Review paper

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Fatigue and interleukin-6 – a multi-faceted relationship

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Abstract

Many connective tissue diseases are characterized by fatigue, which is described in the literature as prostration, weakness, lassitude or asthenia. In many other diseases (autoimmune, neurologic or metabolic) fatigue impinges on daily activities and thus influences the quality of life. Different molecular backgrounds are involved in the development of fatigue. Not only does the immunosuppressive treatment of autoimmune diseases reduce fatigue, but also selective nutritional components may have an effect on secretion of cytokines which are responsible for development of the sensation of tiredness (e.g. secretion of interleukin-6). The beneficial influence of selected food components (such as polyunsaturated omega-3 fatty acids, nutritional antioxidants or adequate fat intake with the diet) on proinflammatory cytokine secretion has been demonstrated in many studies. In this review, the biochemical, neurological and nutritional aspects of fatigue in autoimmune diseases are underlined.

Key words: fatigue, interleukin-6, neuroinflammation, nutritional aspects.

Introduction

Many patients with autoimmune, neurologic or metabolic diseases suffer from fatigue, which they refer to as tiredness, weakness, exhaustion or lack of energy [1, 2]. Generally, in chronic diseases fatigue is usually an element of a depressive syndrome. Conversely, the presence of fatigue increases the risk of depression [3]. Inflammatory processes are characteristic for connective tissue diseases and contribute to the occurrence of both fatigue and depression [1]. The cytokine interleukin-6 (IL-6) is involved in the development of fatigue in both autoimmune and non-autoimmune diseases. It is secreted during acute and chronic inflammatory responses by many cell types, including immune, endothelial, and muscle cells. Elevated levels of IL-6 are observed in connective tissue diseases such as rheumatoid or psoriatic arthritis, Sjögren syndrome and many others [4–6].

Neurologic implications of fatigue

Different molecular aspects of fatigue have been described in the literature. The activation of immune-inflammatory pathways by monocytes and proinflammatory cytokines causes neuroinflammation and neuroprogressive changes and in consequence contributes to fatigue (Fig. 1) [1, 7]. The proinflammatory mechanism of fatigue is also characterized for other somatic disorders, such as reduced sleep quality and excessive daytime sleepiness. However, fatigue is defined as a persistent feeling of physical or mental exhaustion, which is not accompanied by sleepiness and which sleep cannot alleviate [8]. Fatigue can be associated with chronic sleep disorders, which are characterized by increased secretion of proinflammatory cytokines and which contribute to health problems and increased mortality [9]. Interestingly, in these processes IL-6 plays a crucial role and mediates the rapid interplay between the immune system and central nervous system function. This interleukin is called a "sleep factor", because it enhances the sleep drive in accordance with the circadian rhythm (its level is lower during the daytime and higher during the night) [10]. In animal studies, the supply of IL-6 exerted a somnogenic effect [11]. Sleep deprivation leads to an increase in IL-6 and its elevated level is observed during the following

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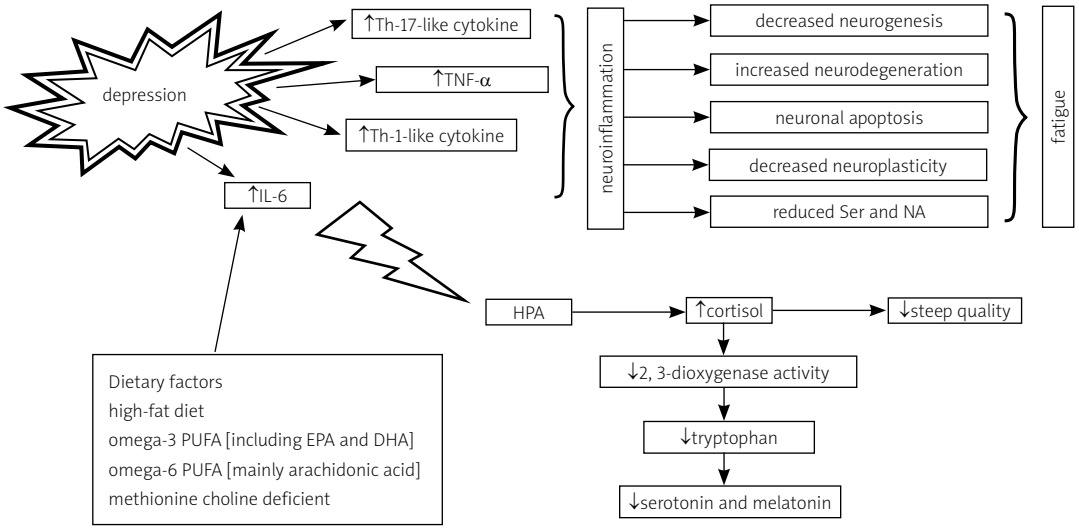


Ser – serotonin; NA – noradrenaline; HPA – hypothalamic-pituitary-adrenal axis, TNF-α – tumor necrosis factor α; PUFA – polyunsaturated fatty acids, EPA – eicosapentaenoic acid; DHA – docosahexaenoic acid; EGCG – epigallocatechin gallate

Fig. 1. Association of fatigue with depression and sleep quality.

day [12]. Moreover, IL-6 stimulates the hypothalamic-pituitary-adrenal (HPA) axis and increases the transitory level of cortisol in the first hours of sleep, and this diminishes sleep quality (Fig. 1) [13]. Increased cortisol levels trigger tryptophan 2,3-dioxygenase activity, and the level of tryptophan decreases, leading to diminished synthesis of serotonin and melatonin [14, 15]. The positive effect of tocilizumab (a humanized anti-IL-6 receptor neutralizing antibody) on fatigue has been reported in the TAMARA [16] and the OPTION studies including rheumatoid arthritis patients [17]. These observations have shown that fatigue is one of the first symptoms which is reduced during initial treatment with biotherapeutic agents (such as etanercept and tocilizumab), while the positive effect of anti-inflammatory medications on joints is observed much later [6, 16, 17].

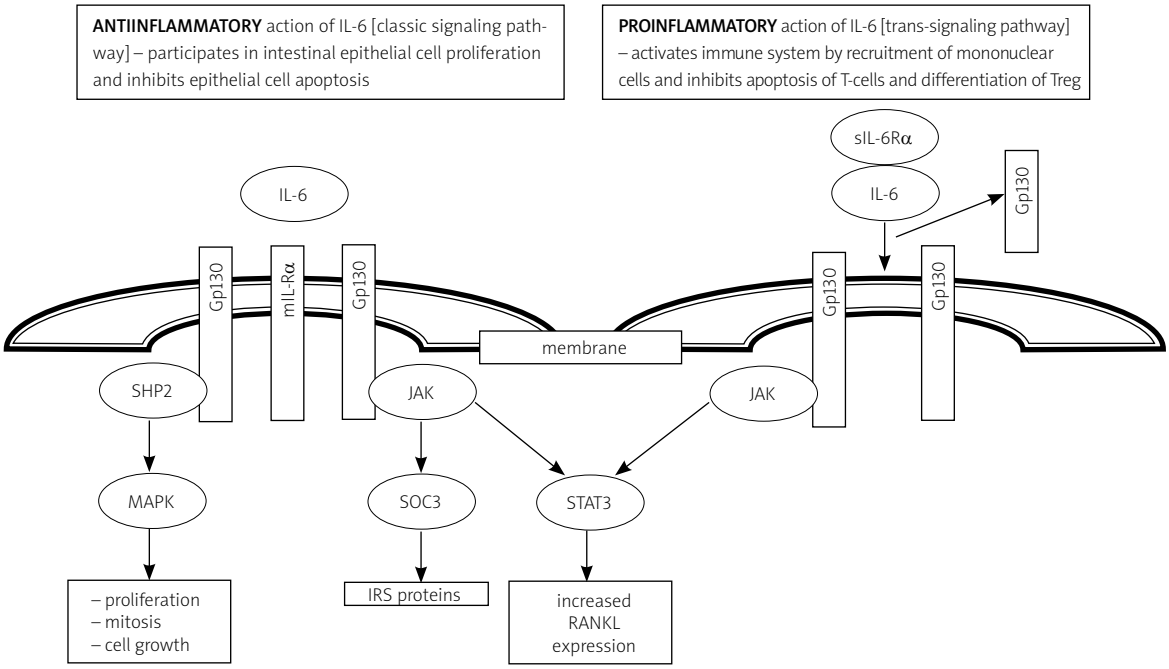
Molecular background of interleukin-6 activity

In many connective tissue diseases (e.g. rheumatoid and psoriatic arthritis), fatigue is associated with increased inflammatory markers, such as IL-6, tumor necrosis factor α (TNF-α), and C-reactive protein (CRP) [5, 18]. In these processes, IL-6 can interact with a ligand-binding receptor, IL-6Rα, either membrane-bound (mIL-6Rα, classical signaling) or in a soluble form (sIL-6Rα, trans-signaling) (Fig. 2). The complex of IL-6 and IL-6R interacts with membrane-bound β-receptor glycoprotein 130 (gp130) complexes containing the cytokine receptor subunit gp130, leading to its dimerization and the consequent activation of the associated JAK kinases [15]. The complex of IL-6 and its soluble receptor stimulates several types of target cells which are unresponsive to IL-6 alone, as they do not express the membrane-bound mIL-6Rα [14, 15]. In consequence, IL-6 reveals both pro- and anti-inflammatory properties [19].

Interestingly, the trans-signaling pattern of IL-6 is also observed in many neurologic cells, such as neurons, astrocytes, microglia, endothelial cells and mast cells in the CNS. These cells produce certain amounts of IL-6, but upon some stimuli (e.g. injury) the synthesis of IL-6 increases [15, 20, 21]. A similar increase in IL-6 level is observed in depression, which is often associated with fatigue [14, 15]. Recent studies have shown that mast cells have an important influence on fatigue development. These cells are crucial not only in allergic reactions, but also in immunity [21] and inflammatory diseases [20]. The stimulation of mast cells increases the release of cytokines, which could contribute to chronic fatigue syndrome characterized by fatigue and malaise [20, 21]. The specific perivascular localization of mast cells in close proximity to neurons suggests their role in fatigue [22].

Fatigue and nutritional components

An elevated level of IL-6 leads not only to fatigue but also to insulin resistance. The chronic administra-



mIL-6R – membrane-bound IL-6 receptor; sIL-6R–soluble-bound IL-6 receptor; STAT3 – signal transducer and activator of transcription 3; SOCS3 – suppressor of cytokine signaling 3; gp130 – the membrane-bound β-receptor glycoprotein 130; IRS – insulin receptor substrate, MAPK – mitogen activated protein kinase; tyrosine phosphatase SHP2 (Src-homology 2 domain-containing phosphatase 2); RANKL – receptor activator of nuclear factor κB ligand

Fig. 2. The action of IL-6 by membrane-bound receptor (classical signaling) or a soluble form (trans-signaling).

tion of IL-6 to mice at levels similar to those found in obese individuals leads to insulin resistance [23]. Consequently, there occurs excessive up-regulation of IL-6/STAT3 signaling, which induces systemic insulin resistance through induction of SOCS3 in various organs (STAT3 – signal transducer and activator of transcription 3; SOCS3 – suppressor of cytokine signaling 3) [23, 24]. Conversely, treatment with tocilizumab decreased glycated hemoglobin HbA_{1c} in diabetic patients with rheumatoid arthritis [25].

The dual activity of IL-6 has been supported in an animal model of hepatic steatosis induced by a methionine choline-deficient (MCD) diet. The treatments with anti-IL-6R antibody caused inhibition of both the classical and trans-signaling pathway (blocking IL-6/GP130 signaling by anti-IL-6 antibodies induced hepatic steatosis, but simultaneously ameliorated liver injury in mouse) [26]. Moreover, the increased body mass influences the feeling of tiredness [23]. The effect of obesity itself on physical fatigue is significant, even after controlling for depression or circulating levels of IL-6 [27]. Thus, an elevated level of IL-6 influences fatigue development in rheumatic diseases, but the presence of increased body mass itself may potentiate this effect [6, 10, 16, 23, 24].

Another reason for increased IL-6 and insulin resistance is increased body mass caused by a lack of physical activity (e.g. a decreased ability to move in arthritis) or side effects of medication (e.g. corticosteroids). Moreover, in patients with rheumatoid arthritis the ratio of fat to lean tissue increases, and usually abdominal deposition of fat is present [18, 26]. This does not mean that all patients with connective tissue diseases suffer from obesity or overweight, but changes in physiological compartments such as lean and fat mass are very often observed [27]. The study of Fried et al. [28] has shown that nearly one third of total circulating IL-6 is secreted by adipocytes, and this is mainly viscerally distributed. Hyperinsulinemia *per se* increases plasma levels of other proinflammatory cytokines such as TNF-α, and induced hepatic production of CRP is present [29]. These changes are responsible for the low-grade inflammation seen in the case of increased amounts of fat tissue [30]. Inflammatory processes induce the Kyn pathway (the 123 kynurenine pathway) – a major metabolic route of tryptophan (Trp) metabolism [31]. Tryptophan is a precursor for serotonin and melatonin. It regulates the energy intake and influences mood changes and fatigue occurrence [32]. If body mass increases, low-grade inflammation is observed and the ratio of Kyn to Trp concentration is el-

evated (this ratio reflects the Trp breakdown rate) [33]. Tryptophan is particularly abundant in oats, milk and other dairy products, chocolate, sesame, red meat and eggs. Increased availability of Trp might enhance serotonin production and reduce depressive symptoms and fatigue [32].

Physical exercise diminishes the level of pro-inflammatory cytokines and thereby enhances Trp levels and reduces circulating IL-6 concentrations [34]. Among overweight and obese adults with knee osteoarthritis, a diet and exercise implemented for 18 months led to reductions in body mass and IL-6 concentrations [35]. However, in connective tissue diseases, the inability to exercise is usually the result of arthritis and disorders of muscles and tendons. Adequate rehabilitation and the adjustment of activity to suit the patient can also reduce the level of pro-inflammatory cytokines and thus may minimize the feeling of tiredness [36].

The secretion of IL-6 also depends on the quality of the diet. Consumption of high-fat food is associated with an elevated level of IL-6 in the plasma of overweight subjects [37]. A significant increase in IL-6 has been observed at 4 and 8 hours after meals [37, 38]. In addition, the level of IL-6 depends on the amount of carbohydrates in a diet. The suppression of postprandial glucose elevation after consumption of a high-carbohydrate meal with an α-glucosidase inhibitor causes a lower postprandial increase in plasma IL-6 concentrations [38]. Reduced IL-6 diminishes fatigue; however, randomized prospective studies are needed to prove the influence of diet on fatigue.

Other nutritional components that should be recommended in autoimmune diseases to reduce inflammation and to diminish the level of IL-6 and fatigue are polyunsaturated omega-3 fatty acids (omega-3 PUFA). The main mechanism that is responsible for the positive influence of omega-3 PUFA on IL-6 concentration is related to nuclear factor κB (NF-κB) and peroxisome proliferator-activated receptors (PPAR) [39]. Polyunsaturated omega-3 fatty acids are a natural ligand of PPAR, which is a ligand-activated transcription factor and regulates gene expression. PPAR can inhibit the activation of NF-κB [40], which stimulates the gene encoding IL-6 [39]. During the inflammatory response oxidative stress processes are also generated and high oxidative stress leads to the activation of NF-κB. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reveal a beneficial (reducing) effect on the oxidative cascade, and thus the antioxidative effect of these acids may also help explain the suppressive effect on IL-6 [41]. Conversely, omega-6 polyunsaturated fatty acids (omega-6 PUFA) reveal an opposing effect and increase the inflammation [42]. It has been found that n-6 polyunsaturated fatty acids (mainly arachidonic acid – an intermediate product of omega-6 PUFA metabolism) can activate NF-κB and in consequence increase IL-6 levels. Similarly, arachidonic acid-derived eicosanoids participate in the regulation of IL-6 and increase the level of this cytokine [43].

As mentioned above, the mast cells located around the vessels in the CNS play a role in fatigue development [20–22]. Certain flavonoids (natural antioxidants) also inhibit mast cells [44, 45] and reveal neuroprotective effects [44]. One of these is quercetin – a flavonol found in many fruits, vegetables, and various kinds of honey. Quercetin reveals not only strong anti-oxidant properties but also anti-inflammatory activity [44, 45]. It inhibits mast cell degranulation and decreases the secretion of TNF-α, IL-6 and IL-8 [46]. However, the study of Bae et al. did not reveal any changes in the blood biomarkers of inflammation (TNF-α, IL-1β, IL-6 and CRP) and disease severity of rheumatoid arthritis patients under conventional medical treatments or dietary supplementation with antioxidants (quercetin + vitamin C and α-lipoic acid) over a period of 4 weeks [47]. Similar to the quercetin-related flavones, luteolin reduces IL-6 release from microglia cells [49]. Thus, these flavonoids may reduce the intensity of fatigue sensation and diminish the inflammation characteristic for autoimmune diseases.

Antioxidative properties are also shown by epigallocatechin gallate (EGCG, found mainly in white and green tea), which inhibits the synthesis of TNF-α, IL-6 and IL-8 [48]. Besides typical antioxidants, other food components may also influence fatigue occurrence. In rheumatoid arthritis the gut microbiota is altered and the supplementation of 10 colony-forming units of *Lactobacillus casei* 01 for eight weeks decreased not only IL-6 levels but also TNF-α and interleukin-12 [50]. Some anti-inflammatory properties are characteristic for ginger, which reduces cytokine synthesis in osteoarthritis. Its derivatives have the potential to control innate immune responses and they reveal anticatabolic properties in chondrocytes (they inhibit both NO production and IL-6 synthesis) [51].

Summary

Fatigue, one of the symptoms of connective tissue diseases, is reduced when the background diseases are treated with specific therapeutics (disease-modifying antirheumatic drugs [DMARDs] or biologic agents). However, the additional beneficial properties of food components, such as polyunsaturated omega-3 fatty acids, nutritional antioxidants, or the reduction of total fat or methionine in the diet, may reduce the inflammation by decreasing the level of proinflammatory cytokines and improve the symptoms, leading to a better physical and mental state. Overall, there is a growing scientific

rationale for the use of dietary supplements as adjuncts in the treatment of the inflammatory state present in many rheumatic diseases. However, prospective randomized large group studies are needed to prove the effectiveness of such treatment.

The authors declare no conflict of interest.

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