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Opinion

Exercise and hormesis: oxidative stress-related adaptation for successful aging

Zsolt Radak[1,*], Hae Young Chung[2] & Sataro Goto[3]
[1]*Exercise Physiology Laboratory, School of Sport Science, Semmelweis University, Budapest Hungary;* [2]*Department of Pharmacology, Pusan National University, Korea;* [3]*Department of Biochemistry, Faculty of Pharmaceutical Sciences, Toho University, Funabashi, Japan; *Correspondence (e-mail: radak@mail.hupe.hu)*

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Abstract

The hormesis theory purports that biological systems respond with a bell-shaped curve to exposure to chemicals, toxins, and radiation. Here we extend the hormesis theory to include reactive oxygen species (ROS). We further suggest that the beneficial effects of regular exercise are partly based on the ROS generating capability of exercise, which is in the stimulation range of ROS production. Therefore, we suggest that exercise-induced ROS production plays a role in the induction of antioxidants, DNA repair and protein degrading enzymes, resulting in decreases in the incidence of oxidative stress-related diseases and retardation of the aging process.

Introduction

In the past few years the hormesis theory has been widely discussed and extended to various fields (Sagan 1989, Minois 2001, Rattan 2001, 2004; Calabrese and Baldwin 2003 a, b; Kaiser 2003; LeBourg 2003). The observation that low doses of toxins and/or radiation can exert beneficial effects in lower organisms resulted in the development of the hormesis theory (Stebbing 1982). Thus, the term hormesis refers to the beneficial effects of low doses of potentially harmful substances. Increasing evidence suggests that hormesis may operate in higher animals as well (Kaiser 2003; Calabrese and Baldwin 2003b). Indeed, low doses of radiation have been shown to increase lifespan in rodents (Caratero et al. 1998) and low doses of certain carcinogens can decrease the development of cancer (Niwa et al. 2002). The concept of hormesis has been extended to the beneficial effects of hypergravity on Drosophila melanogaster (Le Bourg et al. 2003), moderate drinking of alcohol (Calabrese and Baldwin 2003a) and caloric restriction in experimental animals to prevent disease and promote longevity (Sohal and Weindruch 1996). The molecular mechanisms regulating these benefits are largely unknown.

The basis for the hypothesis

Reactive oxygen species (ROS) are physiological products of aerobic metabolism, and are used by organisms for a variety of tasks such as signaling, killing of infectious microorganisms, induction of apoptosis, and stimulation of antioxidant and repair processes (Pani et al. 2000). On the other hand, ROS are also believed to be involved in a number of pathological processes such as atherosclerosis, cancer, ischemia/reperfusion, inflammation, rheumatoid arthritis, cataract, and neurodegenerative diseases, such as Alzheimer's (AD) and Parkinson's. One of the most accepted theories of aging (free radical theory) is also based on the damaging effects of ROS that are considered to be unavoidable byproducts of aerobic

metabolism (Harman 1956). Therefore the question arises, why was a process that results in generation of these byproducts and causes so many problems, selected during the course of evolution?

The typical reaction to ROS can be described by a bell-shaped curve: low concentrations have a stimulating effect (signaling, receptor stimulation, enzymatic stimulation), while a massive level of ROS inhibits enzyme activity and causes apoptosis or necrosis. Skeletal muscle function is a good example, since hydrogen peroxide at a low concentration increases Ca^{++} release from the sarcoplasmic reticulum and force production, whereas a massive increase in hydrogen peroxide concentration results in a sharp decrease in force output (Andrade et al. 2001). When skeletal muscle bundles were incubated with exogenous catalase, force production decreased in a dose dependent manner and exogenous hydrogen peroxide resulted in a gain in force generation (Reid et al. 1993). Hence, the effect of hydrogen peroxide and perhaps some other oxygen species, seems to be hormetic.

Indeed, the pre-conditioning of myocardium by a mild oxidative stress has been repeatedly shown to increase the resistance of the heart against massive oxidative challenge and to have a beneficial effect on physiological function during and after significant oxidative stress (Sun et al. 1996).

Hypothesis

We intend to extend the hormesis theory to the ROS generating effects of exercise. It has been clearly shown that a single bout of exercise above a certain intensity or duration results in increased production of ROS and causes oxidative damage to lipids, proteins, and DNA (Davies et al. 1982, Radak et al. 1999b, McArdle et al. 2004). On the other hand, it is also well established that regular exercise is a preventive measure against oxidative stress- related diseases including cardiovascular diseases, stroke, and certain cancers (Hamilton et al. 2003; Hawkins et al. 2003; Wannamethee et al. 1998). We propose here, that this paradoxical effect is due to the ability of exercise to increase of the formation of ROS to a level that may induce significant, but tolerable, damage that can in turn induce beneficial adaptations, in keeping with the theory of hormesis. We have no doubt that a single bout of exercise increases the generation of ROS, or that ROS play pathophysiological roles in aging, cardiovascular disease, cancer, AD, for example. We do, however, suggest that a low level of ROS or transient increases in ROS could prevent diseases associated with oxidative stress and retard the aging process. Thus, we propose here, that the molecular basis for the preventive effect of regular exercise is due, in part, to intermittent, brief increases in formation of ROS, thereby altering signaling pathways and/or causing molecular damage that can induce adaptive responses that protect against a subsequent stronger stress. In other words, exercise-induced increases in production of ROS may protect against ROS associated diseases. This hypothesis is in accordance with the hormesis theory.

Support for the hypothesis

The oxidative cellular milieu created by exercise activates signal transduction pathways that result in enhancement of endogenous antioxidant systems. Many studies have demonstrated that regular exercise up-regulates the antioxidant system (McArdle and Jackson 2000). Moreover, it also appears that exercise is able to stimulate the oxidative damage repair system (Radak et al. 1999, 2001, 2002, 2003; Sato et al. 2003; Wittwer et al. 2004**).** It has been reported that regular exercise increases the activity of the proteasome complex, which is believed to be responsible for the degradation of oxidatively modified proteins (Radak et al. 1999b, 2002). The proteasome complex has a very important role, namely reduction of oxidatively modified proteins, leading to better and more efficient cell function by a more rapid turnover of proteins (Goto et al. 2001). Faster turnover would not result in just a reduced post-translational period, thus decreasing the chance for oxidative damage, but would also provide a mechanism for damaged proteins to be replaced by intact ones with more efficacious physiological functions (Verbeke et al. 2001, Beedholm et al. 2004). Available evidence suggests that exercise has a preventive role in AD, which might be mediated not just by up-regulated neurotrophins, but also by an increased proteasome activity

(Radak et al. 2001; Mattson et al. 2002) since decreased degradation of β-amyloid peptide has been suggested to be one of the causative factors of AD. Slower β-amyloid degradation is thought to result in increased production of a long form of amyloid β-peptide which self-aggregates and forms insoluble plaques in the brain, resulting in increased ROS production and oxidative damage (Mattson et al. 2002).

Interestingly, the activity of the proteasome complex also responds with a bell-shaped curve to the exposure to hydrogen peroxide, suggesting that the proteasome itself is subject to hormesis when exposed to mild oxidative stress (Sitte et al. 1998).

In addition to an increase in damaged protein degrading systems, the activities of DNA damage- repairing enzymes are also up-regulated by regular exercise (Radak et al. 1999, 2001, 2002, 2003; Sato et al. 2003; Wittwer et al. 2004). The repair process of DNA damage is one of the most important means for survival and vitality of cells (Gilchrest and Bohr 1997). It has been shown in human and animal studies that exercise increases the activity of 8-oxoG DNA glycosylase (hOGG1) (Radak et al. 2002, 2003). Moreover, the level of 8-hydroxydeoxyguanosine (8-OHdG) was lower in leukocytes of regularly exercising humans than in sedentary controls, and the mRNA transcript of the DNA repair enzyme was increased after an exercise bout, indicating that the effect is due to transcriptional stimulation or stabilization of the mRNA (Sato et al. 2003**).** In addition, the recent observation that the expression of DNA repairing genes is up-regulated by endurance training is in accordance with our hypothesis (Wittwer et al. 2004). The finding that caloric restriction, which appears to be the only known method to increase maximal life-span in rodents, decreases the expression of DNA repair genes, may be the result of reduced oxidative stress and related damage (Lee et al. 1999). Therefore, the accumulation of oxidative damage can be decreased either by lowering the generation of ROS (caloric restriction) or by regular exposure to a small amount of ROS (such as mild exercise) that could result in slight oxidative damage, which then leads to up-regulation of repair and antioxidant systems. The damage-induced adaptation theory is not without precedent in exercise physiology (Evans and Cannon 1991).

It is important to emphasize that exercise is not just work or entertainment, but has important physiological implications including improving brain and cardiovascular functions and reducing the incidence of certain cancers and a number of other diseases. Beneficial changes induced by regular exercise may be most prominent in older people (Wannamethee et al. 1998). In addition, moderate oxidative stress, induced by exercise, might up-regulate anti-inflammatory processes and result in modulation of related transcription factors such as NF-kB and AP-1 (Radak et al. 2004). In addition, it appears that single bout of exercise increases the level of tumor necrosis factor-alpha (TNF-α) (Cannon et al. 2001) and resistance exercise training decreases the expression of (TNF-α) in aged skeletal muscle (Greiwe et al. 2001). Hence, it is suggested that decreased (TNF-α) expression in aged skeletal muscle can significantly attenuate the age-associated muscle wasting. Therefore, regular exercise may not only retard the age-associated decline in muscle and bone mass, but, through ROS production, also beneficially affect and retard biological aging.

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