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Pathophysiology of Cancer-Related Fatigue

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Abstract

Cancer-related fatigue (CRF) is influenced and modulated by a number of critical factors, and the mechanism that is both necessary and sufficient to induce development of severe fatigue in patients with cancer has not yet been identified. Specific research efforts on understanding the factors that may contribute to development of CRF have been made, such as studies of the direct effects of tumor burden, the effects of cancer treatment, and other pathophysiological and psychosocial conditions. Compelling new hypotheses regarding the pathophysiology of CRF have been proposed, such as the pro-inflammatory hypothesis, the serotonin hypothesis, the vagal-afferent-activation hypothesis, the anemia hypothesis, and the adenosine triphosphate hypothesis; some of these have been tested in both animal models and humans and some in animals only.

Gaining an understanding of the specific mechanisms related to the development of fatigue in patients with cancer and survivors of cancer requires further investigation. Pathophysiological research in CRF could be applied in the clinic to improve diagnosis of CRF and to enable administration of mechanism-driven interventions. A targeted intervention study with CRF as a primary end point would also be useful.

Introduction

Cancer-related fatigue (CRF) is one of the most common and complex symptoms experienced by patients with cancer, occurring across the spectrum of malignant disease diagnoses and major therapies. Gaining an understanding of the mechanisms underlying this highly prevalent and burdensome symptom is of great interest to researchers and clinicians alike, yet relatively few studies have evaluated the etiology of CRF or the factors that mediate multiple, related physiologic effects.[1,2] The multifactorial and multidimensional nature of CRF has hindered the development of methodologies for evaluating its underlying CRF; consequently, a lack of mechanism-driven clinical trials exploring effective pharmacologic therapies has hampered the effective management of CRF.[3] In sum, CRF is a challenging and controversial subject for both researchers and clinical caregivers, and it is also a significant issue for the many patients with cancer who are unable to get out of bed and function normally.

The pathophysiology of CRF has not been adequately elucidated. Clinical studies have focused on understanding factors that contribute to CRF, including the disease itself, treatments received, and a variety of chronic physical or psychological comorbid conditions, such as anemia, pain, depression, anxiety, cachexia, sleep disturbance, and immobility (Figure 1). Although several mechanisms for the pathophysiology of CRF have been proposed, little progress has been made toward identifying reliable physiological marker(s) as objective measures of fatigue.

CRF has been analyzed from physiological, anatomical, and psychological perspectives.[4] The central governor model posits that fatigue develops in the brain and spinal cord (“central fatigue,” as opposed to “peripheral fatigue,” which occurs in the neuromuscular

junctions and muscle tissues).[5,6] Central fatigue, defined as difficulty in the initiation or maintenance of voluntary activities,[7] 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".[8,9] In this model, to which CRF seems well fitted, fatigue is a complex emotion affected by motivation and drive, fear and anger, and memory of prior activity. It has been proposed that a centrally mediated disorder of perception may underlie many syndromes with symptoms that lack clear pathophysiologic explanations.[4,10] However, although a failure of nonmotor function of basal ganglia has been proposed as one of the potential pathogenic mechanisms of central fatigue,[8] there is little research on human brain imaging of fatigue, and it is unknown if the conscious sensation of fatigue is associated with particular brain locations or related to whole-brain activity. The inherent subjectivity of CRF has limited development of preclinical models.[11]

Establishing the causality of CRF presents numerous difficulties and challenges.[12] First, not all at-risk patients will experience this symptom. According to National Comprehensive Cancer Network (NCCN) guidelines, causes of CRF include the cancer itself, chemotherapy, bone marrow transplants, immunotherapy and radiation therapy, and anemia; factors identified as frequently contributing to CRF include pain, emotional distress, sleep disturbance, anemia, nutritional deficiencies, cardiac deconditioning, and comorbidities.[13] Even so, not all patients with these serious conditions will develop fatigue.[14,15] Variability in disease prognosis and response to cancer or symptom treatment (including placebo effects) may further affect development of this symptom. In addition, CRF is more likely to be caused by a constellation of risk factors (sometimes referred to as a "web of causation") than by a single factor. Complex interplay may be seen between the etiologic agent (eg, cancer treatment, infections, use of central-acting drugs), and host susceptibility. Clinical observations indicate that multiple physical and psychosocial factors are involved for each individual patient.

This paper will review the clinical correlates of CRF development and propose potential mechanisms underlying the pathophysiology of CRF, supported by data related to both single and multiple mechanisms.

Clinical Correlates of Cancer-Related Fatigue

Potential Tumor-Related Causes of CRF

Unusual tiredness often is the first signal that causes people to seek medical care. Significant fatigue often is observed in patients with newly diagnosed cancer, especially patients with renal or small cell lung cancer who develop paraneoplastic syndrome. Patients with advanced-stage cancer may suffer from even more distressing CRF. Progressive cancer directly affects several organ systems and causes neurophysiologic changes in skeletal muscles. Abnormal production of certain substances (eg, inflammatory cytokines)[13,16] may inhibit metabolism or normal muscle function. Decreased availability of metabolic substrates in patients with cancer also be involved.[17] As an example, CRF is one of the main symptoms of cachexia, which presents in approximately 50% of patients with cancer and is characterized by loss of body mass and skeletal muscle that cannot be explained solely by decreased food intake. Cachexia has been associated with increased levels of certain inflammatory cytokines, including interleukins and tumor necrosis factor (TNF-α) and may also be related to abnormalities in energy metabolism.[1,11,18]

Potential Treatment-Related Causes of CRF

Surgery—Fatigue is common after major surgery and delays recovery.[19,20] It is usually attributed to the physiological response to surgery. Postoperative fatigue has been reported

immediately after curative surgery[21–23] and may be related to such factors as having received anesthesia, type of analgesia, decreased ventilatory capacity, immobilization, infection, or anxiety.[24] The mechanisms of postoperative fatigue have been examined only during early times after surgery. Salmon and Hall, in a study of patients who underwent hip arthroplasty, found that the severity of postoperative fatigue was predicted not by physiological changes but by the preoperative level of fatigue.[21] In contrast, Rubin and colleagues have suggested that psychological processes are relevant in the etiology of postoperative fatigue.[19] In particular, their results relating to mood and expectations suggest that somatization may be particularly important in the first few weeks after surgery, whereas cognitive-behavioral factors and cardiovascular deconditioning may be more important in determining later-stage recovery.[19]

Chemotherapy—The nausea, diarrhea, and vomiting induced by chemotherapy can influence CRF symptoms.[1] Chemotherapy-related fatigue may also be associated with anemia or with accumulation of end products from cell destruction.[11] Available evidence supports the correlation between anemia and fatigue.[25,26] Chemotherapy drugs that cross the blood-brain barrier may induce neurotoxicities that produce fatigue.[24] Most patients experience fluctuations in fatigue during high-dose chemotherapy paired with stem cell transplantation, with fatigue increasing as the patients' blood counts approach white blood cell nadir but improving as counts recover.[27] The association of fatigue and chemotherapy has been extensively studied in patients with breast cancer.[28–33] Even existing anemia and fatigue can be exacerbated by chemotherapy and radiotherapy.[34]

Radiotherapy—Fatigue may be the most severe symptom experienced by patients during radiation therapy.[35] Treatment with radiation can lead to anemia, diarrhea, weight loss, anorexia, and chronic pain, any of which can influence fatigue severity.[1] For example, in a longitudinal study of patients with colorectal cancer receiving chemoradiation, the severity of pain before treatment and the severity of diarrhea during treatment predicted the development of severe fatigue.[36] Patients who receive radiotherapy may experience a gradual deepening of fatigue with ongoing treatment.[36,37] Combined modality therapy (eg, concurrent chemotherapy and radiation) is a known risk factor for persistent fatigue.[38]

Biologic-response modification—Patients treated with biologic-response modifiers, such as proinflammatory cytokines, may experience such intense and intolerable fatigue that it limits their ability to continue with these agents.[39–41] Administration of cytokines often results in a "flu-like syndrome" with a set of symptoms that includes fatigue, fever, chills, headache, myalgias, and malaise.[42] The most-studied of these biologic agents is interferon (IFN)-α, which may cause fatigue in approximately 70% of patients and may induce hypothyroidism, which also may cause fatigue, in up to 20% of patients.[43]

Hormone therapy—Side effects of hormone therapy have not been well assessed and are frequently underestimated.[44] Lethargy and lack of energy related to hormone treatment have been reported in patients with breast cancer.[45] Hormone ablation may double the incidence of reported fatigue in patients with prostate cancer, which supports the correlation between gonadotrophin function and fatigue.[46]

CRF in Cancer Survivors

Not only have patients repeatedly identified CRF as the most distressing symptom during the acute phase of cancer treatment but also published literature shows that CRF may continue for years after treatment is completed and even when the cancer is cured. CRF may so affect a cancer survivor's physical and cognitive abilities that he or she is not able to function normally either at work or at home, which can cause significant difficulties.[47,48]

Relationship of Fatigue to Other Symptoms

Although fatigue is often singled out as the most common symptom across many different diseases, it almost always clusters with other significant symptoms. The greater the number of symptoms and perceived disabilities, the more likely clinicians are to identify psychological, behavioral, or social contributors to illness.[10] Cluster analyses of multiple cancer symptoms, such as fatigue, pain, and sleep disturbance, have confirmed this phenomenon.[49,50] This is consistent with observations from cancer patients, who rarely have solitary symptoms during active therapy or with advanced disease and who often experience accompanying medical comorbidities and psychological disorders.[51,52]

Pain and sleep disturbance—The interaction of fatigue with pain and sleep disturbance has been well addressed in the symptom research literature.[47,53–58] Parameter estimates in patients with newly diagnosed lung cancer indicated that the three-way interaction of pain, fatigue, and insomnia was statistically significant.[52] Higher total and subscale fatigue scores were correlated with most components of poorer subjective sleep quality ($r = 0.25–0.42$, $P \leq 0.005$).[58]

Distress and depression—Chronic emotional distress can contribute to development of CRF.[28,29] Proposed mechanisms in this regard include dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis.[59] In an international study of chronic fatigue syndrome in the primary care setting, a temporal relationship between fatigue and depression, when adjusted for demographics, physical morbidity, and intercenter variability, supported the concept that unexplained fatigue and depression might act as independent risk factors for each other.[60] It has also been hypothesized that activation of inflammatory pathways in otherwise healthy individuals may influence individual depression-related symptoms, such as fatigue, insomnia, and anger/hostility.[61,62]

Other pathophysiological conditions—Physical conditions, such as various infections, malnutrition, thyroid dysfunction, and other organ failure could all either cause or contribute to CRF (Figure 1). Multiple physical symptoms interact with affective symptoms, and the patient's perception of illness, coping skills, and mood may have important and long-lasting effects on eventual adaptation to chronic fatigue and should be considered for effective intervention. This is one area where cancer researchers might make good use of the psychology literature, such as the study by Edwards and colleagues on illness representations by patients with chronic fatigue.[63]

Proposed Mechanisms of CRF Pathophysiology

While the underlying etiology of and risk factors for CRF are not fully resolved, the following hypotheses provide independent and overlapping potential mechanisms for the pathophysiology of this complex phenomenon (Figure 1). These proposed mechanisms include proinflammatory cytokines, growth factors, circadian rhythm modulation, HPA-axis disruption, serotonin dysregulation, vagal-afferent activation, anemia, and abnormalities of generation or use of adenosine triphosphate (ATP).[5,16,34,64,65]

Proinflammatory Cytokine Hypothesis

Symptoms reported by patients with cancer undergoing treatment are strikingly similar to characteristics of the evolving animal models of cytokine-induced sickness behavior.[65–67] Sickness behavior refers to clusters of behavioral and physiological responses (eg, hyperalgesia, sleep disturbance, and reduced activity and food intake) observed in animals after physical insult or administration of inflammatory agents or specific proinflammatory cytokines.[68–70] There is growing awareness that cytokines may play a mechanistic role in

CRF as common biologic mechanisms.[35,60,71–73] The theoretical underpinning for the proinflammatory cytokine hypothesis, based on the animal model of inflammation-induced sickness behavior, is that dysregulated inflammation and its downstream toxic effects represent a significant biologic basis for subjectively reported CRF and a cluster of other symptoms.[65,66,74]

Cytokine dysregulation appears to play a part in cancer-related–symptom production. Elevated inflammatory biomarkers (eg, interleukin [IL]-6 and TNF-α) have been shown in studies of persistent fatigue in survivors of breast cancer.[75] These cytokines might be associated with a chronic inflammatory process involving the T-cell compartment.[76] In patients with advanced cancer, cachexia-related tissue catabolism is reported to be mediated by IL-6 and TNF-α.[77]

Increased inflammation is also a prime candidate for the mechanism behind increases in treatment-related symptoms. The insult of cancer treatment, including radiotherapy and chemotherapy, increases production of inflammatory cytokines, especially IL-6 and TNF variants.[78,79] Increases in IL-6 in response to paclitaxel therapy for breast cancer have been associated with reported symptoms.[80] Patients with CRF exhibit elevations in IL-6, IL-1 receptor antagonist (IL-1RA), IL-1, and TNF, along with decreased albumin.[81]

It has been suggested that reduction of this treatment-induced inflammatory response might significantly reduce the morbidity associated with radiotherapy.[82] The use of a TNF inhibitor (etanercept) was associated with significantly less fatigue in patients with cancer, along with a trend for lower mean nuclear factor-kappa B (NF-κB, a cytokine precursor molecule) activity.[83] Prechemotherapy and chemotherapy-induced changes in inflammation in response to chemotherapy have been related to changes in fatigue and quality of life.[84]

Molecules downregulated by cytokines, such as albumin and C-reactive protein (CRP), also show a high correlation with the presence of CRF. For example, fatigue was associated with low albumin in patients with hematologic malignancies and with greater CRP in patients with advanced lung cancer.[85,86]

A recent article reviewed 18 well-designed published studies (N = 1037) to evaluate the strength of evidence supporting the relationship between inflammation and fatigue.[87] Analyses based on weighting according to sample size showed a significant positive correlation between fatigue and levels of circulating inflammatory markers ($r = 0.11$, $P < 0.0001$). Analyses of individual inflammatory markers revealed significantly positive correlations between fatigue and IL-6 ($r = 0.12$, $P = 0.004$), IL-1RA ($r = 0.24$, $P = 0.0005$), and neopterin ($r = 0.22$, $P = 0.0001$). The author proposed that the reason for insignificant correlation with IL-1β or TNF-α was because serum TNF-α was not detectable, possibly due to the sampling process or to storage conditions or duration.[87,88]

Growth Factor Hypothesis

The growth factor hypothesis posits that vascular endothelial growth factor (VEGF) level is associated with treatment-induced fatigue. VEGF is an angiogenic cytokine with high relevance to cancer, stimulating the formation of new blood vessels necessary for tumor growth and metastasis[89] and an independent predictor of poorer survival.[90] Patients with breast cancer undergoing chemotherapy were found to have significantly increased fatigue and reduced quality of life correlated with elevated VEGF and soluble intracellular adhesion molecule-1 levels.[84] Sunitinib is a VEGF receptor inhibitor that is hypothesized to decrease thyroid function by preventing binding of VEGF to normal thyroid cells or impairing thyroid blood flow, which results in thyroiditis. Sunitinib-induced hypothyroidism (without autoantibodies) has been observed in patients with advanced renal cell cancer[91] or

gastrointestinal stromal cancer.[92] Thyroid hormone replacement improved fatigue and other symptoms in 9 of 17 patients with renal cancer.[91]

Circadian Rhythm Modulation Hypothesis

Research examining possible links between circadian rhythms and CRF has focused on secretion rhythms of the stress hormone cortisol and on rest-activity patterns. Preclinical studies have shown that epidermal growth factor receptor (EGFR) ligands, such as transforming growth factor-alpha (TGF-α), inhibit hypothalamic signaling of rhythmic behavior. Clinical observations indicate that elevated levels of TGF-α are associated with fatigue, flattened circadian rhythms, and loss of appetite in patients with metastatic colorectal cancer.[93] A slower decline in salivary cortisol levels correlated with increased fatigue severity was observed in fatigued survivors of cancer over the course of the day.[92] These data support the hypothesis that a symptom cluster of fatigue, appetite loss, and sleep disruption commonly seen in patients with cancer may be related to EGFR ligands, released either by the cancer itself or by the host in response to the stress associated with cancer, and suggest that further examination of their role in the production of symptom clustering is warranted.[95]

Sleep disorders are commonly observed in patients with cancer and may result from altered circadian rest-activity rhythms. An inverse correlation between fatigue and daily activity levels and a positive correlation between fatigue and restless sleep at night have been reported.[31,96] Changes in fatigue between chemotherapy cycles have also been correlated with changes in the rest-activity rhythm.[97] The association between fatigue and circadian disruption was reported as being independent of the presence of depression, although depression did correlate with altered circadian rhythm.

Serotonin Dysregulation Hypothesis

The theory behind dysregulation of serotonin as an explanation of CRF is that cancer and/or treatment cause an increase in brain serotonin (5-hydroxytryptemine [5-HT]) levels in localized regions of the brain and an upregulation of certain 5-HT receptors. This can lead to decreases in somatomotor drive, modified HPA-axis function, and a sensation of decreased capacity to perform physical work.[98–100]

Taken primarily from studies of exercise-induced fatigue or chronic fatigue syndrome, increased evidence supports a role for 5-HT metabolism and neurotransmission in the genesis of central fatigue. Animal studies have shown that 5-HT concentrations increase in the hypothalamus and brain stem with sustained exercise, reaching a maximum at the point of fatigue.[101,102] Similarly, administration of 5-HT to rats produced a dose-related decrease in running endurance,[103] whereas administration of a 5-HT antagonist improved performance.[102] Studies in patients with chronic fatigue syndrome have demonstrated raised plasma levels of free tryptophan, which could potentially lead to high levels of central 5-HT.[104,105] In several human studies, administration of selective serotonin reuptake inhibitors has been shown to reduce the capacity to perform exercise. However, other investigators have shown that central 5-HT concentrations do not influenceCRF.[106,107]

Hypothalamic-Pituitary-Adrenal–Axis Disruption Hypothesis

The HPA axis is the central system regulating release of the stress hormone cortisol. The HPA-dysfunction hypothesis proposes that cancer or its treatment either directly or indirectly cause alterations in HPA function, leading to endocrine changes that either cause or contribute to fatigue.[108,109] Fatigue has been associated with reduced HPA-axis function, such as defective central corticotropin-releasing hormone (CRH) release and downregulation of CRH receptors in response to chronic stress, and with hypocortisolemia in patients with

cancer, chronic fatigue syndrome, and rheumatoid arthritis.[5] Alterations in HPA-axis function may be caused by various factors in patients with cancer. For example, proinflammatory cytokines (e.g., IL-1, IL-6, and TNF-α) and some comorbidities (eg, sleep disturbance) can stimulate the HPA axis.[110,111] Certain cancer treatments (eg, glucocorticoids, radiotherapy, and some chemotherapeutic regimens) may lead to direct suppression of the HPA axis.[112–114] Cortisol has an inhibitory effect on cytokine production; thus, cytokine levels may rise in the presence of reduced cortisol concentrations.[115]

Vagal-Afferent–Activation Hypothesis

Based on animal studies, the vagal-afferent–activation hypothesis suggests that cancer and its treatment cause peripheral release of a spectrum of neuroactive molecules (such as serotonin, cytokines, and prostaglandins) that may activate vagal-afferent nerves.[116–118] The overall effects may manifest as decreased somatic motor output and sustained changes in particular regions of the brain associated with fatigue by induction of IL-1β sickness behavior.[119,120] In response to injection of IL-1β, the vagal-afferent nerves of rats mediate IL-1β production at multiple sites in the central nervous system.[121] Considering the effect of the HPA axis on fatigue, cytokine production in the hypothalamus is especially significant.

Anemia Hypothesis

Cancer-related anemia has a profound impact on patients experiencing the associated complications of fatigue, dyspnea, palpitations, dizziness, and decreased cognitive function.[122] Anemia results in decreased oxygen delivery to tissue, despite the body's attempts to compensate for the effects of a decrease in red blood cells.[123] Hypoxia-related compromise in organ functioning is one of the suspects related to anemia or hemoglobin dysfunction that might cause fatigue.[5] A direct relationship between increases in hemoglobin (within the recommended range) and improvements in fatigue and quality of life has been documented in randomized trials in elderly patients with chronic anemia and in patients with cancer.[124–128]

Adenosine Triphosphate Hypothesis

Feelings of "weakness" and "lack of energy" are reported by patients with cancer, who often have decreased ability to perform mechanical work.[129,130] Cancer or its treatments may lead to a defect in ATP regeneration and the buildup of metabolic byproducts in the neuromuscular junctions and skeletal muscle. ATP is a major source of energy for skeletal-muscle contraction, and a disruption of its metabolism in patients with cancer could decrease their physical abilities. This mechanism of producing fatigue symptoms has been referred to as "peripheral fatigue".[5] Results from pilot studies of agents thought to affect metabolic response or short-term endurance performance in muscle are inconclusive. Whether the "peripheral fatigue" may be a part of CRF is unknown.

Conclusions

Research on understanding the mechanisms underlying both the development and management of CRF has attracted multidisciplinary attention. Specific efforts have been made to understand factors, such as anemia, pain, depression, anxiety, sedating medications (opioids), sleep disturbance, and immobility, that may contribute to fatigue. Compelling new hypotheses regarding the pathophysiology of CRF have been proposed, some with evidence in both animal models and humans and some in animals only. Investigation of these potential mechanisms will contribute to improved understanding of the nature of fatigue, one of the most complicated symptoms experienced by patients with cancer.

Continued research will no doubt improve our understanding of the etiology of CRF. Clearly, CRF is influenced and modulated by a number of critical factors, and the mechanism that is both necessary and sufficient to induce development of severe fatigue in patients with cancer has not yet been identified. Although some effort is being expended to develop objective measures of the physical and cognitive changes caused by fatigue, no well-accepted physiologically or behaviorally objective measures are currently available for diagnostic use. Additionally, whereas fatigue is often objectively described by clinicians as a decrease in performance,[131] it may also result in behavioral manifestations that are more likely to be noted by concerned family members and partners.

Pathophysiological research of CRF could be applied in the clinic to improve diagnosis of CRF and to administration of mechanism-driven interventions. Gaining an understanding of the specific mechanisms related to the development of fatigue in patients with cancer and survivors of cancer requires further investigation. A targeted intervention study with CRF as a primary end point would also be useful.

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At a Glance

- The pathophysiology of cancer-related fatigue (CRF) has not yet been adequately elucidated.
- No physiological markers of CRF have been established from ongoing research with hypotheses proposing underlying mechanisms.
- A web of causation may be reflected in an interaction of etiology and host susceptibility.

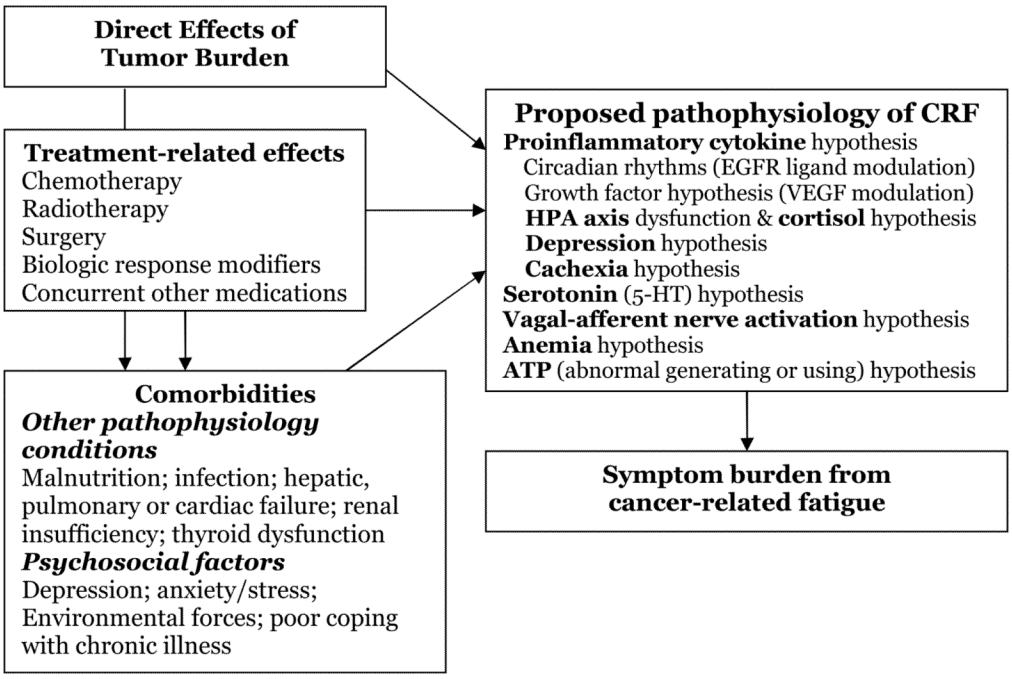

Figure 1. Proposed potential causes of CRF

ATP, adenosine triphosphate; EGFR, epidermal growth factor receptor; HPA, hypothalamic-pituitary-adrenal axis; VEGF, vascular endothelial growth factor.