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Effect of rhIL-6 infusion on GH→IGF-I axis mediators in humans

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Nemet, Dan, Alon Eliakim, Frank Zaldivar, and Dan M. Cooper. Effect of rhIL-6 infusion on GH→IGF-I axis mediators in humans. *Am J Physiol Regul Integr Comp Physiol* 291: R1663–R1668, 2006. First published July 13, 2006; doi:10.1152/ajpregu.00053.2006.—Exercise leads to simultaneous increases in mediators signaling apparently antagonistic functional responses such as growth factors and inflammatory mediators. The aim of the present study was to demonstrate the physiological effect of IL-6 on circulating components of the growth hormone (GH)-insulin-like growth factor-I (IGF-I) axis. Twelve men (ages 26 ± 2 yr) were divided into two groups ($n = 6$ in each group), receiving either albumin or recombinant human (rh) IL-6 infusion. IL-6 was infused via an antecubital vein, and a contralateral antecubital vein was used for blood sampling. The IL-6 dose was chosen to reach plasma levels of IL-6 characteristic of intense exercise (5 μg/h, for 3 h, resulting in plasma levels of 100 pg/ml). Blood samples for GH, GH binding protein, IGF-I, and IGF binding protein (IGFBP)-1 and -3 were collected at baseline, 30 min, and 1, 2, 3, 4, 5, and 8 h after the beginning of the rhIL-6 infusion. IL-6 levels increased only in the rhIL-6-infused group ($P < 0.0005$) and returned to baseline after the infusion was stopped. IL-6 infusion led to a significant increase in GH, peaking 1 h after the beginning of infusion ($P < 0.001$). A decrease in total IGF-I levels was noted only in the rhIL-6-infused group ($P < 0.027$). An initial decrease in IGFBP-1 levels was noted in both groups during infusion ($P < 0.03$). Following the initial decrease, there was a significant increase in IGFBP-1 levels only in the IL-6-infused participants, peaking at 2 after the infusion cessation ($P < 0.001$). IL-6 infusion had no effect on GH binding protein, IGFBP-3, and acid-labile subunit levels. rhIL-6 levels similar to the levels found after strenuous exercise induced a typical exercise-associated GH→IGF-I axis response (increase GH, decreased IGF-I, and elevated IGFBP-1). The results suggest that IL-6 plays a role in the GH→IGF-I response to intense exercise.

exercise; growth factors; inflammatory mediators; cytokines

THERE IS AMPLE EVIDENCE THAT exercise, even in healthy people, leads to simultaneous increases in mediators signaling apparently antagonistic functional responses, such as growth hormone (GH), interleukin-6 (IL-6), and insulin-like growth factor-I (IGF-I). IL-6, produced by the contracting muscle, may serve a unique role as a systemic exercise-associated signaling factor that can, in turn, regulate hormonal and metabolic function throughout the body (27). The goal of this study was to elucidate the physiological effect of IL-6 on GH and IGF-I and their key circulating binding proteins.

GH, the prototypical anabolic hormone, is released in large quantities from the pituitary during intense exercise (15), but so is IL-6, a GH antagonist (10). IGF-I is a GH-dependent growth factor that also plays an important role in the skeletal muscle adaptations to muscle loading and training (1). The circulating IGF-I response to acute exercise is complex and has a biphasic nature characterized by a brief, initial increase, followed by a later decrease mainly after heavy and prolonged exercise tasks (25, 33). These interactions are important, because many of the health effects of exercise seem to be influenced, ultimately, by the fragile balance between inflammatory cytokines and growth factors that are altered by physical activity. Higher levels of circulating IL-6 are negatively correlated with both levels of physical activity and fitness and with IGF-I (4, 16, 41). Moreover, in the elderly, the combination of high IL-6 with low IGF-I and low levels of physical activity is clearly associated with reduced muscle strength, sarcopenia, and increased mortality (26, 30).

IL-6 stimulates GH secretion in a bell-shaped dose-response manner (39). Conversely, in vitro and animal studies show that IL-6 might alter elements of the GH axis, like IGF-I, through a variety of mechanisms, including depression of GH receptor gene expression, leading to GH insensitivity, direct inhibition of IGF-I production, and stimulation of IGF binding proteins (IGFBPs) that act to attenuate IGF-I function (9, 10, 14, 17, 19, 24, 31, 37, 42, 43). To date, no studies have examined the effect of infused, recombinant IL-6 on *1*) IGF-I in its free and bound forms; *2*) IGFBP-1 and -3; and on *3*) GH binding protein (GHBP). In humans, circulating GHBP is the extracellular domain of the GH receptor and, therefore, has been used uniquely as an indicator of GH sensitivity (29).

In the present study, recombinant human (rh) IL-6 or albumin was infused intravenously for 3 h to healthy humans to achieve circulating IL-6 levels comparable to those observed during strenuous, prolonged exercise (34, 40). We determined the effects of the rhIL-6 infusion on key elements of the GH→IGF-I axis, namely GH, GHBP, IGF-I (total and free), and IGFBP-1 and -3. We hypothesized that IL-6 infusion would induce changes in the GH→IGF-I axis, similar to the changes observed following acute strenuous exercise. This will provide evidence that IL-6 plays a major mechanistic role in the GH→IGF-I axis response to exercise. We analyzed serum samples obtained from a recently published human study in which rhIL-6 was infused in healthy, resting subjects (22).

METHODS

Subjects

Twelve young (ages 26 ± 2 yr), healthy, active, but not specifically trained men participated in the study. The subjects were divided into two groups ($n = 6$ in each group), receiving either albumin or rhIL-6 infusion. The study was approved by the Ethical Committee of

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Copenhagen and Frederiksberg Communities, Denmark, and was performed according to the Declaration of Helsinki. Subjects were informed about the possible risks and discomfort involved before giving their written consent to participate. The analysis of deidentified data was performed at the Core Laboratory of the University of California, Irvine, General Clinical Research Center

Protocol

Participants reported to the laboratory at 0700 after an overnight fast. They voided, changed into appropriate hospital attire, and remained supine during the entire experiment. Participants were permitted to consume only water during the experiment. After a 10-min rest, an antecubital vein of one arm was cannulated and used for infusion of rhIL-6 or albumin. An antecubital vein in the contralateral arm was used for blood sampling. The 3-h infusion of rhIL-6 or 20% albumin began between 0800 and 0900.

IL-6 Infusates

The rhIL-6 (Sandoz, Basel, Switzerland) was infused in a dose lower than that reported to be safe in other studies. The IL-6 doses were chosen on the basis of pilot experiments. We aimed to reach plasma levels of IL-6 characteristic of intense exercise or low-grade inflammation (36). The rate of rhIL-6 infusion was 5 μg/h, with albumin used as a vehicle. In the control group, only albumin was infused during the trial.

Blood Analysis

Blood samples were collected at baseline, 30 min, and 1, 2, 3, 4, 5, and 8 h after the beginning of the 3-h rhIL-6 infusion.

GH

GH serum concentrations were determined by ELISA with the use of the DSL-10-1900 Active kit (Diagnostic System Laboratories, Webster, TX). Intra-assay coefficient of variation (CV) was 3.3–4.3%, interassay CV was 6.3–6.5%, and the sensitivity was 0.03 ng/ml.

IGF-I: Total and Free

IGF-I was extracted from IGFBPs using the acid-ethanol extraction method (8). Serum IGF-I concentrations were determined by a two-site immunoradiometric assay using the DSL-5600 Active kit (Diagnostic System Laboratories). IGF-I interassay CV was 3.7–8.2% and intra-assay CV was 1.5–3.4%. Assay sensitivity was 0.8 ng/ml. Free IGF-I was determined by ELISA with the use of the DSL-10-9400 Active kit (Diagnostic System Laboratories). Intra-assay CV was 3.74–4.8%, interassay CV was 6.2–11.1%, and the sensitivity was 0.015 ng/ml.

IGFBPs

IGFBP-1 was measured by coated-tube immunoradiometric assays with the use of the DSL-10-7800 Active kit (Diagnostic System Laboratories). For IGFBP-1, interassay CV was 1.7–6.7%, and intra-assay CV was 2–4%. Assay sensitivity is 0.33 ng/ml. IGFBP-3 serum concentrations were determined by ELISA with the use of the DSL-10-6600 Active kit (Diagnostic System Laboratories). Intra-assay CV was 7.3–9.6%, interassay CV was 8.2–11.4%, and the sensitivity was 0.04 ng/ml.

GHBP

GHBP was measured using the ligand-mediated immunofunctional assay (7). Interassay CV was 9.7–12.9%, and intra-assay CV was 6.3–8.9%. Assay sensitivity was 7.8 pmol/l.

Insulin

Insulin serum levels were determined by ELISA with the use of the DSL-10-1600 Active kit (Diagnostic System Laboratories). Intra-assay CV was 1.3–2.6%, interassay CV was 5.2–6.2%, and the sensitivity was 0.26 μIU/ml.

Acid-Labile Subunit

Acid-labile subunit (ALS) serum levels were determined by ELISA with the use of the DSL Active Total ALS system (DSL-10-82000, Diagnostic Systems Laboratories). Interassay CV was 2.8–8.9%, intra-assay CV was 3.8–7.5%, and the sensitivity was 0.7 ng/ml.

IL-1β

IL-1β serum levels were determined by ELISA with the use of a Quantikine High Sensitivity kit (model HSLB50; R&D Systems, Minneapolis, MN). Interassay CV was 8.2–19.2%, intra-assay CV was 6.4–10.2%, and the sensitivity was <0.1 pg/ml.

Physiological Variables

Heart rate and temperature were measured at the times of blood sampling.

Statistical Analysis

A two-way repeated-measures ANOVA was used to analyze changes over time and between groups. If such analysis revealed significant differences, a Newman-Keuls post hoc test was used to locate the specific differences. Statistical significance was set at $P < 0.05$. Data are presented as means ± SE.

RESULTS

Subject Characteristics

At baseline, no differences in age, weight, height, or body mass index were found between rhIL-6 infusion and control subjects (Table 1). No significant differences in heart rate or body temperature were noted between rhIL-6 and control subjects during and after the rhIL-6 infusion.

Serum Measurements

IL-6. Plasma levels of IL-6 are shown in Fig. 1. The mean level of IL-6 increased to 106.2 ± 9.6 pg/ml at 1 h of infusion in the rhIL-6-infused group ($P < 0.0005$). Albumin infusion did not affect IL-6 levels. Once rhIL-6 infusion was stopped, plasma IL-6 levels decreased rapidly and returned to baseline levels 1 h after infusion cessation.

IL-1β. There were no significant changes and no significant between-group differences in levels of IL-1β.

GH. The effect of rhIL-6 infusion on GH levels is shown in Fig. 2. There was a significant increase in GH plasma level

Table 1. *Participants' characteristics*

	Control	rhIL-6 Infused
Age, yr	27.33±1.5	25.67±2.0
Height, m	1.86±2.2	1.85±1.9
Weight, kg	80.4±3.8	80.0±6.0
BMI, kg/m^2	24.4±1.0	23.3±1.5

rhIL-6, recombinant human interleukin-6; BMI, body mass index. No significant differences were found between control and rhIL-6-infused individuals.

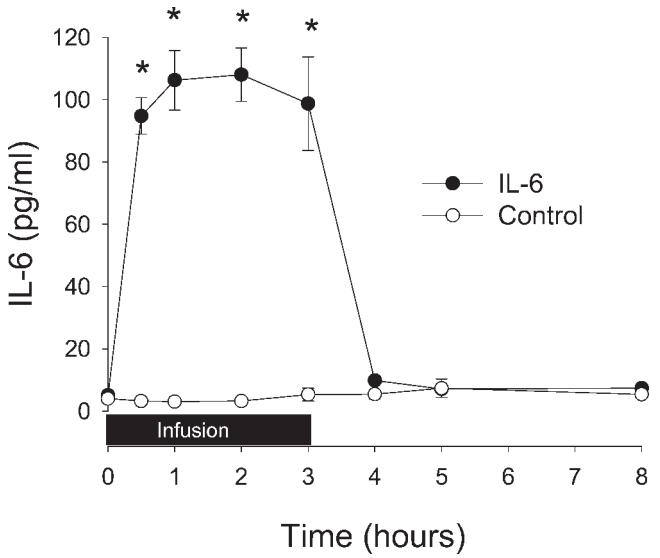

Fig. 1. Plasma interleukin-6 (IL-6) levels before, during, and after infusion of albumin (control) or recombinant human (rh) IL-6. There was a significant increase in IL-6 levels only in the rhIL-6-infused subjects (*$P < 0.0005$).

only in the IL-6-infused subjects (from 0.039 ± 0.008 ng/ml at baseline to 4.32 ± 0.96 ng/ml peak at 1 h, $P < 0.001$).

Total and free IGF-I. The effect of rhIL-6 infusion on plasma levels of total and free IGF-I is shown in Fig. 3. A decrease in total IGF-I levels was noted only in the rhIL-6-infused group (from 291 ± 20 ng/ml at baseline to 228 ± 24 ng/ml at 3 h, $P < 0.027$). Free IGF-I decreased in both groups ($P < 0.005$), and no significant difference was found between the groups.

IGFBP-1. An initial decrease in IGFBP-1 levels was noted in both groups during infusion ($P < 0.03$). Following the initial decrease (10.4 ± 1.9 ng/ml at 3 h, end of IL-6 infusion), there was a significant increase in IGFBP-1 levels only in the IL-6-infused subjects (35.4 ± 4.54 ng/ml), peaking at 2 h after the infusion cessation ($P < 0.001$, Fig. 4).

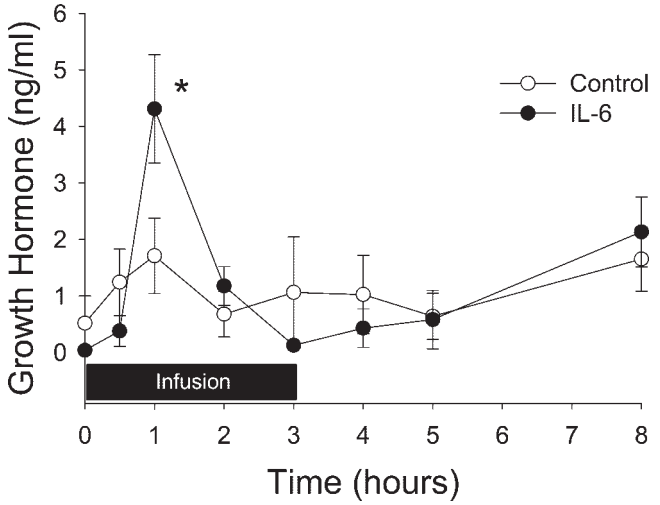

Fig. 2. The effect of rhIL-6 compared with albumin infusion on plasma growth hormone (GH) levels. A significant increase in GH was noted in the rhIL-6-infused subjects (*$P < 0.001$).

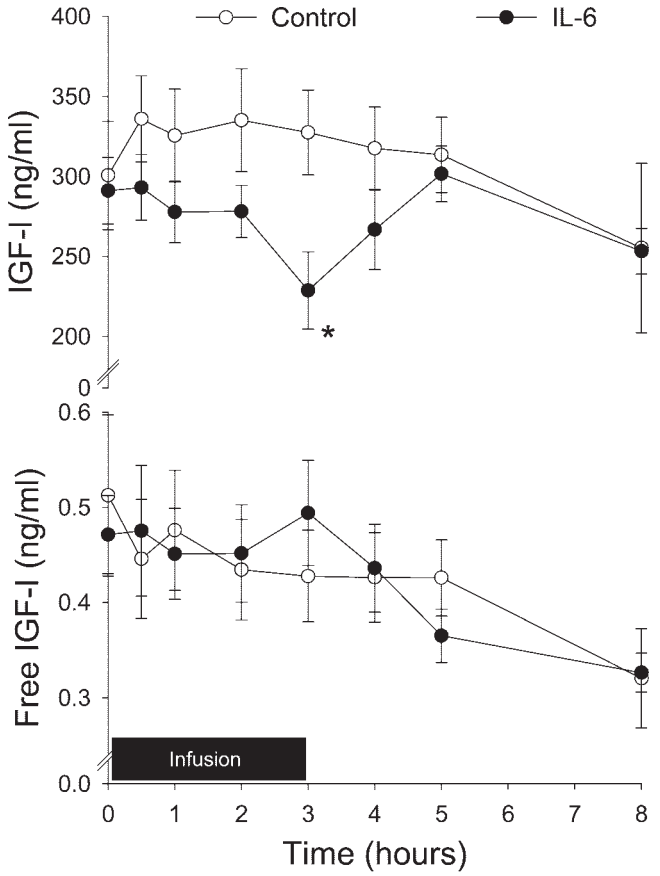

Fig. 3. The effect of rhIL-6 and albumin infusion on plasma total (*top*) and free insulin-like growth factor-I (IGF-I) (*bottom*). A significant decrease in total IGF-I levels was noted in the rhIL-6 infusion group (*$P < 0.027$). Free IGF-I decreased in both groups ($P < 0.005$). No significant between-group difference was found for free IGF-I.

IGFBP-3, GHBP, ALS, and insulin. There were no significant changes and no significant between-group differences in levels of IGFBP-3, GHBP, ALS, or insulin during the intervention.

DISCUSSION

Increasing evidence supports the recent hypothesis that IL-6 produced by contracting skeletal muscle during exercise may act as a systemic signaling protein. We mimicked an intense, exercise-induced IL-6 response by infusing rhIL-6 in resting subjects. Levels of circulating IL-6 achieved were similar to those observed with strenuous, prolonged exercise. In fact, with the exception of pathological conditions like systemic infections, trauma, and burns, exercise may be the only non-pathological state that can cause such high levels of IL-6. Our study confirmed earlier observations that IL-6 infusion leads to increased circulating GH (39). Despite the increase in GH levels, we demonstrated an IL-6 infusion-associated reduction in IGF-I. Interestingly, changes in both GH and IGF-I occurred without changes in GH sensitivity (as reflected by measurements of GHBP). Finally, we found a remarkable increase in IGFBP-1, a functional IGF-I antagonist, but only after the IL-6 infusion had stopped.

GH typically increases substantially with exercise (15); the mechanisms leading to increased GH following exercise are

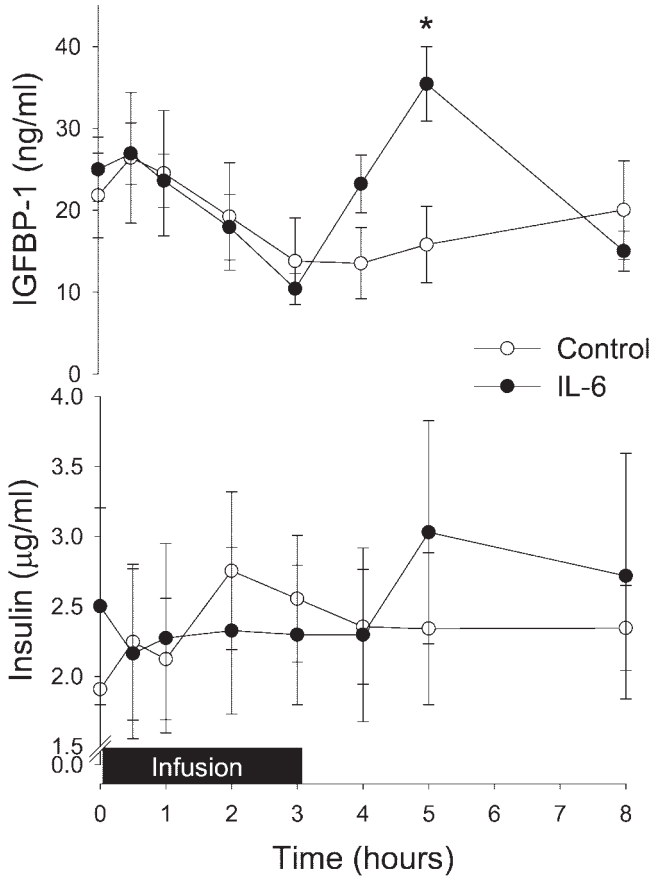

Fig. 4. Plasma IGF binding protein-1 (IGFBP-1) (*top*) and insulin (*bottom*) before, during, and after rhIL-6 or albumin infusion. A significant increase in IGFBP-1 was noted following cessation of the rhIL-6 infusion (*$P < 0.001$). No significant changes were noted for insulin.

not completely understood. Exercise is thought to stimulate GH secretion via its effects on the hypothalamus, and both stimulation of GH-releasing hormone secretion and inhibition of somatostatin release (an inhibitor of GH secretion) have been postulated. Our observation that GH was elevated early during rhIL-6 infusion suggests that inflammatory cytokines may also be involved in the GH secretion following exercise. The GH response observed following IL-6 infusion is abrupt and short and does not continue throughout the period of IL-6 infusion. This is very similar to the GH response observed with exercise in which, following the initial release of GH from the pituitary, even when exercise proceeds, GH levels decline, suggesting exhaustion of the available pituitary GH stores. However, while peak GH levels occurred 1 h following the rhIL-6 infusion, exercise-associated GH peak usually occurs ~30 min from the beginning of exercise (11).

While GH stimulates IGF-I production at the tissue level, it appears that acute changes in IGF-I are not influenced by the typical exercise-associated increase in GH (6). Previous studies, although not entirely consistent, tend to indicate that circulating IGF-I has a biphasic response to acute exercise (3, 6, 13). First, serum levels increase to a small but significant degree in the first 10–20 min, but, as exercise progresses, IGF-I levels fall.

The rhIL-6 infusion can only partially explain the IGF-I response to exercise; rhIL-6 infusion did lead to a late decrease in IGF-I levels. However, no initial increase in IGF-I was noted, suggesting that other mechanisms (e.g., catecholamines, release from marginal pools, etc.) may be responsible for the initial increase in IGF-I. The late reduction in circulating IGF-I levels occurred despite the earlier increase in GH levels, suggesting that the IL-6-associated decrease in IGF-I is GH independent. Similarly, it is now well known that the acute exercise-associated changes in circulating IGF-I levels are also GH independent (3, 33).

Reductions in circulating IGF-I accompany many catabolic states, such as sepsis and burns (21), but the mechanisms for these acute reductions, either during exercise or in other catabolic states, have yet to be elucidated. Low IGF-I level may be indicative of GH resistance. GH resistance is often characterized by reduced levels of the GH receptor. In the present study, we measured circulating GHBP, the extracellular domain of the GH receptor, which is used frequently as an indicator for GH sensitivity reflecting tissue, primarily hepatic, GH receptor levels (5). However, IL-6 infusion had no effect on GHBP levels. With inflammation, multiple postreceptor mechanisms of GH resistance may be induced by cytokines, including IL-6, which reduce GH sensitivity without changing GHBP levels.

Circulating IGF-I is bound to a family of IGFBPs. Some of these binding proteins stimulate (e.g., IGFBP-3, the predominant circulating IGFBP), while others [e.g., IGFBP-1, known to be elevated in systemic inflammatory states (18, 23)] inhibit its anabolic action (28). Interestingly, both IGFBP-3 and IGFBP-1 levels are robustly increased following exercise (25), suggesting that the exercise-associated effects on circulating IGF-I are mediated not only by alteration of the amount of IGF-I, but rather by the effect on its binding proteins and binding protein proteolytic activity (12, 25).

In the present study, IL-6 infusion had no effect on IGFBP-3 (the predominant circulating IGFBP); ALS (part of the IGF-I ternary complex) and IL-6 associated changes in IGFBP-1 occurred only after the IL-6 infusion was stopped and several hours after the changes in IGF-I. These results suggest that the IL-6-associated changes in IGF-I were not mediated by changes in these binding proteins.

IGFBP-1 is found predominantly in tissues, not in circulating blood, and acts primarily to inhibit anabolic effects of IGF-I (28). Circulating IGFBP-1 is elevated in pathological, catabolic states like sepsis and burns, resulting, most likely, from a rapid secretion of IGFBP-1 into the central circulation from the liver (18, 23). The robust IGFBP-1 response to exercise was noted in adults (35) and recently also in prepubertal children (32, 38). Thus the IGFBP-1 response to acute exercise appears to be substantial and reproducible.

IGFBP-1 is known to be highly regulated by insulin, and increased insulin levels are usually associated with reduced circulating IGFBP-1 (28). This inverse relationship was not noted in the present study. Accordingly, both human (20) and animal (2) models have reached the conclusion that IGFBP-1 is elevated with exercise, even when insulin concentrations remain constant. Finally, our data support the evidence that IGFBP-1 may actually be stimulated by inflammatory cytokines (IL-1β, IL-6, and TNF-α) (31). The fact that IGFBP-1 production might be mediated directly by IL-6 suggests that this mechanism may be important for the upregulation of IGFBP-1 seen in catabolic conditions as well as with exercise, both associated with increased circulating concentrations of

this cytokine. In addition, circulating IGFBP-1 levels peaked 2 h after the IL-6 infusion was stopped, and circulating IL-6 levels returned to baseline levels. This suggests that IL-6 might not have only immediate, but also some late effects on key elements of the GH→IGF-I axis. These results may also provide insight into the mechanisms of reduced circulating IGF-I, which is observed in chronic inflammatory states with comparable increases in IL-6, including systemic rheumatoid arthritis and inflammatory bowel disease.

In summary, this study demonstrates that physiological levels of rhIL-6 induce a GH→IGF-I axis response similar to that observed with strenuous exercise. We propose that the effects of intense exercise bouts are to initially create a metabolic state, primarily induced by IL-6, similar in some respects to a GH-resistant, catabolic state often found in sepsis (increased GH, reduced IGF-I, and elevated IGFBP-1). We speculate that, if the individual continues to perform bouts of high-intensity exercise, then the inflammatory nature of the response to single exercise bouts becomes attenuated, permitting an anabolic or training adaptation.

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