

The effects of intensive training on insulin-like growth factor I (IGF-I) and IGF binding proteins 1 and 3 in competitive cyclists: relationships with glucose disposal

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The aim of the present study was to determine whether 4 months of intensified training would result in modified plasma insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 1 (IGFBP-1) or IGFBP-3 in eight competitive cyclists and eight sedentary individuals and to define the relationships of these factors with glucose disposal. Insulin sensitivity and glucose effectiveness – that is, the fractional disappearance of glucose independent of any change in insulinaemia – were measured with the minimal model (mathematical analysis of frequently sampled intravenous glucose tolerance test). Both glucose effectiveness and insulin sensitivity were higher in the cyclists than in the sedentary individuals, but did not increase further with training. IGF-I was higher in the cyclists than in the sedentary group only after training ($P < 0.05$). Plasma IGFBP-1 and IGFBP-3 increased after training (38 and 20%, respectively; $P < 0.05$) in the cyclists and were higher than in the sedentary individuals ($P < 0.05$). IGF-I was negatively correlated with insulin sensitivity before and after training ($r = -0.66$ and -0.67 , respectively; $P < 0.05$) and IGFBP-1 was negatively correlated with glucose effectiveness before and after training ($r = -0.68$ and -0.77 , respectively; $P < 0.05$). Our results show that strenuous endurance training improves the somatotrope axis (growth hormone–IGF) and that IGFBP-1 may be involved in glucose homeostasis, possibly by limiting the exercise-induced increase in glucose disposal, in competitive cyclists.

Keywords: cycling, exercise, glucose disposal, IGFBP-1, IGFBP-3, IGF-I, minimal model.

Introduction

Insulin-like growth factor I (IGF-I) mediates most of the anabolic effects of growth hormone in target tissues (Cuneo and Wallace, 1994; Hussain *et al.*, 1996). Moreover, IGF-I circulates in blood bound to lower molecular weight binding proteins (insulin-like growth factor binding protein: IGFBP) that modulate its availability for action on tissues (Rutamen *et al.*, 1988). A specific role in glucose homeostasis has been proposed for IGF-I and its binding proteins IGFBP-1 and IGFBP-3, since alterations in IGF-I availability may modulate its insulin-like effects (Suikkari *et al.*, 1989; Lewitt *et al.*, 1991; Hopkins *et al.*, 1994). In

addition, constitutive over-expression of IGFBP-1 results in impaired glucose tolerance with normal insulin sensitivity (Rajkumar *et al.*, 1996). Exercise training increases circulating resting IGF-I concentrations (Roelen *et al.*, 1997; Chicharro *et al.*, 2001), but the effects of exercise training on IGFBPs remain poorly documented and little is known about the possible involvement of these factors in exercise-induced modifications in glucose disposal. Recent studies, however, have shown that IGFBP-3 concentrations increased with long-term training in competitive swimmers (Koziris *et al.*, 1999) and that IGFBP-1 concentrations increased with intense endurance exercise in competitive cyclists (Chicharro *et al.*, 2001). Because IGFBP-3 concentration reflects growth hormone secretion, it has been proposed as a marker suitable for evaluating the growth hormone–IGF axis (Blum *et al.*, 1990).

The aims of this study were to determine the influence of strenuous endurance training on plasma

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IGF-I, IGFBP-1 and IGFBP-3 in competitive cyclists and sedentary individuals, and to establish whether a relationship with glucose disposal parameters exists.

Methods

Participants

Eight competitive male cyclists and eight age-matched sedentary males agreed to participate in the study. None were on medication and none had a family history of diabetes or hypertension. None of the sedentary participants took part in competitive sports or in organized leisure-time activities. The physical characteristics of the participants are shown in Table 1.

The participants were asked to fast overnight until their arrival in our hospital unit at 08:00 h for testing, so that the different tests of the protocol could be performed at the same time of day. The cyclists were tested on two occasions, once before the intensified training period (January) and again after it (May). All participants were requested to refrain from exercise in the 3 days before the glucose tolerance test and blood sampling. The cyclists underwent a heavy training programme after an off-season recovery period. During the off-season (approximately 3 months), the cyclists had continued to perform other activities (running, 1 h · week⁻¹; weight training, 2 h · week⁻¹), but at a markedly reduced training intensity and volume (approximately 70%). After a complete and accurate verbal description of the procedure, risks and benefits associated with the study, the participants provided written consent. The cyclists were then tested twice – before and after this 4 month training period. The study was approved by the local ethics committee.

Bicycle training programme

The cyclists performed 17 h of cycling (~500 km) per week during the 4 month training period. This training protocol was carried out according to the following

weekly schedule: Monday, 45 km (recovery); Wednesday, 100–140 km (endurance); Thursday, 30 km (recovery); Friday, 50 km (interval training); Saturday, 100–140 km (endurance and cycling races); and Sunday, 80–100 km (endurance and cycling races). During the first month, the training sessions were performed at a low intensity with a specific target heart of 120–160 beats · min⁻¹. During the next 3 months, the sessions were performed at a high intensity with a minimum target heart rate of 170 beats · min⁻¹ during the interval training sessions and at the end of each uphill climb. The entire training programme was carried out under the control of a cardio-tester.

Body composition

Body composition was assessed with a four-terminal impedance Plethysmograph Dietosystem Human IM-Scan (Lukaski et al., 1985).

Frequently sampled intravenous glucose tolerance test and blood samples

A cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while glucose was administered via the contralateral cephalic vein. Glucose (0.5 g · kg⁻¹ body mass, solution of 30% w/v) was injected slowly over 3 min. Insulin (0.02 units · kg⁻¹ body mass, i.e. 1–2 units) was injected into the vein contralateral to that used for sampling at 19 min. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min after glucose injection. The samples at 1 and 3 min were used for the determination of the early insulin secretory phase (Bouix et al., 1993). The other samples were taken for minimal model calculations (Steil and Bergman, 1991) and were pooled for the determination of basal serum concentrations of IGF-I, IGFBP-1 and IGFBP-3.

Table 1. Baseline characteristics for cyclists before and after training and for sedentary individuals (mean ± standard error)

	Sedentary controls (n = 8)	Cyclists (n = 8)	
		Before training	After training
Age (years)	25.3 ± 0.7	24.4 ± 1.4	—
Height (m)	1.77 ± 0.02	1.80 ± 0.02	—
Mass (kg)	17.4 ± 2.9	12.4 ± 0.6*	12.1 ± 0.4**
$\dot{V}O_{2max}$ (ml · kg ⁻¹ · min ⁻¹)	44.6 ± 2.4	56.5 ± 1.4*	70.3 ± 1.5**#

*Significant differences between sedentary individuals and cyclists before training, $P < 0.05$. **Significant differences between sedentary individuals and cyclists after training, $P < 0.05$. #Significant differences between cyclists before and after training, $P < 0.05$.

All blood samples were immediately placed in a tube containing lithium heparin. The serum was immediately separated by centrifugation at 4°C and was stored at -80°C until analysis.

Measurement of insulin sensitivity and glucose effectiveness

Minimal model analysis of the frequently sampled intravenous glucose tolerance test was done according to Bergman *et al.* (1979) using the TISPAG software from the Department of Physiology, University of Montpellier I (Brun *et al.*, 1995a), which uses a non-linear least-square estimation. This program gave the values of glucose effectiveness and insulin sensitivity. Glucose effectiveness is the fractional disappearance rate of glucose, independent of any insulin response. Insulin sensitivity is an index of the ability of serum insulin to change glucose's own effect on glucose concentration.

Oxygen uptake

After the frequently sampled intravenous glucose tolerance test had been performed, the cyclists were asked to pedal for 5 min at 50 W and for 5 min at 100 W on a cycle ergometer (Bodyguard; Jonas Oglænd, Sandnes, Norway). Maximal oxygen uptake ($\dot{V}O_{2\max}$) was predicted from the submaximal steps according to Åstrand's nomograms (Åstrand and Rodahl, 1986) on the same day as the frequently sampled intravenous glucose tolerance test.

Laboratory measurements

Samples were analysed for serum insulin by a radioimmunoassay kit (SB-INSI-5 from the international CIS). The within-assay coefficient of variation for insulin was determined by repetitive measurements of the same sample and was 6.6%; the between-assay coefficient of variation was 6.2%. The sensitivity (lowest detectable value) was $<1 \mu\text{U} \cdot \text{ml}^{-1}$. Serum glucose was measured with a Beckman glucose analyser, with coefficients of variation of 8.3% (within-assay) and 7.9% (between-assay).

Serum IGF-I was assayed with a Medegenix kit (Belgium), purchased from Sorin Biomedica France. This is a double antibody disequilibrium assay, which includes an ODS-silica extraction procedure for serum samples. After the extraction procedure, the radioimmunoassay is performed by the addition of the sample and rabbit anti-IGF-I, followed by a 2 h incubation at 2-8°C. Iodine-125 IGF-I is then added, followed by a second incubation for 20 h at 2-8°C. The pre-precipitated carrier, second antibody and polyethy-

lene glycol are added in a single step. The assay is centrifuged after the second 2 h antibody incubation at 2-8°C. The detection limit is $2 \text{ nmol} \cdot \text{l}^{-1}$. This assay does not cross-react ($<1\%$) with insulin-like growth factor II, human growth hormone, FGF, TGR or PDGF. The within-assay coefficients of variation range between 9.1 and 10.1%; the between-assay coefficients of variation range between 10.3 and 15.2%.

Serum IGFBP-1 was assayed with the DSL ACTIVE IGFBP-1 coated tube immunoradiometric assay kit (Diagnostic System Laboratories, Inc., USA), purchased from Ciba-Corning France. This is a two-site immunoradiometric assay (IRMA) in which the analyte to be measured is 'sandwiched' between two antibodies. The first antibody is immobilized to the inside wall of the tubes; the other antibody is radiolabelled for detection. The analyte present in patient samples, standards and controls is bound by both antibodies to form a 'sandwich' complex. Unbound materials are removed by decanting and washing tubes. The detection limit is $0.01 \text{ ng} \cdot \text{ml}^{-1}$. Within-assay coefficients of variation range between 3.4 and 6.0%; between-assay coefficients of variation range between 1.0 and 3.5%. No cross-reactivity with IGFBP-2, -3 or -4 has been reported.

Serum IGFBP-3 was assayed with the DSL ACTIVE IGFBP-3 radioimmunoassay kit (Diagnostic System Laboratories, Inc., USA), purchased from Ciba-Corning France. This is a classical radioimmunoassay with competition between a radioactive and a non-radioactive antigen for a fixed number of antibody binding sites. The separation of free and bound antigen is achieved by using a double antibody system. The detection limit is $0.01 \text{ ng} \cdot \text{ml}^{-1}$. Within-assay coefficients of variation range between 5.3 and 6.7%; between-assay coefficients of variation range between 4.2 and 8.0%. No cross-reactivity with IGFBP-1, -2 or -4 has been reported.

Statistical analysis

The data are presented as the mean \pm standard error. The significance of differences between the cyclists and the sedentary individuals was determined using an analysis of variance (ANOVA). If the ANOVA indicated significant differences, these were located by a pairwise multiple comparison procedure (Student-Newman-Keuls test). Pearson correlation analysis was performed. Significance was set at $P < 0.05$.

Results

Table 1 shows that the cyclists and sedentary controls were matched for age and height. However, the cyclists had a lower percent body fat ($P < 0.05$) and a higher

predicted $\dot{V}O_{2\max}$ than the sedentary group ($P < 0.05$; Table 1) and training increased their predicted $\dot{V}O_{2\max}$ by a further 24% ($P < 0.01$; Table 1). Insulin sensitivity and glucose effectiveness were higher in the cyclists than in the sedentary controls ($P < 0.05$; Table 2) and did not change significantly after training. The concentration of IGF-I was higher in the cyclists than in the sedentary group only after training ($P < 0.05$); there was no significant difference in IGF-I concentration in cyclists before and after training (Fig. 1). Plasma IGFBP-1 and IGFBP-3 concentrations were increased after training in the cyclists (38 and 20% respectively; $P < 0.05$) (Fig. 1).

We found a negative correlation between IGF-I concentration and percent body fat in the cyclists ($r = -0.61$, $P < 0.05$ before training; $r = -0.83$, $P < 0.01$ after training) but not in the sedentary controls. Similarly, IGF-I was positively correlated with fat-free mass in the cyclists ($r = 0.76$, $P < 0.03$ before training; $r = 0.57$, non-significant after training) but not the controls.

There was a negative correlation between IGFBP-1 concentration and basal insulinaemia in the cyclists ($r = -0.8$, $P < 0.01$ before training; $r = -0.67$, $P < 0.05$

after training) but not in the sedentary controls. We found no correlation between IGFBP-1 concentration and any of the body composition variables (e.g. percent body fat).

We found correlations between the IGF-IGFBP system and glucose disposal in the cyclists. There was a negative correlation between IGFBP-1 concentration and glucose effectiveness in the cyclists ($r = -0.68$, $P < 0.05$ before training; $r = -0.77$, $P < 0.03$ after training) but not in the controls. Furthermore, IGF-I concentration was negatively correlated with insulin sensitivity in the cyclists ($r = -0.66$, $P < 0.05$ before training; $r = -0.67$, $P < 0.05$ after training) but not in the controls.

Correlations between the IGF-IGFBP system and exercise performance were also noted. IGFBP-3 was correlated with predicted $\dot{V}O_{2\max}$ in the cyclists. This correlation was only found to be significant after training ($r = 0.67$, $P < 0.05$), not before training ($r = 0.37$). Correlations among changes in various parameters before and after training were also studied, with predicted changes in $\dot{V}O_{2\max}$ being positively correlated with changes in IGFBP-3 ($r = 0.67$, $P < 0.05$).

Table 2. Minimal model analysis of intravenous glucose test for cyclists before and after training and for sedentary individuals (mean \pm standard error)

	Sedentary controls ($n = 8$)	Cyclists ($n = 8$)	
		Before training	After training
Resting glucose ($\text{mmol} \cdot \text{l}^{-1}$)	4 ± 0.2	3.8 ± 0.1	3.9 ± 0.1
Resting insulin ($\mu\text{U} \cdot \text{ml}^{-1}$)	9.8 ± 0.7	8.5 ± 0.8	8.4 ± 0.5
Glucose effectiveness ($\% \cdot \text{min}^{-1}$)	2.1 ± 0.4	$3.9 \pm 0.4^*$	$4.1 \pm 0.3^{**}$
Insulin sensitivity ($\mu\text{U} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}$, $\times 10^{-4}$)	6.3 ± 3.3	$15.1 \pm 4.5^*$	$16.1 \pm 5.3^{**}$

*Significant differences between sedentary individuals and cyclists before training, $P < 0.05$. **Significant differences between sedentary individuals and cyclists after training, $P < 0.05$.

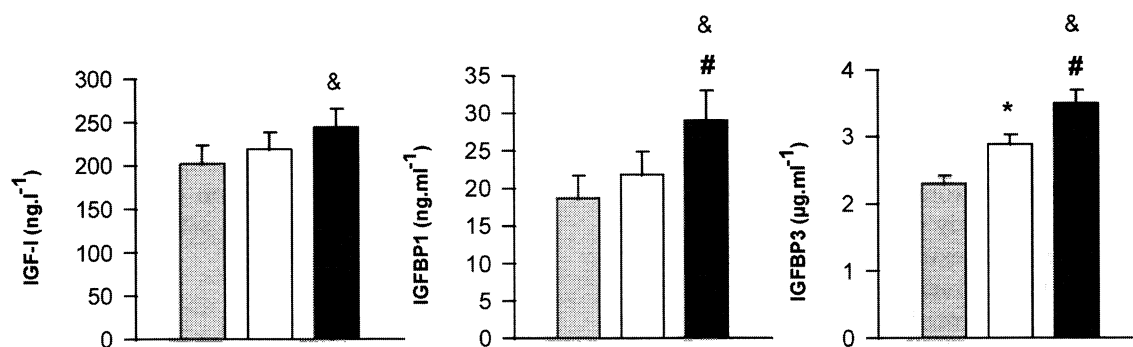


Fig. 1. IGF-I, IGFBP-1 and IGFBP-3 concentrations in sedentary controls (□, $n = 8$) and in cyclists ($n = 8$) before (□) and after (■) training. # $P < 0.05$, before vs after training in cyclists. * $P < 0.05$, sedentary controls vs cyclists before training. & $P < 0.05$, sedentary controls vs cyclists after training.

Discussion

The results of this study show that a 4 month intensified training programme induced a parallel increase in IGFBP-1 and -3 concentrations and aerobic working capacity in competitive cyclists, although no significant increase was noted in IGF-I concentration, insulin sensitivity or glucose effectiveness. The IGF-I concentration, insulin sensitivity and glucose effectiveness were higher in the cyclists than in the sedentary controls only after training, as reported previously (Tokuyama *et al.*, 1993; Roelen *et al.*, 1997; Manetta *et al.*, 2000). Moreover, two correlations suggested a link between IGF status and glucose homeostasis in the cyclists: IGF-I concentration was negatively correlated with insulin sensitivity and IGFBP-1 concentration was negatively correlated with glucose effectiveness.

The effects of exercise and training on IGF-I and its binding proteins, IGFBP-1 and IGFBP-3, remain to be clearly elucidated. Several authors have described an increase in plasma IGF-I after an exercise programme (Roelen *et al.*, 1997; Chicharro *et al.*, 2001), whereas others have reported a decrease (Jahreis *et al.*, 1991; Eliakim *et al.*, 1998). Training has also been reported to increase IGFBP-1 (Hellenius *et al.*, 1995; Chicharro *et al.*, 2001) and IGFBP-3 (Koziris *et al.*, 1999). The discrepancies among these studies can probably be explained by differences in either the participants' training regime, age or body composition status.

In the present study, an improvement in the cyclists' fitness was evidenced by the increase (24%) in predicted $\dot{V}O_{2max}$ as calculated from a submaximal exercise test. Although this index is less sensitive than the direct measurement of $\dot{V}O_{2max}$ during a maximal test, the highly significant increase observed clearly indicates that the training programme, as expected, increased the aerobic working capacity of the cyclists. In addition to this improvement in predicted $\dot{V}O_{2max}$, there were several alterations in the growth hormone-IGF axis.

We were unable to demonstrate a significant increase in IGF-I concentration after training in the cyclists; it was higher in the cyclists than the controls only after this training. The correlation observed between IGF-I and fat-free mass suggests that, among the many other factors that regulate IGF-I concentration, training-induced changes in body composition may also play a role (Copeland *et al.*, 1990; Poehlman and Copeland, 1990). Skeletal muscle has been reported to exhibit large concentrations of IGF-I receptors (Le Bouc, 1996) and to be sensitive to the anabolic effects of this growth factor (Chevenne, 1991). Therefore, the relationship between IGF-I and fat-free mass may, to some extent, reflect the anabolic effects of the training-induced optimization of growth hormone-IGF status, although

this optimization was not evidenced here in circulating IGF-I concentrations. We assume that the lack of a significant increase in IGF-I concentration after training does not rule out the possibility of such an improvement in the growth hormone-IGF status, since a dissociation of the effects of training on circulating concentrations of growth hormone and IGF-I has been reported (Chevenne, 1991). The strong dependence of IGF-I on energetic balance is likely to obscure the relationships between exercise and IGF-I, as shown convincingly by Smith *et al.* (1987). These authors demonstrated that the caloric expenditure induced by strenuous exercise sessions resulted in a decrease in IGF-I concentration similar in magnitude to that induced by the same caloric deficit during food restriction.

An improvement in growth hormone-IGF status was strongly suggested by our IGFBP-1 and IGFBP-3 results. Our findings of a training-induced increase in IGFBP-3 concentration (20%), in accordance with the results of Koziris *et al.* (1999), and a correlation between IGFBP-3 concentration and predicted $\dot{V}O_{2max}$ are in line with earlier studies on young gymnasts (Brun *et al.*, 1995b, 1996a; Bouix *et al.*, 1997). Circulating concentrations of this binding protein were significantly increased after 4 months of intensive training. Since IGFBP-3 is considered to be an integrated index of growth hormone action (Blum *et al.*, 1990), this increase is likely to reflect the training-induced amplification of the secretory activity of the growth hormone-IGF axis that has been reported previously (Cuneo and Wallace, 1994).

This study focused on relationships between IGF-I and glucose disposal after training. The insulin-like effects of IGF-I include glucose transporter recruitment (Suikkari *et al.*, 1989; Hopkins *et al.*, 1994), hypoglycaemic effects (Boulware *et al.*, 1994; Quin *et al.*, 1994) and an *in vivo* direct stimulatory action on glucose uptake by muscle cells (Dardevet *et al.*, 1994). An overall consequence of these effects is that IGF-I increases insulin sensitivity in the body (Zenobi *et al.*, 1993), an effect which is largely due to its action on muscle (Hussain *et al.*, 1996). We were unable to demonstrate any significant improvement in minimal model parameters (either insulin sensitivity or glucose effectiveness) after training. A physiological reason for this limit to the effect of training on carbohydrate disposal is that high insulin sensitivity and glucose effectiveness may result in reactive hypoglycaemia (Tamburrano *et al.*, 1989; Brun *et al.*, 1996b) or exercise hypoglycaemia (Brun *et al.*, 1994). There may thus be a physiological boundary to the effect of training on minimal model parameters, as suggested by us previously (Manetta *et al.*, 2000). An unexpected finding was the negative correlation between insulin sensitivity and IGF-I in the cyclists. Although this

weakly significant correlation could be considered a spurious finding, it may have biological relevance. For instance, there may be a feedback mechanism reducing IGF-I when insulin sensitivity increases to avoid hypoglycaemia, similar to the feedback between insulin sensitivity and insulin secretion (Bergman *et al.*, 1979). However, little is known about this and further investigations are required.

Our results also demonstrated an increase in IGFBP-1 (38%) after endurance training, in accordance with other studies (Hellenius *et al.*, 1995; Chicharro *et al.*, 2001). The strong negative correlation we observed between IGFBP-1 and baseline insulinaemia in the cyclists is consistent with the results of previous studies (Suikkari *et al.*, 1989; Poehlman and Copeland, 1990). It has been reported that insulin regulates circulating concentrations of IGFBPs (Suikkari *et al.*, 1991) and thus IGFBP-1 can be considered as a marker of insulin secretion (Suikkari *et al.*, 1988). On the other hand, IGFBP-1 has been suggested to exert a specific role in glucose homeostasis by controlling free IGF-I concentrations (Baxter, 1991; Lewitt *et al.*, 1991). In addition, Rajkumar *et al.* (1996) demonstrated that over-expression of IGFBP-1 in mice results in impaired glucose tolerance with normal insulin sensitivity. Thus, the negative correlation between IGFBP-1 and glucose effectiveness in our group of cyclists reflects such an involvement of this binding protein in the regulation of glucose disposal. It may be suggested that a rise in IGFBP-1 reduces the non-insulin-dependent component of glucose disposal (which represents the major part of glucose effectiveness) because of a reduction in free IGF-I. IGFBP-1, therefore, appears to prevent IGF-I-induced hypoglycaemia during exercise (Hopkins *et al.*, 1994; Nguyen *et al.*, 1998). Furthermore, it has been reported that fuel metabolism in trained individuals is characterized by a shift towards lipid oxidation and carbohydrate sparing (Brooks and Mercier, 1994). A role for IGFBP-1 in this training-induced metabolic change could be hypothesized.

We have shown that an improvement in working capacity in previously trained cyclists undergoing a 4 month training programme is associated with an increase in IGFBP-1 and IGFBP-3, which is likely to reflect improved function of the growth hormone-IGF axis. However, the effects of training on IGF-I, IGFBP-1 and IGFBP-3 appear to be dissociated. Although IGFBP-3 probably reflects the training-induced enhancement of the growth hormone-IGF axis, IGF-I concentrations are less easy to interpret as they also depend on body composition. Regarding IGFBP-1, our findings suggest that this binding protein plays a role in glucoregulatory adaptations to exercise in competitive cyclists.

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