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.

Chronic fatigue and mitochondrial dysfunction

Mitochondria 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•) 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 handle 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].

The most influential cytokines are considered to be important are TNF-a, 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 [46,60,61]. 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 TNFα 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 (Δψm) 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 TNFα cause pronounced morphological changes in the mitochondria, presumably due to variations in the levels of several mitofusin 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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**References**

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, et al. (1994) The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 121: 953-959.

2. Chazotte B (2001) Mitochondrial Dysfunction in Chronic Fatigue Syndrome. New York: Plenum Publishers.

3. Krupp LB, Pollina DA (1996) Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol 9: 456-460.

4. Norheim KB, Jonsson G, Omdal R (2011) Biological mechanisms of chronic fatigue. Rheumatol 50: 1009-1018.

5. Prins JB, van der Meer JW, Bleijenberg G (2006) Chronic fatigue syndrome. Lancet 367: 346-355.

6. Krupp LB, LaRocca NG, Muiir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46: 1121-1123.

7. Jammes Y, Steinberg JG, Dellaux S, Brégeon F (2009) Chronic fatigue syndrome combines increased exercise-induced oxidative stress and reduced cytokine and Hsp responses. J Intern Med 266: 196-206.

8. Malm C (2002) Exercise immunology: a skeletal muscle perspective. Exerc Immunol Rev 8: 116-167.

9. Maes M, Twisk FN (2010) Chronic fatigue syndrome: Harvey and Wessely’s (bio) psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways. BMC Med 8: 35.

10. Davis MP, Walsh D (2010) Mechanisms of fatigue. J Support Oncol 8: 164-174.

11. McElhone K, Abbott J, Teh LS (2006) A review of health related quality of life in systemic lupus erythematosus. Lupus 15: 633-643.

12. Krupp LB, LaRocca NG, Muiir J, Steinberg AD (1990) A study of fatigue in systemic lupus erythematosus. J Rheumatol 17: 1450-1452.

13. Chen MK (1986) The epidemiology of self-perceived fatigue among adults. Prev Med 15: 74-81.

14. Pawlikowska T, Chalder T, Hirsch SR, Wallace P, Wright DJ, et al. (1994) Population based study of fatigue and psychological distress. BMJ 308: 763-766.

15. Nijroder I, van der Windt D, de Vries H, van der Horst H (2009) Diagnoses during follow-up of patients presenting with fatigue in primary care. CMAJ 181: 683-687.

16. Kim CH, Shin HC, Won CW (2005) Prevalence of chronic fatigue and chronic fatigue syndrome in Korea: community-based primary care study. J Korean Med Sci 20: 529-534.

17. Reeves WC, Jones JF; Maloney E, Heim C, Hoaglin DC, et al. (2007) Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr 5: 5.

18. Bates DW, Schmitt W, Buchwald D, Ware NC, Lee J, et al. (1993) Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Intern Med 153: 2759-2765.

19. Afari N, Buchwald D (2003) Chronic fatigue syndrome: a review. Am J Psychiatry 160: 221-236.

20. Maes M (2009) Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. Curr Opin Psychiatry 22: 75-83.

21. Sivonová M, Zitnanová I, Hlincíková L, Skodácek I, Trebatická J, et al. (2004) Oxidative stress in university students during examinations. Stress 7: 183-188.

22. Bassi N, Amital D, Amital H, Doria A, Shoenfeld Y (2008) Chronic fatigue syndrome: characteristics and possible causes for its pathogenesis. Isr Med Assoc J 10: 79-82.

23. You L, Zhao M, Regenstein JM, Jiao Yan R (2011) In vitro antioxidant activity and in vivo anti-fatigue effect of loach (Mispumus anguillicaudatus) peptides prepared by papain digestion. Food Chem 124: 188-194.

24. Wang L, Zhang HL, Lu R, Zhou YJ, Ma R, et al. (2008) The decapetide CMS001 enhances swimming endurance in mice. Peptides 29: 1176-1182.

25. Costill DL, Pascoe DD, Fink WJ, Robergs RA, Barr SI, et al. (1990) Impaired muscle glycogen resynthesis after eccentric exercise. J Appl Physiol 69: 46-50.
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27. Tan W, Yu QK, Liu YY, Ouyang MZ, Yan MH, et al. (2012) Anti-fatigue activity of polysaccharides extract from Radix Rehmanniae Preparata. Int J Biol Macromol 50: 59-62.

28. Bloomer RJ, Goldfarb AH, Wideman L, McKenzie MJ, Consitt LA (2005) Effects of acute aerobic and anaerobic exercise on blood markers of oxidative stress. J Strength Cond Res 19: 276-285.

29. Finsterer J (2012) Biomarkers of peripheral muscle fatigue during exercise. BMC Musculoskelet Disord 13: 218.

30. Pieczenik SR, Neustadt J (2008) Medication-induced mitochondrial damage and molecular pathways of disease. Exp Mol Pathol 85: 84-92.

31. Wiegman CH, Michaeloudes C, Haji G, Narang P, Clarke CJ, et al. (2015) Oxidative stress-induced mitochondrial dysfunction drives inflammation and airway smooth muscle remodeling in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 136: 769-780.

32. Zanellati MC, Monti V, Barzaghi C, Reale C, Nardocci N, et al. (2015) Mitochondrial dysfunction in Parkinson disease: evidence in mutant PARK2 fibroblasts. Front Genet 6: 78.

33. Neustadt J, Pieczenik SR (2008) Medication-induced mitochondrial damage and disease. Mol Nutr Food Res 52: 780-788.

34. Brand MD, Nicholls DG (2011) Assessing mitochondrial dysfunction in cells. Biochem J 435: 297-312.

35. Schuh RA, Clerc P, Hwang H, Mehrabian Z, Bittman K, et al. (2011) Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev 88: 1243-1276.

36. Wu SJ, Ng LT, Chen CH, Lin DL, Wang SS, et al. (2004) Antihypertension activity of Physalis angulata and P. peruviana extracts and their effects on apoptosis in human Hep G2 cells. Life Sci 74: 2061-2073.

37. Hagl S, Kocher A, Schiborr C, Eckert SH, Ciobanu I, et al. (2013) Rice bran extract protects from mitochondrial dysfunction in guinea pig brains. Pharmacol Res 76: 17-27.

38. Pfeffer G, Chinnery PF (2013) Diagnosis and treatment of mitochondrial myopathies. Ann Med 45: 4-16.

39. Milone M, Wong LJ (2013) Diagnosis of mitochondrial myopathies. Mol Genet Metab 110: 35-41.

40. Hewlett S, Cockshott Z, Byron M, Kitchen K, Tipler S, et al. (2005) Patients’ perceptions of fatigue in rheumatoid arthritis: overwhelming, controllable, ignored. Arthritis Rheum 53: 697-702.

41. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC (1988) Fatigue in multiple sclerosis. Arch Neurol 45: 435-437.

42. Cannon JG, St Pierre BA (1998) Cytokines in exertion-induced skeletal muscle injury. Mol Cell Biochem 179: 159-167.

43. Smith LL (2000) Cytokine hypothesis of overtraining: a physiological adaptation to excess stress? Med Sci Sports Exerc 32: 317-331.

44. Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, et al. (2002) Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. Exerc Immunol Rev 8: 6-48.

45. Hart BL (1988) Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 12: 123-137.

46. Dantzer R, O’Connor JC, Freund GG, Johnson RW, Kelley KW (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9: 46-56.

47. Maes M, Coucke F, Leunis JC (2007) Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome. Neuro Endocrinol Lett 28: 739-744.

48. Geng Y, Hansson GK, Holme E (1992) Interferon-gamma and tumor necrosis factor synergize to induce nitric oxide production and inhibit mitochondrial respiration in vascular smooth muscle cells. Circ Res 71: 1268-1276.

49. Lloyd A, Hickie I, Brockman A, Dwyer J, Wakefield D (1991) Cytokine levels in serum and cerebrospinal fluid in patients with chronic fatigue syndrome and control subjects. J Infect Dis 164: 1023-1024.

50. Katz BZ, Shaishi Y, Mears CJ, Binns HJ (2009) Chronic fatigue syndrome after infectious mononucleosis in adolescents. Pediatrics 124: 189-193.

51. Moe GW, Marin-Garcia J, Konig A, Goldenthal M, Lu X, et al. (2004) In vivo TNF-alpha inhibition ameliorates cardiac mitochondrial dysfunction, oxidative stress, and apoptosis in experimental heart failure. Am J Physiol Heart Circ Physiol 287: H1813-1820.

52. Spruit MA, Thoomeer MJ, Gosselin R, Troosters T, Kasran A, et al. (2005) Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. Thorax 60: 32-38.

53. Nakamura K, Fushimi K, Kouchi H, Mihara K, Miyazaki M, et al. (1998) Inhibitory effects of antioxidants on neonatal rat cardiac myocyte hypertrophy induced by tumor necrosis factor-alpha and angiotensin II. Circulation 98: 794-799.

54. Suematsu N, Tsutsui H, Wen J, Kang D, Ikeuchi M, et al. (2003) Oxidative stress mediates tumor necrosis factor-alpha-induced mitochondrial DNA damage and dysfunction in cardiac myocytes. Circulation 107: 1418-1423.

55. Meier B, Radeke HH, Selle S, Younes M, Sies H, et al. (1989) Human fibroblasts release reactive oxygen species in response to interleukin-1 or tumour necrosis factor-alpha. Biochem J 263: 539-545.
71. Doll DN, Rellick SL, Barr TL, Ren X, Simpkins JW (2015) Rapid mitochondrial dysfunction mediates TNF-alpha-induced neurotoxicity. J Neurochem 132: 443-451.

72. Kim JJ, Lee SB, Park JK, Yoo YD (2010) TNF-alpha-induced ROS production triggering apoptosis is directly linked to Romo1 and Bcl-X(L). Cell Death Differ 17: 1420-1434.

73. Marshall KD, Baines CP (2014) Necroptosis: is there a role for mitochondria? Front Physiol 5: 323.

74. Martin-Garcia J, Goldenthal MJ, Moe GW (2001) Abnormal cardiac and skeletal muscle mitochondrial function in pacing-induced cardiac failure. Cardiovasc Res 52: 103-110.

75. López-Armada MJ, Riveiro-Naveira RR, Vaamonde-Garcia C, Valcárcel-Ares MN (2013) Mitochondrial dysfunction and the inflammatory response. Mitochondrion 13: 106-118.

76. Suematsu N (2003) Oxidative Stress Mediates Tumor Necrosis Factor-alpha-Induced Mitochondrial DNA Damage and Dysfunction in Cardiac Myocytes 107: 1418-1423.

77. Corda S, Laplace C, Vicaud E, Duranteau J (2001) Rapid reactive oxygen species production by mitochondria in endothelial cells exposed to tumor necrosis factor-alpha is mediated by ceramide. Am J Respir Cell Mol Biol 24: 762-768.

78. Chen CC, Tsai SH, Lu CC, Hu ST, Wu TS, et al. (2012) Activation of an NLRP3 inflammasome restricts Mycobacterium kansasii infection. PLoS One 7: e36292.

79. Uthayathas S, Karuppagounder SS, Tamer SI, Parameshwaran K, Degim T, et al. (2007) Evaluation of neuroprotective and anti-fatigue effects of sildenafil. Life Sci 81: 988-992.

80. Glover EI, Martin J, Maher A, Thornhill RE, Moran GR, et al. (2010) A randomized trial of coenzyme Q10 in mitochondrial disorders. Muscle Nerve 42: 739-748.

81. Taylor RW, Schaefer AM, Barron MJ, McFarland R, Turnbull DM (2004) The diagnosis of mitochondrial muscle disease. Neuromuscul Disord 14: 237-245.