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FATIGUE DURING EXERCISE

Zbigniew Szyguła[1], Wojciech Gawroński[1], Michael I. Kalinski[2]

[1]Department of Sports Medicine, University School of Physical Education, Krakow, Poland
[2]School of Exercise, Leisure and Sport, Kent State University, Kent, OH, USA

ABSTRACT

Fatigue is a physiological state occurring during engagement in a physical or mental activity. It lowers performance levels, decreases the speed of movements or causes complete work discontinuation. There are two different patterns of fatigue – one, the pattern being the effect of short-term effort of high-intensity and second, the pattern as the result of long-term exercise. Energetic insufficiency plays an important role in the etiology of muscle fatigue. The other most common changes associated with fatigue are: accumulation of acidic metabolic by-products in working muscles, and finally, the failure of the contractile mechanisms in the muscle fiber. Also described are the alterations in metabolism of some neurotransmitters in central nervous system occurring during exercise, depicted as central fatigue. The paper discusses changes occurring during short-term intensive exercise and long-term exercise, respectively.

Key words: *muscle fatigue, peripheral fatigue, central fatigue, short-term exercise, long-term exercise*

Fatigue is the state of decreased performance ability connected with human activity – both physical and mental. It is the effect of excessive work output and should be treated as physiological occurrence, which protects the organism from harmful consequences that could appear if the exercise were continued. Fatigue can also appear without any physical activity, being the result of sleep-lack or sleepless, jet-leg, etc. The fatigue syndrome often occurs during insignificant exertions and can be affected by such factors as: age, physical activity, infections, circulatory system diseases, etc. Recently, sex differences in muscle fatigue have also been described. Females generally exhibit a greater relative resistance as compare to males and the phenomenon has been observed in a variety of muscles with the use of various of fatigue protocols. Several possible mechanisms have been pointed out for this sex difference such as: muscle mass, substrate utilization, muscle morphology, and neuromuscular activation (14).

Fatigue causes depletion of work effectiveness, decreases in the speed of movements or even complete work discontinuation. It is often observed in athletic performance in situations where a competitor's exertions suddenly break down, the athlete slows down or gives up, regardless of a strong motivation and will to win. With this occurrence, so many questions arise: What has just happened to this athlete's performance? Was it a psychological or a physiological obstacle that was hit? What is "fatigue" and how does it work?

Most research concerning fatigue is limited to the following changes, which occur in working muscles (peripheral fatigue). For a long time it was believed that

muscle acidosis caused by accumulation of metabolic by-products is responsible for exertional pain and the end of work output. Shortage of energetic supplies as a cause of fatigue was also indicated. However, it turns out, new research show that these occurrences are more often combined. The most often described occurrences connected with fatigue and exhaustion are: decrease of energetic reserves in muscles (glycogen, ATP-PCr), accumulation of metabolic by-products in working muscles and increases in intramuscular pH, disorders of muscle contraction or changes in the nervous system (central fatigue). In order to explain the notion of fatigue, few theories have been examined such as the energetic supply depletion theory, acidosis theory, hypo-oxidation theory, intoxication theory, defense theory or catastrophe theory (9, 45).

The topic is still interesting and recently some excellent reviews on fatigue have been published. For more detailed information see publications by Enoka & Stuart (10); Hicks et al.(14), Lambert & Flynn (18), Roberts & Smith (31), Rouillon & Candau (32), Sahlin (34), St Clair Gibson et al. (40), Viru & Pääsuke(45), Walsh (47), describing the phenomenon from different points of view.

The aim of this paper is to introduce the key changes occurring in organism during physical activity contributing to the fatigue phenomenon.

Definition and symptoms of fatigue

Defining fatigue is difficult in itself because of diversity of the forms of exhaustion connected with athletic performance. "Fatigue" is the term often used to describe the feeling of tiredness and inability to perform work. The easiest way to define fatigue is to describe it as a "passing-by" state of lowered work ability caused by activity performance and other related factors. Those other factors include: noise, monotonous activities repeated for some period of time, lack of sleep, high temperature of environment. A definition, which describes fatigue as a physiological occurrence, which protects organism from exhaustion, is also often used. Fatigue can also be characterized as a state of disturbance of the inner functional balance (homeostasis) of an organ or organism induced by physical effort. The more difficult the effort is the more rapidly the homeostasis is disturbed. These disorders more often appear in untrained individuals and are commonly due to unfavorable environmental conditions. Deterioration of inner environment properties can have a negative influence on a particular cell's function, the organ's function, and the whole organism's function, which manifests itself in the lowering of performance intensity and the effectiveness of movements. Many subjective and objective symptoms appear at that time (Table 1). Movements become less fluent, slower and less coordinated. The amount of mistakes made increases, further effort seems futile and production of effort ceases. Fatigue may be considered as protective mechanism against destruction – a kind of muscle wisdom (10, 32). Homeostasis disturbance can be delayed or stopped momentarily in many ways. These methods are: administration of liquids, carbohydrates, branched chain amino acids, cooling of internal temperature, etc. Inner environmental disturbances are recovered after the end of exercise and this process may be supported by proper treatment, like biological renewing.

A biochemical characterization of fatigue describes the occurrence as the decreased ability to utilize energetic sources efficiently – the muscle's failure to generate force and power fast enough to meet metabolic demands. This inability can be a result in numerous local changes

Table 1. *Subjective and objective symptoms of fatigue*

SUBJECTIVE SYMPTOMS OF FATIGUE	OBJECTIVE SYMPTOMS OF FATIGUE
Muscle pain	Reduction in speed and power of muscle contraction
Muscle weaknesses feeling	Lowering of muscular excitability
Feeling of exhaustion	Elongation of reaction time
Dyspnea/Breathlessness	Worsening of movement co-ordination
Thorax pain	Deterioration of movement precision
Dizziness	Raising of body temperature
Nausea	Excessive elevation of heart rate
	Hyperventilation
	Vomits
	Syncope/Fainting

in both working muscles, commonly referred to as peripheral fatigue; and/or changes in ner-vous system are related to central fatigue. However, one should remember that the function of muscles and all movement releasing and controlling systems are interrelated. Functional alterations occurring in any site of regulation in any aspect of the combined structures may cause decrease of muscles ability to generate demanded or expected power (force) output, which can be classified as fatigue.

From the neurophysiological point of view, fatigue could be described as a reduction in efferent motor commands to the active muscles which results in a decline in force or tension (11).

From the biochemical standpoint, fatigue also may be interpreted as alteration hindering ATP (re)synthesis in muscle tissue. Slowing down ATP re-synthesis from one standpoint causes lowering of generated power output, from the standpoint the slowing of muscle relaxation is effected.

Intensity and duration of physical exercise dictates the forms in which fatigue appears. In this review, the changes associated with short-term, high-intensity performance or long-term performance are examined.

Changes that consist for fatigue phenomenon in short-term effort of high-intensity

These changes have local characteristics and mainly consider muscles directly included in performance. Since the main source of energy in short-term effort of high-intensity are the anaerobic metabolic processes, a decrease in high-energetic phosphorus compounds (ATP and PCr) and muscle cells acidosis occur very quickly (35) .

Energetic supply depletion

ATP is a direct energy source for muscle contraction and its relaxation. This occurs as myosin ATP is hydrolyzed to ADP and inorganic phosphorus and so the energy is released. Since intramuscular ATP stores are minimal, this is a contributing factor as to why this compound has to be constantly and quickly regenerated. For immediate ATP regeneration phosphocreatine (PCr) is essential but its extent in muscle is limited. It has been considered that the shortage of PCr in the cytoplasm is

responsible for fatigue (5, 18). However, the stores of ATP and phosphocreatine are not fully depleted in working muscle. Minimal values of ATP and PCr observed at exhaustion were 70% and 10% of resting values, respectively (after 31). In certain fibers nevertheless, ATP decreases by about 80% (39).

Reduction in ATP supply and increased ADP levels in muscle cell inhibit myofibril ATPase, which is responsible for chemical energy transfer to contractility system. Inhibition of myofibril ATPase protects ATP from total depletion. ATPase, which is also functionally coupled with sodium-kalium pump mechanisms responsible for membrane repolarization and excitability of muscle cell, can also be blocked (13).

Acidosis of working muscles

Other important changes occurring during short-term, high-intensity effort is the acidosis of working muscles, which is the effect of accumulation of metabolites from anaerobic metabolism. Lactic acid arises in large amounts as a result of intensive physical activity dissociating to lactate and hydrogen ions, which causes increases in concentration levels in the cell. As the result of the increasing hydrogen H^+ concentrations, intramuscular pH decreases from the resting level 7,1 to the 6,6-6,4 e.g. after a sprinter's run (35, 48) and has been exhibited even lower at 6,15 or 6,0 (35). Enhanced concentration of hydrogen ions in the muscle cell and increasing acidification cause inhibition of muscle function and the decrease of power and strength, both changes contributing to the development of local fatigue. Other possible contributing developments influenced by increasing acidosis include:

- The blockade of glycolytic enzymes, which can contribute to the retardation or interruption of glycolysis and ATP synthesis (5, 35, 48).
- Negative influence on the muscles contraction mechanism by affecting the calcium ion influx, the bonding by troponin and affecting the actin-myosin complex formation (5, 45, 48).
- H^+ ions released to the extracellular space irritate muscles pain receptors (5). As a consequence, reflex enlargement of muscle tension and its relaxation occur causing compression of blood vessels and hampering of oxygen access to the working muscles. This intensification of local oxygen deficiency in tissues is referred to as hypoxia. Hypoxia can be related to reflex blocking of motor conduction (45).

Bangsbo et al. however, suggested that elevated muscle acidosis has not effected negatively muscle glycogen breakdown and lactate production and has little influence on the efficiency of the muscle contractions (2). Instead, they pointed out that accumulation of potassium in muscle interstitium may be the important factor in developing fatigue, though the possible mechanisms are not clear. Although low muscle pH *per se* has not appeared to cause fatigue during intense exercise, a decrease in pH may promote development of fatigue by increasing the release of potassium from the muscle cells (2).

Additionally, hydrogen ions quickly defuse from muscle cell to the blood causing reduction of blood pH and whole list of other side-effects related to the central nervous system such as: pain, nausea, orientation disorders (5).

Changes consisting for fatigue phenomenon in long-term effort

Energetic stores reduction

The main cause of fatigue in efforts lasting more than one hour (but not longer than 4-5 hours) is significant energetic sources reduction (19). According to the po-

pular theory of exhaustion, fatigue development is the effect of an organism's energetic resource decline, which leads to subjective syndromes of fatigue intensification and work discontinuation. In physiological conditions however, including extremely heavy physical effort, total energetic stores diminution never occurs. Muscle glycogen stores may significantly decline but liver glycogen stores will most likely not be totally exhausted (36). Blocking of extramuscular glycolytic enzymes – hexokinase, phosphofructokinase and glycogen phosphorylase - protect from its complete depletion (35). Fatigue can also appear when there are a considerable fat reserves stored up in the organism (25). Examples of extreme starvation also show that proteins can be used as the source of energy. However, as significant muscle glycogen stores decline and glycolytic enzyme blocking leads to a limited ATP re-synthesis, elevated ADP levels can lead to energetic emergency in the muscle cell (33). Such state an energetic crisis can also contribute to such changes as hampered supply of working muscles in oxygen and CO_2 and lactic acid accumulation, which can provoke glycolytic enzymes inhibition (36).

Long-lasting physical effort may also lead to the decline in blood glucose. Because glucose is one of the energetic substances for brain cells, its deficiency in blood causes such manifestations as co-ordination disorders, increases in the amount of mistakes made, orientation disorders, etc (5, 27, 35). Finally, adrenergic syndromes appear which are typical for hypoglycemia. Hypoglycemia and it's symptoms could be effectively prevented when blood glucose homeostasis is maintained via carbohydrate supplementation (27).

Rise of core temperature

If the effort lasts longer than a few minutes, the production of metabolic heat increases significantly. When the effort is taking place in an environment where the temperature and humidity is heightened, the inner organism's temperature raises rapidly. Because humans are homothermal organisms, certain systems, organs, tissues and cells function optimally in the temperature of 37°C. A 2° body-temperature increase disturbs the basic metabolic processes and causes disorder in the cells and organs. A 3° inner-temperature increase above resting levels can cause a complete distraction of physical and psychological processes.

First symptoms of overheating (hyperthermia) include: headaches, confusion, orientation disorders, irrational behavior, weakness, sleepiness and painful muscle spasms. Later, nausea and dizziness occur (43, 44). Hyperthermia leads to deterioration of central nervous system efficiency and alter EEG activity. The rise in core temperature correlates with rating of perceived exertion (28). On the other hand the rise of body temperature leads to a response by the circulatory and respiratory system to intensify efforts according to the task requirements. In muscle cells, oxidative phosphorylation efficiency and ATP level decrease with synchronized rate. There is also an increase of lactate production and acceleration of glycogen depletion in muscles. Effort in hot environment leads to rising of skin temperature and vasodilatation and blood translocation to peripheral vessels. If blood remains in the lower body extremities, a reduction of venous return and arterial hypotension occur. This can result in secondary brain ischaemia and temporary loss of conscious, commonly referred to as syncope (26).

Dehydration

Human organism withstands overheating by sweating, utilizing vaporization as heat is taken away from the skin. When the

sweating is intensified up to 1-1,5l/h (sometimes even up to 3,5l/h) it can initiate a state of dehydration. As a result of such significant dehydration, heat elimination from the organism becomes diminished and inner-temperature begins to rise very rapidly. Moreover, dehydration causes numerous physiological changes, which negatively influence effort skills. Water decrease in muscle also provokes muscle cramping. Lowering of physical efficiency can be the result of circulation system activity due to impaired ability to sustain psychical activity. The more significant the water reduction, the more negative the influence on physical abilities occurs. Even small dehydration (water reduction of approximately 1% of body mass) can deteriorate organism efficiency (19). Reductions of maximal aerobic power, ability to perform supramaximal efforts, muscle resistance, anaerobic efficiency, and work volume have all been properly documented (43, 44). It is considered that water decrease of approximately 3% of body mass, (equivalent to approximately 2100 ml of water in 70 kilo man), is the critical point of dehydration development. From this threshold, significant decreases in performance efficiency are observed (43, 44).

Alterations in electrolyte equilibrium

Alterations in electrolyte equilibrium occurring during physical effort are mainly the effect of electrolyte loss due to sweat and dehydration (19, 29). Similar disorders are also the result of electrolytes movement along intracellular and extracellular space. During prolonged effort, enlarged potassium ion concentration in extracellular space is observed (19, 38). Elevation of potassium ion levels results mainly in a local effect – a decrease in muscle fiber contraction and reduction of cell membrane excitability. Elevated potassium levels in the extracellular space can also have harmful influence on the circulatory system (38).

Muscle pain during and after the effort

During intensified physical effort, sometimes acute pain occurs in working muscles, which is known to quickly disappear after the exertion bout. This pain is mainly associated with the irritation of muscles pain receptors by acidic metabolite accumulation and increased hydrogen ion concentration. Moreover, tissue edema occurs as the result of liquid movement from vessels space to tissues. This edema impairs blood circulation in muscles, making supplementation of oxygen and energetic products difficult. This occurrence is known to block the acidic metabolites inorganic phosphorus and ammonia (48) leading to energetic emergency in working muscle cells. In long-term efforts, decrease of energetic supplies in muscle should be taken into consideration (48). Apart from acute pain, there is also delayed-onset muscle soreness (DOMS) associated with fatigue, which appears in 12-48 hour time frame post-physical effort. The common symptoms of DOMS include muscle-swelling, pain during palpation, decrease of maximal voluntary force, and neuromuscular dysfunction. Few theories are proposed which attempt to explain this phenomenon, but muscle acidosis as a result of this kind of soreness (DOMS) probably has to be excluded. It is pointed out that many eccentric exercises (e.g. running downhill) and certain strength exercises are responsible for cell membrane, contractile protein, and connective tissue destruction (15). Muscle damage may in some cases show up as massive rhabdomyolisis (12, 30). In muscles damage, also free-radicals processes take part. Free radicals generated in enlarged numbers during the effort provoke cell membrane lipid peroxidation and its devastation (37). Biochemical indicators of muscle damage include heightened cell enzymes level in peripheral blood – creatine kinase (CK), lactate dehydrogenase (LDH) - and the presence of myoglobin in urine. Exten-

ded excretion of hydroxyproline in urine evidences changes in connective tissue metabolism. Muscle damage provokes a chain reaction – release of cell proteins from muscle fibers, inflammatory process and healing process further on (5, 48). The inflammatory process is associated with edema, soreness and increase of cell membranes permeability. Further, histamine, serotonin, prostaglandin (PGE_2), nitrogen oxide, cytokine (Interleukin-1, Tumor Necrosis Factor) and interpheron are released, while leukocytes, monocytes, macrophage and neutrophile are accumulated in focus of inflammation (5). The aim of the inflammatory process is the removal of damaged tissue and preparation of the healing area. In this time, tissue edema and chemical mediators irritate nervous receptors causing soreness that lasts from 1 to 3 days after the effort. Damage and pain-related symptoms are more significant in untrained individuals and in athletes after extension of training volume or after introduction of a new form of effort.

The introduction of nucleus magnetic resonance spectroscopy (NMR) into non-invasive muscle metabolism test became significantly useful for widening our knowledge about muscle cell bioenergetics and for the development fatigue mechanism understanding. These types of tests also allowed scientists to identify the significance of such substances as inorganic phosphorus (P_i), ADP, inosine monophosphate, the products of ATP hydrolysis, and their role in the development of muscle fatigue (1, 4, 5, 22, 46). Aside from the indicated factors, other modulators, such as ammonia, lipid acids and derivatives, are being investigated and are thought to play a significant role in fatigue development

Central Fatigue Hypothesis

It has become increasingly clear that the role of the central nervous system (CNS) needs to be better investigated and elucidated in order to explain any functional links and interrelationships between muscle and brain in fatigue (6, 7, 8, 16, 17, 20, 23, 24, 25, 42). Researchers support the assumption suggesting the existence of an important relationship between brain serotonin (5-HT) and central fatigue. The hypothesis has implicated neurotransmitter 5-HT as a possible mediator of central fatigue and its establishment has been due to the high impact of 5-HT on intercommunicative neuronal transmission in the brain at states of exertions or disease. This premise suggested that enhanced brain 5-HT metabolism has an important role in centrally mediated decreases in endurance performance. Further clarification of the mechanisms of central fatigue has led to suggestion to reconsider the assumption that exercise-induced increases in 5-HT precursors supplied to the brain causes decrease in exercise performance. In the recent revision of the hypothesis, it was also suggested that enhanced 5-HT biosynthesis does not by itself initiate central fatigue. Central fatigue has instead been associated with possible impairment of complex neuromodulation and the impaired interaction of central neurotransmitters (42).

Hypotheses have also been proposed concerning other neurotransmitters and neuromodulators such as dopamine (DA), acetylcholine, cytokines and ammonia and their possible role in the mechanisms of central fatigue. The view that DA, a principal neurotransmitter associated with the control of locomotion, is involved in mechanism of central fatigue is receiving increasingly more attention. Data from animal studies (6, 20) suggest that strenuous exercise significantly influence the release, synthesis and metabolism of DA in brain. In the investigations of central fatigue it was particularly difficult to separate the causality from concurrent appearance and

the studies of the metabolism of regional brain DA during exercise have also produced conflicting results. For example, data showing increased striatal DA concentrations after exhaustive exercise has been contrasted with research yielding results of no effects on striatal DA at fatigue. Low ratio of brain 5-HT to DA has been recently implicated to favor improved performance, whereas a high ratio of brain 5-HT to DA has been involved in decreases in performance (8). Exercise training appears to result in diminished basal activity of striatal DA (21). A pharmacological paradigm was utilized in our investigation in order to evaluate the relationship between the nigrostriatal dopaminergic system and running performance by treating mice with methamphetamine (MA) (16). MA produces a major reduction in striatal DA content as well as inhibition of vesicular transporter function in dopaminergic neurons and DA uptake. Treatment with methamphetamine (MA – 20mg/kg x 2h intervals) or its vehicle at 7 days prior to tests of running time to exhaustion were evaluated in 60-day-old CD-1 male mice. Pre-treatment running times were not significantly different between the two groups. MA resulted in significantly decreased running times to exhaustion compared to vehicle-treated controls and a significant reduction in corpus striatal dopamine and DOPAC but not norepinephrine (16). No statistically significant differences in catecholamines were obtained within the hypothalamus. Nor were body weights significantly different between these groups. The data show that a regimen of MA, which results in an approximate 90% depletion of striatal DA, produces a reduction in running time to exhaustion (16).

Transgenic animals have served as valuable models for the study of physiological processes and perturbations in these processes, which result from targeted gene mutations. Mice with a targeted deletion for one of the copies of the neurotrophin-3 (NT3) gene show a number of structural and functional deficits in their cardiac system resulting from a diminished sympathetic innervation. Since NT3 represents a member of the neurotrophin family, which is required for growth, differentiation and survival of neurons, this reduction in sympathetic innervation of +/- NT3 mice is not unexpected. Moreover, significant decreases in sensory neurons within the peripheral nervous system are observed in these +/- NT3 mice. While +/- NT3 mice do not appear to show any salient differences to their wild type littermates and are capable of reproducing, some abnormal postures and movements have been reported in these mice. We were particularly interested in examining basal and post-exercise catecholamine concentrations within selected brain sites of +/+ and +/- NT3 mice. The hypothalamus and corpus striatum were selected for assay due to their importance in generalized metabolic functions and sensorimotor performance, respectively. In addition, catecholamine concentrations were determined within the olfactory bulbs since this area may serve as a control site which would not ordinarily be considered to be affected by exercise. The influence of neurotrophin-3 (NT-3) upon brain catecholamine concentrations and exercise performance were evaluated in mice carrying a targeted single copy inactivation of the NT-3 gene (+/-) (17).

Concentrations of dopamine and norepinephrine within the three brain areas sampled, hypothalamus, corpus striatum and olfactory bulb, were consistently lower in +/- NT3 sedentary mice. Following exercise to exhaustion, the dopamine concentrations of +/- NT3 mice remained lower than their +/+ wild type littermate controls, however, the direction of the changes in dopamine (increases within hypothalamus

and decreases within corpus striatum and olfactory bulb) were very similar between the +/+ and +/- NT3 mice. In contrast to dopamine, the profiles of changes in norepinephrine concentrations following exercise diverged with analyses of these data showing a significant genotype x exercise interaction. The times required for +/- NT3 mice to achieve exhaustion were significantly lower compared with +/+ NT3 mice (17). These data provide evidence for support of a central nervous system catecholaminergic involvement in exercise fatigue that can be studied within the +/- NT3 mouse model.

Future research on possible interactions of various neurotransmitters and neuromodulators during exhaustive exercise is relevant for the explanation of central fatigue, which hypothetically resides external to the muscles and affect exercise performance.

The presented paper attempts to elucidate the extremely complicated fatigue phenomenon to the reader. Unfortunately, scientific literature has not supplied all the answers for questions and doubts in this area yet.

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Address for correspondence:
Dr Zbigniew Szygula
University School of Physical Education
Department of Sports Medicine
P.O. Box 62 (AWF)
31-571 Kraków 49
Poland
wfszygul@cyf-kr.edu.pl