Effect of Low and High Intensity Exercise on Circulating Growth Hormone in Men*

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ABSTRACT

We hypothesized that circulating GH would increase only if a threshold of work intensity [corresponding to the anerobic or lactate threshold (LT)] was exceeded. Ten healthy male volunteers (18–35 yr) first performed ramp-type progressive cycle-ergometer exercise to determine the LT and the maximal oxygen uptake. On subsequent mornings after an overnight fast, each subject performed bouts of 1, 5, and 10 min constant work rate exercise of either high intensity (above LT) or low intensity (below LT). A 1-h interval separated exercise bouts. Gas exchange (breath-by-breath), GH, immunoreactive insulin, glucose, lactate, pyruvate, and epinephrine and norepinephrine were measured at regular intervals. After the 10-min bouts of high compared with low intensity exercise, lactate was 7.2 ± 3.7 mmol/L $vs.$ 1.4 ± 1.3, $P <$ 0.05; epinephrine was $1,113 \pm 519$ pmol/L $vs.$ 496 ± 273, $P < 0.05$; and norepinephrine was 7.89 ± 3.45 nmole/L $vs.$ 2.83 ± 1.34, $P < 0.05$). GH did not increase significantly from preexercise baseline during low intensity exercise ($e.g.$, GH after 10-min low intensity exercise changed from baseline values by 1.5 ± 2.0 μg/L, NS). Although lactate was elevated after 5-min of high intensity exercise, peak GH was significantly elevated (mean increase above baseline of 7.7 ± 2.4 μg/L, $P <$ 0.05) only after 10 min of high intensity exercise (increases in 9 of 10 subjects). The GH increase occurred despite simultaneous increases in both IRI and glucose. A minimum duration of 10 min, high intensity exercise consistently increased circulating GH in adult males. (J $Clin$ $Endocrinol$ $Metab$ **75:** 157–162, 1992)

EXERCISE AFFECTS GH secretory patterns, and this GH effect likely plays a role in growth and in the training phenomenon (1–4). The exercise duration or intensity that will elicit a reproducible and substantial GH pulse in humans is not precisely known. There are reasons to believe that the GH response to increasing work intensity is nonlinear in nature and may be characterized by a threshold. The purpose of this study was to test whether or not a work-intensity threshold could be identified for the GH response.

Although the magnitude of the GH response is related to work intensity (5–8), there is great variability in the reported amplitude and duration of exercise-induced GH response in humans. The variability might be explained by the fact that in previous studies, some subjects exercised below, whereas others worked above a threshold for GH release. The GH response may be correlated to the lactate response to exercise (9–11) which increases in a nonlinear manner with work intensity (12). Finally, other stress responses, $e.g.$ circulating catecholamines, are disproportionately elevated during heavy compared to light exercise (13, 14). We hypothesized that exercise would elicit a significant GH pulse only when the work rate exceeded the anaerobic or lactic acid threshold (high intensity exercise). The latter refers to the work rate above which circulating lactic acid increases (15, 16).

Table 1 reviews 10 studies of the acute GH response to exercise (5, 17–25). It highlights the diversity of approaches used to determine exercise intensity. In most studies, the work rate chosen is equivalent to 60–70% of the subject's maximal oxygen uptake ($\dot{V}O_2$max). By and large, these protocols represent submaximal high intensity exercise since the lactate threshold (LT) occurs between 40–60% of $\dot{V}O_2$max in healthy subjects (26). But some of the subjects may have exercised above and others below their LT for the following reasons. Investigators often used predicted rather than measured $\dot{V}O_2$max, and most did not measure the LT in individual subjects. This, combined with the large intersubject variability of $\dot{V}O_2$max and the LT, may have confounded the investigators' ability to precisely determine work rate intensity.

The duration of the exercise input in previous studies tended to be long (the mean of Table 1 is 44 min). In contrast, naturally occurring patterns of activity in adults and children are shorter. Thus, we specifically examined the effects of short bursts of exercise more likely to mimic physiologically significant patterns of activity.

Subjects and Methods

Subjects (Table 2)

Ten healthy adult male volunteers participated in the study. They ranged in age from 18–35 yr old (mean 27 ± 5 yr). None of the subjects were smokers, suffered from chronic diseases, or took drugs or medications. None of these individuals trained as competitive athletes, but most participated in some form of regular exercise. The study was approved by the institutional Human Subjects' Committee, and each participant granted informed consent.

Protocol

The protocol consisted of three exercise sessions each performed on different days, separated by at least 1 week. On day one each volunteer

TABLE 1. Representative previous studies of the effect of exercise on circulating GH

Ref. no.	Yr	$\dot{V}O_2max$	Lactate threshold	Work intensity	Duration (min)
(17)	1990	Predicted	Not measured	66% $\dot{V}O_2max$	6
(18)	1990	Predicted	Not measured	70% $\dot{V}O_2max$	15
(19)	1990	Measured	Not measured	65% $\dot{V}O_2max$	~90
(20)	1990	Predicted	Not measured	60% $\dot{V}O_2max$	30
(21)	1989	Measured	Measured	Equal to LT	~80
(22)	1988	Measured	Not measured	70% $\dot{V}O_2max$	60
(23)	1987	Not measured	Not measured	1, 1.5, and 2 watt/kg for 5-min periods	15
(24)	1986	Measured	Not measured	60% $\dot{V}O_2max$	60
(5)	1985	Measured	Not measured	63 (10 min), 86 (10 min), 100 (5–7 min)	~26
(25)	1981	Not measured	Not measured	55 watt/m²	60

TABLE 2. Subject age, weight, height, and exercise gas exchange characteristics

Subject	Age (yr)	Wt (Kg)	Ht (cm)	LT (% $\dot{V}O_2max$)	$\dot{V}O_2max$ (ml/min·kg)	LT (ml/min·kg)	Low WR (% $\dot{V}O_2max$)	High WR (% $\dot{V}O_2max$)
1	35	80	178	47	38	18	18	68
2	24	75	180	59	37	22	24	74
3	28	86	185	48	49	23	25	75
4	27	89	185	64	41	26	23	58
5	32	81	178	70	49	35	26	78
6	21	81	190	50	43	21	20	69
7	29	93	196	80	38	30	32	82
8	18	74	187	54	40	22	24	74
9	27	58	173	45	46	21	17	68
10	29	58	170	43	48	21	23	73
Mean	27	78	182	56	43	24	23	72
SD	5	11	8	12	5	5	4	6

performed progressive ramp-type cycle ergometry to determine the $\dot{V}O_2max$ and the LT (see below). The next two sessions consisted of 1-, 5-, and 10-min of constant work rate exercise on the cycle ergometer. An hour of rest separated each exercise burst. For one session, the work rate chosen corresponded to 50% of the difference between the subject's LT and $\dot{V}O_2max$ (high intensity exercise), whereas for the other session all work rates corresponded to 50% of the subject's lactate threshold (low intensity).

For a given session, subjects always performed a fixed sequence of exercise duration (1-, 5-, 10-min), but the order of the exercise intensity (*i.e.* high intensity day, low intensity day) was randomized. We chose this protocol because we anticipated that 10-min exercise bouts would be the most likely to elicit GH responses and it was performed last to minimize possible confounding effects of a prior GH pulse on subsequent pulses. We chose a 1-h interval between exercise bouts. This was a balance between, on the one hand, allowing sufficient time for gas exchange parameters, lactate, and hormones levels to return to baseline, and, on the other hand, minimizing the possibility of spontaneous GH pulses and too prolonged a fasting period.

The subjects arrived at approximately 0800 h on the morning of a low or high intensity exercise study. We chose the morning to perform the study because fewer naturally occurring GH pulses are seen during the morning hours (after about 0800–0900 h). They were instructed to refrain from any exercise and to remain fasted for at least 12 h before the study. An antecubital venous catheter was placed for intermittent blood sampling. Baseline blood samples were taken at 10 and 5 min before the first (1 min) exercise burst. The subject performed the exercise, then samples were taken every 10 min during the rest period. This was repeated after the 5- and 10-min bursts. An additional sample was obtained during exercise (at 5 min) during the last (10-min) exercise period. Breath-by-breath gas exchange measurements were made 5 min before, during, and 10 min after each exercise period.

Gas exchange measurements

The subjects breathed through a mouthpiece connected to a low impedance turbine volume transducer and a breathing valve with a combined dead space of 90 mL. O_2 and CO_2 tensions were determined by mass spectrometry from a sample drawn continuously from the mouthpiece at 1 mL/s. The inspired and expired volumes and gas tension signals underwent analog-to-digital conversion, from which oxygen uptake ($\dot{V}O_2$) (standard temperature pressure dry), CO_2 production ($\dot{V}CO_2$) (standard temperature pressure dry), and minute ventilation ($\dot{V}_E$) (body temperature pressure saturated) were calculated on-line, breath-by-breath as previously described (27). The breath-by-breath data were then interpolated to 1-s time intervals.

Noninvasive determination of LT and $\dot{V}O_2max$

The LT and $\dot{V}O_2max$ were measured noninvasively from the gas exchange data obtained during the progressive exercise. The lactate threshold was defined as the $\dot{V}O_2$ at which the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$) and the end tidal O_2 (PetO₂) increased without an increase in the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$) and the end tidal CO2 (PetCO₂) (28). $\dot{V}O_2max$ was defined as the highest $\dot{V}O_2$ achieved by the subject.

GH, glucose, insulin, lactate, and catecholamines

An in-house RIA was used to measure GH using WHO standard no. 66/217, antisera generated in-house, and hGH from NIDDK for iodination purposes. The GH intraassay variability is less than 10%, interassay variability is 12.6%, and the sensitivity is 0.5 µg/L. Insulin was also measured using an in-house RIA using standard from Wellcome equated to first IRP 66/304, antiporcine antibody from ICN and porcine insulin from Lilly for iodination. The insulin intraassay variability is less than 10%, interassay variability is 11.5%, and the sensitivity 7 pmol/L. Glucose was measured using the Abbott bichromatic analyzer using the Abbott UV glucose kit. The glucose intraassay variability is 2.1% and the interassay variability is 2.4%. Lactate was measured spectrophotometrically using the Behring Stat-pack rapid lactate test. The lactate intraassay variability is 2.8%, the interassay variability is 3.5%, and the

sensitivity is 0.55 mmol/L. Pyruvate was measured enzymatically using the Perkin Elmer luminescence spectrophotometer. Pyruvate intraassay variability is 4% and interassay variability is 12%. Catecholamines [norepinephrine (NE), epinephrine (E)] were measured by the radioenzymatic method. For NE the intraassay variability is less than 10% and the interassay variability is 10.6%, and the sensitivity is 0.12 nmol/L. For E the intraassay variability is less than 10%, interassay is 14.6%, and the sensitivity is 109 pmol/L.

Statistical analysis

Repeated measures analysis of variance was used to describe the patterns of the multiple samples of GH, other hormones, and substrates. Separate analyses were performed for the preexercise values, the peak value, and the Δ (i.e. the difference between peak and preexercise values). The preexercise values were taken as the level of hormone or substrate immediately before the 1-, 5-, or 10-min exercise bout. When analysis of variance (ANOVA) was found to be significant, Duncan's Multiple Range test was used to determine intergroup significance. Unless otherwise stated, values are presented as mean ± SD. A P value less than 0.05 was considered significant.

Results

Gas exchange parameters

The individual subject age, weight, height, and exercise gas exchange characteristics are shown in Table 2. As expected, the $\dot{V}O_2$ reached a steady state during the 5- and 10-min low intensity exercise bouts but not for high intensity exercise (Fig. 1). $\dot{V}O_2$, of course, increased significantly with exercise duration for both low and high intensity exercise. With 10 min of exercise, the peak $\dot{V}O_2$ was 4 and 9 times greater, on average, than baseline for low and high intensity exercise, respectively.

Lactate and pyruvate (Fig. 2)

As expected, lactate concentrations were increased during all durations of high intensity exercise. There were no substantial differences between the two baseline lactate values; however, the lactate levels immediately before the 10-min high intensity exercise bout were slightly but significantly higher ($P < 0.01$) than the baseline levels and than those before the 5-min exercise bouts. The coefficient of variation
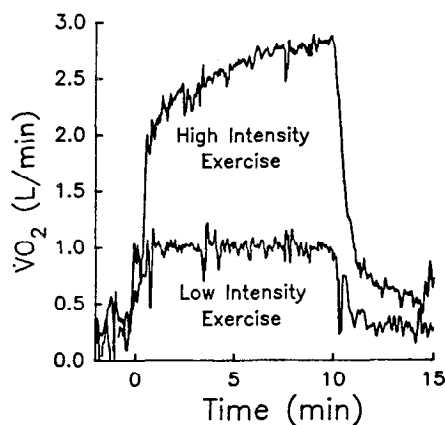
FIG. 1. $\dot{V}O_2$ during low and high intensity exercise in a representative subject. Note that $\dot{V}O_2$ did not achieve a steady state during high intensity (above LT) exercise even though the work rate was constant.
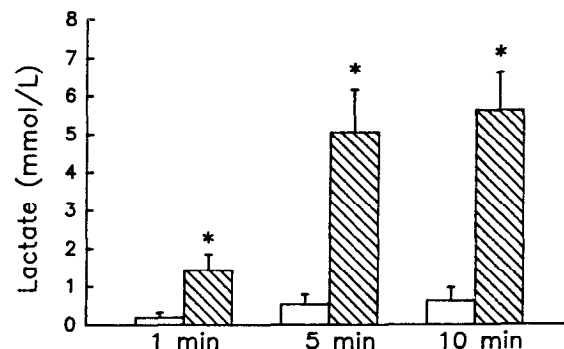
FIG. 2. Mean peak serum lactate levels (minus baseline) and SE after 1, 5, and 10 min of low (hollow bars) and high (hatched bars) intensity exercise. * indicates $P < 0.05$.
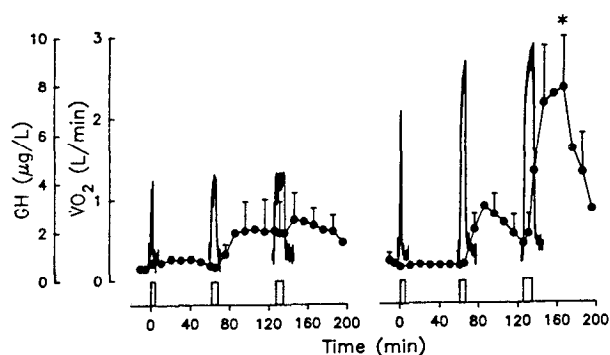
FIG. 3. Mean GH and SE (closed circles) and $\dot{V}O_2$ (lines) after 1, 5, and 10 min of low (left panel) and high (right panel) intensity exercise. * indicates $P < 0.05$. Clear vertical bars represent the exercise bouts. GH significantly increased only after 10 min of high intensity exercise.

for peak lactate among the subjects was 57%. Qualitatively similar results were found for the lactate-to-pyruvate ratios.

GH (Fig. 3)

Spontaneous GH pulses (judged by inordinately elevated preexercise GH with patterns suggesting upward or downward slopes) occurred in only one subject. There were no significant differences between the two baseline GH levels. GH responses to exercise were quite variable in magnitude among the subjects; the ratio of peak pulse to baseline ranged from 0.7 to 14 after low intensity exercise and from 0.5 to 51 after high intensity exercise. After low intensity exercise, exercise-associated increases in GH for the group as a whole were not statistically significant. Two of the 10 subjects had disproportionately greater GH pulses than the others and their GH pulses account by and large for the increase in the mean GH concentration after 5 and 10 min of exercise. After the 10-min high intensity bout there was a significant GH pulse in 9 of 10 subjects (mean peak of 7.7 ± 2.4 μg/L vs. a mean baseline of 1.7 ± 2.4 μg/L, $P < 0.05$). The small increase in GH after 5-min of high intensity exercise was not statistically significant. The coefficient of variation for the peak GH pulse after 10 min in the high intensity range was 85%. After the 10-min high intensity exercise bout, the peak GH pulse occurred at a mean of 29 ± 12 min after the onset of exercise and occurred significantly ($P < 0.05$) later than those

of lactate (15 min), E (10 min), NE (11 min), and insulin (21 min).

Glucose and insulin (Fig. 4)

After low intensity exercise, glucose increased by 0.39 ± 0.11 mmol/L ($P < 0.05$) for 5-min exercise and by 0.28 ± 0.11 mmol/L for 10-min bouts. With high intensity exercise, significant increases ($P < 0.05$) were found after the 1-min (0.28 ± 0.06 mmol/L), 5-min (0.39 ± 0.11 mmol/L), and 10-min (0.61 ± 0.11 mmol/L) protocols. Low intensity exercise had no significant effect on insulin. During high intensity exercise, insulin increased significantly ($P < 0.05$) after the 1-min (29 ± 7 pmol/L), 5-min (50 ± 14 pmol/L), and 10-min (29 ± 7 pmol/L) protocols.

Catecholamines (Fig. 5)

During low intensity protocols, significant increases were found for E after the 10-min exercise bout and for NE after the 1- and 10-min bouts. Both E and NE increased with the high intensity protocols after the 5- and 10-min bouts. The magnitude of the increase in catecholamines after low intensity was substantially less than that observed after the high intensity protocols. The coefficient of variation for peak NE among the subjects was 45% and for epinephrine was 49%.
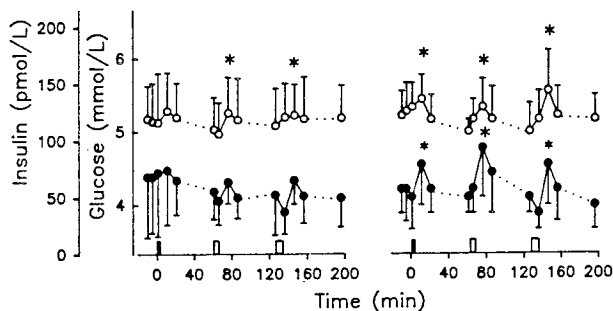

FIG. 4. Mean glucose and SE (*open circles*) and mean insulin and SE (*closed circles*) after 1, 5, and 10 min of low (*left panel*) and high (*right panel*) intensity exercise. * indicates $P < 0.05$ for peak over baseline values. *Clear vertical bars* represent the exercise bouts. Both insulin and glucose increased consistently after high intensity exercise.
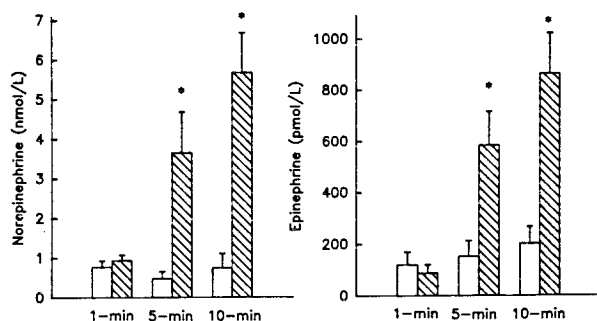

FIG. 5. Mean peak values (minus baseline) ± SE for NE (*left panel*) and E (*right panel*) after 1, 5, and 10 min of low (*hollow bars*) and high (*hatched bars*) intensity exercise. * indicates $P < 0.05$ compared to low intensity exercise.

Discussion

The gas exchange and lactate data demonstrate that we achieved the goal of identifying low- and high-intensity exercise in the subjects. The 10-min period of high-intensity (above the lactate threshold) exercise consistently resulted in bursts of GH secretion in adult males. In contrast, low intensity exercise, including the 10-min protocols, did not elicit significant GH responses. Despite rigorous control over the work rate, our data, like most previous studies, revealed great subject-to-subject variability in the peak GH response achieved (n.b., the coefficient of variation among the subjects was higher for GH than for lactate and catecholamines). Thus, whereas there does appear to be a minimum threshold of exercise duration and intensity necessary for a GH pulse, exercise intensity alone cannot entirely predict the amplitude and duration of the subsequent GH response.

The onset of the GH response to exercise was later and less consistent than the gas exchange, lactate, and other hormonal responses. The elevation in GH induced by exercise lasted far longer than both the 10-min exercise bout itself and the other substrate and hormonal responses studied. The time required to achieve a GH response in our study, between 5 and 10 min, was similar to that observed by Sutton and Lazarus (9) who used a 20-min protocol. The peak GH in their study also occurred at about 30 min after the onset of exercise, *i.e.* after the exercise bout was completed. It appears that 10 min of high intensity exercise are necessary to reliably stimulate pituitary secretion of GH.

The disappearance of GH from the circulation follows a first-order exponential decay (29–32), and reported half-times range from 8.9 min (30) to as high as 27 min (32). A variety of techniques, including deconvolutional analysis (29, 33), has been used to quantify pituitary GH secretion during spontaneous pulses. We constructed a simple single compartment model in which GH is transported from the pituitary to the circulation with first-order kinetics, and follows a first-order disappearance from the plasma. Iterative nonlinear curve-fitting techniques (34) were used to calculate the time constants and the amount of GH secreted from the mean GH levels during and after the 10-min high intensity protocol. The following equation was used:

$$y = A \cdot [e^{-t/\tau_1} - e^{(-t(1/\tau_1 + 1/\tau_2))}]$$

where A represents the GH released consequent to the exercise stimulus, τ_1 corresponds to the disappearance time constant (equivalent to the half-time divided by 0.69) for GH from the plasma compartment, τ_2 corresponds to the time constant of GH release from the pituitary compartment to the plasma, and t is the time in min. (A 5-min delay was included in the model).

A reasonably good fit was seen when 27 min was used as the value for the half-time of plasma GH disappearance (Fig. 6). The analysis predicted a total GH pulse of 0.061 mg when using the mean weight of our subjects (78 kg) and a GH volume of distribution of 4.4% (35). The model suggests a $t\frac{1}{2}$ of the GH release into the plasma of 11 ± 3 min, and a mean GH secretory rate over four half-lives
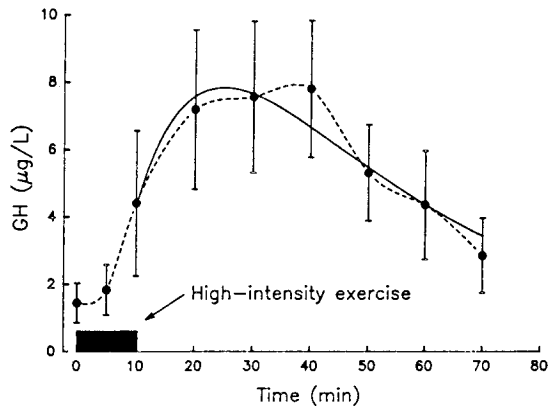
FIG. 6. Mean ± SE for GH (*closed circles*) during and after 10 min of high intensity exercise. The *dashed line* is a cubic splines best-fit curve for the GH data. The *solid line* is the best fit curve for the exponential model as described in the text.

of 0.41 μg/L·min, a value comparable in magnitude to those found from spontaneous pulses (36).

The data show that the GH response to exercise likely has a different mechanism than other known physiological stimuli. Hypoglycemia and/or rapid falls in glucose concentration, for example, cause GH release (37), but, as shown in Fig. 4, subjects remained euglycemic and glucose concentrations tended to increase. Classically, insulin can be used to stimulate GH by inducing hypoglycemia. In our studies, insulin increased significantly following short bursts of high intensity exercise with no evidence of hypoglycemia. It has been reported that insulin decreases during long term exercise (*e.g.* greater than 40 min) (38), but recent data in human subjects during and after short term high intensity exercise demonstrate either no change or, consistent with our results, increases in plasma insulin (39–41). In addition, both insulin and GH were increasing simultaneously following exercise (peak insulin occurred at 21 min; peak GH at 29 min). It would be difficult to conclude from these observations that insulin either directly or indirectly stimulated the exercise-induced GH pulses.

Both E and NE were significantly elevated after both 5- and 10-min of high intensity exercise, while GH was significantly elevated only after 10-min high-intensity exercise. The E and NE responses reflect alterations in neuroadrenergic control known to occur during graded exercise (42, 43); namely, a reduction in parasympathetic tone, an increase in sympathetic tone, and stimulus of adrenal production of epinephrine. The discrepancy between the GH and catecholamine responses, therefore, suggests that neuroadrenergic inputs to the hypothalamus or the pituitary, *i.e.* stress, are not the only modulators of the exercise-associated GH response.

There is mounting evidence to support the idea that exercise-induced GH is important in somatic growth and in the effect of physical training on muscles. Borer *et al.*

(44) demonstrated that exercising hamsters grew at faster rates than did sedentary animals, and the exercising animals had greater frequency and amplitude of spontaneous GH pulses. More recently, Grindeland *et al.* (1) studied the effect of exercise and administration of exogenous GH on muscle growth in hypophysectomized rats recovering from hindlimb suspension. Their preliminary data show that the most marked increases in muscle mass occurred with the combination of exercise and GH. In contrast, the training effect in humans can occur with exercise protocols that are above or below the subject's lactate threshold (45); and DeVol and co-workers (46) showed that training induced muscle hypertrophy with increases in muscle tissue insulin-like growth factor-I messenger RNA even in hypophysectomized animals. Apparently, the growth and hypertrophy observed in response to exercise is modulated by both GH-dependent and GH-independent processes.

Ten minutes of constant work rate, high intensity exercise is a minimum stimulus for consistent GH release in adult males. Whether or not such patterns of activity represent naturally occurring, physiologically important GH stimuli remains unknown. It is intriguing that the character of the exercise stimulus may be as important as the total work done in eliciting the GH response. Vanhelder *et al.* (7) demonstrated that a series of 1-min bursts of very high intensity exercise resulted in a greater GH response than constant work rate exercise (20 min) in which the work expenditure and duration of the two protocols were the same. The importance of the pattern of exercise is highlighted by recent findings that the pulsatile nature of GH release may optimize its overall effect on growth (47). Finally, our data add to the body of evidence that GH pulses in response to exercise, unlike spontaneous GH pulses, are accompanied by increases in other tissue growth mediators (insulin, catecholamines). Perhaps this hormonal "milieu" is as important to growth and training as is the elevation in GH itself.

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