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Reduced exercise-associated response of the GH-IGF-I axis and catecholamines in obese children and adolescents

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THE EMERGING EPIDEMIC OF PEDIATRIC obesity has complex, poorly understood causes (40) and represents a substantial challenge for the long-term health and well-being of children. Many of the detrimental health effects of obesity can be traced to a low-level, chronic inflammatory state, the result of adipocyte cytokine production in the body’s fat stores (8). Many of these adipose-derived mediators have been related to alterations in catecholamines, glucocorticoids, insulin, and growth hormone (GH) (28). Consequently, an increased understanding of the mechanisms that control body composition will be essential to optimally “re-balance” energy intake and expenditure in today’s children and adolescents.

Of particular importance are the ways in which obesity alters the hormonal response to physical activity, a major factor in the distribution of fat and lean tissue in adults and children (27). GH and other elements of the GH→IGF-I axis, key regulators of fat and lean tissue, are markedly sensitive to brief bouts of physical activity and to fitness in general (12). Previous adult studies (19, 45) suggested that the GH response to brief exercise may be attenuated by obesity, but little is known about the effect of obesity on the response of other elements of the GH→IGF-I axis to exercise in general and in particular in adolescents and children in whom the GH→IGF-I activity changes rapidly. It has been suggested that the exercise-associated GH attenuation in adults results from impaired catecholamine response (45). However, whether obesity in otherwise healthy children and adolescents depresses the GH→IGF-I axis by a general central mechanism, or, alternatively, the defect is neuroadrenergic and mediated by a blunted catecholamine responses, is not known.

We hypothesized that, in response to exercise, obese children would have both reduced GH→IGF-I axis and impaired neuroadrenergic function. To test this, we compared the effect of acute exercise in healthy obese and normal-weight children and adolescents on 1) circulating mediators of the GH→IGF-I axis, namely, GH, GH binding protein (GHBp) (the extracellular domain of the GH receptor), total and free IGF-I, and IGF binding proteins (IGFBP)-1 to -4; and 2) circulating mediators of the neuroadrenergic response to exercise, namely, epinephrine (Epi), norepinephrine (NE), and dopamine. In addition, we measured physiological responses to exercise [e.g., peak heart rate, respiratory exchange ratio (RER), and lactate levels] to ensure that the exercise input was comparable in the two groups. This is important because differences in the relative intensity of the exercise input can confound the critical hormonal outcome variables. Finally, because both GH→IGF-I axis hormones and catecholamines play a role in glucose homeostasis during exercise (45), and because obesity is associated with hyperinsulinism, we also measured circulating levels of both glucose and insulin.

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MATERIALS AND METHODS

Subjects

Fifty participants (age range 8–17 yr; 26 girls, 24 boys) were recruited by the University of California Irvine Pediatric Exercise Research Center to participate in this study (Table 1). Twenty-five participants were obese [body mass index (BMI) > 95%], and 25 subjects had BMI percentiles within the normal range (3.5 to 77.8). Individuals participating in competitive sports and individuals with history of any chronic medical conditions or chronic use of any medications were excluded from participation. The Institutional Review Board at the University of California Irvine approved the study. Written, informed assent was obtained from all participants, and their parents gave written consent upon enrollment.

Anthropometric Measurements

Standard, calibrated scales and stadiometers were used to determine height, body mass, and BMI. Since BMI changes with age during normal growth in children, we calculated BMI percentile for each child using the recently published standards from the Centers for Disease Control, National Center for Health Statistics (22). Maturity of the study participants was assessed by a validated self-administered questionnaire that has been widely used as a noninvasive indicator of pubertal status (33, 36).

Body Composition Assessment by Dual-energy X-ray Absorptiometry

Since BMI does not measure lean body mass and does not invariably correlate with fat mass (17), body composition was also measured by dual-energy X-ray absorptiometry (DEXA) using the Hologic QDR 4500 densitometer (Hologic, Bedford, MA). Subjects were scanned in light clothing, while lying flat on their backs. DEXA scans were performed and analyzed using pediatric software. On the days of each test, the DEXA instrument was calibrated using the procedures provided by the manufacturer.

Measurement of Fitness

Each subject performed a cycle ergometer ramp-type progressive exercise test to the limit of his or her tolerance. Subjects were encouraged during the high-intensity phases of the exercise protocol. Gas exchange was measured by breath, and the ventilatory threshold, aerobic threshold, and peak O2 uptake (V\text{O}_2) were calculated using a Sensor Medics metabolic system (7).

<table>
<thead>
<tr>
<th>Exercise Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise consisted of ten 2-min bouts of constant work rate cycle ergometry, with a 1-min rest interval between each of the 10 bouts of exercise. The work rate was individualized for each child and was calculated to be equivalent to the work rate corresponding to 50% between the ventilatory lactate threshold (as determined noninvasively from the ramp-type test) and the peak V\text{O}_2. We have used this protocol in the past to ensure that the exercise input was standardized to physiological indicators of each subject’s exercise capacity (42). The total duration of the exercise session is 30 min (20-min cycling interspersed by 10-min resting).</td>
</tr>
</tbody>
</table>

Blood Sampling and Analysis

Morning (following an overnight fast) pre-, immediately post-, and 120-min postexercise (recovery) blood samples were drawn from an indwelling venous catheter that was inserted 30 min before the first blood draw. Blood samples were immediately spun at 3,000 rpm, at 4°C for 20 min. The serum was separated and stored at −80°C. All pre- and postexercise specimens from each individual were analyzed in the same batch by an experienced technician, who was blinded to the individual’s group (normal weight vs. obese) and to the order of samples.

| 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 3.3–4.5%, interassay CV was 5.5–12.9%, and the sensitivity was 0.03 ng/ml. |
| GHBP. GHB serum levels were measured using ELISA with the use of the DSL-10-4800 Active kit (Diagnostic System Laboratories). Intra-assay CV was 3.2–5.6%, and interassay CV was 5.0–8.0%, and assay sensitivity was 1.69 pmol/l. |
| IGFBP-1 was measured by a coated-tube immunoradiometric assay with the use of the DSL-10-7800 Active kit (Diagnostic System Laboratories). Intra-assay CV was 2–4%, and interassay CV was 1.7–6.7%. Assay sensitivity is 0.33 ng/ml. IGFBP-2 serum concentrations were determined by RIA with the use of the DSL-7100 kit (Diagnostic System Laboratories). Intra-assay CV was 4.7–8.5%, interassay CV was 7.2–7.4%, and the sensitivity was 0.5 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. IGFBP-4 serum concentrations were determined by ELISA with the use of the DSL-10-7300 Active kit (Diagnostic System Laboratories). Intra-assay CV was 2.8–6.4%, interassay CV was 2.3–6.7%, and the sensitivity was 1 ng/ml. |
| Lactate. Serum lactate was measured spectrophotometrically (YSI 1500, Yellow Springs, OH). Intra-assay CV was 2.8%, interassay CV was 3.5%, and the sensitivity was 0.2 mmol/l. |
| Glucose. Serum glucose levels were determined by YSI 2300 STAT Plus analyzer. The assay precision is ±2.0% or 2.5 mg/dl (the higher value of the two). |
| Insulin. Serum insulin 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. |
| Cortisol. Serum cortisol levels were determined by a commercial RIA (Diagnostic Products, Los Angeles, CA). The intra- and interassay CV for this assay were 3.2 and 6.8%, respectively. |

Table 1. Anthropometric characteristics of study participants

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Height, cm</th>
<th>BMI, kg/m²</th>
<th>BMI percentile</th>
<th>Body weight, kg</th>
<th>Body fat, %</th>
<th>Lean body mass, kg</th>
<th>V\text{O}_2peak, ml/kg·min⁻¹</th>
<th>V\text{O}<em>2peak, % \text{V}</em>\text{O}_2peak</th>
<th>LAT, ml/kg·min⁻¹</th>
<th>LAT, % V\text{O}_2peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.8±0.5</td>
<td>153.8±3.4</td>
<td>22.8±4.4</td>
<td>155.2±2.6</td>
<td>44.5±2.8</td>
<td>41.9±1.6</td>
<td>34.9±3.1</td>
<td>12.9±0.9</td>
<td>19.5±0.8</td>
<td>39.4±1.5</td>
<td></td>
</tr>
<tr>
<td>12.3±0.5</td>
<td>29.4±0.2</td>
<td>30.8±1.3</td>
<td>38.9±0.3</td>
<td>76.2±5.0</td>
<td>37.8±1.9</td>
<td>42.9±2.2</td>
<td>22.9±1.5</td>
<td>40.2±2.2</td>
<td>60.4±1.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. H, Hispanic; As, Asian; C, Caucasian; AA, African American; BMI, body mass index; V\text{O}_2peak, peak O2 uptake; LB, lean body mass; LAT, lactate threshold. *p ≤ 0.001, normal-weight vs. obese children.
**Anthropometric and Fitness Data**

Characteristics of the study participants are summarized in Table 1. Body weight, BMI, BMI percentile, body fat, and lean body mass were significantly higher in the obese children. Fitness as expressed by peak VO$_2$ normalized to body weight was significantly lower in the obese children. There were no differences between normal-weight and obese children in peak exercise heart rate, peak exercise serum lactate levels, and peak VO$_2$ normalized to lean body mass (Fig. 1). There was no difference in the RER between normal-weight and obese children (1.07 ± 0.01 vs. 1.09 ± 0.02 in normal-weight and obese participants, respectively).

**GH, GHBP, IGF-I, and IGFBP-3 and -4**

See Table 2 and Fig. 2. **Baseline.** GHBP was significantly greater in obese compared with normal-weight participants. No significant differences were noted at baseline for GH, total and free IGF-I, and IGFBP-3 and -4.

**Exercise.** GHBP was unchanged by exercise in both groups. GH increased significantly in both groups. However, the magnitude of the GH increase was significantly smaller in the obese children. Total IGF-I (but not free) increased significantly following exercise only in obese subjects. No significant exercise-induced change in IGFBP-3 and -4 was found between the groups.

Exercise-associated changes in GH levels were inversely correlated with BMI percentile and body fat. No significant correlations were found between the GH response to exercise and insulin or IGF-I levels (Table 3).

**Catecholamines**

See Table 2 and Fig. 3. **Baseline.** There were no significant baseline differences between the groups in Epi, NE, or dopamine levels.

Table 2. Effects of exercise on several circulating components of the GH-IGF-I axis and cortisol

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight (n = 25)</th>
<th>Obese (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Peak exercise</td>
</tr>
<tr>
<td>Free IGF-1, ng/ml</td>
<td>2.0±0.2</td>
<td>2.2±0.3</td>
</tr>
<tr>
<td>IGFBP-2, ng/ml</td>
<td>190.2±40.3*</td>
<td>211.8±42.8*</td>
</tr>
<tr>
<td>IGFBP-3, ng/ml</td>
<td>3,351.5±199.3</td>
<td>3,597.2±209.7</td>
</tr>
<tr>
<td>IGFBP-4, ng/ml</td>
<td>30.1±2.7</td>
<td>30.6±2.5</td>
</tr>
<tr>
<td>Cortisol, μU/ml</td>
<td>9.8±1.0</td>
<td>10.6±1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. IGFBP, IGF-binding protein. There were no significant effects of exercise on any of the measurements in both groups. *P < 0.05 for differences between normal-weight and obese children.
Epi and NE increased significantly in both obese and normal-weight subjects. However, the magnitude of the increase was significantly smaller in the obese subjects. While dopamine increased in the normal-weight children, no significant increase in dopamine was found in obese subjects.

There was a significant correlation between fitness and the exercise-associated changes in catecholamines (Table 3). There was an inverse correlation between BMI percentiles and percent body fat and the exercise-associated changes in catecholamines.

**Table 3. The relationship between anthropometric characteristics, fitness measures, and baseline insulin and IGF-I levels and exercise-associated changes in circulating GH and catecholamines**

<table>
<thead>
<tr>
<th></th>
<th>GH Changes</th>
<th></th>
<th>Dopamine Changes</th>
<th></th>
<th>Epinephrine Changes</th>
<th></th>
<th>Norepinephrine Changes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>−0.36</td>
<td>0.01</td>
<td>−0.28</td>
<td>0.048</td>
<td>−0.31</td>
<td>0.03</td>
<td>−0.29</td>
<td>0.043</td>
</tr>
<tr>
<td>%Body fat</td>
<td>−0.43</td>
<td>0.002</td>
<td>−0.46</td>
<td>0.0006</td>
<td>−0.49</td>
<td>0.0004</td>
<td>−0.43</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak VO₂/kg</td>
<td>0.28</td>
<td>0.048</td>
<td>0.31</td>
<td>0.03</td>
<td>0.42</td>
<td>0.003</td>
<td>0.47</td>
<td>0.0005</td>
</tr>
<tr>
<td>Peak VO₂/kg LBM</td>
<td>−0.09</td>
<td>NS</td>
<td>0.18</td>
<td>NS</td>
<td>0.5</td>
<td>0.0003</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin</td>
<td>−0.13</td>
<td>NS</td>
<td>−0.18</td>
<td>NS</td>
<td>−0.16</td>
<td>NS</td>
<td>−0.06</td>
<td>NS</td>
</tr>
<tr>
<td>IGF-I</td>
<td>0.03</td>
<td>NS</td>
<td>0.19</td>
<td>NS</td>
<td>0.07</td>
<td>NS</td>
<td>0.15</td>
<td>NS</td>
</tr>
</tbody>
</table>

GH, growth hormone; NS, not significant.
To our knowledge, there have been few studies of GH response to exercise in children (15, 39, 48) and none in which both key GH→IGF-I regulatory elements as well as neuroadrenergic factors were measured simultaneously. We found that both GH→IGF-I axis hormones and neuroadrenergic hormones were influenced by obesity, either at baseline and/or in response to exercise. The major finding of this study was that, in obese children and adolescents, the GH and catecholamine responses to exercise were substantially attenuated (Figs. 2 and 3).

This study highlighted a number of possible mechanisms for the observed blunted GH response to exercise in obese children. First, the lower GH response in the obese children, whose fitness levels are generally lower than normal-weight children (10), cannot be attributed to a smaller magnitude of the exercise stress. This is relevant because, when work is performed above the subject’s lactate anaerobic threshold (heavy exercise, as was done in the present study), relatively small changes in the exercise input can lead to large differences in the response of hormones like GH and catecholamines (14). The similar peak heart rate, RER, serum lactate levels, and peak $\dot{V}O_2$ normalized to lean body mass of the participants (Fig. 1) indicate that we were able to achieve virtually identical metabolic and cardiovascular responses in the maximal exercise test in the two groups. As a consequence, the relative intensity of the interval exercise session was also similar in the two groups.

Increased insulin levels and increased IGF-I levels have also been suggested as possible causes for the reduced GH response to exercise in obese individuals (19). The mechanism of these effects is not fully understood but could be related to downregulation of GH cellular receptors by insulin and IGF-I (23). Consistent with this, baseline insulin levels were significantly higher in the obese children in the present study. Moreover, insulin in obese subjects remained higher, even though insulin significantly decreased with exercise in both groups (Fig. 4), typically encountered with brief bouts of heavy exercise (31). However, there was no correlation between baseline insulin levels and the exercise-associated GH response. Along these lines, there is an inverse relationship between circulating levels of cortisol and GH (30), but cortisol was not different between the two groups at baseline and was not affected by exercise.

With regard to IGF-I, there was no significant difference in preexercise free or total IGF-I between normal-weight and obese subjects. IGF-I levels increased acutely with exercise in the obese subjects [by ~15%, an observation made in healthy subjects previously (4, 38)], although the increase in IGF-I in the normal-weight children was not significant. Similar to insulin, no correlations were found between IGF-I levels (total and free) and the change in the GH response to exercise. Collectively, the data suggest the possibility that the exercise-associated increase in circulating IGF-I levels could play a partial role in the blunted GH response observed in the obese children and adolescents.

In addition, our data do support the idea that the attenuated GH response to exercise is related to an obesity-associated generalized impairment of the adrenergic response to exercise, as was suggested by Vettor et al. (45). Although Epi and NE increased significantly in both the obese and control subjects, the magnitude of the increase was significantly lower in the obese children. While circulating dopamine increased in normal-weight children, no significant increase in dopamine was observed in obesity (Fig. 3). In addition, exercise-associated changes in GH levels were significantly correlated with changes in Epi.
Catecholamines are increased with heavy exercise, in part because of central nervous system mechanisms. Activation of the hypothalamic-pituitary axis and sympathetic-adrenal-medullary activation lead to Epi release from the adrenal medulla and NE and, to a lesser degree, dopamine release, from nerve endings into the circulation (32, 43). Thus exercise shares with other stresses (e.g., psychosocial) some common pathways, leading to increased catecholamine output (49). In addition, the catecholamine response to heavy exercise is further stimulated by systemic changes in acid-base balance and reduced oxygen availability to the working tissues (37).

Remarkably, the increase in circulating dopamine in response to exercise found in healthy children was absent in obese children and adolescents (Fig. 3). Previous studies have demonstrated an increase in circulating dopamine in response to cycle ergometer (29) and resistance exercise (21) in adults, as well as in healthy children (47). Whether the lack of a peripheral dopamine response in obesity is related to a systemic “dopamine deficit” (25, 46) or, alternatively, simply to less stimulation of the sympathetic system in response to exercise has yet to be determined.

There are growing data that blunting central neuroadrenergic pathways can simultaneously attenuate the GH and catecholamine arms of the global stress response. For example, Giordano et al. (16) showed that alprazolam (a benzodiazepine that activates GABA receptors in the brain) inhibited both the GH and catecholamine response to insulin-induced hypoglycemia, and previous studies have shown that benzodiazepines inhibit the catecholamine response to exercise as well (41). Reduced central dopaminergic tone could explain our findings in blunted catecholamines and GH in response to exercise in obese subjects. There are indirect data suggesting that dopamine-2 receptor gene may be abnormal in obese subjects (34), and this could lead to reduced central dopaminergic tone.

Intriguingly, we recently demonstrated a virtually identical pattern of blunted catecholamine responses to exercise in normal-weight children with attention deficit hyperactivity disorder (ADHD) (note: we did not measure GH) (47). Surprisingly, despite the common belief that children with ADHD are physically hyperactive during early childhood, and therefore leaner, Holtkamp et al. (18) demonstrated that the prevalence of obesity in children with ADHD is, in fact, higher compared with the normal population. Similarly, Agranat-Meged and coworkers (1) recently discovered a comorbidity between childhood obesity and ADHD among a subset of children hospitalized for treatment of refractory morbid obesity. They suggested that “…obese children should be screened for ADHD.” Recently, it was shown that the presence of dopamine-4 receptor gene, a variant associated with decreased affinity to dopamine, was higher in obese women who had ADHD, suggesting a genetic linkage between the two common medical conditions (24). The mechanisms responsible for the potential link between childhood obesity and altered neuroadrenergic responses remain unknown.

There were no differences in the response to exercise of the other components of the GH-IGF-I axis that we chose to measure (i.e., GHBP, IGF-I, free IGF-I, and IGFBP-3). Several investigators [e.g., Kanaley and coworkers (19)] speculated that the beneficial effects of exercise in obese subjects might be limited due to the suppressed GH response to exercise. However, it is now well established that many of the health effects of exercise training are mediated by IGF-I and are GH independent (11, 50). Despite the reduced GH response to exercise in obese subjects, levels of total IGF-I did not differ between the two groups (perhaps because of significantly greater GHBP), and IGF-I increased significantly with exercise only in the obese subjects. Thus the attenuated GH response to exercise in obesity appears to be compensated by other hormonal mechanisms. These results also suggest that a limited effect of exercise interventions might be found in a subgroup of obese children with low baseline IGF-I levels and low IGF-I response to exercise [such as seen, for example, in obese children with Prader-Willi syndrome (44)]. This group may possibly benefit from an intensive therapy of both exercise and exogenous GH.

We also found marked effects of obesity on circulating IGFBP-1 and -2. These binding proteins are elevated in catabolic states, tend to antagonize IGF-I physiological function, and contribute to the bioavailability of IGF-I in tissues (35). Circulating levels of both IGFBP-1 and -2 are inversely related to insulin levels, and, consequently, have been found to be low in obese adults and children (2, 3, 12), consistent with our data. Insulin levels decreased following exercise; thus we expected that both IGFBP-1 and -2 would increase. In fact, IGFBP-2 was not significantly affected by exercise, whereas IGFBP-1 significantly decreased (concomitantly with insulin) in both groups. Why the exercise responses for both insulin and IGFBP-1 were parallel and not inverse in the present study is not clear.

As noted, pre- and postexercise insulin levels were significantly elevated in the obese children. The combination of hyperinsulinemia with suppressed GH and catecholamine responses, both counterregulatory hormones, could potentially set the stage for increased risk of hypoglycemia during and after exercise. In fact, none of the participants in our study developed hypoglycemia. Apparently, the counterregulatory hormonal response to hypoglycemia is sufficiently robust and redundant in obese children such that hypoglycemia does not occur in response to exercise, despite the increased glucose demand and the attenuated GH and catecholamine responses.

In conclusion, in response to a metabolically matched exercise input, the GH response to exercise was reduced in obese children and adolescents. This likely resulted in part from changes in IGF-I levels and from baseline hyperinsulinemia found in the obese subjects. In addition, the reduced Epi and NE and the absent dopamine response to exercise in obese subjects suggested the possibility of a centrally mediated attenuation of hypothalamic-pituitary-adrenal axis and/or sympathetic adrenal-medullary function. It is possible that the blunted GH and catecholamine response to exercise leads to reduced carbohydrate and fat utilization during exercise (5, 6) and, as a result, to a greater protein utilization (26). Consistent with this, previous studies have demonstrated that elevated BMI was associated with a reduced training effect in children and adolescents, following a prolonged resistance training intervention (13).

The reduced GH and catecholamine responses to exercise were compensated for such that hypoglycemia did not occur with exercise, despite increased insulin levels in the obese children and adolescents. Thus these results support the use of exercise, even vigorous exercise, as part of the treatment regimen for obese children. Further studies are needed to clarify the mechanistic role of IGF-I, hyperinsulinemia, and the
reduced catecholamine response (in particularly dopamine) for the diminished exercise-associated GH response and the extent to which these hormonal abnormalities persist after weight loss and/or exercise training programs in obese children and adolescents.

REFERENCES


