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Effect of Exercise on Cytokines and Growth Mediators in Prepubertal Children

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ABSTRACT

Many of the anabolic effects of exercise are mediated through insulin-like growth factor-I (IGF-I), but in adolescents, brief exercise training leads to reductions, rather than the expected increase, in circulating IGF-I. Certain cytokines—interleukin-(IL) 1β (IL-1β), IL-6 (IL-6), and tumor necrosis factor-α—are increased by exercise in adults and are known to inhibit IGF-I. To test the hypothesis that these cytokines might play a role in the adaptation to exercise, we measured the acute effects of exercise on selected cytokines and growth factors in 17 healthy 8- to 11-y-old children (4 females). Designed to mimic patterns and intensity of exercise found in the real lives of American children, the exercise protocol consisted of a 1.5-h soccer practice (of which about 40 min constituted of vigorous exercise). Pre- and postexercise urine and saliva samples were obtained in all subjects and both blood and urine in nine subjects. The exercise led to significant increases in circulating tumor necrosis factor-α (18 $\pm$ 7%, $p < 0.05$) and IL-6 (125 $\pm$ 35%, $p < 0.01$) as well as a significant increase in the antiinflammatory cytokine IL-1 receptor antagonist (33 $\pm$ 10%, $p < 0.01$). Urine levels of IL-6 were also substantially increased by exercise (440 $\pm$ 137%, $p < 0.0001$). Circulating levels of IGF-I were reduced to a small but significant degree ($-6.4 \pm 3.2\%$, $p < 0.05$), although IGF-binding protein-1 (known to inhibit IGF-I) was substantially increased (156 $\pm$ 40%, $p < 0.001$). Cytokines are systemically increased after relatively brief exercise in healthy children. This increase may alter critical anabolic agents such as IGF-I and its binding proteins. (***Pediatr Res* 46: 429–434, 1999**)

Abbreviations

c.v., coefficient of variation
IGF-I, insulin-like growth factor-I
IGFBP-1, IGF binding protein-1
IL, interleukin
IL-1ra, IL-1 receptor antagonist
TNF-α, tumor necrosis factor-α

Physical activity is mechanistically linked to anabolic function through the GH-IGF-I axis (GH→IGF-I), a system of growth mediators, receptors, and binding proteins that control somatic and tissue growth in many species (1). Indeed, cross-sectional data from this and other laboratories demonstrate that fitter adolescents and adults have increased GH pulsatility and/or increased circulating IGF-I levels (2–5). Thus, it was surprising to find in a series of prospective studies performed in adolescent males (6) and females (5) that although 5 wk of endurance-type exercise training led to significant increases in muscle mass and cardiorespiratory fitness without any loss in body weight, the training led to decreases, rather than the expected increases, in circulating IGF-I. The data suggested that the initial endocrine response was more consistent with a catabolic, rather than anabolic, adaptation.

The mechanism for this seeming paradox is not yet known. One possibility involves exercise-associated stimulation of specific inflammatory cytokines, namely, IL-1β, IL-6, and TNF-α. The cytokines are a family of low-molecular weight, cell-to-cell mediators that regulate many immune and inflammatory responses (7). IL-1β, IL-6, and TNF-α lower systemic IGF-I levels in a number of ways and may attenuate IGF-I growth effects by increasing levels of those IGF binding proteins that inhibit IGF-I bioactivity (*e.g.* IGFBP-1) (8–13). Previous studies of very strenuous exercise in adult subjects have demonstrated robust increases in the circulating levels of IL-1β, IL-6, and TNF-α (14–19), but whether or not brief bouts of exercise in children similarly affected systemic levels of these inflammatory cytokines had not been previously examined.

Thus, as a first step in identifying a potential mechanistic role for inflammatory cytokines in the IGF-I inhibition associated with exercise training, we hypothesized that relatively brief, real-life exercise would lead to substantial increases in systemic levels of IL-1β, IL-6, and TNF-α. Although it is

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recognized that circulating levels of inflammatory mediators do not necessarily reflect tissue responses, finding an exercise associated increase in circulating cytokines would provide impetus for further studies focused on the source and physiologic effects of these agents.

Factors that stimulate *pro*inflammatory cytokines (*e.g.* TNF-α or IL-6) often elevate antiinflammatory cytokines as well. Accordingly, we examined the effect of exercise on prototypical antiinflammatory cytokines IL-1ra, IL-4, and IL-10. In addition, because cytokine effects are profoundly influenced by catecholamines and corticosteroids (20), we measured the effect of exercise on systemic cortisol (from both the circulation and saliva) and circulating levels of epinephrine and norepinephrine. Finally, because the feasibility of studies in children is enhanced when the least invasive approaches are used, we studied the cytokines response to exercise in urine as well as blood samples.

METHODS

Subject population. Seventeen healthy, nonobese 8- to 11-y-old children (4 females) volunteered to participate in this study. Mean age was 9.7 ± 0.2 y, weight was 33.4 ± 1.3 kg, and height was 142.9 ± 1.6 cm and the subjects were all Tanner 1–2 by history. The protocol was approved by the UCI Institutional Review Board and informed consent as well as ascent were obtained. No subjects were on chronic medication or had taken antiinflammatory agents on the day of the exercise test. All subjects agreed to provide urine and saliva samples immediately before and after the exercise protocol, and nine provided both urine and blood samples pre- and postexercise.

Protocol. The exercise session was designed to mimic a real-life exercise paradigm such as might be encountered in daily activities of the children. To accomplish this, we arranged a 1.5-h soccer practice modeled after typical sessions of this sport which is currently very popular in the community. The soccer practice was coached by one of the UCI team coaches who also had particular experience in working with children. The experimental goal was for the subjects to engage in approximately 40–50 min of vigorous aerobic-type exercise over the 1.5-h period. During the soccer practice, there were many water breaks and brief rest periods, first, to ensure adequate hydration and second, to reflect the intensity and tempo of this type of activity typically found in the community. Heart rate was measured every 15 min in each subject.

The children were instructed to have a light breakfast on the morning of the test, and after this, the participants reported to the laboratory at 0900 h. Urine, saliva, and blood samples were obtained and the subjects proceeded to the soccer practice (on site and adjacent to the Clinical Research Center). After the 1.5-h practice, the subjects jogged back to the Clinical Center where urine, saliva, and blood samples were obtained. There was approximately a 5- to 15-min interval between the end of the jog and the time that the urine, saliva, and blood samples were obtained.

We recognized that this delay introduced a certain confounding factor in our ability to measure known, rapidly changing biochemical markers of exercise intensity such as lactate or catecholamines. However, we believed that at this stage of hypothesis testing it was critical to determine whether or not a cytokine effect could be measured in the types of activities likely to be encountered in the real lives of children. The idea of children engaging in a soccer practice with indwelling catheters (which might have allowed more frequent blood sampling) was not believed to be acceptable.

Blood and urine samples. All blood samples were collected in prechilled Vacutainer tubes via venipuncture with a 21-g "butterfly" blood collection set (Vacutainer, Becton-Dickinson, Franklin Lakes, NJ). Each blood collection tube used contained the appropriate anticoagulant for each variable measured. All tubes were inverted several times and stored on ice until centrifuged at 3000 × *g* for 15 min at 4°C. Aliquots of the resulting plasma were stored at −80°C until analyzed. Urine samples were collected into sterile specimen cups and were placed on ice until the aliquot was frozen at −80°C.

Plasma lactate. Plasma lactate was measured in duplicate, via enzymatic techniques (model 2300stat glucose/L-lactate analyzer, Yellow Springs Instruments, Inc., Yellow Springs, OH). The lactate intra-assay c.v. was 1.7% and the sensitivity was 0.1 mmol/L.

Hematocrit. A capillary tube sample of blood was spun at 3000 rpm for 3 min and the hematocrit was determined in conventional fashion.

IGF-I and IGFBP-1. IGF was extracted from IGFBPs using the acid-ethanol extraction method (21). IGF-I serum concentrations were determined by a two-site immunoradiometric assay using the DSL-5600 Active kit (Diagnostic System Laboratories, Inc., Webster, TX). IGF-I interassay c.v. was 3.7–8.2% and intraassay c.v. was 1.5–3.4%. Assay sensitivity was 0.8 ng/mL.

IGFBP-1 was measured by coated-tube Immunoradiometric Assays (Diagnostic System Laboratories Inc.). Interassay c.v. was 1.7–6.7% and intraassay c.v. was 2–4%. Assay sensitivity was 0.11 ng/mL.

Catecholamines. Blood samples for catecholamines were collected in prechilled tubes, separated in a refrigerated centrifuge, and the plasma stored at −80°C until assay. Epinephrine and norepinephrine were determined by radioenzymatic assay (22). The intra- and interassay coefficients of variation for this assay are 6.5 and 11%, respectively.

Cytokines. We used ELISA kits from R&D Systems (Minneapolis, MN) for all of the cytokine measurements. For TNF-α interassay c.v. was 7.8–10.4%; intraassay c.v. was 5.6–6.1%; and assay sensitivity was 0.180 pg/mL. For IL-6 interassay c.v. was 7.1–29.5%; intraassay c.v. was 3.8–11.1%; and assay sensitivity was 0.094 pg/mL. For IL-1β interassay c.v. was 5.3–9.0%; intraassay c.v. was 1.6–4.0%; and assay sensitivity was 0.059 pg/mL. For IL-1ra, interassay c.v. was 4.4–6.7%; intraassay c.v. was 3.1–6.2%; and assay sensitivity was 22 pg/mL. For IL-4, interassay c.v. was 5.8–10.8%; intraassay c.v. was 4.6–10.1%; and assay sensitivity was 0[illegible] pg/mL. For IL-10 interassay c.v. was 8.1–15.6%; intraassay c.v. was 7.9–13.0%; and assay sensitivity was 0.5 pg/mL.

We measured cytokines in the urine using the above methods. To normalize for changes in urine concentration, cytokine values were normalized to creatinine as has been done by a

number of previous investigators (18). Urine creatinine was measured via colorimetric determination (Sigma Chemical Co. Diagnostics, St. Louis, MO) (23).

Cortisol. Blood samples were collected preand postexercise in 9 subjects and saliva samples in all 17 subjects for subsequent analysis of cortisol. Salivary samples were collected into salivettes (Sarstedt, Sparks, NV). Salivary and serum cortisol levels were determined by a commercial RIA (Diagnostic Products Corporation, Los Angeles, CA). The intra- and interassay coefficients of variation for this assay are 3.2 and 6.8%, respectively.

Statistical analysis. The data were analyzed via planned comparison repeated measures t tests and Pearson product moment correlations. α was set at 0.05. Data are reported as mean ± SE. Standard linear regression techniques were used to quantify correlation coefficients between saliva, blood, and urine levels of cortisol and selected cytokines.

RESULTS

Cardiorespiratory effects of the soccer practice. All 17 subjects completed the 1.5-h practice. Mean HR was 134 ± 4 beats/min during the exercise protocol. Lactate increased by 24.9%, but this did not achieve statistical significance. There was no significant effect of exercise on hematocrit.

Serum growth factors, cytokines (Fig. 1), catecholamines, and cortisol. Significant increases for TNF-α (from the mean preexercise value of 2.50 ± 0.18 pg/mL to the mean postexercise value of 2.88 ± 0.16 pg/mL, $p < 0.05$) and IL-6 (from 1.69 ± 0.34 to 3.24 ± 0.56 pg/mL, $p < 0.01$) were observed (Fig. 1). No significant change was noted for IL-1β (from 2.60 ± 0.86 to 2.00 ± 0.78 pg/mL). There was a significant increase in the antiinflammatory cytokine, IL-1ra (from 233 ± 18 to 298 ± 13 pg/mL, $p < 0.01$). No changes were noted in the antiinflammatory cytokines IL-4 (from 0.13 ± 0.05 to 0.14 ± 0.04 pg/mL, NS) or IL-10 (from 1.91 ± 0.38 to 1.83 ± 0.39 ng/mL, NS). The soccer practice was associated with a small but consistent and significant decrease (−6.4 ± 3.2%) in IGF-I (from 172 ± 26 to 161 ± 25 ng/mL, $p < 0.05$) and a substantial and significant increase (156 ± 40%) in IGFBP-1 (from 57 ± 10 to 124 ± 12 ng/mL, $p < 0.001$).

No significant changes were found in cortisol levels using either salivary (from 0.17 ± 0.09 to 0.22 ± 0.17 μg/dL, NS) or serum (from 8.87 ± 1.54 to 9.79 ± 2.68 μg/dL, NS) measurements. There was a significant correlation between the salivary and serum cortisol levels both pre- and postexercise ($r = 0.97$, $p < 0.001$, and $r = 0.99$, $p < 0.001$, respectively). There was no significant effect of exercise on circulating epinephrine (from 54.37 ± 5.15 to 82.42 ± 14.26, NS) or norepinephrine (from 364.70 ± 36.05 to 380.53 ± 31.26, NS).

Urine levels (Fig. 1). Substantial exercise increases in urine IL-6 (from 60.9 ± 14.8 to 157.9 ± 27.5 pg/mg, $p < 0.001$, all subjects) were observed (Fig. 1). As noted, these data were normalized to urine creatinine levels, and the significant changes were found despite the fact that urine creatinine tended to increase, reflecting the expected increased urine concentration that occurs with exercise. No significant change was observed in TNF-α (24.2 ± 3.15 to 30.18 ± 7.5 pg/mg, NS) or in IL-1ra (from 38, 379 ± 6409 to 58, 460 ± 14, 889 pg/mg, NS).

In the nine subjects who provided both urine and blood samples, we correlated measured levels of cytokines from both sources. There were no significant correlations observed for any of the pro- or antiinflammatory cytokines measured.

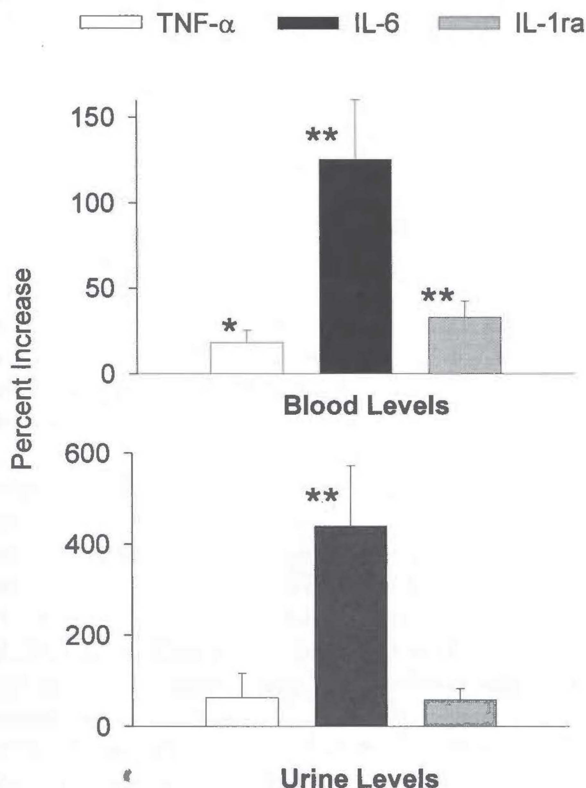

Figure 1. Effect of a soccer practice-type exercise protocol on serum ($n = 9$) and urine ($n = 17$) TNF-α, IL-6, and IL-1ra. Data are expressed as the mean ± SE percent change of each variable. In serum, there were significant elevations in all three of these cytokines with exercise, the most robust response observed for the inflammatory cytokine IL-6. In the urine, a statistically significant and quite substantial response was found for IL-6 alone. (*$p < 0.05$, **$p < 0.01$).

DISCUSSION

This study demonstrates that a substantial increase in systemic inflammatory cytokines occurs in response to vigorous exercise likely to be encountered in daily life activities of many American children. Moreover, the exercise session also led to small but significant reductions in IGF-I and a large increase in IGFBP-1, one of the IGFBPs known to inhibit IGF function. This constellation of findings, namely, a reduced IGF-I and increased IL-6, TNF-α, and IGFBP-1, is also seen when catabolic states are induced by disease such as trauma or burns (24–29). Our data suggest, therefore, that even a relatively brief bout of vigorous exercise in healthy children initiates a hormonal response suggestive of a catabolic environment.

The exercise-associated elevation of these inflammatory cytokines in healthy children may not reflect solely deleterious or catabolic physiologic processes. For example, angiogenesis is one of the most important (and arguably most long lasting) of the known tissue adaptations to exercise, and the capillary response to exercise training appears to be greatest in younger

animals (30). Although the mechanisms of this response in the muscle are not yet fully elucidated, it is clear that vascular growth factors such as fibroblast growth factor-2 and vascular endothelial growth factor are involved (31). Vascular endothelial growth factor, in turn, is stimulated by IL-6 (32). Thus, exercise-associated activation of certain inflammatory cytokines might play an important, and potentially beneficial, role in the adaptation to exercise.

Research into the mechanism and source of the increase in exercise-associated circulating cytokines is still in an early phase. Fielding and coworkers (33) demonstrated increased intramuscular IL-1β immediately after and 5 days after eccentric exercise [*eccentric* exercise occurs when the muscle lengthens although activated; frank muscle injury often occurs with eccentric exercise (34)]. More recently Rohde *et al.* (14), Bruunsgaard *et al.* (17), and Ostrowski *et al.* (19) showed that IL-6 was released specifically from the exercising muscle. In contrast, Papanicolaou *et al.* (35) suggested that the increase in IL-6 postexercise is mediated systemically by catecholamines (which also increase substantially with exercise). The importance of the roles of interacting exercise-associated factors such as hypoxia-reperfusion and oxidative stress, which occur during exercise (36) and can contribute to inflammatory cytokine production (37–39), is not currently known either in adults or in children.

Heavy exercise typically leads to large increases in catecholamines and lactate, and to smaller, but still significant, increases in cortisol in both adults and children. We did not find these increases in our study focused on prepubertal children. For the catecholamines and lactate, the reason may simply be that the clearance of these substances from the systemic circulation is known to be quite rapid. The interval in our study between the end of exercise and blood sampling (about 10–20 min) may have been sufficiently long so that postexercise values of both lactate and catecholamines had begun to return to baseline values. In addition, we speculate that the stop-start nature of the exercise may have enhanced lactate clearance and attenuated the subsequent catecholamine response to each subsequent individual exercise bout. It is noteworthy that systemic, exercise-associated increases of TNF-α and IL-6 may last longer than traditional markers of exercise intensity such as lactate.

Del Corral *et al.* (40) studied salivary and serum cortisol levels in response to 30 min of constant work rate exercise equivalent to 70% of the peak VO_2 in children. They found significant increases in cortisol of roughly 40% by 15 min of exercise that persisted through 15 min postexercise. Although statistical significance was not achieved for salivary cortisol levels, the salivary values in the del Corral study did correlate with serum levels—an observation similar to the one made in our study. In our study, evaluation of pre- and postexercise cortisol levels is confounded due to its diurnal variation. It could be argued, for example, that the fact that we did *not* detect the expected reduction in cortisol levels, *i.e.* between sampling at 0900 h and almost 1200 h, indicates an exercise stimulation of cortisol. A study involving more frequent blood sampling (not feasible in the type of field experiment presented here) and a nonexercising control group will be necessary to more fully determine the acute interaction between exercise associated cytokines and adrenocortical responses.

As noted, inflammatory cytokines do inhibit IGF-I production and stimulate IGFBP-1 (10, 13). We found that vigorous exercise led to significant reductions in IGF-I and an increase in one of its antagonistic binding proteins IGFBP-1. IGFBP-1 levels are known to be inversely correlated with levels of insulin (41). However, previous studies in adults have demonstrated that prolonged heavy exercise leads to reductions in IGF-I and to large, acute increases in IGFBP-1 (42–44), which do not appear to be related to either insulin or glucose levels (not measured in our study).

The mechanism of rapid changes in circulating IGF-I with exercise observed by a number of investigators is not readily apparent (45, 46). In our study, we only measured total IGF-I, but factors such as alterations in bound and unbound ("free") portions of the circulating IGF-I pool could play a role in the observed decrease in IGF-I. Acute exercise in adults is associated with increased IGFBP-3 proteolysis (47), and this could lead to a relatively larger pool of unbound IGF-I. Because unbound IGF-I is more rapidly cleared from the circulation levels of total IGF-I would decrease. The acute effects of exercise on bound and unbound IGF-I or on IGFBP-3 proteolysis have not been studied in children.

We found no effect of acute exercise on antiinflammatory cytokines IL-4 and IL-10, but there was a significant increase in systemic levels of IL-1ra. The latter is a novel member of the cytokine family in that it occupies IL-1 cellular receptor sites but without subsequent signal transduction (48, 49). IL-1ra is stimulated by other cytokines and various bacterial and viral antigens. The mechanism for the elevation of IL-1ra in response to exercise is not clear; however, the IL-1ra increase may reflect an earlier, undetected increase in the inflammatory cytokine IL-1β. Whether or not IL-1ra plays a physiologic role in the acute adjustment or long-term adaptation to exercise has yet to be determined. We believe that this is the first study to show that IL-1ra acutely increases with exercise in children. This is an intriguing finding because both IL-1 and IL-1ra may play a role in bronchial asthma (50, 51), and exercise-induced wheezing is found in the vast majority of patients with childhood asthma (52).

Only a few investigators have studied the effect of exercise on urine cytokines, and all studies done to date have been in adult populations. In adults, IL-6 levels are detectable in the urine and elevated after exercise (53). TNF-α has been shown to increase with exercise in some, but not all, investigations (18). Our data show that urine values for IL-6 showed large increases after exercise. This was qualitatively similar to the serum IL-6 changes, but there was no significant correlation of the magnitude of the change between the two sample sources.

It is noteworthy that the increase in urine concentrations of IL-6 was greater than that observed in the serum. This is not entirely surprising—cytokines are cleared from the systemic circulation into the urine "pool," thus, the cytokine concentration in the urine reflects the integral of cytokine transfer during the interval between the pre- and postexercise voids. It is quite possible that circulating cytokine levels were higher during the

soccer practice than they were when sampled in the postexercise period. Perhaps, these earlier, higher levels in the blood are reflected as higher concentrations in the urine in the immediate postexercise period. Our data do suggest that sampling from urine may, under the right experimental circumstances, serve as a reasonable alternative to blood sampling when attempting to determine the qualitative IL-6 response to exercise in children.

Although the role of cytokines as pathologic mediators has been studied in children, little is known about the maturation of these agents in healthy individuals. Lilic and coworkers (54) recently demonstrated marked differences in cytokine production between children and adults. Using peripheral blood mononuclear cells and *in vitro* cytokine production, these investigators noted that cytokine production was decreased in children compared with adults. The authors suggested that this maturational difference might explain the increased susceptibility to infection recognized in children. Children, like adults, respond to brief exercise with cytokine-associated alterations in immune function characterized by transient leukocytosis, lymphocytosis, and increases in NK cell number and activity (55–57). This, along with the robust IL-6 response reported here, indicates a potential role for exercise as a minimally invasive approach to gauge maturational as well as gender determinants of cytokine and immune responsiveness.

In summary, we demonstrated large increases in inflammatory cytokines IL-6 and TNF-α and the antiinflammatory cytokine IL-1ra after field-type exercise in children. The IL-6 effects were clearly seen in both urine and blood samples. There was a simultaneous decrease in circulating IGF-I and an increase in IGFBP-1. This relatively brief exercise bout in healthy children led to a constellation of findings—increased inflammatory cytokines and reduced IGF-I—typically seen in catabolic states associated with trauma, burns, and sepsis. It is possible that exercise-associated inflammatory cytokine release explains, in part, the reduced IGF-I levels consistently seen after 5 wk of exercise training in healthy adolescents.

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