

Exercise and IL-6 infusion inhibit endotoxin-induced TNF- α production in humans¹

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SPECIFIC AIMS

We hypothesized that IL-6 acts to decrease the production of TNF- α , and given that IL-6 is produced during physical exercise, we further suggested that exercise inhibits TNF production. Thus, the aim of the present study was to determine whether rhIL-6 infusion and physical exercise would inhibit the production of TNF induced by low-grade endotoxemia in humans.

PRINCIPAL FINDINGS

1. Physical exercise and rhIL-6 infusion inhibits endotoxin-induced increase in plasma-TNF- α

To test the hypotheses that IL-6 as well as physical exercise inhibits TNF production, eight healthy males participated in three experiments where they either rested (CON), performed bicycling at 75% of their VO₂ max for 3 h (EX), or were infused with recombinant human IL-6 for 3 h while they rested (rhIL-6). CON and EX were performed in a randomized order, followed by rhIL-6. After 2.5 h the volunteers received a bolus of *Escherichia coli* lipopolysaccharide endotoxin (0.06 ng/kg) i.v. in order to establish a model of low-grade inflammation, which would increase plasma TNF- α concentrations within the normal physiological range. It appears from Fig. 1 that plasma TNF- α differed significantly between groups: exercise vs. rest (ANOVA time \times group $P < 0.0001$) and IL-6 infusion vs. rest (ANOVA time \times group, $P = 0.0001$). In CON, endotoxin administration induced a significant increase in plasma TNF- α concentration (0.0001) (Fig. 1).

2. IL-6 concentrations in the three experiments

IL-6 increased ($P < 0.01$) 10-fold in CON (Fig. 2). Before the endotoxin infusion, plasma levels of IL-6 increased ($P < 0.01$) 19- and 48-fold in EX and rhIL-6, respectively (Fig. 2).

3. Low-dose endotoxin infusion does not induce severe adverse effects and does not induce tolerance

Subjects reported a slight feeling of coldness in their hands in all trials but reported no other side effects. There were no changes in body temperature. To test for possible intolerance to endotoxemia, we conducted pilot work where we administered an identical bolus of endotoxin on 4 separate days without any intervention. There was no difference between the TNF- α levels at the four trials, demonstrating that endotoxin did not induce tolerance. Plasma catecholamines increased in the exercise experiment only (data not shown).

CONCLUSIONS

This study demonstrates that physical exercise inhibits the production of TNF- α elicited by low-grade endotoxemia in humans. We also demonstrate that rhIL-6 infusion at physiological concentrations inhibits endotoxemia-mediated TNF- α production.

The increase in plasma IL-6 was greater in rhIL-6 than Ex (Fig. 2). Nonetheless, the circulating levels of IL-6 were still at a physiological concentration during rhIL-6, since we have observed plasma IL-6 concentrations to be > 100 pg \cdot mL⁻¹ during some forms of strenuous exercise. These findings therefore suggest that exercise-induced IL-6 production may help mediate the effect of exercise on endotoxin-induced TNF- α production. However, other mediators may contribute to the anti-inflammatory effects of exercise. Exercise induces high levels of epinephrine, and epinephrine infusion has been shown to blunt the appearance of TNF- α in response to endotoxin in vivo. Epinephrine infusion induces only a small increase in IL-6, and the mechanism whereby epinephrine inhibits TNF- α production is not clear.

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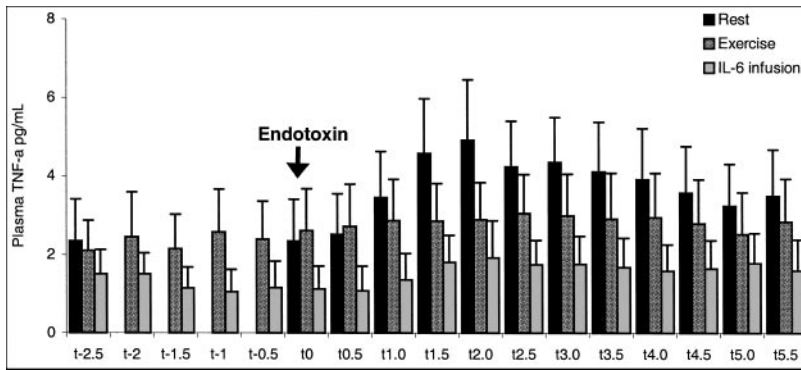


Figure 1. Changes in plasma concentration of tumor necrosis factor α (TNF- α) after i.v. bolus of *E. coli* endotoxin (0.06 ng/kg of body weight) in the same subjects at rest (black bars) during 3 h of ergometer cycling (stippled bars) or during i.v. infusion of interleukin recombinant human IL-6 (gray bars). Means with SE are shown. *P* values for repeated measurements ANOVA are shown.

Although it has been shown that the mobilization of monocytes during exercise is catecholamine dependent, it has been demonstrated that in exercise, monocytes are not the source of IL-6. Therefore, the TNF- α suppressing effect of epinephrine is not likely to involve IL-6. On the other hand, the effect of IL-6 on endotoxin-induced TNF- α production is not catecholamine dependent. During the IL-6 infusion experiment, plasma catecholamines did not change. Thus, epinephrine and IL-6 inhibit the endotoxin-induced appearance of TNF- α via independent mechanisms.

In general, the plasma cytokines found after exercise suggest that exercise induces a strong anti-inflammatory effect. However, the present data provide the first experimental evidence that physical activity exhibits anti-inflammatory activity and may provide a mechanism as to why physical exercise either reduces the susceptibility to or improves the symptoms of diseases associated with low-grade inflammation such as type 2 diabetes and atherosclerosis.

A recent study demonstrated that IL-6-deficient mice develop mature-onset obesity and insulin resistance, which was reversed by administration of IL-6. Thus, the latter study clearly shows that lack of IL-6 (and not the opposite) causes insulin resistance. Given that TNF- α induces insulin resistance, the present findings suggest that exercise may enhance insulin sensitivity through suppression of TNF- α production (Fig. 3).

In summary, our finding that IL-6 infusion inhibits TNF- α production in a human in vivo model implies that IL-6 should be classified as a true anti-inflammatory cytokine as previously suggested. Because exercise increased plasma IL-6 and blunted the endotoxemia-induced increase in TNF- α in a manner similar to that of rhIL-6 infusion, our data provide evidence that exercise is mediating anti-inflammatory activity, and suggest one mechanism as to the beneficial effects of exercise in the treatment of diseases associated with low-grade inflammation. FJ

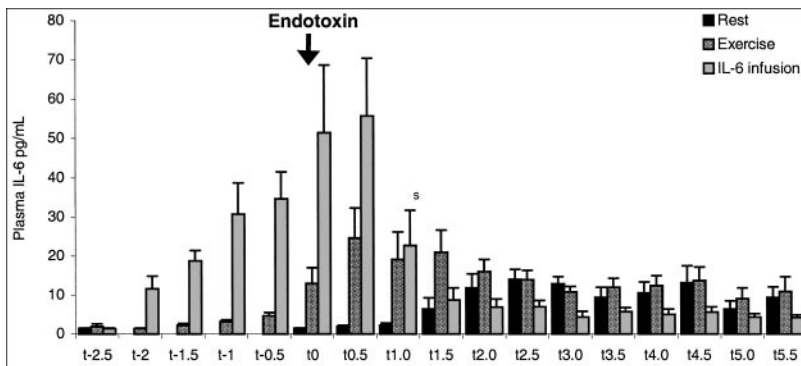


Figure 2. Changes in plasma concentration of IL-6 after i.v. bolus of *E. coli* endotoxin (0.06 ng/kg of body weight) in the same subjects at rest (black bars) during 3 h of ergometer cycling (stippled bars) or during i.v. infusion of interleukin recombinant human IL-6 (gray bars). Means with SE are shown. *P* values for repeated measurements ANOVA are shown.

Figure 3. Schematic diagram depicting production and release of IL-6 from contracting skeletal muscle. The figure illustrates our finding that IL-6 and muscle work inhibit endotoxin-induced TNF production and further illustrates our hypothesis that IL-6 may inhibit TNF-induced insulin resistance and atherosclerosis.

