Growth Hormone Isoform Responses to GABA Ingestion at Rest and after Exercise

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ABSTRACT

POWERS, M. E., J. F. YARROW, S. C. MCCOY, and S. E. BORST. Growth Hormone Isoform Responses to GABA Ingestion at Rest and after Exercise. *Med. Sci. Sports Exerc.*, Vol. 40, No. 1, pp. 104–110, 2007. Oral administration of the amino acid/inhibitory neurotransmitter gamma aminobutyric acid (GABA) reportedly elevates resting serum growth hormone (GH) concentrations. **Purpose:** To test the hypothesis that GABA ingestion stimulates immunoreactive GH (irGH) and immunofunctional GH (ifGH) release at rest and that GABA augments the resistance exercise–induced irGH/ifGH responses. **Methods:** Eleven resistance-trained men (18–30 yr) participated in this randomized, double-blind, placebo-controlled, crossover study. During each experimental bout, participants ingested either 3 g of GABA or sucrose placebo (P), followed either by resting or resistance exercise sessions. Fasting venous blood samples were acquired immediately before and at 15, 30, 45, 60, 75, and 90 min after GABA or P ingestion and were assayed for irGH and ifGH. **Results:** At rest, GABA ingestion elevated both irGH and ifGH compared with placebo. Specifically, peak concentrations of both hormones were elevated by about 400%, and the area under the curve (AUC) was elevated by about 375% ($P < 0.05$). Resistance exercise (EX-P) elevated time-point (15–60 min) irGH and ifGH concentrations compared with rest ($P < 0.05$). The combination of GABA and resistance exercise (EX-GABA) also elevated the peak, AUC, and the 15- to 60-min time-point irGH and ifGH responses compared with resting conditions ($P < 0.05$). Additionally, 200% greater irGH ($P < 0.01$) and 175% greater ifGH ($P < 0.05$) concentrations were observed in the EX-GABA than in the EX-P condition, 30 min after ingestion. GABA ingestion did not alter the irGH to ifGH ratio, and, under all conditions, ifGH represented approximately 50% of irGH. **Conclusions:** Our data indicate that ingested GABA elevates resting and postexercise irGH and ifGH concentrations. The extent to which irGH/ifGH secretion contributes to skeletal muscle hypertrophy is unknown, although augmenting the postexercise irGH/ifGH response may improve resistance training–induced muscular adaptations. **Key Words:** GAMMA AMINO BUTYRIC ACID, RESISTANCE TRAINING, ifGH, AMINO ACID

BASIC SCIENCES

Growth hormone (GH) plays an important role in the growth and maintenance of skeletal muscle, stimulating increases in muscle and cartilage protein synthesis, fatty acid use, and cellular amino acid uptake (11). This peptide hormone is degraded by serum proteases and circulates in multiple molecular forms, only some of which are biologically active (14,25). The intact immunoreactive GH (irGH) molecule possesses two separate receptor-binding domains, both of which are required to dimerize the GH receptor and initiate signal transduction (14,25). Immunofunctional GH (ifGH) represents the fraction of irGH isoforms that contain both binding domains and, theoretically, the fraction that is biologically active. In men, the bulk of irGH and ifGH secretion occurs at night, whereas daytime levels are comparatively low (33). However, several stimuli, including exercise (35) and amino acid administration (7), purportedly alter irGH and/or ifGH secretion.

Both aerobic (29,34) and resistance exercise (23,24,31) have been shown to stimulate irGH and ifGH secretion. Additionally, several amino acids (AA) stimulate irGH secretion when administered intravenously (IV) (3,16). However, the effects of oral AA administration on irGH secretion are inconclusive (5–7,9,15,18). Several factors may account for differences between IV and oral modes of administration, including extended absorption kinetics, differences in interorgan AA transport, and/or liver-induced AA biotransformation, which collectively reduce the peak circulating AA concentrations after AA ingestion (4). Although AA administration may induce irGH release (3), it is unclear whether the circulating concentrations of ifGH, GH isoforms that are capable of dimerizing receptors and inducing signal transduction, increase after supplementation.

Gamma amino butyric acid (GABA) is a commercially available AA supplement and an inhibitory neurotransmitter that seems to directly stimulate GH secretion via centrally mediated mechanisms (5,6). Although GABA administration has been shown to stimulate GH secretion at rest (5,6), no

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study has reported the effects of GABA ingestion on irGH responses after resistance exercise. Additionally, to our knowledge, no reports have documented the ifGH response to GABA administration. On the basis of previous literature, we hypothesized that GABA ingestion would increase circulating irGH and ifGH concentrations at rest and that oral GABA administration would augment the irGH/ifGH response to resistance exercise. Therefore, the purpose of this study was to determine the acute irGH and ifGH responses to GABA ingestion at rest and after resistance exercise.

METHODS

Experimental subjects. Eleven healthy, resistance-trained males (23.6 ± 3.9 yr, 182.3 ± 8.2 cm, 87.5 ± 12.8 kg) participated in this study. Subjects were excluded for self-report of the following: orthopedic injury that would limit participation, a metabolic disease, or nutritional supplement or ergogenic aid use during the previous 2 months. All study participants signed a written informed consent, approved by the university institutional review board.

Study design. This was a randomized, double-blind, placebo-controlled, crossover study. Each subject participated in five sessions, one familiarization and four experimental trials, each separated by 1 wk. The experimental trials consisted of two resting and two exercise bouts completed in a counterbalanced fashion (Fig. 1) to determine the effects of GABA on serum irGH and ifGH concentrations at rest and after resistance exercise. Before each experimental bout, 3000 mg of encapsulated GABA (GNC, Pittsburgh, PA) or an isocaloric placebo (sucrose) was ingested. Throughout the study, participants were instructed to continue their normal daily activities; however, a minimum 24-h layoff from resistance exercise was required before each experimental trial. Additionally, subjects were asked to consume their typical diet throughout the experimental period and to refrain from using any drug or supplement proposed to have an ergogenic effect.

Familiarization session. During the familiarization session, anthropometric measurements (body mass and height) were assessed, using a calibrated medical scale. Additionally, a one-repetition maximum (1RM) was established on 11 selectorized exercise machines (Med-X Corporation, Ocala, FL), including the chest press, lat pulldown, chest fly, seated row, shoulder press, biceps curl, triceps extension, leg press, leg curl, leg extension, and calf raise, according to standard protocol (19). The 1RM results were used to individualize load assignments for subsequent exercise trials.

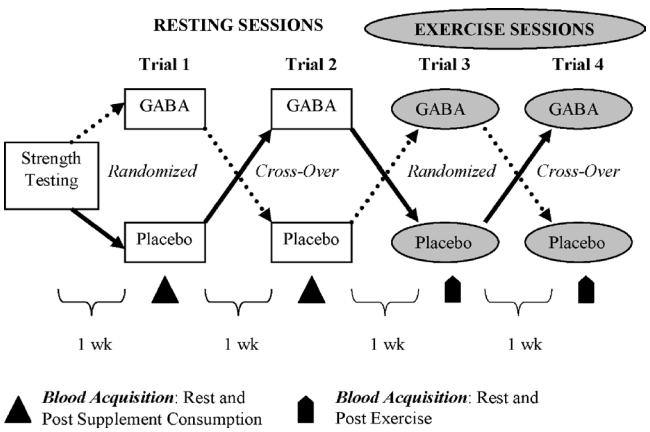

FIGURE 1—Experimental design.

Experimental trials. During all experimental bouts, subjects reported to the laboratory after a 10-h overnight fast to control for possible dietary influences on irGH and ifGH secretion and exercise performance (13). The first two bouts consisted of the resting experimental bouts, during which subjects consumed GABA/placebo and remained at rest for 90 min while blood was acquired. Bouts 3 and 4 consisted of the exercise experimental protocol, during which subjects consumed GABA/placebo, completed the resistance exercise intervention (which lasted about 15 min), and then rested while blood was acquired for 90 min. The resistance exercise intervention involved performing one set each of the 11 previously mentioned exercises. Subjects performed the maximal number of repetitions possible at 70% 1RM, with 1 min of rest between exercises.

Blood acquisition. Blood samples were acquired via catheter from an antecubital forearm vein. Before each experimental trial, subjects rested 15 min in a semirecumbent position before the baseline blood acquisition. During the resting experimental bouts, six additional blood samples were acquired (15, 30, 45, 60, 75, and 90 min) after supplementation. During the exercise experiment, blood was acquired at six time points (1, 15, 30, 45, 60, 75 min) after exercise, which corresponded to the resting trials' acquisition time points. After acquisition, blood was stored at 4°C until centrifugation at 3000*g* for 12 min, after which serum was separated and aliquots were stored at −80°C until analysis. Circadian variability in blood parameters was minimized by collecting all samples between 0700 and 0900 h.

Formulation of supplement. During each experimental trial, four GABA or placebo capsules, identical in appearance, were ingested with 150 mL of water. The GABA-750 supplement was manufactured by GNC (Pittsburgh, PA) and purchased from a local GNC retailer; it consisted of 98% commercially available gelatin encapsulated GABA and 2% silicon dioxide and magnesium stearate (flow agents). The manufacturer verified that each capsule contained 750 mg of GABA, which was isolated from microbiological broth; the GABA was then purified, dried, and encapsulated. Each placebo capsule consisted of 750 mg of 100% sucrose.

Biochemical analyses. Serum irGH was determined by enzyme-linked immunosorbent assays (ELISA) (Diagnostic Systems Laboratories, Inc., Webster, TX). Serum ifGH was determined by a bioactive GH ELISA, using an anti-GH monoclonal antibody and a biotinylated, recombinant, GH-binding protein that binds to GH receptor-binding sites 2

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and 1, respectively, which are present on "immunologically functional" GH molecules (30) (Diagnostic Systems Laboratories, Inc., Webster, TX). The minimal detectable limits of the ELISA were 0.03 $\mu g \cdot L^{-1}$ (irGH) and 0.06 $\mu g \cdot L^{-1}$ (ifGH). All samples were performed in duplicate and in a single run, and the intraassay variances for this study were below 4.3% (irGH) and 5.1% (ifGH).

Data analyses. Separate mixed-model repeated-measures ANOVA were used to determine differences in irGH and ifGH time-point concentrations between conditions. Area under the curve (AUC) was determined using the trapezoidal method, and one-way repeated-measures ANOVA were used to determine differences in AUC and peak irGH and ifGH concentrations. When necessary, the Huynh–Feldt adjustment was used to correct for violations of sphericity. The Tukey's *post hoc* analysis was implemented to verify statistical significance when appropriate. Separate paired *t*-tests (one tailed) were also used to test the hypothesis that GABA would increase the AUC and peak irGH and ifGH concentrations in the resting and exercise conditions. The SPSS 12.0.1 statistical package was used for the statistical analyses. Data are expressed as means ± SE unless otherwise noted. An alpha level of $P \leq 0.05$ was selected as the criterion for statistical significance.

RESULTS

Exercise performance. No difference in the total number of repetitions completed was observed when comparing the exercise–GABA condition (149.22 ± 11.17) with the exercise–P condition (150.89 ± 10.99) ($P > 0.05$).

irGH and ifGH time-point comparisons. Serum irGH concentrations increased approximately 18-fold above the corresponding baseline (preingestion) value during both the exercise–GABA and exercise–P conditions, and they increased approximately 15-fold above baseline during the rest–GABA condition; no differences in irGH concentrations were observed at any time point throughout the rest–P condition (Fig. 2A, B). The irGH responses after the exercise–GABA condition were greater than both the rest–P and the rest–GABA conditions at the 15- to 60-min time points ($P < 0.05$). Similarly, the irGH responses after the exercise–P condition were greater than both the rest–P and rest–GABA conditions at 15–45 min after ingestion ($P < 0.05$). In addition, the irGH response after exercise–GABA was approximately 200% greater than exercise–P at 30 min after exercise cessation ($P < 0.01$) (Fig. 2A, B).

Immunofunctional GH concentrations increased after the exercise–GABA (19-fold), exercise–P (10.5-fold), and rest–GABA (15-fold) conditions; no differences in ifGH concentrations were present in the rest–P condition (Fig. 2A, B). The exercise–GABA ifGH concentrations were greater than both the rest–P and the rest–GABA at 15–60 and 15–45 min after ingestion, respectively ($P < 0.05$). Likewise, the ifGH concentrations in the exercise–P condition were greater than the rest–P (15–60 min after) and the rest–GABA (15–30 min after) ($P < 0.05$). Additionally, the ifGH response after exercise–GABA was 175% greater than exercise–P at 30 min after exercise ($P < 0.05$) (Fig. 2A, B).

irGH and ifGH AUC. The irGH AUC values for the exercise–GABA condition were approximately 480% and 1590% greater than the irGH AUC values during the rest–GABA and rest–*P* values, respectively ($P < 0.01$) (Fig. 3A, B). Similarly, the ifGH AUC values during the exercise–GABA condition were approximately 420% and 1410% greater than the corresponding rest–GABA ($P < 0.05$) and rest–P ($P < 0.01$) values, respectively (Fig. 3A, B). The paired *t*-tests indicated that a significant difference was present between the exercise–GABA and exercise–P conditions for irGH (345.4 ± 124.5 vs 202.1 ± 105.6, $P = 0.02$, one

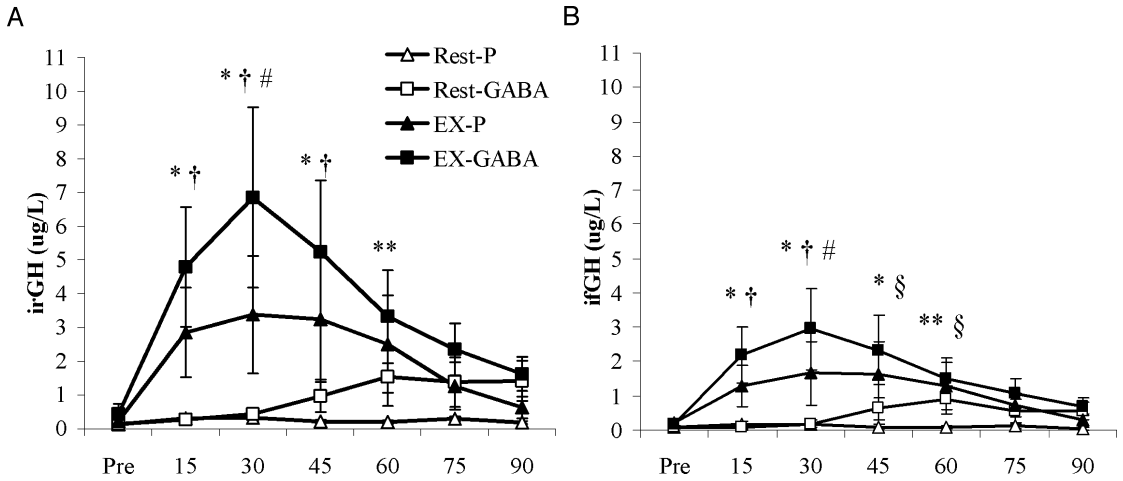

FIGURE 2—Immunoreactive growth hormone (irGH) (*A*) and immunofunctional GH (ifGH) (*B*) time-point concentrations for the rest–placebo (P), rest–GABA, exercise (EX)-P, and EX-GABA conditions. Data are means ± SE. * EX-GABA different from rest–P and rest–GABA ($P < 0.01$); † EX-P different from rest–P and rest–GABA ($P < 0.05$); # EX-GABA different from EX-P ($P < 0.05$); ** EX-GABA different from rest–P ($P < 0.01$); § EX-P different from rest–P ($P < 0.05$).

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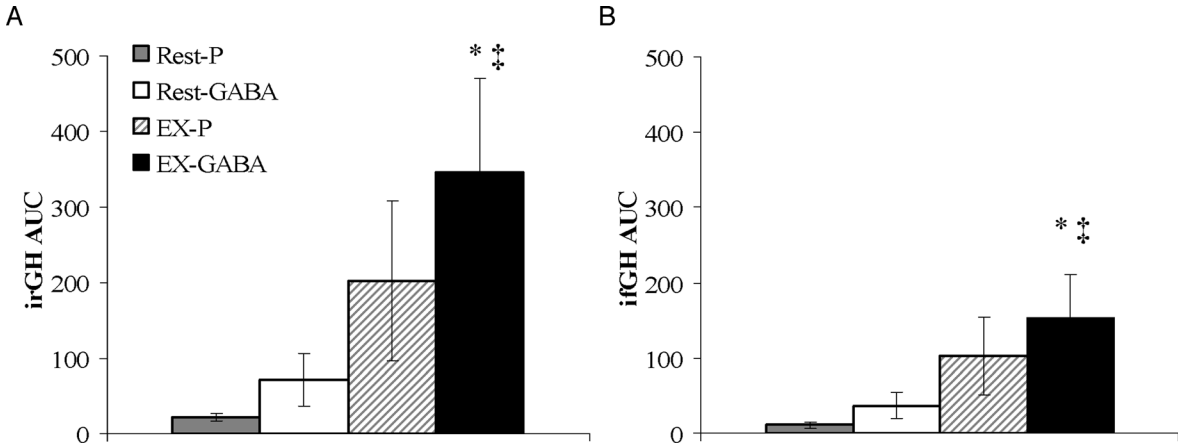

FIGURE 3—Immunoreactive growth hormone (irGH) (*A*) and immunofunctional GH (ifGH) (*B*) area under the curve values (AUC) for the rest–placebo (P), rest–GABA, exercise (EX)-P, and EX-GABA conditions. Data are means ± SE. * Different from rest–P ($P < 0.01$); ‡ different from rest–GABA ($P < 0.01$).

tailed), and a trend towards significance was observed for ifGH (153.6 ± 57.8 vs 102.7 ± 51.2, $P = 0.06$, one tailed) AUC values, respectively. Additionally, a significant difference was present between the rest–GABA and rest–P conditions for ifGH AUC (36.9 ± 17.7 vs 10.9 ± 4.4, $P < 0.05$, one tailed), and a trend towards significance was observed for irGH AUC (71.3 ± 34.5 vs 21.7 ± 5.2, $P = 0.07$, one tailed).

Peak irGH and ifGH response. The peak irGH concentrations for the exercise–GABA condition were approximately 375% and 1650% greater than the peak irGH concentrations during the rest–GABA and rest–P irGH conditions, respectively ($P < 0.01$) (Fig. 4A, B). The peak ifGH concentrations for the exercise–GABA condition were also 300% and 1200% greater than the peak ifGH concentrations during the rest–GABA and rest–P conditions, respectively ($P < 0.01$). Additionally, the exercise–P peak ifGH concentration was approximately 800% greater than the peak ifGH concentration during the rest–P condition ($P < 0.05$) (Fig. 4A, B). The paired-samples *t*-tests indicated that a significant difference was present between the exercise–GABA and exercise–P peak irGH (7.70 ± 2.62 vs 3.94 ± 1.85 $\mu g \cdot L^{-1}$, $P = 0.01$, one tailed) and ifGH (3.47 ± 1.13 vs 2.16 ± 0.93 $\mu g \cdot L^{-1}$, $P = 0.03$, one tailed) concentrations. A significant difference was also present between the rest–GABA and rest–P peak irGH (2.05 ± 0.87 vs 0.47 ± 0.11 $\mu g \cdot L^{-1}$, $P = 0.04$, one tailed) and ifGH (1.13 ± 0.42 vs 0.27 ± 0.10 $\mu g \cdot L^{-1}$, $P = 0.02$, one tailed) concentrations.

irGH to ifGH ratio. The irGH to ifGH ratio was calculated using both the AUC and peak GH responses. No differences were found between the rest–P and rest–GABA (2.83 ± 1.16 vs 2.00 ± 0.96, $P = 0.48$) or the exercise–P and exercise–GABA (2.33 ± 1.04 vs 2.98 ± 1.36, $P = 0.71$) conditions for the AUC GH irGH/ifGH ratios. Additionally, no differences were found between the rest–P and rest–GABA (1.62 ± 0.50 vs 1.14 ± 0.41, $P = 0.49$) or the exercise–P and exercise GABA (1.54 ± 0.38 vs 1.76 ± 0.40, $P = 0.67$) peak GH irGH/ifGH ratios.

DISCUSSION

GABA is an inhibitory neurotransmitter synthesized from L-glutamate in the brain (26). Previous research indicates

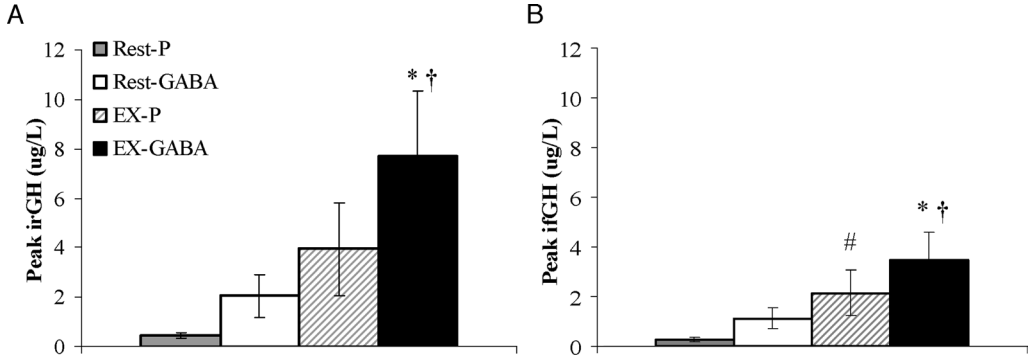

FIGURE 4—Peak immunoreactive growth hormone (irGH) (*A*) and immunofunctional GH (ifGH) (*B*) concentrations for the rest–placebo (P), rest–GABA, exercise (EX)-P, and EX-GABA conditions. Data are means ± SE. * Different from rest–P ($P < 0.01$); † different from rest–GABA ($P < 0.01$); # different from rest–P ($P < 0.05$).

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that GABA ingestion stimulates GH secretion (5,6) and that resistance exercise acutely increases both irGH and ifGH release, the immunologically active forms of irGH (17,23,24,31). For this study, we hypothesized that GABA ingestion would increase both resting and exercise-induced concentrations of irGH and ifGH. The main findings of this study are that 3 g of GABA ingestion augments the resistance exercise–induced irGH/ifGH responses and acutely stimulates both irGH and ifGH secretion at rest.

Our results are consistent with previous reports that administration of either GABA (5,6) or of the GABA-ergic agonist baclofen stimulate GH secretion (21) within 60–90 min of ingestion (6), and they expand on these findings by demonstrating that GABA ingestion stimulates the release of ifGH isoforms at rest (25). Additionally, our results corroborate previous reports that irGH and ifGH concentrations peak at 15–30 min after resistance exercise (18,19), and they concurrently indicate that GABA ingestion augments the resistance exercise–induced increases of both irGH and ifGH. Furthermore, our results seem consistent with previous studies indicating that ifGH represents approximately 50% of postexercise peak and total (AUC) irGH release (23,24). Interestingly, in our study, GABA administration also resulted in elevated AUC and peak irGH and ifGH responses during the resting condition, in a similar ratio of approximately 2:1, indicating that GABA induces the release of biologically active GH isoforms at rest.

Growth hormone is known to have a variety of effects on substrate metabolism, including stimulating fatty acid use and protein synthesis, among others (11). The loss of GH is also known to result in body fat accumulation and skeletal muscle atrophy, which can be attenuated by exogenous GH administration, at least in young subjects (10). As GABA ingestion apparently stimulates irGH and ifGH release, it is certainly possible that the GABA induces lypolytic effects and skeletal muscle protein accretion, via mechanisms directly and/or indirectly related to GH release (11,32). Specifically, after receptor dimerization, GH may *directly* promote fatty acid metabolism, or it may *indirectly* alter skeletal muscle protein synthesis via stimulation of circulating and/or muscle-specific insulin-like growth factor 1 (IGF-1), a central mediator of muscle growth (32). It is apparent that these two IGF-1 pathways induce anabolic responses (11,32), although their relative ergogenic contributions remain to be determined. Given the acute irGH/ifGH responses to GABA ingestion, studies designed to determine the effects of longitudinal GABA supplementation on resting and postexercise irGH/ifGH release, substrate metabolism, and muscle anabolic responses are warranted.

Both resistance exercise and AA supplementation are known to heighten the peak and absolute (AUC) irGH and ifGH responses; however, the relative contributions that the peak and absolute GH responses play in the control of substrate metabolism and protein accretion remain unknown. In our study, both the peak and absolute irGH/ifGH responses followed similar patterns, with the exercise–GABA condition resulting in the greatest peak and absolute GH responses. Because we did not observe a difference in exercise performance between the GABA or placebo exercise condition, it seems that the greater GH responses observed after the exercise–GABA condition were an additive result of both resistance exercise and GABA ingestion on GH secretion. Augmentation of daytime GH release has previously been shown to alter the nocturnal irGH/ifGH release; specifically, Tuckow et al. (31) report that resistance exercise decreases the *peak* nocturnal irGH/ifGH response but results in more frequent burst-like secretions, ultimately having little effect on the integrated AUC nocturnal irGH or ifGH values. It is possible that GABA supplementation may also augment the peak and absolute nocturnal ifGH/ifGH release, through direct (1,27) and/or indirect mechanisms (28); however, this remains to be determined.

Although the results of our present study indicate that GABA increased circulating irGH and ifGH concentrations, we are unsure as to the effects of GABA ingestion on circulating GABA concentrations. Certainly, the stimulation of both irGH and ifGH after GABA ingestion suggests that blood GABA concentrations may have increased with supplementation; however, our results do not exclude the possibility that oral GABA underwent liver-induced biotransformation to other AA, which may also stimulate GH secretion (4,7). We believe that the GH responses observed in our study were directly stimulated by GABA, because oral GABA administration has previously been reported to induce GH secretion by a GABA-ergic pathway (5,6). Additionally, the centrally acting GABA antagonist, pimozide, has been shown to inhibit the GH secretory response to oral GABA, whereas the peripheral antagonist, domperidone, does not inhibit the GH response after GABA ingestion (5), suggesting a *direct*, centrally mediated action of GABA on GH secretion. Further, in humans, oral administration of the GABA agonist sodium valproate causes a robust GH secretion (8), whereas in rats intracerebroventricular injection of GABA stimulates GH secretion (20). Regardless of the mechanism(s) involved, it seems that GABA ingestion results in increased circulating irGH and ifGH concentrations, both at rest and after resistance exercise. Future research examining circulating GABA and AA concentrations after GABA ingestion may assist in determining the metabolic fate of orally consumed GABA.

Growth hormone synthesis and release are primarily regulated by neuroendocrine mechanisms involving growth hormone–releasing hormone (GHRH), ghrelin, and somatostatin (2). GHRH stimulates both the synthesis and release of GH, whereas ghrelin seems to strictly stimulate GH and GHRH release. Conversely, somatostatin suppresses GH release but not GH synthesis (2). The majority of irGH and ifGH secretion occurs during the early hours of sleep in males (33); thus, the anabolic and lypolytic values of the relatively small GABA- and exercise-induced irGH/ifGH responses we observed remain unclear, although, as

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previously discussed, elevated irGH/ifGH concentrations may potentially alter fuel use (12). It is plausible that GABA supplementation stimulated GHRH or ghrelin secretion and/or suppressed somatostatin release, as previously demonstrated in animal models (22,28); however, in our study, we did not attempt to determine the mechanism(s) underlying the GABA-stimulated irGH/ifGH release. Future research designed to determine the hypothalamic response (i.e., GHRH and somatostatin) in animal models and/or the ghrelin response after GABA ingestion may contribute to a better understanding of the mechanism(s) underlying GABA-induced irGH/ifGH release. In summary, GABA ingestion acutely increased resting irGH concentrations and augmented the irGH response to resistance exercise. Additionally, GABA ingestion resulted in the release of ifGH at rest and after resistance exercise, indicating that GABA ingestion stimulates secretion of ifGH isoforms that are capable of dimerizing receptors and inducing signal transduction. In conclusion, GABA-induced irGH/ifGH secretion may alter substrate metabolism and/or enhance the skeletal muscle responses to resistance training, although this remains to be determined.

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