Effects of arginine/lysine supplementation and resistance training on glucose tolerance

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GATER, DAVID R., DENISE A. GATER, JORGE M. URIBE, AND JOY C. BUNT. Effects of arginine/lysine supplementation and resistance training on glucose tolerance. J. Appl. Physiol. 72(4): 1279-1284, 1992.—The purpose of this study was to evaluate and compare the effects of arginine/lysine supplementation (AL) and resistance training (RT) on changes in glucose tolerance and to determine whether alterations were associated with changes in selected hormonal parameters. The study involved 30 physically active college males, ages 20–30 yr, randomly assigned to one of four groups: placebo/control (P/C, n = 7), P/RT (n = 8), AL/C (n = 7), or AL/RT (n = 8). An AL supplement at a daily morning dose of 132 mg/kg fat-free body mass or placebo was administered orally to controls and training groups. During the 10-wk program, exercise subjects participated in a progressive resistance training program stressing all major muscle groups. Three-hour oral glucose tolerance (OGT) tests were performed on each subject before and after the 10-wk intervention to evaluate resting levels and responses of glucose, insulin, and glucagon. OGT parameters did not significantly change after intervention. It was concluded that neither AL supplementation nor RT had a significant effect on OGT.

Once released, hGH can have a number of effects on the body, including growth of tissues and organs through enhanced protein synthesis and glucoregulatory actions. The mechanism by which protein synthesis is triggered within skeletal muscle may involve hGH and/or its messenger IGF-1, which is released from the liver; there is evidence to suggest that both mechanisms have a role (13). Crist et al. (7) demonstrated significant increases in fat-free weight and decreased percent body fat in resistance training (RT) subjects treated with exogenous growth hormone for 6 wk. Growth hormone has also been demonstrated to have diabetogenic actions in animals (1, 5, 18) and in humans (27, 28). It appears that hGH can cause insulin resistance by impairing both the ability of insulin to suppress glucose production and its ability to stimulate glucose utilization, probably at a postreceptor site (27, 28). Chronic elevation of hGH can result in elevated blood glucose levels and hyperinsulinemia. The implied beneficial effects derived from amino acid-induced hGH release may therefore be countered by the detrimental consequences of its diabetogenic effects. Additionally, specific amino acids (particularly arginine) have also been demonstrated to enhance the release of insulin and glucagon (22, 23). Chronic release of these hormones may decrease the sensitivity of their target cells, further compromising glucose tolerance.

Physical activity has been directly correlated with favorable effects on insulin action and/or oral glucose tolerance (OGT) in both endurance (3, 9, 12) and RT athletes (20, 31). It has been hypothesized that increased muscle mass and decreased fat weight, because it would occur after RT, contribute to favorable alterations in glucose tolerance (30).

The purpose of this project was to assess changes in OGT consequent to chronic ingestion of the amino acids arginine and lysine vs. a placebo during a 10-wk period with or without RT. In addition, relationships between glucose tolerance changes and selected hormonal parameters were examined. It was hypothesized that AL supplementation would impair glucose tolerance independent of training status, although to a lesser extent in RT individuals.

METHODS

Experimental Design

Thirty college males (aged 20–30 yr) were recruited and randomly assigned to one of four groups arranged in...
a 2 × 2 factorial design to investigate the effects of RT and arginine/lysine (AL) supplementation on OGT over a 10-wk period. Supplement was provided in double-blind fashion; groups 1 and 2 received a cornstarch placebo while groups 3 and 4 ingested equal amounts of AL (purity > 99.6%) provided by Sigma Chemical. Each morning, subjects drank an oral preparation consisting of 66 mg of each amino acid · kg fat-free body-1 · day-1 or 132 mg cornstarch · kg fat-free body-1 · day-1 diluted in water. Doses were based on pilot studies indicating gastric intolerance at higher levels. Groups 2 and 4 completed a 10-wk RT program, while groups 1 and 3 served as controls (C).

Subjects

To participate, subjects were required to meet specified ranges for body weight (72.5–86.0 kg) and body fat (9–18%) determined from hydrostatic weighing. Nutritional status for the previous 3 mo was assessed by a computer-scanned food frequency questionnaire developed by the University of Arizona Cancer Research Center. All subjects were required to have maintained stable body weight and to have met criteria for percent carbohydrate, fat, and protein components of diet within established guidelines (40–60, 25–40, and 10–20%, respectively). Previous nutritional status information was necessary to avoid recruiting subjects who had been on extreme diets. Subjects also completed food and activity records 1 day/wk for the duration of the study and provided feedback for diet modification. Final criteria required subjects to have had some RT experience, but no formal RT program was to have been implemented for the 3 mo before the study. In addition, any subject with a history of orthopedic injury, diabetes, or renal disease was excluded from the study. A Human Subjects Consent Form approved by the University of Arizona Human Subjects Review Board was signed by each subject before any testing. Of 39 subjects assigned to a group, 9 failed to complete the study, resulting in a 25% drop-out rate. Descriptive characteristics of the remaining subjects are listed in Table 1.

Protocols

Strength parameters, body composition assessment, IGF-1 levels, and the RT protocol have been described previously (11). The effectiveness of the RT program was comparable to that of previous studies (6, 20), as indicated by similar changes in strength parameters and body composition.

Glucose tolerance. Each subject performed an OGT test before and after the 10-wk interventions. Dietary information was collected before the initial OGT test and similar diets were encouraged for the 48 h before the final OGT test; dietary carbohydrate during this time was not recorded. After a 12-h fast, an indwelling catheter with an intravenous saline drip was placed in an antecubital vein between 0700 and 1000. Blood samples (5 ml) were taken at rest, and at 30, 60, 90, 120, and 180 min after the oral ingestion of 100 g glucose in 10 oz of solution to evaluate the responses of plasma glucose, insulin, and glucagon. Posttesting was performed 48 h after the last RT workout and AL supplement.

Plasma Analyses

All subjects had fasting 10-ml blood samples collected from an antecubital vein between 0700 and 1000 before and after the 10-wk training or control period. The blood was collected with the appropriate preservatives and immediately placed on ice; serum was harvested within 1 h and stored at −20°C until assayed. Samples for different assays (including hormonal) were aliquotted to reduce freezing and rethawing.

Glucose. Blood was collected into capillary tubes and immediately analyzed for blood glucose concentration with an automated glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH). A known volume of blood was injected into a collection chamber within the analyzer, which is adjacent to a glucose probe. The corresponding reading was adjusted for hematocrit to yield plasma glucose concentration.

Endocrine. Resting values for insulin and glucagon were measured pre- and posttreatment, and areas under the curves (AUC) were determined by the trapezium rule. Hormonal profiles were determined with radioimmunoassay techniques (RIA). Single-antibody kits (Diagnostic Products Corporation) were used for determination of insulin. Double-antibody kits were used for determination of glucagon (Diagnostic Products). Intra-assay variability for insulin and glucagon ranged from 0.8 to 24.9% and 0.9 to 21.9%, respectively, while interassay variation was 17.1 and 13.0%, respectively. Each assay consisted of a mixture of complete data sets of subjects from different groups. Radioactive levels of 125I for hormonal assays were counted in an LKB Clini-Gamma Counter. Standard curves, using the spline method, and hormone concentrations were calculated with an LKB computer software program.

Statistics

A 2 × 2 factorial experimental design was used to assess the effects of supplementation and RT. Dependent

### Table 1. Descriptive characteristics of groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Pre Weight, kg</th>
<th>Pre % Body Fat</th>
<th>Pre FFB Mass, kg</th>
<th>Pre Total Strength, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/C</td>
<td>7</td>
<td>21.4±0.6</td>
<td>178.8±2.3</td>
<td>76.7±0.5</td>
<td>17.1±1.0</td>
<td>63.6±1.2</td>
<td>318.0±20.2</td>
</tr>
<tr>
<td>P/RT</td>
<td>8</td>
<td>21.4±0.8</td>
<td>177.6±1.7</td>
<td>76.0±2.0</td>
<td>17.8±0.9</td>
<td>62.4±1.3</td>
<td>335.2±17.7</td>
</tr>
<tr>
<td>AL/C</td>
<td>7</td>
<td>23.7±1.2</td>
<td>183.6±2.1</td>
<td>75.5±1.3</td>
<td>14.1±1.4</td>
<td>64.9±1.8 *</td>
<td>312.4±13.2</td>
</tr>
<tr>
<td>AL/RT</td>
<td>8</td>
<td>23.2±0.9</td>
<td>177.5±1.2</td>
<td>72.9±1.6</td>
<td>17.8±1.5</td>
<td>59.8±1.0 *</td>
<td>306.6±11.1</td>
</tr>
</tbody>
</table>

Values are preintervention means ± SE; n, no. of subjects. FFB, fat-free body; P, placebo; C, control; RT, resistance training; AL, arginine/lysine. * Between-group difference, P < 0.05.
variables for assessing glucose tolerance included resting levels and AUCs of glucose, insulin, glucagon, and insulin-to-glucagon ratios (I/G). Analysis of variance was used for comparisons within and between groups. Multiple regression was used to determine to what extent RT and supplementation contributed to observed variability in OGT. Specifically, pre- and posttreatment values, as well as the absolute changes, were assessed for the dependent variables representing these physiological parameters. Percent changes were evaluated if pretreatment values were statistically different. In addition, relationships (zero order and partial correlations) among values and changes in fat-free body (FFB) mass, hormonal, and metabolic variables were evaluated.

RESULTS

Descriptive Characteristics

Initial values for age, height, weight, percent body fat, and FFB weight were similar between all groups, although the AL/RT group had significantly less FFB mass than did the AL/C group (Table 1).

Dietary Profiles

Prestudy dietary profiles (Table 2) were not statistically different between groups except that the AL/RT group had a lower percentage of carbohydrate and higher percentage of protein in its diet than did the P/C group. The AL/C group also had a greater percentage of protein in its diet than did the P/C group. Caloric intake and diet composition during the study were corrected to include the respective supplement taken by each group. Caloric intake during the study was similar between groups and remained isocaloric to prestudy determinations. Diet composition remained similar within groups, except that AL/RT significantly (P < 0.05) increased percent protein. P/C was significantly (P < 0.05) different from both AL/C and AL/RT in absolute carbohydrate and protein consumed; P/RT was also significantly lower in percent protein consumed than AL/RT.

Resting Plasma Profiles

Initial resting glucose levels were similar between groups, and no significant differences were found in resting glucose within or between groups after the 10-wk intervention. Although resting insulin was initially similar between groups, it significantly (P < 0.05) increased in the P/RT after the intervention, which led to a significant (P < 0.05) difference between P/RT and AL/RT in postresting insulin levels. Initial glucagon levels at rest were similar and did not significantly change within or between groups after intervention. Basal I/G was similar between groups; however, postresting I/G was significantly (P < 0.05) higher in the P/RT than in the AL/RT group, although no significant within-group changes were seen.

Glucose Tolerance Parameters

Glucose tolerance was evaluated by the responses of glucose, insulin, glucagon, and I/G ratio after a glucose challenge (Figs. 1-3). Changes in AUCs for each of these variables were also compared among groups. Initial glucose, insulin, and I/G AUCs were similar between groups and did not significantly differ within or between groups after intervention. Glucagon AUC was also similar between groups before intervention; however, after the 10-wk study, significant (P < 0.05) within-group increases were seen for P/C, AL/C, and P/RT, although this did not lead to significant between-group differences.

Prediction of OGT

Potentially significant predictor variables (including training status, supplement status, and dietary, body composition, and endocrine parameters) for evaluating glucose tolerance were tested using multiple regression. The strongest predictor of absolute change in glucose
AUC was absolute change in glucagon AUC, accounting for 12.2% (P < 0.05) of the variability. Although the interaction of training and supplement status was the next strongest predictor of absolute change in glucose AUC, it was not significant (P < 0.08). No significant predictors were found for absolute change in insulin, glucagon, or I/G AUCs.

**DISCUSSION**

Arginine infusion has been shown to stimulate the release of hGH from the anterior pituitary (8, 17, 19, 21, 24). When given in combination with lysine, oral administration of arginine has also been demonstrated to enhance acutely hGH release (14). Glucose tolerance may be impaired through chronic elevation of hGH (27, 28), which causes insulin resistance, presumably at a postreceptor site. Conversely, RT has been demonstrated to increase insulin sensitivity, increase muscle mass, and decrease fat weight (20, 30). Subjects receiving AL supplements with or without RT in the present study were expected to reflect these mechanisms by increasing basal levels and AUCs for glucose, insulin, and, to a lesser extent, glucagon in response to a glucose challenge after the 10-wk intervention. However, no significant within- or between-group changes in basal glucose or AUC were noted after the 10-wk intervention. Similar patterns were observed in the resting insulin and AUCs, except that P/RT significantly (P < 0.05) increased basal insulin after intervention, which made it significantly (P < 0.05) different from AL/RT. Furthermore, basal glucagon was not significantly different after the 10-wk intervention, and although glucagon AUCs increased (P < 0.05) within the P/C, P/RT, and AL/C groups, no significant between-group differences were noted. The results in the present study are somewhat surprising in lieu of past findings, which would suggest changes in glucose tolerance after these types of interventions. A number of factors may have contributed to these observations.

Although arginine administration has been demonstrated to increase hGH release when infused intrave-
ute to observed changes. The present study utilized ran-
dom assignment to exercise and C groups to overcome
this factor, with C groups given the opportunity to use
the RT protocol after the 10-wk study was completed to
maintain motivation. Care was taken to distinguish be-
tween acute and chronic exercise effects on glucose toler-
ance. Immediately after an acute bout of exercise, the
non-insulin-mediated glucose transport in skeletal mus-
cle is increased, augmenting the glucose transport that is
mediated by insulin (10, 15, 16). It has been demon-
strated that the residual effects of a single exercise bout
on glucose transport resolve within hours if carbohy-
drates are consumed but may persist for up to 48 h (16).
The present investigation allowed >48 h postexercise to
pass before measuring glucose tolerance, to minimize the
acute effects of exercise on glucose uptake.

Two cross-sectional studies have suggested relation-
ships between glucose tolerance parameters and body com-
position. Szczypaczewska et al. (20) found that body-
builders with lower percent body fat than C or obese sub-
jects had lower glucose and insulin responses to a 100-g
glucose challenge over 2 h. In comparing weight lifters,
rather, and C subjects, Yki-Jarvinen and Koivistio (31)
demonstrated a significant relationship ($r = 0.54, P<
0.01$) between percent muscle mass and glucose infused
to maintain euglycemia, an indicator of insulin sensitiv-
ity. Unfortunately, the cross-sectional design of these
studies allows for other extraneous variables, including
training status and diet, to contribute to observed differ-
ences.

Despite the random assignment to groups and double-
blind placebo design of the current study, differences in
diet composition were present between groups before
and during the treatment intervention. Diet composition
differences during the study were mostly a reflection of
supplement administration, as the amino acids were re-
corded as dietary protein. Although carbohydrate con-
tent in diet may affect OGT, all subjects consumed a
minimum 150 g carbohydrate each of the 3 days before
the OGT test, as recommended by the American Dia-
betes Association. Furthermore, no significant relation-
ship between diet and OGT parameters was determined by
multiple regression analysis.

Finally, group means did not significantly differ before
or after intervention; however, variability about the
mean was large. Because the number of subjects in each
group was relatively small (7 or 8), the study may not
have attained a statistical power sufficient to demon-
strate significant differences between groups. However,
previous studies with similar sample size and comparable
changes in strength and body composition were able to
demonstrate changes in tolerance after RT (6, 20, 31). No
previous studies examining the effects of AL supplemen-
tation on glucose tolerance have been noted in the litera-
ture.

In conclusion, neither AL supplementation nor RT
had a significant effect on glucose tolerance parameters
after 10 wk of intervention. Furthermore, it is unlikely
that the AL dose employed in this study significantly
altered hGH release, because IGF-1 levels failed to signif-
icantly increase, as reported elsewhere. Finally, although
previous studies have demonstrated relationships be-
tween glucose tolerance parameters and body composi-
tion, those studies failed to provide adequate controls to
eliminate the differential effects of extraneous variables.
The present study overcame these design flaws but was
unable to support the previously reported relationships
between RT and OGT parameters.

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