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Research article

IGF-I and FGF-2 responses to Wingate anaerobic test in older men

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Abstract
Reduced activity of the potent anabolic effectors: insulin-like growth factor-I (IGF-I) and fibroblast growth factor-2 (FGF-2), play a role in aging associated muscle loss. The effect of fitness level on IGF-I and FGF-2 responses to all-out anaerobic exercise in older men was studied. Twenty four healthy older males: 12 higher fit (58 ± 1y) and 12 lower fit (59 ± 1y) underwent the Wingate anaerobic test. Serum levels of IGF-I and FGF-2 were measured before, immediately after exercise, and 50 min into recovery. Immediately post exercise, the average peak power output and serum lactate were higher ($p < 0.05$) in the higher fit (446.0 ± 14.9 kgm·min^{-1} for mean (±SD) peak power and 12.6 ± 1.1 mml·l^{-1} for lactate) compared with the lower fit individuals (284.0 ± 6.5 kgm·min^{-1} and 8.5 ± 0.7 mml·l^{-1}, respectively). Pre-exercise IGF-I was lower and FGF-2 was higher in the higher fit (335.0 ± 54.0 ng·ml^{-1} and 1.6 ± 0.1 ng·ml^{-1}, respectively) compared with lower fit individuals (402.0 ± 50.0 ng·ml^{-1} and 1.4 ± 0.2 ng·ml^{-1}, respectively). Following the anaerobic exercise, in both groups, FGF-2 decreased dramatically ($p < 0.05$); in the higher fit individuals FGF-2 level was 0.4 ± 0.1 pg·ml^{-1} compared to 0.1 ± 0.02 pg·ml^{-1} in the lower fit individuals. In contrast to FGF-2, IGF-I increased transiently to levels of 405.0 ± 62.0 ng·ml^{-1} in the higher fit individuals and to levels of 436 ± 57.0 ng·ml^{-1} in the lower fit individuals. However, the IGF-I elevation was significant ($p < 0.05$) only in the higher fit individuals. In conclusion, the present study demonstrates that during aging, fitness level can alter circulating levels of IGF-I and FGF-2. Furthermore, fitness level can affect the response of both mediators to all-out anaerobic exercise.

Key words: Anaerobic exercise, aging, growth factors; hypertrophy, angiogenesis.

Introduction

It is well established that exercise is a significant determinant of muscle mass and function. The growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis and fibroblast growth factor-2 (FGF-2) are important physiological regulators of fetal and post-natal growth and development (LeRoith, 1991). In healthy individuals the anabolic GH/IGF-I axis maintains muscle mass by suppressing protein degradation, increasing amino acid uptake and stimulating protein synthesis (Rommel et al., 2001). The bioavailability of IGF-I is dependent upon circulating IGF-I and insulin-like growth factor binding protein (IGFBPs) levels. Like IGF-I, FGF-2 is ubiquitously distributed. FGF-2 is one of the most potent mitogens for myoblasts and plays a critical role in myogenesis and capillary angiogenesis during muscle development (Olwin et al., 1994). Furthermore, stress-induced muscle remodeling and repair following extensive pathological injuries are believed to be activated by FGF-2.

Physical exercise has a significant impact on the GH/IGF-I axis. However, data from studies evaluating IGF-I response to exercise are controversial. While some studies have demonstrated no change in circulating IGF-I levels, in many others, exercise induced a transient increase in IGF-I levels resulting from acute release of IGF-I from its binding proteins (BPs) (Kraemer and Ratamess, 2005). Furthermore, IGF-I response depends on exercise type, intensity, and duration as well as training status (Rosendal et al., 2002). Growing evidence suggest that like IGF-I, FGF-2 plays an important role in exercise-induced muscle hypertrophy and angiogenesis. Importantly, recent work suggests the possible synergism of local FGF-2 and circulating IGF-I in regulation of the anabolic adaptation of muscles to exercise (Wilkie et al., 1995).

Physiological age related muscle loss and weakness is referred to as 'sarcopenia'. The etiology is multifactorial and not fully understood. However, during aging there is evidence of declining activity of the GH/IGF-I axis, which is mainly dependent on age-related variations in the hypothalamic control of somatotroph function (somatopause). It has been reported that in older individuals, there is reduced GH production and attenuated IGF-I response to high resistance exercise (Hameed et al., 2003). Furthermore, previous studies have demonstrated a delayed response to FGF-2 with aging satellite cells (Jhonson and Allen, 1995), most probably due to delayed expression of FGF-2 receptors and delayed binding of FGF-2 to the receptors (Brickman et al., 1995).

Anaerobic power is characterized by exposing subjects to a very high degree of sudden strenuous all-out exercise. Little data are available on changes in the levels of IGF-I and FGF-2 following sudden strenuous anaerobic exercise in healthy older subjects. Furthermore, the effect of fitness level on these responses has not been studied yet. We hypothesized that higher fit older men would manifest greater alterations in serum IGF-I and FGF-2 levels following the Wingate anaerobic test, than the lower fit men. Therefore, the purpose of this study was to assess IGF-I and FGF-2 responses to sudden strenuous anaerobic exercise in healthy higher fit and lower fit older men.

Methods

Subjects

Twenty four healthy older males volunteered for this study. Exclusion criteria included: patients with coronary

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artery disease, hypertension, and diabetes and or patients under β-blockers treatment. All subjects had been aerobically active for at least 18 months in a supervised aerobic program (4 times·wk^{-1}). The training is a self-reported program which included running/walking at a pace corresponding to 65% of maximal oxygen consumption ($V0_2$ peak) and controlled by the corresponding heart rate. They were divided evenly into two groups: 12 lower fit (58 ± 1 yrs) men and 12 higher fit (59 ± 1 yrs) men based on their values of $V0_2$ peak. A written informed consent was obtained from each subject, which was approved by the Clinical Science Center Committee on Human Subjects which complies with the Declaration of Helsinki.

Procedure and measurements

Subjects reported to the laboratory 3 times. The first session was devoted to accustoming the subjects to the study procedures. Body fat was assessed as suggested by Behnke and Wilmore (1974) and included total body mass; skinfold fat measurement of the chest axilla, triceps, subscapula, abdomen, suprailium, and front thigh; and circumferences at the shoulder. Total body mass was measured to the nearest 50g and skinfold fat to the nearest 0.5mm. Skinfold fat was measured with a Lange caliper. During the 2nd session subjects were judged free from coronary artery disease by clinical history, absence of major risk factors and by a normal exercise test up to $V0_2$ peak.

During the 3rd session, following warm-up, subjects performed the 30 second all-out Wingate Anaerobic Test (Rubin et al., 2005), utilizing a weight-adjusted Monark cycle-ergometer (Model 864). The subjects were seated on the ergometer with their feet fastened to the pedals by means of racing-type toe-clips, and seat height was adjusted. The anaerobic test consisted of 30 seconds supramaximal pedaling against a resistance determined relative to the subject's body mass at 40 g x kg^{-1} body weight. Subjects commenced pedaling as fast as they could against the inertial ergometer resistance only. The full, predetermined resistance load was applied within 3-4 seconds once inertial resistance had been overcome. Pedal revolution count started at that instant by means of an electro-mechanical counter and subjects maintained an all-out effort throughout the test. Strong verbal encouragement was given to ensure maximal effort. The tests were performed at the same time of the day in order to avoid diurnal variations.

Lactate measurements

Blood samples from an antecubital vein were obtained at rest, at end exercise, and 50 minutes post exercise, for determination of lactate. The sample was immediately transferred to a micro-tube containing 100-µl of 7% perchloric acid. The tubes were centrifuged after standing for at least 1 hour. Twenty microliter aliquots of the supernatant were subsequently used for lactate analysis on the Analox LM3 analyzer (Analox Instruments, England; Reagent Kit No. GMRD-071). Interassay CV was 4.5%, and intra-assay CV was 3.2%.

FGF-2 measurement

Blood samples were obtained from an antecubital vein and plasma was immediately separated by centrifugation and stored for later analysis. Serum FGF-2 concentrations from blood samples were measured at rest, at the end of exercise, and at 50 minutes into recovery. FGF-2 serum concentrations were determined by ELISA with the use of the R&D System Quantikine High Sensitivity kit (R&D System; Minneapolis, MN). Interassay CV was 5.2-10.6%, and intra-assay CV was 4.9-9.9%. Assay sensitivity was 0.27 pg·ml^{-1}. Undetectable levels of FGF-2 were arbitrarily assigned the value 0; however, the statistical analysis reported below was qualitatively the same when we used 0.27 pg·ml^{-1} for those FGF-2 measurements found to be below assay sensitivity.

IGF-I measurement

Blood samples were obtained from an antecubital vein and plasma was immediately separated by centrifugation and stored for later analysis. IGF-I was extracted from IGFBPs using the acid-ethanol extraction method (Daughaday et al., 1987). IGF-I concentrations were determined by a two site Immuno-radiometric Assay (IRMA) using the DSL-5600 Active kit (Diagnostic System Laboratories USA). Briefly, IGF-I was separated from binding proteins by acidic/ethanol precipitation. The RIA used rhIGF-I as standard. Labeled ^{125}IGF-I was used together with polyclonal rabbit antibody to IGF-I (which measures both rhIGF-I and endogenous rat IGF-I. Total serum IGF-I level was measured and expressed in ng·ml^{-1}. The detection limit of the assay is 2.05 ng·ml^{-1}. Interassay CV was 3.5-8.0%, and intra-assay CV was 1.3-3.2%. Plasma insulin levels were determined using a Phadeseph Kit (Parmacia, Uppsala, Sweden). Plasma glucose levels were determined using an EML 105 analyser (Radiometer, Copenhagen, Denmark).

Statistical analysis

The responses of the physiological variables during exercise in the two groups were compared by two-way ANOVA with repeated measures. Statistical significance was set at $p < 0.05$. If F was significant, a post-hoc Tukey test was used when appropriate to perform single degree of freedom comparisons. Graphical data are presented as mean ± SD

Results

All individuals completed the anaerobic Wingate test. Seven individuals, two higher fit and five lower fit, experienced ECG abnormality (e.g. S-T segment depression). The 17 other individuals completed the exercise challenges without difficulties or abnormal symptoms. Mean descriptive data are presented in Table 1. No significant differences were noted between the groups with respect to height and weight. However, body fat percent was significantly higher and lean body mass was significantly lower in the lower fit compared to the higher fit individuals. Immediately post-exercise, there was a significant difference ($p < 0.05$) between the groups regarding peak power.

Table 1. Subjects' physical characteristics measurements. Data are means (±SD).

Variables	Higher Fit (n = 12)	Lower Fit (n = 12)
Age (years)	59.0 (1.0)	58.0 (1.0)
Height (m)	1.73 (.02)	1.74 (.02)
Weight (kg)	71.1 (3.0)	71.7 (3.0)
Fat (%)	15.1 *	19.1
LBM (kg)	60.4 *	58.0
VO_2 max ($ml \cdot kg^{-1} \cdot min^{-1}$)	45.1 (2.3) *	39.9 (3.5)
PP (watts)	446.0 (14.9) *	284.2 (6.5)

* $p < 0.05$ between groups. Abbreviations: LBM = Lean Body Mass, PP = Peak Power.

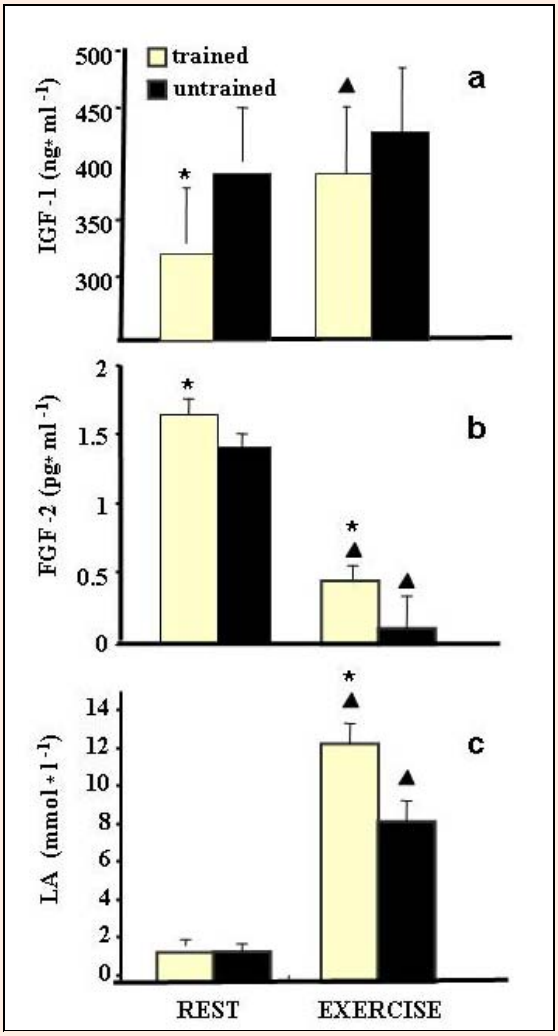

Figure 1. Effect of Wingate anaerobic exercise on serum IGF-I, FGF-2, and lactate levels. a) Pre-exercise IGF-I level was significantly lower in the higher fit compared to the lower fit group. Following the Wingate anaerobic exercise, a significant transient increase in the level of IGF-I was observed only in the higher fit group. b) Pre-exercise FGF-2 level was significantly higher in the higher fit compared to the lower fit group. Following the Wingate anaerobic exercise, FGF-2 decreased significantly to almost undetectable levels in both groups. c) At peak anaerobic exercise, a significant difference in lactate level was observed between the groups. * $p < 0.05$ between the groups. Δ $p < 0.05$ between rest and peak anaerobic exercise.

The effect of Wingate anaerobic exercise on serum IGF-1, FGF-2 and lactate are shown in Figures 1 a-c respectively. At rest, significant ($p < 0.05$) differences were noted between the groups with regard to IGF-1 and FGF-2 levels. Pre-exercise IGF-I levels were significantly lower while pre-exercise FGF-2 levels were significantly higher in the higher fit compared to the lower fit individuals. In both groups, IGF-I increased transiently from rest to immediately post- exercise. However, the increase was significant ($p < 0.05$) only in the higher fit group. In contrast to IGF-I response, in both groups there was a significant ($p < 0.05$) drop in serum FGF-2 immediately after exercise. However, post-exercise FGF-2 levels were significantly higher in the higher fit compared to the lower fit group. Fifty minutes into recovery, IGF-1 levels returned to resting levels while FGF-2 levels remained significantly ($p < 0.05$) lower in both groups. Lactate increased significantly ($p < 0.05$) from pre- to post-exercise in both groups. However, compared to the lower fit individuals, the higher fit individuals showed significantly ($p < 0.05$) higher levels of post-exercise lactate.

Discussion

In the present study we evaluated the effect of fitness level on IGF-I and FGF-2 responses following all-out anaerobic exercise in healthy older men. We found fitness level dependent alterations in the response of older individuals to the Wingate anaerobic exercise regarding the levels of IGF-I and FGF-2. The study demonstrates that higher fit compared to lower fit older men had lower pre-exercise serum levels of IGF-I and higher pre-exercise FGF-2 levels. Following the Wingate anaerobic exercise, there was a transient elevation in the level of IGF-I in both higher fit and lower fit individuals. However, IGF-I elevation was significant only in the higher fit individuals. Contrary to IGF-I, post exercise levels of FGF-2 decreased dramatically to almost undetectable levels in both groups and remained low for 50 minutes into recovery. Our data suggests that during aging, fitness level is an important determinant of growth factors responses to exercise. By modulating the anabolic effects of growth factors, fitness level may have positive effects on aging associated skeletal muscle loss.

IGF-I response to either acute or chronic physical activity remains unclear (Kraemer and Ratamess, 2005). Based on several studies done in healthy young adults, there is an increase in circulating IGF-I in response to different types of exercise; either aerobic, resistance or heavy ergometer cycling (Cappon et al., 1994; Kraemer et al., 2004; Kraemer et al., 1991; Rubin et al., 2005). However, most studies dealing with the acute response of IGF-I to resistance exercise have shown no change in serum IGF-I level (Chandler et al., 1994; Kraemer et al., 1995). The chronic adaptation of circulating IGF-I in response to

physical training is controversial as well. While a few studies have reported no change in resting levels of IGF-I following short-term resistance training (Hansen et al., 2001; Kraemer et al., 1999; Walker et al., 2004), other studies have shown elevations in IGF-I during short/long term resistance training programs (Rubin et al., 2005), particularly during high-volume training (Koziris et al., 1999; Marx et al., 2001). Furthermore, IGF-I increased following endurance type physical training (Roelen et al., 1997) and triathlon training (Maimoun et al., 2004). The mechanism of this response has not been fully resolved and likely involves both increased skeletal muscle IGF-I release and increased clearance rate of IGF-I from IGFBPs (Kraemer and Ratamess, 2005).

As noted, there are not many studies on IGF-I response to exercise in older age during which the activity of the GH/ IGF-I system declines. Specifically, the response of older individuals to acute all-out anaerobic exercise has not yet been investigated. In the few studies conducted to date in older individuals, controversial results have been obtained (Hagberg et al., 1988; Ravaglia et al., 2001; Tissandier et al., 2001). Our data show an elevation in post exercise IGF-I level in the higher fit compared to the lower fit older individuals, suggesting that despite a decline in GH/IGF-I axis in older age, IGF-I response to acute exercise improves among better fit subjects. The exercise-induced anabolic adaptations of skeletal muscle are mostly attributed to IGF-I. Given that IGF-I regulation is involved in aging-associated 'sarcopenia', and that anaerobic muscle activity is represented in many daily life activities of the elderly, our results highlight the clinical significance of IGF-I regulation during aging, and further support the notion that exercise training especially for older individuals can be beneficial.

Surprisingly, we found 17% reduction in pre-exercise circulating IGF-I in the higher fit compared to the lower fit older individuals. The discrepancy between higher levels of IGF-I in healthy young after two weeks of strenuous physical training (Roelen et al., 1997) and our data showing lower levels of IGF-I in higher fit compared to lower fit older individuals might be explained by the finding of higher IGFBP-1 levels in older age (Benbassat et al., 1997). Unlike IGF-I response, pre-exercise FGF-2 was 14% higher in the higher fit compared to the lower fit older individuals and decreased dramatically (75% reduction in the higher fit group and 93% reduction in the lower fit group), in response to the all-out anaerobic exercise, remaining low for at least 50 min into recovery. Similar results have been obtained by Eliakim et al., (2000) and Nemet et al., (2002), who found a significant reduction in circulating FGF-2 in healthy young individuals following a single wrist flexion exercise. Eliakim et al., (2000) hypothesized that exercise promotes a marked reduction in circulating FGF-2 by inducing increased binding of FGF-2 to endothelial and muscle cells receptors resulting in redistribution and local 'capture'. However, in none of these studies was the effect of exercise training evaluated. Previous studies employing either knee-extensor ergometer training or intense intermittent endurance training have analyzed the adaptation of human skeletal muscle to exercise training at the transcriptional level. Since there was a slight or no change in the level of skeletal muscle FGF-2 mRNA (Jensen et al., 2004), increased synthesis does not seem to be the mechanism responsible for the elevation in pre-exercise circulating FGF-2. However, in vitro studies on differentiated human skeletal muscle cultures have demonstrated that mechanical load induces sarcoplasmic wounding and FGF-2 release from myofibers with a linear correlation between the degree of mechanical load and the amount of myofiber wounding and FGF-2 release (Clarke et al., 1993; Clarke and Feedback, 1996). In light of these results, it is possible that prolonged training imitates mechanical load by causing myofiber damage and FGF-2 release into circulation. The resulting increase in circulating FGF-2 might be an important compensatory mechanism during aging, in which the anabolic effects of FGF-2 are reduced by decreased binding affinity and by the delayed expression of local FGF-2 receptors (Brickman et al., 1995).

We speculate that the changes in IGF-I and FGF-2 may have positive anabolic effects on the induction of muscle and capillary growth, resulting in muscle hypertrophy and angiogenesis. Thus, the fitness induced alteration in IGF-I and FGF-2 levels may counteract the process of skeletal muscle loss, by modulating their positive anabolic effects, on skeletal muscle. This may have clinical implications during aging in which the declined activity of growth factors is a major determinant of the loss of muscle strength and function.

Conclusion

The present study suggests that during aging, fitness level can alter circulating levels of IGF-I and FGF-2 and can affect the response of both mediators to all-out anaerobic exercise. Future studies are desirable to elucidate the mechanisms behind these changes.

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Key points

- The present study suggests that during aging, fitness level can alter circulating levels of IGF-I and FGF-2.
- Furthermore, fitness level can affect the response of both mediators to all-out anaerobic exercise.
- Anaerobic muscle activity is represented in many daily life activities of elderly individuals.
- This may have clinical implications during aging, where the declined activity of growth factors is a major determinant of the loss of muscle strength and function.

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