Anaerobic Exercise and Oxidative Stress: A Review

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Catalogue Data
Bloomer, R.J.; and Goldfarb, A.H. (2004). Anaerobic exercise and oxidative stress: A review. **Can. J. Appl. Physiol.** 29(3): 245-263. © 2004 Canadian Society for Exercise Physiology.

Key words: *antioxidants, free radicals, training, lipid peroxidation, protein carbonyls*
Mots-clés: *antioxydants, radicaux libres, entraînement, peroxydation lipidique, groupement carbonyle peptidique*

Abstract/Résumé

Oxidative stress and subsequent damage to cellular proteins, lipids, and nucleic acids, as well as changes to the glutathione system, are well documented in response to aerobic exercise. However, far less information is available on anaerobic exercise-induced oxidative modifications. Recent evidence indicates that high intensity anaerobic work does result in oxidative modification to the above-mentioned macromolecules in both skeletal muscle and blood. Also, it appears that chronic anaerobic exercise training can induce adaptations that act to attenuate the exercise-induced oxidative stress. These may be specific to increased antioxidant defenses and/or may act to reduce the generation of pro-oxidants during and after exercise. However, a wide variety of exercise protocols and assay procedures have been used to study oxidative stress pertaining to anaerobic work. Therefore, precise conclusions about the exact extent and location of oxidative macromolecule damage, in addition to the adaptations resulting from chronic anaerobic exercise training, are difficult to indicate. This manuscript provides a review of anaerobic exercise and oxidative stress, presenting both the acute effects of a single exercise bout and the potential for adaptations resulting from chronic anaerobic training.

L'exercice aérobie, on le sait bien maintenant, cause un stress par oxydation qui entraîne des dommages intracellulaires aux protéines, aux lipides, et aux acides nucléiques de même qu'au système du glutathion. On connaît cependant beaucoup moins les effets de l'exercice

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anaérobie sur le stress par oxydation. D'après des études récentes, un travail anaérobie intense cause du stress par oxydation aux macromolécules nommées plus haut et localisées dans les cellules musculaires et le sang. Par contre, un entraînement anaérobie chronique peut susciter des adaptations contribuant à atténuer ce stress par oxydation. Ces adaptations se limiteraient à l'accroissement des défenses antioxydantes et/ou à la diminution des substances pro-oxydantes produites au cours et à la suite de l'effort physique. Dans ces études sur le stress par oxydation, cependant, on a eu recours à diverses formes d'exercice anaérobie et à diverses méthodes de dosage. Il est donc difficile de tirer des conclusions définitives concernant le locus et le niveau des dommages aux macromolécules de même que les adaptations suscitées par l'entraînement anaérobie chronique. Ce texte est une synthèse des études sur l'exercice anaérobie et le stress par oxydation traitant des ajustements et des adaptations à ce type d'effort physique.

Introduction

Oxidative stress may be defined as a condition in which the cellular production of pro-oxidants exceeds the physiological capacity of the system to render reactive species inactive. The processing of reactive oxygen and nitrogen species (RONS) is carried out by the body's endogenous antioxidant defense system, in conjunction with exogenous antioxidants consumed through diet. The generation of RONS, such as singlet oxygen (·O), superoxide radical ($O_2^{\cdot -}$), hydroxyl radical (·OH), and peroxynitrite (ONO_2^-) occur as a consequence of normal cellular metabolism and seem to be increased under conditions of both psychological and physical stress (Sen et al., 1994). While regular exercise training is indeed associated with numerous health benefits, it can also be viewed as an intense physical stressor that might lead to increased oxidative cellular damage, likely due to enhanced production of RONS (Knight, 1999; Sen et al., 1994). Such cellular damage is often represented by modifications to various macromolecules, including proteins, lipids, and nucleic acids, and appears to occur as a result of high intensity exercise of moderate to long duration.

Oxidative damage to proteins involves oxidation of amino-acid side chains and fragmentation of polypeptides, as all amino acids are vulnerable to metal-catalyzed oxidation. Protein oxidation is most often represented by the formation of carbonyl derivatives and may lead to loss of catalytic or structural function, making these proteins susceptible to proteolytic degradation (Levine and Stadtman, 2001).

Regarding lipids, such oxidative modifications result in the chain reaction sequence known as lipid peroxidation, involving degradation of polyunsaturated fatty acids and phospholipids. Assessment of lipid peroxidation in vivo has included the study of conjugated dienes as well as lipid hydroperoxides (LOOH), as early propagation and termination phase products, respectively. With regard to the specific lipid peroxidation end products, there has been extensive measurement of thiobarbituric acid reactive substances (TBARS), an indirect marker of lipid peroxidation, in addition to the assessment of a major aldehyde, the 3-carbon chain malondialdehyde (MDA). MDA is generally regarded as a more precise measurement of lipid peroxidation than TBARS. This is because the assay for TBARS measures aldehyde breakdown products. Some of the aldehyde products are MDA,

while some reactants are nonfunctional aldehydes unrelated to lipids. However, there are limitations with the MDA assay as well, since not all lipid peroxidation products generate MDA, and MDA may be produced by reactions other than lipid peroxidation (Jenkins, 2000). An increase in lipid peroxidation may lead to impairments in normal physiological function, i.e., loss of membrane fluidity, increased membrane permeability with loss of cytosolic proteins, and alteration in enzyme function.

Specific to DNA, RONS associated damage may involve both strand breaks as well as single base modifications (to both mitochondrial and nuclear DNA), potentially leading to mutagenesis (Halliwell and Gutteridge, 1989). Additionally, researchers have routinely studied glutathione status as a marker of oxidative stress within biological systems, as this seems to be one of the most reliable indices of exercise-induced oxidant production (Sen, 2001a).

On the surface, the generation of RONS resulting from acute exercise and the subsequent oxidation of cellular macromolecules appears to be somewhat troubling. This is especially true in light of the fact that RONS have been suggested as being involved in the pathology of numerous diseases. However, it should be noted that their presence may simply be a consequence of disease rather than an overt cause (Knight, 1999).

Despite these observations, it has been demonstrated that regular exercise training appears to upregulate antioxidant defense mechanisms, providing additional "protection" during times of intense physical stress (Powers et al., 1999). Such an adaptation functions to attenuate the typical rise in protein, lipid, DNA, and glutathione oxidation following a single bout of exercise, which appears to be true for both aerobic and anaerobic exercise (Radak et al., 2001). The fact that oxidation of these macromolecules seems to be attenuated vs. eliminated by the training adaptation suggests either that such adaptations may not be possible through exercise training alone (Radak et al., 2001) or that elimination would not be physiologically favorable. There is certainly evidence for the latter, since RONS in biological systems regulate a variety of key molecular mechanisms that may be linked with signal transduction, immunity, cell-cell adhesion, cell proliferation, inflammation, metabolism, and apoptosis (Hensley and Floyd, 2002; Sen, 2001b). Because of these observations, it seems important to maintain an appropriate homeostasis between RONS production and removal.

With this brief overview, most of the evidence has implicated aerobic exercise as the major culprit of increased oxidative stress, likely related to the fact that most researchers have exclusively studied this form of physical activity. In fact there are several excellent reviews on the subject of aerobic exercise-induced oxidative stress (Goldfarb, 1993; Konig et al., 2001; Radak et al, 2001). To the contrary, while it is becoming increasingly clear that acute bouts of anaerobic exercise can also lead to an oxidative stress, as evidenced by the production of oxidatively modified macromolecules, we know of no published review on the subject. Such information should be made available, as more and more individuals are becoming involved in regular anaerobic exercise through resistance training. Therefore the purpose of this review is to present an overview of the literature related to anaerobic exercise-induced oxidative stress. It should be noted that with the exception of two studies focusing on DNA oxidation (Radak et al., 1999; Schiffl et

al., 1997) only protein, lipid, and glutathione oxidation have been studied in response to anaerobic exercise. Thus the subsequent text is largely devoid of discussion on nucleic acid oxidation.

Furthermore, the following discussion does not include investigations utilizing a downhill running program, because such protocols, while typically inducing muscle damage and subsequent inflammation which may increase the generation of RONS, are clearly not anaerobic. If individuals or animals are capable of maintaining a particular exercise intensity for 60 to 90 minutes, as is typical in most studies employing downhill protocols, the prescription by definition is aerobic in nature. Such studies have been reviewed elsewhere (Radak et al., 2001).

Anaerobic Exercise-Induced Oxidative Stress

While it is fairly well accepted that RONS production and subsequent modification of proteins, lipids, and DNA can occur in response to aerobic exercise, largely due to a disturbance in electron transport leading to an increased leakage of superoxide radicals, information on the production of RONS as a result of acute anaerobic exercise is lacking. However, in addition to electron leakage, it has been suggested that oxidative stress specific to anaerobic exercise (e.g., isometric, eccentric, resistance, and sprint training) may be mediated through various other pathways (Jackson, 2000): xanthine and NADPH oxidase production, prostanoid metabolism, ischemia/reperfusion, phagocytic respiratory burst activity, disruption of iron-containing proteins, and alteration of calcium homeostasis. The production of RONS via these pathways may result in part from eccentric muscle actions, which commonly produce muscle injury (McHugh et al., 1999). It is likely that the production of RONS during and after anaerobic exercise involves several pathways, which collectively lead to their presence in biological samples analyzed. Figure 1 presents a schematic of the possible RONS-generating pathways related to anaerobic exercise.

ISOMETRIC EXERCISE

The influence of anaerobic exercise on markers of oxidative stress in humans was examined by Sahlin et al. (1992), who studied the effect of isometric knee extensions at 30% maximal voluntary contraction (MVC) on blood and muscle markers of oxidative stress. The exercise was intermittent (10 sec on, 10 sec off) and was performed for 80 minutes or until subjects were too exhausted to continue. Blood samples and biopsies of the quadriceps muscle were taken before exercise and at 20-min intervals throughout the exercise session (at 20, 40, 60, 80 min) and were analyzed for MDA, total glutathione (TGSH), and oxidized glutathione (GSSG). Except for an increase in TGSH in blood (greatest at 80 min), no changes were noted for any other variables in either blood or muscle, suggesting that no oxidative stress occurred during isometric leg exercise. However, since intensity of activity is important for eliciting an increase in RONS and oxidative stress (Leaf et al., 1997; Lovlin et al., 1987), it is possible that the protocol used was of too low of an intensity to produce any real change in the variables measured.

Alessio et al. (2000) reported an increase in LOOH immediately after and one hour after isometric handgrip exercise performed at 50% MVC for 45 sec on,

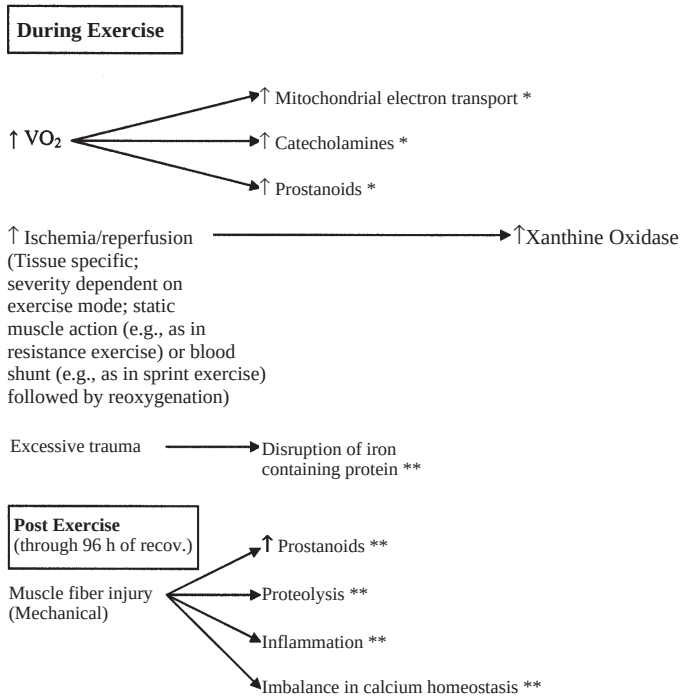

Figure 1. Potential mechanisms of increased RONS production related to an acute bout of anaerobic exercise. *Note*: RONS production and subsequent oxidation mainly following sprint exercise (*) and eccentric biased resistance exercise (**). RONS production pathways may overlap in all anaerobic exercise modes. Xanthine oxidase appears to be a ubiquitous agent in all anaerobic exercise modes.

45 sec off until the contraction phase duration reached roughly 15 min; this time was matched to that of subjects' treadmill run time so that both exercise modes could be compared. Despite the increase in LOOH, however, only a mere 12% increase was observed for protein carbonyls (PC) immediately after exercise, suggesting that isometric handgrip exercise, as done in this study, may increase lipid peroxidation while only slightly affecting protein oxidation.

Two recent investigations also examined the role of isometric handgrip exercise on oxidative stress. Dousset et al. (2002) had their subjects perform at 60% MVC until exhaustion (42 ± 5 sec) and noted an increase in blood TBARS, suggesting an oxidative stress. Steinberg et al. (2002) reported that a 3-min period at an intensity of 100% MVC, using a duty cycle of 1 sec on and 1 sec off, could influence circulating TBARS and GSH. Both TBARS and GSH (reduced glutathione) were assessed before exercise and for up to 30 min postexercise. The results indicated an increase in TBARS, greatest at 5-min postexercise, with a concomitant decrease in GSH, greatest at 20-min postexercise.

Collectively, the results with respect to isometric exercise suggest that oxidative stress can be induced, especially with moderate to high intensity handgrip exercise. It has been proposed that this oxidative stress may be largely related to an acute state of ischemia/reperfusion and the production of xanthine oxidase (Hellsten, 2000). Decreased levels of ATP, perhaps mediated by strenuous exercise involving an acute state of ischemia followed by reperfusion, lead to high intracellular levels of ADP, which promote ADP degradation and the conversion of xanthine dehydrogenase to the superoxide radical-generating enzyme xanthine oxidase. The formation of xanthine oxidase usually occurs in the presence of hypoxanthine, acting as a substrate for both xanthine and xanthine dehydrogenase. In addition, there is an activation of calcium-dependent proteases, which increase when calcium homeostasis is compromised, perhaps as a result of muscle injury. Thus, generation of RONS via the xanthine oxidase pathway likely involves high intensity exercise conditions whereby muscle is metabolically compromised and perhaps damaged (i.e., ATP degradation is greater than ATP generation and calcium homeostasis is compromised).

Elevations in both plasma and tissue levels of xanthine oxidase (Hellsten et al., 1988; 1997; Radak et al., 1996; Vina et al., 2000) and hypoxanthine (Ihara et al., 2001) have been reported in several studies after either isometric or dynamic exhaustive anaerobic exercise. Such elevations in xanthine oxidase have been associated with a rise in lipid peroxidation resulting from anaerobic exercise (Radak et al., 1996). Further evidence for the role of xanthine oxidase in mediating increased RONS was presented by Vina and colleagues (2000), who reported that inhibition of xanthine oxidase with allopurinol prevented exercise-induced oxidation of glutathione in both humans and rats. Taken together, these findings suggest that while there may be multiple pathways for RONS generation owing to acute exercise, xanthine oxidase seems to be a major factor specific to high intensity anaerobic work.

However, given that high concentrations of xanthine oxidase have also been associated with elevations in plasma and tissue lactate levels during and after anaerobic exercise, the oxidation of macromolecules may not be imminent. This is because, as has been reported, lactate ions may possess antioxidant properties (Groussard et al., 2000). Thus, with both a rise in xanthine oxidase and lactate during and after anaerobic exercise, it is possible that lactate ions provide some protection against oxidation of certain structures. In fact, Hellsten and colleagues (1997) reported significant elevations in muscle xanthine oxidase after eccentric exercise without any change in muscle MDA. This finding underscores the complexity of the system in regulating both the production and processing of RONS with acute exercise.

ECCENTRIC EXERCISE

Aside from isometric exercise, eccentric (lengthening) muscle actions have been used to examine oxidative stress. It is likely that the eccentric actions induce muscle damage, which may lead to increased RONS through a variety of biochemical pathways including inflammatory processes and a loss in muscle calcium homeostasis (Jackson, 2000).

Lee and Clarkson (2003) recently noted an increase in plasma TGSH through 120 hours following a bout of 50 maximal eccentric muscle actions with the elbow flexors. However, the increase was observed only in those persons with low plasma TGSH at baseline (<2.5 $\mu M \cdot L^{-1}$), while subjects with values greater than 3.8 $\mu M \cdot L^{-1}$ demonstrated no change. Saxton and colleagues (1994) reported oxidative stress following both eccentric and concentric (shortening) muscle actions. Subjects were asked to perform both eccentric and concentric actions of the elbow flexors as well as the knee extensors; lipid and protein oxidation were measured. Different limbs were used for eccentric and concentric protocols, and the protocols were separated by several weeks.

Blood samples following the arm protocols, and muscle biopsies following the leg protocols, were taken before and for up to 10 and 2 days postexercise, respectively. A nonsignificant change was noted for both TBARS and conjugated dienes following the arm protocols, with no change noted for MDA in muscle. However, concentric activity increased PC in muscle immediately following exercise, with no change noted for eccentric exercise. This raises the question as to whether or not dynamic isotonic (eccentric/concentric) exercise would be a greater stimulus of oxidative stress than either exercise by itself. To date, however, only two studies have assessed lipid peroxidation resulting from isotonic exercise (McBride et al., 1998; Surmen-Gur et al., 1999), yielding mixed results.

Our laboratory recently demonstrated an increase in plasma PC and a slight nonsignificant decline in GSH in the days following a bout of 60 eccentric actions with the elbow flexors; no change was noted for other markers of glutathione status in the blood (Lee et al., 2002). Child et al. (1999) reported no change in MDA either in blood or muscle in subjects after 70 eccentric actions with the knee extensors. Hellsten et al. (1997) noted similar findings for MDA in muscle following repeated eccentric actions with the knee extensors, as did Lenn et al. (2002), who found no change in MDA or TBARS following 50 eccentric actions with the elbow flexors. No change was noted in TGSH or GSSG (Bryer & Goldfarb, 2001) from 70 eccentric actions of the elbow flexors at 1.75 $rad \cdot s^{-1}$ (60° sec) at 100% MVC. In contrast to the above, however, Childs et al. (2001) demonstrated an increase in two markers of lipid peroxidation, LOOH and 8-isoprostane, during the 4 days following 30 eccentric actions with the elbow flexors, suggesting that eccentric exercise can increase lipid peroxidation during the subsequent days of recovery.

Specific to DNA oxidation, only Radak et al. (1999) have studied the impact of eccentric exercise on 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of DNA oxidation. In their study the subjects completed 200 eccentric actions with the knee extensors; 8-OHdG was assessed in the quadriceps muscle via biopsy sample at 24 hours postexercise. A significant increase in 8-OHdG was noted at this time, suggesting that eccentric exercise can cause DNA oxidative damage. Thus there does not seem to be consensus on the effects of eccentric resistance exercise on markers of oxidative stress. It is possible that differences in the biomarkers of study (e.g., DNA, glutathione, lipid), the assay techniques for the specific markers used (e.g., MDA, LOOH), and the degree of muscle activation affecting the level of oxidative stress might explain some of the discrepancies in the literature.

ISOTONIC (ECCENTRIC/CONCENTRIC) RESISTANCE EXERCISE

Only three studies to date have assessed oxidative stress resulting from isotonic resistance exercise (Boyer & Goldfarb, 1996; McBride et al., 1998; Surmen-Gur et al., 1999). An increase in blood MDA was noted in the 2 days following a full-body resistance training protocol (McBride et al., 1998), whereas no change was reported in blood MDA 6 min following the performance of 20 maximal eccentric/concentric actions with the knee extensors (Surmen-Gur et al., 1999). No change was noted for TBARS (Boyer & Goldfarb, 1996) following heavy full-body resistance exercise performed to failure. The differences in the protocols may have contributed to the discrepancy in the results. Clearly, more work is needed to aid our understanding of the potential role of isotonic resistance exercise in generating increased oxidative stress, especially since this form of anaerobic exercise is the one most widely prescribed as a component of a well rounded fitness program.

SPRINT EXERCISE

Several other researchers have used sprint exercise as a form of anaerobic work to study oxidative stress responses. In the first study of its kind, Alessio et al. (1988) examined lipid peroxidation in rat skeletal muscle immediately following a 1-min sprint performed at 45m/min. Both TBARS and LOOH were noted to be higher than values found for control animals at rest, suggesting that a minimal volume of high intensity sprint exercise can increase lipid peroxidation.

In a recent study, Kayatekin et al. (2002) had mice perform 15 sprints at 35m/min for 30 sec each so they could study oxidative stress in both skeletal muscle and liver during the 24-hr postexercise period. While TBARS increased acutely (i.e., at 30 min and 3 hrs postexercise) in skeletal muscle, no change was noted in liver, suggesting a tissue-specific response. Radak et al. (1998) used rats to study the effect of anaerobic running on PC content in the lung. One hour following exercise, PC was noted to be elevated above resting control values, indicating oxidative damage to proteins as a result of anaerobic exercise.

Only a few studies utilizing sprint protocols have been undertaken in humans. Most recently, Groussard and co-workers (2003) showed an increase in lipid radical production during the 40-min postexercise period in male physical education students following a 30-sec cycle sprint (Wingate test). The technique utilized for detecting lipid radical production was electron spin resonance spectroscopy, which is the most specific and direct method for measuring free radical species. While an increase was observed for lipid radical production, no increase was seen in TBARS, which Groussard et al. suggested was due to postexercise clearance from the plasma.

Marzatico et al. (1997) studied sprint athletes following the performance of six sprints (150 meters) and noted elevated plasma MDA at 6 to 48 hrs postexercise, and plasma conjugated dienes at 6 hrs postexercise. Similarly, Thompson et al. (2001) studied trained athletes after a 90-min shuttle run of intermittent walking, jogging, and sprinting, and found increased levels of plasma MDA. Inal and colleagues (2001) noted a decrease in blood GSH following a 100-meter swim sprint, leading them to suggest an increased oxidative stress imposed on the glutathione system. While not using a sprint exercise protocol, Ortenblad and colleagues (1997)

found no change in MDA in either muscle or blood in trained and untrained subjects following a strenuous jumping protocol.

Only Schiffl et al. (1997) have sought to study DNA oxidation resulting from sprint exercise. The subjects in their study performed two exhaustive sprints, and blood samples were taken prior to exercise and at 2 days postexercise. The number of micronuclei in 3,000 binucleated blood lymphocytes was assessed as a marker of DNA damage and was noted to be increased compared to resting levels at both the 24- and 48-hr postexercise time points.

In summary and based on the available evidence, although results are largely mixed (Tables 1, 2, and 3), it appears that anaerobic exercise, whether it involves isometric, eccentric, isotonic, or sprint training, can induce oxidative damage to proteins, lipids, DNA, and glutathione. This appears to be true in several tissues, albeit a tissue-specific response, such as the presence of modified macromolecules, has been noted in blood, skeletal muscle, and lung. From the literature, it should be noted that only two studies assessing macromolecule oxidation in human skeletal muscle have shown an increase in either protein or DNA oxidation, with none demonstrating an increase in lipid oxidation. Studies showing increased oxidative stress in human blood have been specific to lipid oxidation, with only one study reporting increased protein oxidation and one other study reporting increased DNA oxidation. Future investigations should focus on assessment in both tissue and blood if possible, in addition to including various oxidative stress indices, as the oxidative stress response may differ depending on the tissue or fluid of analysis and the macromolecule of study.

It is probable that exercise intensity and duration, the time of postexercise sample collection, the load on the muscle, the alteration of blood flow, and the site of measurement would influence the results. It is also possible that ischemic/reperfusion of the active skeletal muscle during or after the exercise could be involved in this oxidative stress. Because researchers have chosen to use a wide variety of exercise protocols in addition to assay procedures, it is not possible at this time to draw more specific conclusions as to the exact extent and location of oxidative macromolecule damage resulting from anaerobic exercise.

Anaerobic Exercise-Induced Oxidative Stress Adaptations

While anaerobic exercise can increase oxidation of macromolecules, potentially leading to tissue damage, chronic training can induce adaptations that attenuate the exercise-induced oxidative stress. However, just as exercise intensity must be great enough during an acute bout to elicit oxidative stress, the same seems true for generating these training adaptations. The stimulatory effect of physical exercise on RONS generation appears to be an important phenomenon of the exercise-induced adaptation process (Radak et al., 2000). The increased antioxidant enzyme activity in response to training is apparently due to the system's need to generate antioxidants to facilitate protection against RONS. Additionally, the decrease in RONS markers may also be due to repeated and prolonged exposure to high RONS generation, resulting in alterations in the production of these RONS.

Perhaps very light intensity exercise fails to induce adaptations because the generated RONS are adequately eliminated by the antioxidant defense system

Table 1 Human Studies on Effects of Anaerobic Isotonic or Isometric Resistance Exercise on Markers of Oxidative Stress

Reference	Tissue	Subjects	Activity	Marker	Effect
Alessio et al. (2000)	Blood	12 trained M or F	Isometric handgrip exercise at 50% MVC intermittently for ~15 min	PC	–
				MDA	–
				LOOH	↑
				ORAC	–
Boyer & Goldfarb (1996)	Blood	12 untrained M	Full body resist. trng program (8 exerc, 3 sets each to failure)	TBARS	–
Bryer & Goldfarb (2001)	Blood	18 untrained M	70 max eccentric actions with elbow flexors	TGSH	–
				GSSG	–
Child et al. (1999)	Blood	8 untrained M or F	70 max eccentric actions with knee extensors	MDA	–
				TAC	–
	Skeletal muscle			MDA	–
				TAC	↑
Childs et al. (2001)	Blood	14 untrained M	30 eccentric actions at 80% MEF with elbow flexors	SOD	↑
				GPx	–
				LOOH	↑
				8-isoprastane	↑
Dousset et al. (2002)	Blood	8 M	Isometric handgrip exercise at 60% MVC until exhaustion (42±5 sec)	TBARS	↑
				RAA	↓
Hellsten et al. (1997)	Blood	7 untrained M	5 sets of 300-s duration max eccentric actions with knee extensors	TAC	–
	Skeletal muscle			MDA	–
				XO	↑
Lee & Clarkson (2003)	Blood	60 non-resistance-trained M or F	50 max eccentric actions with elbow flexors	TGSH	↑
Lee et al. (2002)	Blood	8 non-resistance-trained M	60 max eccentric actions with elbow flexors	PC	↑
				TGSH	–

				GSH ↓
				GSSG –
				GSSG/TGSH–
Lenn et al. (2002)	Blood	22 non-resistance-trained M or F	50 max eccentric actions with elbow flexors	MDA –
				TBARS –
McBride et al. (1998)	Blood	12 resist-trnd M	Full body resistance training program (8 exercises, 3 sets each to failure)	MDA ↑
Radak et al. (1999)	Skeletal muscle	12 F	200 eccentric actions at 60% MIF with knee exten.	8-OHdG ↑
Sahlin et al. (1992)	Blood	7 M	Isometric knee extension exercises at 30% MVC for 80 min intermittently	MDA –
				TGSH ↑
				GSSG –
	Skeletal muscle			TGSH –
				GSSG –
Saxton et al. (1994)	Blood	14 non-resistance-trained M	70 max eccentric or concentric actions with elbow flexors	TBARS –
				CG –
	Skeletal muscle		80 max eccentric or concentric actions with knee extensors	MDA –
				PC(concentric only) ↑
Steinberg et al. (2002)	Blood	7 M	Isometric handgrips, 100% MVC for 3 min intermittently	TBARS ↑
				GSH ↓
Surmen-Gur et al. (1999)	Blood	9 untrained M	Max test on bike, then 20 max eccent/concent. actions with knee extensors	MDA –
				SOD –
				GPx –

Definitions: MDA, malondialdehyde; PC, protein carbonyls; TGSH, total glutathione; GSH, reduced glutathione; GSSG, oxidized glutathione; CAT, catalase; GPx, glutathione peroxidase; SOD, superoxide dismutase; LOOH, lipid hydroperoxides; ORAC, oxygen radical absorbance capacity; GST, glutathione-S transferase; CG, conjugated dienes; TBARS, thiobarbituric acid reactive substances; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; TAC, total antioxidant capacity; XO, xanthine oxidase; RAA, reduced ascorbic acid; MVC, maximal voluntary contraction; MIF, maximal isometric force; MEF, maximal eccentric force; ↑, increase w/exercise; ↓, decrease w/exercise; –, no change w/ exercise.

Table 2 Human Studies on Effects of Anaerobic Sprint or Jump Exercise on Markers of Oxidative Stress

Reference	Tissue	Subjects	Activity	Marker	Effect
Groussard et al. (2003)	Blood	8 M	30-sec max sprint on cycle (Wingate test)	TBARS GSH SOD GPx Lipid radicals	↓ ↓ ↓ – ↑
Inal et al. (2001)	Blood	9 M or F swimmers	100-meter swim	CAT GPx GSH	↑ ↑ ↓
Marzatico et al. (1997)	Blood	12 M untrained or sprinters	6 × 150-m sprints	MDA CD SOD GPx CAT	↑ ↑ ↑ ↑ –
Ortenblad et al. (1997)	Blood Skeletal muscle	8 jump-trained & 8 untrained M	6 bouts of jumping at 30 sec each	MDA MDA	– –
Schiffl et al. (1997)	Blood	6 M or F, trained or untrained	Two exhaustive sprints	DNA damage via # of micronuclei	↑
Thompson et al. (2001)	Blood	9 trained M	90-min shuttle run (intermittent walk, jog, sprint)	MDA	↑

See note under Table 1.

(Radak et al., 2001). Presumably, the adaptations result from the cumulative effects of repeated exercise bouts of sufficient intensity and duration. Therefore the reduced oxidative stress resulting from chronic training may originate from the enhanced antioxidant defense system. The level of oxidative damage after an acute exercise bout may not be totally eliminated but rather attenuated (Miyazaki et al., 2001; Neiss et al., 1996). As suggested by Radak et al. (2001), this upregulation in protective defenses often parallels the rise in RONS production after exercise. Without an adequate rise in antioxidant protection, the potential for cellular damage resulting from RONS production would be increased.

The following section gives an overview of those studies that have examined enhanced protection against anaerobic exercise-induced oxidative stress as a result of regular anaerobic exercise training. Because they have focused on adap-

Table 3 Animal Studies on Effects of Anaerobic Exercise on Markers of Oxidative Stress

Reference	Tissue	Subjects	Activity	Marker	Effect
Alessio et al. (1988)	Skeletal muscle	8 untrained male rats	1-min sprint at 45m/min	TBARS	↑
				LOOH	↑
Kayatekin et al. (2002)	Skeletal muscle	55 untrained male mice	15 sprints at 35m/min for 30 sec	TBARS	↑
				SOD	–
				GPx	–
	Liver			TBARS	–
				SOD	–
				GPx	–
Nagasawa et al. (2000)	Skeletal muscle	12 untrained male rats	Electrical stimulation at both low and high frequencies	PC	↑ (low only)
				TBARS	–
				SOD	–
				GPx	–
				GST	–
Radak et al. (1988)	Lung	12 untrained male rats	Two 5-min runs at 30m/min, then incremenental run to exhaustion	PC	↑

See note under Table 1.

tations following chronic isotonic (eccentric/concentric) resistance and sprint exercise, only these areas will be discussed. The adaptations may be specific to increased antioxidant defenses (e.g., upregulation of antioxidant enzymes and thiols, generally assessed at rest), suppression of radical generation, and/or reduced markers of oxidative stress during and after exercise. A more detailed review of this topic has been presented elsewhere (Radak et al., 2001).

ISOTONIC (ECCENTRIC / CONCENTRIC) RESISTANCE EXERCISE

Vincent et al. (2002) studied the role of high intensity exercise on glutathione status in addition to total thiols and lipid peroxidation following an acute exercise bout. Older adults, mean age 64 years, participated in a resistance training protocol of 14 exercises; they performed each exercise for one set at either 50% or 80% (low vs. high intensity) of their one-repetition maximum (1-RM) three times a week. A third group of subjects served as untrained controls. Before and after 6 months of training, all subjects underwent a graded exercise test (GXT) on a treadmill to impose an acute stress. Blood samples were taken before and immediately after the GXT both prior to and after the 6-month training period. It was shown

that 6 months of training resulted in an attenuated TBARS and LOOH response to GXT in both training groups, with minimal change observed in thiols at rest or postexercise. However, as Vincent et al. measured serum thiols rather than whole blood thiols, where the majority of thiols are found (Michelet et al., 1995), it is uncertain whether chronic resistance training can effectively increase blood thiol status. Furthermore, they did not measure glutathione status or lipid peroxidation after the final bout of resistance training. Thus it is unclear whether the anaerobic training could have attenuated lipid peroxidation following an anaerobic work bout. It is possible that the adaptations are specific to the mode of exercise creating the stress and do not have as great a carryover to other forms of exercise. Unfortunately, this was not determined in their study.

Rall and co-workers (2000) also examined resistance-training adaptations on oxidative stress. Both younger (22–30 yrs) and older (65–80 yrs) adults, in addition to persons with rheumatoid arthritis (25–65 yrs), participated in a 12-week resistance training program consisting of three sets at 80% 1-RM for all major muscle groups. Measurement of 8-OHdG was assessed at baseline and at some point beyond 24 hours after the last exercise session to determine whether chronic training could attenuate resting levels of DNA oxidation. While baseline 8-OHdG was greater in those with rheumatoid arthritis, only a slight nonsignificant change from baseline values was observed for older healthy adults or those with rheumatoid arthritis as a result of the training program. For reasons unclear, however, younger healthy adults were only assessed at baseline. Therefore it is uncertain whether training as outlined in their study had an effect on basal 8-OHdG in this population.

SPRINT EXERCISE

Hellsten et al. (1996) examined the effects of 7 weeks of sprint cycle training on the activity of the antioxidant enzymes glutathione peroxidase (GPx), glutathione reductase (GR), and superoxide dismutase (SOD) in human muscle. During the first 6 weeks the subjects trained three times per week, while Week 7 included a twice-a-day, 7-days-a-week protocol. Results revealed no significant increase in enzyme activity in the vastus lateralis following the first 6 weeks; however, an increase was noted for GPx and GR at 24 hrs following Week 7, which returned to baseline by 72 hrs posttraining. These results suggest that exercise volume, in addition to intensity, is important for promoting an adaptation in antioxidant enzyme activity. Further, the increase in activity of these antioxidant enzymes was transient and likely due to the increased oxidative stress imposed on the system during periods of higher volume work in the 7th week. Unfortunately, it is impossible to conclude whether the alterations were solely related to the increased volume of work during Week 7.

Ortenblad et al. (1997) compared jump-trained (elite volleyball players) and untrained subjects at rest and following a jumping protocol in regard to muscle and blood antioxidant status and MDA levels. Resting activities of SOD, GPx, and GR from skeletal muscle were higher for trained vs. untrained subjects. In contrast, no differences were noted in these blood markers between groups. Further, despite the different antioxidant enzyme activities in muscle, neither muscle nor

blood levels of MDA differed between groups following the exercise test. Therefore, while jump training may increase antioxidant enzyme activity in muscle, the increase does not appear to be associated with any attenuation of MDA following an acute exercise stress. However, since MDA did not increase above resting levels in either group, it is debatable as to whether the test protocol itself was strenuous enough to elicit increased lipid peroxidation. A more demanding protocol may be needed to determine whether or not trained subjects are better protected against lipid peroxidation resulting from strenuous anaerobic exercise.

Atalay et al. (1996) studied the effect of sprint training on TGSH, glutathione enzymes, and SOD in heart and skeletal muscle. Following 6 weeks of high intensity sprint training (interval running for 30 sec at 65–95meters/minute) in rats, there was an increase of TGSH in muscle (mainly fast and mixed fiber muscles), and an increase of GPx, glutathione-S transferase (GST), and GR in skeletal muscle and heart. Despite these changes, training did not alter SOD activity in any tissue examined. These findings suggest that high intensity sprint training increased antioxidant defenses in a tissue-specific manner by increasing TGSH in skeletal muscle and upregulating components of the glutathione system in muscle and heart. However, these animals trained at speeds up to 95m/min at an 8% incline, an intensity suggested to approximate 200% of a laboratory rat's $\dot{V}O_2max$. Whether similar results could be obtained in humans is presently unknown.

In summary, it appears that chronic anaerobic exercise training stimulates increased antioxidant production as well as potentially suppressing exercise-induced oxidative stress. This assumes that the anaerobic exercise is of sufficient intensity and duration to elicit an increase in RONS, as this seems to trigger an adaptive protection. However, whether attenuated oxidation following an exercise stressor is due to upregulation of antioxidant defenses, suppression in radical generation, or decreased production of oxidants via other pathways both during and after exercise is presently unknown. Regarding the upregulation in specific antioxidant enzymes, the precise role of each of these in providing cellular protection to macromolecules is presently unknown. Whether observed changes in tissue or blood would provide cross-protection in other areas is also unknown. Clearly, more work is needed to ascertain the extent of protection via antioxidant defenses in individuals undergoing chronic moderate to high intensity anaerobic training.

Conclusion

From the available evidence it appears that high intensity anaerobic exercise can lead to acute oxidative stress. The degree of oxidative stress appears to be attenuated by chronic anaerobic training due to an increase in endogenous antioxidant production, a decrease in RONS generation, or a combination of both processes. More research is needed to confirm the few studies that have been published. More work is also needed to confirm that anaerobic exercise training can modify specific macromolecules related to oxidative stress, as only a few studies have been published to date.

It should be noted that when assessing biological systems, any given assay procedure is merely capturing a snapshot of what is occurring at that particular time. It is quite possible that when taking a single sample following a bout of

exercise, the generation of RONS and associated alterations to macromolecules could be missed, either by taking the sample too late or by not waiting long enough for secondary generation of RONS to occur and interact with these macromolecules. This is particularly true considering anaerobic exercise in which oxidative stress values may be altered as a function of the delayed injury due to inflammation and intramuscular calcium imbalance, which may manifest their changes only several hours or days after the exercise. Therefore, future investigations should take repeated samples following a bout of exercise, possibly up to 48 hrs into recovery. Such a time-course analysis should allow for better representation of the oxidative status of the system.

Further, as clearly expressed by several researchers, no one assay can accurately represent the entire process of oxidation within cells (Jenkins, 2000; Witt et al., 1992). As such, it is best to include assays specific to oxidation of several macromolecules (e.g., protein, lipids, DNA) rather than simply lipids, which has in the past been commonplace in the literature on exercise. Furthermore, as the various markers of lipid peroxidation may represent different phases of the chain reaction sequence, the inclusion of two or more of these markers (e.g., MDA and LOOH) should be considered. In this way we can obtain a better understanding in regard to overall cellular damage, and the response of these macromolecules to acute anaerobic exercise and anaerobic training. More studies are also needed to ascertain whether these potential alterations with anaerobic training are transferable to other exercises which induce an increase in RONS. Finally, the endogenous antioxidant status of subjects, as well as the potential influence of dietary antioxidants, is often not presented in the literature. Thus the protective effect of these antioxidant defenses could have influenced some of the results in these studies, and this possibility needs to be considered in future work.

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Received March 7, 2003; accepted in final form November 26, 2003.