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Mechanisms of Cancer-Related Fatigue

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ABSTRACT

Cancer-related fatigue (CRF) is one of the most prevalent symptoms patients with cancer experience, both during and after treatment. CRF is pervasive and affects patients' quality of life considerably. It is important, therefore, to understand the underlying pathophysiology of CRF in order to develop useful strategies for prevention and treatment. At present, the etiology of CRF is poorly understood and the relative contributions of the neoplastic disease, various forms of cancer therapy, and comorbid conditions (e.g., anemia, cachexia, sleep disorders, depression) remain unclear. In any individual, the etiology of CRF probably involves the dysregulation of several physiological and biochemical systems. Mechanisms proposed as underlying CRF include 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and ATP metabolism, hypothalamic–pituitary–adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation. Currently, these hypotheses are largely based on evidence from other conditions in which fatigue is a characteristic, in particular chronic fatigue syndrome and exercise-induced fatigue. The mechanisms that lead to fatigue in these conditions provide a theoretical basis for future research into the complex etiology of this distressing and debilitating symptom. An understanding of relevant mechanisms may offer potential routes for its prevention and treatment in patients with cancer.
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Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

In a healthy person, fatigue occurs as an indispensable sensation that prompts the desire to rest. This response has probably evolved to protect against overexertion, which can lead to permanent tissue damage, or to promote healing. Fatigue associated with cancer or its treatment is distinct from the typical fatigue that most people experience as a result of normal daily life. Unlike typical fatigue, cancer-related fatigue (CRF) is disproportionate to exertion level and is not relieved by rest or sleep [1,2]. CRF has been defined as a "persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning" [3,4].

CRF is extremely common, with most studies reporting prevalence rates above 60% and some studies reporting rates of up to 90% [5]. CRF is also persistent, in that it may be present at diagnosis, increase during therapy, and continue for months or years following the completion of therapy. CRF is frequently reported as the most distressing symptom associated with cancer and its treatment, even more so than pain, nausea, or vomiting. Thus, this symptom can have an immensely negative impact on patients' quality of life and daily activities. Until recently, fatigue in patients with cancer was underrecognized and undertreated because attention has been focused on other common symptoms, such as nausea and pain. This article reviews the current hypotheses and evidence for the etiology of CRF.

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What Is Fatigue?

Fatigue is a highly subjective multidimensional experience. Individuals may perceive fatigue as physical tiredness or exhaustion, a need for reduced activity, reduced motivation, and/or mental fatigue [6]. Much of what is known about fatigue focuses on physical fatigue as it relates to exercise (i.e., muscle response). From this perspective, fatigue is defined physiologically as the inability to maintain power output [7], and is perceived as a sensation of weakness—even when the muscle is not being used—and/or a sense of greater effort required to accomplish a task. Additionally, fatigue includes psychological dimensions such as mental fatigue and reduced motivation. Mental fatigue can be expressed as a reduced capacity for attention, concentration, and learning, as well as a disturbance in short-term memory [8].

The basic mechanisms of fatigue have been broadly categorized into two main components: peripheral and central. Peripheral fatigue, which occurs in the neuromuscular junctions and muscle tissues, results in the inability of the peripheral neuromuscular apparatus to perform a task in response to central stimulation. Mechanisms implicated in peripheral fatigue include a lack of ATP and the buildup of metabolic by-products. Central fatigue, which develops in the central nervous system (CNS), arises from the progressive failure to transmit motor neuron impulses [9]. Central fatigue has been defined as difficulty in the initiation or maintenance of voluntary activities [10]. Central fatigue thus manifests as "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" [11,12].

The sensation of fatigue may arise from peripheral signals mediated by afferent nerves in the muscles or closely related structures (e.g., tendons and joints) and/or by activation of central pathways in the cerebral cortex. Conversely, an individual's perception of effort appears to be linked more to the effort required to generate force than to the magnitude of the force exerted. The perception of effort may involve a central mechanism of signaling from the motor cortex to the primary somatosensory cortex [13,14]. However, the relationship between the sensations of effort and fatigue has not yet been elucidated.

Mechanisms Underlying Cancer-Related Fatigue

Fatigue has been studied in normal (exercise) conditions and in the context of chronic diseases, including chronic fatigue syndrome and rheumatoid arthritis. However, there are limitations to extrapolating results of these studies to CRF because different etiologic factors are likely to be involved.

Serotonin Dysregulation

One hypothesis proposed to explain CRF is that cancer and/or cancer treatment causes an increase in brain serotonin (5-HT) levels and/or upregulation of a population of 5-HT receptors, leading to reduced somatomotor drive, modified hypothalamic–pituitary–adrenal (HPA) axis function, and a sensation of reduced capacity to perform physical work [15]. 5-HT has numerous functions, including control of appetite, sleep, memory, learning, temperature regulation, mood, behavior, cardiovascular function, muscle contraction, endocrine regulation, and depression, and there is increasing evidence for a role for 5-HT in the genesis of central fatigue. In particular, research in exercise-induced fatigue and chronic fatigue syndrome implicates 5-HT dysregulation in the etiology of central fatigue.

5-HT Levels and Central Fatigue

Exercise increases the concentration of tryptophan, the precursor of 5-HT, in the brain, leading to increased synthesis of 5-HT by some neurons. The increased concentration of 5-HT could result in physical and mental fatigue during prolonged exercise [16–18]. Studies in patients with chronic fatigue syndrome have demonstrated raised plasma levels of free tryptophan, which could potentially lead to high central 5-HT levels [19,20]. Animal studies have shown that sustained exercise increases 5-HT levels in the hypothalamus and brain stem [21]; however, the site(s) at which 5-HT is elevated in humans during exercise is not well understood. The rate-limiting step for synthesis of 5-HT in the brain is the transport of tryptophan into the brain. Tryptophan and branched-chain amino acids (BCAAs) compete for entry into the brain via a transporter [22]. During exercise, BCAAs are taken up by muscle cells. One hypothesis suggests that increased levels of central 5-HT during exercise are caused by a reduction in circulating BCAAs, which allows more tryptophan to enter the brain [23,24]. In addition, exercise increases the concentration of plasma free fatty acids that displace tryptophan from albumin, thus generating more available unbound tryptophan in plasma [25]. Animal studies have shown that 5-HT concentrations increase during sustained exercise, reaching a maximum at the point of fatigue [21,26]. From studies in humans, Blomstrand and colleagues [27–29] and Mittleman and colleagues [30] reported that supplementation with BCAAs before and during exercise was associated with improved physical and mental performance. Other studies in humans, however, have failed to find a link between BCAA supplementation and delayed onset of physical fatigue or increased exercise capacity [31–35].

Alterations in central serotonergic transmission are associated with fatigue during exercise. Animal studies have shown that administration of 5-HT produced a dose-related decrease in running endurance [36], while a 5-HT antagonist improved performance [26]. In several human studies, administration of selective serotonin reuptake inhibitors (SSRIs) has been shown to reduce the capacity to perform exercise. In two separate studies using healthy subjects, administration of the SSRI paroxetine (20 mg) prior to cycling exercise was associated with earlier exhaustion compared with placebo [33,37]. Similar outcomes were observed with fluoxetine administration [38]. Conversely, Strachan and colleagues [39] showed that acute administration of paroxetine had no effect on exercise performance. Although considerable evidence suggests a role for 5-HT metabolism and/or neurotransmission in fatigue associated with various conditions, other investigators have shown that central 5-HT concentrations do not influence CRF [40,41].

Changes in 5-HT Receptors and Fatigue

Changes in 5-HT receptors may also contribute to fatigue. Patients with chronic fatigue syndrome may have enhanced serotonergic responses, possibly due to upregulation and/or hypersensitivity of postsynaptic 5-HT_{1A} receptors in the hypothalamus [42–44]. Cleare and colleagues [45] have also reported evidence of decreased 5-HT_{1A} receptor numbers or affinity in chronic fatigue syndrome. Other evidence suggests a disruption of the interaction between the HPA axis and the serotonergic system in chronic fatigue syndrome [46]. This disrupted interaction may arise either from decreased responsiveness of the 5-HT_{1A} receptors responsible for controlling the HPA axis at the hypothalamic level or from reduced pituitary responsiveness [47]. Treatment with 5-HT_3 receptor antagonists, such as granisetron and ondansetron, which relieve fatigue associated with chronic fatigue syndrome and chronic liver disease, may be a promising intervention for CRF [48–51].

Dysregulation of Central 5-HT Metabolism and Cancer-Related Fatigue

Dysregulation of central 5-HT metabolism or function may be a contributing factor in CRF. There is evidence that proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, can influence 5-HT metabolism. Evidence suggests the existence of a feedback loop between TNF-α and central 5-HT [52] in which peripherally synthesized TNF-α causes an increase in 5-HT release into the synaptic space [53]. In addition, TNF-α can increase 5-HT transporter function, resulting in increased clearance of 5-HT from the synaptic space [54,55]. Conversely, 5-HT can decrease TNF-α synthesis. The feedback loop in the CNS may become dysregulated in patients with pathologic conditions or in response to cancer therapies [52].

Possible means by which systemic cytokines could influence the CNS include activation of peripheral afferent nerves (see below for further discussion) and the production of neuromediators, such as prostaglandins, at the blood–brain interface [56]. In addition, proinflammatory cytokines, such as interleukin (IL)-1β, interferon (IFN)-α, IFN-γ, and TNF-α, may directly or indirectly stimulate indoleamine 2,3-dioxygenase to alter 5-HT metabolism [57].

HPA-Axis Dysfunction and Cancer-Related Fatigue

Another potential etiology of fatigue is the disturbance of the HPA axis. Low levels of circulating cortisol have been observed in patients with chronic fatigue syndrome [47]. The HPA-axis dysfunction hypothesis proposes that cancer, and/or cancer treatment, alters the function of the HPA axis, resulting in endocrine changes that cause or contribute to fatigue.

The HPA axis (Fig. 1) is the central regulatory system controlling release of the stress hormone cortisol. Corticotropin-releasing hormone (CRH) is secreted from the paraventricular nucleus of the hypothalamus in response to physical or psychological stress. It acts synergistically with arginine vasopressin (antidiuretic hormone [ADH]) to release corticotropin (adrenocorticotropic hormone [ACTH]) from the anterior pituitary. ACTH in turn stimulates the release of cortisol from the adrenal cortex. Cortisol exerts a multitude of biological effects, including regulation

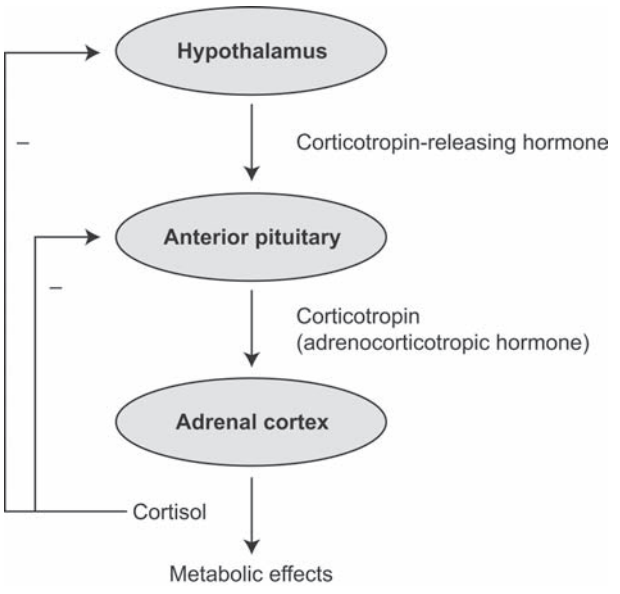

Figure 1. Schematic representation of the hypothalamic–pituitary–adrenal axis.

of blood pressure, cardiovascular function, carbohydrate metabolism, and immune function. Cortisol also exerts a negative feedback on the HPA axis at the level of the hippocampus, hypothalamus, and pituitary. Serum cortisol concentrations show diurnal variation, typically being highest after waking and then declining throughout the day.

In fact, animal experiments have shown that different types of stress induce different changes in HPA-axis activity. Physical and/or psychological stresses tend to *increase* hypothalamic CRH expression [58–60], while chronic inflammation (i.e., biological stress) tends to *reduce* central CRH synthesis and release [61]. Animal models of a variety of conditions, including rheumatoid arthritis, systemic lupus erythematosus, and cholestatic liver disease, support the possible relationship among chronic inflammatory response, defective CRH synthesis/release, and fatigue [61–64].

In humans, fatigue has also been linked to reduced HPA-axis function and hypocortisolemia in multiple clinical conditions, including cancer, chronic fatigue syndrome, and rheumatoid arthritis. Despite the frequent coexistence of depression and fatigue in patients with cancer, depression is actually associated with hypercortisolemia [65,66]. By contrast, in conditions manifesting with fatigue, such as chronic fatigue syndrome, mild hypocortisolemia has been observed [47]. Although the specific HPA-axis dysfunction in chronic fatigue syndrome is unclear, possible explanations include defective central CRH release, downregulation of CRH receptors in response to chronic stress, and reduced cortisol output [67–69].

Some evidence indicates altered HPA-axis function in CRF. As with chronic fatigue syndrome, some studies have indicated that CRF may be associated with reduced cortisol output [70,71]. Bower and colleagues [70] measured morning (8–10 a.m.) serum cortisol levels in women who survived breast cancer (mean time from diagnosis, ≤5.5 years). Women who experienced fatigue had significantly lower serum cortisol levels than those who did not report fatigue. In another study, the same investigators applied the Trier Social Stress Test to breast cancer survivors (mean time since diagnosis, 8.4 years) to induce activation of the HPA axis [72]. The results showed that women with fatigue had a significantly blunted response to the stressor, as measured by salivary cortisol levels, compared with women without fatigue (Fig. 2) [71]. Currently, possible correlations between high cortisol levels and CRF are inconclusive [73,74]. Discrepancies between studies may be due to differences in patient groups, type of sample, and timing of sample collection [73]. The diurnal rhythm, rather than overall cortisol levels, may be more significant with respect to the disturbances in HPA-axis function seen in patients with cancer, as discussed in the following section.

At present, the relationship among cancer, fatigue, and dysregulation of the HPA axis is unclear. Changes in the HPA axis may be caused by a number of different factors relevant to neoplastic disease. Proinflammatory cytokines, such as IL-1, IL-6, and TNF-α, are potent stimulators of the HPA axis [57]. Cortisol levels are controlled by the interaction of 5-HT with the HPA axis at the level of the hippocampus, hypothalamus, and pituitary, where stimulation of 5-HT_{1A} receptors signals the release of CRH, ADH, and ACTH [75]. In addition, there may be direct suppression of the HPA axis by cancer therapies, such as glucocorticoids, radiotherapy, and some forms of chemotherapy [76–78]. In turn, HPA-axis function influences immune cell development, maturation, and trafficking, and cytokine production, including production of proinflammatory cytokines [73,79]. Cortisol, for example, has a suppressive effect on proinflammatory cytokine production, and hence reduced cortisol levels allow cytokine levels to rise [80]. Although the current hypothesis proposes that HPA-axis disruption may cause CRF, there is also the possibility that comorbid conditions, such as sleep disturbance, may cause changes in the HPA axis [81]. The role of comorbid conditions in CRF is likely to be an important area for future research.

Circadian Rhythm Disruption

Another potential process by which cancer may cause fatigue is circadian rhythm disruption. Circadian rhythms are endogenous genetically- and physiologically-based patterns that are controlled by the body's "biological clock." These rhythms typically have a 24-hour cycle and are sensitive to

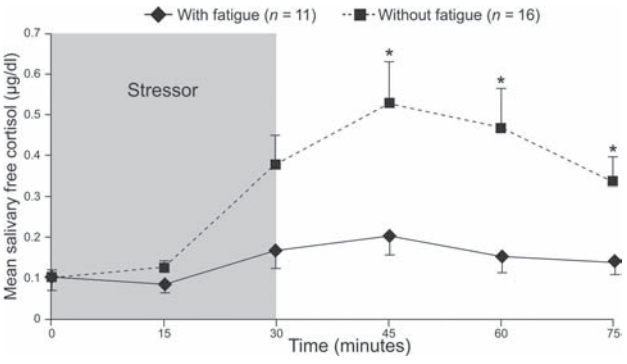

Figure 2. Mean salivary free cortisol levels before, during, and after application of the Trier Social Stress Test in women who survived breast cancer and who were grouped according to whether or not they still experienced fatigue. Error bars represent one standard error. *$p < .05$. Reproduced from Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom Med 2005;67:277–280, with permission from Lippincott Williams & Wilkins.

many environmental (e.g., alterations in light and dark) and psychological factors (e.g., stress, anxiety, and illness).

Several alterations in circadian function have been demonstrated in patients with cancer. These include changes in endocrine rhythms (e.g., cortisol, melatonin, and prolactin secretion), metabolic processes (e.g., temperature and circulating protein levels), the immune system (e.g., levels of circulating leukocytes and neutrophils), and rest–activity patterns [73,82–89]. Types of rhythm alteration include diminished amplitude, phase shifts, period changes, and erratic peaks and troughs. Patients with advanced cancer tend to demonstrate the greatest rhythm alterations [84,86,88].

Research examining possible links between circadian rhythms and CRF has focused on cortisol secretion rhythms and rest–activity patterns. Bower and colleagues [73] investigated the change in salivary cortisol levels between the morning on awakening and the late evening in women who survived breast cancer (mean time since diagnosis, >6 years). The subgroup of patients with fatigue was found to have a significantly flatter diurnal cortisol slope than the subgroup without fatigue. Further investigation showed that patients with fatigue tended to have a slower decline in cortisol levels over the course of the day, and that increased fatigue severity correlated with flatter slope plots.

Sleep disorders are common in patients with cancer [90] and may arise from altered rest–activity rhythms. Berger [91] and Mormont and colleagues [85,92] measured relative levels of activity in patients with breast or colorectal cancer using actigraphy. Both research groups showed an inverse relationship between fatigue and activity levels during the day and a positive relationship between fatigue and restless sleep at night. A relationship between the quality of 24-hour rest–activity rhythms and fatigue was also observed: patients with inconsistent and/or dampened circadian rhythms tended to experience greater fatigue than patients with better defined rhythms [93–96]. For example, Roscoe and colleagues [96] demonstrated a significant correlation between more consistent patterns of sleep and activity (measured over a 72-hour period using actigraphy) and lower fatigue scores in patients with breast cancer (Fig. 3). Furthermore, changes in fatigue between chemotherapy cycles correlated with changes in the circadian rest–activity rhythm. Notably, this study found that the association between fatigue and circadian disruption was independent of the presence of depression, even though depression correlated with disrupted circadian rhythm.

The causes of cancer-related circadian dysregulation may include genetic factors, psychosocial, environmental, and behavioral influences, and effects of the tumor on host rhythm regulation [84,86]. Altered neuroimmunologic responses could mediate associations among cancer (and its treatments), circadian rhythms, and fatigue [95]; however, the cause-and-effect relationship is likely to be complex. Diurnal changes in cortisol are known to change the number and function of immune cells, which could affect the suppression of proinflammatory cytokine production [80,97]. In addition, flattened cortisol rhythms in patients with breast cancer have been shown to be associated with altered immune function [89,98].

Muscle Metabolism/ATP Dysregulation

Patients' perceptions of CRF are often described as feelings of "weakness" and "lack of energy." Such subjective feelings are likely to relate, at least in part, to peripheral fatigue (i.e., the muscles have a reduced capacity for contractile response). The negative correlation between physical function and CRF has been confirmed by objective measurement of physical performance [99,100]. One hypothesis to explain this aspect of CRF is that cancer and/or its treatment leads to a defect in the mechanism for regenerating ATP in skeletal muscle, thereby compromising the ability to perform mechanical tasks (Fig. 4) [15].

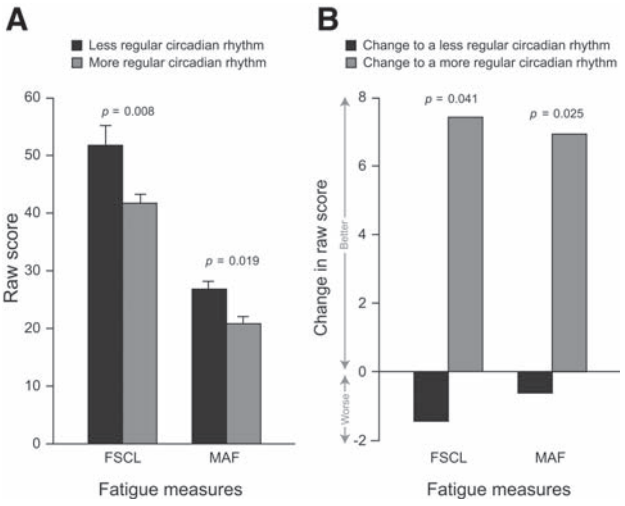

Figure 3. Fatigue in patients with breast cancer undergoing chemotherapy. Patients were grouped according to their circadian consistency, based on an evaluation of the degree of similarity of an individual's rest–activity patterns across 3 days. **(A):** Fatigue scores 1 week after patients' second on-study treatment. Higher scores indicate greater symptom severity. **(B):** Changes in fatigue from patients' second to fourth on-study treatments by median split on change in circadian consistency. Adapted from Roscoe JA, Morrow GR, Hickok JT et al. Temporal interrelationships among fatigue, circadian rhythm and depression in breast cancer patients undergoing chemotherapy treatment. Support Care Cancer 2002;10:329–336. Abbreviations: FSCL, Fatigue Symptom Checklist; MAF, Multidimensional Assessment of Fatigue.

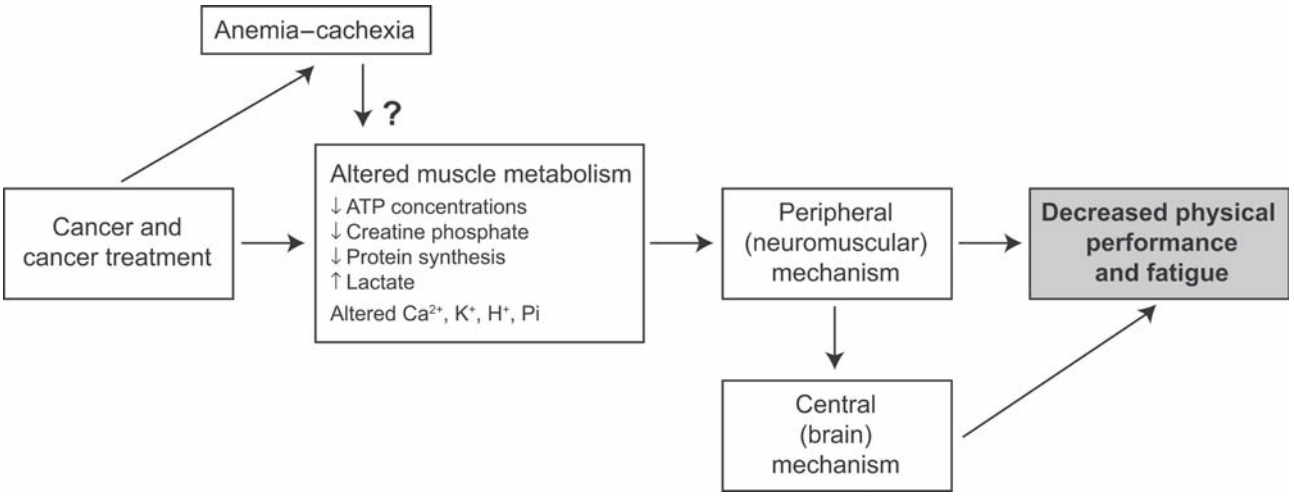

Figure 4. Possible involvement of skeletal muscle metabolism changes in the genesis of cancer-related fatigue. Adapted from Andrews PLR, Morrow GR, Hickok JT et al. Mechanisms and models of fatigue associated with cancer and its treatment: Evidence of pre-clinical and clinical studies. In: Armes J, Krishnasamy M, Higginson I, eds. Fatigue in Cancer. Oxford: Oxford University Press, 2004:51–87.

ATP is the major source of energy for contraction of skeletal muscle. Hydrolysis of the high-energy phosphate bonds in ATP releases energy; in normal circumstances, the ATP is then replenished. Depletion or failure to replenish ATP compromises muscle function. Studies investigating muscle fatigue in patients with chronic fatigue syndrome showed reduced oxidative muscle metabolism [101], depleted cellular ATP associated with a dysregulated 2′,5′-oligoadenylate synthetase/RNase L pathway [102], and impaired synthesis of ATP [103]. In addition, reduced skeletal muscle concentrations of ATP and creatine phosphate have been noted in patients with chronic renal failure, who often report fatigue and weakness as symptoms of their illness [104].

Evidence is limited for the disruption of ATP metabolism in the muscles of patients with cancer. Patients with cancer often have reduced energy intake, due to alterations in appetite and adverse effects of treatment (e.g., anorexia–cachexia), which may limit ATP repletion. Increased levels of uncoupling proteins, accompanied by reduced levels of ATP, have been reported in the skeletal muscle of patients with cancer [105,106]. Furthermore, it has been proposed that patients with cancer, particularly those with anorexia–cachexia, have altered muscle protein metabolism [107].

Studies investigating ATP depletion provide further evidence of an association between altered ATP metabolism and fatigue. A randomized clinical trial in patients with advanced non-small-cell lung cancer showed that ATP infusions improved muscle strength as well as some aspects of quality of life, such as tiredness [108]. In addition, Forsyth and colleagues [102] conducted a randomized, double-blind, placebo-controlled, crossover study to test the hypothesis that administration of nicotinamide adenine dinucleotide (NAD), a key coenzyme in the formation of ATP, could alleviate symptoms in patients with chronic fatigue syndrome. NAD, administered orally in its reduced form (NADH), decreased fatigue and improved quality of life [102]. Depending on the extent of ATP depletion in CRF, NAD administration may be a promising therapeutic strategy.

Vagal Afferent Nerve Activation

Vagal afferent nerves may also play a role in the development of fatigue. The vagal nerve comprises a large proportion of afferent fibers that communicate signals from the viscera to the brain stem, and it supplies efferent parasympathetic fibers to visceral organs such as the heart and stomach. The vagal afferent nerve hypothesis proposes that cancer and/or its treatment causes a peripheral release of neuroactive agents that activate vagal afferent nerves, leading to suppression of somatic muscle activity and induction of "sickness behavior."

Several animal studies have provided evidence of a vagosomatic inhibitory reflex. The earliest report of such an effect was by Schweitzer and Wright [109], who showed that electrical stimulation of the central terminus of the vagal nerve in cats was associated with a reduction in the knee-jerk reflex. Subsequent animal studies showed that activation of vagal afferent nerves to the lungs or to the abdomen caused reflex inhibition of somatomotor activity, including reflex activation of skeletal muscles and exercise-induced electromyogram activity [110–116]. Other studies have shown that a variety of substances, such as 5-HT, cytokines, and prostaglandins, can stimulate vagal afferent nerves [117–120]. The purpose of the abdominal vagal afferent suppression of somatic muscle activity is unknown;

however, evidence suggests that the function of pulmonary afferent suppression is to limit exercise when pulmonary congestion occurs [114,121,122]. The existence of a vagosomatic inhibitory reflex has yet to be confirmed in humans but, if present, the resultant decrease in skeletal muscle tone would be perceived as a general weakness (i.e., an inability to complete a motor task or a feeling that greater effort was needed than usually required or expected) [15].

Vagal afferent nerves may also mediate the induction of "sickness behavior" by peripheral cytokines. Cytokine-induced "sickness behavior" occurs in response to infection and includes symptoms such as fatigue, increased sleep, malaise, listlessness, inability to concentrate, subjective feelings of poor memory, fever, and decreased appetite. Animal studies have shown that "sickness syndrome" can be induced by intraperitoneal injection of lipopolysaccharide or IL-1β [123–126]. Further animal studies have shown that the vagal nerve mediates induction of IL-1β production in the brain stem, hippocampus, and hypothalamus in response to intraperitoneal injections of IL-1β [127]. Given the potential involvement of the HPA axis in the genesis of fatigue, induction of cytokines in the hypothalamus is of particular interest. One might hypothesize that CRF is a result of a reflex inhibition of skeletal muscle activity caused by the secretion of proinflammatory cytokines and/or 5-HT in peripheral areas where vagal afferent nerves terminate. How vagal afferent activation might contribute to the long-term persistence of CRF is unclear.

Cytokine Dysregulation

Proinflammatory cytokines, such as TNF-α and IL-1β, are implicated in many of the mechanisms proposed for the etiology of fatigue associated with cancer and various illnesses [56]. Experimental or therapeutic administration of proinflammatory cytokines is known to induce "sickness behavior" [128–133]. In particular, TNF has been shown to be associated with alterations in CNS neurotransmission, leading to behavioral changes such as lethargy and anorexia [134]. IFN-α, which is used in the treatment of a number of malignancies, is also associated with fatigue [135,136].

Cancer and its treatment (chemotherapy, surgery, radiotherapy, biologic therapies) are associated with increases in plasma levels of cytokines, especially TNF-α, IL-1β, and IL-6 [137–140]. One published clinical study has examined possible correlations between serum cytokine levels and fatigue in patients with cancer [141]. No correlation was found between IL-6, IL-1β, or TNF-α and fatigue, even though a correlation between IL-6 levels and flu-like symptoms was observed in patients with breast cancer undergoing chemotherapy with paclitaxel. In that study, measurements were made at only three time points during one treatment cycle, rather than at regular intervals throughout the cycle, which could explain the lack of correlation between serum cytokine levels and fatigue. Support for the role of cytokines in the etiology of fatigue comes from reports of elevated TNF-α and IL-6 levels in patients with chronic fatigue syndrome [129,142,143]. Furthermore, monoclonal antibody treatment to block proinflammatory cytokine activity has been shown to ameliorate fatigue associated with Castleman's disease and rheumatoid arthritis, and could serve as a new intervention for CRF [144–146].

Contribution of Comorbid Conditions Associated with Cancer-Related Fatigue

CRF often occurs as part of a cluster of symptoms and is accompanied by conditions that are likely to contribute to the development of fatigue. The most common of these symptoms include anemia, cachexia, depression, and sleep disorders.

Anemia

Anemia (a hemoglobin level of <12 g/dl) may occur as a result of either neoplastic disease or cancer treatment. It is identified by the National Comprehensive Cancer Network as one of the treatable factors that may contribute to CRF [3]. The incidence of anemia in patients with cancer varies by type, stage, and duration of the disease and its treatment [147]. Although occurring less frequently than fatigue, anemia is a common complication of myelosuppressive chemotherapy [147]. On average, over one third of patients become anemic after three cycles of chemotherapy [148]. The cause of anemia associated with cancer is multifactorial. Bleeding, hemolysis, bone marrow infiltration, and nutritional deficiencies may all contribute to the development of anemia in patients with cancer. In addition, inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IFN-γ, inhibit erythropoiesis, which leads to decreased production of erythrocytes, resulting in anemia and fatigue [149–151].

Many studies have demonstrated a relationship between anemia and fatigue [148,152–155]. Hemoglobin function may be altered by changes in the membrane transport characteristics of erythrocytes, such as changes in potassium, chloride, and magnesium ion fluxes, in response to neoplastic disease or cancer therapy. Support for this hypothesis comes from the fact that the lifespan of erythrocytes is reduced in cancer-related anemia [156] and from evidence that erythrocyte magnesium levels may play a role in chronic fatigue syndrome [157]. The mechanism by which anemia or hemoglobin dysfunction might cause fatigue in patients with cancer is unknown; however, hypoxia-related impairment of organ function has been suggested [158].

Cachexia

Cachexia is a wasting disease that involves loss of both adipose tissue and skeletal muscle mass, leading to anorexia, weight loss, fatigue, impaired function, and shortened survival time. Cancer cachexia is common, affecting approximately 50% of all patients with cancer and up to 85% of patients with certain cancers, such as gastric and pancreatic cancer [159,160]. The etiology of cancer cachexia is complex and involves not only a reduction in nutrient intake, but also tumor-induced metabolic alterations, including protein catabolism and reduced protein synthesis in skeletal muscle. The tissue catabolism occurring in cachexia is thought to be mediated by cytokines (TNF-α and IL-6) [161–163] and tumor catabolic products, such as lipid-mobilizing factor and proteolysis-inducing factor [162]. Proinflammatory cytokines may also induce the release of CRH, which has a powerful anorexigenic effect [164]. Potential therapies aimed at preventing skeletal muscle wasting, such as anticatabolic agents, may help alleviate CRF.

Depression

Though less prevalent than fatigue, depression is common in patients with cancer. Many studies have reported strong correlations between the incidence of depression and fatigue in patients with cancer [128,132,165–170]. Some evidence suggests a common etiology for depression and fatigue. For example, depression is known to be a predisposing factor for the development of chronic fatigue syndrome [171]. In contrast, other investigators have concluded that CRF and depression are independent conditions with patterns that differ over time. In a study of patients undergoing radiotherapy, fatigue was found to increase over the course of treatment, whereas depression decreased [172]. Neither condition was found to be predictive of the other. As previously discussed, several investigations have noted distinctions between depression and fatigue with regard to disrupted rest–activity rhythms [96], 5-HT dysfunction [40,41], and altered HPA-axis activity [65,66]. Hence, it is currently unclear whether fatigue and depression arise through a common pathway.

Sleep Disorders

Strong correlations have been reported between fatigue and sleep disorders in patients with cancer [90]. Sleep disorders may arise via several of the mechanisms discussed above, including HPA-axis and circadian rhythm disruption, serotonin metabolism alterations, and changes in cytokine expression. The HPA axis plays a key role in the regulation of sleep. Likewise, CRH may affect several aspects of sleep, including depth of sleep, slow-wave sleep, rapid eye movement (REM) sleep, and waking. Studies in both humans and animals have shown that CRH increases electroencephalograph frequency and decreases slow-wave sleep, resulting in lighter sleep and greater wakefulness [173,174]. In healthy individuals, excess cortisol reduces REM sleep. However, results from studies in patients with Addison's disease have suggested that some degree of cortisol secretion is necessary to initiate and maintain REM sleep [81,175]. CRH is also associated with waking, suggesting that sleeping and waking depend on a balance between endogenous cortisol levels and CRH suppression [176].

As previously mentioned, dysregulation of HPA-axis function and cortisol release have been linked with sleep disorders. Cancer therapy has also been associated with dysregulation of the HPA axis and hypocortisolemia. For example, patients with breast cancer receiving chemotherapy show significant differences in cortisol, melatonin, and serotonin levels compared with both disease-free individuals and patients with cancer who are not receiving treatment [177,178]. Furthermore, there is considerable evidence supporting the involvement of cytokines in sleep disorders. Several studies have demonstrated that the cytokines TNF-α and IL-6 are elevated in disorders associated with excessive daytime sleepiness, such as sleep apnea, narcolepsy, and idiopathic hypersomnia [81,179,180]. Overexpression of cytokines, including IL-1, IL-6, and TNF-α, by cancer cells and as part of the immunologic response has been demonstrated in patients with cancer and in their response to cancer therapy [181]. Similarly, there is evidence supporting the involvement of IL-6 and TNF-α in the development of fatigue. This emerging area of research connecting sleep disorders with CRF is discussed in greater depth in an accompanying article [90].

Summary

The etiology of CRF is multifactorial and most likely involves the dysregulation of several interrelated physiological, biochemical, and psychological systems, thus presenting considerable challenges for patients, researchers, and clinicians. The disorder, or combination of disorders, causing CRF may differ among individuals, phases of disease, and types of treatment. Several mechanisms for the development of CRF have been proposed, which may aid in the development of therapies to combat this debilitating symptom. Future research needs to focus on understanding the interrelationships among the various cancer-related symptoms and the similarities and differences in fatigue experienced in different conditions.

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Disclosure of Potential Conflicts of Interest

G.R.M. has acted as a consultant for MGI Pharma and Cephalon.

References

1 Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. Support Care Cancer 1996;4:82–96.

2 Morrow GR, Shelke AR, Roscoe JA et al. Management of cancer-related fatigue. Cancer Invest 2005;23:229–239.

3 Mock V, Atkinson A, Barsevick A et al. NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology (Williston Park) 2000;14:151–161.

4 Watson T, Mock V. Exercise as an intervention for cancer-related fatigue. Phys Ther 2004;84:736–743.

5 Cella D, Davis K, Breitbart W et al. Cancer-related fatigue: Prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol 2001;19:3385–3391.

6 Ahlberg K, Ekman T, Gaston-Johansson F et al. Assessment and management of cancer-related fatigue in adults. Lancet 2003;362:640–650.

7 Newsholme EA. Application of principles of metabolic control to the problem of metabolic limitations in sprinting, middle-distance, and marathon running. Int J Sports Med 1986;7(suppl 1):66–70.

8 Ronnback L, Hansson E. On the potential of glutamate transport in mental fatigue. J Neuroinflammation 2004;1:22.

9 Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001;81:1725–1789.

10 Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004;363:978–988.

11 Chaudhuri A, Behan PO. Fatigue and basal ganglia. J Neurol Sci 2000;179:34–42.

12 Okada T, Tanaka M, Kuratsune H et al. Mechanisms underlying fatigue: A voxel-based morphometric study of chronic fatigue syndrome. BMC Neurol 2004;4:14.

13 Enoka RM, Stuart G. Neurobiology of muscle fatigue. J Appl Physiol 1992;72:1631–1648.

14 McCloskey DI. Kinesthetic sensibility. Physiol Rev 1978;58:763–820.

15 Andrews PLR, Morrow GR, Hickok JT et al. Mechanisms and models of fatigue associated with cancer and its treatment: Evidence of pre-clinical and clinical studies. In: Armes J, Krishnasamy M, Higginson I, eds. Fatigue in Cancer. Oxford: Oxford University Press, 2004:51–87.

16 Newsholme EA, Acworth IN, Blomstrand E. Amino acids, brain neurotransmitters and a functional link between muscle and brain that is important in sustained exercise. In: Benzi G, ed. Advances in Myochemistry. London: John Libbey Eurotext, 1987:127–133.

17 Davis JM, Bailey SP. Possible mechanisms of central nervous system fatigue during exercise. Med Sci Sports Exerc 1997;29:45–57.

18 Fernstrom JD, Fernstrom MH. Exercise, serum free tryptophan, and central fatigue. J Nutr 2006;136(suppl):553S–559S.

19 Badawy AA, Morgan CJ, Llewelyn MB et al. Heterogeneity of serum tryptophan concentration and availability to the brain in patients with the chronic fatigue syndrome. J Psychopharmacol 2005;19:385–391.

20 Castell LM, Yamamoto T, Phoenix J et al. The role of tryptophan in fatigue in different conditions of stress. Adv Exp Med Biol 1999;467:697–704.

21 Blomstrand E, Perrett D, Parry-Billings M et al. Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat. Acta Physiol Scand 1989;136:473–481.

22 Blomstrand E. A role for branched-chain amino acids in reducing central fatigue. J Nutr 2006;136(suppl):544S–547S.

23 Newsholme EA, Blomstrand E. Tryptophan, 5-hydroxytryptamine and a possible explanation for central fatigue. Adv Exp Med Biol 1995;384:315–320.

24 Newsholme EA, Blomstrand E. Branched-chain amino acids and central fatigue. J Nutr 2006;136(1 suppl):274S–276S.

25 Chaouloff F, Elghozi JL, Guezennec Y et al. Effects of conditioned running on plasma, liver and brain tryptophan and on brain 5-hydroxytryptamine metabolism of the rat. Br J Pharmacol 1985;86:33–41.

26 Bailey SP, Davis JM, Ahlborn EN. Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. J Appl Physiol 1993;74:3006–3012.

27 Blomstrand E, Hassmen P, Newsholme EA. Effect of branched-chain amino acid supplementation on mental performance. Acta Physiol Scand 1991;143:225–226.

28 Blomstrand E, Hassmen P, Ekblom B et al. Administration of branched-chain amino acids during sustained exercise – effects on performance and on plasma concentration of some amino acids. Eur J Appl Physiol Occup Physiol 1991;63:83–88.

29 Blomstrand E, Hassmen P, Ek S et al. Influence of ingesting a solution of branched-chain amino acids on perceived exertion during exercise. Acta Physiol Scand 1997;159:41–49.

30 Mittleman KD, Ricci MR, Bailey SP. Branched-chain amino acids prolong exercise during heat stress in men and women. Med Sci Sports Exerc 1998;30:83–91.

31 Cheuvront SN, Carter R 3rd, Kolka MA et al. Branched-chain amino acid supplementation and human performance when hypohydrated in the heat. J Appl Physiol 2004;97:1275–1282.

32 Davis JM, Welsh RS, De Volve KL et al. Effects of branched-chain amino acids and carbohydrate on fatigue during intermittent, high-intensity running. Int J Sports Med 1999;20:309–314.

33 Struder HK, Hollmann W, Platen P et al. Influence of paroxetine, branched-chain amino acids and tyrosine on neuroendocrine system responses and fatigue in humans. Horm Metab Res 1998;30:188–194.

34 van Hall G, Raaymakers JS, Saris WH et al. Ingestion of branched-chain amino acids and tryptophan during sustained exercise in man: Failure to affect performance. J Physiol 1995;486:789–794.

35 Watson P, Shirreffs SM, Maughan RJ. The effect of acute branched-chain amino acid supplementation on prolonged exercise capacity in a warm environment. Eur J Appl Physiol 2004;93:306–314.

36 Bailey SP, Davis JM, Ahlborn EN. Effect of increased brain serotonergic activity on endurance performance in the rat. Acta Physiol Scand 1992;145:75–76.

37 Wilson WM, Maughan RJ. Evidence for a possible role of 5-hydroxytryptamine in the genesis of fatigue in man: Administration of paroxetine, a 5-HT re-uptake inhibitor, reduces the capacity to perform prolonged exercise. Exp Physiol 1992;77:921–924.

38 Davis JM, Bailey SP, Jackson DA et al. Effects of a serotonin (5-HT) agonist during prolonged exercise to fatigue in humans. Med Sci Sports Exerc 1993;25:S78.

39 Strachan AT, Leiper JB, Maughan RJ. Paroxetine administration failed [corrected] to influence human exercise capacity, perceived effort or hormone responses during prolonged exercise in a warm environment. Exp Physiol 2004;89:657–664.

40 Morrow GR, Hickok JT, Roscoe JA et al. Differential effects of paroxetine on fatigue and depression: A randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. J Clin Oncol 2003;21:4635–4641.

41 Roscoe JA, Morrow GR, Hickok JT et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 2005;89:243–249.

42 Bakheit AM, Behan PO, Dinan TG et al. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. BMJ 1992;304:1010–1012.

43 Cleare AJ, Bearn J, Allain T et al. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. J Affect Disord 1995;34:283–289.

44 Sharpe M, Hawton K, Clements A et al. Increased brain serotonin function in men with chronic fatigue syndrome. BMJ 1997;315:164–165.

45 Cleare AJ, Messa C, Rabiner EA et al. Brain 5-HT_{1A} receptor binding in chronic fatigue syndrome measured using positron emission tomography and [^{11}C]WAY-100635. Biol Psychiatry 2005;57:239–246.

46 Dinan TG, Majeed T, Lavelle E et al. Blunted serotonin-mediated activation of the hypothalamic–pituitary–adrenal axis in chronic fatigue syndrome. Psychoneuroendocrinology 1997;22:261–267.

47 Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. Endocr Rev 2003;24:236–252.

48 Drapkin R, Barolo JL, Blower PR. Effect of granisetron on performance status during high-dose interferon therapy. Oncology 1999;57:303–305.

49 Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. Lancet 1999;354:397.

50 Spath M, Welzel D, Farber L. Treatment of chronic fatigue syndrome with 5-HT_3 receptor antagonists – preliminary results. Scand J Rheumatol Suppl 2000;113:72–77.

51 The GK, Prins J, Bleijenberg G et al. The effect of granisetron, a 5-HT_3 receptor antagonist, in the treatment of chronic fatigue syndrome patients—a pilot study. Neth J Med 2003;61:285–289.

52 Morrow GR, Andrews PLR, Hickok JT et al. Fatigue associated with cancer and its treatment. Support Care Cancer 2002;10:389–398.

53 Clement HW, Buschmann J, Rex S et al. Effects of interferon-gamma, interleukin-1 beta, and tumor necrosis factor-alpha on the serotonin metabolism in the nucleus raphe dorsalis of the rat. J Neural Transm 1997;104:981–991.

54 Mossner R, Heils A, Stober G et al. Enhancement of serotonin transporter function by tumor necrosis factor alpha but not by interleukin-6. Neurochem Int 1998;33:251–254.

55 Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology 2006;31:2121–2131.

56 Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: Mechanisms and implications. Trends Neurosci 2002;25:154–159.

57 Wichers M, Maes M. The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. Int J Neuropsychopharmacol 2002;5:375–388.

58 Aguilera G. Regulation of pituitary ACTH secretion during chronic stress. Front Neuroendocrinol 1994;15:321–350.

59 Chappell PB, Smith MA, Kilts CD et al. Alterations in corticotropin-releasing factor-like immunoreactivity in discrete rat brain regions after acute and chronic stress. J Neurosci 1986;6:2908–2914.

60 Imaki T, Nahan J-L, Rivier C et al. Differential regulation of corticotrophin-releasing factor mRNA in rat brain regions by glucocorticoids and stress. J Neurosci 1991;11:585–599.

61 Shanks N, Harbuz MS, Jessop DS et al. Inflammatory disease as chronic stress. Ann N Y Acad Sci 1998;840:599–607.

62 Harbuz MS, Rees RG, Eckland D et al. Paradoxical responses of hypothalamic corticotropin-releasing factor messenger ribonucleic acid (mRNA) and CRF-41 peptide and adenohypophysial proopiomelanocortin mRNA during chronic inflammatory stress. Endocrinology 1992;130:1394–1400.

63 Swain MG, Maric M. Defective corticotropin-releasing hormone mediated neuroendocrine and behavioral responses in cholestatic rats: Implications for cholestatic liver disease-related sickness behaviors. Hepatology 1995;22:1560–1564.

64 Swain MG, Patchev V, Vergalla J et al. Suppression of hypothalamic–pituitary–adrenal axis responsiveness to stress in a rat model of acute cholestasis. J Clin Invest 1993;91:1903–1908.

65 Duval F, Mokrani MC, Monreal-Ortiz JA et al. Cortisol hypersecretion in unipolar major depression with melancholic and psychotic features: Dopaminergic, noradrenergic and thyroid correlates. Psychoneuroendocrinology 2006;31:876–888.

66 Maes M, Lin A, Bonaccorso S et al. Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder and patients with major depression, but not in patients with fibromyalgia. Acta Psychiatr Scand 1998;98:328–335.

67 Cleare AJ, Miell J, Heap E et al. Hypothalamo–pituitary–adrenal axis dysfunction in chronic fatigue syndrome, and the effects of low-dose hydrocortisone therapy. J Clin Endocrinol Metab 2001;86:3545–3554.

68 Demitrack MA, Dale JK, Straus SE et al. Evidence for impaired activation of the hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab 1991;73:1224–1234.

69 Scott LV, Medbak S, Dinan TG. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. Acta Psychiatr Scand 1998;97:450–457.

70 Bower JE, Ganz PA, Aziz N et al. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002;64:604–611.

71 Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom Med 2005;67:277–280.

72 Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993;28:76–81.

73 Bower JE, Ganz PA, Dickerson SS et al. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology 2005;30:92–100.

74 Lundström S, Fürst CJ. Symptoms in advanced cancer: Relationship to endogenous cortisol levels. Palliat Med 2003;17:503–508.

75 Chaouloff F. Physiopharmacological interactions between stress hormones and central serotonergic systems. Brain Res Brain Res Rev 1993;18:1–32.

76 Del Priore G, Gurski KJ, Warshal DP et al. Adrenal function following high-dose steroids in ovarian cancer patients. Gynecol Oncol 1995;59:102–104.

77 Morrow GR, Hickok JT, Andrews PL et al. Reduction in serum cortisol after platinum based chemotherapy for cancer: A role for the HPA axis in treatment-related nausea? Psychophysiology 2002;39: 491–495.

78 Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK et al. Assessment of the hypothalamo–pituitary–adrenal axis in patients treated with radiotherapy and chemotherapy for childhood brain tumor. J Clin Endocrinol Metab 2003;88:3149–3154.

79 McEwen BS, Biron CA, Brunson KW et al. The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine and immune interactions. Brain Res Brain Res Rev 1997;23: 79–133.

80 Petrovsky N, McNair P, Harrison LC. Diurnal rhythms of pro-inflammatory cytokines: Regulation by plasma cortisol and therapeutic implications. Cytokine 1998;10:307–312.

81 Vgontzas AN, Chrousos GP. Sleep, the hypothalamic–pituitary–adrenal axis, and cytokines: Multiple interactions and disturbances in sleep disorders. Endocrinol Metab Clin North Am 2002;31:15–36.

82 Focan C, Focan-Henrard D, Collette J et al. Cancer-associated alteration of circadian rhythms in carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) in humans. Anticancer Res 1986;6:1137–1144.

83 Levin RD, Daehler MA, Grutsch JF et al. Circadian function in patients with advanced non-small-cell lung cancer. Br J Cancer 2005;93: 1202–1208.

84 Mormont MC, Levi F. Circadian-system alterations during cancer processes: A review. Int J Cancer 1997;70:241–247.

85 Mormont MC, De Prins J, Levi F. [Study of circadian rhythms of activity by actometry: Preliminary results in 30 patients with metastatic colorectal cancer.] Pathol Biol (Paris) 1996;44:165–171. French.

86 Sephton S, Spiegel D. Circadian disruption in cancer: A neuroendocrine-immune pathway from stress to disease? Brain Behav Immun 2003;17:321–328.

87 Singh R, Singh RK, Mahdi AA et al. Studies on circadian periodicity of urinary corticoids in carcinoma of the breast. In Vivo 1998;12:69–73.

88 Touitou Y, Levi F, Bogdan A et al. Rhythm alteration in patients with metastatic breast cancer and poor prognostic factors. J Cancer Res Clin Oncol 1995;121:181–188.

89 Touitou Y, Bogdan A, Levi F et al. Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: Relationships with tumour marker antigens. Br J Cancer 1996;74:1248–1252.

90 Roscoe JA, Kaufman ME, Matteson-Rusby SE et al. Cancer-related fatigue and sleep disorders. ***The Oncologist*** 2007;12(suppl 1):35–42.

91 Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. Oncol Nurs Forum 1998;25:51–62.

92 Mormont MC, Hecquet B, Bogdan A et al. Non-invasive estimation of the circadian rhythm in serum cortisol in patients with ovarian or colorectal cancer. Int J Cancer 1998;78:421–424.

93 Mormont MC, Waterhouse J. Contribution of the rest–activity circadian rhythm to quality of life in cancer patients. Chronobiol Int 2002;19: 313–323.

94 Mormont MC, Waterhouse J, Bleuzen P et al. Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. Clin Cancer Res 2000;6:3038–3045.

95 Rich T, Innominato PF, Boerner J et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest–activity patterns in patients with metastatic colorectal cancer. Clin Cancer Res 2005;11:1757–1764.

96 Roscoe JA, Morrow GR, Hickok JT et al. Temporal interrelationships among fatigue, circadian rhythm and depression in breast cancer patients undergoing chemotherapy treatment. Support Care Cancer 2002;10: 329–336.

97 Kronfol Z, Nair M, Zhang Q et al. Circadian immune measures in healthy volunteers: Relationship to hypothalamic–pituitary–adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med 1997;59: 42–50.

98 Sephton SE, Sapolsky RM, Kraemer HC et al. Diurnal cortisol rhythm as a predictor of breast cancer survival. J Natl Cancer Inst 2000;92: 994–1000.

99 Brown DJ, McMillan DC, Milroy R. The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer. Cancer 2005;103:377–382.

100 Lee JQ, Simmonds MJ, Wang XS et al. Differences in physical performance between men and women with and without lymphoma. Arch Phys Med Rehabil 2003;84:1747–1752.

101 McCully KK, Natelson BH, Iotti S et al. Reduced oxidative muscle metabolism in chronic fatigue syndrome. Muscle Nerve 1996;19:621–625.

102 Forsyth LM, Preuss HG, MacDowell AL et al. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. Ann Allergy Asthma Immunol 1999;82:185–191.

103 Lane RJ, Barrett MC, Taylor DJ et al. Heterogeneity in chronic fatigue syndrome: Evidence from magnetic resonance spectroscopy of muscle. Neuromuscul Disord 1998;8:204–209.

104 Pastoris O, Aquilani R, Foppa P et al. Altered muscle energy metabolism in post-absorptive patients with chronic renal failure. Scand J Urol Nephrol 1997;31:281–287.

105 Collins P, Bing C, McCulloch P et al. Muscle UCP-3 mRNA levels are elevated in weight loss associated with gastrointestinal adenocarcinoma in humans. Br J Cancer 2002;86:372–375.

106 Isaksson B, Rippe C, Simonoska R et al. Obstructive jaundice results in increased liver expression of uncoupling protein 2 and intact skeletal muscle glucose metabolism in the rat. Scand J Gastroenterol 2002;37: 104–111.

107 Giordano A, Calvani M, Petillo O et al. Skeletal muscle metabolism in physiology and in cancer disease. J Cell Biochem 2003;90:170–186.

108 Agteresch HJ, Dagnelie PC, van der Gaast A et al. Randomized clinical trial of adenosine 5′-triphosphate in patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000;92:321–328.

109 Schweitzer A, Wright S. The anti-strychnine action of acetylcholine, prostigmine and related substances, and of central vagus stimulation. J Physiol 1937;90:310–329.

110 Coleridge JC, Coleridge HM. Afferent vagal C fibre innervation of the lungs and airways and its functional significance. Rev Physiol Biochem Pharmacol 1984;99:1–110.

111 DiCarlo SE, Collins HL, Chen C-Y. Vagal afferents reflexly inhibit exercise in conscious rats. Med Sci Sports Exerc 1994;26:459–462.

112 Kalia M. Effects of certain cerebral lesions on the J reflex. Pflugers Arch 1973;343:297–308.

113 Kawasaki K, Kodama M, Matsushita A. Caerulein, a cholecystokinin-related peptide, depresses somatic function via the vagal afferent system. Life Sci 1983;33:1045–1050.

114 Paintal AS. Vagal sensory receptors and their reflex effects. Physiol Rev 1973;53:159–227.

115 Pickar JG, Hill JM, Kaufman MP. Stimulation of vagal afferents inhibits locomotion in mesencephalic cats. J Appl Physiol 1993;74:103–110.

116 Pickar JG. The thromoboxane A_2 mimetic U-46619 inhibits somatomotor activity via a vagal reflex from the lung. Am J Physiol 1998;275: R706–R712.

117 Blackshaw LA, Grundy D. Effects of 5-hydroxytryptamine on discharge of vagal mucosal afferent fibres from the upper gastrointestinal tract of the ferret. J Auton Nerv Syst 1993;45:41–50.

118 Blackshaw LA, Grundy D. Effects of 5-hydroxytryptamine (5-HT) on the discharge of vagal mechanoreceptors and motility in the upper gastrointestinal tract of the ferret. J Auton Nerv Syst 1993;45:51–59.

119 Ek M, Kurosawa M, Lundeberg T et al. Activation of vagal afferents after intravenous injection of interleukin-1β: Role of endogenous prostaglandins. J Neurosci 1998;18:9471–9479.

120 Niijima A. The afferent discharges from sensors for interleukin-1β in the hepatoportal system in the anaesthetized rat. J Auton Nerv Syst 1996;61:287–291.

121 Davies SF, McQuaid KR, Iber C et al. Extreme dyspnea from unilateral pulmonary venous obstruction. Demonstration of a vagal mechanism and relief by right vagotomy. Am Rev Respir Dis 1987;136:184–188.

122 Paintal AS. Sensations from J receptors. News Physiol Sci 1995;10:238–243.

123 Hansen MK, Krueger JM. Subdiaphragmatic vagotomy blocks the sleep- and fever-promoting effects of interleukin-1β. Am J Physiol 1997;273: R1246–R1253.

124 Johnson DR, O'Connor JC, Dantzer R et al. Inhibition of vagally mediated immune-to-brain signaling by vanadyl sulfate speeds recovery from sickness. Proc Natl Acad Sci U S A 2005;102:15184–15189.

125 Kapas L, Hansen MK, Chang HY et al. Vagotomy attenuates but does not prevent the somnogenic and febrile effects of lipopolysaccharide in rats. Am J Physiol 1998;274:R406–R411.

126 Opp MR, Toth LA. Somnogenic and pyrogenic effects of interleukin-1β and lipopolysaccharide in intact and vagotomized rats. Life Sci 1998;62:923–936.

127 Hansen MK, Taishi P, Chen Z et al. Vagotomy blocks the induction of interleukin-1β (IL-1β) mRNA in the brain of rats in response to systemic IL-1β. J Neurosci 1998;18:2247–2253.

128 Blesch KS, Paice JA, Wickham R et al. Correlates of fatigue in people with breast or lung cancer. Oncol Nurs Forum 1991;18:81–87.

129 Borish L, Schmaling K, DiClementi JD et al. Chronic fatigue syndrome: Identification of distinct subgroups on the basis of allergy and psychologic variables. J Allergy Clin Immunol 1998;102:222–230.

130 Holmes GP, Kaplan JE, Gantz NM et al. Chronic fatigue syndrome: A working case definition. Ann Intern Med 1988;108:387–389.

131 Moldawer NP, Figlin RA. Tumor necrosis factor: Current clinical status and implications for nursing management. Semin Oncol Nurs 1988;4:120–125.

132 Piper BF, Lindsey AM, Dodd MJ et al. The development of an instrument to measure the subjective dimension of fatigue. In: Funk SG, Tornquist EM, Champagne MT et al., eds. Key Aspects of Comfort: Management of Pain, Fatigue, and Nausea. New York: Springer, 1989:199–208.

133 Winningham ML, Nail LM, Burke MB et al. Fatigue and the cancer experience: The state of the knowledge. Oncol Nurs Forum 1994;21:23–36.

134 Benzing T, Brandes R, Sellin L et al. Upregulation of RGS_7 may contribute to tumor necrosis factor-induced changes in central nervous function. Nat Med 1999;5:913–918.

135 Capuron L, Gumnick JF, Musselman DL et al. Neurobehavioral effects of interferon-alpha in cancer patients: Phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 2002;26:643–652.

136 Raison CL, Demetrashvili M, Capuron L et al. Neuropsychiatric adverse effects of interferon-α: Recognition and management. CNS Drugs 2005;19:105–123.

137 Bianco JA, Appelbaum FR, Nemunaitis J et al. Phase I–II trial of pentoxifylline for the prevention of transplant-related toxicities following bone marrow transplantation. Blood 1991;78:1205–1211.

138 Greenberg DB, Gray JL, Mannix CM et al. Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. J Pain Symptom Manage 1993;8:196–200.

139 Hallahan DE, Haimovitz-Friedman A, Kufe DW et al. The role of cytokines in radiation oncology. In: DeVita VT, Hellman S, Rosenberg SA, eds. Important Advances in Oncology. Philadelphia: Lippincott, 1993:71–80.

140 Hong JH, Chiang CS, Campbell IL et al. Induction of acute phase gene expression by brain irradiation. Int J Radiat Oncol Biol Phys 1995;33:619–626.

141 Pusztai L, Mendoza TR, Reuben JM et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. Cytokine 2004;25:94–102.

142 Chao CC, Gallagher M, Phair J et al. Serum neopterin and interleukin-6 levels in chronic fatigue syndrome. J Infect Dis 1990;162:1412–1413.

143 Patarca R, Klimas NG, Lugtendorf S et al. Dysregulated expression of tumor necrosis factor in chronic fatigue syndrome: Interrelations with cellular sources and patterns of soluble immune mediator expression. Clin Infect Dis 1994;18(suppl 1):S147–S153.

144 Nishimoto N, Kanakura Y, Aozasa K et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005;106:2627–2632.

145 Omdal R, Gunnarsson R. The effect of interleukin-1 blockade on fatigue in rheumatoid arthritis—a pilot study. Rheumatol Int 2005;25:481–484.

146 Weinblatt ME, Keystone EC, Furst DE et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial. Arthritis Rheum 2003;48:35–45.

147 Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: Incidence and treatment. J Natl Cancer Inst 1999;91:1616–1634.

148 Glaspy J, Degos L, Dicato M et al. Comparable efficacy of epoetin alfa for anemic cancer patients receiving platinum- and nonplatinum-based chemotherapy: A retrospective subanalysis of two large, community-based trials. ***The Oncologist*** 2002;7:126–135.

149 Dicato M. Anemia in cancer: Some pathophysiological aspects. ***The Oncologist*** 2003;8(suppl 1):19–21.

150 Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. Blood 1992;79:1987–1994.

151 Jelkmann W, Wolff M, Fandrey J. Modulation of the production of erythropoietin by cytokines: In vitro studies and their clinical implications. Contrib Nephrol 1990;87:68–77.

152 Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: A new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol 1997;34(suppl 2):13–19.

153 Demetri GD, Kris M, Wade J et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: Results from a prospective community oncology study. Procrit Study Group. J Clin Oncol 1998;16:3412–3425.

154 Littlewood TJ, Bajetta E, Nortier JW et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001;19:2865–2874.

155 Yellen SB, Cella DF, Webster K et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63–74.

156 Bron D. Biological basis of cancer-related anaemia. In: Marty M, Pecorelli S, eds. Fatigue and Cancer. European School of Oncology Scientific Updates, 5. Amsterdam: Elsevier, 2001:45–50.

157 Cox IM, Campbell MJ, Dowson D. Red blood cell magnesium and chronic fatigue syndrome. Lancet 1991;337:757–760.

158 Mercuriali F, Inghilleri G. Treatment of anaemia in cancer patients: Transfusion of rHuEPO. In: Marty M, Pecorelli S, eds. Fatigue and Cancer. European School of Oncology Scientific Updates, 5. Amsterdam: Elsevier, 2001:185–200.

159 DeWys WD, Begg C, Lavin PT et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980;69:491–497.

160 Tisdale MJ. Wasting in cancer. J Nutr 1999;129(suppl 1S):243S–246S.

161 Argiles JM, Busquets S, Lopez-Soriano FJ. Cytokines as mediators and targets for cancer cachexia. Cancer Treat Res 2006;130:199–217.

162 Tisdale MJ. Biology of cachexia. J Natl Cancer Inst 1997;89:1763–1773.

163 Tisdale MJ. Molecular pathways leading to cancer cachexia. Physiology (Bethesda) 2005;20:340–348.

164 Connan F, Lightman SL, Landau S et al. An investigation of hypothalamic–pituitary–adrenal axis hyperactivity in anorexia nervosa: The role of CRH and AVP. J Psychiatr Res 2007;41:131–143.

165 Bower JE, Ganz PA, Desmond KA et al. Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18:743–753.

166 Jacobsen PB, Hann DM, Azzarello LM et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: Characteristics, course, and correlates. J Pain Symptom Manage 1999;18:233–242.

167 Jacobsen PB, Stein K. Is fatigue a long-term side effect of breast cancer treatment? Cancer Control 1999;6:256–263.

168 Jamar SC. Fatigue in women receiving chemotherapy for ovarian cancer. In: Funk SG, Tournquist EM, Champagne MT et al., eds. Key Aspects of Comfort: Management of Pain, Fatigue and Nausea. New York: Springer, 1989:224–228.

169 Morrow GR, Pandya K, Barry M et al. Chemotherapy-induced fatigue and patient-reported psychological depression. Proc Am Soc Clin Oncol 1992;11:383.

170 Jacobsen PB, Donovan KA, Weitzner MA. Distinguishing fatigue and depression in patients with cancer. Semin Clin Neuropsychiatry 2003;8:229–240.

171 Wessely S, Hotopf M, Sharpe MC. Chronic Fatigue and Its Syndromes. New York: Oxford University Press, Inc., 1999:1–456.

172 Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: How are they related? Support Care Cancer 1998;6:101–108.

173 Ehlers CL, Reed TK, Henriksen SJ. Effects of corticotrophin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. Neuroendocrinology 1986;42:467–474.

174 Holsboer F, von Bardeleben U, Steiger A. Effects of intravenous corticotropin-releasing hormone upon sleep-related growth hormone surge and sleep EEG in man. Neuroendocrinology 1988;48:32–38.

175 Friess E, Tagaya H, Grethe C et al. Acute cortical administration promotes sleep intensity in man. Neuropsychopharmacology 2004;29:598–604.

176 Chang FC, Opp MR. Corticotropin-releasing hormone (CRH) as a regulator of waking. Neurosci Biobehav Rev 2001;25:445–453.

177 Payne JK. The trajectory of fatigue in adult patients with breast and ovarian cancer receiving chemotherapy. Oncol Nurs Forum 2002;29:1334–1340.

178 Payne J, Piper B, Rabinowitz I et al. Biomarkers, sleep and fatigue characteristics in women with breast cancer. Proceedings of the Seventh National Conference on Cancer Nursing Research, 2003.

179 Maier SF, Watkins LR. Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev 1998;105:83–107.

180 Vgontzas AN, Papanicolaou DA, Bixler EO et al. Evidence of corticotrophin-releasing hormone (CRH) deficiency in patients with idiopathic hypersomnia: Clinical and pathophysiological implications. Presented at the 79th Endocrine Society Meeting, Minneapolis, MN, June 11–14, 1997.

181 Kurzrock R. Cytokine deregulation in cancer. Biomed Pharmacother 2001;55:543–547.