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Exercise-induced hormesis and skeletal muscle health ☆

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ABSTRACT

Hormesis refers to the phenomenon that an exposure or repeated exposures of a toxin can elicit adaptive changes within the organism to resist to higher doses of toxin with reduced harm. Skeletal muscle shows considerable plasticity and adaptions in response to a single bout of acute exercise or chronic training, especially in antioxidant defense capacity and metabolic functions mainly due to remodeling of mitochondria. It has thus been hypothesized that contraction-induced production of reactive oxygen species (ROS) may stimulate the hormesis-like adaptations. Furthermore, there has been considerable evidence that select ROS such as hydrogen peroxide and nitric oxide, or even oxidatively degraded macromolecules, may serve as signaling molecules to stimulate such hermetic adaptations due to the activation of redox-sensitive signaling pathways. Recent research has highlighted the important role of nuclear factor (NF) κB, mitogen-activated protein kinase (MAPK), and peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α), along with other newly discovered signaling pathways, in some of the most vital biological functions such as mitochondrial biogenesis, antioxidant defense, inflammation, protein turnover, apoptosis, and autophagy. The inability of the cell to maintain proper redox signaling underlies mechanisms of biological aging, during which inflammatory and catabolic pathways prevail. Research evidence and mechanisms connecting exercise-induced hormesis and redox signaling are reviewed.

1. Introduction

Hormesis is a biological concept which states that exposure to a low dose of a noxious or toxic agent can bring about results deemed beneficial to the long-term welfare of the organisms [1]. According to the recent literature, a biological phenomenon can be called hormesis if it fulfills the following conditions: (1) it shows a biphasic dose-relationship in which the response to low dose is opposite to the response to a high dose; (2) the concentration and effects of the low dose are measurable, i.e., are not due to placebo [2]; and (3) the factors acting on the biological system are present in natural environment [2]. Among the various hormetic agents are hypoxia, heat, starvation, pro-oxidants, and other types of stress such as pain, sleeplessness, noise, and cold [3,4]. Although exercise itself is not a specific hormetic stimulus, numerous biochemical and physiological changes take place during exercise at the cell, organ and circulatory levels that have been shown to elicit hormetic responses. Thus, exercise has been suggested to have hormesis-like benefits [5,6]. It is interesting to note that studies on the efficacy and mechanism of exercise-induced hormesis are increasing in recent years. Among the various best-known hormetic effects studied to date are upregulation of antioxidant network, mitochondrial adaptation, cardiac protection against ischemia-reperfusion, heat tolerance, adaptation to low energy substrates (especially blood sugar), and muscle hypertrophy in response to blood flow restriction [7].

Redox signaling induced by intrinsic generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is closely related to exercise-induced hormesis [8,9]. This is because mild oxidative stress, resulting from the imbalance between ROS and RNS generated during muscular contraction and the endogenous antioxidant defense system, can activate specific cellular pathways that lead to various adaptations including, but not limited to, post-translational enzyme activation/inhibition, modulation of transcription factors (TF) and cofactors (via covalent modification and association/dissociation), up-or downregulation of gene transcription, and altered potential epigenetic mechanisms [10,11]. Hydrogen peroxide (H_2O_2) and nitric oxide (NO) serve as the most important signaling molecules due to their mild chemical reactivity, relative stability, and diffusiability [12–15]. An important paradigm of redox signaling is based on reversible modification of

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cysteine residues on specific enzymes which subsequently control downstream enzymes and pathways [9]. However, concurrent definition of redox signaling is not strictly limited to sulfhydryl modification but includes modification of protein function due to the electron transfer process. Phosphorylation/dephosphorylation via kinases and phosphatases, acetylation/deacetylation, methylation and sulfoxidation, are also potential covalent modulations in the process of redox signaling.

For the past several decades, the Free Radical Theory of Aging first proposed by Harman [16] took the center stage of aging research. It was later modified to Mitochondrial Theory of Aging pointing to a critical role of ROS of mitochondrial origin in the progression of aging. Over the past two decades, however, evidence has continued to merge that increased ROS generation and accumulation of oxidatively damaged macromolecules cannot explain biological aging as previously thought [17]. Thus, there is some confusion as to how acute and long-term physical exercise, which increases ROS generation and renders macromolecule to oxidative modification, would impact on the health and longevity of the aging population, who are encouraged to be more physically active. Furthermore, since aging directly affects metabolic rate, mitochondrial structure and turnover, ROS generation, and antioxidant defense capacity, it is conceivable that cell redox signaling patterns and intensity among the older individuals would be different from those of the young ones. Finally, aged individuals may perceive “low dose” of toxins and stress differently than the young individuals, i.e., aging may alter the shape of the inverted U curve typical of a hormetic effect, as well as the “breaking point”, i.e., the point where the curve dramatically changes its direction. This in turn can impact on physiological function and performance of the elderly people. Obviously, the topic to be reviewed is quite broad and complex. In order to keep in line with the purpose of his special Olympic Issue of FRBM focusing on Human Performance and Redox Signaling in Health and Disease, the current review will focus on those exercise-induced hormetic effects for which redox signaling is experimentally proven to be the underlying mechanism. Also, primary attention will be given to the skeletal muscle, an organ vital for physical function and performance. For more complete review, the readers are referred to several recent articles on hormesis [7,17,18].

1.1. Exercise-induced hormesis in antioxidant systems: role of redox signaling

1.1.1. Exercise adaptation of antioxidant system

At the very early stage of free radical research, it was reported that wild animals and birds display higher antioxidant enzyme activities than their domestic counterparts [19]. It was speculated that frequent muscular activity associate with the life pattern of the former was responsible for the observed difference in antioxidant defense, and this hypothesis was later experimentally confirmed with animals involved in exercise training. Numerous studies in the 1980–90's showed that exercise-training promoted an increase in key antioxidant enzymes in skeletal muscle [20–24]. Furthermore, trained animals or humans were found to have lower level of oxidative damage such as lipid peroxidation than their sedentary counterparts when subjected to similar related workload (%VO_2max) [25]. Interestingly, exercise intensity was found to determine the magnitude of adaptation of a particular antioxidant enzyme such as superoxide dismutase (SOD), such that when daily running time and treadmill speed and grade were increased, so did SOD activity in the muscle [26]. However, as exercise intensity reached maximal level, SOD activity leveled off. Besides SOD, glutathione (GSH) antioxidant system were also altered by training [27,28]. Training adaptation of GPX was found to be muscle fiber specific, with the type 2a fibers which have moderate antioxidant defense to be more responsive than type 1 fibers, which have higher antioxidant capacity [29]. To examine the biological consequence of this training adaptation, respiratory function of isolated muscle mitochondria from endurance trained and sedentary rats were examined after being exposed to equal dose of H_2O_2 [30]. “Trained” mitochondria demonstrated a higher rate of state 3 respiration and respiratory control index (RCR) compared to those from sedentary rats, indicating a greater resistance to ROS insult. In addition to SOD and GPX, the rate-limiting enzyme for GSH synthesis, γ-glutamylcysteine synthetase (GCS), was reportedly induced by training in muscle and liver [31,32]. As a result, muscle and hepatic GSH contents, as well as GSH export under cardiac ischemic insult, were increased in the trained state.

Inducible form of nitric oxide synthase (iNOS) has shown clear adaptation in response to endurance training [33,34]. Increased NO production can have dual consequences: NO can react with superoxide radicals to form peroxynitrite thereby inflicting strong oxidative damage, whereas NO is also known to exert vasodilative effect to increase blood flow to muscle thus indirectly enhance muscle antioxidant defense during exercise [35,36].

The definition of antioxidant enzyme may be broadened to including those which indirectly protect the organisms from oxidative damage, such as enzymes removing modified lipids (phospholipase A2), repairing oxidatively damaged DNA (8-oxoG DNA glycosylase-1, OGG), and selectively degrading damaged proteins (proteases). Exercise training has been shown to induce some of these enzymes and thus reducing the impact of exercise-induced ROS to these macromolecules. However, the discussion of these enzymes to acute and exercise is beyond the scope of the current review.

1.1.2. Mechanism of antioxidant adaptation to exercise

Although muscular contraction during exercise was found to increase ROS generation in as early as 1980s [37,38], the idea that exercise-generated ROS can directly induce antioxidant enzyme adaptation remained a hypothesis [37]. An important breakthrough was reported by Hollander et al. [39] showing that exercise training could increase the protein content of mitochondrial SOD (SOD2), but not cytosolic SOD. The data indicated that training induced antioxidant enzyme activity is caused by accumulation of enzyme protein, and related to mitochondrial generation of ROS. Oh-ishi et al. [40] and Gore et al. [41] were the first to report that an acute bout of exhaustive exercise could alter mRNA level of antioxidant enzymes. Shortly after, Hollander et al. [42] demonstrated that a single bout of running significantly increased mRNA of SOD2, the first evidence that exercise can change the gene expression of an antioxidant enzyme. Furthermore, Roberts et al. (1999) showed that iNOS mRNA level could be increased after an acute bout of exercise [43]. Later, a studied by Gomez-Cabrera confirmed the above findings showing that mRNA levels of both MnSOD and iNOS were elevated after acute exercise [44]. Despite these insightful discoveries, how exercise can activate the gene expression of SOD2 and other antioxidant enzymes remains unclear in the 1990s.

In 2001, Zhou et al. [45] reported a significant finding, demonstrating in C2C12 muscle cells that nuclear factor (NF) κB plays a critical role in the response of SOD, catalase and GPX to H_2O_2 treatment. While H_2O_2 induced a dose-responsive elevation of NFκB binding, NFκB-driven luciferase activity and mRNA level of GPX, deletion and mRNA silencing of κB binding sites on the DNA promoter abolished the H_2O_2 effects. A few years after, Ji et al. [46] reported that an acute bout of exercise activated NFκB binding in rat skeletal muscle, with a peak activation at 2–4 h after exercise. The experiments also showed that both IκB and IκB kinase (IKK) were phosphorylated after exercise, whereas P50/P65 was transported into the nucleus. It is now clear that SOD2