HORMESIS-LIKE BENEFITS OF PHYSICAL EXERCISES DUE TO INCREASED REACTIVE OXYGEN SPECIES

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Received on 10 October, 2016.
Accepted on 02 November, 2016.
Published on 30 December, 2016.

Abstract

During normal metabolism, the body produces unstable molecules, the most common of which are the reactive oxygen species (ROS). Increased number of ROS, called oxidative stress, is capable to damage cells. To be able to combat the adverse effects of free radicals, human body triggers the massive production of different antioxidants or accelerates their intake from foods. Scientific studies have demonstrated that long intense exercise such as endurance training, may cause an overwhelming of body's antioxidant defenses, leading to excessive oxidative stress and harmful outcomes. On the other hand regular exercise in intensity and duration has a wide range of beneficial effects on the body, by producing healthy amounts of oxidative stress. Contrary to what is believed until now, oxidative stress is beneficial in small amounts. In fact it's essential, because prompts the body cells to become stronger over time by increasing antioxidants and thus provide protection against potential injury or cellular damage. The beneficial consequences of regular exercise and harmful outcomes of exhaustive exercise due to amount of ROS production fit well with the concept of hormesis. It states that exposure to a low dose of a noxious or toxic agent can bring about results believed beneficial to the long-term welfare of the organisms. According to literature, physical inactivity combined with poor nutrition, excessive smoking and alcohol consumption leads to impairment in physiological functions and reduces the whole body resistance to oxidative stress, and can be regarded as one of the end points of the exercise associated hormesis curve. Moreover, it seems that physical inactivity through molecular pathways could facilitate the incidence of oxidative stress-related diseases. Therefore it seems that the human being is not designed to be inactive for survival.

Keywords: exercise, hormesis, reactive oxygen species

Background

Life exists by maintaining a complex dynamic equilibrium or homeostasis that is constantly challenged by intrinsic or extrinsic adverse forces, the stressors. When faced with excessive physical or emotional stress, a subject's adaptive responses attain a relatively stereotypic nonspecific nature, referred as ''the general adaptation syndrome''. It predicts that cells, tissues, and organisms can experience three stages when a stressor is increased: alarm, resistance or adaptation, and exhaustion [Tsigos & Chrousos, 2002; Lawler et al., 2016]. Research over the past 30 years is consistent with the notion that response and adaptations to oxidative stress also follow the conceptions of the general adaptation syndrome [de Magalhaes & Church, 2006; Lawler & Hindle, 2011]. For instance, cells and integrative biological systems respond to moderate redox challenges by increasing antioxidant enzymes

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and other protective proteins (e.g., heat shock proteins) [Das et al., 1993; Omar & Pappolla, 1993; Radak et al., 2008].

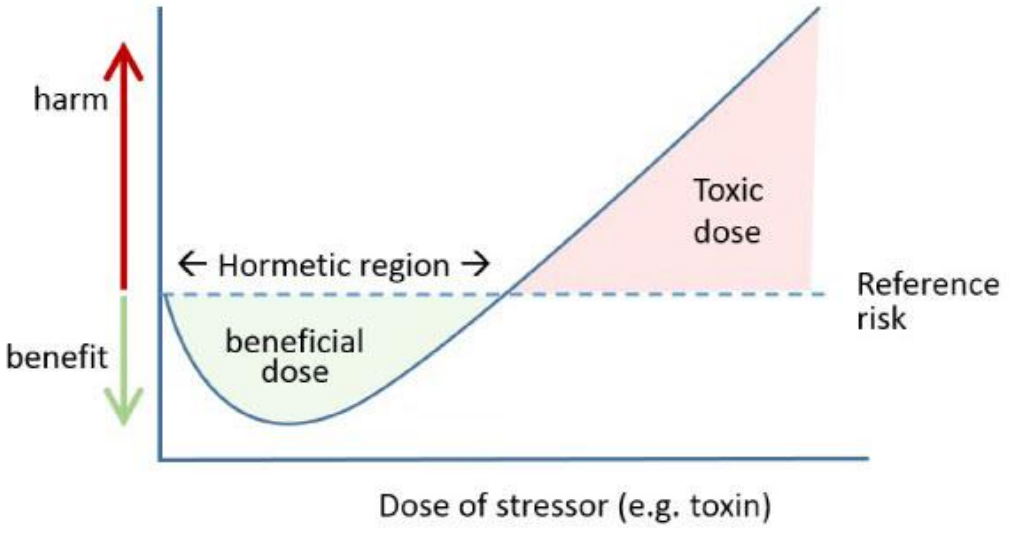
It is well known that during the physical exercises mechanical, metabolic, and oxidative stress are increased and at high levels of intensity they could be injurious. Thus it is not surprising that levels of many proteins involved in protection against stressors are increased in response, either acutely or as an adaptation to repeated or habitual bouts of exercise in skeletal muscle and the heart [Locke et al., 1995; Samelman, 2000; Khassaf et al., 2001; Kim et al., 2015b]. Physiological response and adaptations to stressors experience with exercise provide protection against potential injury or cellular damage. A cellular objective is thus to maintain homeostasis within a desired cellular and organism tolerance.

An acute bout of exercise increases skeletal muscle and cardiac levels of reactive oxygen species (ROS) production and oxidative stress. The term "exercise preconditioning" or "hormesis" was first evident in the literature in an article by Radak *et al*. (2000), where the authors described resistance to oxidative stress in the myocardium induced by exercise training. Exercise preconditioning is now recognized to be critical in not only reducing oxidative stress during exercise, but also reducing oxidative stress and damage due to ischemia-reperfusion, reducing glucose intolerance and insulin resistance, as well as attenuating skeletal muscle atrophy [Radak et al., 2000; Ding et al., 2005; Dupont-Versteegden et al., 2006; Fontana et al., 2010; Lawler et al., 2016]. Therefore, the focus of this review is hormesis-like benefits of physical exercises due to increased ROS.

The hormesis theory

In toxicology, hormesis is a dose – response phenomenon characterized by a low-dose stimulation and high-dose inhibition. It is a non-monotonic / biphasic dose response, with specific dose response features resulting in either a J-shaped or an inverted U-shaped dose response curve (Fig. 1) [Calabrese and Baldwin, 2003]. From biological point of view, hormesis is a concept which states that exposure to a low dose of a noxious or toxic agent can bring about results believed beneficial to the long-term welfare of the organisms [Calabrese et al., 2013]. 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 [Jargin, 2015]; and (3) the factors acting on the biological system are present in natural environment [Jargin, 2015].

Fig. 1. Non-monotonic / biphasic dose response, with specific dose response features resulting in either a J-shaped or an inverted U-shaped dose response curve.



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Among the various hormetic agents are hypoxia, heat, starvation, pro-oxidants, and other types of stress such as pain, sleeplessness, noise, and cold [Marques et al., 2009; Le Bourg, 2009]. 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 [Radak et al., 2005; Ji et al., 2006]. 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 [Peake et al., 2015].

In recent years the hormesis theory has been extended specifically to the mitochondria (mitohormesis) [Ristow and Zarse, 2010; Yun and Finkel, 2014], with the concept being that mild perturbations in mitochondrial homeostasis coordinate a nuclear and cytosolic response that leaves the whole cell less susceptible to future perturbation. Such responses are not limited to acute cytoprotective mechanisms but can induce long-term metabolic alterations and stress resistance. During exercise mitochondria metabolism is increased to meet the energy demands of the exercise task. It is well seen especially in endurance sports where more oxygen is needed. In theory, the higher the metabolic rate and energy needs, the more free radicals the mitochondria will produce. Therefore, if the mitochondria are capable of regulating their own, as well as cell-wide and possibly system-wide, responses to changes in homeostasis it stands to reason that mitohormesis signaling would be a central mechanism regulating exercise-mediated adaptation.

ROS production

Reactive oxygen species are physiological products of aerobic metabolism. They are used by organisms for a variety of tasks such as signaling, metabolizing of xenobiotics, initiating apoptosis, and stimulation of antioxidant and repair processes [Pani et al., 2000]. On the other hand, ROS are also involved in a number of pathological processes such as inflammation, rheumatic arthritis, atherosclerosis, ischemia / reperfusion, cancer, and neurodegenerative diseases such as Alzheimer and Parkinson diseases. It is also believed that the damaging effects of ROS are in the foundation of the most accepted theory of aging [Harman, 2006]. Interestingly, some literature data showed that certain conditions that result in low levels of exposure to free radicals or free radical-generating systems, such as radiation, could lead to extension of the life span [Sagan, 1989; Kaise, 2003]. Caloric restriction, which is the only known method to extend both mean and maximal life span, can be regarded as a mild stressor [Ristow and Schmeisser, 2011].

Regular physical exercise, which has been proven to increase mean life span, could also serve as a stimulating stressor for ROS production. However, free radicals are also created through other pathways, and are not always related to the oxygen needs. Several studies have shown that despite much higher oxygen intakes during aerobic exercise, anaerobic exercise (sprinting, weight lifting, etc) can produce similar levels of oxidative damage. Indeed, there is little doubt that the generation of ROS is increased during exercise [Davies et al., 1992; Alessio and Goldfarb, 1988; Radak et al., 1999, 2001]. However, mounting epidemiological data have proven that exercise decreases the incidence of oxidative stress-associated diseases [Radak, 2004]. This phenomenon is not a paradox; it is a result of exercise-induced adaptation (Fig. 2). Recent studies suggest that redox signaling induced by intrinsic generation of ROS and reactive nitrogen species (RNS) is closely related to exercise-induced hormesis [Ji, 2008; Schieber, 2014]. This is because mild oxidative stress, resulting from the imbalance between ROS and RNS generated during

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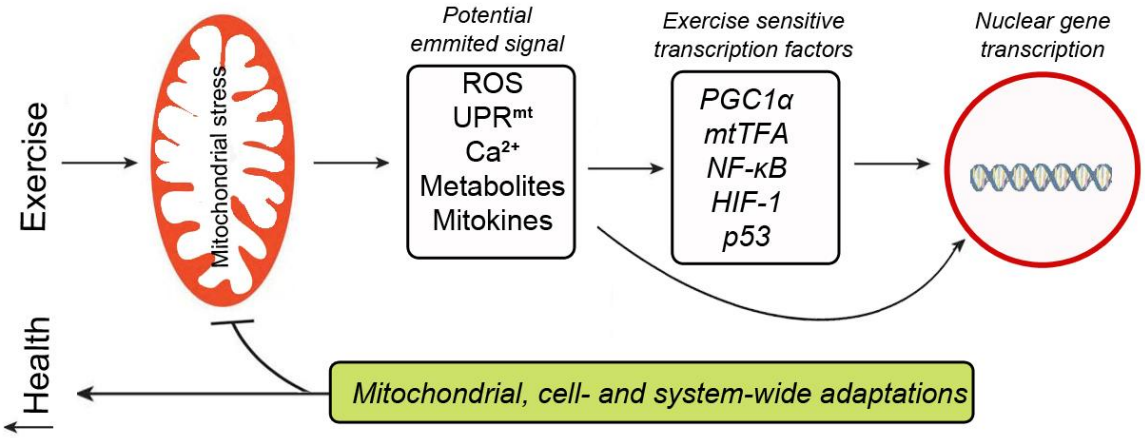
muscular contraction and the endogenous antioxidant defense system, can activate specific cellular pathways that lead to various adaptations including, but not limited to, posttranslational enzyme activation/inhibition, modulation of transcription factors (TF) and cofactors, up- or downregulation of gene transcription, and altered potential epigenetic mechanisms [Powers and Jackson, 2008; Alleman et al., 2014].

Fig. 2. Potential mitohormetic response to exercise. Exercise induces mitochondrial stress and as a result signals are sent from the mitochondrion to the nucleus to induce mitochondrial specific, cell- and potentially system-wide adaptive responses which protect the cell against subsequent stress (mitohormesis). Potential signals emitted by mitochondria during or immediately following exercise may include, but are not limited to, changes in ROS, reactive oxygen species Ca^{2+}, UPRmt, metabolic metabolites and mitokine levels. These may act directly to initiate a transcriptional response in the nucleus or via signaling intermediates such as protein kinases (not depicted in this figure) and exercise-sensitive transcription factors. PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; mtTFA, mitochondrial transcription factor A; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; HIF-1, hypoxia inducible factor (According to Merry & Ristow, 2016).



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 [Pourova, 2010; Collins et al., 2012]. An important paradigm of redox signaling is based on reversible modification of cysteine residues on specific enzymes which subsequently control downstream enzymes and pathways [Schieber and Chandel, 2014]. 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. Most importantly, the exercise-induced oxidative challenge-associated adaptation is systemic. These beneficial consequences of regular exercise are in sharp contrast to the effects of exhaustive exercise on unprepared tissues that results in, apparently, harmful outcomes. These consequences of exercise fit well with the concept of hormesis (Fig. 3) [Radak et al., 2008].

Extending life span by increasing oxidative stress

A considerable number of findings in various organisms suggest that reduction of oxidative stress is associated with prolongation of life expectancy [Ristow and Schmeisser, 2011]. Consequently, ROS-lowering interventions were widely proposed as an antiaging strategy in humans. Antioxidants, a group of synthetic or naturally occurring substances, which are

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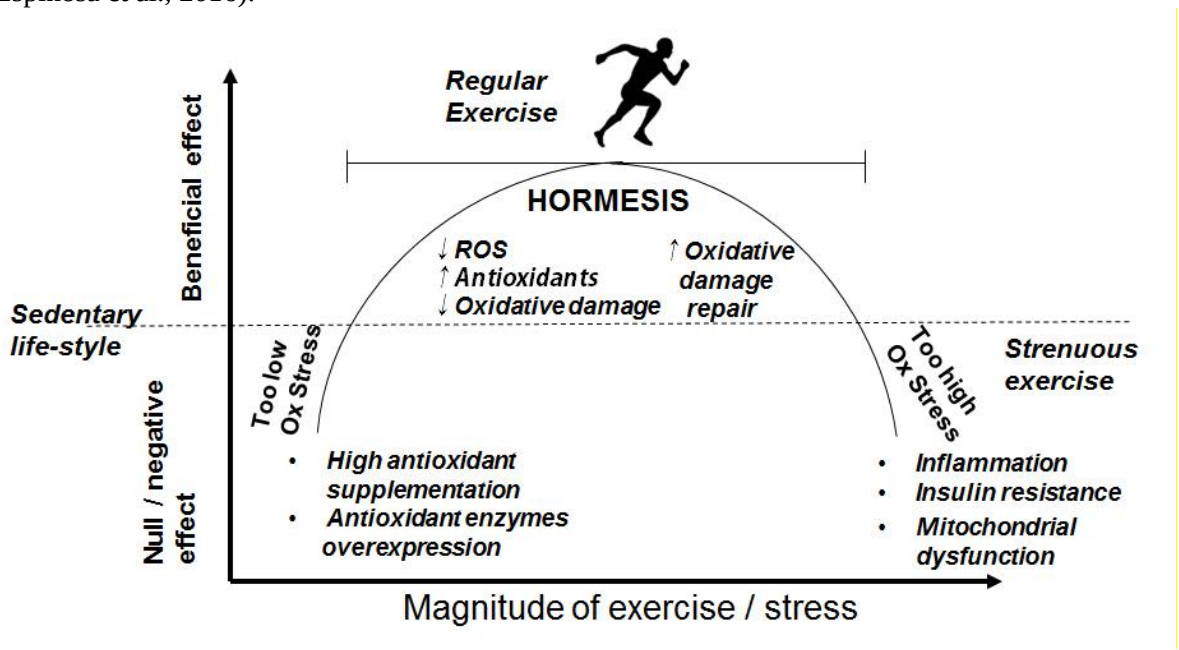
capable of scavenging free radicals, were extensively examined in that regard.

Fig. 3. Hormesis and exercise. Dose response theoretical curve depicting ROS production. ROS participates as physiological agents that are necessary for normal function in skeletal muscle. An excess ROS levels is present in pathological processes, being probably the cause of damage in striated muscle. An oxidative status that is too low leads to a lack of benefits and may be detrimental for health. Ox, oxidative; ROS, reactive oxygen species. (according to Pingitore et al., 2015 and Espinosa et al., 2016).



Unexpectedly, several prospective clinical intervention studies were unable to show a positive association between supplementation with antioxidants and health-beneficial effects. Whereas most studies found a lack of effect in regards to health promotion in humans [Buring and Manson, 2007; Katsiki and Manes, 2009; Lin et, 2009; Song et al., 2009], other reports even suggest that antioxidants may promote cancer growth [Bardia et al., 2008; Myung et al., 2010]. Moreover, supplementation with antioxidants has been linked to increased incidence of a number of diseases with adverse effects on human longevity [Bjelakovic et al., 2007; Ward et al., 2007; Lippman et al., 2009].

According to recent literature data, activation of stress response pathways as well as induction of defense mechanisms has been discussed as representing the underlying life-span-extending mechanisms [Sharma et al., 2010; Zuin et al., 2010; Yang and Hekimi, 2010; Woo and Shadel, 2010]. It should be noted that endogenously produced ROS presumably not only induce ROS defense enzymes, but also increase activities of enzymes that protect from damage beyond ROS. Consistent with the concept of mitohormesis, glucose restriction leads to an increase in mitochondrial activity accompanied by an increase in respiration-derived ROS. This ROS signal is able to induce conserved downstream processes that culminate in an overall adaptive response, represented by an improvement in antioxidant capacity and finally longevity. Cotreatment with antioxidants inhibits ROS signal transduction and prevents the adaptive response. Thus, glucose-restriction-mediated longevity is abolished. Therefore, interventions that induce mitochondrial function seem to be promising in regard to regulation of life expectancy. Accordingly, moderate physical activity, an intervention that is known to be health beneficial in a broad spectrum [Warburton et al., 2006; Manini et al., 2006; Lanza et al., 2008], is assumed to cause induction of mitochondrial metabolism and ROS production [Davies et al., 1982; Chevion et al., 2003; Powers and Jackson, 2008]. Moreover, health-promoting effects were demonstrated to be reduced if subjects exposed to

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physical activity were cotreated with antioxidant supplements [Gomez-Cabrera et al., 2008; Ristow et al., 2009]. On the other hand, physical inactivity leads to impairment in physiological functions and reduces the whole body resistance to oxidative stress. Moreover, it seems that physical inactivity through molecular pathways could facilitate the incidence of oxidative stress-related diseases, such as cardiovascular diseases, cachexia, atherosclerosis, cancer, ischemia/reperfusion, inflammation, rheumatic arthritis, and neurodegenerative diseases such as Alzheimer and Parkinson diseases. Therefore it seems that the human being is not designed to be inactive for survival.

Conclusions

Hormesis is now considered by many scientists as a valid hypothesis, and is "fashionable" in a way, there is a risk to dogmatically apply this concept even when it is not appropriate. Therefore, hormesis should not become a "new religion" [Thayer et al., 2005]. It is necessary to consider not only the beneficial effects of a mild stress, but also the negative ones [Le Bourg, 2009]. It is now thought that all types of exercise, whether aerobic or anaerobic, have the potential to produce ROS and thus induce oxidative stress. Of course, exercise-induced oxidative stress is influenced by several other factors, including the mode of exercise (duration, intensity, and frequency), specific biomarkers chosen, time course of tissue sampling, age, training status, and dietary intake. Since the optimal level of ROS production (i.e., mild to moderate oxidative stress) may function as an indispensable mechanism in exercise-related hormetic adaptive responses, a strategy to maintain exercise-induced oxidative stress within the most suitable range must be established. In other words, it is necessary that exercise-induced oxidative stress is dynamically regulated within a physiological regulatory range to ensure redox homeostasis. As a result, only the regular exercise in intensity and duration has a wide range of beneficial effects on the body and fit well with the concept of hormesis. It enhances mitochondrial activity and subsequently increase ROS formation that ultimately induce an adaptive response (increased defense mechanisms and improved stress resistance), which culminates in metabolic health and extended longevity. Thus, contrary to what is believed until now, oxidative stress is beneficial in small amounts. In fact it's essential, because prompts the body cells to become stronger over time by increasing antioxidant defense mechanisms. However, it is difficult to identify the threshold between beneficial physiological oxidative stress and pathological oxidative stress for each individual. To specifically obtain exercise-mediated benefits, new surrogate markers to predict the individual threshold of oxidative stress may also be required. Although the detailed role of oxidative stress in the mechanism of exercise-induced hormetic adaptations in humans remains to be completely elucidated, there is no doubt that exercise induced oxidative stress, a tool for "hormesis" and "adaptive response", has tremendous potential to upregulate various biological functions.

References

1. **Alessio, HM, Goldfarb, AH.** (1988). Lipid peroxidation and scavenger enzymes during exercise: adaptive response to training. J Appl Physiol, 64:1333–1336.
2. **Alleman, RJ, Katunga LA, Nelson MA, Brown DA, Anderson EJ.** (2014). The "Goldilocks Zone" from a redox perspective - adaptive vs. deleterious responses to oxidative stress in striated muscle. Front Physiol, 5:358.
3. **Bardia, A, Tleyjeh IM, Cerhan JR, Sood AK, Limburg PJ, Erwin PJ, Montori VM.** (2008). Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. Mayo Clin Proc, 83(1):23-34.

Corresponding author: Christos D. Papageorgiou, e-mail: chrispapag@gmail.com

4. **Bjelakovic, G, Nikolova D, Gluud L, Simonetti R, Gluud C**. (2007). Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 297:842–857.
5. **Buring, JE, Manson, J.E.** (2007). A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. Arch Intern Med, 167:1610–1618.
6. **Calabrese, EJ, Iavicoli I, Calabrese V.** (2013). Hormesis: its impact on medicine and health, Hum Exp Toxicol, 32:120–152.
7. **Calabrese, EJ.** (2006). The failure of dose–response models to predict low dose effects: a major challenge for biomedical, toxicological and aging research. Biogerontology, 7:119–122.
8. **Calabrese, EJ, Baldwin LA.** (2003). Toxicology rethinks its central belief. Nature, 421:691–692.
9. **Chevion, S, Moran DS, Heled Y, Shani Y, Regev G, Abbou B, Berenshtein E, Stadtman ER, Epstein Y.** (2003). Plasma antioxidant status and cell injury after severe physical exercise. Proc Natl Acad Sci USA, 100:5119–5123.
10. **Collins, Y, Chouchani ET, James AM, Menger KE, Cochemé HM, Murphy MP.** (2012). Mitochondrial redox signalling at a glance. J Cell Sci, 125(Pt 4):801-6.
11. **Das, DK, Engelman RM, Kimura Y.** (1993). Molecular adaptation of cellular defences following preconditioning of the heart by repeated ischaemia. Cardiovasc Res, 27**:**578-584.
12. **Davies, KJ, Quintanilha AT, Brooks, GA, Packer L.** (1982). Free radicals and tissue damage produced by exercise. Biochem Biophys Res Commun, 107:1198–1205.
13. **Ding, YH, Young CN, Luan X, Li J, Rafols JA, Clark JC, McAllister JP, Ding Y.** (2005). Exercise preconditioning ameliorates inflammatory injury in ischemic rats during reperfusion. Acta Neuropathol**,** 109:237-246.
14. **Dupont-Versteegden, EE, Fluckey JD, Knox M, Gaddy D, Peterson CA.** (2006). Effect of flywheel-based resistance exercise on processes contributing to muscle atrophy during unloading in adult rats. Journal of applied physiology, 101:202-212.
15. **Fontana L, Klein S, Holloszy JO.** (2010). Effects of long-term calorie restriction and endurance exercise on glucose tolerance, insulin action, and adipokine production. Age (Dordr), 32:97-108.
16. **Gomez-Cabrera, MC, Domenech E, Romagnoli M, Arduini A, Borras C, Pallardo F.V, Sastre J, Vina J.** (2008). Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. Am J Clin Nutr, 87:142–149.
17. **Harman, D.** (2006). Free radical theory of aging: an update: increasing the functional life span. Ann NY Acad Sci, 1067:10–21.
18. **Jargin, SV.** (2015). Hormesis and homeopathy: the artificial twins. J Intercult Ethnopharmacol, 4:74–77.
19. **Ji, LL, Gomez-Cabrera MC, Vina J.** (2006). Exercise and hormesis: activation of cellular antioxidant signaling pathway. Ann NY Acad Sci, 1067:425-35.
20. **Ji, LL.** (2008). Modulation of skeletal muscle antioxidant defense by exercise: Role of redox signaling. Free Radic Biol Med, 44(2):142-52.
21. **Kaise, RJ.** (2003). Hormesis: a healthful dab of radiation? Science, 302:378.
22. **Katsiki, N, Manes C.** (2009). Is there a role for supplemented antioxidants in the prevention of atherosclerosis? Clin Nutr, 28:3–9.
23. **Khassaf, M, Child RB, McArdle A, Brodie DA, Esanu C, Jackson MJ.** (2001). Time course of responses of human skeletal muscle to oxidative stress induced by nondamaging exercise. Journal of applied physiology, 90:1031-1035.

Corresponding author: Christos D. Papageorgiou, e-mail: chrispapag@gmail.com

24. **Kim, JS, Lee YH, Choi DY, Yi HK.** (2015). Expression of Heat Shock Proteins (HSPs) in Aged Skeletal Muscles Depends on the Frequency and Duration of Exercise Training. J Sports Sci Med, 14:347-353.
25. **Lanza, IR, Short DK, Short KR, Raghavakaimal S, Basu R, Joyner MJ.** et al**.** (2008). Endurance exercise as a countermeasure for aging. Diabetes 57:2933–2942.
26. **Lawler, JM, Rodriguez DA, Hord JM.** (2016). Mitochondria in the middle: Exercise preconditioning protection of striated muscle. J Physiol, doi: 10.1113/JP270656.
27. **Le Bourg, E.** (2009). Hormesis, aging and longevity. Biochim. Biophys. Acta (BBA) - General Subjects, 1790:1030–1039.
28. **Lin, J, Cook NR, Albert C, Zaharris E, Gaziano JM, Van Denburgh M, Buring JE, Manson JE.** (2009). Vitamins C and E and beta-carotene supplementation and cancer risk: a randomized controlled trial. J Natl Cancer Inst, 101:14–23.
29. **Lippman, SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM.** et al., (2009). Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA, 301:39–51.
30. **Locke, M, Noble EG, Tanguay RM, Feild MR, Ianuzzo SE, Ianuzzo CD.** (1995). Activation of heat-shock transcription factor in rat heart after heat shock and exercise. Am J Physiol, 268**,** C1387-1394.
31. **Manini, TM, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M.** et al. (2006). Daily activity energy expenditure and mortality among older adults. JAMA,296:171–179.
32. **Marques, FZ, Markus MA, Morris BJ.** (2009) Hormesis as a pro-healthy aging intervention in human beings? Dose-Response, 8:28–33.
33. **Myung, SK, Kim Y, Ju W, Choi HJ, Bae WK.** (2010). Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials. Ann Oncol, 21:166–179.
34. **Omar, R, Pappolla M**. (1993). Oxygen free radicals as inducers of heat shock protein synthesis in cultured human neuroblastoma cells: relevance to neurodegenerative disease. Eur Arch Psychiatry Clin Neurosci, 242:262-267.
35. **Pani, G, Colavitti R, Bedogni B, Anzevino R, Borrello S, Galeotti T.** (2000). A redox signaling mechanism for density-dependent inhibition of cell growth. J Biol Chem 275: 3889–38891.
36. **Peake, JM, Markworth JF, Nosaka K, Raastad T, Wadley GD, Coffey VG.** (1985) Modulating exercise-induced hormesis: Does less equal more? J Appl Physiol, 119(3):172-89.
37. **Pourova, J, Kottova M, Voprsalova M, Pour M.** (2010). Reactive oxygen and nitrogen species in normal physiological processes.Acta Physiol (Oxf), 198(1):15-35.
38. **Powers, SK, Jackson MJ.** (2008). Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev, 88:1243–1276.
39. **Radak, Z, Chung HY, Goto S.** (2008). Systemic adaptation to oxidative challenge induced by regular exercise. Free Radic Biol Med, 44:153-159.
40. **Radak, Z, Chung HY, Goto S.** (2005). Exercise and hormesis: oxidative stress-related adaptation for successful aging. Biogerontology, 6(1):71-75.
41. **Radak Z, Sasvari M, Nyakas C, Pucsok J, Nakamoto H, Goto S.** (2000). Exercise preconditioning against hydrogen peroxide-induced oxidative damage in proteins of rat myocardium. Archives of biochemistry and biophysics, 376:248-251.
42. **Radak, Z,** ed. (2004). Exercise and diseases, Aachen: Meyer & Meyer Verlag.
43. **Radak, Z, Pucsok J, Mecseki S, Csont T, Ferdinandy P.** (1999). Muscle soreness-induced reduction in force generation is accompanied by increased nitric oxide content and DNA damage in human skeletal muscle. Free Radic Biol Med, 26:1059–1063.

Corresponding author: Christos D. Papageorgiou, e-mail: chrispapag@gmail.com

44. **Radak, Z, Taylor AW, Ohno H, Goto S.** (2001). Adaptation to exercise- induced oxidative stress: from muscle to brain. Exerc Immunol Rev, 7:90–107.
45. **Ristow, M, Schmeisser S.** (2011). Extending life span by increasing oxidative stress. Free Radic Biol Med, 51(2):327-336.
46. **Ristow, M, Zarse K.** (2010). How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis). Exp Gerontol, 45(6):410-418.
47. **Ristow, M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M, Stumvoll M, Kahn CR, Blüher M.** (2009). Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci USA, 106:8665–8670.
48. **Sagan, LA.** (1989) On radiation, paradigms, and hormesis. Science, 245:574-621.
49. **Samelman, TR.** (2000). Heat shock protein expression is increased in cardiac and skeletal muscles of Fischer 344 rats after endurance training. Exp Physiol, 85:92-102.
50. **Schieber, M, Chandel NS.** (2014). ROS function in redox signaling and oxidative stress. Curr Biol, 24(10):R453-62.
51. **Sharma, PK, Agrawal V, Roy N.** (2010). Mitochondria-mediated hormetic response in life span extension of calorie-restricted Saccharomyces cerevisiae. Age, 33:143–154.
52. **Song, Y, Cook NR, Albert CM, Van Denburgh M, Manson JE.** (2009). Effects of vitamins C and E and beta-carotene on the risk of type 2 diabetes in women at high risk of cardiovascular disease: a randomized controlled trial. Am J Clin Nutr, 90:429–437.
53. **Thayer KA, Melnick R, Burns K, Davis D, Huff J.** (2005). Fundamental flaws of hormesis for public health decisions, Environ Health Perspect, 113:1271–1276.
54. **Tsigos, C, Chrousos GP.** (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res, 53(4):865-71.
55. **Warburton, DE, Nicol CW, Bredin SS.** (2006). Health benefits of physical activity: the evidence. Can Med Assoc J, 174:801–809.
56. **Ward, NC, Wu JH, Clarke MW, Puddey IB, Burke V, Croft KD, Hodgson JM.** (2007). The effect of vitamin E on blood pressure in individuals with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. J Hypertens, 25: 227–234.
57. **Woo, DK, Shadel GS.** (2011). Mitochondrial stress signals revise an old aging theory. Cell, 144:11–12.
58. **Yang, W, Hekimi S.** (2010). A Mitochondrial superoxide signal triggers increased longevity in Caenorhabditis elegans. PLoS Biol, 8:e1000556.
59. **Yun, J, Finkel T.** (2014). Mitohormesis. Cell Metab, 19(5):757-66.
60. **Zuin, A, Carmona M, Morales-Ivorra I, Gabrielli N, Vivancos AP, Ayte J, Hidalgo E.** (2010). Lifespan extension by calorie restriction relies on the Sty1 MAP kinase stress pathway. EMBO J, 29:981–991.

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