

Impact of acute exercise intensity on pulsatile growth hormone release in men

By: Cathy J. Pritzlaff, [Laurie Wideman](#), Judy Y. Weltman, Robert D. Abbott, Margaret E. Gutgesell, Mark L. Hartman, Johannes D. Veldhuis, and Arthur Weltman

Pritzlaff, C.J., Wideman, L., Weltman, J.Y., Abbott, R.D., Gutgesell, M.E., Hartman, M.L., Veldhuis, J.D. and Weltman, A. 1999. Impact of acute exercise intensity on pulsatile growth hormone (GH) release in men. *Journal of Applied Physiology* 87 (2): 498-504. PMID: 10444604

Made available courtesy of the American Physiological Society:

<https://doi.org/10.1152/jappl.1999.87.2.498>

***© 1999 American Physiological Society. Reprinted with permission. No further reproduction is authorized without written permission from APS. This version of the document is not the version of record. Figures and/or pictures may be missing from this format of the document. ***

Abstract:

To investigate the effects of exercise intensity on growth hormone (GH) release, 10 male subjects were tested on 6 randomly ordered occasions [1 control condition (C), 5 exercise conditions (Ex)]. Serum GH concentrations were measured in samples obtained at 10-min intervals between 0700 and 0900 (baseline) and 0900 and 1300 (exercise+ recovery). Integrated GH concentrations (IGHC) were calculated by trapezoidal reconstruction. During Ex subjects exercised for 30 min (0900–0930) at one of the following intensities [normalized to the lactate threshold (LT)]: 25 and 75% of the difference between LT and rest (0.25LT and 0.75LT, respectively), at LT, and at 25 and 75% of the difference between LT and peak (1.25LT and 1.75LT, respectively). No differences were observed among conditions for baseline IGHC. Exercise+recovery IGHC (mean \pm SE: C = 250 ± 60 ; 0.25LT = 203 ± 69 ; 0.75LT = 448 ± 125 ; LT = 452 ± 119 ; 1.25LT = 512 ± 121 ; 1.75LT = $713 \pm 115 \mu\text{g} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$) increased linearly with increasing exercise intensity ($P < 0.05$). Deconvolution analysis revealed that increasing exercise intensity resulted in a linear increase in the mass of GH secreted per pulse and GH production rate [production rate increased from 16.5 ± 4.5 (C) to $32.1 \pm 5.2 \mu\text{g} \cdot \text{distribution volume}^{-1} \cdot \text{min}^{-1}$ (1.75LT), $P < 0.05$], with no changes in GH pulse frequency or half-life of elimination. We conclude that the GH secretory response to exercise is related to exercise intensity in a linear dose-response pattern in young men.

Keywords: lactate threshold | endocrinology | pituitary | somatotropin

Article:

The growth hormone (GH) response to acute exercise has been studied extensively, with most investigators reporting that acute bouts of exercise increase the plasma concentration of GH (4-6,20). Available studies suggest that intensity and duration of acute exercise, work output during exercise, muscle mass used during exercise, fitness, and training state may all influence, in part,

the GH response to exercise (3-6, 20, 21, 23). Furthermore, the level of aerobic fitness and prior training are related to the amount of GH released over a 24-h period (30, 34, 35).

Exercise intensity may play a key role, with exceeding of a particular threshold of exercise intensity needed before a significant rise in serum GH concentration occurs (4-6). Although a threshold concept has been supposed, no study has examined this proposition systematically. Felsing et al. (6) suggested that this exercise intensity threshold may correspond to the lactate threshold (LT). Recent indirect data from our laboratory also support the notion that the LT may be an important intensity for eliciting a training response (32, 35) and may also be related to GH release during exercise (36), possibly through (central) catecholamine release (36). In the present study, we examined the effects of exercise intensity on GH secretion in young men. We hypothesized that the GH secretory response to exercise would be attenuated until an exercise intensity equal to or greater than the LT was reached.

METHODS

Subjects. Ten recreationally active men [mean age = 26 ± 1.1 (SE) yr; mean height, 178 ± 1.7 cm; mean weight, 83.4 ± 2.8 kg] provided voluntary written informed consent, as approved by the Human Investigation Committee of the University of Virginia, before entering the study. Each subject underwent a detailed medical history and physical examination, and no subject had a history of pituitary, renal, hepatic, or metabolic disease. The subjects were nonsmokers, did not abuse alcohol, and were not taking any medication known to affect GH secretion. Screening laboratory data revealed normal hematologic, renal, hepatic, metabolic, and thyroid function. Subjects refrained from exercise for 24 h before each evaluation.

Experimental design. Each subject completed a treadmill test to assess level of cardiovascular fitness and underwent hydrostatic weighing to determine body density (and percent body fat) at the Exercise Physiology Laboratory of the General Clinical Research Center (GCRC). Subjects were then evaluated on six separate occasions, five with exercise and one at rest; the order of study conditions was assigned in a randomized fashion. The admissions were scheduled at least 7 days apart, and no more than two admissions over a 2-mo period were allowed (to ensure that guidelines for blood withdrawal were not exceeded). Exercise consisted of 30 min of constant-load exercise at a predetermined velocity. Treadmill velocity was set at 25 and 75% of the difference between the $\dot{V}O_2$ at LT and $\dot{V}O_2$ at rest (0.25LT and 0.75LT, respectively); at LT (LT); and 25 and 75% of the difference between the $\dot{V}O_2$ at LT and peak $\dot{V}O_2$ ($\dot{V}O_{2\text{ peak}}$) (1.25LT and 1.75LT, respectively), on the basis of results obtained during a prior LT/ $\dot{V}O_{2\text{ peak}}$ protocol (see below).

Body composition. Body density was assessed by hydrostatic weighing (18). Each subject was weighed in air on an Accu-weigh beam scale accurate to 0.1 kg and subsequently weighed underwater on a Chatillon autopsy scale accurate to 10 g. Residual lung volume was measured by using an O_2 -dilution technique (40). The computational procedure of Brozek et al. (2) was used to determine percent body fat from body density measurements.

LT/ $\dot{V}O_{2\text{ peak}}$. A continuous treadmill (Quinton Q 65 treadmill) exercise protocol with increasing velocity until volitional fatigue was used to assess LT and $\dot{V}O_{2\text{ peak}}$. The initial velocity was set at

100 m/min with increases in velocity of 10 m/min every 3 min. Open-circuit spirometry was used to collect metabolic data (SensorMedics model 2,900Z metabolic measurement cart, Yorba Linda, CA). Heart rate was determined via a Marquette Max-1 electrocardiograph. An indwelling venous cannula was inserted into a forearm vein before testing, and blood samples were taken at rest and during the last 15 s of each stage for the measurement of blood lactate concentration (Yellow Springs Instruments 2700 Select Biochemistry Analyzer, Yellow Springs, OH). The test was terminated when the subject reached volitional exhaustion. $\dot{V}O_{2\text{ peak}}$ was chosen as the highest $\dot{V}O_2$ attained.

Determination of LT. The blood lactate-velocity relationship that was obtained from the LT/ $\dot{V}O_{2\text{ peak}}$ protocol was used to estimate the LT. Velocity at LT was determined by plotting blood lactate concentration against treadmill velocity and was chosen as the highest velocity obtained before the curvilinear increase in blood lactate concentration with increasing velocities. An elevation in blood lactate concentration of at least 0.2 mM (the error associated with the lactate analyzer) above baseline was required for LT determination. $\dot{V}O_2$ associated with velocity LT was then determined (33).

Exercise/control days. Subjects were admitted to the GCRC on the evening before the exercise/control studies. Subjects were required to consume their evening meal at or before 1700, and then received a standardized snack (500 kcal) at 2000. The nutrient composition of the snack was 55% carbohydrate, 15% protein, and 30% fat. Subjects were allowed to consume water ad libitum. To avoid the confounding effects of meals on GH secretion, subjects then fasted until the end of the study (9, 10). At 2100, an intravenous cannula was placed bilaterally in each forearm vein.

Subjects remained at the GCRC after eating their snack and were asked to turn lights off by 2300 (10, 11). Beginning at 0700, blood samples were withdrawn every 10 min until 1300 for later measurement of serum GH concentrations. After 2 h of baseline blood sampling, subjects began their exercise bout or remained at rest (C). The exercise bout began at 0900 and continued until 0930. During the exercise bout, blood lactate was measured every 10 min, and metabolic data were measured minute by minute. On completion of exercise, subjects resumed bed rest until 1300. Subjects were then fed and discharged.

GH analysis. Serum GH concentrations were measured in duplicate by using an ultrasensitive chemiluminescence assay (13). The optimized assay consists of 200 μ l serum assayed in duplicate with 200 μ l GH antiserum, overnight shaking incubation, robotic pipetting, and automated washing of the antibody-coated polystyrene beads (Nichols Laboratories, San Juan Capistrano, CA). All samples from a subject were assayed together to eliminate interassay variability. Assay sensitivity defined as 4 SDs above the zero-dose tube was 0.005 μ g/l, and that defined as 2 SDs above the zero-dose tube was 0.002 μ g/l (13). Recombinant human GH (22,000 Da) was used as the reference standard. No serum GH measurements from these subjects fell below 0.005 μ g/l at any time, and no more than 5% of all measurements were below 0.015 μ g/l. The within-assay coefficients of variation ranged from 4.5 to 13%. Within-sample SDs were calculated in each subject's series of 222 samples as dose-dependent values defined by a power function relating the within-sample SD to the mean sample GH concentration (for deconvolution analysis described below).

Integrated serum GH concentrations (IGHC) were calculated as previously described (26). A multiple-parameter deconvolution method was employed to derive quantitative estimates of attributes of GH secretory events and monoexponential GH half-life from the measured serum GH concentrations (25). In this analysis we used resting, exercise, and postexercise data. The inclusion of a long postexercise period was based on the fact that peak GH concentrations are typically observed at the end of exercise or within 40-min postexercise and the need to have several GH half-lives to apply the analysis. We assumed that individual GH pulses are approximated algebraically by a Gaussian distribution of secretory rates (25). Basal secretion was estimated for each admission (13, 30). GH secretory pulses were considered significant if the fitted amplitude could be distinguished from zero (i.e., pure noise) with 95% statistical confidence. The GH secretory pulse half duration (duration at half-maximal amplitude), GH half-life of elimination, and GH distribution volume were assumed to be constant throughout the study period for each individual. The mass of GH secreted per pulse was estimated as the area of the calculated secretory pulse [$\mu\text{g/l}$ of distribution volume ($\mu\text{g/l}_v$) \times min] (25). The endogenous pulsatile GH production rate was estimated as the product of the number of secretory pulses and the mean GH mass secreted per pulse.

Statistical analysis. ANOVA with repeated measures was used to determine mean differences for $\dot{V}O_2$ and blood lactate concentration. Whenever mean differences were observed, means comparisons (corrected for correlated data by using Huynh-Feldt epsilons) were examined. To examine the relationship between GH response and exercise intensity, separate regression models were estimated for each of the 10 study subjects with the GH response regressed on exercise intensity. Separate models were estimated within subjects because of the intraindividual correlation that existed between the GH responses across levels of exercise intensity. Such methods, while likely to be conservative, were thought to be appropriate because of the limited sample size that was available for estimating intraindividual correlation structures. Simple linear regression was also used, because in comparison with more complex models that allow for curvature, departures from linearity were not apparent. To determine whether a GH response changed significantly with exercise intensity, the 10 slopes associated with exercise intensity from the individual regression models were then subjected to a Wilcoxon signed-rank test (12). Similar methods were used to examine the association between each of the deconvolution parameters and exercise intensity. The association between exercise+recovery (0900–1300) integrated serum GH concentrations and exercise intensity was further assessed by adding each deconvolution parameter to the within-subject regression models. To determine whether the relationship between a GH response and exercise intensity was independent of a deconvolution parameter, the slopes associated with exercise intensity in the adjusted models were again subjected to a Wilcoxon signed-rank test. All data are presented as means \pm SE.

RESULTS

Subject characteristics. Subjects' $\dot{V}O_2$ at LT was 2.72 ± 2.6 l/min (32.6 ± 2.6 ml \cdot kg⁻¹ \cdot min⁻¹), $\dot{V}O_{2\text{ peak}}$ was 3.93 ± 0.19 l/min (47.9 ± 2.2 ml \cdot kg⁻¹ \cdot min⁻¹), $\dot{V}O_{2\text{ LT}}/\dot{V}O_{2\text{ peak}}$ was 0.68 ± 0.4 , and percent body fat was $19.3 \pm 1.9\%$. As expected, $\dot{V}O_2$ at LT and $\dot{V}O_{2\text{ peak}}$ were strongly correlated with one another ($r = 0.79$).

V_{o2} and blood lactate concentration during constant-load exercise. One-way ANOVA with repeated-measures and post hoc analyses revealed that $\dot{V}O_2$ and blood lactate concentrations increased ($P < 0.05$) across all exercise intensities. The mean $\dot{V}O_2$ at each exercise intensity was 1.01 ± 0.08 l/min at 0.25LT; 1.85 ± 0.14 l/min at 0.75LT; 2.45 ± 0.18 l/min at LT; 2.98 ± 0.21 l/min at 1.25LT; and 3.55 ± 0.31 l/min at 1.75LT. These $\dot{V}O_2$ values corresponded to 26, 47, 62, 76, and 90% of $\dot{V}O_{2\text{ peak}}$, respectively. Thus, whether data were examined relative to LT or relative to $\dot{V}O_{2\text{ peak}}$, linear increments in exercise intensity were observed. Mean blood lactate values were 0.65 ± 0.05 mM at 0.25LT; 0.93 ± 0.11 mM at 0.75LT; 1.52 ± 0.16 mM at LT; 2.53 ± 0.40 mM at 1.25LT; and 4.94 ± 0.40 mM at 1.75LT ($P < 0.05$).

GH release. Figure 1 shows the mean serum GH concentrations during blood sampling at 10-min intervals over 6 h during C, 0.25LT, 0.75LT, LT, 1.25LT, and 1.75LT conditions. No differences were observed among conditions for baseline IGHC (0700–0900) ($P = 0.20$) (data not shown). Mean IGHC values during exercise+recovery were as follows: C = $250 \pm (\text{SE}) 60$; 0.25LT = 203 ± 69 ; 0.75LT = 448 ± 126 ; LT = 452 ± 119 ; 1.25LT = 512 ± 121 ; 1.75LT = $713 \pm 115 \mu\text{g} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$. The individual relationships between exercise intensity and IGHC during exercise+recovery (0900–1300) are shown in Fig. 2. Within-subject regression revealed that IGHC increased significantly with each exercise intensity in a linear pattern ($P = 0.002$). This was the case when IGHC was plotted against either %LT (Fig. 2A) or % $\dot{V}O_{2\text{ peak}}$ (Fig. 2B). There was no suggestion from the data that any of the individual GH responses increased differently across the ranges of exercise intensity. For each increase in exercise intensity corresponding to 0.25LT, exercise+recovery IGHC (4 h) would be expected to increase by $\sim 70 \mu\text{g} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$.

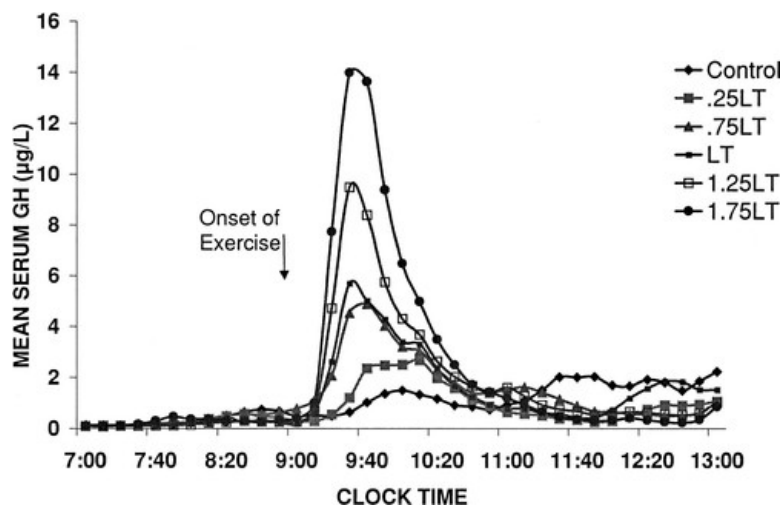


Fig. 1. Mean serum growth hormone (GH) concentrations during blood sampling at 10-min intervals over 6 h during control (C); 25 and 75% of difference between $\dot{V}O_2$ uptake ($\dot{V}O_2$) achieved at lactate threshold (LT) and $\dot{V}O_2$ at rest (0.25LT and 0.75LT, respectively); and 25 and 75% of difference between $\dot{V}O_2$ at LT and peak $\dot{V}O_2$ (1.25LT and 1.75LT, respectively) conditions. Values are means \pm SE; $n = 10$ subjects.

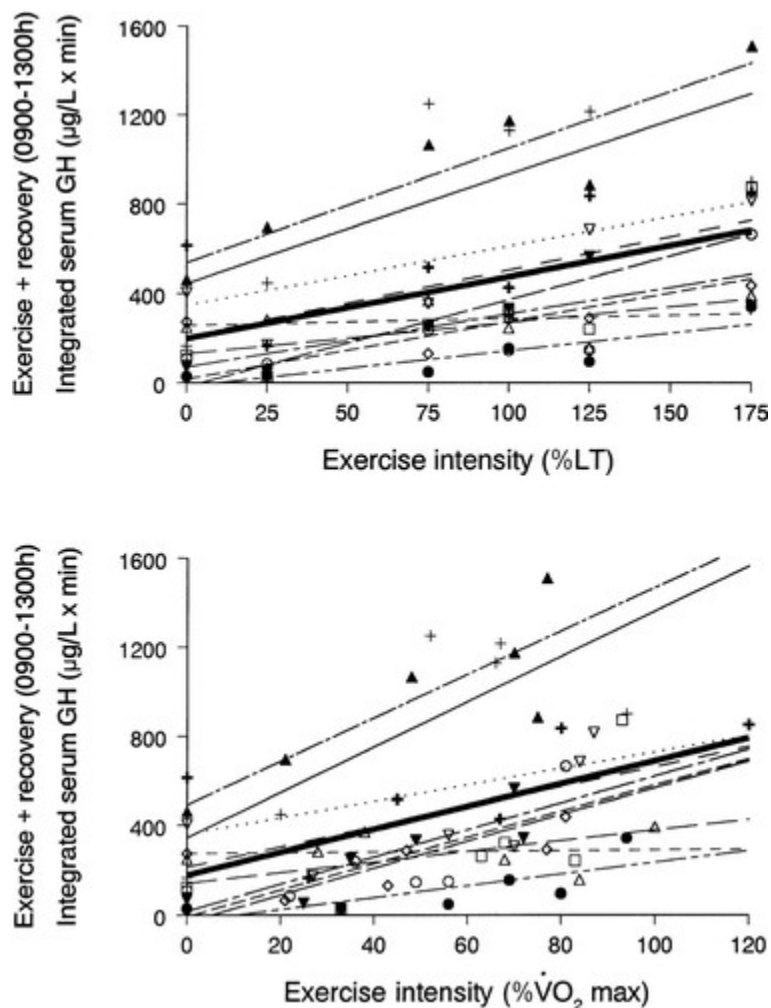


Fig. 2. Relationship between exercise intensity expressed as %LT (*top*) and %maximal $\dot{V}O_2$ ($\dot{V}O_{2\max}$; *bottom*) and integrated serum GH concentration ($\mu\text{g} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$; exercise+recovery, 0900–1300). Symbols represent individual concentrations for 10 subjects across 6 levels of exercise intensity. Thick solid line is derived from average of intercepts and slopes from within-subject regression (thin solid, dashed, and dotted) lines. Integrated serum GH increases significantly with exercise intensity ($P = 0.002$).

For the remaining analyses, we chose to express exercise intensity relative to the LT on the basis of the following: 1) the strong correlation observed in the present study and reported previously between LT and $\dot{V}O_{2\text{peak}}$ (32, 33); 2) data in the literature that suggest that LT may be a marker for GH release (6, 35, 36); and 3) data that suggest that LT is an important marker of submaximal fitness and a strong predictor of endurance performance (32).

Table 1 shows the results of the multiparameter deconvolution analysis of serum GH concentrations between 0700 and 1300 as well as the mean slopes and intercepts from the regression models. GH production rate, mass of GH secreted per pulse, and GH secretory pulse amplitude all increased significantly with increasing exercise intensity ($P = 0.014$, $P = 0.028$, $P = 0.004$, respectively), whereas GH secretory pulse half duration declined significantly with each

exercise intensity ($P = 0.002$). There were no significant associations between exercise intensity and any other deconvolution parameter. The regression models indicated that GH production rate during the 6-h period would be expected to increase by $\sim 2.6 \mu\text{g} \cdot \text{l}_v^{-1} \cdot \text{min}^{-1}$ for each increase in exercise intensity corresponding to 0.25LT. This was accounted for by an increase in the mass of GH secreted per pulse ($0.5 \mu\text{g}/\text{l}_v$ for each increase in exercise intensity corresponding to 0.25LT), with no change in the number of GH secretory pulses or the GH half-life of elimination. The amplitude (maximal rate) of GH secretory pulses increased by $\sim 0.04 \mu\text{g} \cdot \text{l}_v^{-1} \cdot \text{min}^{-1}$ with each 0.25LT increase in exercise intensity, whereas the secretory pulse half duration decreased by ~ 1.1 min with each increase in exercise intensity of 0.25LT. Thus, with increasing exercise intensities, GH secretory pulses were of shorter duration but greater amplitude. The positive relationship between exercise+ recovery IGHC (0900–1300) and exercise intensity remained statistically significant after adjustment for each of the deconvolution parameters, with the exception of GH secretory pulse amplitude ($P = 0.106$), suggesting that increased pulse amplitude is the primary statistical determinant of the increase in IGHC with increasing exercise intensity.

Table 1. Effects of increasing exercise intensity on specific measures of GH secretion and half-life during 6 h (0700–1300) as determined by multiple-parameter deconvolution analysis and regression analyses

Variable	C	0.25LT	0.75LT	LT	1.25LT	1.75LT	x-Slope	x-Intercept
GH basal secretion, $\mu\text{g}/\text{l}_v$	0.004 ± 0.001	0.009 ± 0.004	0.005 ± 0.001	0.004 ± 0.001	0.004 ± 0.001	0.004 ± 0.001	-0.0014 ± 0.001	0.0063 ± 0.002
GH secretory pulses	6.4 ± 0.6	4.8 ± 0.3	5.4 ± 0.8	5.3 ± 0.5	5.4 ± 0.4	4.5 ± 0.5	-0.64 ± 0.43	5.83 ± 0.42
GH mean inter-pulse interval, min	45.9 ± 8.2	61.7 ± 6.7	45.5 ± 6.9	49.3 ± 7.6	62.3 ± 6.1	76.2 ± 12.5	12.48 ± 6.5	46.41 ± 5.2
GH secretory pulse half duration, min	22.3 ± 1.9	25.1 ± 2.9	20.8 ± 1.9	16.9 ± 0.8	17.6 ± 0.5	16.7 ± 1.1	$-4.57 \pm 0.9^*$	23.7 ± 1.2
GH half-life, min	13.7 ± 1.7	14.3 ± 1.5	15.0 ± 0.9	16.7 ± 1.2	14.7 ± 1.1	15.3 ± 0.9	0.942 ± 0.75	14.2 ± 0.9
Mass of GH/pulse, $\mu\text{g}/\text{l}_v$	2.7 ± 0.6	4.0 ± 1.8	4.2 ± 1.1	3.4 ± 0.5	4.2 ± 1.2	7.4 ± 1.0	$1.99 \pm 0.89^*$	2.65 ± 0.95
GH secretory pulse amplitude, $\mu\text{g}/\text{l}_v$	0.12 ± 0.02	0.12 ± 0.04	0.19 ± 0.05	0.19 ± 0.03	0.24 ± 0.05	0.43 ± 0.06	$0.17 \pm 0.04^*$	0.08 ± 0.03
GH production rate, $\mu\text{g} \cdot \text{l}_v^{-1} \cdot \text{min}^{-1}$	16.5 ± 4.5	9.2 ± 1.3	17.9 ± 4.2	18.6 ± 4.1	24.0 ± 7.0	32.1 ± 5.2	$10.5 \pm 3.5^*$	10.9 ± 2.5

Values are means \pm SE; $n = 10$ men. C, control; 0.25 lactate threshold (LT) and 0.75LT, 25 and 75% of the difference between the \dot{V}_{O_2} achieved at LT and the \dot{V}_{O_2} at rest; LT, at lactate threshold; 1.25LT and 1.75LT, 25 and 75% of the difference between the \dot{V}_{O_2} achieved at LT and peak \dot{V}_{O_2} ; GH, growth hormone; l_v , liter of distribution volume; x-slope, mean of the slopes from the 10 individual regression lines; x-intercept, mean of the intercepts from the 10 individual regression lines. * $P < 0.05$.

Because the GH response to exercise appeared to be completed by 90 min, we examined the 90-min mean serum GH concentration after the stimulus (0900–1030), the absolute maximal serum GH peak response over that same interval, and the summed mass of GH secreted per pulse from 0900 to 1030 (exercise+1-h recovery). These data are shown in Fig. 3. Statistical analyses revealed that 90-min mean serum GH (A), peak GH (B), and the summed mass of GH secreted per pulse (C) increased significantly with exercise intensity ($P = 0.004$, $P = 0.002$, and $P = 0.006$, respectively). For each added increase in exercise intensity in the amount of 0.25LT, 90-min mean serum GH would be expected to increase an average of $0.73 \mu\text{g}/\text{l}$, peak GH would be expected to increase an average of $1.7 \mu\text{g}/\text{l}$, and the summed GH mass secreted per pulse would be expected to increase an average of $3.1 \mu\text{g}/\text{l}_v$ over the 90 min.

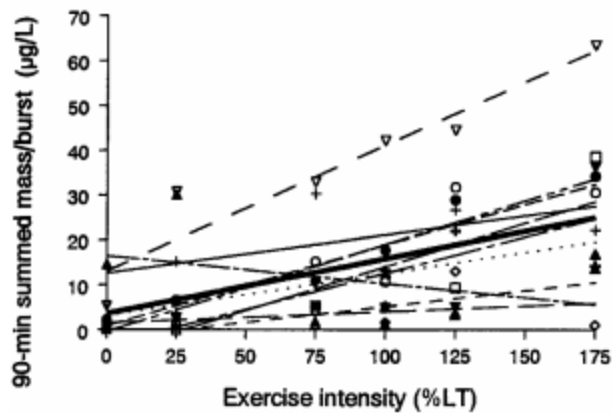
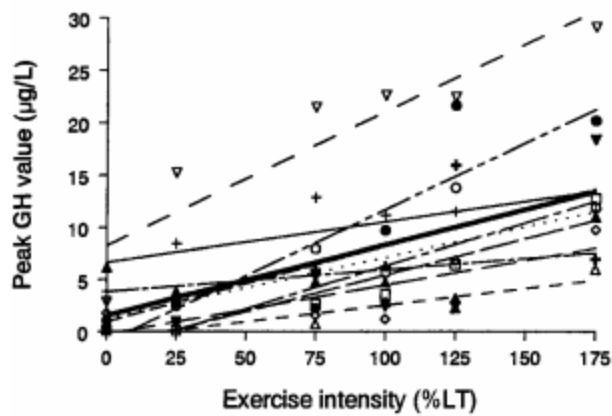
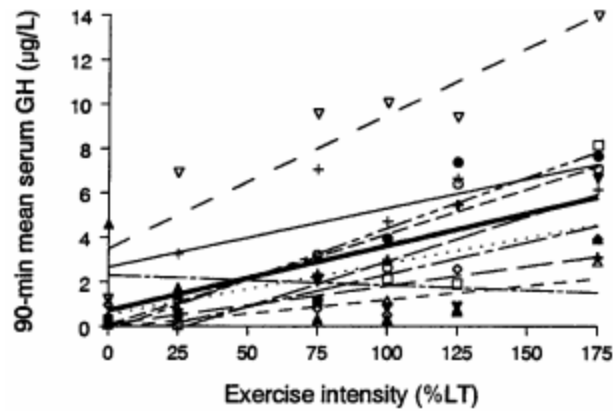


Fig. 3. Mean serum GH concentration (*top*), absolute maximal serum GH peak response (*middle*), and summed GH mass secreted per pulse (*bottom*) over a 90-min interval (exercise+1-h recovery, 0900–1030h) according to exercise intensity. Thick solid line is derived from average of intercepts and slopes from within-subject regression (thin solid, dashed, and dotted) lines. Mean serum GH at 90 min, peak GH, and summed mass secreted per pulse increase significantly with exercise intensity ($P = 0.004, P = 0.002$, and $P = 0.006$, respectively).

DISCUSSION

Although an acute bout of exercise of appropriate intensity will evoke a large increase in serum GH concentrations (3-6, 17, 23, 36), little quantitative information is available regarding the precise relationship between specific levels of exercise intensity and the magnitude of the GH response. We had postulated a threshold relationship between intensity of exercise and the GH secretory response to exercise and that the GH response to exercise would be relatively attenuated until an exercise intensity equal to or greater than the LT was reached. Accordingly, five exercise intensities were chosen in the present study so that the relationship between exercise intensity and GH release could be evaluated systematically.

The major findings of the present study support the hypothesis that the GH secretory response to exercise is related positively to exercise intensity. The GH secretory response to exercise rose with increasing exercise intensities below or equal to LT and was followed by a continuing increase in IGHC above LT (Fig. 2). Notably, exercise intensities below the LT resulted in a stimulation of GH release. Thus, in contrast to our stated hypothesis of a threshold relationship between exercise intensity and the GH response (i.e., no rise or a gradual increase in GH release at intensities below LT and a much greater increase in GH release at intensities above LT), it appears that a linear dose-response relationship exists between exercise intensity and the GH secretory response.

Multiple-parameter deconvolution analysis was employed to examine whether the increase in IGHC with increasing exercise intensities was due to increased GH secretion, decreased clearance of GH, or both. The major assumptions of deconvolution analysis have been well established in the published literature both technically and experimentally (27). In particular, the two principal assumptions are, first, that the half-life is subject specific and invariant across a sampling session, which we have been able to document in test-retest studies (7). The second assumption is that GH is secreted in bursts, which has now been demonstrated in humans by direct catheterization of the inferior petrosal sinus (24). Other indirect data also indicate burstlike secretion on the basis of high-frequency of blood sampling at 30-s intervals overnight (11).

The present analysis indicated that exercise-enhanced IGHC was mechanistically attributable to a linear increase in the mass of GH secreted per pulse with increasing exercise intensity. The latter reflected a linear increase in secretory pulse amplitude and occurred despite a small but linear decrease in secretory pulse half duration [Table 1; the mass per pulse is controlled jointly and linearly by pulse amplitude and duration (29)]. There was no major effect of exercise intensity on the number of secretory GH episodes or the calculated GH half-life during the 6-h sampling period. These findings are consistent with our previous report of the effect of repeated exercise bouts on attributes of GH secretory pulses (17).

Exercise elicited an apparent alteration in the pulse width of GH secretion with GH secretory pulses of shorter duration, but greater amplitude. In principle, this GH secretory pattern change is consistent with concurrent amplification of GHRH (and/or cosecretagogue) release and more rapid-onset reciprocal somatostatin inhibition during intense exercise (8). Reciprocal intrahypothalamic connections between GHRH and somatostatin-secreting neurons (39) will allow for possible rapid stimulation of somatostatin release by GHRH neuronal activation, as has been inferred, for example, in vitro in bovine brain explant experiments (38). Thus exercise may

activate GHRH and, secondarily, somatostatin secretion, with the latter appropriately timed to maximize the mass of GH released per pulse. Indeed, pulsed GHRH infusions in young men also remarkably abbreviated the duration of evoked GH secretory bursts (14). Modeling experiments also indicate the mechanistic feasibility of this hypothesis from a feedback network perspective (22).

Although it is possible that exercise may induce changes in GH-binding protein, to our knowledge there are no evident changes in GH-binding protein concentrations associated with exercise. The GH-binding proteins are thought to represent the extracellular domain of the GH receptor and are high-affinity binding proteins. There is no particular reason why their intravascular distribution should be greatly changed in the course of exercise. In addition, any major alteration in the binding protein level would be predicted on mathematical grounds to alter the GH half-life, as reported earlier in modeling studies (28). In fact, we do not observe this (see Table 1).

Although the present data suggest that a relationship exists between exercise intensity normalized against the LT and GH release, we cannot suggest a causal relationship. Because infusions of lactate do not stimulate GH release (21), it is unlikely that circulating lactate itself is responsible for the GH response to exercise. The LT may be a marker for other physiological events, e.g., intramuscular acidosis, mechano- or chemoreceptor activation, or relative muscle ischemia, and so on (31), which are more closely related to the stimulation of GH secretion during exercise. For example, changes in blood lactate and catecholamine release follow similar patterns in response to exercise (37). We hypothesize that the GH response to exercise is more strongly related to the central nervous system drive underlying the evident catecholamine responses. Indeed, sympathetic activity may be an important mediator of the GH response to acute exercise (5, 10, 23, 36), with greater sympathetic activity (reflected peripherally by epinephrine and norepinephrine release) associated with greater GH responses to exercise (19, 20). Presently, the precise relationship between peripheral plasma catecholamine concentrations and the activity of central adrenergic neurons (presumptively, α_2) that regulate GH secretion is unknown, although the blood GH and catecholamine responses to exercise training are parallel (36). Because the sympathetic (catecholaminergic) and parasympathetic (cholinergic) autonomic pathways (8) may, in part, regulate GH release during exercise, studies to systematically investigate the direct relationship between intensity of exercise and the central neuronal adrenergic outflow are warranted.

Although the present data may have implications for exercise prescription, it is unknown whether the greater stimulation of GH secretion with increasing exercise intensity will lead to greater clinical benefits. Administration of human GH to GH-deficient adults and abdominally obese men has been reported to reduce abdominal/visceral obesity, improve insulin sensitivity, affect lipoprotein and bone metabolism favorably, lower diastolic blood pressure, and increase muscular strength (1, 15, 16). Because exercise intensity appears to be linearly related to increases in endogenous GH secretion, we hypothesize that higher training intensities will have greater clinical utility than lower training intensities. This is based on the use of a 30-min exercise prescription. However, it is possible that longer-duration exercise at lower intensity may also be of clinical benefit. In addition, this conjecture should be tempered by the qualification

that the effects of exercise intensity on GH release in women, GH-deficient, and older and/or obese subjects may not be comparable to the present observations in young healthy men.

In summary, the present study indicates that, in young men, the magnitude of GH release rises linearly with increasing exercise intensity, with an apparent dose-response relationship observed between exercise intensity normalized against the LT and GH release. This augmentation of GH production rates with increasing intensity of exercise is attributable mechanistically to an increase in the mass of GH secreted per pulse. This appears to be a highly specific neuroendocrine response, as the number of GH secretory pulses and the GH half-life are not affected by exercise intensity.

The authors thank Greg Scharer and David Boyd of the University of Virginia General Clinical Research Center (GCRC) for computing assistance, Ginger Bauler of the GCRC Core Assay Lab, and Sandra Jackson and the nurses of the GCRC for expert clinical care.

Note

This study was supported in part by National Institutes of Health Grants NIA R01-AG14799 (to J. D. Veldhuis) and RR-00847 to the GCRC.

References

1. Bengtsson, B., S. Eden, L. Lonn, H. Kvist, A. Stokland, G. Lindstedt, I. Bosaeus, J. Tolli, L. Sjostrom, and O. G. Isaksson. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J. Clin. Endocrinol. Metab.* 76: 309–313, 1992.
2. Brozek, J., F. Grande, J. T. Anderson, and A. Keys. Densitometric analysis of body composition of men from girth measurements: revision of some quantitative assumptions. *Ann. NY Acad. Sci.* 110: 113–140, 1963.
3. Bunt, J. C., R. A. Boileau, J. M. Bahr, and R. Nelson. Sex and training differences in human growth hormone during prolonged exercise. *J. Appl. Physiol.* 61: 1796–1801, 1986.
4. Chang, F. E., W. G. Dodds, M. Sullivan, M. H. Kim, and W. B. Malarkey. The acute effects of exercise on prolactin and growth hormone secretion: comparison between sedentary women and women runners with normal and abnormal menstrual cycles. *J. Clin. Endocrinol. Metab.* 62: 551–556, 1986.
5. Chwalbinska-Moneta, J., H. Krysztofiak, A. Ziembra, K. Nazar, and H. Kaciuba-Uscilko. Threshold increases in plasma growth hormone in relation to plasma catecholamine and blood lactate concentrations during progressive exercise in endurance-trained athletes. *Eur. J. Appl. Physiol.* 73: 117–120, 1996.
6. Felsing, N. E., J. A. Brasel, and D. M. Cooper. Effect of low and high intensity exercise on circulating growth hormone in men. *J. Clin. Endocrinol. Metab.* 75: 157–162, 1992.

7. Friend, K., A. Iranmanesh, and J. D. Veldhuis. The orderliness of the growth hormone (GH) release process and the mean mass of GH secreted per burst are highly conserved in individual men on successive days. *J. Clin. Endocrinol. Metab.* 81: 3746–3753, 1996.
8. Giustina, A., and J. D. Veldhuis. Pathophysiological basis of the neuroregulation of the somatotrophic (GH) axis in experimental animals and the human. *Endocrine Rev.* In press.
9. Hartman, M. L., J. D. Veldhuis, M. L. Johnson, M. M. Lee, K. G. M. M. Alberti, E. Samojlik, and M. O. Thorner. Augmented growth hormone (GH) secretory burst frequency and amplitude mediate enhanced GH secretion during a two day fast in normal men. *J. Clin. Endocrinol. Metab.* 74: 757–765, 1992.
10. Hartman, M. L., J. D. Veldhuis, and M. O. Thorner. Normal control of growth hormone secretion. *Horm. Res.* 40: 30–47, 1992.
11. Holl, R., M. L. Hartman, J. D. Veldhuis, W. Taylor, and M. O. Thorner. Thirty second sampling of plasma growth hormone (GH) in man: correlation with sleep stages. *J. Clin. Endocrinol. Metab.* 72: 854–861, 1991.
12. Hollander, M., and D. A. Wolfe. *Nonparametric Statistical Methods*. New York: Wiley, 1973, p. 27–33.
13. Iranmanesh, A., B. Grisso, and J. D. Veldhuis. Low basal and persistent pulsatile growth hormone secretion are revealed in normal and hyposomatotropic men studied with a new ultrasensitive chemiluminescence assay. *J. Clin. Endocrinol. Metab.* 78: 526–535, 1994.
14. Iranmanesh, A., S. South, A. Y. Liem, D. Clemmons, M. O. Thorner, A. Weltman, and J. D. Veldhuis. Impact of age, percentage body fat, and serum testosterone concentration on the somatotrophic response to a three-day exogenous growth-hormone-releasing-hormone (GHRH) clamp. *Eur. J. Endocrinol.* In press.
15. Johannson, G., G. Grimby, K. S. Sunnerhagen, and B. Bengtsson. Two years of growth hormone (GH) treatment increase isometric and isokinetic muscle strength in GH-deficient adults. *J. Clin. Endocrinol. Metab.* 82: 2877–2883, 1997.
16. Johannson, G., P. Marin, L. Lonn, M. Ottosson, K. Stenlof, P. Bjorntorp, L. Sjostrom, and B. Bengtsson. Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism, and reduces diastolic blood pressure. *J. Clin. Endocrinol. Metab.* 82: 727–732, 1996.
17. Kanaley, J. A., J. Y. Weltman, J. D. Veldhuis, A. D. Rogol, M. L. Hartman, and A. Weltman. Human growth hormone response to repeated bouts of aerobic exercise. *J. Appl. Physiol.* 83: 1756–1761, 1997.
18. Katch, F. I., E. D. Michael, and S. M. Horvath. Estimation of body volume by underwater weighing: description of a simple method. *J. Appl. Physiol.* 23: 811–813, 1967.

19. Kjaer, M., P. A. Farrell, N. J. Christensen, and H. Galbo. Increased epinephrine response and inaccurate glucoregulation in exercising athletes. *J. Appl. Physiol.* 61: 1693–1700, 1986.
20. Kozlowski, S., J. Chwalbinska-Moneta, M. Vigas, H. Uscilko, and K. Nazar. Greater serum GH response to arm than to leg exercise performed at equivalent oxygen uptake. *Eur. J. Appl. Physiol.* 52: 11–135, 1983.
21. Lugar, A., B. Watschinger, P. Duester, T. Svoboda, M. Clodi, and G. P. Chrousos. Plasma growth hormone and prolactin responses to graded levels of acute exercise and to a lactate infusion. *Neuroendocrinology* 56: 112–117, 1992.
22. Straume, M., L. Chen, M. L. Johnson, and J. D. Veldhuis. Systems-level analysis of physiological regulatory interactions controlling complex secretory dynamics of growth hormone axis: a connectionistic network model. *Methods Neurosci.* 28: 270–310, 1995.
23. Thompson, D. L., J. Y. Weltman, A. D. Rogol, D. L. Metzger, J. D. Veldhuis, and A. Weltman. Cholinergic and opioid involvement in release of growth hormone during exercise and recovery. *J. Appl. Physiol.* 75: 870–878, 1993.
24. Veldhuis, J. D. Issues in quantifying pulsatile neurohormone release. In: *Methods in Neuroendocrinology: The Cellular and Molecular Neuropharmacology Series*, edited by L. D. Van de Kar. Boca Raton, FL: CRC, 1998, p. 181–203.
25. Veldhuis, J. D., M. Carson, and M. Johnson. The pituitary gland secretes in bursts: appraising the nature of glandular secretory impulses by simultaneous multiple-parameter deconvolution of plasma hormone concentrations. *Proc. Natl. Acad. Sci. USA* 84: 7686–7690, 1987.
26. Veldhuis, J. D., and M. Johnson. Cluster analysis: a simple, versatile, and robust algorithm for endocrine pulse detection. *Am. J. Physiol.* 250 (Endocrinol. Metab. 13): E486–E493, 1986.
27. Veldhuis, J. D., and M. L. Johnson. Specific methodological approaches to selected contemporary issues in deconvolution analysis of pulsatile neuroendocrine data. *Methods Neurosci.* 28: 25–92, 1995.
28. Veldhuis, J. D., M. L. Johnson, L. M. Faunt, M. Mercado, and G. Baumann. Influence of the high-affinity growth hormone (GH)-binding protein on plasma profiles of free and bound GH and on the apparent half-life of GH. *J. Clin. Invest.* 91: 629–641, 1993.
29. Veldhuis, J. D., A. B. Lassiter, and M. L. Johnson. Operating behavior of dual or multiple endocrine pulse generators. *Am. J. Physiol.* 259 (Endocrinol. Metab. 22): E351–E361, 1990.
30. Veldhuis, J. D., A. Y. Liem, S. South, A. Weltman, J. Weltman, D.A. Clemmons, R. Abbott, T. Mulligan, M. L. Johnson, S. Pincus, M. Straume, and A. Iranmanesh. Differential impact of age, sex steroid hormones, and obesity on basal versus pulsatile growth hormone secretion in

men as assessed in an ultrasensitive chemiluminescence assay. *J. Clin. Endocrinol. Metab.* 80: 3209–3222, 1995.

31. Vissing, J., S. F. Vissing, D. A. MacLean, B. Saltin, B. Quistorff, and R. G. Haller. Sympathetic activation in exercise is not dependent on muscle acidosis. *J. Clin. Invest.* 101: 1654–1660, 1998.

32. Weltman, A., R. L. Seip, D. Snead, J. Y. Weltman, E. M. Haskvitz, W. S. Evans, J. D. Veldhuis, and A. D. Rogol. Exercise training at and above the lactate threshold in previously untrained women. *Int. J. Sports Med.* 13: 257–263, 1992.

33. Weltman, A., D. Snead, P. Stein, R. Seip, R. Schurrer, R. Rutt, and J. Y. Weltman. Reliability and validity of a continuous incremental treadmill protocol for the determination of lactate threshold, fixed blood lactate concentrations, and $\dot{V}O_2\text{max}$. *Int. J. Sports Med.* 11: 26–32, 1990.

34. Weltman, A., J. Y. Weltman, M. L. Hartman, R. D. Abbott, A. D. Rogol, W. S. Evans, and J. D. Veldhuis. Relationship between age, percentage body fat, fitness, and 24-hour growth hormone release in healthy young adults: effects of gender. *J. Clin. Endocrinol. Metab.* 78: 543–548, 1993.

35. Weltman, A., J. Y. Weltman, R. Schurrer, W. S. Evans, J. D. Veldhuis, and A. D. Rogol. Endurance training amplifies the pulsatile release of growth hormone: effects of training intensity. *J. Appl. Physiol.* 72: 2188–2196, 1992.

36. Weltman, A., J. Y. Weltman, C. J. Womack, S. E. Davis, J. L. Blumer, G. A. Gaesser, and M. L. Hartman. Exercise training decreases the growth hormone (GH) response to acute constant-load exercise. *Med. Sci. Sports Exerc.* 29: 669–676, 1997.

37. Weltman, A., C. M. Wood, C. J. Womack, S. E. Davis, J. L. Blumer, J. Alvarez, K. Sauer, and Gaesser, G. A. Catecholamine and blood lactate responses to incremental rowing and running exercise. *J. Appl. Physiol.* 76: 1144–1149, 1994.

38. West, C. R., K. J. Lookingland, and H. A. Tucker. Regulation of growth hormone-releasing hormone and somatostatin from perfused, bovine hypothalamic slices. III. Reciprocal feedback between growth hormone-releasing hormone and somatostatin. *Domest. Anim. Endocrinol.* 14: 358–366, 1997.

39. Willoughby, J. O., M. Brogan, and R. Kapoor. Hypothalamic interconnections of somatostatin and growth hormone releasing factor neurons. *Neuroendocrinology* 50: 584–591, 1989.

40. Wilmore, J. H. A simplified method for the determination of residual lung volume. *J. Appl. Physiol.* 27: 96–100, 1969.