective polysomnographic studies of sleep disturbance often do not correlate well with the patient's subjective complaints of sleep problems [99,101]. In any event, patients should be asked about their sleep hygiene, and in some cases a trial of a night-time hypnotic may be beneficial with respect to daytime fatigue.

## SUMMARY

The complaint of fatigue is extremely common in patients with chronic disease, and can be the most debilitating part of a disease. Moreover, it is clear that the genesis of the symptom of fatigue in chronic disease is complex and poorly understood, although the cause of fatigue is very likely to be multifactorial. Currently there is very little to be offered from a therapeutic standpoint to specifically treat fatigue in the patient with chronic disease. Moreover, the study of fatigue in chronic disease is complicated by the subjective nature of this complaint and the inaccessibility of the human brain to study. In this regard, animal models of chronic disease may prove to be invaluable in ultimately dissecting out the neural mechanisms which contribute directly to the genesis of central fatigue, and may provide direction for future therapeutic intervention. In the future, potential pharmacological interventions for treating fatigue associated with chronic disease are likely to be developed. These therapies may target defective central corticotropin-releasing-hormone-related pathways, abnormal neurotransmission or cytokines.

## ACKNOWLEDGMENTS

M.G.S. is funded by the Medical Research Council of Canada and the Alberta Heritage Foundation for Medical Research.

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Received 9 February 2000/15 March 2000; accepted 30 March 2000