Exercise-dependent growth hormone release is linked to markers of heightened central adrenergic outflow

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Abstract:

To test the hypothesis that heightened sympathetic outflow precedes and predicts the magnitude of the growth hormone (GH) response to acute exercise (Ex), we studied 10 men [age 26.1 ± 1.7 (SE) yr] six times in randomly assigned order (control and 5 Ex intensities). During exercise, subjects exercised for 30 min (0900–0930) on each occasion at a single intensity: 25 and 75% of the difference between lactate threshold (LT) and rest (0.25LT, 0.75LT), at LT, and at 25 and 75% of the difference between LT and peak (1.25LT, 1.75LT). Mean values for peak plasma epinephrine (Epi), plasma norepinephrine (NE), and serum GH concentrations were determined [Epi: 328 ± 93 (SE), 513 ± 76, 584 ± 109, 660 ± 72, and 2,614 ± 579 pmol/l; NE: 2.3 ± 0.2, 3.9 ± 0.4, 6.9 ± 1.0, 10.7 ± 1.6, and 23.9 ± 3.9 nmol/l; GH: 3.6 ± 1.5, 6.6 ± 2.0, 7.0 ± 2.0, 10.7 ± 2.4, and 13.7 ± 2.2 µg/l for 0.25, 0.75, 1.0, 1.25, and 1.75LT, respectively]. In all instances, the time of peak plasma Epi and NE preceded peak GH release. Plasma concentrations of Epi and NE always peaked at 20 min after the onset of Ex, whereas times to peak for GH were 54 ± 6 (SE), 44 ± 5, 38 ± 4, 38 ± 4, and 37 ± 2 min after the onset of Ex for 0.25–1.75LT, respectively. ANOVA revealed that intensity of exercise did not affect the foregoing time delay between peak NE or Epi and peak GH (range 17–24 min), with the exception of 0.25LT ($P < 0.05$). Within-subject linear regression analysis disclosed that, with increasing exercise intensity, change in (Δ) GH was proportionate to both ΔNE ($P = 0.002$) and ΔEpi ($P = 0.014$). Furthermore, within-subject multiple-regression analysis indicated that the significant GH increment associated with an antecedent rise in NE ($P = 0.02$) could not be explained by changes in Epi alone ($P = 0.77$). Our results suggest that exercise intensity and GH release in the human may be coupled mechanistically by central adrenergic activation.

Keywords: catecholamines | epinephrine | norepinephrine

Article:

Although an acute bout of exercise of appropriate intensity will evoke a large increase in serum GH concentrations (2,6, 8, 10, 19,21, 23, 29, 33,37, 38, 39, 41,42), few quantitative correlates are available to link central nervous-system activation with growth hormone (GH) release to greater exercise intensities. We recently reported a linear dose-response relationship between exercise intensity and incremental GH release in young men across a wide span of exertional intensities beginning below the lactate threshold (LT) (29). On the basis of these data, we hypothesized that progressive augmentation of GH release at higher exercise intensities may be mediated by antecedent but proportionate changes in neurotransmitter activity.

Epinephrine (Epi), norepinephrine (NE), acetylcholine, GABA, and opioids have been variously suggested as plausible neuromodulators of GH release during exercise (13). Our laboratory and those of others have reported that, during acute progressively incremental exercise, blood catecholamine concentrations rise with increasing exercise intensity (26, 28, 30,40). Such observations suggest that heightened central nervous system sympathetic outflow may contribute to the GH secretory response to acute exercise. In the present study, we used a series of acute exercise bouts of varying intensity, assigned in random order on separate study days, to examine the relationship between the simultaneously monitored release of GH and NE or Epi during exercise and recovery. This randomized block design was intended to obviate any serial confounds otherwise possibly introduced by a schedule of continuously increasing exercise intensity in the same setting, and it may also minimize anticipatory confounds. We hypothesized that, if increased sympathetic activity is an important mediator of the GH response to exercise (e.g., via α_2-central adrenergic neurons), greater sympathetic outflow, as reflected peripherally by NE and Epi release, should precede in time and correlate in incremental amounts with heightened GH secretory responses to exercise.

METHODS

Rationale. The present design uses randomly ordered independent variable-intensity exercise sessions conducted at the same time of day in a controlled nutritional context to test the relative timing of NE and Epi release and GH secretion in young men. This strategy was intended to limit any ad seriatim carryover effects. By imposing a large (sub- vs. supra-LT) range of exercise intensities, we explore the relationship, if any, between incremental NE and/or Epi release and incremental GH secretion. Individual regression analyses in 10 subjects are used to establish the consistency of observed relationships.

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 Health System, before entering the study. Each subject underwent a detailed medical history and physical examination, and no subject had a history of pituitary, renal, hepatic, metabolic, or other systemic disease. The subjects were nonsmokers, did not abuse alcohol, and were not taking any medication known to affect GH secretion. Screening laboratory chemistry revealed normal hematologic, renal, hepatic, metabolic, and thyroid function. Subjects refrained from exercise for 24 h before each evaluation. An estimate of statistical power was determined a priori for $n = 10$ with approximate

statistical power of 85% for detecting a 50% treatment effect of exercise at $P = 0.05$ by using serum GH concentration as the measured response variable.

Experimental design. Each volunteer first completed a treadmill test to assess level of cardiovascular fitness and underwent hydrostatic weighing to determine body density at the Exercise Physiology Laboratory of the General Clinical Research Center (GCRC). Subjects were then evaluated on six separate and randomly ordered occasions, five with exercise and one at rest. The admissions were scheduled at least 7 days apart, and no more than two admissions were allowed within 2 mo (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 O_2 uptake ($\dot{V}o_2$) at the LT and $\dot{V}o_2$ at rest (0.25LT and 0.75LT, respectively), at LT (LT) and at 25% and 75% of the difference between the $\dot{V}o_2$ at LT and peak $\dot{V}o_2$ ($\dot{V}o_{2\,peak}$) (1.25LT and 1.75LT, respectively), on the basis of results obtained during a prior LT and $\dot{V}o_{2\,peak}$ protocol (see *LT* and *$\dot{V}o_{2\,peak}$* below).

Body composition. Body density was assessed by hydrostatic weighing (20). 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 (43). The computational procedure of Brozek et al. (1) was used to determine percent body fat from body density measurements.

LT and $\dot{V}o_{2\,peak}$. A continuous treadmill (Quinton Q 65 treadmill) exercise protocol with increasing velocity until volitional fatigue was used to assess LT and $\dot{V}o_{2\,peak}$. 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 (model 2900Z metabolic measurement cart, SensorMedics, 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 (2700 Select biochemistry analyzer, Yellow Springs Instruments, Yellow Springs, OH). The test was terminated when the subject reached volitional exhaustion. $\dot{V}o_{2\,peak}$ was chosen as the highest $\dot{V}o_2$ attained.

Determination of LT. The blood lactate-velocity relationship that was obtained from the LT/$\dot{V}o_{2\,peak}$ 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 (36).

Exercise and control days. Subjects were admitted to the GCRC on the evening before the exercise and control studies to allow for adaptation to the unit and a uniform overnight fast. 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 possible confounding effects of meals on GH secretion, subjects then fasted until the end of the study (15). At 2100, intravenous cannulas were placed bilaterally in each forearm vein.

Subjects remained at the GCRC after eating their snack and were asked to turn lights off by 2300 (16). Volunteers were awakened at 0600. At this time, basal metabolic parameters were measured for 30 min by using a Delta-Trac bedside metabolic unit (SensorMedics, Anaheim, CA). Beginning at 0700, blood samples were withdrawn every 10 min until 1300 for later measurement of serum GH concentrations. Beginning at 0800, blood samples were withdrawn every 20 min until 1300 for later catecholamine analysis. After 2 h of baseline blood sampling, subjects began their exercise bout or remained at rest (control). The exercise bout began at 0900 and continued until 0930. During the exercise bout, blood lactate was also measured every 10 min. Metabolic data were measured minute-by-minute by using open-circuit spirometry (model 2900Z metabolic measurement cart, SensorMedics). At the end of the study (1300) subjects were fed and discharged from the unit.

GH analysis. GH concentrations in all serum samples (0600–1200) were measured by using a recently validated ultrasensitive (0.005 µg/l threshold) chemiluminescence-based assay (Nichols, San Juan Capistrano, CA) (7, 18, 35). The chemiluminescent assay detects predominately the 22-kDa form of GH, with 34% cross-reactivity with 20-kDa GH (methionylated). The median intra-assay coefficient of variation (CV) for the GH assay was 6.0%, and the interassay CV was 9.9%. Secretory data are expressed per unit distribution volume in each subject, thereby mirroring GH concentration bathing the target tissue.

Catecholamine analysis. Plasma catecholamine analysis was performed by using a modification of the procedure published by Bioanalytic Systems (BAS; LCEC Application Note no. 14). Blood samples (4 ml) were collected in Vacutainer tubes containing EDTA and transferred to polypropylene tubes containing an EGTA-glutathione stabilizer (20 ml/ml of blood). The stabilizer tubes, prepared before the admission, were kept at −70 C until analyzed for catecholamine content.

The determination of plasma Epi and NE concentrations was performed by using HPLC with electrochemical detection. Plasma samples were thawed on ice and adsorbed to 50 mg of acid-washed alumina buffered to pH 8.65 with 1 M Tris buffer containing 2% EDTA. After being shaken for 10 min, the alumina was sedimented by centrifugation and washed twice with deionized water. After the second wash, the alumina was resuspended in deionized water and transferred to a 2-µm-pore-size regenerated cellulose microfilter. The filter was centrifuged for 3 min at low speed, and the filtrate was discarded. The filter was then transferred to a clean centrifuge tube, and catecholamines were eluted with 0.2 ml of 0.1 M perchloric acid. This eluate was injected directly onto the HPLC column.

Chromatographic analysis was performed by using a BAS 400 liquid chromatography system with electrochemical detection utilizing a glassy carbon working electrode with an applied potential of +650 mV. The mobile phase consisted of 0.17 M monochloroacetic acid and 0.12 M NaOH containing 200 mg/l SDS. A BAS 3m Phase 11 ODS column (100 × 3.2 mm) was used and maintained at 30°C with a heater block. The solvent flow rate was 0.9 ml/min. Peak areas

were quantified by using a Varian model 4270 integrator set to an attenuation of 16 and a chart speed of 0.5 cm/min.

An internal standard dihydroxybenzylamine was used in the analysis, and the ratio of the area of the catecholamine peak to the area of the dihydroxybenzylamine peak was used to calculate the catecholamine concentrations. The limits of detectability for both Epi and NE were 136 pmol/l. The percent recovery for the extraction of NE and Epi was 85 and 77%, respectively. Epi and NE values were corrected for the internal standard. The within-day CVs for Epi and NE were 1.25 and 3.7% respectively; the between-day CVs were 3.4 and 4.7%, respectively. This assay was sensitive enough to measure all resting and exercise catecholamine levels.

Statistical analysis. ANOVA with repeated measures was used to determine whether the difference between the times of the plasma Epi or NE peak concentrations and the serum GH peak concentration was consistent, independently of exercise intensity.

Separate regression models were estimated for each of the 10 study subjects with the incremental change in serum GH concentration (peak − baseline) regressed against *1*) the change in plasma NE, *2*) the change in plasma Epi (simple-regression models), and *3*) the change in NE and Epi (multiple-regression model).

The set of 10 slopes associated with the individual regression models was then evaluated by the Wilcoxon signed-rank test against a null hypothesis of a zero median slope for the group (17).

RESULTS

All data are presented as means ± SE.

Subjects' $\dot{V}_{O_2}$ at LT averaged 2.72 ± 0.18 l/min (32.6 ± 2.6 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}), $\dot{V}_{O_2 peak}$ was 3.93 ± 0.19 l/min (47.9 ± 2.2 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}), $\dot{V}_{O_2}$ at LT/$\dot{V}_{O_2 peak}$ was 0.68 ± 0.4, and percent body fat was $19.3 \pm 1.9\%$. As expected, $\dot{V}_{O_2}$ at LT and $\dot{V}_{O_2 peak}$ were strongly correlated ($r = 0.79$)

$\dot{V}_{O_2}$ 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 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 $\dot{V}_{O_2 peak}$, respectively. Whether data were examined relative to LT or relative to $\dot{V}_{O_2 peak}$, 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 ($P < 0.05$). These mean data as well as the 6-h GH data have been presented previously (29).
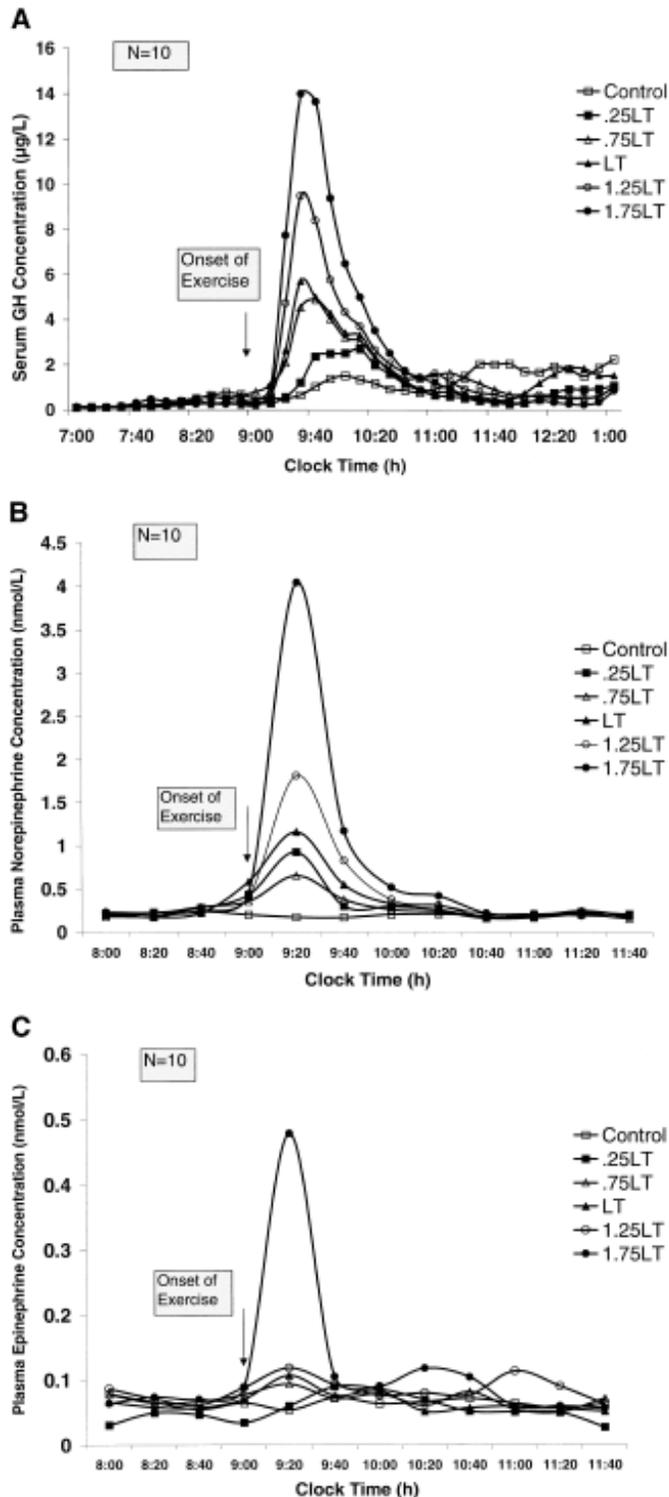
Fig. 1. Serum growth hormone (GH; *A*) and plasma norepinephrine (NE; *B*) and epinephrine (Epi; *C*) concentrations during repetitive blood sampling over 6 h at rest (control) and during separate exercise sessions assigned with randomly ordered intensities of 0.25, 0.75, 1.0, 1.25, and 1.75 of the individual lactate threshold (LT). 0.25LT and 0.75LT, 25 and 75% of the difference between the O_2 uptake achieved at LT and the O_2 uptake at rest; LT, at LT; 1.25LT and 1.75LT, 25 and 75% of the difference between the O_2 uptake achieved at LT and peak O_2 uptake. Values are means ± SE; $n = 10$ men. Catecholamine values between 12:00 and 1:00 were negligible and are not shown.

Figure 1 shows the mean serum GH (*A*), and plasma NE (*B*) and Epi (*C*) concentrations during blood sampling over 6 h during control, 0.25LT, 0.75LT, LT, 1.25LT, and 1.75LT conditions. A similar dose-response pattern was observed for GH and NE, in which increasing exercise intensity resulted in an increase in GH and NE. Although Epi rose with increasing exercise intensity, the effects of exercise intensity on Epi release were most pronounced when the 1.75LT intensity was reached.

Table 1 shows peak concentrations of GH, NE, and Epi in relation to exercise intensities of 0.25LT, 0.75LT, LT, 1.25LT, and 1.75LT. ANOVA revealed the following: *1*) for peak GH, all exercise comparisons were significantly different with the exception of 0.25LT vs. 0.75LT, 0.75LT vs. LT, and 1.25LT vs. 1.75LT;*2*) for peak NE, all exercise comparisons were significantly different with the exception of 0.25LT vs. 0.75LT and LT, 0.75LT vs. LT, and LT vs. 1.25LT; and *3*) for peak Epi, the 1.75LT exercise condition was significantly different from all other exercise intensities, but no other exercise comparisons were different. Analysis of the sets of individual within-subject regression models revealed that peak GH, NE, and Epi increased significantly with each exercise intensity in a simple linear manner ($P = 0.002, P = 0.002$, and $P = 0.004$, respectively).

Table 1. Peak serum growth hormone and plasma norepinephrine and epinephrine concentrations attained over 6 h during 0.25LT, 0.75LT, LT, 1.25LT, and 1.75LT exercise conditions

Exercise Intensity	GH, μg/l	NE, nmol/l	Epi, pmol/l
0.25LT	3.6 ± 1.5*	2.3 ± 0.2*	328 ± 93*
0.75LT	6.6 ± 2.0*†	3.9 ± 0.4*†	513 ± 76*
LT	7.0 ± 2.0†	6.9 ± 1.0†‡	584 ± 109*
1.25LT	10.7 ± 2.4‡	10.7 ± 1.6‡	660 ± 72*
1.75LT	13.8 ± 2.2‡	23.9 ± 3.9§	2,614 ± 579†

Values are means ± SE for 10 men. GH, growth hormone; NE, norepinephrine; Epi, epinephrine; 0.25LT and 0.75LT, 25 and 75% of the difference between the O_2 uptake achieved at lactate threshold (LT) and the O_2 uptake at rest; LT, at LT; 1.25LT and 1.75LT, 25 and 75% of the difference between the O_2 uptake achieved at LT and peak O_2 uptake. Values with no shared superscripts are significantly different (ANOVA, $P < 0.05$).

Table 2. Time to peak (from the onset of exercise) for serum growth hormone and plasma norepinephrine and epinephrine and the time delay between peak NE and EPI and peak GH

Exercise Intensity	Time to Peak GH, min	Time to Peak NE and Epi, min	Time Delay Between Peak GH and Peak NE and Epi, min
0.25LT	54.0 ± 6.4*	20.0 ± 0.0	34.0 ± 6.4*
0.75LT	44.0 ± 4.5†	20.0 ± 0.0	24.0 ± 4.5†
LT	38.0 ± 3.9†	20.0 ± 0.0	18.0 ± 3.9†
1.25LT	38.0 ± 3.9†	20.0 ± 0.0	18.0 ± 3.9†
1.75LT	37.0 ± 1.5†	20.0 ± 0.0	17.0 ± 1.5†

Values are means ± SE for 10 men. Values with no shared superscripts are significantly different (ANOVA, $P < 0.05$).

Table 2 summarizes the times to peak for GH, NE, and Epi as well as the latency between peak NE or Epi and peak GH. The time to peak GH was not affected by exercise intensity, with the exception of the 0.25LT condition, in which time to peak GH was significantly greater than for

all other exercise intensities. Peak plasma NE and Epi occurred 20 min after the onset of exercise in all subjects and always preceded peak GH. With the exception of the 0.25LT condition, intensity of exercise did not affect the time delay between peak NE or Epi and peak GH.

The individual relationships between the increment (from baseline to peak) in GH vs. the change in NE and Epi are shown in Figs. 2 and 3, respectively. The group relationships are derived from the average of intercepts and slopes from within-subject regression results. With increasing exercise intensity, the change in GH was linearly related to the change in NE ($P = 0.002$) and to the change in Epi ($P = 0.014$). Multiple-regression analysis to account for NE and Epi covariance revealed that the GH rise associated with an increase in NE ($P = 0.02$) could not be explained by changes in Epi alone ($P = 0.77$); i.e., NE rises contributed independently to the GH incremental response.
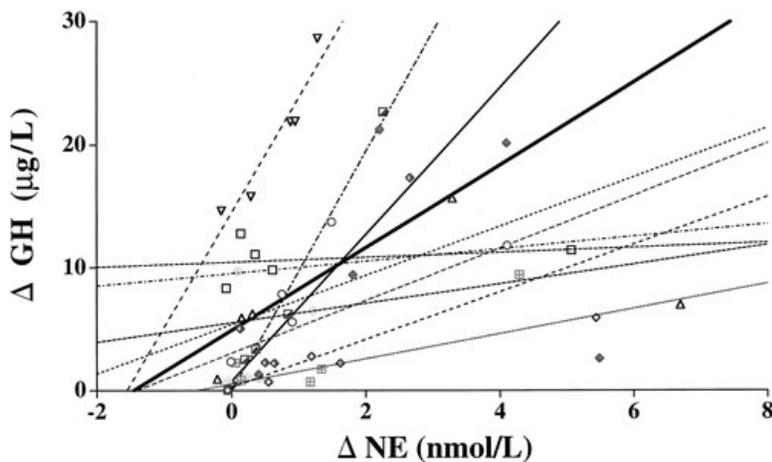
Fig. 2. Individual (and group, solid line) relationships between the incremental changes (from baseline to peak, Δ) in serum GH and plasma NE concentrations in 10 young men studied at different exercise intensities assigned in random order (Fig. 1).
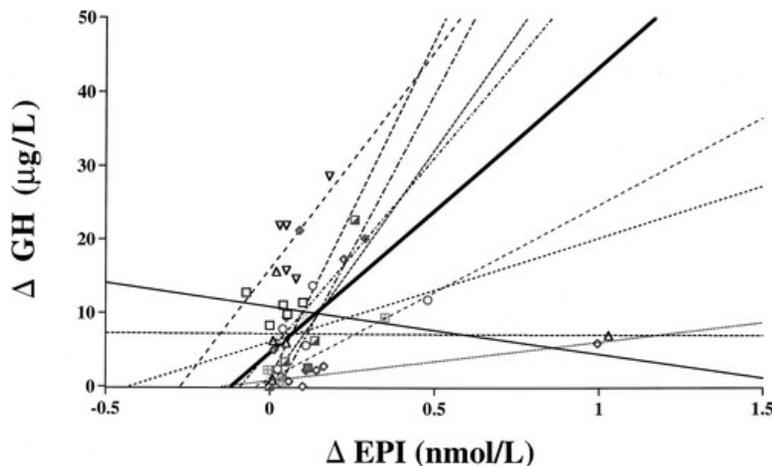
Fig. 3. Individual (and group, solid line) relationships between the incremental changes (from baseline to peak) in serum GH and plasma Epi concentrations in 10 young men studied at different exercise intensities assigned in random order (Fig. 1).

DISCUSSION

Although many clinical studies have attempted to discern the individual contributions of various neurotransmitters to exercise-induced GH release, no single mechanism has emerged as primary. Indeed, catecholamines, muscarinic agents, opiatergic pathways, GABA-ergic receptors, and so forth may all modify GH secretion (5, 11, 13,22, 25, 32). For example, available experimental evidence suggests that α_2-adrenergic pathways may limit somatostatin release (15) and stimulate GH-releasing hormone release, thus triggering GH secretion. Conversely, β_2-adrenergic agonists likely block GH secretion by eliciting somatostatin release (13). Although the effects of changing adrenergic activity on GH release during exercise are less well understood, blood concentrations of both Epi and NE rise with escalating exercise intensity (26, 28, 30,40). Catecholamines can directly stimulate GH secretion from rodent pituitary tissue in vitro (13). In addition, central nervous system hypothalamic adrenergic activity may modulate the exercise-driven release of GH. In support of the second notion, both nonselective (propranolol) and cardioselective (metoprolol) β_1-adrenergic receptor blockers can significantly augment the GH response to exercise (34). Conversely, salbutamol and broxaterol (both selective β_2-agonists) suppress the exercise-induced release of GH (12). Thus we postulate that exercise favors *1*) an increase in stimulatory α_2-adrenergic tone and *2*) partial suppression of inhibitory β_2-adrenergic tone. However, the effects of α-receptor blockade on exercise-stimulated GH are less clear, because not all papers report that phentolamine (a nonspecific α-receptor antagonist) suppresses GH release during exercise (14,24, 31).

The present study shows that peripheral markers of heightened adrenergic outflow precede and are quantitative physiological correlates of exercise-intensity-dependent GH release in humans. First, peak plasma concentrations of NE and Epi always preceded maximal GH release. The zenith of NE and Epi in blood always occurred during the ongoing exercise stimulus, whereas peak serum GH concentrations developed toward the end of or after exercise. A wide range of intensities of exercise did not influence the time delay between peak NE or Epi and peak GH appearance in the blood (~20 min), with the exception of the lowest exercise intensity of 0.25LT. However, at the latter intensity, GH responses did not differ significantly from control (Fig. 1; $P > 0.29$). Second, with increasing exercise intensity, the increment (change from baseline to peak) in GH was linearly related to the increment in NE ($P = 0.002$) and that in Epi ($P = 0.014$) (Figs. 2 and 3). Multiple-linear regression analysis to allow for expected correlations between NE and Epi release revealed that the dominant relationship was between incremental changes in GH and NE ($P = 0.02$), rather than Epi ($P = 0.77$). We interpret these findings to indicate that higher exercise intensities may drive increased GH release in part by central adrenergic activation. It should be noted that, whereas NE and Epi were sampled every 20 min and GH every 10 min (to stay within institutional review board guidelines for blood withdrawal), partial censoring of the exact timing of the NE or Epi peaks would not influence their consistent appearance before GH (Fig.1*A*). In addition, the different distribution volumes for these analytes would not alter their strong linear relationships, because we regressed incremental NE or Epi against incremental GH release (Figs. 2 and 3). Nonetheless, hormone-specific deconvolution analysis to correct for unequal disappearance rates, if applied to even more intensively sampled time series, would likely portray the absolute latencies in endogenous appearance times even more accurately.

Although not addressed by the present study, cholinergic, opiatergic, and other pathways can also modulate GH release. Cappa et al. (3) reported that pyridostigmine (an indirect cholinergic agonist) and exercise stimulated GH release additively. We corroborated that oral pyridostigmine, alone or in combination with the opiate receptor antagonist naltrexone, can potentiate exercise-induced GH release (33). In addition, although atropine (a muscarinic-receptor blocker) inhibits the GH response to exercise (4), this agent also inhibits GH secretion in response to virtually all stimuli (13). The role of opioids in the control of exercise-induced GH release is more controversial. Moretti et al. (27) reported that high doses of naloxone (an opiate-receptor antagonist) completely blocked exercise-induced GH release in well-trained competitive athletes. In contrast, Coiro et al. (9) and analyses from our laboratory (33) noted that naloxone and naltrexone, respectively, did not inhibit exercise-stimulated GH release in subjects who were not trained athletes. Naltrexone also did not alter the rise in GH concentrations stimulated by pyridostigmine (33), which would speak against a major interaction between opiatergic and cholinergic pathways in the exercise effect (33).

In conclusion, the present analysis of the intensity-dependent effects of a physiological exercise stimulus identifies precedent and proportionate increases in markers of central adrenergic outflow and exercise-induced GH release in young men. Comodulatory effects of cholinergic and/or opiatergic signals are not excluded by these findings. Indeed, exercise may alter the activity of several neurotransmitter pathways concurrently or in succession (13).

Note

References

1. Brozek J, Grande F, Anderson JT, and Keys A. Densitometric analysis of body composition of men from girth measurements: revision of some quantitative assumptions. Ann NY Acad Sci 110: 113–140, 1963.

2. Bunt JC, Boileau RA, Bahr JM, and Nelson R. Sex and training differences in human growth hormone during prolonged exercise. J Appl Physiol 61: 1796–1801, 1986.

3. Cappa M, Grossi A, Benedetti S, Drago F, Loche S, and Ghigo E. Effect of the enhancement of cholinergic tone by pyridostigmine on the exercise-induced growth hormone release in man. J Endocrinol Invest 16: 421–424, 1993.

4. Casanueva FF, Villaneuva L, Cabranes JA, Cabezas-Carrato J, and Fernandez-Cruz A. Cholinergic mediation of growth hormone secretion elicited by arginine, clonidine, and physical exercise in man. J Clin Endocrinol Metab 59: 526–530, 1984.

5. Cella SG, Picotti GB, and Mueller EE. Alpha 2-adrenergic stimulation enhances growth hormone secretion in the dog: a presynaptic mechanism? Life Sci 32: 2785–2792, 1983.

6. Chang FE, Dodds WG, Sullivan M, Kim MH, and Malarkey WB. 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.

7. Chapman IM, Hartman ML, Straume M, Johnson ML, Veldhuis JD, and Thorner MO. Enhanced sensitivity growth hormone chemiluminescence assay reveals lower postglucose nadir GH concentrations in men than women. J Clin Endocrinol Metab 78: 1312–1319, 1994.

8. Chwalbinska-Moneta J, Krysztofiak H, Ziemba A, Nazar K, and Kaciuba-Uscilko H. 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.

9. Coiro V, Volpi R, Maffei ML, Caoazza A, Caffarri G, Capretti L, Colla R, and Chiodera P. Opioid modulation of the gamma-aminobutyric acid-controlled inhibition of exercise-stimulated growth hormone and prolactin secretion in normal man. Eur J Endocrinol 131: 50–55, 1994.

10. Felsing NE, Brasel JA, and Cooper DM. Effect of low and high intensity exercise on circulating growth hormone in men. J Clin Endocrinol Metab 75: 157–162, 1992.

11. Ghigo E, Bellone J, Arvat E, Mazza E, Cella SG, Brambilla F, Mueller EE, and Camanni F. Effect of a- and b-adrenergic agonists and antagonists on growth hormone secretion in man. J Neuroendocrinol 2: 157–159, 1990.

12. Giustain A, Malerba M, Bresciani E, Desenzani P, Licini M, Zaltieri G, and Grassi V. Effect of two b2-agonist drugs, salbutamol and broxaterol, on the growth hormone response to exercise in adult patients with asthmatic bronchitis. J Endocrinol Invest 18: 847–852, 1995.

13. Giustina A and Veldhuis JD. Pathophysiological basis of the neuroregulation of the somatotropic (GH) axis in experimental animals and the human. Endocr Rev 19: 717–797, 1998.

14. Hansen AP. The effect of adrenergic blockade on the exercise-induced serum growth hormone rise in normals and juvenile diabetics. J Clin Endocrinol Metab 33: 807–812, 1971.

15. Hartman ML. Physiological regulators of growth hormone secretion. In: Growth Hormone in Adults, edited by Juul A and Jorgensen JOL. Cambridge, UK: Cambridge Univ. Press, 2000, p. 5–35.

16. Holl R, Hartman ML, Veldhuis JD, Taylor W, and Thorner MO. Thirty second sampling of plasma growth hormone (GH) in man: correlation with sleep stages. J Clin Endocrinol Metab 72: 854–861, 1991.

17. Hollander M and Wolfe DA. Nonparametric Statistical Methods. New York: Wiley, 1973, p. 27–33.

18. Iranmanesh A, Grisso B, and Veldhuis JD. 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.

19. Kanaley JA, Weltman JY, Veldhuis JD, Rogol AD, Hartman ML, and Weltman A. Human growth hormone response to repeated bouts of aerobic exercise. J Appl Physiol 83: 1756–1761, 1997.

20. Katch FI, Michael ED, and Horvath SM. Estimation of body volume by underwater weighing: description of a simple method. J Appl Physiol 23: 811–813, 1967.

21. Kozlowski S, Chwalbinska-Moneta J, Vigas M, Uscilko H, and Nazar K. Greater serum GH response to arm than to leg exercise performed at equivalent oxygen uptake. Eur J Appl Physiol 52: 131–135, 1983.

22. Lancranjan I and Marback P. New evidence for GH modulation by alpha-adrenergic system in man. Metabolism 26: 1225–1229, 1977.

23. Lugar A, Watschinger B, Duester P, Svoboda T, Clodi M, and Chrousos GP. Plasma growth hormone and prolactin responses to graded levels of acute exercise and to a lactate infusion. Neuroendocrinology 56: 112–117, 1992.

24. Martin JB. Neural regulation of growth hormone secretion. Medical progress report. N Engl J Med 288: 1384–1393, 1973.

25. Mauras N, Blizzard RM, Thorner MO, and Rogol AD. Selective b1-adrenergic receptor-blockade with atenolol enhances basal and growth hormone releasing hormone mediated growth hormone release in man. Metabolism 36: 369–372, 1987.

26. Mazzeo RS and Marshall P. Influence of plasma catecholamines on the lactate threshold during graded exercise. J Appl Physiol 67: 1319–1322, 1989.

27. Moretti C, Fabri A, Gnessi L, Cappa M, Calzolari A, Fraioli F, Grossman A, and Besser GM. Naloxone inhibits exercise-induced release of PRL and GH in athletes. Clin Endocrinol (Oxf) 18: 135–138, 1983.

28. Podolin DA, Munger PA, and Mazzeo RS. Plasma catecholamine and lactate response during graded exercise with varied glycogen conditions. J Appl Physiol 71: 1427–1433, 1991.

29. Pritzlaff CJ, Wideman L, Weltman JY, Abbott RD, Gutgesell ME, Hartman ML, Veldhuis JD, and Weltman A. Impact of acute exercise intensity on pulsatile growth hormone release in men. J Appl Physiol 87: 498–504, 1999.

30. Schneider DA, McGuiggin ME, and Kaminmori GH. A comparison of the blood lactate and plasma catecholamine thresholds in untrained male subjects. Int J Sports Med 13: 562–566, 1992.

31. Sutton J and Lazarus L. Effect of adrenergic blocking agents on growth hormone responses to physical exercise. Horm Metab Res 6: 428–429, 1974.

32. Tatar P and Vigas M. Role of alpha-1 and alpha-2 adrenergic receptors in the GH and prolactin response to insulin-induced hypoglycemia in man. Neuroendocrinology 39: 275–281, 1980.

33. Thompson DL, Weltman JY, Rogol AD, Metzger DL, Veldhuis JD, and Weltman A. Cholinergic and opioid involvement in release of growth hormone during exercise and recovery. J Appl Physiol 75: 870–878, 1993.

34. Uusitupa M, Siitonen O, Harkonen M, Gordin A, Aro A, Hersio K, Johansson G, Korhonen T, and Rauramaa R. Modification of the metabolic and hormonal response to physical exercise by beta-blocking agents. Ann Clin Res 14: 165–167, 1982.

35. Veldhuis JD, Liem AY, South S, Weltman A, Weltman J, Clemmons DA, Abbott R, Mulligan T, Johnson ML, Pincus S, Straume M, and Iranmanesh A. Differential impact of age, sex steroid hormones, and obesity on basal vs. pulsatile growth hormone secretion in men as assessed in an ultrasensitive chemiluminescence assay. J Clin Endocrinol Metab 80: 3209–3222, 1995.

36. Weltman A, Snead D, Stein P, Seip R, Schurrer R, Rutt R, and Weltman JY. Reliability and validity of a continuous incremental treadmill protocol for the determination of lactate threshold, fixed blood lactate concentrations, and V̇ O2 max. Int J Sports Med 11: 26–32, 1990.

37. Weltman A, Weltman JY, Hartman ML, Abbott RD, Rogol AD, Evans WS, and Veldhuis JD. 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.

38. Weltman A, Weltman JY, Schurrer R, Evans WS, Veldhuis JD, and Rogol AD. Endurance training amplifies the pulsatile release of growth hormone: effects of training intensity. J Appl Physiol 72: 2188–2196, 1992.

39. Weltman A, Weltman JY, Womack CJ, Davis SE, Blumer JL, Gaesser GA, and Hartman ML. Exercise training decreases the growth hormone (GH) response to acute constant-load exercise. Med Sci Sports Exerc 29: 669–676, 1997.

40. Weltman A, Wood CM, Womack CJ, Davis SE, Blumer JL, Alvarez J, Sauer K, and Gaesser GA. Catecholamine and blood lactate responses to incremental rowing and running exercise. J Appl Physiol 76: 1144–1149, 1994.

41. Wideman L, Weltman JY, Shah N, Story S, Bowers CY, Veldhuis JD, and Weltman A. Gender impact on the GH response to exercise. In: Sex-Steroid Interactions With Growth Hormone, edited by Veldhuis JD and Giustina A. New York: Springer-Verlag, 1999, p. 261–276.

42. Wideman L, Weltman JY, Shah N, Story S, Veldhuis JD, and Weltman A. Effects of gender on exercise-induced growth hormone release. J Appl Physiol 87: 1154–1162, 1999.

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