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Full Length Research Paper

Effect of alpha-lipoic acid and time- of-day on interleukin-6 response to exhaustive exercise in humans

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Circadian rhythms have an influence on human performance. Interleukin-6 is a cytokine which plays a role in muscle energy homeostasis during physical exercise. This study tested the effect of diurnal variation and alpha-lipoic acid, a natural thiol antioxidant, on skeletal muscle contractile properties, interleukin-6 response and oxidative damage. Male subjects (n=26) performed isokinetic exercise in different time-of-day. Next, the subjects were supplemented with alpha-lipoic acid for two weeks and the exercise tests were repeated. Blood samples were analyzed at baseline and immediately after exercise. Leg extensor muscle parameters were compared with time-of-day. Maximal work per single repetition and total work values were higher in the afternoon time, suggesting a time-of-day effect. Serum interleukin-6 levels increased in response to exercise, but were not associated with time-of-day. Alpha-lipoic acid did not have a significant effect on any of the measured parameters. Diurnal variations during exhaustive eccentric exercise seem to reflect muscle contractile work capacity. Exercise increases serum interleukin-6 levels irrespective of diurnal variation.

Key words: Diurnal variation, lipoic acid, interleukin-6, muscle performance.

INTRODUCTION

Muscle performance and contractile capacity is affected by the time-of-day (TOD) and type of muscle contraction, and is dependent on the muscle groups tested (Gauthier et al., 1996; Shephard, 1984). TOD has been shown to influence both aerobic performance (Atkinson and Reilly, 1996; Atkinson et al., 2005), and anaerobic power and capacity (Melhim, 1993; Souissi et al., 2002). Moreover, both concentric and eccentric strength parameters were measured at different TOD peak at early evening (Souissi et al., 2002: Wyse et al., 1994). Only few studies have investigated TOD effects in muscle contractile properties during acute exhaustive short-term isokinetic eccentric exercise (Atkinson and Reilly, 1996; Atkinson et al., 2005), but without conclusive results.

Eccentric type of exercise has been used as a specific training model in sports for muscle strength improvement during training sessions or after a skeletal muscle injury. Moreover, eccentric contractions are involved in all activities where the contracting muscles exert braking to control motion of the body in daily activities. The highest increase in peak torque has been shown to occur in the eccentric training (+18%) as compared to the respective concentric exercise (+2%) (Seger et al., 1998). On the other hand, eccentric training induces greater post-exercise muscle damage and may have negative impact on training performance (Allen, 2001). Furthermore, due to the observed variations in the muscle performance during a solar day (Souissi et al., 2002), the vulnerability of skeletal muscle tissue to exercise-induced muscle damage may differ by TOD.

Interleukin- 6 (IL- 6) is considered as a marker of inflammation and an immunomodulatory cytokine produced mainly by the cells of the immune system. However, IL-6 is also secreted by the skeletal muscle and plasma levels of IL-6 may rise up to 100-fold after strenuous physical exercise (Pedersen et al., 2001). IL-6 may also improve skeletal muscle energy supply and assist in the maintenance of stable blood glucose levels by stimulating lipolysis in the adipose tissue and augmenting hepatic glycogenolysis (Pedersen and Febbraio, 2007; Pedersen et al., 2003) . With respect to skeletal muscle metabolism in different types of muscle contractions, the energy cost is likely to be different (Kirwan et al., 1992), and this may also exert variable effects on IL-6 response. A previous study has also presented evidence for diurnal changes to IL-6 concentrations in healthy subjects and patients with depression (Alesci et al., 2005).

Alpha-lipoic acid is a potent thiol antioxidant that acts as a cofactor in the pyruvate dehydrogenase complex and has shown to be beneficial in conditions associated with increased oxidative stress (Ziegler et al., 1999). Moreover, alpha-lipoic acid has been demonstrated to enhance muscle phosphocreatine levels and muscle total creatine concentrations (Burke et al., 2003), suggesting a potential enhancing effect on short-term exercise. However, the effects of alpha-lipoic acid on isokinetic exercise performance are unknown.

Reliable parameters are needed for monitoring optimal intensity of eccentric training in order to minimize exercise-induced muscle damage and improve training outcomes. The present study sought further evidence on TOD, muscle fatigue and energy balance relationships during the acute exhaustive eccentric exercise and more specifically, to test the effect of alpha-lipoic acid in response to acute exercise, and whether IL-6 response could be implemented as a performance parameter on muscle contractile properties during acute exhaustive eccentric exercise.

MATERIALS AND METHODS

Study subjects

The subjects were healthy male volunteers (n=26, age 23.3±4.1 years, BMI 23.3±3.4 kg/m^2), and who were informed on the purpose of the study and gave written consent. The research plan was approved by the Ethics Committee of the University of Suleyman Demirel Turkey. The subjects were without a history of knee injury and not involved in a regular weight-training program, and instructed not to consume any caffeine-containing drinks or nutritional supplements during the study. Before the exercise tests, a morning-eveningness questionnaire (Horne and Ostberg, 1976; Punduk et al., 2005) was applied to all subjects who were subsequently divided into two groups based on their circadian type: the “moderately morning type” (n=12) and “intermediate type” (n=14) group.

Alpha-lipoic acid supplementation

The subjects consumed 1200 mg of alpha-lipoic acid (Solgar, Leonia, NJ, USA) per day divided in two 600 mg doses in capsule form for two weeks after completion of the first round of exercise tests involving no supplementation. The subjects were instructed to divide the daily dosage in half so that 600 mg was taken with meals in the morning and another 600 mg of alpha-lipoic acid in the evening time. All subjects tolerated well the alpha-lipoic acid and reported no adverse effects.

Exercise protocol

One week before the exercise tests, the subjects visited the laboratory and were instructed to the exercise tests. They also performed one exercise session to familiarize with the protocol and the measurement apparatuses. The subjects were instructed to consume a light meal about two hours before the exercise tests to avoid sudden alterations in blood glucose and subjective energy levels.

Following a 20 min rest, blood samples (8 ml) were drawn from the antecubital vein in Vacutainer tubes. Next, the subjects performed a light warm-up for 5 min at 60W pedalling, followed by brief stretching. After the warm-up, the subjects were seated on a computer controlled isokinetic dynamometer (CYBEX CSMi, Stoughton, MA, USA) which had been calibrated prior to every test. The subjects were positioned sitting with the backrest at 90° and were instructed to grip the sides of the seat during the test. Thigh, pelvis and trunk of the subjects were stabilized with straps. An adjustable lever arm was attached to the leg by padded cuff just proximal to the lateral malleolus. The axis of rotation of the dynamometer arm was positioned just lateral to the lateral femoral epicondyle. Gravity correction to torque at 45° (0° = straight leg) were calculated by the computer software. In this position, after three maximal familiarisation repetitions with 120°/s angular velocities, the subjects performed one hundred eccentric maximal voluntary contractions (MVC) for extensor muscles of the dominant knee at the same angular velocities (120°/s). The range of motion was standardized from 10 to 90° during the test. The subjects were verbally encouraged to produce maximal efforts. After the exercise, the subjects remained seated while the post-exercise blood samples were collected. Haemoglobin levels were determined in all samplings to control for alterations in plasma volume.

The subjects performed the exercise test twice without alpha-lipoic acid supplementation, either in the morning time or in the evening time, depending on their randomisation, and then again after two weeks with alpha-lipoic acid supplementation. For the second test, the time of the exercise test was changed accordingly. The morning test started at 8:00 a.m. while the evening test started at 4:30 p.m. The two test sessions were separated by a 7 to 10 day period which allowed the subjects to fully recover from the previous exercise test. Throughout the study, the subjects did not consume any medications or alcohol, and were requested to avoid strenuous physical activity at least 24 h before each test session.

Biochemical analyses

Serum was separated from whole blood and stored frozen at -80°C until assayed. IL- 6 concentrations in serum were analyzed by commercial high sensitivity ELISA kit according to the manufacturer’s instructions (QUANTIKINE HS, R and D Systems, Minneapolis, MN, USA), and the Data are expressed as pg/ml. Assay specifications were as follows: sensitivity limit 0.16 pg/ml, and maximum intra- and interassay CV% was 5.9 and 9.8%, respectively.

Oxygen radical absorbing capacity (ORAC) was assayed according to the previously published method (Prior et al., 2003). Fluorescein was used as a target of free radical attack with 2,2’-azobis(2-amidinopropane) dihydrochloride as a peroxyl radical generator. TROLOX (Sigma-Aldrich, Milwaukee, WI, USA) was used as a standard. The results were calculated using the differences of areas under the fluorescence decay curves between the blank and the sample, and quantified according to standards. Data were expressed as mol.

For protein carbonyl measurements, the samples were first derivatized with 2,4- dinitrophenyl hydrazine to form a Schiff base for production of the corresponding hydrazone, which was recorded spectrophotometrically at an absorbance between 360 to 385 nm according to a previous method and standardized to total protein concentration (Reznick and Packer, 1994). Data were expressed as nmol/mg of protein.

Statistical analysis

Statistical significance was determined by using paired t- test and Pearson's product-moment correlation coefficient, and set at $p<0.05$. Data are presented as means ± standard deviation (SD) unless stated otherwise.

RESULTS

Muscular performance

The subjects showed TOD variations on muscular performance with higher contractile force of the extensor muscles in the evening time as compared to the morning time, and the single repetition work values were significantly higher in the evening time (p=0.021; Figure 1A). Similarly, total work performed during 100 MVC was significantly higher in the evening time as compared to the morning time (p=0.003, Figure 1B).

Supplementation with alpha-lipoic acid had no significant effect on these physical performance parameters (Figures 1A and 1B).

Serum interleukin-6 levels

Serum IL-6 levels were significantly increased in response to acute isokinetic exercise at the end of the exercise session when compared to baseline values (p=0.018, Figure 2). However, no TOD effect on IL-6 levels was observed, as the difference between the morning time and evening time (baseline) values were non-significant (mean morning time value 1.79 ng/ml vs. mean evening time value 1.78 ng/ml; p=0.95).

No significant correlations were found between serum IL-6 levels and muscle work performance (data not shown). In addition, IL-6 levels were unaffected by the alpha-lipoic acid supplementation (Figure 2).

Markers of oxidative damage

Blood antioxidant capacity (ORAC) and protein carbonyl formation were not significantly affected in response to bouts of isokinetic exercise or with alpha-lipoic acid supplementation (Table1).

DISCUSSION

The present study reports diurnal variation of leg extensor muscle contractile work capacity during eccentric type of exercise. Previously, a TOD effect on isokinetic performance variables (peak torque, average power, maximal work) have been noted at different angular velocities with peak values in the early evening time (Gauthier et al., 2001; Souissi et al., 2002, Wyse et al., 1994). Moreover, Wyse et al. (1994) and Gauthier and coworkers (1996) showed TOD variation in muscle strength during concentric contractions with the amplitude ranging from 5 to 12% depending on the exercising muscle and/or angular velocity used. However, the effects of TOD variations on muscle contractile capacity during eccentric contraction have remained largely unknown. Evidently, the present results demonstrated diurnal variation on performed work values during eccentric contractions, whereas the peak torque values were not significantly affected by TOD.

Among the frequently presented factors to explain diurnal variation effects on muscular peak torque, some authors have suggested causality between muscle temperature and peak torque fluctuation with nearly 5% reduction in peak torque when muscle temperature was dropped by 1°C (Atkinson et al., 1993; Bernard, 1988). In addition, Febbraio et al. (1996) showed that an increase of 1.9°C in muscle temperature improved glycogenolysis, glycolysis and high energy phosphate degradation by the muscle during exercise. The authors also hypothesized that an elevated muscle temperature increased the ATP turnover rate associated with exercise, and/or changes in the aerobic/anaerobic contribution to ATP resynthesis (Febbraio et al., 1996). Moreover, rectal and muscle temperature have shown lowest values in morning hours, and to progressively increase towards afternoon and evening hours (Deschenes et al., 1998; Reilly and Brooks, 1990). Hence in these studies, the lower early morning muscle peak torque values could be partly explained by muscle temperature at this TOD. Accordingly, in the present study, the higher eccentric contraction work values observed in the evening time may reflect the diurnal variations to muscle temperature. Nevertheless, core or intramuscular temperatures were no registered during the present study.

This study also explored whether diurnal variation may influence serum IL-6 levels after acute exhaustive isokinetic eccentric exercise. To avoid any interference by fasting, the subjects were studied in a post-absorptive state. IL-6 has been suggested to be produced as a result of muscle contractions and that the release of IL-6 is dependent on the intensity of the muscle activity and the number of muscle fibers involved in the contraction, specifically the concentric and the eccentric contraction (Pedersen et al., 2001). The present data provide evidence that IL-6 levels are increased also after a short

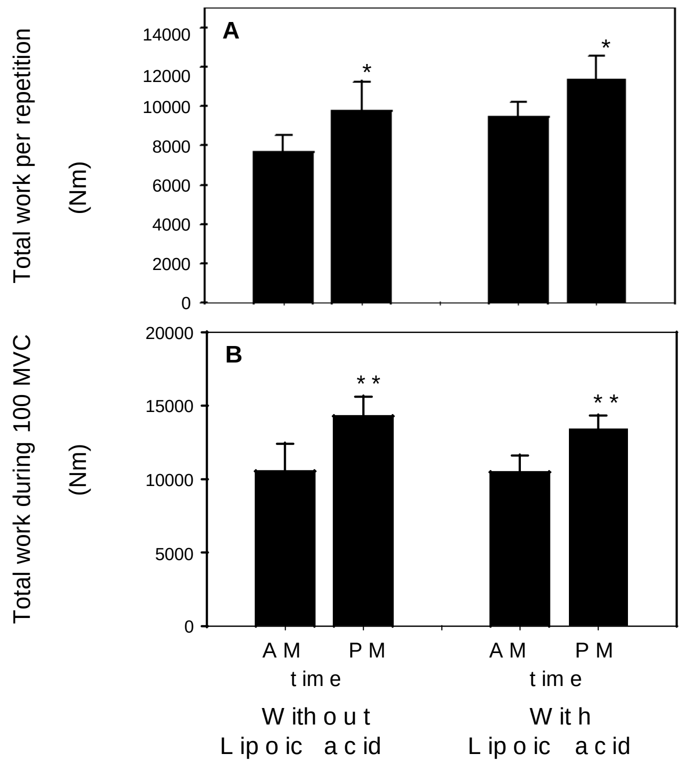

Figure 1 Time-of-day effects on muscle eccentric work capacity. A: maximal work performed per single repetition, and B: during 100 maximal voluntary contractions (MVC) in the morning (AM) and evening (PM) time without or with alpha-lipoic acid supplementation. Data are mean ± SD (n=26). Paired t-test: *p< 0.05; **p< 0.01.

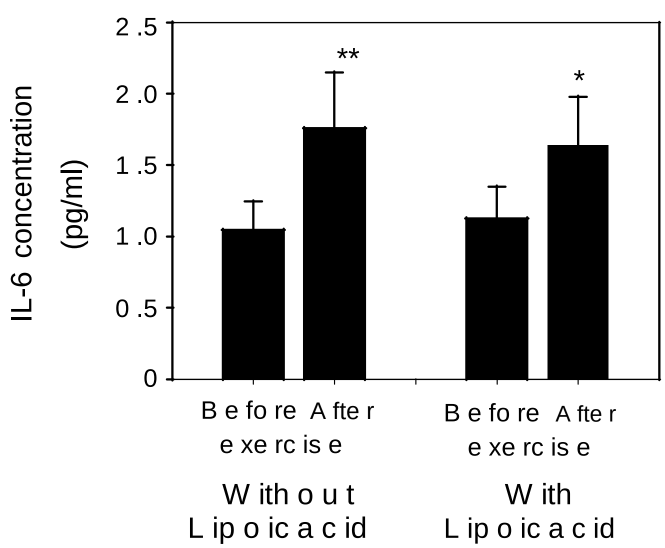

Figure 2 Interleukin-6 response to acute eccentric exercise. Serum IL-6 levels before and immediately after exhaustive isokinetic eccentric exercise without or with two week alpha-lipoic acid supplementation. Data are mean ± SD (n=26). Paired t-test: *p< 0.05; **p< 0.01.

Table 1. Effect of isokinetic eccentric exercise without or with alpha-lipoic acid supplementation on markers of antioxidant capacity (ORAC) and protein oxidation (protein carbonyls) in serum. Data are mean ± SD (n=26).

	Without Lipoic acid		With Lipoic acid	
	Before exercise	After exercise	Before exercise	After exercise
ORAC (mol)	44.09 ± 2.95	46.57 ± 2.14	40.62 ± 2.26	41.89 ± 1.56
Protein carbonyls (nmol/mg of protein)	4.73 ± 0.69	5.52 ± 0.81	4.82 ± 0.72	4.93 ± 0.84

bout of isokinetic eccentric exercise. Elevated IL-6 has been shown to selectively stimulate lipolysis in the skeletal muscle, whereas the adipose tissue remains unaffected (Wolsk et al., 2010). Considering skeletal muscle metabolism in different types of exercise, notably concentric and eccentric, the energy cost is likely different (Kirwan et al., 1992). Moreover, the eccentric type of exercise shows association with increased insulin resistance and impaired post-exercise muscle glycogen resynthesis (Allen, 2001; Costill et al., 1990, Doyle et al., 1993; Widrick et al., 1992) and transiently decreases skeletal muscle glucose transport (Asp et al., 1996; 1995) . The concentric type of exercise, on the other hand, has been shown to improve skeletal muscle insulin sensitivity (Richter et al., 1989). It is tempting to speculate whether IL-6 acts as a key regulator of insulin sensitivity in the skeletal muscle, similar to the adipokine leptin (Dyck et al., 2006). IL-6 has also been linked to activation of the AMP-activated protein kinase (AMPK), which stimulates fatty acid oxidation and increases glucose uptake in the skeletal muscle (Kahn et al., 2005), and enhances mitochondrial biogenesis through the transcriptional coactivator PCG-1alpha, which may be involved in the increased mitochondrial content by physical exercise.

Alpha-lipoic acid has been shown to enhance thiol antioxidant defences and decrease exercise-induced oxidative stress in the skeletal muscle (Kinnunen et al., 2009b). Moreover, alpha-lipoic acid has also been used to treat diabetic complications (Ziegler et al., 1999). Interestingly, alpha-lipoic acid may also decrease post-exercise lactic acid accumulation (Kinnunen et al., 2009a), indicating a potential benefit for delayed fatigue in short-term anaerobic exercise. However, contrary to set hypothesis, the present results suggest that no beneficial effects can be gained from supplementation with alpha-lipoic acid for exercise performance and exercise-induced IL-6 response. In the present study, alpha-lipoic acid was used at a dose of 1200 mg per day for two weeks before the exercise tests and blood biochemical analysis. As humans also synthesize alpha-lipoic acid, it is not a required micronutrient, such as vitamin C. Moreover, the relationships between supplemental and therapeutic doses of alpha- lipoic acid have not been clearly defined. Nevertheless, because alpha-lipoic acid supplementation was neither associated with improved exercise performance nor had any effect on serum IL-6 response or blood antioxidant capacity, it can be concluded that lipoic acid is ineffective for improving short-term exhaustive exercise performance. Furthermore, a recent study suggests that vitamin E and alpha-lipoic acid supplementation may in fact suppress skeletal muscle mitochondrial biogenesis, regardless of training status (Strobel et al., 2010).

The present results must be interpreted with awareness of the fact that the number of subjects was modest; however, a very homogenous population was analyzed. In addition, same subjects were analyzed with and without alpha-lipoic acid supplementation to take into consideration any diet- or lifestyle-associated, or other yet unidentified but potentially confounding factors.

Conclusion

The present results provide evidence that serum IL-6 response is altered by isokinetic eccentric exercise. Knowledge on IL-6-dependent actions in the circulatory system and for human exercise performance is still far from complete because they are merely associations without established causative link. More research is needed to determine the impact of exercise on skeletal muscle IL-6 secretion depending on the TOD.

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