Oral arginine attenuates the growth hormone response to resistance exercise

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Collier, S. R., E. Collins, and J. A. Kanaley. Oral arginine attenuates the growth hormone response to resistance exercise. J Appl Physiol 101: 848–852, 2006. First published June 1, 2006; doi:10.1152/japplphysiol.00285.2006.—This study investigated the combined effect of resistance exercise and arginine ingestion on spontaneous growth hormone (GH) release. Eight healthy male subjects were studied randomly on four separate occasions [placebo, arginine (Arg), placebo + exercise (Ex), arginine + exercise (Arg + Ex)]. Subjects had blood sampled every 10 min for 3.5 h. After baseline sampling (30 min), subjects ingested a 7-g dose of arginine or placebo (blinded, randomly assigned). On the exercise days, the subject performed 3 sets of 9 exercises, 10 repetitions at 80% one-repetition maximum. Resting GH concentrations were similar on each study day. Integrated GH area under the curve was significantly higher on the Ex day (508.7 ± 169.6 min·ng/ml; P < 0.05) than on any of the other study days. Arg + Ex (260.5 ± 76.8 min·ng/ml) resulted in a greater response than the placebo day but not significantly greater than the Arg day. The GH half-life and half duration were not influenced by the stimulus administered. The GH secretory burst mass was larger, but not significantly, on the Arg, Ex, and Arg + Ex days than on the placebo day. Endogenous GH production rate (Ex > Arg + Ex > Arg > placebo) was greater on the Ex and Arg + Ex days than on the placebo day (P < 0.05) but there were no differences between the Ex and Arg + Ex days. Oral arginine alone (7 g) stimulated GH release, but a greater GH response was seen with exercise alone. The combined effect of arginine before exercise attenuates the GH response. Autonegative feedback possibly causes a refractory period such that when the two stimuli are presented there will be suppression of the somatotrope.

endocrine; somatotrope; resistance exercise

EXERCISE USUALLY EVOKES a large increase in growth hormone (GH) concentrations (13, 14, 22, 30, 32), and many believe that this increase in GH will promote gains in muscle mass and strength gains (5). Additionally, the intravenous infusion of arginine in men (1) and women (21) has shown dramatic increases in GH by 8- and 20-fold, respectively. Arginine has been shown to increase basal GH secretion by inhibiting endogenous somatostatin release (10), whereas the specific mechanism responsible for the exercise-induced GH release has not been elucidated. Moderate-intensity exercise may enhance cholinergic tone (11, 15), which may potentiate the GH response by suppressing hypothalamic secretion of somatostatin and enhancing the response to GH-releasing hormone (GHRH) (3, 26). During higher intensity exercise, augmented hypothalamic secretion of GHRH may occur in addition to suppression of hypothalamic somatostatin activity. If the exercise-induced GH release is preferentially mediated by somatostatin withdrawal and arginine works via a similar mechanism, then it is possible that neither exercise nor oral arginine results in complete somatostatin withdrawal. Thus, theoretically, arginine plus exercise should evoke an even larger GH increase. Supporting this hypothesis, a recent study (31) using a 30-g infusion of arginine administered 30 min before aerobic exercise (0800) resulted in an increased GH secretion compared with exercise alone.

However, the literature is not consistent concerning the GH response to exercise and oral arginine ingestion. One study found a 2.7-fold increase in GH concentrations after 1.5 g of arginine + 1.5 g of ornithine, but when combined with exercise the GH response was not higher than with exercise alone (25). Another study (9) has shown that ingestion of a combination of amino acids over several days during a weight training circuit workout did not enhance GH release in highly trained weight lifters. Furthermore, one report (18) noted a trend for a decrease in the GH response when arginine and exercise were combined. This response may be similar to the reduction of the GH response after repeated GHRH stimulation (2, 4), due to a downregulation of somatotropes (2, 4). Arginine may stimulate the GH secretion by inhibition of endogenous somatostatin release (10), but if the subsequent stimuli of exercise is too close together there may be autonegative feedback. These conflicting results between studies may be due to differences in methodology between the protocols, different exercise modes (resistance vs. aerobic exercise), or differences in the frequency of blood sampling.

The aim of this study was to ascertain whether the stimulatory influence of oral arginine ingestion on GH release would be enhanced by a subsequent bout of resistance exercise. We studied the impact of arginine (Arg) alone, exercise (Ex) alone, and arginine + exercise (Arg + Ex) on the GH response in young healthy male subjects in a randomized controlled study. This study assessed the contribution of an exogenous secretagogue on GH release, as well as the effect from exercise. Also, if exercise provided a further reduction of somatostatin, then one would have to assume that the somatostatin mechanism was not saturated (7) or that exercise worked through another mechanism.

METHODS

Study Subjects

Eight young male subjects (age 18–25 yr) volunteered to participate in this research study, and each signed an informed consent approved by the Institutional Review Boards of Syracuse University and SUNY Upstate Medical University (Syracuse, NY). All subjects were healthy, with no major chronic diseases such as diabetes, cardiovascular disease, atherosclerosis, hypertension, or dyslipidemia. Subjects were physically active, and most participated informally in resistance exercise training. All subjects were nonsmokers.

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Experimental Procedures

Subjects visited the Human Performance Laboratory at Syracuse University on five occasions. A medical history and a physical activity questionnaire were completed on the first visit. The subjects also had their one-repetition maximum (1 RM) measured for eight muscle groups. During visits 2–5, subjects were required to come to the Human Performance Laboratory for a 3.5-h period, and blood samples were drawn every 10 min. Using a randomized double-blind design for the placebo and arginine days, and a randomized administration of the exercise days, the subjects either had a placebo, Arg, placebo + Ex or Arg+Ex intervention. Dietary intake on the evening prior was noted, and subjects were asked not to change their dietary habits throughout the study and on the day before testing.

Resistance exercise. Subjects were initially tested for their 1 RM on the following exercises: lateral pulldown, leg extension, bench press, and back extension. On the subsequent study days with exercise, the subjects completed 3 sets of 10 repetitions at 80% of 1 RM. A 1.5-min rest interval with a small rest period is needed to stimulate a GH response. If a 1.5-min rest was given between each set, resulting in the exercise lasting 55 min to complete. If the subjects could not complete the full set, they were assisted by a spotter so each achieved 10 repetitions per set. This load and rest period were selected based on previous work by Kraemer and colleagues (16), who have shown that a high-intensity work interval with a small rest period is needed to stimulate a GH response.

Anthropometrics. Whole body air displacement plethysmography (Bod Pod, Life Measurement, Concord, CA) was used to assess body composition (8). Height and weight were measured using a stadiometer (to the nearest 0.5 cm) and a beam balance platform scale, respectively. Body mass index was calculated as weight (kg) divided by height (m) squared.

Study day. During visits 2–5, subjects came to the Human Performance Laboratory at 0700, after an overnight 12-h fast. A heparin lock was placed in the antecubital vein of the subject’s arm by a registered nurse and kept patent by a saline flush. Thirty minutes after the heparin lock was placed, blood samples were drawn every 10 min for the next 3.5 h. On all study days, after 30 min of taking resting blood samples, subjects ingested either a placebo or 7 g of arginine, which was encapsulated and has been shown previously to evoke a GH response (6). The l-arginine and the placebo were obtained through Eckerd Drug (Greenbush, NY). They floated and encapsulated the l-arginine or placebo into gel caps. On the exercise days, 30 min after arginine ingestion, the subjects completed 3 sets of the 10 resistance exercises. After the exercise, the subjects sat quietly as they did on the control day. Subjects were not allowed to sleep or eat during the recovery period.

Blood sampling and analysis. Blood was collected in a 5-ml EDTA tube, centrifuged, aliquoted, and frozen at a temperature of −80°C and later assayed for GH concentrations. Using a validated ultrasensitive (0.005 μg/l threshold) chemiluminescence-based assay (Nichols Institute Diagnostics, San Juan Capistrano, CA) (32), GH concentrations were determined in all samples in duplicate. This assay primarily detects the 22-kDa form of GH with a 4% cross-reactivity with 20-kDa GH. The intra- and interassay coefficients of variation for the assay were 6.7% and 7.8%, respectively. To avoid any changes in assay variability, all hormone samples of the four visits for each subject were analyzed in the same assay. All samples were run in duplicate.

Statistical Analysis

Calculation of the integrated GH hormone concentration [area under the curve (AUC)] was determined by the use of a trapezoidal method (version 2.01; GraphPad Prism, San Diego, CA) and is reported in absolute values (baseline hormone concentration: y = 0). To determine the quantitative estimates of attributes of GH secretion from the measured GH concentrations during the 3.5-h period, a multiple-parameter deconvolution method was employed. This method uses a validated two-component endogenous GH kinetics model (28) consisting of a rapid GH half-life of 3.5 min and a slow-phase GH half-life of 20.8 min. A fractional (slow/total) decay amplitude of 0.63 was used (28).

A one-way ANOVA with repeated measures was performed to examine the effects of the intervention on the GH concentrations. If a significant main effect was observed, a Tukey’s test was used for post hoc comparisons. The data are reported as means ± SE, and significance was determined at an α level of 0.05.

Sample size for the present study was based on previous data from our laboratory gathered under similar conditions. For these calculations, the STATA statistical software package was used (College Station, TX), and eight subjects were required to give us adequate statistical power at a P < 0.05. With relatively small sample size, rather large differences may not reach statistical significance and result in type II error with other secondary variables. Therefore, effect sizes (partial η², which represents the proportion of total variation attributable to the factor, partialing out other factors from the total nonerror variation) for deconvolution analysis variables are reported as an additional statistical parameter to aid the reader in interpretation of the findings.

RESULTS

The mean age of the subjects was 20.4 ± 1.2 yr, mean height was 179.2 ± 2.4 cm, and mean weight was 79.2 ± 3.0 kg. These subjects were not overweight and had a body mass index of 24.2 ± 0.7 kg/m². Their percent body fat was 17 ± 1.8%.

On all study days, there was no significant difference in the fasting GH concentrations before the stimuli being administered (placebo 0.17 ± 0.01, Arg 0.22 ± 0.03, Ex 0.38 ± 0.10, Arg+Ex 0.24 ± 0.06 μg/l). A typical pattern of response on each study day is shown in Fig. 1. Three of the subjects showed increases in GH levels between arginine ingestion and exercise, but only one subject had a significant peak in GH levels as determined by deconvolution analysis in this time period. Peak blood GH concentrations were found ~60 min after the arginine ingestion on both the Ex and Arg+Ex day and remained elevated until the end of exercise, at which point the blood concentrations decayed toward resting concentrations. On both study days, the GH concentrations were still slightly elevated at the end of the sampling period. The peak GH

![Graph](image-url)
concentrations on the Ex day (7.0 ± 1.9 μg/l) were greater than Arg+Ex (4.7 ± 1.3 μg/l), which was greater than Arg alone (3.5 ± 1.7 μg/l) and the placebo day (1.1 ± 1.7 μg/l). These data show that the peak serum GH concentrations were 222, 437, and 652% greater on the arginine, Arg+Ex, and Ex day compared with the placebo day. The peak serum concentrations were significantly greater than the placebo day on both the Arg + Ex and Ex days (P < 0.05). Figure 2 presents the data for the total integrated GH AUC for the 3 h postbaseline on each study day. The integrated AUC also revealed that the exercise day resulted in a greater GH response (P < 0.05) than was seen on the Arg + Ex day. This GH response was ~50% higher on the Ex day than the Arg + Ex day, and ~65% higher than on the Arg day.

Deconvolution analysis of the GH secretory responses is shown in Table 1. The basal GH secretion was similar on all study days. The calculated GH half-life was not influenced by the stimulus administered (η = 0.19), nor was the GH half duration (η = 0.12). The number of GH pulses were increased slightly with on the Arg + Ex day compared with the placebo day, but this increase was not significant (η = 0.12). The GH secretory pulse mass was larger on the Arg, Ex, and Arg+Ex days than the placebo day, but this was not significantly greater (η = 0.24). Similarly, the order of the magnitude of response for the endogenous GH production rate (Ex > Arg+Ex > Arg > placebo) was similar to that seen with the GH pulse mass (Fig. 2). Production rate was significantly greater on the Ex (14.2 ± 4.3 μg/l·4 h) and Arg+Ex (9.9 ± 3.6 μg/l·4 h) day than on the placebo day (2.7 ± 1.5 μg/l·4 h; P < 0.05), but there were no differences between these 2 study days. The GH secretory pulse amplitude was not found to be different by stimulus (η = 0.27).

**DISCUSSION**

Previous studies have shown that putative inhibitors of somatostatin outflow will suppress GH autonegative feedback, enhancing GH release (10, 23). One such inhibitor is L-arginine. The present study examined the combined effects of 7-g oral arginine ingestion and resistance exercise and demonstrated that oral arginine increases the GH levels acutely similar to our laboratory’s previous report (6) but that resistance exercise alone causes a greater GH response than arginine alone. In contrast to our hypothesis, Arg+Ex attenuated the GH response compared with Ex alone.

Earlier studies (6, 25) have reported that oral arginine ingestion induces a GH response, which is similar to studies using intravenous administration (1, 21, 31). In the present study, we found an ~115% increase in GH AUC with 7-g oral arginine, which was similar to our laboratory’s previous work (6). The absolute increase in GH levels was less than seen by Wideman and associates (31), but they utilized a larger and intravenous dose of arginine. In contrast, Ex alone resulted in a sixfold increase in GH levels compared with the twofold increase with Arg+Ex. Compared with Arg, Ex resulted in greater changes in the secretory characteristics, such that the GH production rate was ~40% greater and the pulse amplitude was ~60% greater on the Ex day with a slightly shorter GH secretory pulse half duration. Although the number of pulses, the mass of GH secreted per pulse, half life, and pulse amplitude were not significantly different from the Arg day, they would account for the dramatically greater AUC that was observed on the Ex day. The dramatic difference in the GH response between exercise and arginine ingestion may have been because of differences in the mechanism of GH release (6, 18, 29, 31) or because the exercise stimulus was much greater than the arginine stimulus.

The regulatory augmentation mechanism of arginine on GH release is by suppressing somatostatin (10). Although the regulatory control of GH release is well understood at rest, it is unclear during exercise. Some evidence has suggested that exercise works by the same mechanism as arginine and suppresses somatostatin release. More recently, however, using pyridostigmine, deVries et al. (7) have established that the exercise-induced GH response is not due to complete inhibition of hypothalamic somatostatin release but that exercise also stimulates other potentiating factors (e.g., GHRH or ghrelin). Other potential mechanisms that have been investigated are adrenergic and cholinergic stimulation, metabolic acidosis, and the metaboreflex (3, 12, 15, 19, 26, 29).

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**Table 1. Comparison of deconvolution GH variables between the 4 study day conditions**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Arginine</th>
<th>Exercise</th>
<th>Arginine + Exercise Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal GH secretion rate, μg/l·min⁻¹</td>
<td>0.068±0.002</td>
<td>0.070±0.002</td>
<td>0.057±0.002</td>
<td>0.076±0.004</td>
</tr>
<tr>
<td>GH half-life, min</td>
<td>12.7±1.5</td>
<td>13.4±2.1</td>
<td>18.3±2.4</td>
<td>13.6±1.3</td>
</tr>
<tr>
<td>GH secretory pulse half duration, min</td>
<td>18.7±2.3</td>
<td>28.9±6.9</td>
<td>23.6±7.2</td>
<td>33.3±7.5</td>
</tr>
<tr>
<td>GH secretory pulses per 4 h</td>
<td>1.8±0.7</td>
<td>1.4±0.4</td>
<td>2.3±0.5</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>GH secretory pulse mass, μg/l</td>
<td>1.0±0.4</td>
<td>9.2±6.6</td>
<td>10.2±3.4</td>
<td>10.7±4.0</td>
</tr>
<tr>
<td>GH production rate, μg/l·4 h</td>
<td>2.7±1.5</td>
<td>8.5±5.7</td>
<td>14.2±4.3*</td>
<td>9.9±3.6*</td>
</tr>
<tr>
<td>GH pulse amplitude, μg/l·min⁻¹</td>
<td>0.07±0.03</td>
<td>0.24±0.16</td>
<td>0.56±0.27</td>
<td>0.33±0.33</td>
</tr>
</tbody>
</table>

Values are means ± SE for subjects. GH, growth hormone. *P < 0.05 vs. placebo.
Both exercise and arginine are known to be clear stimulators of GH release independently in most individuals, but the research is unclear whether the combined effect of Arg+Ex potentiates the GH response. An earlier study (25) observed that the administered doses (1.5 g arginine + 1.5 g lysine) were adequate to stimulate a GH response on a nonexercise day but that ingestion immediately before exercise did not alter the exercise-induced GH response in young men, compared with exercise alone. Additionally, 4 days of a combined L-arginine, L-ornithine, and L-lysine supplementation (2 g/day) to weight lifters did not alter their 24-h GH levels compared with the placebo day (9). Subsequent work (18) also noted that 5 g of arginine alone increased the GH response but that in young subjects exercise caused the greatest increase in GH levels, with a tendency for a blunted GH response when arginine was combined with exercise. This blunting was not observed in older subjects, who had a much smaller GH response initially. Similarly, we observed an attenuated GH response when arginine and exercise were combined. In some of these earlier studies arginine was used in combination with other amino acids, so it was difficult to assess the impact of arginine alone. Furthermore, we used a higher dose than in the earlier studies because our laboratory’s previous work demonstrated at ~7 g of arginine was needed to get a definitive GH response (6). The present study is the first to demonstrate that an adequate dose of oral arginine can stimulate an almost threefold increase in GH levels in combination with exercise, but this was ~50% less than observed on the exercise alone day.

The diminished GH response with Arg+Ex compared with exercise alone may be due to a few possibilities. First there may be autonegative feedback on the somatotrope from the arginine ingestion. This suppressed response is in agreement with early work by Ghigo et al. (10), showing that repeated GHRH administration leads to a progressively decreasing somatotrope response (17, 20, 24), due to a receptor or postreceptor downregulation (10). Second, there is evidence that the somatotrope has a refractory period to repeated GHRH stimulation due to elicitation of an autonegative feedback likely mediated by enhanced release (17, 20, 24, 27). Possibly the decreased response to the exercise may have been due to the timing of the exercise after the ingestion of arginine. The exercise was initiated 30 min postingestion, and this may have been the time period where there was the strongest negative feedback on the somatotrope, resulting in a blunted response to the exercise. Our data support this because we found an increasing GH levels in five of the eight subjects before exercise. Although the specific mechanism of GH release is not known with exercise, it is believed to be similar to arginine with suppression of hypothalamic secretion of somatostatin.

Our finding of a blunted GH response with Arg+Ex is in contrast to those of Wideman et al. (31), who found an approximate doubling of GH secretory burst mass by arginine plus exercise vs. exercise after arginine bolus injection. They speculated that arginine infusion partially overcomes the β-adrenergic or other inhibition otherwise induced by exercise itself. This may have been the mechanism in the Wideman et al. study, which used 30 g of intravenous arginine 30 min before exercise. Speculatively, this may have overwhelmed the system such that the β-adrenergic stimuli from exercise was minimized. Our lower dose of oral arginine was selected because our laboratory’s earlier study (6), which found that higher doses caused gastrointestinal distress in a large percentage of subjects. With this lower dose it may allow the β-adrenergic stimuli to be more dominant. Additionally the route of administration is important to consider. Because intravenous administration does not rely on absorption rates, it is most likely that the intravenous arginine stimulates the hypothalamic-pituitary axis rapidly and started to clear this region thus minimizing the effect of autonegative feedback on a subsequent stimulus to the hypothalamus. Although our laboratory’s earlier work (6) indicated that in 30-min GH levels begin to increase, different rates of absorption may have resulted in a more prolonged stimulus to the hypothalamic-pituitary axis, which may have desensitized it to the subsequent exercise stimulus. Thus the route of arginine administration is very important when trying to establish the arginine effects on the hypothalamic-pituitary axis.

Much of the previous literature on arginine (1, 21, 31) has employed intravenous administration and has shown a large GH response, such that arginine infusion is now used as a provocative test for testing for GH release. Interpreting these intravenous data where large boluses of arginine were administered may be misleading when trying to compare results with oral arginine administration. Our findings demonstrate that both oral arginine ingestion alone (7 g) and intense resistance exercise stimulate GH release with a greater response from the exercise stimulus. The administration of oral arginine before exercise attenuates the GH response, suggesting that the exercise-induced GH release works through a different mechanism than arginine alone and that possibly the autonegative feedback causes a refractory period such that when the two stimuli are presented there will be a suppression of the somatotrope.

GRANTS

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