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Growth hormone responses to varying doses of oral arginine

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Abstract

Intravenous (IV) arginine invokes an increase in growth hormone (GH) concentrations, however, little is known about the impact of oral arginine ingestion on the GH response.

Objective: The purpose of this study was to determine the dose of oral arginine that elicits an optimal GH response and to determine the time course of the response.

Design: Eight healthy males (18–33 years – 24.8 ± 1.2 years) were studied on 4 separate occasions. Following an overnight fast at 0700 h, a catheter was placed in a forearm vein. Blood samples were taken every 10 min for 5 h. Thirty minutes after sampling was initiated, the subject ingested a dose of arginine (5, 9 or 13 g) or placebo (randomly assigned).

Results: Mean resting GH values for the placebo, 5, 9 and 13 g day were 0.76, 0.67, 2.0 and 0.79 μg/L ($n = 6$), respectively. Integrated area under the curve was not different with 13 g (197.8 ± 65.7 min μg/L), yet it increased with 5 and 9 g compared with the placebo (301.5 ± 74.6, 524.28 ± 82.9 and 186.04 ± 47.8 min μg/L, respectively, $P < 0.05$). Mean peak GH levels were 2.9 ± 0.69, 3.9 ± 0.85, 6.4 ± 1.3 and 4.73 ± 1.27 μg/L on each day for the placebo, 5, 9 and 13 g days.

Conclusion: In conclusion, 5 and 9 g of oral arginine caused a significant GH response. A 13 g dose of arginine resulted in considerable gastrointestinal distress in most subjects without augmentation in the GH response. The rise in GH concentration started ~30 min after ingestion and peaked ~60 min post ingestion.

Keywords: Growth hormone; Amino acids; Arginine

1. Introduction

Arginine is a semi-essential amino acid that serves many purposes in the human body. Intravenous (IV) studies consistently show a large GH response when an arginine bolus is introduced [1,2]. IV arginine administration is used clinically as a provocative test to establish GH deficiencies [2–4], and the doses used to stimulate GH release range from 2 to 40 g. Oral arginine, however, has been used primarily by the athletic population in efforts to enhance the exercise-induced GH response, yet little is known about the effects of oral arginine on GH release. Administration of oral arginine for 30 days has been shown to increase resting GH levels in postmenopausal women [5]. Acute administration of oral arginine has been reported to increase [6] or have no impact on GH secretion [7]. Previous research has administered doses ranging from 1.2 to 17 g/day [5–8], and has frequently used only one sample to determine GH levels. However, no studies have examined the impact of various doses of oral arginine on the GH response. Potentially, studies administering too small of a dose of arginine may not observe a true GH response or the changes in GH levels may have been missed because of inadequate sampling. Thus, understanding the dose of oral arginine that elicits a GH response and the time course of the metabolic response after ingestion could lead to future studies investigating correct supple-

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mentation strategies and combining it with exercise. Therefore, the purpose of this study was to investigate the dose–response relationship of oral arginine on the resting GH response using frequent blood sampling, and to determine the time to the start of the GH response and the time to peak GH levels.

2. Methods

Eight healthy young males (age 18–33 years) participated in this study and signed a consent approved by the Syracuse University Institutional Review Board. The mean height, weight, age, and body mass index (BMI) were 179.2 ± 2.4 cm, 78 ± 3 kg, 24.8 ± 1.2 years and 20.2 ± 0.7 kg/m^2, respectively. None of the subjects were taking any medications prior to and during the study, and all subjects were non-smokers.

Each subject reported to the Human Performance Laboratory on 4 occasions (placebo, 5, 9 and 13 g day). Subjects reported to the lab following an overnight fast at 0700 h. A heparin lock was placed in a forearm vein, and 30 min after the placement of the cannula, blood sampling began. Blood was sampled every 10 min for the next 5 h. Thirty minutes after the start of blood sampling, the subject drank a lemon juice mixture (8 drops of lemon juice) in 6 ounces of water with a predetermined dose of 5, 9 or 13 g of arginine (Experimental and Applied Sciences Incorporated, Golden, CO), or placebo added. The placebo was just the lemon juice and water. These trials were randomized and blinded. During the study, subjects remained awake and fasted, and could drink water ad libitum.

Blood was chilled and spun in a centrifuge at 1300 rpm for 15 min. The plasma was aliquotted and frozen at −80 °C until it was assayed. All samples from the same subjects were run in the same assay and in duplicate using a validated ultrasensitive (0.005 μg/L threshold) chemiluminescence-based assay (Nichols, San Juan Capistrano, CA, [9]). The chemiluminescent assay detects predominately the 22-kDa form of GH with a 34% cross-reactivity with 20-kDa GH. The intra-assay coefficient of variation (CV) for the GH assay was 7.9% and the interassay CV was 8.4%.

Statistics. A one-way ANOVA with repeated measures was employed to determine the effect of arginine dose on the GH response over time (SPSS v10.1, Chicago, IL). Integrated area under the curve (AUC) for the 5 h of sampling, peak values and the time of onset of the first peak was determined using Prism software (GraphPad 3, San Diego, CA). Baseline GH levels were determined by taking the mean values of the first 30 min of sampling (4 samples) prior to arginine ingestion. All data are expressed as mean ± SE, with an alpha level set at 0.05 a priori.

3. Results

The purpose of this study was to establish a dose response curve and a timeline after the ingested arginine elicits a GH response. For adequate absorption of oral arginine, it must be mechanically transported from the gut into the blood for a GH response to occur. Because the GH iAUC responses comprised a bimodal distribution, we categorized the subjects into those who had a GH response across provocations (responders) and those who did not (nonresponders). Two non-responders experienced GI distress on all study days except the placebo day, and these subjects had <25% of the group mean GH response. Therefore, the data analysis was conducted on six individuals. Resting GH concentrations on each study day were not different between the placebo, 5, 9 and 13 g day (0.76 ± 0.66, 0.67 ± 0.42, 2.0 ± 1.12 and 0.79 ± 0.73 μg/L, respectively) and were in the normal range. On the placebo day there were small changes in GH levels, which were in the normal range of variability for a fasted subject. Fig. 1(a) reveals the integrated area under the curve for each subject by study day. Most subjects showed an increased GH response with arginine ingestion, except on the 13 g day, as high doses of amino acids can cause GI distress due to the osmotic movement of water into the stomach and intestine [10]. On the 13 g day,

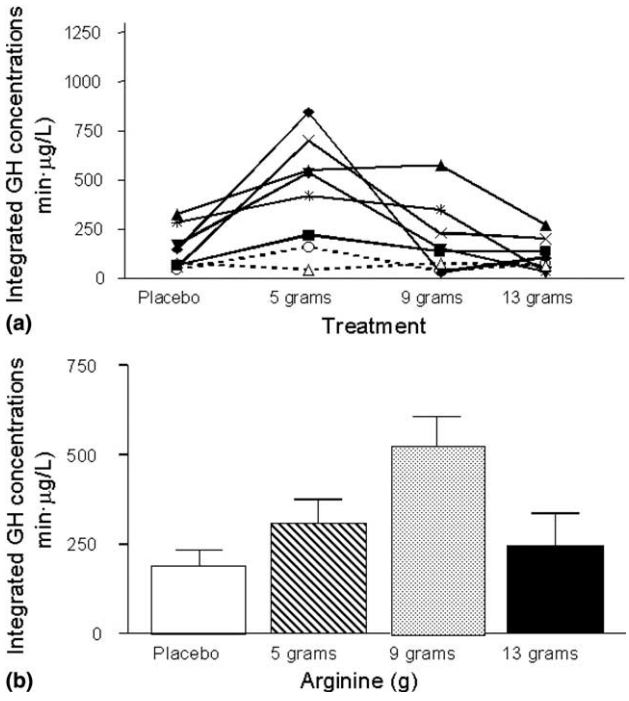

Fig. 1. (a) The integrated GH concentrations on each study day for each subject. The dashed lines represent the 2 subjects who were non-responders. The solid lines represent the 6 subjects included in the analysis. (b) The mean integrated GH concentrations on each study day. *$p < 0.05$ vs. placebo day, $n = 6$.

there was GI distress in all but 1 of our subjects and potentially much of the arginine was excreted before it was absorbed [11], thus on this day only a small change in GH was observed. A significant increase in the integrated AUC ($p < 0.05$) was observed on the 5 and 9 g days compared to the placebo day (Fig. 1(b)). The AUC for GH on the placebo day was 186 ± 47.8 min μg/L, compared to 301 ± 74.6 min μg/L on the 5 g day and 524 ± 82.9 min μg/L on the 9 g day ($p < 0.05$), with no significant difference in the GH response between the 5 and 9 g days. Peak GH concentrations were higher on the 5 g (3.9 ± 0.9 μg/L) and 9 g day (6.4 ± 1.3 μg/L) as compared the peak levels seen on the placebo day (2.9 ± 0.7 μg/L, $P < 0.05$). The time to the start of the GH rise was ~30 min after arginine ingestion, with peak GH levels at ~60 min post arginine consumption.

4. Discussion

Exogenous arginine administration elicits a profound GH response particularly when administered as an IV bolus (1,2,4), but a paucity of research has examined the effects of oral arginine on GH concentrations, and no studies have been conducted to establish if there is a dose response relationship. Our data indicated that 5 and 9 g of oral arginine results in a significant GH response compared to placebo, while 13 g of arginine had a substantially lesser effect. The rise in GH occurred at ~30 min after ingestion, with a peak in GH concentration ~60 min after ingestion.

Arginine is known to potentiate the maximal pituitary somatotroph responsiveness to GHRH, and increases GH release on the hypothalamic level by suppression of endogenous somatostatin release [2]. The trend for a progressively larger GH response with increasing arginine doses implies that an increased arginine concentration can be absorbed and carried in the bloodstream to the hypothalamus. Likewise, the pituitary must have the capability of not only suppressing somatostatin concentrations to varying degrees but to also release more GH with a greater arginine signal. Arginine administration resulted in a 45% greater GH response with 9 g than 5 g but this was not statistically significant. Thus the pituitary was capable of releasing more GH with the higher dose of arginine. Likewise using IV doses of 1/12, 1/6 and 1/4 g of arginine per pound of body weight, Merimee et al. [12] saw an increase in GH levels with each increasing dose. The lowest dose (1/12 g per pound body weight) had no significant increase in men but 1/6 g increased the GH levels and 1/4 g even further.

Consistent with previous literature we found an increase in GH levels with oral arginine. Blum et al. [5] reported a 72% increase in resting GH levels when 9 g of oral arginine was administered daily over a four-week period, and Isidori et al. [6] found ~6 μg/L increase in GH levels when 1.2 g of oral arginine was administered. In contrast IV arginine administration has been shown to result in more dramatic increases in GH concentrations. Wideman et al. [4] reported increases from ~2.4 to 32 μg/L when 30 g of arginine was infused over 30 min in men. Some studies [7] have reported no change in GH levels with oral arginine administration and other studies have shown that when used in combination with other amino acids, an even greater GH response is invoked [6]. A combination of arginine and lysine elicited an increase in plasma GH that was about 5× higher than arginine alone (63 μg/L vs. 10 g/L; lysine alone 7.8 μg/L). Possibly combining amino acids may be more effective in evoking a GH response because it ensures at least one amino acid will be absorbed and able to be transported to the hypothalamus.

Discrepancies between the studies in the GH responses reported are possibly due to the inclusion of 'non-responders' in the findings. In our study of 8 subjects, we identified two individuals who suffered substantial GI distress on every study day which is consistent with Blum and associates [5] who noted that in one of ten subjects had no increase in resting GH levels with 30 days of arginine use.

The previous research has focused on the intravenous administration of arginine, therefore the time course of the GH response in this study may not be consistent with previous studies. Studies using intravenous arginine [13,14] showed that doses larger than 30 g of intravenous arginine invoked a rise in GH levels in ~20 min. Similarly, we observed that a rise in GH occurred at ~30 min post-ingestion and that peak values were found ~60 min post-ingestion. Consistent with our findings, Isadori et al. [6] observed a GH peak at 30 and 60 min when administering 1.2 g of oral arginine in 15–20 year old males [6]. Further we observed that the time of increase in GH levels was not altered by arginine dose nor was the peak GH level. While intravenous introduction of the bolus is a faster method of introducing arginine into the bloodstream, oral arginine was only about 10 min slower at inducing the GH rise.

Aging has been associated with a decrease in muscle mass that is paralleled by a decrease in GH levels. Enhancing muscle mass has been associated with GH administration, therefore, potentially increasing GH levels with a supplement such as arginine may be beneficial [14]. To enhance performance, athletes are already trying to stimulate GH levels using arginine supplements in an attempt to increase GH, which may increase IGF-I levels and thus increase muscle mass. Our data indicates that oral arginine can result in a rise in GH levels, and the timing of this dose may be important. From our data, it was concluded that the initial rise in GH concentrations occurs at approximately 30 min after

arginine ingestion. Peak GH concentrations are then seen 30 min after the onset of the initial GH rise. This suggests that if used in combination with exercise, the exercise bout should commence 30 min after the arginine ingestion. Further both 5 and 9 g of oral arginine elicited a significant GH response in most individuals, but a high dose of oral arginine (13 g) may increase GH levels but there is an increased incidence of GI distress. It also needs to be noted that "non responders" to arginine ingestion do exist and will skew the results when examining the impact of oral arginine.

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