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Review

Exercise, oxidative stress and hormesis

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Abstract

Physical inactivity leads to increased incidence of a variety of diseases and it can be regarded as one of the end points of the exercise-associated hormesis curve. On the other hand, regular exercise, with moderate intensity and duration, has a wide range of beneficial effects on the body including the fact that it improves cardio-vascular function, partly by a nitric oxide-mediated adaptation, and may reduce the incidence of Alzheimer's disease by enhanced concentration of neurotrophins and by the modulation of redox homeostasis. Mechanical damage-mediated adaptation results in increased muscle mass and increased resistance to stressors. Physical inactivity or strenuous exercise bouts increase the risk of infection, while moderate exercise up-regulates the immune system. Single bouts of exercise increases, and regular exercise decreases the oxidative challenge to the body, whereas excessive exercise and overtraining lead to damaging oxidative stress and thus are an indication of the other end point of the hormetic response. Based upon the genetic setup, regular moderate physical exercise/activity provides systemic beneficial effects, including improved physiological function, decreased incidence of disease and a higher quality of life.

Keywords: Exercise; Oxidative stress; Hormesis

1. Introduction

The thesis of the hormesis theory is that biological systems respond to the exposure to chemicals, toxins, and radiation with a bell-shaped curve. In toxicology, hormesis is a dose–response phenomenon characterized by a low dose of stimulation, high dose of inhibition, resulting in either a J-shaped or an inverted U-shaped dose–response, which is a non-monotonic response (Calabrese and Baldwin, 2001, 2002; Cook and Calabrese, 2006). Recently, we have extended the hormesis theory to free radical species, which appear to plateau when modulated by aging or physical exercise (Radak et al., 2005) Therefore, we have proposed that exercise modulates free radicals and the effects can be described by the hormesis curve.

The most important effect of exercise on the body is the adaptation process. As any stressor, a single bout of exercise has the capability to induce adaptation, although only in a restricted number of incidences, due to the limited time frame and the characteristics of the loading (Radak et al., 2001c). According to the original stress theory,

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developed by Selye (1956), for a chronic stressor the body replies with a decreased (alarm reaction), and then with an increased resistance (stage of resistance), which is followed by exhaustion of the body (stage of exhaustion). Therefore, chronic stressors could be very dangerous since the resting period, which is obligatory for recovery and efficient stress response, is missing. Using extremely long-duration exercise as an example, such as 18–24 consecutive hours of running or swimming, even in superbly trained individuals, the body can suffer serious ''exhaustion'' which could jeopardize the health of the individuals.

On the other hand, under normal conditions, exercise bouts are followed by rest periods and during rest the body has the capability to cope with the exercise ''stressor'' and as a result, adaptation takes place (Radak et al., 2001c). Indeed, the adaptive effects of regular exercise are systemic and, depending on the characteristics of exercise, the effects are specific. In skeletal muscle, for example, a single bout of long-term aerobic exercise decreases the concentration of glycogen, whereas the normal exercise-induced adaptation to a training regimen is an increase in glycogen concentration which significantly exceeds the level which is found in untrained muscle. Similarly, intensive anaerobic exercise increases the level of lactic acid, which can be as high as 20–25 mmol/l in the blood, but regular anaerobic exercise-associated adaptation enhances the ability to cope with lactic acid by enhancing its elimination.

Regular exercise is carried out for the sole purpose of bringing about adaptation. One of the end points of the exercise-related hormesis curve is physical inactivity, which unfortunately is associated with our modern ''civilized'' life-style. It is well documented that physical inactivity is associated with increased incidence of a variety of diseases and pathological conditions, including cardiovascular diseases, Type II diabetes, muscular atrophy, Alzheimer's and Parkinson's diseases and obesity (Booth and Lees, 2007).

Interestingly, the beneficial effects of exercise are highlighted according to the human genetic setup, and physical activity has been an important and necessary part of our every day life (Goto and Radak, 2005). Hunting, gathering, fighting and mobility were part of every day life some 100 years ago, and as a result the human genetic pool favors physical activity. Modern life-style, on the other hand, at least in industrialized nations, has essentially eliminated physical activity in the work place. Modern technology and fad diets have resulted in the extensive appearance of life-style-related diseases, which easily can be treated and prevented with regular physical activity (Goto and Radak, 2005; Radak et al., 2004b).

Excessive exercise or overtraining, the other end point of the hormesis curve, increases the risk of disease and jeopardizes health. Indeed, it is also well established that during overtraining the adaptation process fails, and this is primarily due to incomplete recovery from the exercise bouts and, as a result, some maladaptation occurs (Ogonovszky et al., 2005).

Since the present review is limited in length and thus unable to cover the extremely complex systemic adaptation to exercise or fully describe the effects of physical inactivity and overtraining, only some of the most important topics have been selected.

2. Exercise and fatigue

Regular exercise is an interval stressor. During exercise, metabolic, mechanical and psychological loading result in a wide range of alteration in different organs. During rest, the body recovers, compensates and/or over-compensates the effects of the exercise-stressor. It is a well-known physiological fact that exercise must attain a certain level of stress for adaptation to occur. Indeed, if the exercise-induced stress does not reach this threshold, adaptation will not occur. Low-level exercise loading can be effective in case of low level physical fitness but for well trained individuals a high level of exercise stress is obligatory. Adaptation will not occur without fatigue. The level of fatigue is important, since extreme fatigue could cause very significant cellular alterations, even irreversible ones, and the recovery period after extreme fatigue could be too long, which makes it difficult to establish an exercise regimen. On the other hand, if, following fatigue, inadequate time for recovery is not accounted for, overtraining could occur. This would result in decreased physiological performance, a disturbance of hormonal processes, a depressed immune function, an increased susceptibility to infection, and an increased incidence of many diseases (Angeli et al., 2004; Armstrong and VanHeest, 2002; Lakier Smith, 2003; Moeller, 2004; Nederhof et al., 2006; Smith, 2000). Inflammation, which is a protective process, and necessary for the healing process to occur, can be deregulated and the generation of inflammatory and anti-inflammatory cytokines could be the causative factors of the overtraining syndrome (Smith, 2000). Overtraining is a maladaptive process, which can seriously endanger health and decrease the ability to maintain homeostasis. There is no question that overtraining is an end point of the exercise-associated hormesis curve.

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3. Muscle soreness and muscle hypertrophy

Exercise with unaccustomed loading often results in muscle soreness, which is associated with structural damage to the sarcomeres, disruption of desmin and the myofilament network, splitting of the Z-band and increased intramuscular pressure detected by slit-catheter (Friden et al., 1984, 1986, 1988). This damage activates inflammatory processes, increases DNA binding of NF-κB, activates proteases of the proteasome complex, so that degradation of damaged proteins will be enhanced (Malm et al., 2004; Peake et al., 2006; Goto and Radak, 2005). It appears that this adaptive micro damage evokes the repair process. Hence, after the remodeling, the sarcomere will be stronger and better able to withstand mechanical stress. Therefore, as a result of this muscular adaptation, the same level of loading would not result in muscle soreness, decrease in maximal force production, or inflammation (Radak et al., 1999b).

According to our current understanding of muscular hypertrophy, exercise loading has to reach a certain level, which is above 60% of the maximal performance, in order to stimulate the process of hypertrophy (Macintyre, 1987). The enhanced secretion of anabolic hormones, growth hormone, testosterone and IGF-1, is an important factor to increase protein synthesis and this does not happen if the loading is sub-threshold (Goto and Radak, 2005). All types of muscle fibers are capable of hypertrophy, although in the case of fast fibers, the increase of protein synthesis is dominant, while slow fibers decrease the rate of protein degradation to gain greater size (Goldspink, 1991).

It is claimed (Goldspink, 1991), that when the protein content of myofibrils increases and when they are under high tension, longitudinal splitting takes place, which results in new filaments being formed. As a consequence of this increased mechanical stress, the myofibrillar mass is subdivided, because the Z-bands, where the actin filaments are anchored, are not able to withstand the increased tension. Therefore, it appears that muscular hypertrophy is mediated by high mechanical tension that causes micro damage. Extreme mechanical stress, on the other hand, disintegrates sarcomeres, and ruptures tendo-muscular junctions, which leads to apoptosis and necrosis, which, even if recovered after a long period, would not cause increased muscle size, or enhanced physiological function (Armand et al., 2003; Friden and Lieber, 1998; Koskinen et al., 2002).

Therefore, both muscle soreness and muscular hypertrophy can be described by the hormetic curve. Muscle soreness is associated with decreased physiological function. As a result of this adaptive damage and after remodeling, this would lead to improved performance. Similarly, for the splitting of myofibrils, tension is necessary which causes damage to the Z-band and the formation of daughter filaments occurs. The damage-induced adaptation results in increased muscle mass. If the damage is too large it can cause necrosis, or apoptosis and un-recoverable alterations can occur. If the stimulus is missing or not strong enough, the adaptation process would not have been necessary, and thus the physiological function would remain unchanged.

4. Adaptive gene expression in exercise

Two types of physical activity, i.e. resistance exercise and endurance training, cause adaptive responses of gene expression in nuclear and mitochondrial genomes in the skeletal muscle. The changes of gene expression are modulated by a variety of transcription factors constituting the basis of different or common mechanisms of adaptation in the two paradigms. One of the most prominent changes induced by physical activities is upregulation of mitochondrial energy metabolism. The increase involves transcriptional regulation of genes for mitochondrial proteins encoded in the nuclear genome by the peroxisome-proliferator-activated receptor (PPAR) gamma co-activator-1 alpha (PGC-1α) and control of mitochondrial gene expression by the mitochondrial transcription factor A (Tfam) (Hood, 2001). Endurance exercise activates PGC-1α, leading to phenotypes such as increased mitochondrial biogenesis and efficient muscle contraction (Baar, 2004; Joseph et al., 2006). On the other hand, exercise causes an increase in AMP concentration due to massive consumption of ATP sufficient to activate AMP kinase (AMPK) by phosphorylation via a yet unknown mechanism (Atherton et al., 2005). Expression of PGC-1α is induced by AMPK by an uncharacterized mechanism, thus the AMPK–PGC-1α signaling pathway is apparently being involved in adaptive responses to endurance training that results in mitochondrial biogenesis (Atherton et al., 2005). PGC-1α is also involved in fiber-type switching from glycolytic to oxidative fibers and the abundance of contractile proteins (Sandri et al., 2006). Thus, PGC-1α is shown to lend resistance to muscle atrophy, providing a mechanism for protecting age-related sarcopenia by exercise.

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In addition to the impact on energy homeostasis, exercise inevitably increases ROS and NOS generation that can be harmful to unprepared tissues but may also activate adaptive responses to oxidative stress inducing antioxidant defense systems by upregulation of responsible gene expression (Powers et al., 1999; Ji et al., 2006). An acute bout of exercise activates the transcription factor NF-κB (nuclear factor kappa B) to enhance transcription of genes for antioxidative enzymes such as mitochondrial Mn superoxide dismutase (MnSOD) and inducible nitric oxide synthase (iNOS) via increased generation of ROS (Hollander et al., 2001; Hemmrich et al., 2003). Regular exercise also increases antioxidant defenses in the skeletal muscle upregulating SOD and glutathione peroxidase gene expression, thereby adapting stronger oxidative stresses (Powers and Lennon, 1999; Leeuwenburgh and Heinecke, 2001). It thus appears that ROS serves as messengers in exercise-induced adaptive gene expression. Franco et al. reported that myotubes exposed to H_2O_2 exhibit upregulation of mRNA for antioxidant enzymes (catalase, glutathione peroxidase, Cu, ZnSOD and MnSOD), suggesting that ROS is involved in the adaptive upregulation of antioxidant gene expression by exercise (Franco et al., 1999). In support of this suggestion, Khassaf et al. (2003) found that supplementation of vitamin C, a nutritional antioxidant, attenuates antioxidant defense including increase in shock protein (HSP) 70 in human lymphocytes and skeletal muscle. Similarly, the active isoform of another dietary antioxidant vitamin E and vitamin C inhibits induction of the mRNA of HSP 72, an important component of cellular protection, by exercise in human skeletal muscle (Fischer et al., 2006). Gomez-Cabrera et al. (2005) reported that the induction of antioxidative enzyme MnSOD and iNOS induced by exhaustive exercise is abolished by allopurinol, an inhibitor of xanthine oxidase, in the skeletal muscle of rats. Since the expression of these enzymes appears to be dependent on NF-κB that is activated by ROS, the adaptive process is suggested to be induced by ROS (Gomez-Cabrera et al., 2005). These findings illustrate essential roles of ROS in protective adaptation induced by exercise. Too much generation of ROS in unaccustomed muscles is obviously harmful while the modest generation by regular exercise is apparently beneficial to upregulating defense mechanisms against oxidative stress, thus forming a basis of hormetic effects of exercise.

5. Exercise and the immune system

There is an accumulating body of evidence which suggests that exercise induces considerable alterations to the immune system (Chung et al., 2005). The interaction between exercise-associated stress and the immune system provides an excellent opportunity to study hormesis in this unique condition (Pedersen and Hoffman-Goetz, 2000; Chung et al., 2005). In general, exercise of a high intensity or long duration can cause immunosuppression and increased susceptibility to infection. Indeed, upper respiratory tract infections are often reported after strenuous exercise (Heath et al., 1992). This level of exercise load is associated with glutamate debt, which could alter the efficiency of the immune system (Lehmann et al., 1995). As well, long-term exercise results in increased secretion of cortisol, which also could lead to immunosuppresion (Okutsu et al., 2005; Smith and Myburgh, 2006) since cortisol likely plays a role in maintaining the neutrophilia and lymphopenia after prolonged exercise. As a result, the activity of natural killer cells is suppressed to below the pre-exercise values, especially after exercise of a high intensity or long duration, when the lowest natural killer cell activity is measured 2–4 h after the strenuous exercise bouts (Pedersen et al., 1990). Therefore, exercise of high intensity or long duration creates an ‘‘open window’’ which indicates a higher risk of infection. On the other hand, exercise of moderate intensity and duration generally can be regarded as an up-regulator of the immune system, leading to increased resistance against infection and a lower risk of appearance of disease, including certain types of cancer (Chung et al., 2005; Radak et al., 2005; Woods et al., 2006).

6. Exercise and free radicals

Exercise can increase the generation of ROS and this is especially true for single bouts of exercise (Alessio and Goldfarb, 1988; Alessio et al., 1988; Davies et al., 1982; Radak et al., 1999b). As a consequence of increased concentration of ROS, oxidative damage of lipids, proteins and DNA have been reported following single bouts of exercise (Alessio et al., 1988; Davies et al., 1982; Gomez-Cabrera et al., 2006; Ikeda et al., 2006; Ji et al., 2006; Mahoney et al., 2005; Paroo et al., 2002; Poulsen et al., 1998; Radak et al., 1995, 1996, 1998, 1999b, 2004a; Russell et al., 2005). Redox sensitive transcription factors and signaling pathways are induced by exercise, and these pathways are obligatory for adaptive responses to occur.

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An interesting finding has been reported by Gomez-Cabrera et al. (2005), which demonstrates that administration of allopurinol, a potent inhibitor of xanthine oxidase, prevents exercise-induced adaptation. This observation underlines the importance of ROS, at least in the concentration generated during exercise, to induce adaptation, and questions the uncontrolled administration of antioxidants.

There is ample evidence to suggest that regular exercise increases the activity of antioxidant enzymes and increased levels of ROS appear to be necessary during the exercise session. In addition to the first line of antioxidant enzymes, the second line, the oxidative damage repair systems, are important to minimize the dangerous effects of ROS (Crawford and Davies, 1994; Davies, 1986). It has been demonstrated that regular exercise increases the activity of proteasome complex in the myocardium, and decreases the level of carbonylated proteins. Administration of hydrogen peroxide for 2 weeks, every second day, to sedentary rats, resulted in increased activity of the proteasome, and the carbonyl concentration increased. On the other hand, hydrogen peroxide treatment did not increase the oxidative protein damage in the heart, but the induction of proteasome activity was most prominent, indicating that exercise increases the resistance against oxidative stress and also increases the efficiency of the repair process (Radak et al., 2000). This observation can be extended to DNA as well, since our data suggest that marathon running increased the activity of OGG1, the enzyme which preferentially repairs 8-hydroxydeoxyguanosine (8-OHdG) in skeletal muscle of runners (Radak et al., 2003). The up-regulation of the activity of DNA repair enzymes could be an important means by which exercise decreases the DNA damage in nuclei (Radak et al., 1999a, 2002, 2005, 2007).

Exercise also has a large impact on the availability and bioactivity of endothelial-derived nitric oxide (NO). The stimulus for endothelial NO production is the increased flow through the vessels, which results in shear stress and increased activation of endothelial nitric oxide synthase (Kojda and Hambrecht, 2005; McAllister and Laughlin, 2006). NO then acts as a vasodilator. Exercise results in increased blood flow and shear stress, and increased bioactivity of NO (Clarkson et al., 1999; McAllister and Laughlin, 2006). Data suggest that at least 10 weeks of exercise training are necessary to significantly improve endothelium-dependent vasodilation in healthy young man (Clarkson et al., 1999), while for patients with depressed NO bioactivity, even 4 weeks of training is beneficial (Hambrecht et al., 2000a,b; Hamilton et al., 2001; Hambrecht et al., 2000). There is an intriguing relationship between NO and ROS, especially with regards to superoxide. NO at low concentrations serves as an antioxidant, while at high concentrations, the end product of superoxide and NO interaction results in peroxynitrite ($ONOO^-$) which is very reactive and highly cytotoxic (Pacher et al., 2007).

Although the available information on exercise load-dependent bioactivity of NO is still sparse, data indicate that low intensity exercise may fall below the threshold level which is necessary to improve NO-related vascular function (Goto et al., 2003; Bergholm et al., 1999). Interestingly, exercise of a very high intensity could also have little effect on vascular function, since the bioavailability of NO can be abolished through scavenging by ROS generated at high intensity exercise (Goto et al., 2003).

Therefore, the effects of exercise on ROS production, NO and dependent vascular function fit the hormesis curve.

It is our view that the ROS-generation effects of exercise are very important, because this process can initiate adaptive processes, which result in lower base levels of ROS, increased activity of antioxidant and damage repair enzymes, and lower levels of oxidative damage (Radak et al., 2005). This ROS mediated adaptation could play a significant role by which exercise decreases the incidence of ROS-associated diseases, including specific cardiovascular diseases, stroke, Alzheimer disease, and certain types of cancer (Perry et al., 2005; Radak et al., 2005; Mattson and Magnus, 2006; Mattson and Wan, 2005; Yu and Chung, 2006).

7. Exercise and aging

In the present review, we have been discussing the relationship of exercise to the context of hormesis. The link between exercise and aging can also fit the hormesis curve. Generally, during aging, the ability of the body to maintain homeostasis decreases, and regular exercise increases the ability to cope with a variety of stressors. Aging is associated with significant decreases in physical activity, which in turn facilitate the aging process. Aging is a very complex process, which affects each organ, and even each cell differently. The mass and function of skeletal muscle decrease. However, it has been shown that regular exercise significantly prevents this age-associated loss (Roos et al., 1997). Recently, it has become clear, that exercise also has a very similar beneficial effect on brain function (Mattson, 2005; Radak et al., 2001a). There is evidence that physical inactivity raises the incidence of Alzheimer disease, one of the

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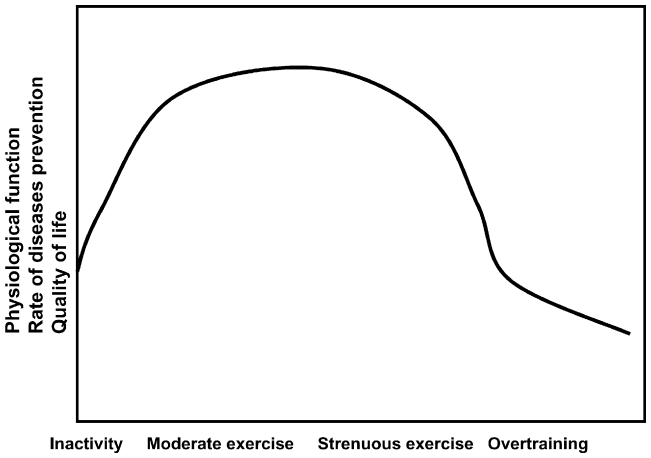

Fig. 1. Typical hormesis curve and the effects of exercise. Moderate exercise increases the physiological function of different organs, increases the rate of prevention against diseases and improves quality of life. Physical inactivity and strenuous exercise and overtraining increases the risk of diseases and decreases physiological function.

most well-described age-related disorders (Booth and Lees, 2007; Booth et al., 2002; Feher and Lengyel, 2006; Taylor and Poston, 2006; Thompson, 2006; Wendel-Vos et al., 2004). Muscular activity results in increased capillarization and better oxygen supply to different regions of the brain, and, naturally, the increased metabolic activity of neurons results in increased oxygen uptake, which probably is associated with increased activity of antioxidant and oxidative damage repairing enzymes (Cotman and Berchtold, 2002; Fabel et al., 2003; Radak et al., 2001a, 2006). Moreover, physical activity results in up-regulation of neutrophins, which not only enhance brain function but play a critical role in cell survival, and increase resistance against a variety of stressors (Mattson and Wan, 2005; Mattson et al., 2004; Mattson, 2005).

A causative relationship has been shown between the accumulation of carbonyl groups in amino acid residues, due to the interaction with ROS, and specific brain functions (Carney et al., 1991; Radak et al., 2001b). We have shown that regular exercise can increase the activity of proteasome complex, which is responsible for the degradation of carbonylated and other damaged proteins. A recent study by Lazarov et al. (2005) has shown that physical activity reduced the β-amyloid content in the brain of transgenic mice and this is due to the increased activity of neprilysin.

The systemic effects of exercise can also be observed in the liver, in which single bouts of exercise significantly increase the level of ROS and cause oxidative damage to lipids (Davies et al., 1982; Radak et al., 1995, 1996). Furthermore, we have demonstrated that regular exercise decreases the ROS concentration in liver, and attenuates the age-associated increase in ROS and the associated oxidative damage (Radak et al., 2004a). In addition, the DNA binding of NF-κB, which is one of the most potent inflammatory transcription factors, is modified by aging, and regular exercise and has a rejuvenating effect in the context of NF-κB.

Therefore, the available information suggests regular exercise at moderate intensity can retard the aging process and ameliorate the insidious onset of age-associated diseases.

8. Conclusion

The response of biological systems to stressors can be described by a U-shaped curve. Physical exercise also evokes this hormesis curve-response by the organism. The two end-points of the hormesis curve are inactivity and overtraining, and both of these result in decreased physiological function (Fig. 1). Normal and positively adapted function of the organism can be achieved with regular moderate exercise bouts. The effects of exercise on the immune system, free radicals, muscle function, vascular function and aging appear to fit the hormesis curve.

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