REVIEW / SYNTHÈSE

Hormetic effects of regular exercise in aging: correlation with oxidative stress

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Abstract: To explore mechanisms of the beneficial consequences of regular exercise, we studied the effects of regular swimming and treadmill exercise on oxidative stress in the brain and liver of rats. Protein carbonyl was significantly reduced and the activity of proteasome was upregulated in the brain extracts of young and middle-aged animals after 9 weeks of swimming training. Furthermore, their cognitive functions were significantly improved. In separate experiments, the activation of transcription nuclear factor κB was attenuated in the liver of old rats after 8 weeks of regular treadmill exercise and the DNA binding activity of glucocorticoid receptor reduced with age was restored, suggesting that inflammatory reactions are alleviated by the regimen. This was accompanied by upregulation of the glutathione level and reduced reactive oxygen species generation. Similar training reduced the 8-oxodeoxyguanosine content in the nuclear and mitochondrial DNA of the liver of old rats. Thus, these findings, together with reports of other investigators, suggest that moderate regular exercise attenuates oxidative stress. The mild oxidative stress possibly elicited by regular exercise appears to manifest a hormesis-like effect in nonmuscular tissues, constituting beneficial mechanisms of exercise by adaptively upregulating various antioxidant mechanisms, including antioxidative and repair–degradation enzymes for damaged molecules. Importantly, the adaptation induced by regular exercise was effective even if initiated late in life.

Key words: rat, aging, regular exercise, liver, brain, protein carbonyl, NF-κB, 8-oxodG, OGG1, hormesis.

Résumé : Nous analysons les effets de la nage et de la course pratiquées régulièrement sur le stress oxydatif observé dans le cerveau et le foie de rats afin d'approfondir les mécanismes associés aux bienfaits de la pratique régulière de l'activité physique. On observe une diminution de la concentration des protéines carbonylées et une régulation à la hausse de l'activité des protéasomes dans les tissus extraits du cerveau de rats jeunes et d'âge moyen après neuf semaines d'entraînement à la nage. De plus, on a observé une amélioration de leurs fonctions cognitives. Dans d'autres études, on observe dans le foie de rats âgés une diminution de l'activation des facteurs de transcriptions nucléaires NF-kB après huit semaines d'entraînement à la course sur tapis roulant; de plus, on observe la restauration de l'activité de fixation de l'ADN du récepteur glucocorticoïde, ce qui suggère une diminution des réactions inflammatoires causée par la pratique régulière d'activité physique. On observe en outre une augmentation de la concentration de glutathion (GSH) et une diminution des espèces oxygénées radicalaires (ROS). Un entraînement du même type cause une diminution du contenu en 8-hydroxydésoxyguanosine (8-oxodG) dans l'ADN du noyau et des mitochondries du foie de rats âgés. Somme toute, ces observations ainsi que celles des autres chercheurs suggèrent que la pratique régulière d'activité physique modérée atténue le stress oxydatif. Le léger stress oxydatif probablement causé par la pratique régulière d'activité physique semble accompagné d'une action hormétique dans les tissus autres que musculaires; on attribue le bienfait apporté par l'exercice physique à la bonification, au fil de la pratique, des mécanismes antioxydatifs incluant le travail des enzymes antioxydatives et de réparation/dégradation des molécules endommagées. Notons-le de façon importante, cette adaptation causée par la pratique régulière d'activité physique se manifeste même si la pratique est introduite tard dans la vie.

Mots-clés : rat, vieillissement, pratique régulière d'activité physique, foie, cerveau, protéines carbonylées, NF-kB, 8-oxodG, OGG1, hormèse.

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Introduction

The free radical theory of aging proposed by Harman (1956) predicts that radicals endogenously generated in oxygen-related metabolisms or induced by exogenous stimuli such as irradiation, smoking, and environmental pollutants, or possibly food components are major factors that drive aging. Radicals produced in a body include a variety of reactive oxygen species (ROS), reactive nitrogen species (RNS), and their derivatives (Pryor et al. 2006). The ROS and RNS modify cellular components and are, therefore, potentially harmful, causing aging and age-related diseases (Martin et al.1996; Beckman and Ames 1998). However, ROS and RNS also play essential roles in cellular homeostasis (Chandel et al. 1998; Maemura et al. 2005) and thus should not be regarded as "bad guys" that are to be eliminated as much as possible as current anti-aging strategies tend to claim (Olshansky et al. 2002; Dangour et al. 2004; Hadley et al. 2005).

Biological aging is accompanied by increased accumulation of altered proteins, lipids, and nucleic acids caused mainly by ROS and RNS. A focus to intervene in the aging process, therefore, has been on reducing the oxidatively modified molecules with antioxidative treatments by natural and synthetic compounds (Schaffer et al. 2006). Despite extensive studies on such attempts, no strong success has been reported (Dangour et al. 2004; Howes 2006). Dietary restriction and regular exercise are alternative approaches. Anti-aging effects of dietary restriction including extension of mean and maximum life span are well established in rodent models, in which oxidative stress is shown to be reduced (Sohal and Weindruch 1996; Hunt et al.2006), but it is controversial whether it is also true in human (Demetrius 2006; Le Bourg and Rattan 2006; Fontana et al. 2004). Epidemiological studies have shown that a physically active lifestyle has various health benefits in reducing the risk of age-associated diseases such as cardiovascular disorders, type 2 diabetes, cancer, and dementia, preventing sarcopenia and osteoporosis, and improving activities of daily life in elderly people that include upregulation of cognitive function (Singh 2002; Abbott et al. 2004; Larson et al. 2006). Paradoxically, however, physical exercise increases oxygen consumption and can induce oxidative stress. This apparently paradoxical outcome of exercise has been proposed to be owing to upregulation of the antioxidative and repair capacities of cells that are induced by mild oxidative stress as a form of hormesis (Navarro et al. 2004; Radák et al. 2005; Judge et al. 2005). Here, we summarize briefly our studies on the attenuation of oxidative stress by regular exercise in the brain and liver of middle-aged and old rats.

Effects of regular exercise on oxidative status in the brain

Protein carbonyl generated by oxidation of amino acid residues has been conveniently measured by the reaction with 2,4-dinitrophenylhydrazine as a marker to study the oxidative status of cells (Stadtman 1992; Goto et al. 1999). We have evaluated effects of regular exercise on the oxidation of the brain proteins in young and middle-aged male rats, measuring reactive protein carbonyls (Radák et al. 2001). Young (4 week-old) and middle-aged (14 month-old) animals were subjected to 60–90 min of swimming exercise per day for 5 days a week. The trained animals showed improved cognitive functions in passive and active avoidance tests in both age groups after the training period. The functional changes were accompanied by a decrease in the protein carbonyl in the brain.

Proteasome is involved in the degradation of altered proteins, such as oxidatively modified ones, as well as normal short-lived proteins including cell cycle regulators (Hershko 2005; Ciechanover 2005). The proteasome activity was upregulated in the brain of the trained animals as compared with the sedentary controls, suggesting that the increased proteasome activity is responsible for the decrease in the oxidatively modified proteins (Radák et al. 2001). These findings are consistent with the report that age-related decrease in the cognitive function and increase in protein carbonyls in the brain of gerbils were reversed in the old animals by treatment with a spin trap compound, N-tert-butyl-α-phenylnitrone, with concomitant increase in proteasome activity (Carney et al. 1991; but see Floyd et al. 2002 for an alternative mechanism of N-tert-butyl-α-phenylnitrone action).

It is interesting to note that a potentially beneficial effect of regular exercise is observed in tissue such as the brain that may not be expected to be influenced significantly compared with muscle tissues, suggesting that its effect is systemic. In recent years, it has been reported that long-term physical activity increases cell proliferation and neurogenesis in some regions of the mouse brain (van Praag et al.1999; Brown et al. 2003). Most remarkably, physical exercise reduced beta-amyloid deposition in the brains of transgenic model mice for Alzheimer's disease by upregulating the activity of neprilysin that degrades the beta-amyloid. These findings suggest that regular exercise may reduce the risk of other neurodegenerative diseases as well (Tillerson et al. 2003; Lazarov et al. 2005; Adlard et al. 2005; Pang et al. 2006). Z. Radák et al. describe beneficial effects of exercise in the brain function in more detail elsewhere in this issue of this journal.

Effects of regular exercise on oxidative status in the liver

Ever since Davies et al. (1982) demonstrated that exhaustive exercise induces free radical generation in the liver and skeletal muscles, numerous reports have been published on the increased oxidative stress induced by exercise (Vollaard et al. 2005). On the other hand, exercise training is reported to produce an adaptive response to oxidative stress, as studied primarily on skeletal muscles (Hollander et al. 1999; Rinaldi et al. 2006).The information is limited, however, on whether moderate regular exercise invokes oxidative stress or, conversely, produces adaptation to the stress in old organisms. Therefore, we studied the impact of regular exercise using old (28 month-old) and middle-aged (18 month-old) rats. They were subjected to regular treadmill running, 5 days a week for 8 weeks. The maximum oxygen uptake increased by about 40% in both age groups (Radák et al. 1999). The ROS level was significantly higher in the old sedentary groups than in the middle-aged counterparts (Radák et al. 2004). The regular exercise tended to

Table 1. Potential mechanisms of beneficial outcomes of regular exercise in the liver and brain of rats.

Organ	Outcome
Liver	1. The nuclear and mitochondrial DNA oxidation (8-oxodG) is reduced.
	2. The nuclear DNA repair activity (OGG1) is upregulated.
	3. The glucocorticoid receptor binding to its responsive DNA element is increased.
	4. The GSH content is increased.
	5. The NF-κB binding to its responsive DNA element is reduced.
Brain	1. The protein oxidation (carbonyl modification) is attenuated.
	2. The proteasome activity is upregulated.

attenuate this age-related increase. The reduced glutathione (GSH) is an important regulator of the redox status of tissues and in plasma during exercise (Leeuwenburgh and Ji 1995). The GSH reserve is reduced by exhaustive exercise not only in the skeletal muscle but also in the liver (Lew et al. 1985). In the present experiment, the hepatic redox status evaluated by GSH level showed a more than 2-fold increase in exercised groups in both middle-aged and old rats. Kakarla et al. (2005) also reported an increase in the GSH content of the liver of middle-aged (12 month-old) rats after 12 weeks of exercise training. Thus, the cellular milieu was shifted to a less oxidative state by regular exercise, even in middle-aged and old rats.

In view of the reduced oxidative stress in the liver, we expected that the redox-sensitive nuclear transcription factor-kappa B (NF-κB) is influenced by regular exercise. NF-κB is normally complexed with the inhibitory protein IκBα in the cytoplasm and triggers the synthesis of inflammatory cytokines (such as interleukin-6) and enzymes (including cyclooxygenase 2 and inducible nitric oxide synthase) upon dissociation from the inhibitor, translocation into the nucleus, and binding to the target genes (Haddad 2002; Piva et al. 2006). The DNA binding activity for NF-κB in nuclear extracts of the liver, detected by electrophoretic mobility shift assay, was significantly attenuated in the exercised old rats compared with the sedentary age-matched controls, with a concomitant increase in the amount of cytoplasmic IκBα (Radák et al. 2004). It is thus suggested that inflammatory response is alleviated in the liver of old animals by the exercise regimen, by virtue of the reduced oxidative stress and NF-κB activation. Since NF-κB is involved in carcinogenesis (Karin 2006), the attenuation of its activation may possibly explain a part of the mechanisms of the anticancer effect of regular exercise. Additionally, in contrast to the increased level of the neutrophil by acute exercise (Quindry et al. 2003), we found that the age-related increase in the neutrophil level in the blood is decreased by the regular exercise, the finding being consistent with roles of regular exercise in reducing inflammatory processes (Matsuura et al., unpublished results; Kobayashi et al., unpublished results).

Glucocorticoids have anti-inflammatory activities, suppressing inflammatory reactions in chronic diseases such as asthma and rheumatoid arthritis. The glucocorticoid-bound receptor (GR) influences gene expression of the inflammation-related proteins directly or indirectly via interaction with other transcription factors (Adcock 2000). The GR translocated to the nucleus inhibits gene expression of inflammatory cytokines including interleukin-1β and tumor necrosis factor-α, and enzymes responsible for inflammatory processes such as inducible nitric oxide synthase and cyclooxygenase 2 (Adcock 2000). In view of the above finding on NF-κB, it was of interest to study the effects of regular exercise on the GR. We found that the binding activity of the GR to the responsive DNA element (GRE) was significantly decreased in the liver of sedentary-aged animals compared with their young counterparts, but the regular exercise partially restored the decrease in the old animals (R. Abe et al., unpublished results). This finding is consistent with the view that regular exercise attenuates inflammation. Interestingly, the GR can directly interact with NF-κB, competing for the binding site in inflammatory genes (Ray and Prefontaine 1994; Smoak and Cidlowski 2004). It is thus likely that the upregulation of GR binding and the downregulation of NF-κB binding synergistically attenuate the expression of inflammation-related genes in exercised animals.

An active lifestyle is known to reduce the risk of cancer, a major cause of death in elderly people (Blair et al. 1989). Oxidative stress in the nuclear and mitochondrial DNA is thought to cause carcinogenesis and aging (Balaban et al. 2005; Harman 1972; Loft and Poulsen 1996). 8-Oxoguanine (8-oxoG), the abundant form of oxidative DNA base modifications, can lead to a GC→TA transversion type of mutagenesis (Cheng et al. 1992). We have, therefore, studied the effect of regular exercise on the oxidative modification of the nuclear and mitochondrial DNA and its repair in the liver of aged rats (Nakamoto et al. 2007). Rats at 21 months of age were subjected to 8 weeks of regular treadmill running. The amount of 8-oxodG (deoxynucleoside of 8-oxoG) in the nuclear and mitochondrial DNA of the liver in sedentary controls was 2- and 1.5-fold higher in the 2 organelles, respectively, than that in young adult animals (11 months old). The mitochondrial DNA showed a 10-fold higher content of the oxidative lesion than the nuclear DNA. 8-OxodG was reduced to levels of the young animals in both nuclear and mitochondrial DNA by the exercise. The activity of the repair enzyme 8-oxoguanine DNA glycosylase 1 (OGG1) for the lesion was decreased in the nucleus, but not in mitochondria, with age; it was upregulated significantly by the exercise in the nucleus but downregulated in mitochondria. Thus, the repair activity was differentially regulated by exercise. The upregulation of OGG1 activity in the nucleus suggests that the reduced oxidative damage to the nuclear DNA is, at least partly, owing to the increased repair. The reason for the downregulation of mitochondrial OGG1 activity, despite the reduction of DNA oxidation, is not clear. It is, however, possible that the activity had been upregulated in early stages of the training, but was reduced later as an adaptation when the oxidative damage was reduced. Consis-

tent with our present observation that the mitochondrial OGG1 activity is downregulated by regular exercise, Ji (1993) has reported that mitochondrial GSH peroxidase is decreased in chronically trained animals, in that both enzymes are protective against oxidative stress. Thus, reduced oxidative damage to DNA appears to be one of the mechanisms for the anticancer and anti-aging effects of a physically active lifestyle. Our major findings are summarized in Table 1.

Conclusion

Our findings and reports of other investigators have suggested that moderate regular exercise attenuates oxidative stress via mild generation of ROS (Goto et al. 2004; Ji et al. 2006; Judge et al. 2005; Radák et al. 2005). Thus, regular exercise can be a form of hormesis (Calabrese 2004; Goto 2004) in that, whereas excessive generation of ROS by exhaustive exercise is obviously harmful to unprepared cells, regular exercise that generates a moderate amount of ROS can induce an adaptive response to cope with stronger stress that may be encountered in the future. To retard age-related physiological decline and reduce morbidity in elderly people, regular exercise may be superior to pharmacological anti-aging medicine by upregulating various antioxidant systems including antioxidant enzymes, repair enzymes, and enzymes for degradation of potentially harmful damaged molecules. It is important to note that exercise-induced adaptive response appears effective even when training is initiated late in life.

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