

Mechanism of Mitochondrial Dysfunction during Chronic Fatigue

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Abstract

A clinically defined condition characterized by persistent, severe, disabling fatigue lasting more than six months that is not reversed by sleep is regarded as chronic fatigue (CF). Fatigue is a complex phenomenon determined by several factors, including psychological health but at the biochemical level fatigue is related to the metabolic energy available to tissues and cells, mainly through mitochondrial respiration. Fatigue is the most common symptom of poorly functioning mitochondria. therefore dysfunction of these organelles may be the cause of the fatigue seen in CF. There is a great progress in the molecular understanding of mitochondrial disorder but the relation of mitochondrial dysfunction with CF and the underlying mechanism is not identified well in addition treatment of fatigue is still inadequate. In this review we try to summarize the relation between CF with mitochondrial dysfunction and determine the underline mechanism.

Keywords: Chronic fatigue; Mitochondria; ROS; TNF- α

Introduction

Chronic fatigue can be defined as an overwhelming sense of tiredness, which causes lack of energy, reduction in ability of body to work accompanied by feeling of exhaustion extreme physical or mental tiredness, resulting from severe stress and hard physical or mental work. [1-5]. It is different from normal experiences such as tiredness or sleepiness [4,6]. Fatigue can occur due to several reasons it can appear with stress or exhaustive exercise. [5,7,8] Fatigue causes various neurological, psychiatric and systemic diseases, it associated with a wide variety of conditions such as cancer, HIV infection (AIDS), chronic inflammatory disorder, Parkinson's, multiple sclerosis, amyotrophic lateral sclerosis, aging, and depression [4,9,10].

Chronic fatigue is a severe and distressing phenomenon to the patient by interfering with the patient's life, including social withdrawal, family conflicts and work disability [11,12]. Fatigue is a common symptom in the community, with up to half of the general population reporting fatigue in large surveys [13,14]. Worldwide nearly 10% of the general population suffered due to fatigue [15-18]. It also is reported by at least 20% of patients seeking medical care [19,20].

There are several different mechanisms for the occurrence of fatigue. Viral and bacterial, infections, psychosocial and physical stressors can be important factors for fatigue symptoms [7,9,21-23], it can also result from exhaustion of energy sources such as glucose and glycogen due to intense exercise [24-26]. Over accumulation of serum lactic acid and blood urea nitrogen will also result in metabolic disorders leading to fatigue [25,27]. Moreover intense exercise can cause accumulation of reactive free radicals which will lead the body in a state of oxidative stress and bring injury to the body by attacking large molecules and cell organs leading to physical fatigue [24,25,28,29].

Chronic fatigue and mitochondrial dysfunction

Mitochondrial dysfunction is a characteristic of disease. It has been implicated in nearly all pathologic and toxicologic conditions [30]. Several diseases and conditions are associated with dysfunction of the mitochondrion, such as Cancer, Alzheimer's disease, Parkinson's disease, schizophrenia, diabetes, chronic fatigue syndrome, non-alcoholic steatohepatitis etc. [31-35].

Fatigue is a complex phenomenon determined by several factors, including psychological health but at the biochemical level fatigue is related to the metabolic energy available to tissues and cells, mainly through mitochondrial electron transport [36], Fatigue is the most common symptom of poorly functioning mitochondria, The classic symptoms of persistent and debilitating fatigue, chronic muscle weakness, and myalgia are consistent with mitochondrial dysfunction in other diseases of known mitochondrial etiology [2]. Most fatigue patients report mental concentration impairment and cognitive deficits, which are also seen in mitochondrial dysfunctions [36,37]. Therefore dysfunction of these organelles may be the cause of the fatigue seen in chronic fatigue. Thus the integrity of mitochondrial membranes is critical to cell function and energy metabolism. More specifically, muscle fatigue with exercise intolerance is a multifactorial process characterized by failure to maintain an expected level of force during sustained or repeated muscle contraction, and is considered a common symptom of mitochondrial diseases [10,29,38-41].

Effect of reactive oxygen species in mitochondria during chronic fatigue

Mitochondria are crucial organelles for the production of energy by efficient aerobic energy metabolism and for the control of signaling cascades and they are suggested as being a primary regulator of autophagy in skeletal muscle [42] The predominant physiological function of mitochondria is the generation of energy as a form of ATP and heat by oxidative phosphorylation Mitochondria produce more than 90% of our cellular energy through metabolic processes called the

Krebs or citric acid cycle, and the electron transport chain (ETC) [30,33,34].

ROS are generated in all cells undergoing aerobic metabolism, although multiple compartments and enzymes contribute to the overall oxidative burden, Mitochondria are known to be a major physiological source of ROS, which are generated during oxidative phosphorylation occurring mainly at complexes I and III due to the release of electrons by NADH and FADH into the ETC [30,43-46]. ROS include several harmful species, such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (HO^\cdot) generated by mitochondrial respiration, as well as cellular enzymatic reactions in response to environmental stimuli [30,47].

The cell possesses antioxidant defense systems to counteract damaging ROS these are enzymatic antioxidants such as catalase, superoxide dismutase (SOD), glutathione peroxidase, and non-enzymatic antioxidants such as ascorbic acid (vitamin C), α -tocopherol (vitamin E) and β -carotene [30,43,48]. Under normal physiological conditions, this mitochondrial antioxidant defense system can adequately handles the potentially detrimental effects of ROS derived from energy metabolism, this cellular free-radical scavenging enzymes neutralize excess ROS and repair the enzymes that reverse ROS-mediated damage [36,48]. However, when these enzymes cannot convert ROS such as the superoxide radical to H_2O fast enough, oxidative damage occurs and accumulates in the mitochondria [29,30,49].

If the increase in free radicals is greater than the ability to neutralize them, ROS will attack cellular structures located near the sites where ROS are generated [30,44,48]. Functional imbalance between ROS levels and antioxidant concentrations can be caused by various disease states such as cancer, cardiovascular diseases, brain dysfunction, inflammatory diseases, neurodegenerative diseases, ischemia-reperfusion injury, and aging [43,48,50,51].

During the development of chronic fatigue oxidative damage impairs mitochondrial function. For example, in chronic fatigue syndrome patients there is evidence of oxidative damage to mitochondrial DNA and lipids [37]. Alterations of mitochondrial efficiency and function are mainly related to alterations in mitochondrial content, Failure in the electron transport system leads to the production of reactive oxygen species (ROS) such as hydrogen peroxide that can damage macromolecules and thus lead to dysfunctional cell components or even apoptosis [52]. Failure to maintain mitochondrial function results in failure to generate energy and increased free-radical production, converging mitochondrial permeability transition, mitochondrial depolarization, intracellular glutathione depletion and cytochrome c release and this will result energy impairment, oxidative stress, and also early apoptotic cell death. The diverse pro-apoptosis stimuli leading to disease [51,53,54].

Effect of inflammatory cytokines on mitochondria during chronic fatigue

Inflammation is associated with fatigue, it is common in acute infections as well as fatigue frequently reported among patients with inflammatory diseases such as multiple sclerosis and rheumatoid arthritis [4,55,56]. Moreover muscle tissue damage after physical exercise will induce an inflammatory response, studies have demonstrated exhaustive exercise can cause flu-like symptoms such as fever, chills, fatigue, myalgia, headache and appetite loss, these might be associated with hypercytokinemia [57-59].

The most influential cytokines are considered to be important are TNF- α , IL-1 and, IL-6 play a big role in the inflammatory response, and are crucial both in defense against infection and in development of autoimmune disease [4,59]. Pro-inflammatory cytokines in animals act on the brain during infection and other inflammatory states to cause sickness behaviour. This phenomenon is characterized by drowsiness, loss of appetite, decreased activity and withdrawal from social interaction and represents a change of behaviour theorized to enhance survival of infection [4,60,61]. Fatigue in humans could be considered a part of this biologically triggered coping mechanism.

Psychological stressors can induce the cytokine network and ROS pathway. ROS elevation as a result of inflammatory responses can cause damage to membrane fatty acids, functional proteins, DNA or mitochondria, which further aggravate the fatigue [9,21,62] In cancer patients, there is evidence that cytokines play a key role in the fatigue. HIV infection also is characterized by fatigue accompanied by clinical signs of inflammation [9].

Increased levels of proinflammatory cytokines due to bacterial or viral infection as well as stress trigger oxidative damage that can generate fatigue symptoms, including fatigue, a flu-like malaise, pain, symptoms of irritable bowel syndrome, and neurocognitive disorders [9]. There is plenty of evidence to indicate the effect Cytokines on mitochondrial function, Administration of cytokines to smooth muscle cells in culture reportedly inhibits mitochondrial respiration [63]. Related evidence suggests that cytokine imbalances occur in chronic fatigue and other chronic diseases [29,64,65]. Studies by Chazotte showed cytokine can lower mitochondrial membrane potential in human cells [2].

Inflammatory cytokine also mediated increases of ROS directly to inhibit mitochondrial respiration. They have been associated *in vitro* with mitochondrial dysfunction and increased ROS generation reducing complex III activity in the ETC, increasing ROS production resulting damage to mtDNA, alter mitochondrial membrane permeability and mitochondrial enzymatic dysfunction and also associated with muscle fatigue [29,33,66-70].

Tumor necrosis Factor α (TNF- α)

Muscle fatigue was associated with increased serum levels of TNF- α , studies revealed TNF- α which has a profound effect causing a marked and prolonged decrease on mitochondrial and cellular bioenergetics during chronic fatigue. The plasma concentration of TNF- α has been reported to rise several hours later after the finishing of intensive exercise though significant increases immediately after exercise were absent [29,59,67]. TNF-alpha have showed effect on membrane potentials of human cell lines was examined in relation to a possible role in CFS [2].

TNF- α level has been shown to be a key element for detection of mitochondrial dysfunction [30,33,71,72]. ROS have an important function in cell survival and cell death triggered by TNF- α signaling, and the main source of ROS generation required for TNF- α -induced cell death is the mitochondria [70,72,73]. TNF- α results in mitochondrial dysfunction by reducing complex III activity in the ETC, increasing ROS production and causing damage to mtDNA [33,71,73,74]. TNF- α generates ROS at the mitochondrial inner membrane, which may easily result in the progressive destruction of the mtDNA, possibly because of its proximity to the site of ROS production TNF α also decreased complex III activity of mitochondria which might be because of its higher susceptibility to ROS-induced

damage or due to decrease of the mtDNA copy number leads to a decrease in complex III activity decrease [33,71,73,74]. Moreover the activity of complex I, ATP production, and mitochondrial membrane potential ($\Delta\psi_m$) has shown to be affected due to TNF- α [75]. Therefore, complex I together with complex III have been suggested to be major sources of ROS. TNF- α displayed to mediate cardiac myocyte mtDNA damage and mitochondrial dysfunction *via* the overproduction of ROS [76]. A study by Corda and his clique revealed that TNF- α can induces a rapid increase in mitochondrial ROS production in human endothelial cells [77]. Studies with isolated cells implicated the effects of pro-inflammatory cytokines TNF- α in the generation of reactive oxygen species in mitochondria, altered mitochondrial membrane permeability and in mitochondrial enzymatic dysfunction as both early events and critical to the physiological mechanism of TNF- α action [74,76,77].

In addition, Studies with cells treated with TNF- α have recently shown that the mitochondrial cytochromes are critical targets of TNF- α action. Ceramide, another mediator of TNF- α function, has been reported to selectively inhibit complex III activity in isolated cardiac mitochondria [74]. Moreover, in adipocytes, the changes induced by TNF α cause pronounced morphological changes in the mitochondria, presumably due to variations in the levels of several mitofusion proteins [78].

Summary

Even though fatigue decreases the quality of life in people there are only few pharmacological drugs or therapies available for the treatment of fatigue [1,16-18,79]. Vitamins, minerals, and other metabolites supplementation may be a target Therapies for treatment of mitochondrial dysfunction and fatigue since they are necessary cofactors for the synthesis and function of mitochondrial enzymes and other compounds that support mitochondrial function [30,38,68,80,81]. Nevertheless the treatment of mitochondrial dysfunction and chronic fatigue is still inadequate, and their role in the treatment of the majority of these patients remains unclear.

Science mitochondrial dysfunction relate to almost all kinds of diseases, also fatigue is a common symptom seen in many kind of disease mitochondrial target therapy is the best choice for treatment of multiple disease including fatigue. Generally chronic fatigue is mainly related to mitochondrial dysfunction by increasing TNF- α level as well as attacking mitochondrial component through ROS induced lipid peroxidation and also by triggering damage in both inner and outer mitochondrial membranes, and disturbing mitochondrial dynamic network. Further studies needed to be done on in depth analysis of fatigue targeting mitochondrial dysfunction to determine the overall molecular mechanism and detailed signaling pathway in relation to TNF- α induced ROS generation and lipid peroxidation.

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