Interleukin-6 Is a Novel Factor Mediating Glucose Homeostasis During Skeletal Muscle Contraction

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The mechanisms that mediate the tightly controlled production and clearance of glucose during muscular work are unclear, and it has been suggested that an unidentified "work factor" exists that influences the contraction-induced increase in endogenous glucose production (EGP). The cytokine interleukin (IL)-6 is released from skeletal muscle during contraction. Here we show that IL-6 contributes to the contraction-induced increase in EGP. Six men performed 2 h of bicycle exercise on three separate occasions, at a relatively high intensity (HI) or at a low intensity with (LO + IL-6) or without (LO) an infusion of recombinant human IL-6 that matched the circulating concentration of IL-6 seen in HI exercise. The stable isotope 6,6 $^2H_2$ glucose was infused to calculate EGP (rate of glucose appearance [R_a]), whole-body glucose disposal (rate of glucose disappearance [R_d]), and metabolic clearance rate (MCR) of glucose. Glucose R_a, R_d, and MCR were higher ($P < 0.05$) at HI than at LO. Throughout exercise at LO + IL-6, glucose R_a and R_d were higher ($P < 0.05$) than LO, even though the exercise intensity was identical. In addition, MCR was higher ($P < 0.05$) at LO + IL-6 than at LO at 90 min. Insulin, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone were identical when comparing LO + IL-6 with LO. These data suggest that IL-6 influences glucose homeostasis during exercise. Our results provide potential new insights into factors that mediate glucose production and disposal and implicates IL-6 in the so-called "work factor."
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Skeletal muscle contraction is a powerful stimulus for glucose disposal, with the increase in muscle glucose uptake being greater than that elicited by maximal insulin stimulation (1). To maintain glucose homeostasis and avoid hypoglycemia during muscular work, the increase in glucose uptake is accompanied by a rise in endogenous glucose production (EGP), most, if not all, of which is derived from the liver (2). Regulation of the contraction-induced increase in EGP has been the focus of a vast number of studies over the past 40 years. In general, it is accepted that during exercise at a moderate intensity, glucoregulation is primarily mediated by an increase in the portal venous glucagon-to-insulin ratio (3,4). Coker et al. (5) demonstrated that a mechanism independent of changes in pancreatic hormones contributes toward a modest stimulation of the net splanchnic glucose output during moderate and heavy exercise in humans. In addition, whereas cortisol (6), epinephrine (7,8), adrenergic neural stimulation (9–11), and combined epinephrine and norepinephrine infusion (12) have been proposed to be major neurohumoral mediators of EGP during exercise, they cannot account for the rapid increase. Indeed, studies have been unable to fully elucidate the precise mediator(s) of contraction-induced EGP. As far back as 1961, Goldstein (13) suggested that muscle cells possess a "humoral" component, and two more recent studies (5,7) have concluded that an as yet unidentified factor released from contracting muscle cells may contribute to the increase in hepatic glucose production.

Work from our group demonstrated that the cytokine interleukin (IL)-6 is produced in, and subsequently released from, contracting muscle (14,15), and it has been hypothesized that this may indeed be a factor contributing to EGP (16) during exercise. In the present study, we tested the hypothesis that the IL-6 produced by contracting skeletal muscle may contribute to the increase in EGP necessary to maintain blood glucose homeostasis when the uptake of blood glucose by skeletal muscles is increased by prolonged exercise by infusing recombinant human (rh) IL-6 during prolonged exercise.

RESEARCH DESIGN AND METHODS

Six healthy recreationally active men (age 24 ± 1 years, weight 75.8 ± 2.2 kg, height 182 ± 2 cm) volunteered for this study, after having the procedures fully explained to them, being made aware of all possible risks, and providing written informed consent. The study was approved by the Ethical Committee of Copenhagen and Frederiksberg Communities, Denmark, and performed according to the Declaration of Helsinki.

Pre-experimental protocol. Subjects visited the laboratory and performed an incremental exercise test on a cycle ergometer (Lode, Groningen, the Netherlands) until they reached volitional exhaustion. Peak pulmonary oxygen uptake ($V\text{O}_{2peak}$) averaged 50.3 ± 3.5 ml · kg^{-1} · min^{-1}.

Experimental protocol. After at least 7 days, subjects attended the laboratory on three subsequent occasions separated by at least 7 days. On the first occasion, subjects performed the high-intensity (HI) trial, which involved bicycle exercise for 120 min at a workload equivalent to 70% of $V\text{O}_{2peak}$. Plasma IL-6 was subsequently determined, and the subjects performed two further trials at a workload equivalent to 40% of $V\text{O}_{2peak}$ with (LO + IL-6) or without

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EGP, endogenous glucose production; FFA, free fatty acid; HI, high intensity; IL, interleukin; LO, low intensity; MCR, metabolic clearance rate; rh, recombinant human.

(LO) the infusion of rhIL-6, which was infused at a dose intended to mimic the circulating IL-6 response seen in the HI group. We were able to calculate the infusion rate of IL-6 based on pilot experiments and previous studies (17–19) in which we infused rhIL-6 in the basal state. As in previous experiments, rhIL-6 (Sandoz Pharmaceuticals, Basel, Switzerland) was delivered in 2% sterile human albumin. The latter two trials were performed in random order, and albumin was infused as a sham control in LO and HI. Apart from the infusion of rhIL-6, the protocol for each trial was identical.

Subjects attended the laboratory at 0800, after an overnight fast, and rested quietly on a bed before the antecubital vein from each arm and a dorsal hand vein were cannulated for the infusion of rhIL-6, the glucose tracer, and/or blood sampling. Blood samples were obtained from the dorsal hand vein cannula, and the hand was kept in a heating blanket throughout the entire experiment so that the venous samples were arterialized. This was confirmed by measuring O_2 saturation in each sample. All samples were >90% O_2 saturated. After a basal blood sample was obtained, a primed (36 μmol/kg) continuous (0.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) infusion of the stable isotope 6,6 $^2H_2$ glucose commenced and subjects remained supine for ~115 min. After 105 min, blood samples were obtained every 5 min until 120 min to ensure steady-state basal enrichments of the tracer. After ~115 min, subjects mounted the bicycle ergometer, and at 120 min (0 min before exercise), the tracer infusion rate was doubled and the infusion of rhIL-6 or sham commenced. Subjects then cycled continuously for 120 min. They were permitted to drink water ad libitum, and the temperature of the laboratory was maintained at 20–22°C throughout the experiment.

Blood sampling and analysis. Blood samples were obtained every 30 min during exercise for the measurement of IL-6, glucose, 6,6 $^2H_2$ glucose enrichments, lactate, free fatty acids (FFAs), insulin, and glucagon. Additional samples were collected at 30 and 60 min after exercise for the measurement of glucose, 6,6 $^2H_2$ glucose enrichments, and lactate. Growth hormone, cortisol, epinephrine, and norepinephrine were measured immediately before exercise and at 60 and 120 min during exercise. Blood samples were collected into precooled glass tubes containing lithium heparin for the measurement of all metabolites and hormones except the catecholamines. For these analyses, blood was collected into precooled tubes containing 30 μl of a preservative consisting of ethylene glycol-*bis* (β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid and reduced glutathione. Plasma glucose lactate and FFAs were measured by automated analyses (Cobas, Fara, Roche, France), and plasma insulin (Insulin RIA 100; Amersham Pharmacia Biotech, Uppsala, Sweden), glucagon (Linco Research, St. Charles, MO), cortisol (Diagnostic Products, Los Angeles, CA), growth hormone (LDN, Nordhorn, Germany), and catecholamines (Biostrategy, Auckland, New Zealand) were all determined by radioimmunoassay.

Plasma IL-6 concentration was measured using a high-sensitivity enzyme-linked immunosorbent assay kit (no. HS600; R&D, Minneapolis, MI), which detects total IL-6 independent of binding to soluble receptors, with a sensitivity of ~0.094 pg/ml (intra-assay coefficient of variation <11.1% and inter-assay coefficient of variation <16.5%).

Plasma 6,6 $^2H_2$ glucose enrichments were determined by gas chromatography mass spectrometry (GC column, CP-SIL 8CB; Chromopack, Middelburg, the Netherlands). Briefly, 250 μl water and 3 ml chloroform-methanol (2.3:1, vol/vol) were added to 150 μl plasma, mixed, and spun in a centrifuge for 15 min at 4°C. The supernatant was decanted and washed by adding 1 ml water (pH 2) and 2 ml chloroform before being spun again. The upper layer was dehydrated and derivatized with the addition of butylboronic acid and pyridine (100 mg:10 ml, wt/vol) and incubated at 95°C for 30 min. Thereafter, 250 μl acetic anhydride was added and incubated at 20–22°C for 90 min. The deuterium enrichment of glucose was determined by split injection (1:30) of 1-μl samples using the previously described gas chromatography mass spectrometry. Rates of glucose appearance (R_a) and glucose disappearance (R_d) were determined from changes in the percentage of enrichment in the plasma of the isotope calculated using the one pool, non–steady-state model of Steele et al. (20), assuming a pool fraction of 0.65 and estimating the apparent glucose space as 25% of body mass. The metabolic clearance rate (MCR), which represents the rate of plasma required to clear a set amount of glucose, was calculated by dividing R_d by the plasma glucose concentration.

Statistical analysis. Data from the three experimental trials were statistically analyzed using a two-way (trial × time) ANOVA with repeated measures (Statistica, Tulsa, OK), with significance accepted with a P value of <0.05. If analyses revealed a significant interaction, a Newman-Keuls post hoc test was used to locate specific differences. Data are presented as means ± SE.

RESULTS

The V_{O_2}, V_{CO_2}, respiratory exchange ratio, heart rate, and absolute workload were higher ($P < 0.05$) throughout exercise in HI compared with LO and LO + IL-6. No differences, however, were observed in these measures when comparing LO with LO + IL-6 (Table 1).

TABLE 1
Mean V_{O_2}, V_{CO_2}, respiratory exchange ratio, heart rate, and absolute workload during 120 min of bicycle exercise at HI, LO, or LO + IL-6

	HI	LO	LO + IL-6
V_{O_2} (ml/min)	2,718 ± 40	1,587 ± 53*	1,652 ± 33*
V_{CO_2} (ml/min)	2,517 ± 49	1,274 ± 45*	1,383 ± 30*
Respiratory exchange ratio	0.93 ± 0.01	0.84 ± 0.02*	0.84 ± 0.01*
Heart rate (bpm)	140 ± 1.9	113 ± 2.9*	113 ± 2.3*
Work load (W)	191 ± 4.7	110 ± 3.2*	110 ± 3.9*

Data are means ± SE ($n = 6$). *Difference ($P < 0.05$) from HI.

As predicted, exercise at 40% $V_{O_{2peak}}$ (LO) did not result in any increase in plasma IL-6. This was in contrast with exercise at 70% $V_{O_{2peak}}$ (HI), where IL-6 increased ($P < 0.05$) after 60 min of exercise and remained elevated. During LO + IL-6, rhIL-6 was sufficient to elevate ($P < 0.05$) plasma IL-6, such that the levels were higher ($P < 0.05$) throughout exercise in this trial compared with LO. Although plasma IL-6 was higher ($P < 0.05$) at 30 and 60 min in LO + IL-6 compared with HI, this was transient, and no differences were observed at 90 or 120 min when comparing these trials. In addition, neither mean plasma IL-6 nor peak plasma IL-6 differed when comparing HI with LO + IL-6 (Fig. 1). Plasma IL-6 was higher ($P < 0.05$) after 60 min of exercise in HI compared with LO. Although plasma IL-6 was higher in five of six subjects after 30 min in HI compared with LO, values were not significant using ANOVA. If, however, values were compared at this point using a paired t test, the results were significantly higher in HI compared with LO.

Plasma glucose content was not affected by exercise in HI for most of the experiment. However, at 120 min and 30 min into recovery, plasma glucose fell ($P < 0.05$) in the HI group compared with resting levels. In contrast, in the LO and LO + IL-6 groups, plasma glucose was maintained during exercise and recovery. As a consequence, plasma glucose concentration was lower ($P < 0.05$) in the HI group compared with LO and LO + IL-6 groups at 120 min of exercise and 30 min into recovery (Fig. 2). Both plasma R_a and R_d were increased ($P < 0.05$) by exercise in all trials, before returning to resting levels by 30 min of recovery. As expected, the magnitude of the increases in both R_a and R_d was higher ($P < 0.05$) in HI compared with LO. Importantly, however, was the observation that both R_a and R_d were higher ($P < 0.05$) when comparing LO + IL-6 with LO. In addition, there were no differences in R_a or R_d when comparing HI with LO + IL-6 (Fig. 2). The MCR was higher ($P < 0.05$) throughout exercise in the HI group compared with both the LO and LO + IL-6 groups. In addition, there was a slightly higher MCR in LO + IL-6 compared with LO throughout exercise, with the difference reaching statistical significance at 90 min of exercise (Fig. 2).

There were no differences observed in plasma lactate at rest when comparing the three trials. During exercise, however, plasma lactate was elevated ($P < 0.05$) in the HI group, such that the concentrations of this metabolite

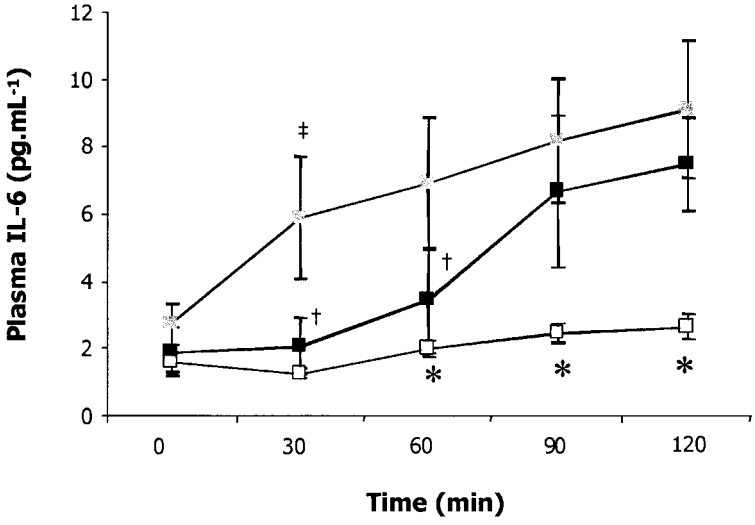

FIG. 1. Plasma IL-6 during 120 min of bicycle exercise at 70% Vo_{2peak} (HI, ■) or 40% Vo_{2peak} without (LO, □) or with (LO + IL-6, ▨) rhIL-6 infusion. *Difference ($P < 0.05$) from HI and LO + IL-6; †difference ($P < 0.05$) from LO + IL-6; ‡difference ($P < 0.05$) from LO. Data are means ± SE ($n = 6$).

were higher ($P < 0.05$) during this period compared with LO and LO + IL-6. Plasma lactate declined ($P < 0.05$) after exercise in the HI group. No differences were observed for this metabolite when comparing LO with LO + IL-6, neither was plasma lactate elevated during exercise in these latter trials (Fig. 3). Plasma FFAs were not different at rest or during exercise in any trial. During recovery, FFAs were higher ($P < 0.05$) in HI compared with LO and LO + IL-6. FFAs during the latter trials were not different at any point (Fig. 3).

The concentrations of circulating hormones were not different when comparing any trial at rest. Growth hormone, cortisol, glucagon, epinephrine, and norepinephrine were all higher ($P < 0.05$), whereas insulin was lower ($P < 0.05$), throughout exercise in the HI group compared with the LO and LO + IL-6 groups. Importantly, the concentrations of these hormones were practically identical when comparing LO with LO + IL-6 (Fig. 4).

DISCUSSION

It has been known for some time that contracting skeletal muscle releases IL-6 in marked quantities, but to date, the biological role of contraction-induced skeletal muscle IL-6 release has been largely unidentified. These data indicate that IL-6 is a protein that mediates EGP during exercise and therefore suggest that IL-6 may be an important protein released during exercise to aid in the maintenance of glucose homeostasis. In addition, because MCR was also higher during exercise in LO + IL-6 compared with LO, our data also indicate that IL-6 may increase whole-body glucose disposal independent of glucose production.

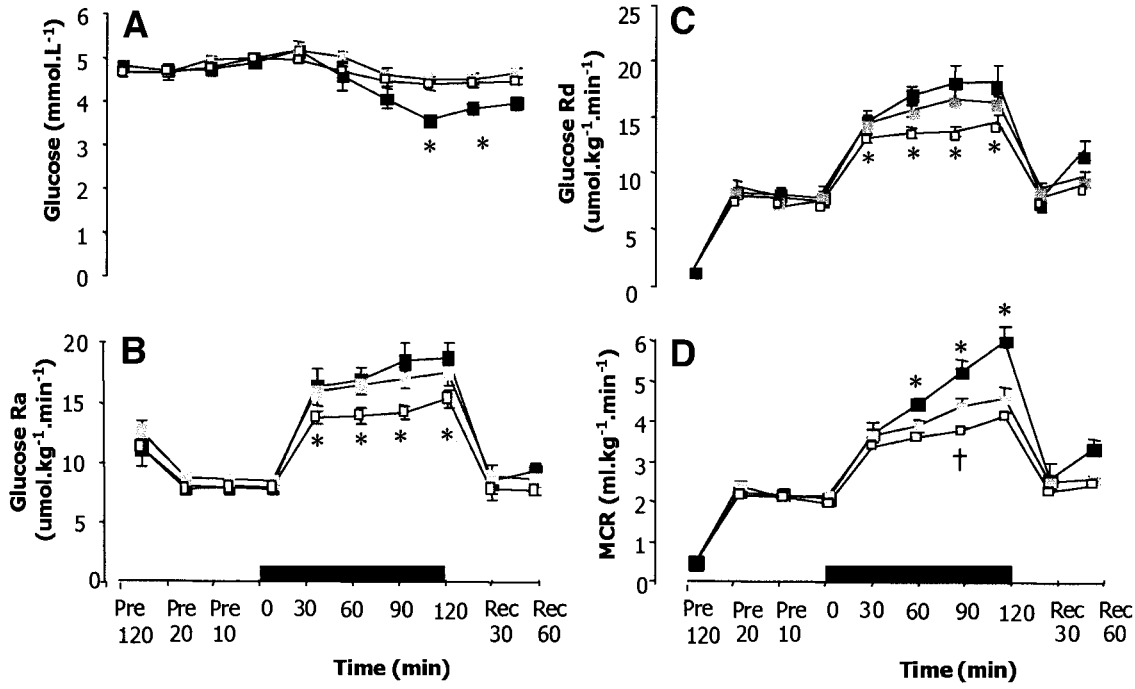

FIG. 2. Plasma glucose (*A*), R_a (*B*), R_d (*C*), and glucose MCR (*D*) during 120 min of bicycle exercise (and 60 min of recovery) at 70% Vo_{2peak} (HI, ■) or 40% Vo_{2peak} without (LO, □) or with (LO + IL-6, ▨) rhIL-6 infusion. *Difference ($P < 0.05$) from HI and LO + IL-6; †difference ($P < 0.05$) from LO + IL-6. Data are means ± SE ($n = 6$).

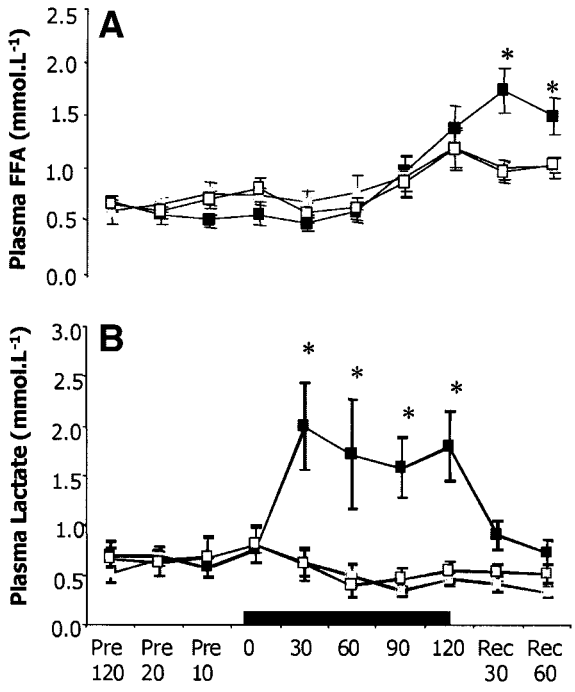

FIG. 3. Plasma FFA (*A*) and lactate (*B*) during 120 min of bicycle exercise at 70% $V\text{O}_{2\text{peak}}$ (HI, ■) or 40% $V\text{O}_{2\text{peak}}$ without (LO, □) or with (LO + IL-6, ▨) rhIL-6 infusion. *Difference ($P < 0.05$) from LO and LO + IL-6. Data are means ± SE ($n = 6$).

These data provide novel insights into factors that mediate glucose production and disposal and suggest a role for IL-6 that implicates it in the so-called "work factor."

Although our data indicate that IL-6 is a factor contributing to the increase in EGP, it is clear that it is not solely responsible for mediating glucose homeostasis during exercise. This is clear because during exercise in LO, glucose R_a markedly increased from rest at the onset of exercise (Fig. 2), even though plasma IL-6 did not increase during this trial (Fig. 1). These data are consistent with previous investigations that demonstrate that during low- to moderate-intensity exercise, EGP and glucose homeostasis are mediated primarily by the portal venous glucagon-to-insulin ratio (3,4). In addition, it must also be noted that while there was a tendency for IL-6 to be higher in the HI group compared with the LO group, at 30 min, the results were not statistically significant (Fig. 1), although EGP was significantly elevated in HI at this point (Fig. 2). In the present study, we could not place catheters into the portal vein because this procedure necessitates surgery. However, because plasma glucagon did not change in LO, but insulin fell ($P < 0.05$) during this trial, it is likely that the portal venous glucagon-to-insulin ratio increased during exercise, and this would primarily account for the increase in EGP.

The regulation of glucose homeostasis during more intense exercise has been the subject of considerable debate, and despite the fact that Kreisman et al. (12) recently suggested that catecholamines are the prime mediators of EGP during very intense exercise, our data suggest that IL-6 plays a role at exercise conducted at 70% $V\text{O}_{2\text{peak}}$. Of note, in two recent studies (5,7) conducted at this workload, the authors could not fully account for the factors that mediated EGP and concluded that an as yet unidentified factor released from contracting muscle cells may contribute to the increase in hepatic glucose production. We propose this to be IL-6. It is also noteworthy that during more intense exercise (~80% $V\text{O}_{2\text{peak}}$), control of EGP is more complex, even compared with exercise conducted at the intensity used in the present study, because the pancreatic hormones appear to play less of a role. We recently conducted a study where we used a combined α- and β-adrenergic blockade during exercise at ~80% $V\text{O}_{2\text{peak}}$ to examine whether adrenergic mechanisms mediate the abrupt rise in EGP. We found no effect of combined blockade on R_a and again speculated that an unknown factor may be mediating this effect (11). It is noteworthy that leg IL-6 release increases as a function of exercise intensity (21). Although speculative, our data raise the possibility that IL-6 may play a more significant role in regulating EGP as exercise intensity increases.

It appears from our data that IL-6 is mediating its effects directly and not via changes in circulating hormones, because all of the measured glucoregulatory hormones were remarkably similar when comparing LO with LO + IL-6 and yet EGP was markedly higher in the latter trial. We acknowledge, however, that our hormonal measures were not obtained from the portal circulation and that there could be differences when comparing portal insulin and glucose concentrations with those measured in the peripheral circulation. Although we have previously measured (19) no effect of IL-6 on circulating pancreatic hormone levels at rest, no studies have measured the effect of this cytokine on portal pancreatic hormone levels. We must also acknowledge that we slightly overestimated our infusion rate early during exercise (Fig. 1), and this must be considered when comparing our glucose flux data in LO + IL-6 with HI.

If, however, IL-6 is mediating its effects on EGP directly, what is the mechanism? There is some evidence to suggest that IL-6 may have a marked influence on hepatic glucose metabolism. IL-6 has been shown (22) to inhibit glycogen synthase activity and accelerate glycogen phosphorylase activity in isolated rat hepatocytes. In contrast, we have recently demonstrated (18) that rhIL-6 infusion into healthy young men at rest does not affect glucose turnover. It appears, therefore, that in humans, IL-6 may only increase EGP during exercise and in the basal state. Although this is somewhat surprising, there are several possibilities that may account for these observations. First, because the absolute glucose flux rates in the basal state are relatively low, it is possible that current methods for measuring glucose turnover in humans may lack the sensitivity to detect small differences. In this respect, it should be noted that although we did not previously measure any effect of rhIL-6 infusion on EGP, others have shown (23) that injection of rhIL-6 into humans increases EGP and fasting blood glucose concentration in a dose-dependent manner. Therefore, we cannot rule out the possibility that in the current study, the higher flux rates during exercise made the effect of rhIL-6 on glucose turnover easier to quantify.

It is also possible that a cofactor associated with exercise might be necessary for IL-6 to exert its effect on glucose metabolism. Epinephrine is a powerful mediator of glucoregulation during exercise. We hypothesized that

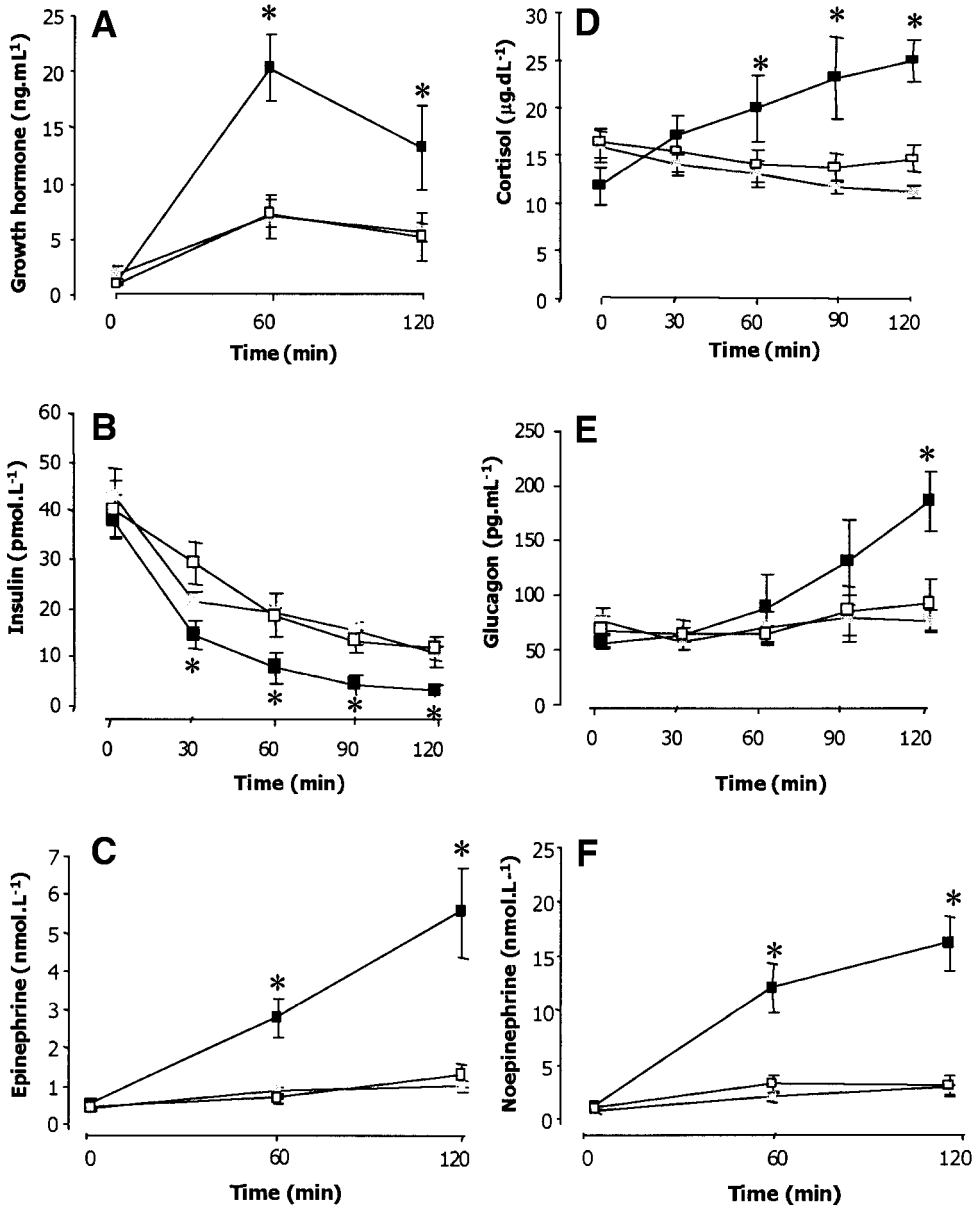

FIG. 4. Plasma growth hormone (*A*), insulin (*B*), epinephrine (*C*), cortisol (*D*), glucagon (*E*), and norepinephrine (*F*) during 120 min of bicycle exercise at 70% Vo_{2peak} (HI, ■) or 40% Vo_{2peak} without (LO, □) or with (LO + IL-6, ▨) rhIL-6 infusion. *Difference ($P < 0.05$) from LO and LO + IL-6. Data are means ± SE ($n = 6$).

this may be the factor. Therefore, in preliminary experiments, we incubated HEPG2 cells with IL-6, epinephrine, or a combination of these two compounds and measured glucose in the culture medium. We saw no evidence of glucose release being different whether cells were incubated in IL-6, epinephrine, or a combination (data not shown). Therefore, our tissue culture experiments could shed no light on this hypothesis. It is also possible that lactate may have to be elevated because lactate would provide the substrate for gluconeogenesis to proceed. In the present experiment, plasma lactate was not elevated during LO + IL-6, making this hypothesis unlikely. However, it is important to note that plasma lactate is only a measure of the balance between lactate production and clearance, and because we have no measure of lactate flux across the hepatosplanchnic viscera, we cannot rule out the possibility that lactate is indeed a cofactor needed for IL-6 to exert its effect on EGP during exercise.

Finally, it must be noted that glucose homeostasis is a reflection of the tight balance between R_a and R_d. During exercise in HI, the MCR was higher ($P < 0.05$) compared with the other trials. This was not surprising because leg glucose uptake increases during exercise in an intensity-dependent manner (24). Importantly, however, at 90 min of exercise, the MCR was higher ($P < 0.05$) in LO + IL-6 than in LO. These data indicate that whole-body glucose disposal was being affected by IL-6 infusion independent of the increase in glucose because of elevated R_a. There are few data to suggest that IL-6 may increase glucose disposal, and indeed some studies suggest that IL-6 may induce insulin resistance (25). However, Stouthard et al. (26) demonstrated that acute IL-6 treatment increased

both basal and insulin-stimulated glucose uptake in an adipocyte cell line. Our data suggest that during exercise, IL-6 may play a role in enhancing whole-body glucose disposal. This may indeed be the primary effect of IL-6, and the increase in EGP may be secondary to increased whole-body glucose disposal.

It should be noted that although R_d was significantly increased when comparing LO + IL-6 with LO, the average R_d was 16.9 vs. 14.6 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, respectively. If we assume an active muscle mass of 20 kg during this type of exercise and that all of the glucose taken up by the tissues is oxidized, the difference in glucose oxidation over the course of the exercise is ~5.5 mmol glucose. This is unlikely to be significant in terms of total substrate oxidation over the duration of 120 min of exercise.

In conclusion, our data suggest that IL-6 contributes to the exercise-induced increase in glucose production and clearance in humans. Our results appear not to be attributed to changes in the hormonal milieu, since circulating insulin, glucagon, epinephrine, norepinephrine, cortisol, or growth hormone were identical when comparing LO + IL-6 with LO. Our results provide new insight into factors that mediate glucose production and disposal and suggest an entirely novel role for IL-6 that implicates it in the so-called "work factor."

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