IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans

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Steensberg, Adam, Christian P. Fischer, Charlotte Keller, Kirsten Møller, and Bente Klarlund Pedersen. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab* 285: E433–E437, 2003; 10.1152/ajpendo.00074.2003.—The purpose of the present study was to test the hypothesis that a transient increase in plasma IL-6 induces an anti-inflammatory environment in humans. Therefore, young healthy volunteers received a low dose of recombinant human (rh)IL-6 or saline for 3 h. Plasma IL-6 levels during rhIL-6 infusion were ~140 pg/ml, corresponding to the levels obtained during strenuous exercise. The infusion of rhIL-6 did not induce enhanced levels of the proinflammatory cytokine TNF-α but enhanced the plasma levels of the two anti-inflammatory cytokines IL-1 receptor agonist (IL-1ra) and IL-10 compared with saline infusion. In addition, C-reactive protein increased 3 h post-rhIL-6 infusion and was further elevated 16 h later compared with saline infusion. rhIL-6 induced increased levels of plasma cortisol and, consequently, an increase in circulating neutrophils and a decrease in the lymphocyte number without effects on plasma epinephrine, body temperature, mean arterial pressure, or heart rate. In conclusion, this study demonstrates that physiological concentrations of IL-6 induce an anti-inflammatory rather than an inflammatory response in humans and that IL-6, independently of TNF-α, enhances the levels not only of IL-1ra but also of IL-10. Furthermore, IL-6 induces an increase in cortisol and, consequently, in neutrocytosis and late lymphopenia to the same magnitude and with the same kinetics as during exercise, suggesting that muscle-derived IL-6 has a central role in exercise-induced leukocyte trafficking.

cytokines; C-reactive protein; tumor necrosis factor-α; neutrophils and lymphocytes; interleukin-1 receptor agonist

INTERLEUKIN (IL)-6 has initially been classified as a proinflammatory cytokine, mainly because it increases in the early course of an infection. However, it was recently suggested that IL-6 should be classified as an anti-inflammatory cytokine (32). In vitro studies (9), as well as animal studies (16, 18), suggest that IL-6 inhibits TNF-α production. Studies in IL-6 knockout mice have demonstrated that these mice possess a compromised ability to control the proinflammatory cytokine response to injected endotoxin (35). Recently, we demonstrated that infusion of recombinant human (rh)IL-6 to healthy volunteers inhibited low-grade endotoxin-induced TNF-α production (25a). A number of epidemiological studies have shown increased levels of both TNF-α and IL-6 in aging (4), in obese individuals (2), and in patients with type 2 diabetes (13, 17, 24, 34). Furthermore, plasma concentrations of IL-6 have been shown to predict total and cardiovascular mortality in population-based studies (25). It is, however, not known whether chronically elevated levels of IL-6 are causally related to atherosclerosis, obesity, and insulin resistance. On the basis of evidence that IL-6 exerts anti-inflammatory effects, it is likely that the elevated plasma IL-6 found in these individuals represents low-grade inflammation, rather than its cause.

We have used exercise as a model for the study of metabolic and immunological interactions (for reviews see Refs. 22 and 23). During strenuous exercise, several cytokines transiently increase in plasma along with changes in circulating immune cells (21). The increase in IL-6 during exercise precedes that of other cytokines examined (20). Therefore, IL-6 is likely to play a central role in the cytokine cascade. The IL-6 gene is expressed within and released from contracting muscles (30), especially when intramuscular glycogen is low (14, 26). There is evidence to suggest that one function of muscle-derived IL-6 during exercise is to work as a hormone by increasing substrate mobilization (15). In addition, muscle-derived IL-6 may also induce anti-inflammatory effects. High plasma concentrations of IL-6 induce the expression of the IL-1 receptor antagonist (ra) (33), a cytokine that antagonizes the effects of the proinflammatory cytokine IL-1 (8). Whether IL-6, independently of TNF-α, induces IL-10, one of the other major anti-inflammatory cytokines, is not known. Injection of IL-6 into humans increases plasma adrenocorticotropic hormone and plasma cortisol (3, 31). Moreover, both the pituitary corticotrophs and adrenocortical cells express IL-6 receptors, and IL-6 is able to induce an increase in cortisol both directly and indirectly (3).

Acute elevations in plasma IL-6 either by infusion of IL-6 or by exercise are therefore likely to stimulate the

anti-inflammatory environment, thereby reducing any ongoing inflammatory processes in the host. These same subjects, however, might consequently also experience immune impairment and enhanced susceptibility to infections.

Exercise induces highly stereotyped changes in leukocyte subpopulations. Thus the number of neutrophils increases during and after exercise, whereas the lymphocyte number increases during exercise and decreases in the postexercise period (22). Whereas the initial changes can be ascribed to the effect of catecholamines (29), the prolonged changes in leukocyte numbers are most likely mediated through an effect of muscle-derived IL-6 on cortisol production.

In the present study, a low dose of rhIL-6 or saline was infused for 3 h into healthy humans. The plasma IL-6 levels obtained were comparable to those observed during strenuous prolonged exercise (21). Any changes in cortisol, lymphocytes, neutrophils, C-reactive protein (CRP), IL-10, IL-1ra, and TNF-α were measured in the blood during the infusion and in the hours after it. We hypothesized that IL-6 infusion would induce an increase in plasma IL-1ra and IL-10, plasma CRP, and cortisol as well as a consequent increase in neutrophil and decrease in lymphocyte numbers, without any changes in TNF-α.

METHODS

Subjects. Twelve healthy, active, but not specifically trained males participated in the study. The subjects were divided into two groups, receiving either saline or rhIL-6 infusion. The mean ($\pm$SE) ages of the two groups were 23 $\pm$ 1 and 24 $\pm$ 1 yr, without any significant differences. The study was approved by the Ethical Committee of 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.

Protocol. Subjects reported to the laboratory at 0700 after an overnight fast. They voided, changed into appropriate hospital attire, and remained supine during the entire experiment. They were permitted to consume only water during the experiment. After 10 min, the femoral arteries of both

legs were cannulated as previously described (26). One femoral arterial catheter was used for the infusion of rhIL-6 or saline. The other arterial line was used for blood sampling. At ~1000, the 3-h infusion of rhIL-6 or saline commenced.

IL-6 infusates. The rhIL-6 (Sandoz, Basel, Switzerland) was infused in a dose lower than that reported to be safe in other studies (31). 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. The rate of rhIL-6 infusion was 30 μg/h, with saline used as a vehicle. Saline was infused during the control trial.

Blood analysis. Blood samples for IL-6, IL-10, IL-1ra, and TNF-α were measured by high-sensitivity ELISA, as previously described (21), and CRP, blood lymphocytes, and neutrophils were measured by standard laboratory procedures. Plasma epinephrine was measured by HPLC, and plasma cortisol (Diagnostic Products, Los Angeles, CA) was analyzed by radioimmunoassay, as previously described (27).

Physiological variables. Heart rate and mean arterial pressure (MAP) were measured every 60 min by use of electrocardiography and sphygmomanometry, respectively. Temperature was also measured at these time points via a tympanic probe.

Statistics. All data are presented as means $\pm$ SE; n = 6. Plasma IL-6, IL-1ra, IL-10, and TNF-α values were log transformed to obtain a normal distribution. To analyze changes over time and between groups, a two-way repeated-measures analysis of variance (RM-ANOVA) was used. If such analysis revealed significant differences, a Newman-Keuls post hoc test was used to locate the specific differences. $P < 0.05$ was accepted as significant.

RESULTS

At steady state during saline and rhIL-6 infusions, plasma IL-6 concentrations were ~4 and 140 pg/ml, respectively. At the cessation of the rhIL-6 infusion, plasma IL-6 declined rapidly toward preinfusion levels within the first hour. Plasma epinephrine, heart rate, MAP, and temperature were not affected by IL-6 infusion or time, as shown in Table 1.

Infusion of rhIL-6 did not affect the levels of TNF-α in the plasma (Fig. 1*A*). The two cytokines IL-10 and IL-1ra significantly increased ($P < 0.05$) during the rhIL-6 infusion compared with saline and preinfusion,

Table 1. *Plasma IL-6, plasma epinephrine, temperature, MAP, and heart rate before, during, and after saline or low-dose rhIL-6 infusion*

	Trial	Preinfusion	Infusion			Postinfusion		
			1 h	2 h	3 h	4 h	5 h	6 h
Plasma IL-6, pg/ml	Saline	3 ± 1	4 ± 1	4 ± 1	5 ± 1	5 ± 1	7 ± 2	6 ± 1
	rhIL-6	2 ± 1	147 ± 12*†	130 ± 5*†	152 ± 14*†	12 ± 3*†	8 ± 2	8 ± 2
Plasma epinephrine, mmol/l	Saline	0.81 ± 0.19	0.76 ± 0.11	0.56 ± 0.15	0.62 ± 0.24	0.43 ± 0.08	0.30 ± 0.08	0.82 ± 0.16
	rhIL-6	0.88 ± 0.13	0.66 ± 0.08	0.68 ± 0.015	0.71 ± 0.05	0.56 ± 0.03	0.61 ± 0.05	0.92 ± 0.15
Temperature, °C	Saline	36.7 ± 0.2	36.7 ± 0.2	37.0 ± 0.2	37.0 ± 0.2		37.0 ± 0.2	37.1 ± 0.2
	rhIL-6	36.5 ± 0.3	36.5 ± 0.3	36.8 ± 0.2	36.9 ± 0.2		37.2 ± 0.1	37.1 ± 0.1
MAP, mmHg	Saline	81 ± 3	80 ± 3	82 ± 4	84 ± 4		81 ± 4	84 ± 2
	rhIL-6	88 ± 4	87 ± 3	89 ± 4	84 ± 2		80 ± 3	87 ± 2
Heart rate, beats/min	Saline	63 ± 2	63 ± 3	63 ± 2	65 ± 2		64 ± 3	62 ± 3
	rhIL-6	65 ± 6	68 ± 5	79 ± 5	76 ± 7		76 ± 6	74 ± 5

Values are means ± SE; n = 6. MAP, mean arterial pressure; rh, recombinant human. *Difference from preinfusion; †difference from saline infusion ($P < 0.05$).
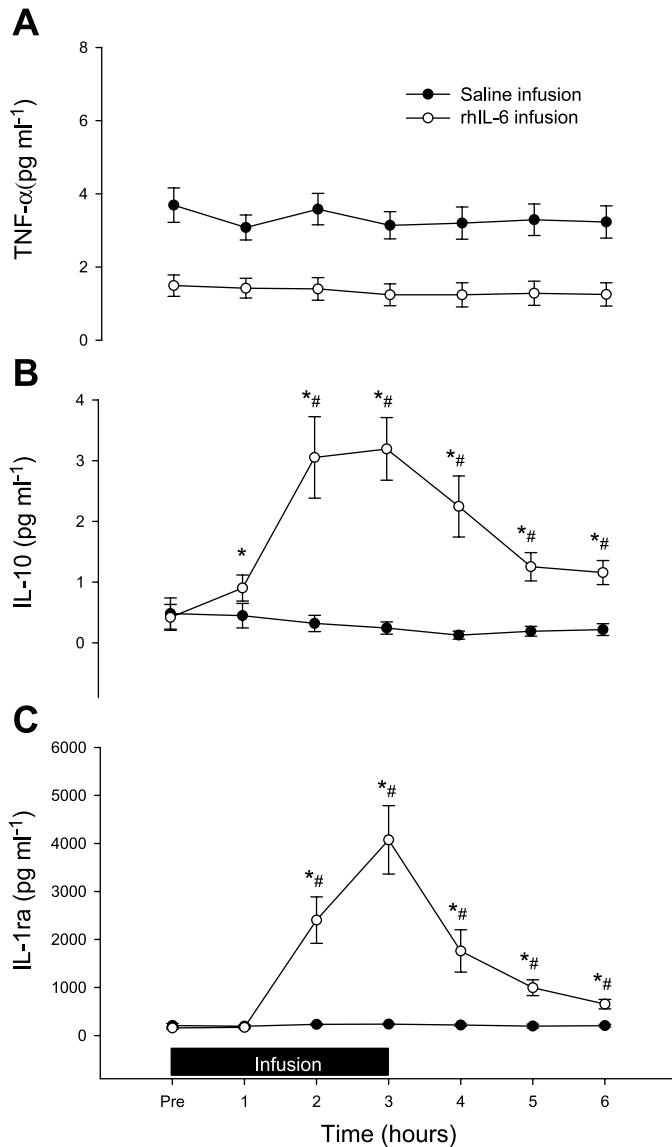
Fig. 1. Plasma TNF-α (*A*), plasma IL-10 (*B*), and IL-1 receptor agonist (IL-1ra, *C*) before, during, and after 3-h infusion of either saline or a low dose of recombinant human (rh)IL-6. Values are means ± SE; *n* = 6. *P* < 0.05: *difference from preinfusion; #difference from saline infusion.
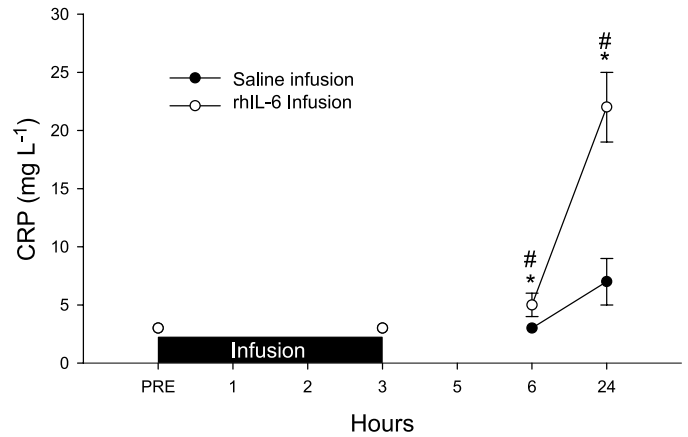

Fig. 2. Plasma C-reactive protein (CRP) before, during, and after 3-h infusion of either saline or a low dose of rhIL-6. Values are means ± SE; *n* = 6. *P* < 0.05: *difference from preinfusion; #difference from saline infusion.
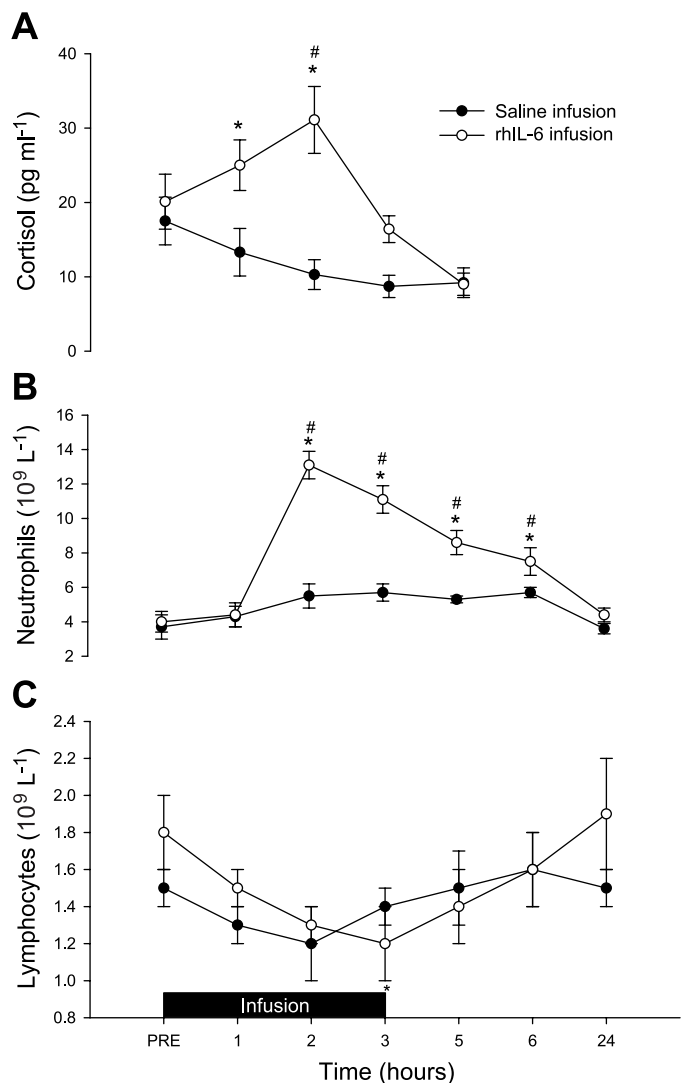

Fig. 3. Plasma cortisol (*A*), circulating neutrophils (*B*), and lymphocytes (*C*) before, during, and after 3-h infusion of either saline or a low dose of rhIL-6. Values are means ± SE; *n* = 6. *P* < 0.05: *difference from preinfusion; #difference from saline infusion.

with ~8-fold and ~26-fold increases, respectively. At the cessation of the infusion, the plasma concentrations of both cytokines declined toward basal levels (Fig. 1, *B* and *C*). Plasma CRP was increased (*P* < 0.05) 3 h after the cessation of the rhIL-6 infusion, reaching 22 ± 3 mg/l 16 h later (Fig. 2).

Plasma cortisol increased (*P* < 0.05) during rhIL-6 infusion and declined toward basic levels at the cessation of infusion (Fig. 3*A*). The number of circulating neutrophils increased (*P* < 0.05) during the rhIL-6 infusion, peaking 2 h into the infusion (13.1 ± 0.8 × 10^9/l) compared with control (5.5 ± 0.7 × 10^9/l). The next day, circulating neutrophils were back to preinfusion numbers (Fig. 3*B*). The lymphocyte number declined modestly (*P* < 0.05) during the rhIL-6 infusion but did not change during saline infusion (Fig. 3*C*).

DISCUSSION

The findings from the present study support the hypothesis that IL-6 is an anti-inflammatory cytokine. This is suggested by its very high plasma concentrations observed during infections and by its release from contracting skeletal muscle during exercise. In this study, we show that an acute experimental elevation of plasma IL-6 induced a transient increase in the plasma levels of the two anti-inflammatory cytokines IL-1ra and IL-10 and cortisol and caused a delayed increase in plasma CRP. This took place without any effect on the levels of plasma TNF-α, plasma catecholamines, temperature, MAP, or heart rate, thus indicating that an important function of IL-6 is to limit the potentially injurious effects of sustained inflammation.

IL-6 is known to inhibit an endotoxin-associated increase in TNF-α in humans (25a). Because we found that IL-6 infusion did not decrease the basal plasma levels of TNF-α, it is possible that IL-6 influences circulating levels of TNF-α by inhibiting dynamic TNF-α production or release. However, we cannot exclude the possibility that treatment with IL-6 for days would have an effect on the basal plasma levels of TNF-α, especially in individuals who have higher basal plasma levels of TNF-α, such as aged or obese subjects or patients with type 2 diabetes.

To our knowledge, this is the first study to demonstrate that IL-6, independently of TNF-α, induces the release of IL-10. Others have demonstrated that supraphysiological doses of IL-6 concentrations induce IL-1ra in humans (33). The only known biological role of IL-1ra is its ability to bind to the IL-1 receptor and thereby inhibit the function(s) of IL-1α and IL-1β (8). IL-1ra is mainly produced by monocytes and macrophages after stimulation with lipopolysaccharide (8) or the cytokines IL-4, IL-6, IL-10, and IL-14 (7). IL-10 is produced by Th2 lymphocytes, monocytes, and B cells, and it inhibits several immune pathways. Moreover, IL-10 is a potent inhibitor of Th1-, monocyte-, and macrophage-derived cytokines (19). In addition, IL-10 attenuates the surface expression of TNF-α receptors (6, 12). The finding that plasma CRP was higher 16 h postinfusion than after 3 h demonstrates a prolonged anti-inflammatory effect of the rhIL-6 infusion. CRP and other acute-phase proteins are anti-inflammatory and immunosuppressive mediators (32). Moreover, in in vivo models, CRP can inhibit polymorphonuclear (PMN) leukocyte infiltration (11) and attenuate vascular injury induced by stimulated PMN leukocytes (1). In an in vitro model (10), CRP inhibits intracellular calcium mobilization and superoxide production by alveolar macrophages.

The IL-6-induced increase in plasma cortisol is in agreement with previous findings (3, 31); therefore, the increase in circulating neutrophils found in this study is likely to be caused by the increase in plasma cortisol. Cortisol increases the circulating pool of neutrophils by inhibiting their ability to bind to the endothelial membrane (5) and to infiltrate into the tissue. Hence, the increased neutrophil number during rhIL-6 infusion is a sign of anti-inflammatory cortisol action. Exercise increases circulating neutrophils to a similar extent (29). It is therefore likely that muscle-derived IL-6 mediates this effect. A small decrease in the circulating pool of lymphocytes toward the end of rhIL-6 infusion supports the observation that the late lymphopenia seen during the recovery from exercise (29) may also be caused by IL-6. Exercise-induced disappearance of type 1 cytokine-producing cells from the circulation (28) may be related to elevated levels of IL-10. Also, the plasma IL-1ra and IL-10 increases seen during exercise (21) are likely to be mediated by IL-6.

In conclusion, this study demonstrates that physiological concentrations of IL-6 induce an anti-inflammatory rather than a proinflammatory response in humans and that IL-6, independently of TNF-α, enhances the levels not only of IL-1ra but also of IL-10. Furthermore, IL-6 stimulates cortisol release and thus produces neutrocytosis and lymphopenia of the same magnitude and pattern as are seen during intense exercise. This suggests that muscle-derived IL-6, in addition to its metabolic effects, plays a key role in exercise-induced leukocyte trafficking.

DISCLOSURES

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