

UDC 577.334, 577.171.7, 57.032

doi: 10.15330/jpnu.2.1.61-69

OXIDATIVE STRESS IN MUSCLE GROWTH AND ADAPTATION TO PHYSICAL EXERCISE

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Abstract. In a few last decades oxidative stress detected in a variety of physiological processes where reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a central role. They are directly involved in oxidation of proteins, lipids and nucleic acids. In certain concentrations they are necessary for cell division, proliferation and apoptosis. Contractile muscle tissue at aerobic conditions form high ROS flow that may modulate a variety of cell functions, for example proliferation. However, slight increase in ROS level provide hormetic effect which may participate in adaptation to heavy weight training resulted in hypertrophy and proliferation of skeletal muscle fibers. This review will discuss ROS types, sites of generation, strategies to increase force production and achieve skeletal muscle hypertrophy.

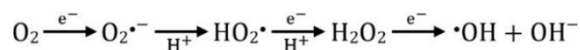
Keywords: oxidative stress, reactive oxygen species, muscle hypertrophy.

1. INTRODUCTION

In modern society, healthy people are often associate with sports lifestyle. Regular training provides a lot of benefits from enhancing immune system, metabolism and muscle force to normalizing blood pressure, body weight etc. No matter in what type of sport people are engaged their muscles always produce reactive oxygen species (ROS) in a greater or lesser extent. The reason for this lies in the mechanism of energy production. Mitochondria produce ATP during oxidative phosphorylation and therefore the generation of ROS occurs. ROS are chemically reactive molecules that formed as a natural byproduct of the normal metabolism of oxygen. In certain circumstances their levels may increase and significantly damage cell components. These ROS molecules act as oxidants leading to myoblast apoptosis or stimulators of proliferation to increase force and endurance of muscle fiber. High ROS formation occurs during intense muscle contractions and myogenesis inhibition [19, 26]. Low-to-moderate ROS levels lead to activation of growth factors, receptors, signal transduction cascades, and transcriptionally regulated genes linked to proliferation. Character of action depends on ROS type and place of its formation. Hormonal stimulation is also an important part in increasing strength and endurance of skeletal muscle.

2. ROS CLASSIFICATION AND SITES OF ITS FORMATION

The most common types of ROS are: superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical (HO^{\bullet}), singlet oxygen (1O_2) [37]. Formation of these ROS types begins with superoxide anion. Further, hydroperoxyl radical, hydrogen peroxide and hydroxyl radical forms in below presented scheme:



The main source of superoxide anion in the cell is the mitochondrial electron transport chain [34]. It is considered that the place of superoxide anion formation in mitochondrial electron transport chain is ubiquinone Q-cycle [27]. In this cycle ubiquinone accepts electrons from cytochrome b on the matrix side of the inner mitochondrial membrane, becoming a free radical compound – ubisemihinon. While accepting protons and electrons, ubisemihinon is reduced to ubiquinol, which translocates to the cytoplasmic side of the mitochondrial membrane. Here ubiquinol again oxidized to ubisemihinon by transferring one electron to cytochrome c1 through an intermediary Fe-S-containing protein [9]. At the last step reaction ubisemihinon reduce cytochrome b, thus transforming to ubiquinone. Some electrons can escape from ETC, especially from complexes I and III [31] and its leakage is greater during basal respiration state compared to maximal ADP-stimulated respiration [16]. Other sites of superoxide generation represented in transverse tubules, sarcolemma and sarcoplasmic reticulum by skeletal muscle NADP(H) oxidases [38, 50]. To provide NADP(H) oxidase activity after contraction, regulatory subunit p40^{Phox} translocates from cytoplasm to sarcolemma [42]. Following muscle contraction, superoxide anion has been detected in the extracellular space [51]. NADP(H) oxidase activity can be stimulated by calcium-dependent and independent forms of phospholipase A₂ in both cytosol and mitochondria [32]. The last notable superoxide-producing enzyme in skeletal muscle is xanthine oxidase [21]. This enzyme catalyzes the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. Xanthine oxidase can also act on certain other aldehydes, purines and pterins. For instance, it efficiently converts 1-methylxanthine, a metabolite of caffeine. Caffeine is widely used before training as mental stimulator and its action may demand xanthine oxidase activity. Xanthine oxidation provides uric acid when oxygen atom from molybdenum transferred to xanthine. The reformation of the active molybdenum center occurs by the addition of water [29].

Hydrogen peroxide is one of the most persistent form of ROS with a comparably long half-life and it freely diffuses at a relatively large distance from cite of its formation [49]. In response to specific signals mitochondria produced H_2O_2 by activation of p66^{Shc} protein [30]. It functions as a redox enzyme that generates mitochondrial H_2O_2 and causes swelling of mitochondria and apoptosis. p66^{Shc} uses mitochondrial reduction equivalents from ETC by direct oxidation of cytochrome c. These data suggest that H_2O_2 generation in mitochondria is not just a by-product of respiration, but also the product of specific enzymes, such as p66^{Shc}. H_2O_2 interaction with copper or iron ions leads to the formation of hydroxyl radical which is highly reactive with a strong oxidizing potential and can damage carbohydrates, lipids, aromatic amino acid residues on proteins. Skeletal muscles produce HO^{\bullet} during intermittent static contraction.

Nitric oxide (NO) is synthesized by nitric oxide synthases from *L*-arginine with formation of *L*-citrulline. This process requires reducing equivalents of NADPH. Both the neuronal NOS (nNOS) and the endothelial NOS (eNOS) isoforms are expressed in skeletal muscle [23]. nNOS is thought to be localized in the subsarcolemmal region of skeletal muscle and at the neuromuscular junction. eNOS is uniformly distributed in muscle fibers and vessel wall [24]. *L*-Arginine is considered a dietary supplement that improves arterial vessels tone, which depends on blood pressure and nutrition of tissues, including muscle. A blood pressure decrease was observed with both *L*-arginine enriched by natural foods and oral *L*-arginine supplementation [46]. Serum total cholesterol, triglyceride decreased

and HDL cholesterol increased only in case with oral *L*-arginine supplementation. Lack of arginine and insufficient activity of NO-synthase manifested in increased blood pressure.

3. SKELETAL MUSCLE FORCE PRODUCTION AND HYPERTROPHY

One of the most common effect of weight training is increase in force production. Skeletal muscle generates a number of reactive oxygen species that are increased during contraction. ROS and NO are well established compounds involved in contractile force production. Both of them demonstrate a positive impact at specific cellular levels. For example, low-to-moderate ROS levels promote full and even increased force production in unfatigued muscle [39], while antioxidant supplementation decreases this parameter [7]. NO also modulates force production at submaximal contraction intense [36], but does not involved in maximal force production. Role of ROS and RNS in fatigue postponing is controversial. Some studies report positive effect of ROS and RNS scavenging in promotion of longer contractile activity. For example, NAC (*N*-acetylcystein) administration increases duration of contractile activity and delay onset of muscle fatigue [45, 28]. Other study conclude that under physiologically relevant conditions, the recovery of force after fatigue could not be improved with antioxidants or with a nitric oxide synthase inhibitor [6]. Neither vitamin C nor vitamin E supplementation improves exercise performance in humans. Further, no beneficial effects have been observed with the combination of vitamins C and E [1, 3]. However, one report indicate improved recovery from diaphragm fatigue [10].

Progressive overload of skeletal muscle leads to adaptation in the way of increased size and amount of contractile proteins. Strength training resulted in muscle injury. Satellite cells found in outside of the muscle fibers between the basal lamina (basement membrane) and the plasma membrane (sarcolemma) of muscle fibers proliferate to these sites resulted in fusion between themselves or with muscle fibers. This process depends on nitric oxide and lies in the increasing of cross-sectional muscle area or hypertrophy. Muscle cells increase in thickness and number by division and differentiation [47]. Satellite cells fusion with muscle fibers resulted in providing additional nuclei to increase the myofilaments number. This satellite cell activation and proliferation period lasts up to 48 hours after muscle injury [15] and maintained at higher levels after several weeks of training [22]. Satellite cells express Pax7 and inactivation of Pax7 results in severe depletion of these muscle stem cells [43]. They are classified as myogenic stem cells because of their ability to maintain their own population by self-renewal. Muscle growth and regeneration highly dependent on satellite cells, because their number is not restored after ablation.

Insulin-like growth factor 1 (IGF-1) is a downstream effector of growth hormone (GH). IGF-1 closely linked to protein synthesis and repair. Mechano growth factor, a splice variant of IGF-1, suggested to play crucial role in muscle growth in response to strength training. Mechano growth factor causes muscle hypertrophy in response to a mechanical stimulus by activating muscle satellite cells and increasing the upregulation of protein synthesis through IGF-1 receptor. ROS has a critical function in muscle hypertrophy via MAPK signaling and action of IGF-I. A recent study found that the ingestion of a leucine-enriched essential amino acid-carbohydrate mixture resulted in significant increase in muscle protein synthesis, reduced AMPK phosphorylation, increased Akt/PKB and mTOR phosphorylation, increased mTOR signaling to its downstream effectors increasing both S6K 1 and 4E-BPI phosphorylation, and reduced eEF2 phosphorylation [13].

Many athletes face with a reduction in the protective function of the immune system. This results in decreased physical performance or even risk to fall ill. Some researchers have demonstrated that the leukocytes and lymphocytes have been increased due to stress of exercise. Muscle injury stimulate macrophages activity, which are necessary to provide adequate response by secreting cytokines and growth factors [35]. Interleukin-1, Interleukin-6 and tumor necrosis factor alpha are responsible for protein breakdown, an increased production of prostaglandins and removal of damaged muscle cells. It has been reported that caffeine ingestion prior to exercise enhances the activation of both the

hypothalamic-pituitary-adrenal axis and the autonomic nervous system, which in turn, may affect the immune response to exercise. Nonessential amino acid *L*-glutamine is highly utilized by cells of the immune system for proliferation, antigen presentation, phagocytosis, cytokine, nitric oxide and superoxide production [33]. Thus, *L*-glutamine supplementation may provide additional protection and boost the efficiency of the immune system.

Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone and combined with exercise, increase fat-free mass, muscle size and strength in normal men with previous weight-lifting experience who were on standardized diets [2]. Using AAS provide higher resistance to muscle fatigue during training. Authors speculate, that it can be the effect of blocking cortisol action, since cortisol level increases in response to steroid administration [17]. Cortisol is a steroid hormone, which is produced in the adrenal cortex of the kidney in response to stress. Increase in cortisol is related to an increased rate of protein catabolism, in a way of breaking down muscle proteins, inhibiting skeletal muscle hypertrophy [18]. Receptor binding and susceptibility to biotransformation govern androgenic anabolic steroids efficacy.

AAS and GH are widely administrated by athletes and bodybuilders to increase muscle hypertrophy and strength [11]. Extremely high doses or long period of use may cause tumorigenesis, water retention, hyperglycemia, testicular atrophy, gynecomastia, myocardial infarction, heart failure and many other side effects. Some AAS are directly involved in oxidative stress appearance. For example, repeated low level administration of turinabol and methanabol had no significant effects on oxidative stress markers, while the high dose created oxidative stress and myocardial dysfunction in young rabbits [14]. Authors emphasize high hazard from high doses of these AAS, especially in young human subjects. In addition, nandrolone decanoate administration to male rats induces oxidative stress, seminiferous tubules dysfunction, and sperm DNA fragmentation [48] and disrupts redox homeostasis in liver, heart and kidney of male Wistar rats [12]. For instance, acute effects of nandrolone decanoate do not promote the production of ROS and even possess some anti-oxidative potential [20]. Anabolic steroid stanozolol decreases mitochondrial ROS generation during acute exercise [41]. High doses of GH also involved in detrimental effects related to energy metabolism and oxidative stress [44], whereas close-to-physiological levels prevents memory deficits in early stages of the neurodegenerative process and slow down adverse effects of immobilisation in old rats muscle tissue [5, 40].

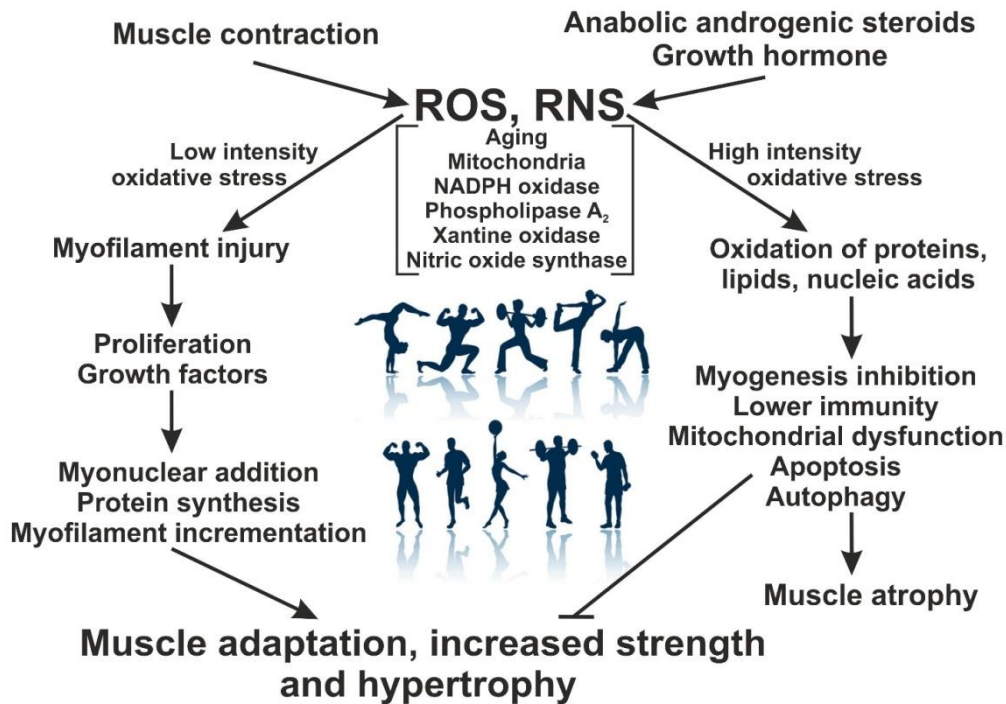


Fig 1. Possible role of ROS/RNS in muscle growth and adaptation to physical exercise. Muscle contraction, anabolic androgenic steroids and growth hormone cause induce changes in ROS and RNS levels. Low intensity oxidative stress promotes hypertrophy and adaptation of myofibers through stimulation of proliferation and action of growth factors. This provides additional nuclei and increases the myofilaments number, enhances protein synthesis and as a result myofilament incrementation. Oxidative stress of high intensity causes unfavorable oxidation of proteins, lipids and nucleic acids. Oxidation of this macromolecules decreases myogenesis, immunity, mitochondrial functions and stimulate apoptosis and autophagy. These degenerative processes results in muscle atrophy.

4. CONCLUSIONS

Oxidative stress is directly involved in contractile muscle force production, proliferation and hypertrophy. Many muscle processes need ROS and RNS for its functions. To achieve muscle hypertrophy hormone therapy does not required. Yes, it would take more time and will require close attention to details, such as training methodology, nutrition and recovery, but keeps healthspan or even improve it. Nowadays allot of non-hormonal supplements available in the markets of sport nutrition. Some of them work, some of them is just a waste of money. Nonetheless, well established creatine monohydrate, BCAAs, *L*-glutamine, *L*-carnitine, *L*-arginine- α -ketoglutarate and weight training combined with of course protein whey enhance muscle hypertrophy and force production [8, 25, 4].

ACKNOWLEDGEMENTS

The author is grateful to Dr. O. Lushchak for critical reading of the manuscript.

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Received: 04.03.2015; **revised:** 07.04.2015.

Юркевич І.С. Оксидативний стрес при м'язовому рості та адаптації до фізичних навантажень. *Журнал Прикарпатського університету імені Василя Стефаника*, **2** (1) (2015), 61–69.

За останні десятиліття було встановлено роль вільних радикалів в багатьох фізіологічних процесах. Активовані форми кисню (АФК) та активовані форми нітрогену (АФН) безпосередньо задіяні в цих процесах. Вони беруть участь в окисленні білків, ліпідів та ДНК. В певних концентраціях вони необхідні для клітинного поділу, проліферації та індукції апоптозу. М'язова тканина в аеробних умовах генерує велику кількість АФК, які можуть модулювати різні клітинні функції. Проте, невелике збільшення рівня АФК створює горметичний ефект, який може забезпечити адаптацію до силового

тренування, яке призводить до гіпертрофії і проліферації скелетних м'язових волокон. У цьому огляді ми зупинимося на класифікації АФК, місцях їх утворення, стратегіях для збільшення сили і гіпертрофії скелетних м'язів.

Ключові слова: оксидативний стрес, активні форми кисню, гіпертрофія м'язів.