Growth Hormone Release During Acute and Chronic Aerobic and Resistance Exercise: Recent Findings

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Abstract:

Exercise is a potent physiological stimulus for growth hormone (GH) secretion, and both aerobic and resistance exercise result in significant, acute increases in GH secretion. Contrary to previous suggestions that exercise-induced GH release requires that a 'threshold' intensity be attained, recent research from our laboratory has shown that regardless of age or gender, there is a linear relationship between the magnitude of the acute increase in GH release and exercise intensity. The magnitude of GH release is greater in young women than in young men and is reduced by 4–7-fold in older individuals compared with younger individuals. Following the increase in GH secretion associated with a bout of aerobic exercise, GH release transiently decreases. As a result, 24-hour integrated GH concentrations are not usually elevated by a single bout of exercise. However, repeated bouts of aerobic exercise within a 24-hour period result in increased 24-hour integrated GH concentrations.

Because the GH response to acute resistance exercise is dependent on the work-rest interval and the load and frequency of the resistance exercise used, the ability to equate intensity across different resistance exercise protocols is desirable. This has proved to be a difficult task. Problems with maintaining patent intravenous catheters have resulted in a lack of studies investigating alterations in acute and 24-hour GH pulsatile secretion in response to resistance exercise. However, research using varied resistance protocols and sampling techniques has reported acute increases in GH release similar to those observed with aerobic exercise.

In young women, chronic aerobic training at an intensity greater than the lactate threshold resulted in a 2-fold increase in 24-hour GH release. The time line of adaptation and the mechanism(s) by which this training effect occurs are still elusive. Unfortunately, there are few studies investigating the effects of chronic resistance training on 24-hour GH release.

The decrease in GH secretion observed in individuals who are older or have obesity is associated with many deleterious health effects, although a cause and effect relationship has not been established. While exercise interventions may not restore GH secretion to levels observed in young, healthy individuals, exercise is a robust stimulus of GH secretion. The combination of exercise and administration of oral GH secretagogues may result in greater GH secretion than

exercise alone in individuals who are older or have obesity. Whether such interventions would result in favourable clinical outcomes remains to be established.

Article:

Growth hormone (GH) is secreted by the anterior pituitary in a pulsatile pattern. GH secretion is regulated by two hypothalamic peptides: GHreleasing hormone (GHRH), which stimulates GH synthesis and secretion, and somatostatin, which inhibits GH release without affecting GH synthesis.[1,2] Many of the metabolic effects of GH are mediated by insulin-like growth factor (IGF)-I, which is synthesised in the liver under GH control and exerts a rapid negative feedback on GH release. In addition, recent data suggest that a GH secretagogue receptor, expressed in somatotroph cells in the anterior pituitary and hypothalamus, may also mediate the stimulation of GH secretion via a signal transduction pathway that is distinct from that of GHRH. Both synthetic GH-releasing peptides (GHRPs) and endogenous GHRP-like neuropeptides (e.g. ghrelin) may activate this receptor and the endogenous GHRP-like neuropeptides may be involved in the regulation of GH secretion.[1-3]

Human growth hormone (hGH) represents a family of proteins rather than a single hormone and over 100 forms of GH have been identified in plasma,[4] with apparently different physiological functions.[5] In the circulation, the dominant form of GH is a 22kD protein. However, approximately 10% of circulating GH is a 20kD protein and there are also various lower molecular weight fragments of GH.[4] All of these may be immunoactive in some GH immunoassays. However, in order for GH to be biologically active, it must be able to dimerize two GH receptors on the cell surface. This requires that two specific binding regions of the GH molecule be present in order to bind to two GH receptors. The proportion of intact GH molecules in the circulation varies between 50–95% of immunoactive GH, as measured by polyclonal competitive radioimmunoassays (RIA).[6] Thus, polyclonal RIAs tend to yield serum GH concentrations that are higher than many of the assays employing monoclonal antibodies. However, the various commercially available monoclonal assays in use today employ different antibodies with different specificity for the various molecular forms of GH.[6,7] Thus, the measurement of GH concentration using various assay techniques can result in vastly discrepant results. Although several bioassay techniques have also been used to assess GH levels[8-11] these are not widely available.

The isoforms of GH that are measurable in the circulation may be altered by muscle afferent stimulation,[12] acute aerobic[13] and heavy resistance exercise.[14] Some of these changes are detected only by bioassay.[12] After fractionation, 71–75% (for pre- and post-exercise samples, respectively) of GH was found in the <30 kDa fraction.[14] This review will focus on studies that have used immunoassay as the technique for assessing GH concentration, since it is used most commonly. The authors recognise that immunoassay procedures have limitations for inference about the actual ‘bioavailable’ and ‘functional’ GH that leads to downstream GH signalling in target tissues in response to exercise. To this end, the development of immunofunctional assays, such as that described by Strasburger et al.[10] or Ikeda et al.,[11] are likely to become more critical for assessing the ability of different types of exercise to actually affect changes in the downstream signalling pathway of GH, ultimately leading to changes in protein expression.

GH deficiency in adults with hypothalamic or pituitary disease leads to altered body composition[15] and has been associated with increased risk of premature cardiovascular disease.[16] In addition, GH deficiency is linked to reduced exercise capacity,[17] insulin resistance,[18] dyslipidaemia,[19,20] vascular dysfunction[21] and reduced left ventricular mass and lower ejection fractions.[22] In GH deficient adults, the beneficial effects of administration of hGH include increased lean body mass and decreased fat mass, reduced abdominal/visceral obesity, favourable effects on lipoprotein and bone metabolism and improved patient perception of quality of life.[23-27] Several studies have reported significant improvements in aerobic exercise capacity with GH replacement in adults with GH deficiency.[28-31] These may be the result of increased left ventricular mass and cardiac ejection fraction.[32,33] However, the ability of exogenous GH administration to increase muscular strength in GH-deficient adults has been less consistently demonstrated, with some studies reporting improvements[17,28,34] and others reporting little or no change.[35,36] For a more complete review of the effects of GH replacement in adults with growth hormone deficiency, see Carroll et al.[37] or Simpson et al.[38]

GH production and release decreases with age[39,40] by approximately 14% per decade after the age of 40 years[41] and is decreased in conditions such as obesity.[42,43] Many age related changes in GH secretion resemble those seen in GH-deficient adults including: reduced muscle mass and exercise capacity, increased body fat especially abdominal visceral fat, unfavourable lipid and lipoprotein profiles, reduction in bone mineral density, and increased risk of vascular disease. However, treatment of healthy older adults with GH results in less impressive benefits than is observed in adults with GH deficiency due to hypothalamic or pituitary disease. In general, GH treatment of older adults results in changes in body composition (increased lean body mass, decreased fat mass and decreased abdominal fat) but no improvement in exercise performance.[44-49] Data from a recently completed clinical trial at the University of Virginia investigating the effects of GH administration with and without exercise training in older adults confirm these previous findings.[50,51]

Many physiologic factors alter pulsatile GH secretion, including age, gender, body composition, sleep, nutrition, exercise and serum concentrations of gonadal steroids, insulin and IGF-I. Among these various factors, the amount of abdominal visceral fat is the most important predictor of the 24-hour integrated GH concentration.[52] However, this review is limited to the effects of exercise on GH release. The reader should consult the review by Hartman[2] for a more comprehensive overview of the effects of these other physiological factors on GH release. These other factors should be taken into account when reviewing the literature regarding the effects of exercise on GH secretion.

Exercise is a potent stimulus of GH release in young adults. Since decreased GH secretion in aging and other conditions such as obesity is associated with many detrimental health effects it can be suggested that the use of regular exercise as a stimulus for GH release may have positive effects on health and well being. Initial studies[50,53-56] evaluating the GH response to exercise performed minimal sampling and compared GH concentrations pre- and post-exercise. It is now well known that GH secretion from the anterior pituitary is pulsatile and that more frequent sampling regimens are necessary to assess the effects of stimuli on GH release. Thus, the primary purpose of this paper is to review findings on the effects of acute and chronic aerobic

and resistance exercise on GH release. In addition, where available, we will discuss the effects of exercise on GH pulsatility.

Acute Aerobic Exercise

Initial studies of the growth hormone response to aerobic exercise reported that GH release occurs as a result of exercise with initial elevation of GH observed approximately 15 minutes into exercise and peak values attained at or near the end of exercise.[53-55] Recent studies, using more frequent sampling techniques to measure the inherent pulsatile pattern of GH release, support the contention that aerobic exercise of appropriate intensity and duration is a potent physiological stimulus for GH release in young adults.[57-60] The pattern of GH release to acute aerobic exercise is depicted in figure 1.

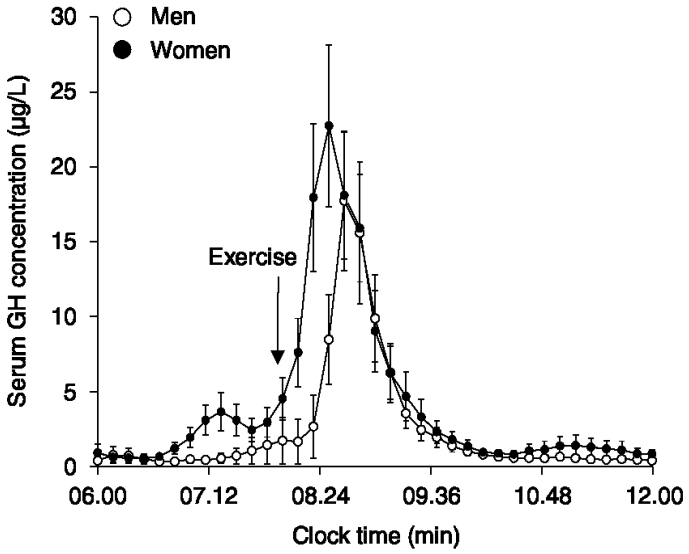

Fig. 1. Mean serum growth hormone (GH) response patterns for men and women during exercise; n = 9 in each group. Values are means ± standard error (reproduced from Wideman et al.,[59] with permission).

Women have higher GH concentrations at rest, greater basal GH secretion, greater 24-hour integrated area under the concentration-time curve (AUC) and less orderly GH release.[1,59,61-65] Although the general pattern of exercise-induced GH release is similar in men and women,[53,66] more recent studies have demonstrated gender differences in the GH response to exercise.[59,60] Women exhibit an anticipatory response to exercise and a more rapid attainment of peak GH concentrations with exercise.[59,60,67] Because these studies employed morning exercise, it is possible that these findings are related to the increase in morning ambulatory-induced GH release in young women compared with young men.[61] Nevertheless, the response to exercise is likely independent of circadian rhythm, as time of day does not influence the GH response to exercise in young men.[68] While young women and men both attain large increases in GH concentrations during exercise, the increase from baseline is significantly higher for men than women,[60,66] even though the absolute change in exercise-induced AUC is similar.[59]

Exercise intensity has been suggested as a key modifier of exercise-induced GH release. It has been suggested that a threshold of exercise intensity may be necessary for GH release.[69-71] In contrast, recent studies from our laboratory[58,67] indicate that the magnitude of GH release rose linearly with increasing intensity of exercise in young men and young women. We also observed that the incremental increase in GH release with increasing exercise intensity was greater in young women than in young men.[67] This concept is illustrated in figure 2. Using deconvolution analysis, this increase was shown to be attributable to an increase in the mass of GH secreted per pulse in both genders.[58,67]

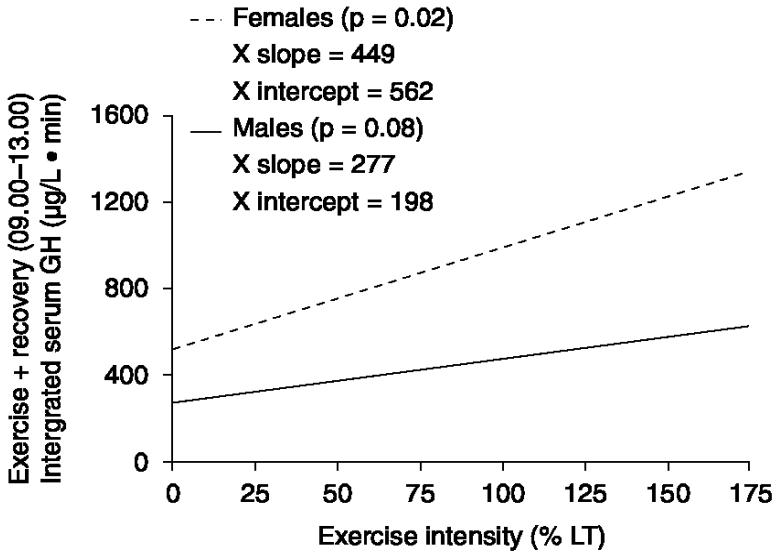

Fig. 2. Mean slope and intercept values when the growth hormone (GH) response was regressed on exercise intensity in young men and women. The male data were taken from Pritzlaff et al.[58] (reproduced from Pritzlaff-Roy et al.,[67] with permission). **LT** = lactate threshold.

Although it has been shown that a single, acute aerobic exercise session results in an increase in GH release during and immediately following exercise, the effects of acute exercise on 24-hour GH release have not been well described. A transient decrease in GH release is observed following the increase in GH secretion associated with a bout of aerobic exercise.[68] As a result, 24-hour integrated GH concentrations are not usually elevated by a single bout of exercise.[72] However, we have shown that three 30-minute bouts of exercise (separated by 1 or 3.5 hours) resulted in a 60% increase in 24-hour integrated GH AUC compared with the control day.[73] Repeated bouts of exercise within 60 minutes of each other did not result in attenuation of exercise-induced GH release, suggesting that exercise may 'break through' GH auto-negative feedback. When the 24-hour time frame was further divided into day and night, the daytime GH AUC was increased by approximately 150% compared with rest, whereas the night-time GH AUC was not different for exercise or rest.[73] Similarly, Kern et al.[74] observed that mean nocturnal GH concentrations, measured every 15 minutes for 8 hours, did not differ after a single bout of daytime moderate or intense aerobic exercise, compared with the control condition. Recently, Ronsen et al.[75] also reported a more pronounced GH response to a second bout of

exercise on the same day, although frequent blood sampling was completed only during the second exercise session. Thus, while GH concentrations at the end of the second exercise session were higher than at the end of the first session, no comparisons of GH AUC or mean GH concentration can be made for the two sessions.

Several studies have specifically investigated the influence of time of day on exercise-induced GH release.[68,76-79] The exact time of day chosen for exercise varied, but generally comparisons of GH release were made between morning, afternoon, evening and nocturnal (usually midnight) exercise sessions. GH release[76-79] and GH secretion parameters (as assessed by deconvolution analysis)[68] were unaffected by time of day and this observation persisted regardless of the intensity of acute exercise (high, moderate) or the mode of exercise (stair climbing, arm ergometry, cycling, treadmill) employed. Kanaley et al.[68] reported that exercise at any time of day resulted in an approximately 2-fold increase in GH secretion rate and mass of GH secreted per pulse, with no effect on GH half-life. Recently, our laboratory reported that one 30 minute bout of exercise as well as three 10 minute bouts of exercise (spread throughout the day) resulted in similar increases in 24-hour GH release (approximately 1.4-fold in those without obesity and approximately 1.2-fold in those with obesity).[80] Interestingly, Galassetti et al.[79] reported that even when plasma glucose levels were controlled with clamping, morning exercise reduced the GH, adrenaline (epinephrine), noradrenaline (norepinephrine) and cortisol response to afternoon exercise in men. Conversely, morning exercise followed by afternoon exercise in women resulted in preservation of or increased response of GH, adrenaline, noradrenaline and cortisol.[79] These findings underscore the need to further investigate gender differences in exercise- induced GH release.

In contrast to our findings in young adults, when the GH response to exercise intensity was examined in older men and women, we found that the GH response to exercise was blunted in older individuals.[81,82] In men, the slope values for the relationship between GH release during exercise and recovery and exercise intensity was 3.9-fold higher in younger than older men. Furthermore, the GH response to exercise in the older men was attenuated until the highest exercise intensity was reached.[81] Similarly, exercise-stimulated GH secretion in postmenopausal women was 5.7–7.3-fold lower than that attained in exercising premenopausal women.[82] This attenuation in exercise stimulated GH release was observed in postmenopausal women both with and without oestrogen supplementation, suggesting that aging, independent of estrogen status, impairs the GH secretory response.[82] These data suggest that in older individuals exercise may need to be used in combination with other provocative stimuli of GH release (i.e. a GH secretagogue) to obtain GH levels similar to those observed in young adults. Table I provides a summary of studies that have investigated the effects of acute aerobic exercise on GH release.

Other investigators have also reported that older individuals have decreased exercise-induced GH release.[83,84] These decrements in exercise- stimulated GH release may be due to excessive somatostatin (SRIH) release and/or diminished GHRH secretion[1] or a reduction in the endogenous GHRP-like ligand. A recent study by Marcell et al.[83] reported that pyridostigmine, which may indirectly suppress SRIH, administered 30 minutes prior to exercise augmented GH AUC by 74 and 24% in young men, and by 224 and 59% in older men during maximal and submaximal exercise, respectively. While the fractional increase in GH AUC was greater in

Table I. Summary of the effects of acute aerobic exercise on acute and 24h growth hormone (GH) release

Study	Participants	Effect on acute GH release	Effect on 24h GH release
Wideman et al.[59]	M and W; 18-35y	Time to peak GH; W < M	NA
Wideman et al.[60]	M and W; 18-35y	Pattern of GH release; M = W	NA
Pritzlaff-Roy et al.[67]	M and W; 18-35y	Peak GH value; M = W	NA
		↑ in GH AUC; M = W	
		GH secretory pulse mass; ↑	
Bunt et al.[66]	M and W; 21-30y	Fold change from rest; M > W	NA
Wideman et al.[60]	M and W; 18-35y		
Pritzlaff et al.[58]	M and W; 18-35y	↑ GH release with ↑ intensity; W > M	NA
Pritzlaff-Roy et al.[67]	M and W; 18-35y		
Kanaley et al.[73]a	M; 21-29y		↑ 24h AUC
			↑ daytime GH
Marcell et al.[83]	M; 18-24y and 60-76y	↑ GH release; young > old	NA
Zaccaria et al.[84]	M and W; <25y and >40y	↑ GH release; young > middle-age	NA

a 24h GH AUC included three exercise bouts.

AUC = area under the concentration-time curve; **M** = men; **NA** = not available; **W** = women.

older versus younger men, the absolute magnitude of the change was similar, suggesting that pyridostigmine was equally effective in both groups at counteracting SRIH inhibition of GH release.[83] Gusenoff et al.[85] investigated the interrelationships of cortisol and GH secretory dynamics at rest in healthy older men and women. They reported that postmenopausal women have reduced cortisol-GH pattern synchrony (increased cross-ApEn score; a measure of coupling between two signals over a specified time frame) than men of the same age, even though orderliness of GH release was similar in older men and women. Thus, with aging, a deterioration of coordinated neuroendocrine function may occur.[85]

GH release at rest and during exercise is also reduced in individuals with increased body fat.[43,80,86] When comparing various pharmacologic and physiologic stimuli, the magnitude of the GH response to exercise in individuals with obesity is greater than that observed with levodopa or clonidine,[87,88] but similar to that observed with GHRH, pyridostigmine or arginine.[87,89-92] However, the exercise-induced GH response in individuals with obesity is less than that observed after stimulation with GHRP or combined secretagogues.[87,89,91] Thus, the same metabolic factors that attenuate the GH response to pharmacological stimuli may also inhibit the GH response to exercise in individuals with obesity.[2]

Acute Resistance Exercise and Growth Hormone (GH) Release

Studies of the acute GH response to resistance exercise have been hampered by the difficulty of equating intensity levels across individuals and studies, maintaining patent intravenous catheters throughout exertion and obtaining blood samples without interfering with resistance exercise. Most studies have sampled pre-exercise, at some time intervals during exercise and at varying intervals postexercise for up to several hours. Regardless of the sampling intervals or the resistance protocol employed, the pattern of GH release is similar. In all cases, the GH concentration peaks at or slightly after the termination of exercise and returns to baseline levels by 90 minutes postexercise.[93-102] This pattern is similar to that observed for the GH response to acute aerobic exercise.

Notably, to our knowledge, no reports are available regarding the effects of acute resistance exercise on pulsatile 24-hour GH secretion. Nindl et al.[99] investigated GH pulsatility in young men for 12 hours following acute heavy resistance exercise performed in the late afternoon (15.00–17.00). The pattern of GH release during the 12 hours following exercise is shown in figure 3. GH levels were significantly elevated for the 20 minutes immediately after acute heavy resistance exercise and then gradually declined over the next 30 minutes, so that by 1 hour postexercise, GH concentrations were similar to those observed during the control day.[99] Acute heavy resistance exercise influenced the temporal pattern of overnight GH pulsatile release, such that GH release was lower in the first half of sleep, but higher in the second half.[99] Additionally, this exercise resulted in lower maximal GH values and lower mean peak amplitude, even though overall mean GH values were not significantly reduced.[99]

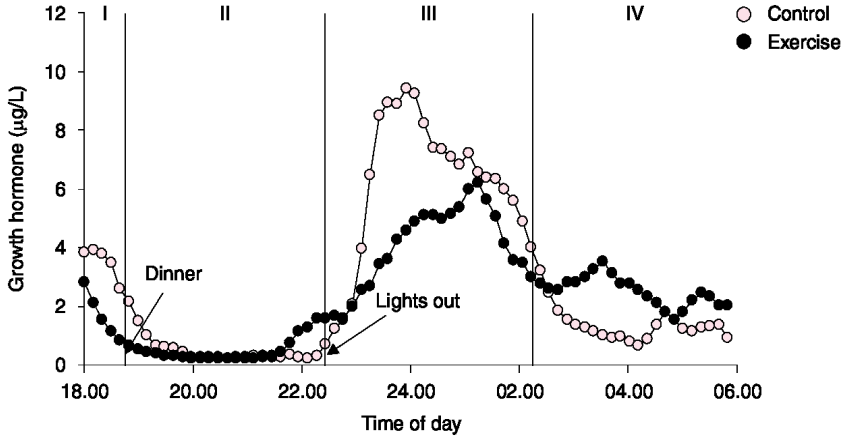

Fig. 3. Composite pulsatility human growth hormone profiles between the control day and after heavy resistance exercise conditions in young men. The profile was partitioned into four segments (labelled I–IV) based on feeding time, lights out time and the time for the observed divergence between the exercise and control conditions (reproduced from Nindl et al.,[99] with permission).

An in-depth study of the GH response to different resistance exercise protocols was completed by Kraemer et al.[94] This study investigated six different heavy resistance exercise protocols (HREP) and observed sizeable variation in the GH response to the different protocols in young men. Generally, resistance exercise protocols with high total work and short rest intervals or high repetitions with moderate power (70% or greater), resulted in the greatest GH response. [94,102,103] The same HREP were used to examine the acute GH response of young women to resistance exercise.[97] In women, shortening the duration of the sets or increasing the rest period between sets did not result in significant stimulation of GH release and by 90 minutes postexercise, GH concentrations fell below baseline values. The largest GH responses were observed with the resistance protocols that minimised rest, were of longer duration and were combined with moderately heavy resistance.[97] Similarly, Mulligan et al.[104] found that when women performed multiple sets of resistance exercise GH release was greater and more prolonged than with a single set of resistance exercise. When Kraemer et al.[98] investigated the effect of menstrual cycle phase on resistance exercise-induced GH release, they observed a greater GH response

during the luteal phase compared with the follicular phase. Further, when GH AUC was normalised for fat-free mass and total work done, there was no gender difference in GH release. In general, resistance exercise with higher total volume resulted in a greater GH response than resistance exercise with lower total volume. [94,96,97] In contrast, Takarada et al.,[101] reported that GH increased approximately 290-fold over resting GH values in response to very low intensity resistance exercise (20% 1 repetition maximum [RM]) when vascular occlusion occurred simultaneously. This extreme increase in GH may be due to regional accumulation of metabolites without considerable tissue damage.[101]

Although acute resistance exercise results in increased GH release,[83,94,96,97,101,103,105-108] the GH response to resistance exercise is influenced by the work-rest intervals, and the load and frequency of the resistance exercise that is used.[94,102,103] Additionally, as observed with aerobic exercise- induced GH release, the interindividual response to acute resistance exercise is highly variable.[100] These results indicate that comparisons of the GH response to acute resistance exercise between studies should be made with extreme caution. In addition, future studies should attempt to equalise total work when comparing resistance exercise protocols and should assess the effect of resistance exercise on the daily (24-hour) pulsatile release of GH. Comparison of the physiological mechanisms involved in the increase of GH after acute aerobic versus acute resistance exercise, may also be important as these two training techniques clearly result in different phenotypic responses in humans.

Similar to responses observed with acute aerobic exercise, most reports suggest that acute resistance exercise results in increased GH release in elderly men and women.[83,109,110] As expected, peak GH values and integrated GH AUC were markedly attenuated in older individuals compared with younger individuals.[83,110] However, one report[93] did not find increased GH release with acute heavy resistance exercise in older men or women. As depicted in figure 4, while elderly participants did not respond with increased GH release, young and middle-aged men and women had substantial increases in GH release (approximately 200- and 20-fold, respectively). This disparity in stimulation of GH release in different age groups may be due to methodological differences, particularly, differences in total work done or intensity of exercise. Weltman et al.[81] reported that for older men, intensity of aerobic exercise had to reach the highest workload before substantial increases in GH were observed. It is possible that the workload or intensity must be 'relatively' much greater in older individuals (compared with younger individuals) in order to achieve substantial increases in GH release with resistance exercise. Table II provides a summary of studies that have investigated the effects of acute resistance exercise on GH release.

Clearly, acute resistance exercise of appropriate intensity and duration results in increased GH release in all age groups. Dependent on the protocol employed, the average peak GH concentration attained during acute resistance exercise in young men and women ranges between 5–25 μg/L.[93-97,99,100,104,108,110,111] Similarly, the average peak GH concentration attained during acute aerobic exercise is also between 5–25 μg/L.[58-60,66,67,69,70,83,112-115] When extremely high intensity aerobic work (90% maximal oxygen uptake [V.O2max]) is employed, mean GH concentrations as high as 50 gg/L have been reported.[112] Thus, the magnitude of the GH response is similar with either acute aerobic or resistance exercise of appropriate intensity and duration. Ideally, a comparison of the GH response to both acute

Table II. Summary of the effects of acute resistance exercise on acute and 24h growth hormone (GH) release

Study	Participants	Effect on acute GH release	Effect on 12h GH release
Vanhelder et al.[102]	M; 20-40y	↑ GH release; peak (GH) at end of exercise; return to baseline; 90 min	NA
Kraemer et al.[94]	M; <35y		
Kraemer et al.[96]	M; <35y and W; <30y		
Kraemer et al.[95]	M; <30y		
Kraemer et al.[97]	W; <30y		
Kraemer et al.[98]	W; 20-28y		
Kraemer et al.[108]	M; 30 and 62y		
Raastad et al.[100]	M; <30y		
Takarada et al.[101]	M; 20-22y		
Hakkinen and Pkarinen[93]	M; 30, 50 and 70y	↑ GH release in 30 and 50y	NA
	W; 30, 50 and 70y	No ↑ GH release in 70y	
Pyka et al.[110]	M; <40 and >60y	Peak GH; young > old	NA
	W; <40 and >60y	GH AUC; young > old	
Nindl et al.[99]	M; 18-25y		GH AUC; exercise = control
			Mean GH; exercise = control
			Peak amplitude; ↓
			Maximum GH value; ↓

AUC = area under the concentration-time curve; **M** = men; **NA** = not available; **W** = women.

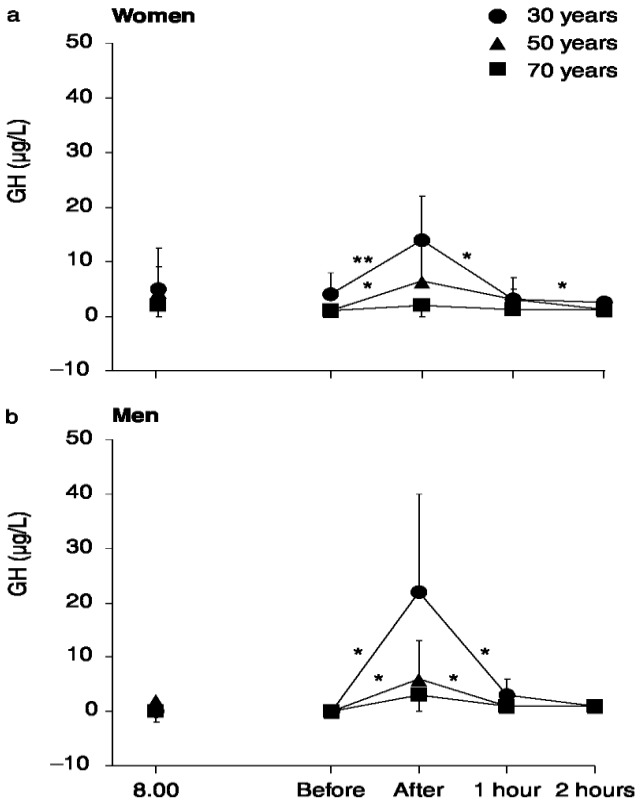

Fig. 4. Mean (± standard deviation) values for serum growth hormone (GH) concentrations on the morning (08.00), before (12.00) and after a heavy resistance exercise session, and during the recovery for 2 hours in: (**a**) women at three different age groups; and (**b**) men at three different age groups (reproduced from Hakkinen and Pakarinen,[93] with permission). * = $p < 0.05$; ** = $p < 0.01$.

aerobic and resistance exercise should be made within the same individuals. To our knowledge, no such study exists.

Chronic Endurance Training and GH Release

Studies have shown that endurance training reduces the exercise-induced GH release in response to acute constant load exercise when the absolute workload was unchanged.[115,116] These data suggest that the GH response to exercise is influenced to a greater degree by relative exercise intensity than by absolute exercise intensity. In young eumenorrhoeic women who participated in endurance training for 1 year, a nearly 2-fold increase in spontaneous 24-hour integrated serum GH concentrations was observed provided some of the training was at an intensity above the lactate threshold (LT).[117] In middle-aged and young competitive cyclists, progressive endurance training for 4 months resulted in similar increases for maximal oxygen consumption. However, neither the young nor middle-aged participants had an increase in acute exercise-induced GH release in response to maximal aerobic exercise on a cycle ergometer.[84] The middle-aged cyclists had a much lower GH response to acute maximal exercise than the young cyclists both before and after training. It should be noted that no comparisons to sedentary age-matched controls were made and the effect of progressive endurance training on spontaneous 24- hour GH release was not examined in this study.

Although relatively few studies have prospectively evaluated the effect of exercise training on the GH-IGF-I axis in older adults, it appears that GH secretion may be less responsive to exercise training. In a study of older men (aged 50–78 years), serum IGF-I concentrations did not differ between a group of marathon runners and age- matched sedentary controls.[118] Similarly, a sustained programme of moderate-intensity resistance exercise training in elderly individuals for 1 year failed to increase serum IGF-I levels.[119] We studied the effects of 1 year of exercise training (either supervised aerobic training [4 days/wk] or supervised strength training [3 days/wk]) in healthy older (aged 59–79 years) adults and observed no significant change in 24-hour integrated GH concentrations.[50] The lack of effect of training on the GH-IGF-I axis in these older individuals may have been attributable to: (i) lack of a sufficient training stimulus; (ii) lack of change in percentage body fat and abdominal visceral fat (both of which are correlated with GH release in older adults); and/or (iii) intrinsic aging of the GH-IGF-I axis.

Chronic Resistance Training and GH Release

Studies investigating the effect of chronic resistance training on GH release have shown that resting levels of GH are unchanged with resistance training.[56,107,108,119-123] Hurley et al.,[124] investigated the effect of 10 weeks of resistance training on resting 24-hour GH release in young men and observed a reduced daytime mean GH concentration compared with pre-training. Samples were taken hourly but averaged for 24-hour, daytime and night-time means. In this study, the investigators did not calculate an integrated GH AUC for the pre-, mid- or post-training GH concentrations. Marx et al.,[120] measured the resting GH response to low-volume circuit training and high-volume periodised resistance training in young women. Both training regimens resulted in significant improvements in muscular performance after 12 weeks, but only the high-volume periodised resistance training resulted in improvements in strength, power and speed after 24-weeks of training. Neither training regimen resulted in changes in resting GH levels in young women.[120] This may be due to the fact that only a single GH sample was taken pre-training, and after 12 or 24 weeks of training.

Several studies have reported that the effect of chronic progressive resistance training on the GH response to acute resistance exercise is similar pre- and post-training in both men and women.[107,121] Craig et al.[56] reported that young men increased GH concentrations 5-fold in response to an acute bout of resistance exercise and this increased to approximately 6-fold after training. However, Kraemer et al.[108] reported that training resulted in lower GH concentrations during late recovery (30 minutes postexercise) in young men, even though the response during the acute bout was similar to pre-training. Recently, Kraemer et al.[111] trained participants for 19 weeks on a lower-body resistance training programme that involved only concentric work or both concentric and eccentric work and then detrained them for 4 weeks. The GH response to acute concentric and acute eccentric work was measured pre- and post-training and after de-training. The groups that trained concentrically had a greater GH response to acute concentric work compared with acute eccentric work, while the group that trained both concentric and eccentric muscle actions had a greater GH response to acute eccentric work. Interestingly, detraining resulted in a reduced GH response to acute concentric work in the groups that trained concentrically, with no reduction of the GH response to acute eccentric work with detraining. However, in the group that trained both concentric and eccentric muscle action, detraining resulted in a greater GH response to acute concentric work compared with post-training, while the GH response to acute eccentric work was reduced compared with post- training. These results indicate that the GH response to acute exercise in men is sensitive to the type of muscle action used during training.[111] Here again, the use of a single GH sample for the assessment of GH release provides only limited insight due to the pulsatile nature of GH secretion.

Although the American College of Sports Medicine[125] recommends the addition of resistance exercise to a programme of regular aerobic training, there are few studies that assess the effect of concurrent strength and endurance training on hormone concentrations. A recent study by Bell et al.,[126] noted that the resting GH concentration did not change during 12 weeks of either strength training alone, endurance training alone or concurrent strength and endurance training, despite the fact that changes in strength and $\dot{V}O_{2\,max}$ were observed. Again, the use of a single sample at any timepoint for the assessment of GH release likely confounded the results. No assessment of the GH response to either acute aerobic or resistance training was determined pre- or post-training.

Resistance training has become a popular intervention for elderly individuals in an effort to try to slow, decrease or even reverse the age-related declines in strength and functional ability that occur with aging. Craig et al.,[56] reported that while elderly males had increased GH concentrations to an acute bout of resistance exercise, chronic progressive resistance training for 12 weeks did not increase the response to acute exercise. Similar findings were reported by Pyka et al.,[119] after 1 year of resistance training in elderly men. These findings have been corroborated by several other newer studies.[108,109,127] We also reported that 1 year of resistance training did not result in an increase in 24-hour GH release in older men.[50] It has been repeatedly shown that the type of resistance exercise and the total work completed are crucial for the exercise-induced increase in GH release to occur. It is possible that the intensity and volume of resistance training that is required to produce a training effect in older adults is not a feasible workload for them to complete regularly without injury. Further, more complete investigations of the 24-hour GH response to resistance exercise and training are needed before conclusions can be made about the usefulness of resistance training for elevating GH in elderly individuals.

Interestingly, several studies showed strength gains in elderly individuals without changes in GH,[108,109,127,128] which suggests that factors other than GH (likely neuromuscular adaptations) may be important in producing these functional responses in elderly individuals.

Neuroendocrine Control

The neuroendocrine mechanisms involved in exercise-induced release of GH have not been completely elucidated and are complex in nature, although the effect appears to occur via hypothalamic input. The mechanism would putatively involve GHRH release and/or somatostatin withdrawal and possibly, natural GHRP-like ligand release (e.g. ghrelin) or some combination of these mechanisms (figure 5). A complete review of this topic is beyond the scope of this review and readers are referred to Giustina and Veldhuis[1] for more in-depth coverage of the possible neuroendocrine mechanisms involved in the control of exercise-induced GH release.

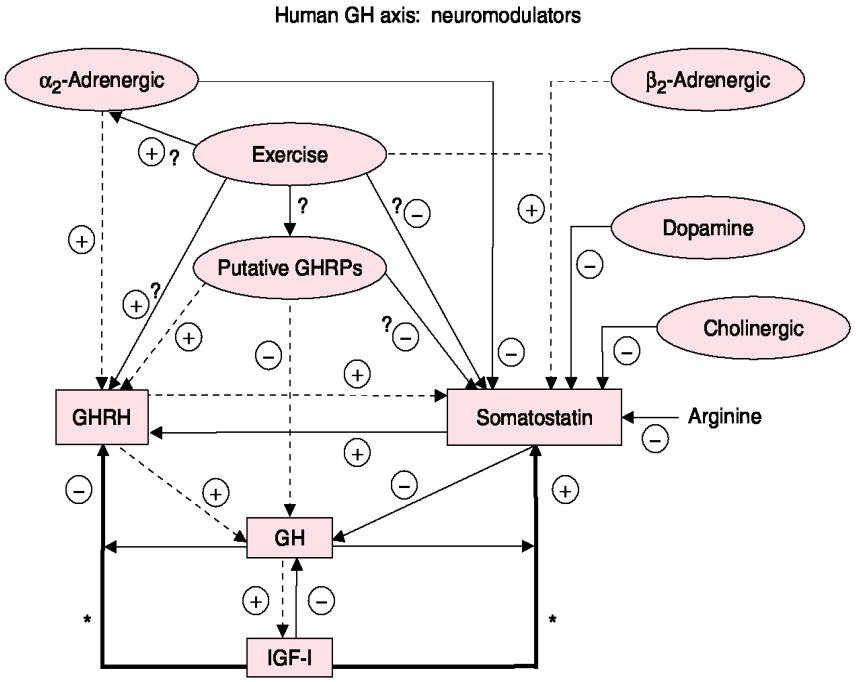

Fig. 5. Schematic representation of the possible interactions or mechanisms that control exercise-induced growth hormone (GH) release (adapted from Giustina and Veldhuis,[1] with permission). **GHRH** = GH releasing hormone; **GHRPs** = GH-releasing peptides; **IGF-I** = insulin-like growth factor-I; * indicates the possibility that exercise modifies the normal autonegative feedback control of GH on GHRH and somatostatin; + denotes stimulation; – denotes inhibition.

The stimulation of GH secretion by exercise likely involves multiple neuroregulatory responses in the GH axis,[60] as well as a variety of peripheral feedback signals. Several neurotransmitters have been implicated but the final common pathway likely involves either stimulation of GHRH secretion and/or inhibition of somatostatin release (see Giustina and Veldhuis[1]). Sympathetic activity may be an important mediator of the GH response to acute exercise, possibly via activation of central α_2-adrenergic neurons.[1] Weltman et al.[129] demonstrated that peak plasma adrenaline and nor- adrenaline concentrations preceded the peak in serum GH concentrations. Multiple regression analysis revealed that prior increases in noradrenaline with resulting significant increments in GH could not be explained by adrenaline alone.[129] In creases in serum GH and catecholamines with exercise are also similarly affected by exercise training.[115]

Additionally, ghrelin, cholinergic and opioid pathways may also be involved.[1] Current evidence favours a modulatory effect of cholinergic pathways on the GH response to exercise with a less important role for opioid pathways.[1,130] The role of endogenous ghrelin in the stimulation of GH release in response to exercise has not been elucidated, however, one study has measured the plasma ghrelin response to 45 minutes of aerobic exercise at lactate threshold.[131] Plasma ghrelin levels remained unchanged from baseline throughout exercise and 3 hours of recovery (~150 pmol/L), indicating that exercise is not associated with changes in plasma ghrelin.

GH Signalling and Exercise

The regulation of energy metabolism by GH is believed to be mediated by direct interaction of GH with the GH receptor (GHR) on target cells.[132] GHRs are found in many tissues throughout the body, including liver, muscle, adipose and kidney.[133] Our understanding of the signal transduction systems that mediate GH action is limited, but it is known to involve GHR dimerisation, activation of Janus kinases, mitogen activated protein kinases and the signal transducers and activators of transcription signalling pathways.[134] An excellent review of GH signalling and the use of trans- genic models to understand the complex biological actions of GH is provided by Kopchick et al.[134] GH regulation during exercise at the neuroendocrine level is clearly multifactorial. While chronic aerobic and resistance training clearly results in different phenotypic responses in both men and women, the literature reviewed in this paper supports the view that both acute aerobic and resistance exercise produces a similar GH response (i.e. GH concentration peaks at or near the end of exercise with GH concentration returning to baseline by approximately 90 minutes postexercise).

Clearly, one could argue that chronic aerobic or resistance training has divergent cumulative effects resulting in different phenotypic responses. However, we must consider the possibility that exercise-induced elevations in immunoassayable GH alone, may not be an adequate indicator of the role that GH plays in producing cellular changes that result in these different phenotypic responses. As suggested in the introduction, alternative assay techniques may be required to assess the importance of the changes induced by exercise. Further, several studies in rats have shown that sexually dimorphic differences in plasma GH profiles (i.e. males have intermittent GH secretion with periods of secretory quiesence, while females have continuous GH release), result in sexually dimorphic gene expression in the liver, that ultimately results in sexually dimorphic differences in whole-body growth patterns.[135-137] Consequently, one must consider the possibility that changes in the pulsatile release patterns of GH may play an important role in the ability of aerobic and resistance training to induce such divergent phenotypic responses. Clearly, one of our greatest challenges is to link exercise-induced changes in GH pulsatility to downstream GH signalling changes and ultimately, changes in protein production. The phenotypic differences that result from chronic aerobic or resistance training may, in part be dependent on subtle changes in GH pulsatility that lead to diminutive, but important changes in the GH signalling pathway.

Conclusion

Exercise is a potent stimulus for GH release, particularly in younger men and women. However, the GH response to exercise appears to be reduced in older adults, as well as in those with obesity. The mechanisms underlying this reduction in GH have not been elucidated but may include primary effects on the hypothalamus and pituitary, as well as potential lifestyle or

metabolic factors (e.g. increased visceral fat). In older adults, an exercise intervention alone is unlikely to restore GH secretion to levels observed in young individuals, particularly if aging has a primary effect on the hypothalamus that results in decreased GH secretion. Since this marked reduction in GH secretion is associated with unfavourable clinical profiles, interventions designed to reverse the effects of aging on GH secretion may result in favourable changes in risk factors for chronic disease. Since the administration of an oral GH secretagogue enhances GH secretion in older individuals at rest, it is possible that a combination of exercise and an oral GH secretagogue in older individuals may increase GH secretion to levels observed in young adults. However, the ability of this increase to produce longterm clinical benefits is unknown.

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