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REVIEW ARTICLE

The pathophysiology of cancer-related fatigue: current controversies

C. M. O'Higgins[1,2,3] · B. Brady[3,4] · B. O'Connor[3,4] · Declan Walsh[1,3,4,5] · R. B. Reilly[1,2,6]

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Abstract

Fatigue is one of the most common and debilitating cancer symptoms, and is associated with impaired quality of life. The exact pathophysiology of cancer-related fatigue (CRF) is poorly understood, but in any individual, it is likely multifactorial and involves inter-related cytokine, muscular, neurotransmitter, and neuroendocrine changes. Underlying CRF mechanisms proposed include central and peripheral hypotheses. Central mechanisms include hypotheses about cytokine dysregulation, hypothalamic-pituitary-adrenal-axis disruption, circadian rhythm disruption, serotonin, and vagal afferent nerve function while peripheral mechanisms include hypotheses about adenosine triphosphate and muscle contractile properties. Currently, these hypotheses are largely based on evidence from other conditions in which fatigue is characteristic. The purpose of this article is to provide a narrative review of the literature and present the current controversies in the pathophysiology of CRF, particularly in relation to central and peripheral hypotheses for CRF. An understanding of pathophysiology may facilitate direct and simple therapeutic interventions for those with cancer.

Keywords Cancer-related fatigue · Pathophysiology · Proinflammatory cytokines · Hypothalamic-pituitary-adrenal axis · Neuromuscular abnormalities · Serotonin

Introduction

Cancer-related fatigue

Cancer-related fatigue (CRF) is one of the most common and debilitating symptoms, through all stages of the cancer trajectory and into survivorship [1, 2]. Unlike the typical fatigue that healthy people experience, CRF can occur suddenly, is disproportionate to exertion, and not relieved by rest or sleep [1]. It has a major effect on quality of life [2]. CRF prevalence can vary from 15 to 99% [3]; these variable prevalence estimates are due to different definitions, imprecise fatigue criteria, varied assessment methodology, and/or the influence of specific disease sites and anti-cancer treatments [4, 5]. CRF can occur as part of symptom clusters which include anorexia-cachexia and neuropsychological disorders [5].

The aim of this article is to conduct a narrative review of the literature and present the current controversies in the pathophysiology of CRF, particularly in relation to central and peripheral hypotheses for CRF.

Definition

A challenge concerning CRF is that a clear distinction between the terms exhaustion, fatigue, lack of energy, tiredness, and weakness has not been made, despite there being conceptual differences. The word "fatigue" may describe both an objective decrease in physical or mental performance and a

✉ Declan Walsh
Declan.Walsh@carolinashealthcare.org

C. M. O'Higgins
ohiggici@tcd.ie

[1] School of Medicine, Trinity College Dublin, Dublin, Ireland

[2] Trinity Centre for Bioengineering, Trinity College Dublin, Dublin, Ireland

[3] Academic Department of Palliative Medicine, Our Lady's Hospice and Care Services, Dublin, Ireland

[4] School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland

[5] Department of Supportive Oncology, Levine Cancer Institute, Carolinas HealthCare System, School of Medicine, University of North Carolina at Chapel Hill, Charlotte, NC, USA

[6] School of Engineering, Trinity College Dublin, Dublin, Ireland

subjective mental state. Several definitions of CRF have been proposed. The European Association for Palliative Care defines CRF as "a subjective feeling of tiredness, weakness or lack of energy" [6]. This definition was chosen to reflect the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) fatigue subscale that assesses tiredness, weakness, and lack of energy [6, 7]. However, the EAPC definition fails to include all aspects of CRF, related symptoms, or the impact on quality of life.

The National Comprehensive Cancer Network (NCCN) which has been adopted by the American Society of Clinical Oncology Clinical Practice Guidelines [7] has the most comprehensive and commonly used definition: "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity, and significantly interferes with usual functioning." This definition is stronger due to inclusion of the multidimensional aspects of CRF. While this is the most commonly used definition, there is no universally agreed definition of CRF. A universal definition of fatigue is important for development of treatment guidelines and research in oncology, supportive care, and palliative medicine.

Assessment

Current evaluation is based on subjective uni- or multidimensional questionnaires like the Brief Fatigue Inventory (BFI), which assesses severity on a scale of 0–10; the EORTC QLQ-C30, which assesses severity and quality of life; and the Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F) or Piper Fatigue Scale (assessing behavioral, affective, sensory, and cognitive/mood attributes of fatigue) [7–9]. While these questionnaires are validated in the cancer population, they are subjective measures with different domains and dimensions, and gather varied information. There is neither a "gold standard" for CRF diagnosis and quantification, nor consensus about the best treatment to manage it. There is also a difficulty in separating disease- and treatment-related fatigue. A detailed universal characterization of CRF is necessary to improve diagnostic evaluation and management strategies. It is important to identify symptom dimensions like the onset and duration to distinguish between acute and chronic fatigue. Those with chronic fatigue typically require more intensive evaluation and management focused on both short- and long-term goals. Other important fatigue descriptors or dimensions include severity, daily pattern, frequency, exacerbating and palliative factors, associated distress, interference with daily activities, and comorbid symptoms [3].

Pathophysiology

Despite the high prevalence, severity, and distress of CRF, the pathological mechanism remains unknown. The pathogenesis appears complex and multi-factorial, involving the interaction of cognitive, emotional, psychosocial, and somatic factors, with highly variable clinical expression. Several individual mechanisms may explain the causation of CRF, which may be considered central and/or peripheral in origin.

Central fatigue (Fig. 1) originates in the central nervous system (CNS) which generates signals that control voluntary movement. Central fatigue may occur from progressive failure to transmit these CNS neuronal impulses. It is characterized by the failure to complete physical and mental tasks (that require self-motivation and internal cues) without demonstrable cognitive failure or motor weakness [10, 11]. Peripheral fatigue is manifested by an inability of muscle to perform a task in response to central stimulation [10–12]. This may arise at either the neuromuscular junction or within muscle, perhaps due to adenosine triphosphate (ATP) dysfunction or accumulated muscle metabolites [10–13]. Central mechanisms include hypotheses about cytokine, hypothalamic-pituitary-adrenal-axis, circadian rhythm, serotonin, and vagal afferent nerve function while peripheral mechanisms include hypotheses about ATP and muscle contractile properties (Fig. 1) [10, 14–17].

These hypotheses are mainly derived from either animal models or limited human studies of CRF and other clinical conditions where fatigue is typical: myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), exercise-induced fatigue, or rheumatoid arthritis (RA) (Table 1 and Table 2). Controversy surrounds the relative contribution and degree of interactivity of central and

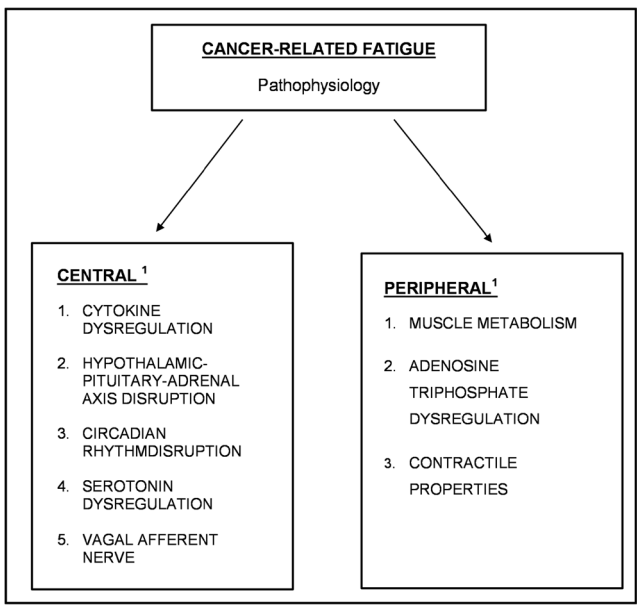

Fig. 1 Summary of proposed pathophysiology of CRF

Table 1 Fatigue hypotheses in various conditions

Hypotheses	Chronic fatigue syndrome	Cancer-related fatigue	Exercise	Rheumatoid arthritis
Cytokine response	X	X	X	X
Hypothalamic-pituitary-adrenal axis	X	X		X
Circadian rhythm dysregulation	X	X		
Serotonin dysregulation	X	X	X	
Vagal afferent nerve activation		X		
Muscle metabolism/ATP dysregulation	X	X		

peripheral factors to fatigue due to lack of evidence and objective assessment.

Methods

This article is a narrative overview to synthesize the current literature on etiology of CRF. A search of the electronic databases PubMed, Science Direct, Scopus, and CINAHL from January 1, 1998 to January 1, 2018 was conducted. A subject librarian was consulted in order to identify and assign the appropriate search terms before beginning. Titles and abstracts were searched for terms which included "cancer-related fatigue," "fatigue," "circadian rhythm modulation," "hypothalamic-pituitary-adrenal axis," "HPA axis," "muscle wasting," "pathophysiology," "proinflammatory cytokines," "serotonin dysregulation," and "vagal afferent nerve."

Inclusion and exclusion criteria

Searches were restricted to articles written in English (this was to ensure that information was not lost in translation), conducted in humans, and in the last 20 years with full text available (within the resources available). Reference lists of relevant articles were also hand-searched. Articles were excluded if they were abstracts only, editorials, or letters to the editor.

Discussion

A full list of studies referenced is included in Table 3, and 4. Several hypotheses for CRF have been proposed (Fig. 1), each of which will now be explored in detail. The hypotheses are listed in approximate order of significance with the influence of cytokines discussed first due to mounting evidence on their importance. They are also a common factor running through all the hypotheses (Table 2 and Fig. 3).

Central hypotheses

Cytokine dysregulation hypothesis

There is increased evidence that ongoing inflammation plays a crucial role in CRF. Cytokines are one category of signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis. This signaling changes behavior, neural activity, and psychological processes. Cytokines and mediators with "peripheral" effects may also have prominent CNS actions. Cytokines convey to the brain that an infection has occurred in the periphery; this can occur via the traditional endocrine route (from the blood) or direct neural transmission through the afferent vagus nerve [38]. This then causes changes from the release of inflammatory mediators that act on the brain to induce feelings of "sickness." Sickness behavior refers to adaptive behavioral changes, like depression, fatigue, lethargy, and loss of appetite [39].

Fatigued cancer patients and survivors have significantly higher serum levels of proinflammatory cytokine markers than non-fatigued survivors or healthy controls [47]. Cytokines such as C-reactive protein (CRP), interleukin-1 receptor antagonist (IL-1ra), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interferons (IFNs), neopterin, soluble tumor necrosis factor receptor 2 (sTNF-RII), and tumor necrosis factor-alpha (TNFα) may induce central fatigue (through mechanisms which include anemia, cachexia, and depression), and peripheral fatigue through mitochondrial impairment [2, 10, 22, 35, 36, 40, 47]. The underlying mechanism with the most significance for CRF remains unclear.

Increased cytokine activity may occur from tissue damage after chemotherapy, radiation, or both. It is still unclear whether this cytokine activity produces or just exacerbates CRF. Importantly, previous literature indicates that enhanced proinflammatory cytokine signaling dysregulation not only represents a significant basis for subjective symptoms in CRF but also intersects with several other hypotheses (see below). These include a direct influence on HPA axis dysregulation, altered serotonin metabolism, and possibly vagal afferent activation. Therefore, enhanced proinflammatory cytokine activity likely plays a central etiological role in CRF [2, 15, 22, 35, 36, 47].

Table 2 Hypotheses and their impact

Hypothesis affected by cancer and/or anti-cancer treatment	Impact on	May result in
Cytokine dysregulation	Circadian rhythm	Anorexia
	Comorbidities	Anemia
	HPA axis	Cachexia
	Neurotransmitters (5-HT)	Increased fatigue
	Vagal nerve	Increased or decreased HPA function
		Increased inflammation
		Sarcopenia
		Sleep disorders
Hypothalamic-pituitary-adrenal axis disruption	Circadian rhythm	Comorbidities
	Cytokines	Depression
	Comorbidities	Increased fatigue
	Neurotransmitters (5-HT)	Increased inflammation
		Sleep disorders
Circadian rhythm disruption	Cytokines	Depression
	HPA axis	Increased fatigue
	Comorbidities	Increased inflammation
	Neurotransmitters (5-HT)	Rest-activity cycle disruption
		Sleep disorders
Serotonin dysregulation	Circadian rhythm	Anorexia
	HPA axis	Cachexia
	Cytokines	Circadian rhythm disruption
	Vagal nerve	Decreased capacity to work
	Motor drive	HPA function
		Increased fatigue
		Increased inflammation
		Pain
		Vagal nerve activation
Vagal afferent nerve activation	Cytokines	Increased fatigue
	HPA axis	Increased inflammation
	Stomach muscle activity	Sickness behavior
	Neurotransmitters (5-HT)	Sleep disorders
Muscle metabolism/dysregulation	ATP regeneration	Anorexia
	Comorbidities	Cachexia
	Protein metabolism	Decreased ATP regeneration
	Physical performance (skeletal muscle)	Decreased protein
		Decreased muscle performance
		Increased fatigue
		Increased inflammation
		Sarcopenia

Previously published studies that assessed the association between inflammatory markers and treatment-fatigue lacked consistency, perhaps due to data collection procedures, or the use of non-standard and/or low-sensitive assays [22, 35, 47]. A 2016 systematic review on cytokines [37] identified that a varying set of cytokines (IL-6, IL-1Ra, TGFβ, TNFα, sTNF-RII) are differentially linked with CRF according to the numerous types of chemotherapy regimens. However, findings from each study were not consistent enough to draw a significant conclusion. Future work should include further

Table 3 List of cancer studies and reviews

Author and year	Title	Study type	Population
Agteresh et al. (2000a) [18]	Pharmacokinetics of intravenous ATP in cancer patients	Primary research, cross-sectional	Advanced non-small-cell lung cancer
Agteresh et al. (2000b) [19]	Effects of ATP infusion on glucose turnover and gluconeogenesis in patients with advanced non-small-cell lung cancer	Primary research, longitudinal	Non-small-cell lung cancer
Alexander et al. (2010) [20]	Evaluation of central serotonin sensitivity in breast cancer survivors with cancer-related fatigue syndrome	Primary research, longitudinal. Double-blind, randomized	Breast cancer survivors
Bower et al. (2005) [21]	Diurnal cortisol rhythm and fatigue in breast cancer survivors	Primary research, longitudinal	Breast cancer survivors
Bower et al. (2009) [22]	Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer	Primary research, longitudinal	Breast and prostate cancers
Cai et al. (2014) [23]	Evidence of significant central fatigue in patients with cancer-related fatigue during repetitive elbow flexions till perceived exhaustion	Primary research, cross-sectional	Advanced cancers
Kirkova et al. (2010) [5]	Cancer symptom clusters—a dynamic construct	Observational study	Advanced cancers
Kurz et al. (2012) [24]	Fatigue in patients with lung cancer is related with accelerated tryptophan breakdown	Primary research, cross-sectional	Lung cancer
Levin et al. (2005) [25]	Circadian function in patients with advanced non-small-cell lung cancer	Primary research, longitudinal	Non-small-cell lung cancer
Morrow et al. (2003) [26]	Differential effects of paroxetine on fatigue and depression	Primary research, randomized, double-blind trial	Cancers
Parker et al. (2008) [27]	Sleep/wake patterns of individuals with advanced cancer measured by ambulatory polysomnography	Primary research, longitudinal	Advanced cancers
Pertl et al. (2013) [15]	C-reactive protein predicts fatigue independently of depression in breast cancer patients prior to chemotherapy	Primary research, longitudinal	Breast cancer
Prinsen et al. (2015) [13]	The role of central and peripheral muscle fatigue in post-cancer fatigue: a randomized controlled trial	Primary research, longitudinal	Cancer survivors
Schmidt et al. (2016) [28]	Cancer-related fatigue shows a stable association with diurnal cortisol dysregulation in breast cancer patients	Primary research, longitudinal	Breast cancer patients
Schrepf et al. (2013) [29]	Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability	Primary research, longitudinal	Ovarian cancer
Serra et al. (2017) [30]	Resistance training reduces inflammation and fatigue and improves physical function in older breast cancer survivors	Primary research, longitudinal	Breast cancer survivors
Sephton et al. (2013) [31]	Diurnal cortisol rhythm as a predictor of lung cancer survival	Primary research, longitudinal	Lung cancer
Sultan et al. (2017) [32]	Worsening of rest-activity circadian rhythm and quality of life in female breast cancer patients along progression of chemotherapy cycles	Primary research, longitudinal	Breast cancer
Tell et al. (2014) [33]	Day-to-day dynamics of associations between sleep, napping, fatigue, and the cortisol diurnal rhythm in women diagnosed as having breast cancer	Primary research, longitudinal	Breast cancer
Weinrib et al. (2010) [34]	Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer	Primary research, cross-sectional	Ovarian cancer
Yavuzsen et al. 2009 [12]	Cancer related fatigue: central or peripheral?	Primary research, cross-sectional	Cancers
Barsevick et al. (2010) [2]	I'm so tired: biological and genetic mechanisms of cancer-related fatigue. Quality-of-life research	Clinical synthesis review	Cancers
Berger et al. (2015) [1]	Cancer-related fatigue	NCCN guideline review	Cancers
Bower et al. (2013) [35]	Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications	State-of-the-science review	Cancers
Bower et al. (2014) [7]	Screening, assessment, and management of fatigue in adult survivors of cancer	Systematic review	Cancers
Coussens et al. (2002) [36]	Inflammation and cancer	Narrative review	Cancers
Eyob et al. (2016) [37]	Impact of chemotherapy on cancer-related fatigue and cytokines in 1312 patients: a systematic review of quantitative studies	Systematic review of quantitative studies	Cancers
Hofman et al. (2007) [3]	Cancer-related fatigue: the scale of the problem	Narrative review	Cancers
		Narrative review	Cancers

Table 3 (continued)

Author and year	Title	Study type	Population
Jager et al. (2008) [38]	The pathogenesis of cancer related fatigue: could increased activity of proinflammatory cytokines be the common denominator?		
Kelley et al. (2003) [39]	Cytokine-induced sickness behavior	Narrative review	Cancers
Kurzock et al. (2001) [40]	The role of cytokines in cancer-related fatigue	Narrative review	Cancers
LaVoy et al. (2016) [41]	Exercise, inflammation, and fatigue in cancer survivors	Narrative review	Cancer survivors
Minton et al. (2013) [4]	Cancer-related fatigue and its impact on functioning	State-of-the-art review	Cancers
Mortimer et al. (2010) [9]	Studying cancer-related fatigue: report of the NCCN scientific research committee	NCCN guidelines	Cancers
Neefjes et al. (2013) [42]	Aiming for a better understanding and management of cancer-related fatigue	State-of-the-science review	Cancers
Roscoe et al. (2007) [43]	Cancer-related fatigue and sleep disorders	Systematic review	Advanced cancers
Ryan et al. (2007) [16]	Mechanisms of cancer-related fatigue	Narrative review	Cancers
Saligan et al. (2015) [14]	The biology of cancer-related fatigue: a review of literature	Systematic review	Cancers
Schubert et al. (2007) [44]	The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review	Quantitative review	Cancers
Seyidova-Khoshnabi et al. (2011) [8]	Review article: a systematic review of cancer-related fatigue measurement questionnaires	Systematic review of CRF questionnaires	Cancers
Wang et al. (2008) [17]	Pathophysiology of cancer-related fatigue	Narrative review	Cancers

investigation of pharmaceutical agents (e.g., etanercept, infliximab, glucocorticoids) that block proinflammatory markers (e.g., TNF-α, IL-1B) which would broaden our understanding of cytokine dysregulation in CRF.

Hypothalamic-pituitary-adrenal axis disruption hypothesis

This hypothesis proposes that cancer (or its treatment) disrupts the normal HPA axis either directly or indirectly causing endocrine changes that induce CRF. Physical and/or psychological stresses increase hypothalamic corticotrophin-releasing hormone (CRH) expression, while chronic inflammation (i.e., biological stress) reduces central CRH synthesis and release [14–17]. The HPA axis normally regulates the release of the stress hormone cortisol in response to physical or psychological stress (Fig. 2). In addition, cortisol has important biological effects; these include the regulation of the cardiovascular system, including blood pressure, immune system function, and metabolism. Cortisol also inhibits cytokine

Table 4 Studies and reviews involving chronic illnesses

Author and year	Title	Study type	Population
Forsyth et al. (1999) [45]	Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome	Primary research, randomized, double-blind, placebo-controlled crossover study	Chronic fatigue syndrome
Hansen et al. (1998) [46]	Vagotomy blocks the induction of interleukin-1β (IL-1β) mRNA in the brain of rats in response to systemic IL-1β	Primary research	Animal study (no human studies available)
Meeusen et al. (2007) [47]	Amino acids and the brain: do they play a role in "central fatigue"?	Integrative review	Healthy individuals and chronic illnesses
Siemionow et al. (2004) [48]	Altered central nervous system signal during motor performance in chronic fatigue syndrome	Primary research, cross-sectional	Chronic fatigue syndrome
Dantzer et al. (2014) [49]	The neuroimmune basis of fatigue	Narrative review	Chronic illnesses
Davis et al. (2010) [10]	Mechanisms of fatigue	State-of-the-art review	Chronic illnesses
Gandevia et al. (2001) [11]	Spinal and supraspinal factors in human muscle fatigue	Narrative review	Healthy individuals and chronic illnesses
Radbruch et al. (2008) [6]	Fatigue in palliative care patients—an EAPC approach	EAPC guidelines, review	Palliative care

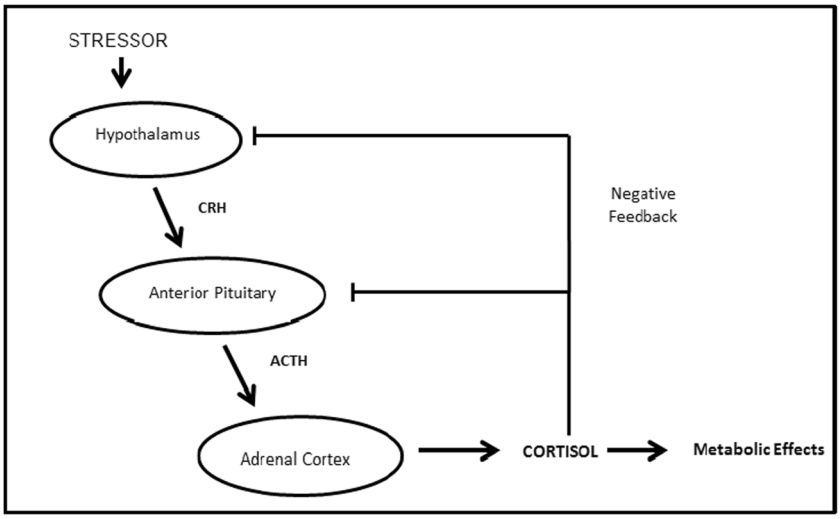

Fig. 2 Hypothalamic-pituitary-adrenal axis hypothesis. The HPA axis normally regulates the release of the stress hormone cortisol in response to physical or psychological stress. Stress stimulates corticotrophin-releasing hormone (CRH) release from the hypothalamus. CRH acts with arginine vasopressin to release adrenocorticotropic hormone (ACTH) from the pituitary. ACTH in turn increases cortisol release from the adrenal glands. Cortisol then exerts a negative feedback on the HPA axis

production. This with immune response suppression helps protect the individual from a lethal overactivation of the immune system, and minimizes tissue damage from inflammation.

The HPA axis has a key role in regulation of cytokine production and potent anti-inflammatory effects via a negative feedback control loop. Proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α), serotonin levels, and sleep disturbances may disrupt the HPA axis [14, 42]. Sleeplessness and fatigue can affect it via a 24-h increase of adrenocorticotropic hormone (ACTH) and cortisol secretion, serotonin can affect the axis by impaired ACTH release, and an acute release of proinflammatory cytokines (IL-1, IL-6, and TNF-α) stimulates the HPA axis with increased cortisol levels. In contrast, chronic cytokine exposure decreases HPA axis stimulation with lower cortisol activity and a blunted circadian rhythm. Elevated cytokine levels, HPA axis, and circadian disruption can lead to CRF. This connects to the cytokine hypothesis of CRF (above) and suggests that decreased cortisol levels may increase cytokine production (through a feedback loop). Hypocortisolemia has also been observed in cancer, and other illnesses like RA and CFS. Previous studies suggest that CRF could at least in part be due to low-cortisol output [29].

Certain cancer treatments like glucocorticoids, radiotherapy, and some chemotherapy drugs can also suppress the HPA axis, and the consequent blunted stress response may secondarily reduce energy levels. The increased circulating cytokines and cortisol is somewhat of a paradox as glucocorticoids are known to suppress cortisol and inflammatory cytokine production. At present, the relationship between cancer, CRF, and HPA dysregulation is controversial and several factors are evident. The changes in the HPA axis in cancer could be secondary to other various disease-related factors like anticancer treatment, excess proinflammatory cytokines (IL-1, IL-6, and TNF-α), or comorbid conditions like sleep disturbance.

Considering the influence of the HPA axis on fatigue, cytokine production in the hypothalamus is particularly significant [16, 17, 42]. The role of the HPA axis in CRF would be better understood through more frequent longitudinal measures of cortisol and glucocorticoid levels, before, during, and after treatment.

Circadian rhythm dysregulation hypothesis

Circadian rhythms are physical, mental, and behavioral changes that follow a 24-h cycle. They are sensitive to environmental changes like light and dark, stress or illness, and alter with age. The central circadian system regulates various behaviors which include arousal, body temperature regulation, hormone secretion, and sleep. In addition to these behaviors, circadian rhythms regulate rhythms of the immune system, which may disrupt/increase cytokine production or tumor-associated cytokines (IL-6, TNF-α, TGF-α).

Circadian rhythms and quality of life are considered by some to be important predictors of cancer prognosis [32]. In healthy individuals, cortisol levels display a diurnal pattern like the rest-activity cycle, with a peak in the morning, declining slowly throughout the day [14, 16, 17, 21]. Cortisol provides the individual with energy during the stress response with acute elevations occurring after brief stressors. Altered diurnal cortisol secretion and disrupted circadian rhythms are both indicative of HPA axis dysfunction, which in turn has been linked to increased cytokine signaling and fatigue in various clinical conditions. For example, a flattened circadian cortisol cycle is observed in those with chronic fatigue syndrome [28, 29, 31, 34]. With chronic stressors, the negative feedback system that regulates cortisol becomes impaired, with chronically elevated cortisol levels (particularly at night) due to the loss of diurnal rhythm. Cancer or its treatment certainly affects this system and disrupts an individual's arousal or sleep patterns (likely by altering cortisol rest-activity levels).

CRF subjects have significantly altered cortisol circadian levels; i.e., greater fatigue is associated with flatter diurnal slopes and a slower decline of evening cortisol [28, 29, 31, 34]. A study in those with advanced lung cancer showed that the 24-h urine cortisol level increased during treatment. In addition to this, higher overall values were found across the 24-h cycle, but with erratic peaks and troughs [25]. Another study observed higher evening cortisol levels and a significantly flatter slope among 130 breast cancer patients compared to non-fatigued participants [33]. Cancer patients often report poor sleep quality and insomnia leading to altered rest-activity patterns [50] and decreased quality of life [32]. Actigraphy studies and polysomnography demonstrated that circadian rhythm differs significantly in fatigued participants compared to controls [27, 34, 43]. Those with CRF show abnormal sleep patterns, with higher than expected wakefulness during normal sleep times and extensive sleep periods during normal activity times [27, 43].

Limitations to these studies include small sample size, and short-term measurements over 1 or 2 days, rather than continuous assessment over several weeks. The current evidence therefore suggests that circadian rhythm disruption accompanied by abnormal cortisol levels are reflected in altered rest-activity patterns and contribute to CRF. However, the higher cortisol levels in CRF may be secondary to stress or disrupted rest/activity cycles as a result of fatigue. Alternatively, the higher-cortisol pattern and fatigue may not be directly linked but instead triggered by a primary HPA axis disruption as cortisol is closely linked to energy production and regulation, along with many other vital behaviors and bodily functions [21].

Serotonin dysregulation hypothesis

High brain serotonin (5-HT) levels or upregulation of serotonin receptors may be involved in CRF. Fatigue could be caused by either an abnormally high or low level of brain 5-HT which in turn lowers cortisol output [38], whereas in contrast, there may be an optimal 5-HT level without fatigue. This intersects with the hypocortisolemia and proinflammatory cytokine theories as described above.

5-HT and its receptors influence each other and the HPA axis. This occurs by regulation of upstream CRH via serotonin receptor activation in the paraventricular nucleus of the hypothalamus which secondarily increases cortisol and cytokine levels, decreases somatomotor drive, alters HPA function, and lowers physical work capacity [2, 14, 16, 17, 38, 42]. 5-HT has well-known effects, causing drowsiness and lethargy, regulating eating and digestion, muscle contraction, and sleep and waking depending on which 5-HT receptor and brain area is activated [51].

Low levels of 5-HT are related to sleep disturbances and mood disorders, which are common in cancer. One hypothesis is that *low* 5-HT levels decrease both the stimulation and responsiveness of the hypothalamic 5-HT receptors (5-HT-1A) [38]. This may occur due to elevated proinflammatory cytokines activating the tryptophan- and 5-HT-degrading enzyme indoleamine 2,3-dioxygenase (IDO). This in turn would lower HPA axis activity and impair cortisol production.

Another theory is that chronically *increased* 5-HT levels could disrupt the HPA axis lowering cortisol production; it is thought that these persistently high 5-HT levels may be from high proinflammatory cytokines [2, 38, 42]. Serotonin neurotransmission can also be impaired by inflammation from cytokine-induced activation of indoleamine 2,3-dioxygenase. This metabolizes (the serotonin precursor) tryptophan into kynurenine, which lowers 5-HT levels due to enhanced 5-HT reuptake. Kynurenine is further metabolized into neurotoxic metabolites that may play a role in depression and are associated with fatigue in lung cancer [24, 41, 49].

The known relationship between depression and fatigue raises a third proposed mechanism of 5-HT dysregulation in CRF. Yet, clinical trials of paroxetine and buspirone, a selective serotonin reuptake inhibitor and selective serotonin agonist, respectively, to treat chemotherapy fatigue did not show any benefit for fatigue, although 5-HT levels should have increased [20, 26]. This suggests that fatigue is unaffected by brain 5-HT level correction, and either the psychomotor retardation evident in depression differs from that of CRF or changes have already occurred before treatment.

The challenge with the 5-HT hypothesis is that brain neurotransmission activity cannot be directly measured and 5-HT levels are not readily available, so direct evidence is absent. However, while there have only been a few studies with the use of anti-depressants as treatment for fatigue, these suggest that serotonin is not the primary causative factor. This hypothesis is mainly derived from animal or non-cancer studies but even then the results conflict. Further research is needed into 5-HT dysregulation and CRF with examples including longitudinal testing, 24-h urine analysis, cerebral spinal fluid (CSF) levels, or imaging techniques like positron emission tomography (PET). For PET scanning, a specialized radioligand could measure serotonin, e.g., 3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile, labeled with carbon 11 (C-DASB) binds to the serotonin transporter. This would allow relatively direct inferences to be made about serotonin levels.

Vagal afferent nerve activation

In addition to supplying several visceral organs with parasympathetic efferents, the vagal nerve contains 80–90% afferent fibers that convey visceral autonomic, motor, and sensory functions to the brain stem [2, 4, 14–17, 41]. Vagal afferents can be activated by peripheral neurotransmitter (cytokines, interleukins, prostaglandins, and serotonin) release caused by cancer or its treatment. These afferents reduce somatic

motor activity, modulate somatic muscle tone, and also cause continuous plastic changes in brain areas associated with fatigue, like the hypothalamus. Activated vagal afferents may also cause "sickness behavior" from the release of peripheral cytokines like IL-1β [2, 15–17, 49].

Animal studies reveal sickness behavior from administration of intraperitoneal IL-1β (which causes vagal nerve activation). This administration of intraperitoneal IL-1β induces IL-1β production in the brain stem, hippocampus, and hypothalamus [2, 15–17, 42, 46]. This response can be decreased or eliminated completely by a subdiaphragmatic vagotomy [46]. Other animal studies suggest that vagal nerve afferents (activated by proinflammatory cytokines or 5-HT) cause reflex inhibition of somatomotor activity in muscles, and this contributes to CRF and subjective weakness [2, 15–17, 46, 49].

This hypothesis also links the cytokine, HPA axis, muscle activity, and serotonin hypotheses of CRF. There are no human studies to support this, and such studies to clarify the role of vagal afferents in CRF are required. Future studies to assess vagal afferent nerve should include known methods of assessing vagal nerve activity, i.e., examination of reflex-mediated changes, blood pressure, and heart rate variability (low HRV indicates low vagal tone and thus parasympathetic underactivity) [41]. Considering the involvement of the HPA axis in fatigue and CRF, the role of the vagus nerve in stimulating cytokine production in the hypothalamus could be investigated.

Peripheral hypotheses

Muscle metabolism dysregulation

Fatigue in healthy and diseased individuals is associated with skeletal muscle structure and functional abnormalities [10, 11]. Muscle fatigue is defined as "any exercise induced reduction in the ability to exert muscle force or power regardless of whether or not the task can be sustained." Patients often describe their fatigue as "feelings of weakness" and/or a "constant lack of energy"; this likely occurs as a result of peripheral rather than central fatigue [10, 13]. For peripheral hypotheses of CRF, two particular mechanisms are proposed.

Adenosine triphosphate

The ATP dysregulation hypothesis proposes that cancer or its treatment damages the sarcoplasmic reticulum with increased intracellular calcium levels and/or impaired mitochondrial mechanisms for regeneration of skeletal muscle, thereby compromising the individual's ability to perform physical tasks [10–13, 16, 52]. Sarcoplasmic reticulum dysregulation may cause CRF due to lower protein synthesis or metabolite accumulation (ATP, chloride, inorganic phosphate, lactic acid, magnesium, potassium, and reactive oxygen species). An accumulation of metabolites can directly or indirectly produce metabolic fatigue within the neuromuscular junction or muscle fibers through the following:

- Interference with the release of calcium from the sarcoplasmic reticulum [2, 10, 16].
- Reduction of the sensitivity of contractile molecules actin and myosin to calcium or ATP dysregulation [2, 10, 16, 45].

ATP is a major source of energy for skeletal muscle contraction, and normally, it is quickly replenished with cellular ATP formed in the mitochondria by oxidative phosphorylation. Failure to replenish ATP will compromise muscle function and decrease ability for physical work, resulting in subjective fatigue. In addition, those with cancer often have reduced energy intake due to changes in appetite and adverse effects of treatment which can lead to anemia and nutritional deficiencies which affects ATP generation. People with cancer anorexia/cachexia have altered muscle protein metabolism [10], which is manifested by increased muscle protein catabolism leading to loss of muscle mass. This potentially reduces ATP regeneration and precipitates fatigue.

Evidence of ATP dysregulation in cancer is limited [18, 19]. One study [19] investigated ATP infusion in non-small-cell lung cancer (NSCLC), while another study [45] investigated the efficacy of nicotinamide adenine dinucleotide + hydrogen (NADH) for CFS symptoms. NADH is the reduced form of the coenzyme nicotinamide adenine dinucleotide (NAD), a key coenzyme of oxidative phosphorylation. NAD triggers energy production through ATP generation. Both of these trials demonstrated improved fatigue, muscle strength, quality of life, and weight gain; however, these effects were short lived. Further trials should investigate the potential use of ATP/NADH as treatment agents in CRF. While there is some evidence to support their use, they are currently not utilized.

Contractile properties

Two studies in CRF [23, 52] and one in CFS [48] compared muscle contractile properties to healthy volunteers. CRF participants and healthy controls performed a sustained isometric elbow flexion contraction of the right arm at 30% maximal level until self-perceived exhaustion. Electromyographic signals of the elbow flexor and extensor muscles were recorded during this sustained contraction. These studies showed that those with CRF and CFS fatigued earlier in motor tasks, but did not show contractile property changes. This suggested central activation failure in CRF and CFS. A recent study [30] showed that resistance training reduced the effects of fatigue and inflammation in breast cancer survivors with

fatigue. This inflammatory change once more provides a link to the cytokine hypothesis of CRF.

Limitations in these studies included mixed cancer populations, single assessment, small study samples, and not taking CNS stimulant or depressant medications into account. More longitudinal objective investigations with larger sample sizes are needed to distinguish central from peripheral CRF. These objective investigations could include electrical muscle stimulation, fatiguing motor tasks while recording electromyography (EMG) and electroencephalography (EEG) simultaneously to assess both central and peripheral contributions to fatigue, and muscle biopsies.

Summary

Fatigue presentation may be influenced by the interaction of cognitive, emotional, psychosocial, and somatic factors with a highly variable pattern of clinical expression. In an attempt to explain CRF, several hypotheses have been proposed (Table 2 and Fig. 3) [14]. These hypotheses suggest that simultaneous complex biochemical, physiological, and psychological dysregulation of important biological systems contribute. While biochemical and physiological abnormalities related to fatigue are identified, it is not clear whether these mechanisms are the underlying cause or just linked to CRF and its associated symptoms. It is difficult to completely separate each hypothesis from one another as they are inter-dependent (Fig. 3).

Although not the only common feature throughout all the proposed hypotheses, there is increased evidence that cytokines play a crucial role. IL-1B, IL-6, and TNF-a influence nearly every step of the signaling pathway and several feedback loops, with proinflammatory cytokine mediators active in the HPA axis, circadian rhythm, serotonin metabolism, and vagal afferent activation. Cytokines may also be indirectly involved in CRF-related issues like anemia, anorexia, cachexia, depression, and sarcopenia.

The HPA axis is an important regulator of cortisol and cytokine production and has potent anti-inflammatory effects. Serotonin influences the HPA axis and potentially also plays a role in the anorexia-cachexia syndrome. Serotonin release can also be triggered by pain, which is another extremely common cancer symptom.

The circadian rhythm, regulated by the hypothalamus, is known to be affected by cortisol, cytokine, and serotonin levels. Distorted circadian rhythms can also affect the HPA axis.

Feelings of weakness and lack of energy are reported in CRF, and patients often have a decreased ability to do physical work, referred to as peripheral fatigue. This may be due to ATP dysregulation or buildup of metabolic by-products in the neuromuscular junction or muscle. However, studies examining muscle dysfunction and ATP have not drawn definitive conclusions, and those looking at contractile properties have suggested a more central origin of CRF.

The limited numbers of studies to date that have investigated these hypotheses are generally lacking and have not yet been conducted in all the relevant patient groups, for all aspects of fatigue (e.g., severity vs duration, pre- and post-treatment). Our knowledge of the factors that cause or contribute to CRF, though complex and controversial, continues to evolve. A neuroendocrine cause of CRF is especially attractive as it could facilitate direct and simple therapeutic interventions. However, additional research is required to elucidate the specific cause(s), as well as more research into cytokine dysregulation, where evidence seems to be the strongest.

Cancer-related fatigue is a serious problem that impairs patients physically, psychologically, and socially. While it

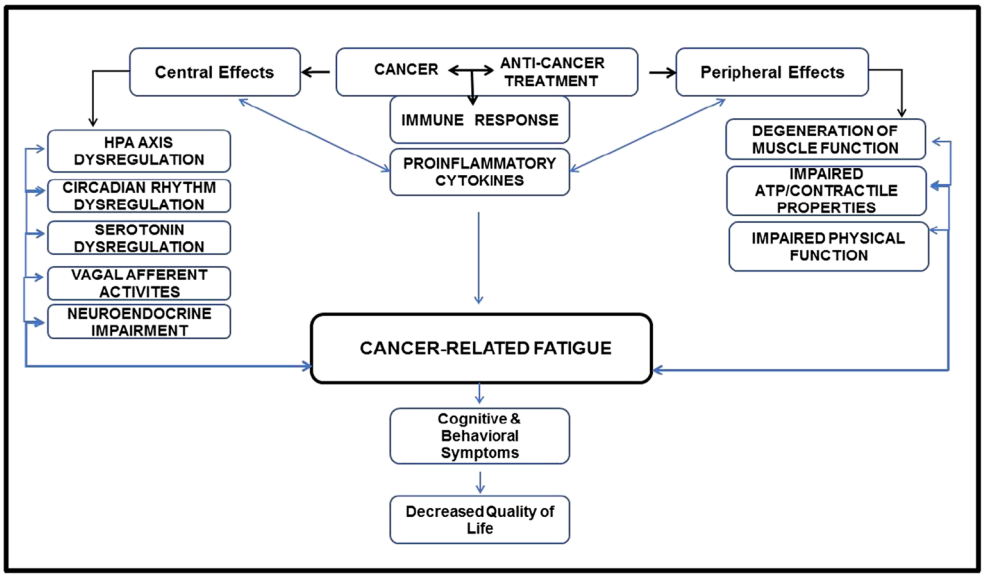

Fig. 3 This review shows that cancer and/or its treatment induce a cascade of simultaneous complex biochemical, physiological, and psychological dysregulation of important biological systems in an individual. This cascade of events, in both the central and peripheral nervous system, results in cancer-related fatigue which is manifested with cognitive and behavioral symptoms, and a decreased quality of life

has been referred to as a decrease in performance (i.e., peripheral fatigue), there are also behavioral and central manifestations that occur. Frequent, longitudinal studies should assess patients before, during, and after treatment. Finally, a comprehensive clinical assessment of the relationship between CRF and other cancer-related symptoms and co-morbid conditions (like depression, pain, and sleep disorders) is important to advance our understanding of the complex pathophysiology behind CRF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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