Available online at www.sciencedirect.com
SCIENCE DIRECT®
Growth Hormone & IGF Research 13 (2003) 225–238
www.elsevier.com/locate/ghir

Review

Growth hormone responses to sub-maximal and sprint exercise

Keith Stokes*

Department of Sport and Exercise Science, University of Bath, Bath BA2 7AY, UK

Received 9 July 2002; received in revised form 21 March 2003; accepted 21 March 2003

Abstract

Exercise is a potent stimulus for growth hormone (GH) release and a single bout of exercise can result in marked elevations in circulating GH concentrations. The magnitude of the GH response to exercise will vary according to the type, intensity and duration of exercise as well as factors such as the age, gender, body composition and fitness status of the individual performing the exercise. However, the mechanisms regulating GH release in response to exercise are not fully understood. This review considers the GH responses to sub-maximal and sprint exercise and discusses the factors that might affect GH release along with the mechanisms that have been proposed to regulate exercise-induced GH release.

Keywords: Prolonged exercise; High-intensity exercise; Repeated exercise; Metabolic responses; Endocrine; Human

1. Why is growth hormone of interest to an exercise physiologist?

In recent years a great deal of attention has been paid to the abuse of growth hormone (GH) in sport, and whilst this alone might attract the interest of an exercise physiologist, there are other reasons why GH is studied in sport and exercise physiology. Growth hormone is a potent anabolic agent, and the natural response to exercise is, therefore, of great interest to sports performers who are trying to maximise the anabolic effect of their training regimen. Similarly, with the decline of resting circulating GH levels being a natural part of the ageing process, the use of exercise as an intervention to contribute to the maintenance of functional capacity could have a major impact in the current climate of an ageing western society. Indeed, even a brief search on the Internet provides evidence of the level of interest in what are termed ''GH supplements'' as a so-called ''fountain of youth''. Exercise might offer an alternative to these supplements as well as providing a multitude of other health benefits. Therefore, there are many reasons why it is important to understand the relationship between exercise and GH release, and this review will attempt to describe the natural response to acute bouts of exercise.

However, the study of the relationship between exercise and GH release is complicated by a number of factors. First, historically and currently there have been a wide range of assays available for the measurement of GH. This makes the comparison of findings from different studies difficult. The Growth Hormone Research Society has suggested that including a clear statement of methodology when reporting assay data might reduce this problem [1]. In addition, to improve standardisation, it has been recommended that the GH reference preparation should be a recombinant 22 kDa human GH (IRP 88/624 [1] or IRP 98/574 [2]), each with a specific activity of 3 IU/mg rather than previously used pituitary derived reference preparations.

Second, although it is hoped that strict controls are in place in studies reporting on GH responses to exercise, it is possible that GH pulses as a result of the stress of venous section, or stress related to anticipation might affect the results. For example, some authors have reported increased levels of GH following arterial and venous puncture [3,4]. A further difficulty in comparing the findings of different studies relates to the fact that some studies report GH release using measures such as

* Tel: +44-1225-384190; fax: +44-1225-383275.
E-mail address: k.stokes@bath.ac.uk.

1096-6374/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S1096-6374(03)00016-9

integrated GH concentrations and maximum GH concentrations, whilst others assess GH secretion using cluster analysis or deconvolution analysis. These will give different insights into the relationship between exercise and GH. In addition, whilst it is clear that exercise alters circulating GH concentrations and that GH has important actions in growth and metabolism, there is little available evidence how GH alters cellular signalling in tissues to mediate these actions. It is important that this issue is addressed in order that the mechanisms of GH action are better understood.

2. The GH response to different types of exercise

One of the problems when studying the relationship between intense exercise and GH release is that there are a number of different types of exercise that can be used. For the purpose of this review, the terms sub-maximal exercise and sprint exercise will be used, although even within these categories there are a number of additional subdivisions. Sub-maximal exercise is any exercise that is below the maximal aerobic capacity, or maximal oxygen uptake ($\dot{V}O_2$max). As such, sub-maximal exercise includes any mode of exercise (e.g., walking, running, swimming, cycling) that is typically sustainable for more than about 5 min. It appears that low-intensity exercise (50% of the lactate threshold) does not elicit GH secretion, whilst high-intensity exercise (50% of the difference between the lactate threshold and $\dot{V}O_2$max) stimulates a GH response [5] suggesting that a threshold intensity of exercise must be reached before a significant increase in GH concentration can be detected. However, there has been no systematic study of this threshold concept, and recent evidence suggests that the GH response to sub-maximal treadmill running displays a linear dose–response relationship as GH secretion increases with rising intensity [6]. There is a similar lack of literature reporting the effect of sub-maximal exercise duration, when intensity is maintained, on the GH response. However, in general, GH levels have been reported to peak at or near the end of sub-maximal exercise. Table 1 gives some examples of the GH response to sub-maximal treadmill running.

Sprint exercise is sometimes erroneously termed supra-maximal since it is above $\dot{V}O_2$max, or anaerobic exercise since the energy for this form of exercise is predominantly from anaerobic metabolism, although these terms are inaccurate for a number of reasons. Indeed, the suggestion that exercise can be "supra"-maximal is clearly paradoxical, and there is now evidence that there can be a large aerobic contribution to sprint exercise. This review will use the term sprint exercise. As with endurance exercise, running, cycling, swimming and other modes of exercise can be included in the sprint exercise category, as long as it is performed at an intensity that is sustainable for only a short period of time (up to about 60 s). Table 2 gives examples of the GH response to all-out sprinting on a cycle ergometer and on a treadmill. It is clear from these examples that the GH response to sprint exercise is influenced by duration of exercise [7]. In addition, mode of exercise may effect the GH response, for example, treadmill sprinting where both arms and legs are active, has been suggested to elicit a greater GH response than sprint cycling, where movement is concentrated in the lower limbs, since a larger muscle mass is employed [8].

3. Factors influencing exercise-induced GH release

The mechanisms regulating GH secretion are yet to be fully elucidated. However, it would appear that a combination of hypothalamic release of GH releasing hormone (GHRH), withdrawal of somatostatin and release of a GH releasing peptide (GHRP), such as the

Table 1
Examples of the mean peak GH response to sub-maximal exercise

Sub-maximal exercise	Subjects	Exercise	Peak [GH] (μg/l)
Kanaley et al. [73]	8 F (non-obese)	30 min @ 70% $\dot{V}O_2$ peak	13.7
	11 F (LBO)	30 min @ 70% $\dot{V}O_2$ peak	6.8
	12 F (UBO)	30 min @ 70% $\dot{V}O_2$ peak	3.5
Pritzlaff et al. [6]	10 M (young active)	30 min @ 26% $\dot{V}O_2$ peak	~2.5
		30 min @ 47% $\dot{V}O_2$ peak	~4.5
		30 min @ 62% $\dot{V}O_2$ peak	~5.5
		30 min @ 76% $\dot{V}O_2$ peak	~9.5
		30 min @ 90% $\dot{V}O_2$ peak	~14
Pritzlaff-Roy et al. [64]	8 F (young active)	30 min @ 33% $\dot{V}O_2$ peak	~7
		30 min @ 49% $\dot{V}O_2$ peak	~12
		30 min @ 62% $\dot{V}O_2$ peak	~17
		30 min @ 76% $\dot{V}O_2$ peak	~22
		30 min @ 86% $\dot{V}O_2$ peak	~26

F, female; M, male; LBO, lower body obese; UBO, upper body obese.

Table 2
Examples of the mean peak GH response to sprint exercise

Sprint exercise	Subjects	Exercise	Peak [GH] (μg/l)
Nevill et al. [21]	5 F (ST)	30 s all-out treadmill sprint	26.9
	6 F (ET)	30 s all-out treadmill sprint	10.4
	6 M (ST)	30 s all-out treadmill sprint	44.0
	6 M (ET)	30 s all-out treadmill sprint	15.9
Stokes et al. [7]	9 M (young active)	6 s all-out cycle sprint	4.0
		30 s all-out treadmill sprint	18.5
Stokes et al. [8]	10 M (young active)	30 s all-out treadmill sprint	20.4

F, female; M, male; ST, sprint trained; ET, endurance trained.

putative endogenous GHRP-like ligand Ghrelin, mediate the effects of a number of candidate stimuli. During and after exercise there are a number of potential stimuli for GH release, but the factors that determine the magnitude of GH release remain unclear. Various mechanisms regulating the GH response to exercise have been proposed, as reviewed in the following sections.

3.1. Increased blood lactate concentrations

A promising candidate for regulating the secretion of GH in exercise was identified when a correlation between blood lactate concentrations and GH concentrations was observed [9]. In a study employing arm cranking exercise, leg bicycle exercise and treadmill running, at an intensity eliciting similar oxygen consumption in all trials, serum GH concentrations were also found to be positively correlated with blood lactate concentrations [10]. Furthermore, significant correlations were found between plasma lactate and plasma GH during 20 min of continuous "aerobic" exercise and during 20 min of intermittent "anaerobic" exercise of nearly equal external work, with significantly higher plasma lactate and plasma GH concentrations following "anaerobic" exercise [11].

However, another study employing continuous and intermittent exercise of equal external work identified a similar GH response in each trial, with a divergent pattern of blood lactate accumulation [12]. The difference in the results of these two trials was attributed to the fact that "anaerobic" exercise was not employed by Karagiorgos et al. [12], reflected by higher measured blood lactate concentrations in the study of Van Helder et al. [11]. Further evidence that the GH response to exercise is independent of lactate accumulation in the blood is that artificial manipulation of blood lactate levels using sodium lactate [13,14] have been shown to have no consistent effect on GH concentration. Indeed, both Van Helder et al. [11] and Kozlowski [10] reflected on the findings of Sutton et al. [14] using sodium lactate, and accepted that their results should not be considered to demonstrate a causal link between blood lactate and serum GH concentrations. Instead, it is possible that a mechanism that stimulates anaerobic metabolism might result in an increase in blood lactate concentrations whilst also providing a signal for GH release.

3.2. Increased hydrogen ion concentration in the blood

It has been suggested that any stimulus for GH release associated with lactate accumulation would be more likely to act through hydrogen ion (H^+) accumulation [15]. Sutton et al. [14] studied the role of acid–base balance during exercise in the regulation of the exercise-induced GH response. Acidotic, alkalotic and control conditions were considered during a ~45 min graded exercise test to exhaustion. Although in the first 20 min of the exercise test acidosis resulted in a significantly higher circulating GH concentration than the alkalotic or control conditions, this did not extend to the second 20 min or the last 5 min stage. It was therefore concluded that, although exercise is a clear stimulus for GH release, the stimulatory mechanism acts independently of blood $[H^+]$.

However, it was not clear whether the same conclusion could be drawn for short-term, high-intensity exercise. Therefore, male subjects were administered $NaHCO_3$ or NaCl placebo in a randomised double-blind counterbalanced experiment with a crossover design [15]. All-out high intensity exercise of 90 s duration resulted in a larger and faster rise in serum GH concentrations in the placebo trial in all 10 subjects. Correlation analysis in the placebo trial alone demonstrated significant correlation between highest measured "peak" GH and both peak $[H^+]$ and peak lactate concentrations. Overall correlations, combining data from both trials, showed that highest measured "peak" GH concentration was correlated with peak $[H^+]$ but not peak lactate concentration, suggesting that the GH response to high intensity exercise is more highly associated with peak venous $[H^+]$ than with peak venous lactate concentration. The use of combined oral and intravenous administration of either or NaCl placebo during an incremental exercise test to exhaustion identified that $NaHCO_3$ administration tended to suppress exercise-induced GH release at rest and during recovery from

exercise, except for the peak value at 60 min which was similar in the two trials [16]. However, the mechanism by which an acute rise in blood $[H^+]$ acts as a stimulus for GH release is not clear.

3.3. Oxygen demand/availability ratio

It is known that GH levels increase as oxygen demand increases and a significant correlation between initial O_2 deficit and peak GH concentrations during 1 h of cycle ergometer exercise has been identified [17]. In addition, Raynaud et al. [18] demonstrated that individuals dwelling at sea level who were non-adapted to hypoxia had a greater GH response to exercise under acute hypoxic conditions and when exercising at altitude than when exercising under normal conditions. This highlights a possible role for oxygen availability in regulating the GH response to exercise. However, under hypoxic conditions, it would be expected that exercise would induce a greater metabolic response, and, therefore, it might not be hypoxia per se that is regulating GH release. In fact, Raynaud et al. [18] did report a higher blood lactate response under hypoxic conditions and when exercising at altitude than when exercising in normoxic conditions.

Therefore, it was suggested that the GH response to exercise might be proportional to the ratio of oxygen demand to oxygen availability (D/A ratio) [19]. The D/A ratio was applied to the results of previously published research, and a highly significant relationship between the GH response and the D/A ratio for continuous "aerobic" and intermittent "anaerobic" exercise [11] was identified [19]. Perhaps more surprisingly, there was a highly significant relationship between GH and the D/A ratio in the data of Karagiorgos et al. [12]. This finding was despite the fact that originally the results of that study identified no significant relationship between blood lactate concentrations and the GH response to exercise or even between the oxygen deficit in continuous exercise and serum GH concentrations. The data from these studies [11,12], as well as those from other previously published studies [18,20], were combined and resulted in the demonstration of a close association between the D/A ratio and the GH response to exercise for a wide range of exercises [19]. The relationship between the D/A ratio and GH release was proposed to suggest that differences in oxygen demand and supply at the muscle site might regulate GH release via muscle metabolic receptors [19].

3.4. Afferent signals from muscle metabolic receptors

It might be that a combination of factors related to anaerobic metabolism are involved in controlling GH release [21]. However, the finding that there is no relationship between externally administered lactate and GH release [13,14] is evidence that systemic metabolic disturbance might not regulate GH, and Karagiorgos et al. [12] found no correlation between any anaerobic metabolite or oxygen deficit and GH concentration. Even if anaerobic metabolites in the blood do not have a role to play in the regulation of exercise-induced GH release, this would not preclude the possibility that they are detected in the muscle [10,11,19,21–23].

It has been suggested that neural afferent signals from muscle metabolic receptors, activated by local changes in lactate concentration, oxygen concentration or pH, might participate in the activation of catecholamine release [24,25]. Van Helder et al. [19] cited the close association between GH and the D/A ratio as support for the suggestion that similar metabolic receptors occur in the muscle with a role in GH regulation during exercise. Ischaemic exercise, resulting in enhanced accumulation of lactate in the muscle, has been associated with a twofold increase in GH concentrations compared to normal exercise and this was attributed to the activation of muscle receptors [23]. However, Kjaer et al. [26] blocked afferent nerve activity by epidural anaesthesia in order to test the hypothesis that afferent nervous activity from exercising muscle regulates GH release. Epidural blockade had no effect on the GH response to exercise, yet it was postulated that afferent nervous activity might still have a role to play in the regulation of exercise-induced GH release, since elevated central motor activity might compensate for the reduction in afferent sensory signals.

If afferent feedback from muscle metabolic receptors contributes to the regulation of GH release, then exercising under hypoxic conditions would be expected to exaggerate metabolic changes in contracting muscle and enhance the GH response to exercise. Epidural anaesthesia would blunt this response, yet Kjaer et al. [27] demonstrated that epidural anaesthesia during leg cycling exercise at $\sim$50% $\dot{V}O_2$max under hypoxic conditions enhanced, rather than blunted, the exercise-induced GH response. Epidural anaesthesia also reduced muscle strength and increased perceived exertion, suggesting a role for "central command" in the exercise-induced GH release, rather than regulation by afferent feedback from receptors in exercising muscle.

3.5. Motor centre activity

Activity in motor centres may directly stimulate pituitary hormone release, including GH, during exercise [10,26,28,29]. Administration of tubocurarine is reported to induce a partial neuromuscular blockade, which increases voluntary effort during exercise and therefore necessitates higher activity in motor centres [30]. Kjaer et al. [28] administered tubocurarine prior to exercise and demonstrated higher motor activity, measured through an increased rate of perceived exertion,

compared to exercise without tubocurarine administration. At the same time exercise with tubocurarine elicited a greater GH response than exercise alone, suggesting that central motor activity might play a role in the regulation of the GH response to exercise. In a further study using epidural anaesthesia to block afferent nerve activity, decreased muscle strength and higher rates of perceived exertion during exercise with epidural blockade inferred increased motor centre activity [26]. Since epidural anaesthesia had no apparent effect on the GH response to exercise it was suggested that this increase in motor centre activity compensated for the lack of afferent nervous input.

However, Kjaer et al. [29] did not observe any decrease in the GH response to exercise with both afferent sensory blockade by epidural anaesthesia combined with electrically induced cycling, to offset motor centre activity. These results suggested that blood-borne humoral feedback mechanisms and autonomic (i.e., spinal) reflexes are capable of inducing the GH response to exercise. It was postulated that a decrease in plasma glucose, as observed in this study, was of great importance in the control of the GH response to exercise. A further study by Kjaer et al. [31] compared electrically induced leg cycling in tetraplegic humans with voluntary arm cranking at a work rate similar to that achieved during the involuntary leg stimulation trials. It was observed that GH concentrations increased as a result of voluntary arm exercise, but not with involuntary leg stimulation. These results support the suggestion that an intact central nervous system and activity in motor centres, as well as afferent nerves from exercising muscles, are needed for the GH response to exercise. In addition, arm cranking exercise appeared to result in an exaggerated GH response, probably due to higher motor centre activity relative to work output, since the subjects' arm muscles were weakened by partial paralysis. This finding provides further support for a role of motor centre activity in the regulation of the GH response to exercise. These studies do not consider a possible role of psychological perception of exercise and the associated stress signalling which might parallel motor centre activity. However, the potential importance of motor centre activity in regulating GH release in response to exercise is evident.

3.6. A proprioceptive mechanism

Another potent pituitary growth factor has been identified that cannot be measured by standard GH immunoassay and that has apparently distinct mechanisms regulating its release [32]. This growth factor has been labelled as bioassayable GH (BGH) to differentiate between it and immunoassayable GH (IGH) since the method measures GH activity using changes in tibial epiphyseal width in hypophysectomised rats as an in vivo bioassay [33]. The assay is understood to measure variants of GH other than 22 kDa GH, and various lines of evidence suggest that BGH is distinct from IGH [33]. However, the physiological significance of BGH, beyond linear bone growth [32], is yet to be elucidated.

It has recently been suggested that skeletal muscle proprioceptor afferents might contribute to the regulation of BGH release, since electrical stimulation has been shown to result in increased release of BGH, but not IGH, in rats [34]. Vibration-induced activation of muscle spindle afferents in the tibialis anterior, but not the soleus, has also been shown to result in elevated plasma BGH concentrations in human [35]. Immunoassayable GH was not altered by vibration of either muscle. These studies suggest that there is a proprioceptive mechanism by which the release of BGH is regulated, whilst no such mechanism exists for IGH. However, performing an all-out 30 s sprint on a cycle ergometer at fast ($\sim$160 rpm) pedalling rates has been shown to result in a greater IGH response when compared with pedalling at slower ($\sim$130 rpm) pedalling rates with 9 out of 10 subjects following this pattern of response, although the difference was not significant ($P = 0.05$) [8]. This is despite the fact that there are no differences in the blood [8,36] or muscle [36] metabolic responses to sprinting at different pedalling rates. It is, therefore, possible that a proprioceptive mechanism might contribute to the regulation of IGH, as well as BGH, release.

3.7. Catecholamines

During progressively incremental exercise, blood catecholamines, adrenaline (A) and noradrenaline (NA) have been shown to rise with increasing exercise intensity [37]. In addition, catecholamines can directly stimulate GH release from rat pituitary tissue in vitro [38]. In exercising humans, a significant positive correlation between plasma [NA] and serum GH concentrations has been identified [10]. These findings were supported by those of Chwalbinska-Moneta et al. [39] who also demonstrated significant correlations between catecholamine concentrations and serum GH concentrations during and after an incremental exercise test. In addition, the GH-threshold identified by Chwalbinska-Moneta et al. [39] during incremental exercise was reported to occur at a similar work load as what was identified as both the [A]-threshold and the [NA]-threshold, as well as the lactate threshold.

Peripheral markers of heightened adrenergic outflow, that is [A] and [NA], have been shown to precede and correlate with exercise-induced GH concentrations [40]. A time delay between peak-[A] or peak-[NA] and peak-[GH] of $\sim$ 20 min was identified and changes in exercise intensity did not alter this interval. In addition, increasing intensity resulted in a linear relationship

between the increment (change from baseline to peak) in GH and the increment in A as well as the increment in NA. Multiple linear regression showed that the dominant relationship was between incremental changes in GH and NA. These results suggest that higher exercise intensities might drive increased GH secretion, at least in part, by central adrenergic activation [40]. However, It has been suggested that a decrease in pH in contracting muscles due to accelerated lactate production and associated metabolic changes may stimulate the sympathetic outflow by neural afferent signals from muscle metabolic receptors causing rapid release of catecholamines [24,25]. Catecholamines released following afferent signals from muscle metabolic receptors might, in turn, play a role in the regulation of GH release.

3.8. Change in core temperature

Brenner et al. [41] identified the importance of motor centre activity in the regulation of exercise-induced GH release, but suggested that the role of the increase in core temperature associated with exercise cannot be ruled out. An early study identified greater GH release in seven out of nine subjects when exercising for 20 min at a temperature of 21 °C compared with 4 °C [42]. Later studies support this finding, and it has been shown that the use of a thermal clamp technique during exercise halves the GH response, whilst passive heating results in similar patterns of both temperature change and serum GH concentrations to those seen in exercise in cold conditions [43].

Using a single subject, Buckler et al. [42] reported that there was a significant positive correlation between the rate of change in core temperature and the rate of change in GH concentrations. A similar finding was identified when 30 min of cycling was performed at room temperature (23 °C) compared with hot conditions (40 °C) [41]. Based on this evidence, the rate of rise in body temperature during exercise might be more important than the magnitude of change, and a sufficiently slow rise in core temperature might not elevate GH concentrations [42]. However, it has also been suggested that a threshold exists whereby increases in core temperature not exceeding 0.5 °C do not elicit increases in systemic GH concentrations, whilst increases greater than 0.6 °C result in significant increases in circulating GH concentrations [44]. In addition, when revisiting earlier work [43] a core temperature threshold for activation of GH release was reported to exist at around 38–38.5 °C, whereafter a significant exponential relationship between elevations in core temperature and GH was identified [44].

3.9. Summary

From the discussion above it is clear that there are a number of factors which might contribute to the regulation of GH release as a result of exercise. It is possible that the exact mechanism regulating GH release is dependent on the form of exercise being performed, and it certainly appears that environmental factors, such as temperature have an impact upon the GH response to exercise. A proposed model for the regulation of exercise-induced GH release would be that, at the onset of exercise, impulses in motor centre elicit a workload dependent increase in GH secretion [28]. Blood-borne metabolic error signals and/or neural afferent signals from muscle metabolic receptors, proprioceptive feedback and, at higher exercise intensities, central adrenergic activation might then feed back to modulate further GH release.

4. Roles of GHRH and somatostatin in the GH response to exercise

It has been proposed that relatively low intensity exercise induces moderate GH responses through activation of the central cholinergic system, resulting in a reduction in hypothalamic somatostatin release [45]. However, it appears that there is an upper limit to this process and at higher exercise intensities, once hypothalamic somatostatinergic tone is completely suppressed, further increases in GH release must be mediated by an increase in GHRH secretion.

The importance of the inhibition of somatostatinergic tone as a result of exercise was demonstrated by Di Luigi et al. [46], who observed a suppression of the GH response to treadmill exercise, at 60% $\dot{V}O_2$max, following pretreatment with the somatostatin analogue octreocide, in humans. In contrast, administration of the somatostatin inhibitor, pyridostigmine, has been shown to enhance exercise-induced GH release [47,48], suggesting that pyridostigmine and exercise might act independently in eliciting the GH response to strenuous exercise [48]. Administration of GHRH at the start of an incremental exercise test lasting 25 min, with an additional stage at 100% $\dot{V}O_2$max until exhaustion has also been shown to have an additive effect on the GH response [45]. However, co-administration of GHRH and GH-releasing peptide-2 (GHRP-2) at the start of exercise further potentiated GH release [45], as did the administration of GHRP-2 before 30 min of exercise [49]. It is possible that GHRP-2 acts via a mechanism potentiating the effect of endogenous GHRH and/or by opposing the central actions of somatostatin [49].

Growth hormone releasing peptides (e.g., GHRP-2) act through specific receptors [50] for which a specific endogenous ligand has been identified and named ghrelin [51]. Ghrelin has been shown to stimulate GH release in a dose-dependent manner with a potency similar to that of GHRH in culture, and intravenous injection of ghrelin into male rats has been shown to

induce GH release [51]. These findings suggest that ghrelin circulating in the blood might elicit GH release, however, in healthy human adults and in GH-deficient adults, sub-maximal exercise did not result in significant changes in plasma ghrelin concentration despite eliciting GH release [52]. Therefore, it would appear that there is a role for an endogenous GHRP-like ligand (ghrelin) in regulating the GH response to exercise, but that systemic ghrelin is not involved [52].

5. Large inter-individual variation in the GH response to exercise

It has often been reported that there is a great degree of inter-individual variation in the GH response to exercise [7,18,53], and when individuals work at the same sub-maximal exercise intensity relative to their maximal exertion, this variation remains, suggesting that inter-individual variation is not due to exercise intensity [53]. One approach that has been taken is to divide subjects into responders and non-responders [54], but this is sometimes difficult as, for example, there appears to be a continuum of GH responses to sprint exercise [7].

Variations in the GH response to an exercise stimulus are mainly due to differences in the time to peak response, and the maximal value [4,7]. However, despite large inter-individual variation, within an individual the GH response to sub-maximal exercise has been shown to be similar over several months at a range of intensities [4]. In addition, integrated (area under the curve) GH concentrations following a single 30 s sprint on a cycle ergometer had a standard error of measurement of 2.9 ± 54.3 μg l^{-1} [55]. There is, therefore a certain intrasubject reliability in the GH response to sub-maximal and sprint exercise.

6. Roles of gender, age and body composition in the GH response to exercise

6.1. Gender

A number of studies have considered the sex-related differences in GH secretion in rats. Jansson et al. [56] described high amplitude GH pulses with low GH concentrations between pulses in male rats compared with less regular pulses with higher interpulse concentrations in females. The role of GHRH and somatostatin in these different secretory patterns of male and female rats was studied by Painson and Tannenbaum [57] using passive immunisation with specific antisera. In female rats, a single acute dose of anti-somatostatin serum resulted in increased plasma GH concentrations at all time points for 6 h after administration, as well as an increase in GH peak amplitude, GH nadir levels, and overall mean 6 h GH levels. In contrast, an acute dose of anti-somatostatin serum to male rats increased only GH nadir levels. In addition, administration of an acute dose of anti-GHRH serum raised GH nadir levels in females but had no effect in males. These findings suggest that the secretory pattern of somatostatin plays an important role in the sexually dimorphic GH secretion patterns in rats.

Women have been identified as having greater daytime GH serum concentrations [58] and greater 24 h GH secretion [59,60] than men although higher integrated serum GH concentrations in young women have been shown to be strongly influenced by serum oestradiol concentrations [59]. Jaffe et al. [61] compared GH secretion in women in the early follicular phase of the menstrual cycle, when oestrogen levels are comparable between sexes, with GH secretion in men and found it to be similar in both groups. In addition, a positive correlation between plasma oestradiol concentrations and GH secretion was identified [61]. These findings suggest that higher oestradiol concentrations in women, rather than sex per se, result in greater GH secretion in women than in men. However, the level(s) at which oestradiol exerts its regulatory control is not clear [62]. The apparent importance of oestradiol in determining average daily GH secretion means that women using the contraceptive pill will have markedly different daily GH secretion from women not using the contraceptive pill, and that different formulations of contraceptive pill may mediate different effects depending on their oestradiol content.

Despite the fact that total secretion rates are similar for males and females matched for age, relative adiposity and oestradiol concentrations, there do appear to be differences in patterns of GH secretion between men and women [60,61]. Specific patterns of GH secretion are regulators of GH bioactivity in rats and therefore the importance of the GH secretory pattern in the regulation of GH action in humans has been considered [63]. Women have been shown to have more GH pulses with interpulse concentrations twice as high as those of men. These reported higher interpulse GH concentrations in women than in men bears a similarity to the differences in GH secretory patterns in male and female rats [56]. In addition, GH secretion in men has been found to be dominated by large nocturnal pulses with relatively low GH secretion throughout the rest of the day. In contrast, women had a much more uniform pulsatile pattern of secretion throughout the day, spending nearly twice as much time in active GH secretion than men [61]. It is possible that the differences in the pattern of GH secretion between men and women are attributable to a lesser role of somatostatin in women [61]. In any case, it appears that the pattern of GH secretion might impact upon important aspects of growth and metabolism in humans [63].

Wideman et al. [53] reported that women had greater serum GH concentrations at rest and during 30 min of high-intensity sub-maximal exercise, despite the women performing their trials in the early-follicular phase, when oestradiol levels are similar between men and women. The higher serum GH concentrations were attributed to increased mass per secretory burst in women than men, and women also reached peak GH concentrations earlier in exercise. Despite these differences, the relative responses to a single bout of sub-maximal exercise were similar between men and women [53]. With increases in exercise intensity, GH secretion has been shown to increase in a linear dose–response relationship in both men [6] and women [64] (see Table 1). However, women were found to have a greater GH response to exercise at all intensities, and it was also found that women reached peak GH concentrations earlier in exercise than men [6].

6.2. Age

There is evidence that the pituitary GH pool is preserved with increased age yet daily GH secretion rate has been negatively correlated with age [65,66]. This age-related fall in GH secretion appears to be more pronounced in men than in women [37]. However, which aspect, or aspects, of secretion rate contribute to the observed changes in secretion rate with age (mass of secretory burst, frequency of secretory burst or basal secretion rate) is not entirely clear. Iranmanesh et al. [65] observed age to be a major negative statistical determinant of GH burst frequency and also endogenous GH half-life. However later research found that GH secretory burst amplitude varied inversely with age, without identifying any significant correlation between age and burst frequency or endogenous GH half-life [66]. From the results of that study Veldhuis et al. [66] suggested that the primary impact of age, acting with altered body composition, is to diminish the amount or mass of GH secreted per burst, possibly mediated by an increase in somatostatinergic inhibitory tone and/or decreased activity of hypothalamic GHRH. In addition, Veldhuis et al. [66] used an approximate entropy statistic to evaluate the relative degree of serial orderliness or regularity of 24 h serum GH concentration profiles and observed a reduced regularity of GH secretion with age. This suggests that with increasing age there is disruption in the pathways directing GH secretion, possibly as a result of a reduction in the co-ordination of the secretion of GHRH and somatostatin.

It has been estimated that for men with a normal body mass index (BMI), an indirect measure of body fatness, each decade of increasing age reduces the GH production rate by 14% and the GH half-life by 6% [65]. Vahl et al. [67] studied the significance of age on the pharmacokinetics of a single fixed dose exogenous pulse, mimicking endogenous conditions, in normal adults and found age to be the most important predictor of GH area under the curve in all subjects with lower GH area under the curve in older individuals, along with a greater metabolic clearance rate (MCR). However, more recently it was shown that the administration of a body weight adjusted GH bolus resulted in there being no correlation between age and MCR [68].

There is a paucity of literature regarding the effect of ageing on the GH response to sub-maximal and sprint exercise, although there is some evidence that the growth hormone response to resistance exercise is blunted with age [69]. The major limitation of work in this area is the fact that younger individuals tend to be able to do more work in a bout of exercise than older individuals.

6.3. Body composition

Mean (24 h) serum GH concentration has been demonstrated to be negatively correlated with percentage body fat allied with a progressive increase in entropy of 24 h GH profiles with increasing percentage body fat [66]. Abdominal adiposity has been associated with decreased spontaneous 24 h GH secretion [70], and it has been estimated that each unit increase in BMI, at a given age, reduces the daily secretion rate by 6% [65]. Recently, it has been shown that abdominal visceral fat (AVF), measured using single-slice computed tomography scans, is a strong predictor of 24-h GH secretion, with an inverse, curvilinear relationship between AVF and 24-h GH secretion independent of age and gender [71]. In fact, the results of this study suggest that factors affecting GH secretion such as age and gender might exert their influence in part via effects on AVF [71].

Intra-abdominal fat mass has been shown to be the major determinant of stimulated GH secretion in healthy non-obese adults [72], suggesting that abdominal adiposity might also alter the GH response to exercise. In fact, obese women have been shown to have a reduced GH response to sub-maximal exercise when compared with non-obese women [73] (see Table 1). Six hour integrated GH concentrations were half as great in those with upper body obesity compared with those with lower body obesity, although no statistically significant differences were identified when subjects were separated by body fat distribution. In the same study, 16 weeks of aerobic training did not alter the GH response to exercise despite improvements in aerobic capacity, although no changes in fat mass were identified [73]. The evidence seems to suggest, therefore, that high body fat percentage and, in particular, high levels of AVF, will result in reduced GH responses to exercise.

In addition to gender, age and body composition factors such as sex-steroid hormones, nutritional status, physical fitness/exercise training, quality and quantity of sleep and medication use might also affect exercise-induced GH secretion. All of these factors must be

considered in the design and interpretation of experimental research.

7. Effect of time of day on exercise-induced GH release

A 20 min incremental treadmill running test, with the last 5 min at 90% $\dot{V}O_2$max, has been shown to induce an increase in GH regardless of whether the exercise was performed in the morning (between 07:00 and 08:00 h) or the afternoon (between 15:00 and 16:00 h) in women [74]. Peak GH concentrations were measured at the end of each exercise bout and returned to resting levels 20 min after exercise and no changes were identified in either the magnitude or the pattern of the exercise-induced GH response in the morning or afternoon. These results agree with a study showing no diurnal variation in GH release in response to insulin-induced hypoglycaemia [75]. Scheen et al. [22] compared continuous bed-rest with 3 h of high (60% $\dot{V}O_2$max) and low (40% $\dot{V}O_2$max) intensity, arm cranking and leg cycling exercise at three different times of day, where exercise was initiated at approximately 05:00, 14:30 and 23:30 h. The results of this study demonstrated that exercise elicits a clear GH response regardless of time of day with 5- to 6-fold increases in plasma GH concentrations. In addition, there was no difference in the magnitude of the exercise-induced GH response at three different times of day suggesting that there is no diurnal rhythm in the GH response to prolonged sub-maximal exercise.

Similar findings were also reported for moderately trained young men, who performed 30 min of treadmill exercise on three separate occasions at 07:00, 19:00 and 24:00 h. No significant difference in the magnitude of the GH response was identified for these three trials, although the increase in serum GH concentrations was followed by a period of suppression of GH secretion in the 07:00 and the 19:00, but not the 24:00 h trial [76]. It would appear, therefore, that exercise is a robust stimulus that can overcome underlying diurnal rhythms. However, both low- and moderate- intensity sub-maximal exercise have been shown to suppress GH release in the first part of nocturnal sleep, when GH concentrations are usually at their peak, and increases GH release in the second part of sleep, when GH concentrations are normally lower, without altering total GH release [77].

7.1. Effect of repeated bouts of exercise on GH release

There is a great deal of evidence suggesting that GH, like a number of other hormones, regulates its own secretion via a negative feedback mechanism, although the nature of this autoregulation is not entirely clear. A number of possibilities exist and the role of GH autofeedback, increased somatostatinergic tone and/or decreased GHRH release, increased circulating FFA and modulation by IGF-I have all been considered.

Lanzi and Tannenbaum [78] found spontaneous GH release to be inhibited within 1 to 2 h after a single subcutaneous injection of rGH in rats, and it remained completely suppressed for up to 4 h after the rGH injection. They also demonstrated no difference in the duration or magnitude of attenuation of the GH response according to an acute (single subcutaneous injection) or chronic (5 day) injection regimen. Passive immunisation with specific somatostatin antiserum reversed the rGH-induced blunting of the spontaneous GH response by restoring the amplitude of the GH secretory bursts. The fact that immunoneutralisation of somatostatin prevented the attenuation of spontaneous GH release after GH pre-treatment provides strong support for a role for somatostatin in GH autoregulation. However, since the normal pattern of pulsatile GH secretion was not restored by passive immunisation with somatostatin antiserum, the possibility of a GH-induced inhibitory effect on hypothalamic GHRH cannot be discounted.

In a further study Lanzi and Tannenbaum [79] also demonstrated a role for somatostatin in the attenuation of exogenous GHRH-induced GH release in rats. Serial injections of GHRH at 2 h intervals elicited 4- to 6-fold increases in GH release when GHRH was administered at times of peak spontaneous GH release, but only a minimal GH response was observed during trough periods. There was no evidence of desensitisation of somatotropes since high GH responsiveness to exogenous GHRH was maintained at a time of spontaneous secretory episode following a previous exogenous GHRH challenge during a trough period. These results demonstrate the importance of the cyclical increase in endogenous hypothalamic somatostatin secretion in preventing desensitisation of the pituitary to GHRH. In the same study a single subcutaneous rGH injection 3 h prior to GHRH administration severely attenuated the GHRH-induced GH response. Passive immunisation with specific somatostatin antiserum reversed the blunted GH response and completely restored GH responsiveness to GHRH. This was consistent with the contention that GH feedback is exerted, at least in part, by somatostatin. In addition, the understanding that GH receptor mRNA is colocalised in somatostatin-positive neurons in the periventricular nucleus of the rat hypothalamus [80] further supports these findings.

In normal adults repeated GHRH administration has been shown to result in an attenuated GH response to the second stimulus [81]. However, the administration of arginine, which acts to suppress somatostatin release, with the second bolus of GHRH restored the responsiveness of the somatotroph and, in fact, even potentiated the GH response. This suggests that the attenuation of the GH observed using repeated boluses of GHRH

alone was not due to a GHRH-induced reduction in the size of the pool of GH available for release. In addition, the fact that arginine administration reinstated the GHRH-induced GH response following the second stimulation implies an important role for somatostatin in GH autoregulation.

The GH response to repeated bouts of exercise has also been studied, and Kanaley et al. [82] demonstrated an augmented GH response to repeated bouts of 30 min exercise at 70% $\dot{V}O_2$max separated by either 60 min or 210 min of recovery. Each exercise bout resulted in a distinct GH pulse and the apparent progressive increase in GH response tended to be greater with a longer (210 min) recovery period. The augmented response with repeated bouts of exercise provided evidence that the depletion of pituitary stores with repeated stimuli to GH release is unlikely. Jaffe et al. [83] supported this viewpoint, suggesting that pituitary GH content far exceeded the amount of GH released in their study and yet they demonstrated a suppression of the GH response to repeated GHRH administration. The GH response to the second of two 65 min bouts of exercise at 70% $\dot{V}O_2$max separated by 3 h of recovery has also been shown to result in a greater GH response than a single 65 min bout of exercise at 70% $\dot{V}O_2$max [84]. From these results it would appear that exercise provides sufficient stimulus to overcome the autonegative feedback demonstrated using pharmacological interventions [82].

However, Cappon et al. [85] demonstrated that the GH response to 10 min of constant power cycling exercise, at an intensity corresponding to 50% of the difference between the lactate threshold and $\dot{V}O_2$max, was dramatically attenuated as a result of previous exercise bouts. In addition, they demonstrated an acute, GH independent, exercise-induced increase in IGF-I. A purified IGF-I preparation has been shown to inhibit GH release from pituitary cells in culture [86], and the infusion of rhIGF-I has also been demonstrated to suppress pulsatile and GHRH-stimulated GH secretion in male subjects [61]. There is an apparent role for somatostatin in this long-loop feedback, since Berelowitz et al. [86] also observed IGF-I to stimulate a dose-related release of somatostatin from hypothalamic explants. However intraventricular IGF infusion in ewes had no effect on GH secretion, whereas intrapituitary infusion resulted in the inhibition of GH release [87] providing strong evidence for a direct effect of IGF-I at the level of the pituitary.

However, Cappon et al. [85] found that exercise-induced IGF-I levels were not significantly higher than baseline within 30 min of recovery, whilst the recovery between exercise bouts was 50 min, suggesting that IGF-I did not play a role in the attenuation of the GH response to exercise in their study. In addition, it would appear that exercise-induced IGF-I would not have a role in the regulation of the exercise-induced GH response in exercise bouts separated by more than 30 min. Lanzi and Tannenbaum [78] also measured IGF-I and did not observe an increase in plasma IGF-I concentration, but reported GH release to be suppressed for 4 h after rGH administration in rats. This implies that the GH negative feedback loop can function independently of IGF-I, although there does remain the possibility that locally synthesised IGF-I in the pituitary gland might play a role.

Cappon et al. [85] also considered GH autoinhibition, whereby GH feeds back on itself directly, however, this seemed unlikely as GH was only slightly elevated at the end of each recovery period. Alternatively, an increase in FFA as a result of the first exercise bout might have blocked GH release directly at the pituitary level [88]. The potential role of FFA in the GH feedback loop was studied by Pontiroli et al. [89]. Infusion of methionyl-GH (met-GH) blocked the response to exogenous GHRH and administration of acipimox, an antilipolytic agent, and pyridostigmine, to block hypothalamic somatostatin release, did not restore the GH response to GHRH. This indicates that inhibition of the GH response to GHRH can occur independently of circulating plasma FFA levels and hypothalamic somatostatin release and was probably mediated by GH autofeedback at the pituitary gland.

Repeated sprint exercise has also been shown to result in an attenuated GH response when GH is still elevated immediately prior to a second sprint [8]. In this study, the GH response to the second sprint was attenuated in 6 out of 10 subjects who displayed moderate to large increases in serum GH concentrations following the first sprint, and whose GH levels remained elevated before the second sprint. A GH response to the second sprint was identified in two of the subjects and, in both cases, the GH response to the first sprint was moderate and GH had returned to pre-exercise levels before the second sprint. This suggests that GH autoinhibition can be responsible for the suppression of GH release in repeated sprint bouts with 60 min between sprints. Increasing the recovery period between sprints to 240 min, by which time serum GH had returned to pre-exercise levels, resulted in a partial recovery of the GH response to a second sprint [90].

8. Effect of training on acute GH release

A number of studies have concluded that exercise training has no effect on resting GH concentrations when comparing sedentary individuals and athletes [91–94], sprint-trained and endurance-trained athletes [21] and following endurance training [95]. However, the endogenous pulsatility of GH concentrations makes the measurement of "resting" GH concentrations almost meaningless. In addition, it is likely that in some of the

studies considering the effect of training on resting GH concentrations the assays employed would have been unable to satisfactorily measure the low levels of GH associated with human subjects at rest [66].

Some studies have considered the effect of training state on the GH response to an acute bout of exercise. There is little agreement between these studies as to whether exercise training increases [93,95] or decreases [91,96,97] the GH response to a single exercise bout. The GH response to a 30 min run at 60% of $\dot{V}O_2$max was found to be significantly greater in runners (minimum mileage of 40 miles per week) compared with moderately active controls [93]. In agreement with these findings, the GH response to a standard swimming training session (15×200 m with 20 s rest between sets) was enhanced in nine top-level male endurance swimmers (national team members) following 18 weeks of training despite no change in swimming velocities during these sets [95]. In addition, it has been shown that endurance-trained athletes have a greater GH response to insulin-induced hypoglycaemia than untrained individuals [92].

However, an incremental sub-maximal cycling test has been shown to elicit a smaller GH response in well-trained compared with untrained cyclists [91]. In addition, six weeks of sub-maximal exercise training was associated with a 45% reduction in the GH response to a 20 min constant load cycle ergometer test [96]. In this study, absolute power output was the same in pre- and post-training tests and over the training period power output expressed as a percentage of maximum power output decreased from 82% to 70%. These findings suggest that, in sub-maximal exercise, there might be a critical relative exercise intensity required to elicit GH release [96]. Six weeks of combined speed and speed-endurance training has also been found to result in a smaller exercise-induced GH response to a 30 s sprint on a cycle ergometer compared with pre-training despite a 5% increase in mean power output during the sprint [97]. Weltman et al. [96] suggested that reduced exercise-induced GH concentrations following training may be a result of a combination of reduced GH secretion and enhanced GH clearance. In support of this contention is the suggestion that the half-life of endogenous GH is shorter in exercising than resting individuals [98].

However, the effect that exercise training has on the GH response to exercise is not entirely clear and might depend on a number of factors including the type and frequency of training and the duration of the training period. In addition, only three of the studies mentioned [91,93,97] compared the response of trained individuals with untrained control subjects and of these only one [97] completed longitudinal study incorporating a control group. It would appear, therefore, that further research is required in this area before a meaningful conclusion can be drawn.

9. Summary

This review has focussed on the natural GH response to intense exercise, and has identified a number of the factors that influence exercise-induced GH release. Fig. 1 summarises these factors, although it is accepted that this list might not be exhaustive, and that the mechanisms of action and relationships between many of these factors are not fully understood. It is clear, therefore, that further research is needed in order to determine the stimulus for exercise-induced GH secretion in response to a single bout of exercise, as well as to understand the effect of multiple bouts of exercise on

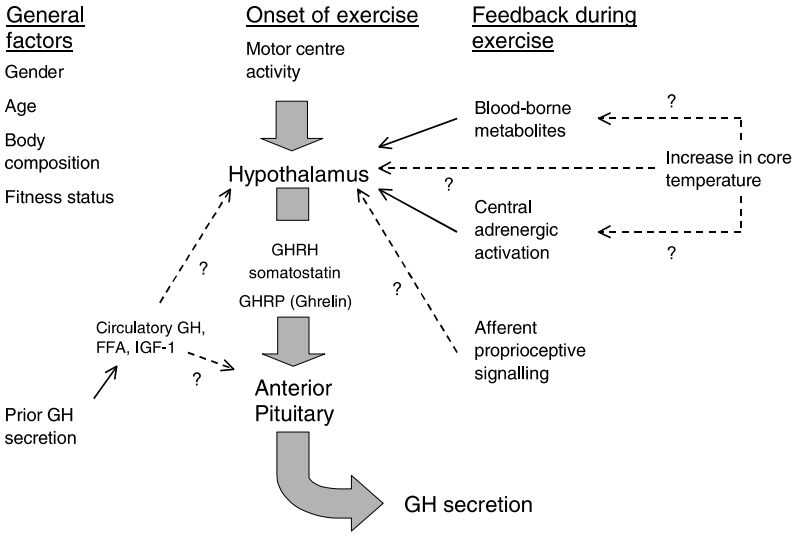

Fig. 1. Summary of the factors affecting the GH response to intense exercise.

the GH response to exercise, both in a single day, and as part of a programme of training. A better understanding of these factors could be of benefit to sports performers, but also to normal individuals attempting to slow the process of ageing.

Acknowledgements

The author thanks Dr. Mary Nevill, Dr. Henryk Lakomy, and Prof. George Hall for the assistance given in the preparation of this review.

References

[1] Growth Hormone Research Society, Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society, J. Clin. Endocrinol. Metab. 85 (2000) 3990–3993.
[2] J. Seth, A. Bristow, Standardisation of human growth hormone (hGH) assays, Available from http://www.ukneqas.org.uk/nib-scgh.pdf (accessed 1 December 2002) 2000.
[3] G. Copinschi, M. Hartog, J.M. Earll, R.J. Havel, Effect of various blood sampling procedures on serum levels of immunoreactive human growth hormone, Metab. Clin. Exp. 16 (1967) 402–409.
[4] J. Raynaud, A. Capderou, J.P. Martineaud, J. Bordachar, J. Durand, Intersubject variability in growth hormone time course during different types of work, J. Appl. Physiol. 55 (1983) 1682–1687.
[5] N.E. Felsing, J.A. Brasel, D.M. Cooper, Effect of low and high intensity exercise on circulating growth hormone in men, J. Clin. Endocrinol. Metab. 75 (1992) 157–162.
[6] C.J. Pritzlaff, L. Wideman, J.Y. Weltman, et al., Impact of acute exercise intensity on pulsatile growth hormone release in men, J. Appl. Physiol. 87 (1999) 498–504.
[7] K.A. Stokes, M.E. Nevill, G.M. Hall, H.K.A. Lakomy, The time course of the human growth hormone response to a 6 s and a 30 s cycle ergometer sprint, J. Sports Sci. 20 (2002) 487–494.
[8] K.A. Stokes, M.E. Nevill, G.M. Hall, H.K.A. Lakomy, Growth hormone response to repeated maximal cycle ergometer exercise at different pedaling rates, J. Appl. Physiol. 92 (2002) 602–608.
[9] J.R. Sutton, J.D. Young, L. Lazarus, J.B. Hickie, J. Maksvytis, The hormonal response to physical exercise, Austr. Ann. Med. 18 (1969) 84–90.
[10] S. Kozlowski, J. Chwalbinska-Moneta, M. Vigas, H. Kaciuba-Uscilko, K. Nazar, Greater serum GH response to arm than leg exercise performed at equivalent oxygen uptake, Eur. J. Appl. Physiol. 52 (1983) 131–134.
[11] W.P. VanHelder, R.C. Goode, M.W. Radomski, Effect of anaerobic and aerobic exercise of equal duration and work expenditure on plasma growth hormone levels, Eur. J. Appl. Physiol. 52 (1984) 255–257.
[12] A. Karagiorgos, J.F. Garcia, G.A. Brooks, Growth hormone response to continuous and intermittent exercise, Med. Sci. Sports 11 (1979) 302–307.
[13] M.S. Vigas, S. Nemeth, L. Jurcoricora, J. Mikula, L. Komadel, The importance of lactate in exercise-induced growth hormone release in man. Radioimmunoassays: methodology and applications in physiology and clinical studies, Horm. Metab. Res. 5 (Suppl) (1974) 166–169.
[14] J.R. Sutton, N.L. Jones, C.J. Toews, Growth hormone secretion and acid–base alteration at rest and during exercise, Clin. Sci. Mol. Med. 50 (1976) 241–247.
[15] S.E. Gordon, W.J. Kraemer, N.H. Vos, J.M. Lynch, H.G. Knuttgen, Effect of acid–base balance on the growth hormone response to acute high-intensity cycle exercise, J. Appl. Physiol. 76 (1994) 821–829.
[16] A.N. Elias, A.F. Wilson, S. Naqvi, M.R. Pandian, Effects of blood pH and blood lactate on growth hormone, prolactin, and gonadotropin release after acute exercise in male volunteers, Proc. Soc. Exp. Biol. Med. 214 (1997) 156–160.
[17] C. Lassarre, F. Girard, J. Durand, J. Raynaud, Kinetics of human growth hormone during submaximal exercise, J. Appl. Physiol. 37 (1974) 826–830.
[18] J. Raynaud, L. Drouet, J.P. Martineaud, J. Bordachar, J. Coudert, J. Durand, Time course of plasma growth hormone during exercise in humans at altitude, J. Appl. Physiol. 50 (1981) 229–233.
[19] W.P. VanHelder, K. Casey, M.W. Radomski, Regulation of growth hormone during exercise by oxygen demand and availability, Eur. J. Appl. Physiol. 56 (1987) 628–632.
[20] J.R. Sutton, Hormonal and metabolic responses to exercise in subjects of high and low work capacities, Med. Sci. Sports 10 (1978) 1–6.
[21] M.E. Nevill, D.J. Holmyard, G.M. Hall, et al., Growth hormone responses to treadmill sprinting in sprint- and endurance-trained athletes, Eur. J. Appl. Physiol. 72 (1996) 460–467.
[22] A.J. Scheen, O.M. Buxton, M. Jison, et al., Effects of exercise on neuroendocrine secretions and glucose regulation at different times of day, Am. J. Physiol. 274 (1998) E1040–E1049.
[23] M. Viru, E. Jansson, A. Viru, C.J. Sundberg, Effect of restricted blood flow on exercise-induced hormone changes in healthy men, Eur. J. Appl. Physiol. 77 (1998) 517–522.
[24] D.L. McCloskey, J.H. Mitchell, Reflex cardiovascular and respiratory responses originating in exercising muscle, J. Physiol. 224 (1972) 173–186.
[25] M. Kjaer, Epinephrine and some other hormonal responses to exercise in man, J. Sports Med. 10 (1989) 2–15.
[26] M. Kjaer, N.H. Secher, F.W. Bach, S. Sheikh, H. Galbo, Hormonal and metabolic responses to exercise in humans: effect of sensory nervous blockade, Am. J. Physiol. 257 (1989) E95–E101.
[27] M. Kjaer, B. Hanel, L. Worm, et al., Cardiovascular and neuroendocrine responses to exercise in hypoxia during impaired neural feedback from muscle, Am. J. Physiol. 277 (1999) R76–R85.
[28] M. Kjaer, N.H. Secher, F.W. Bach, H. Galbo, Role of motor center activity for hormonal changes and substrate mobilization in humans, Am. J. Physiol. 253 (1987) R687–R695.
[29] M. Kjaer, N.H. Secher, J. Bangsbo, et al., Hormonal and metabolic responses to electrically induced cycling during epidural anesthesia in humans, J. Appl. Physiol. 80 (1996) 2156–2162.
[30] E. Asmussen, S.H. Johansen, M. Jorgensen, M. Nielsen, On the nervous factors controlling respiration and circulation during exercise-experiments with curarization, Acta. Physiol. Scand. 63 (1965) 343–350.
[31] M. Kjaer, S.F. Pollack, T. Mohr, et al., Regulation of glucose turnover and hormonal responses during electrical cycling in tetraplegic humans, Am. J. Physiol. 271 (1996) R191–R199.
[32] S. Ellis, M.A. Vodian, R.E. Grindeland, Studies on the bioassayable growth hormone-like activity of plasma, Recent Prog. Horm Res. 34 (1978) 213–238.
[33] G.E. McCall, K.L. Gosselink, A.J. Bigbee, R.R. Roy, R.E. Grindeland, V.R. Edgerton, Muscle afferent-pituitary axis: a novel pathway for modulating the secretion of a pituitary growth factor, Ex. Sport Sci. Rev. 29 (2001) 164–169.
[34] K.L. Gosselink, R.E. Grindeland, R.R. Roy, et al., Skeletal muscle afferent regulation of bioassayable growth hormone in the rat pituitary, J. Appl. Physiol. 84 (1998) 1425–1430.

[35] G.E. McCall, R.E. Grindeland, R.R. Roy, V.R. Edgerton, Muscle afferent activity modulates bioassayable growth hormone in human plasma, J. Appl. Physiol. 89 (2000) 1137–1141.
[36] P.W. Cherry, H.K.A. Lakomy, L.H. Boobis, M.E. Nevill, Rapid recovery of power output in females, Acta. Physiol. Scand. 164 (1998) 79–87.
[37] A. Weltman, C.M. Wood, C.J. Womack, et al., Catecholamine and blood lactate responses to incremental rowing and running exercise, J. Appl. Physiol. 76 (1994) 1144–1149.
[38] A. Giustina, J.D. Veldhuis, Pathophysiological basis of the neuroregulation of the somatotropic (GH) axis in experimental animals and the human, Endocr. Rev. 19 (1998) 717–797.
[39] J. Chwalbinska-Moneta, H. Krysztofiak, A. Ziemba, K. Nazar, 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. Phyisol. 73 (1996) 117–120.
[40] A. Weltman, C.J. Pritzlaff, L. Wideman, et al., Exercise-dependent growth hormone release is linked to markers of heightened central adrenergic outflow, J. Appl. Physiol. 89 (2000) 629–635.
[41] I.K.M. Brenner, J. Zamecnik, P.N. Shek, R.J. Shephard, The impact of heat exposure and repeated exercise on circulating stress hormones, Eur. J. Appl. Physiol. 76 (1997) 445–454.
[42] J.M.H. Buckler, The relationship between changes in plasma growth hormone levels and body temperature occurring with exercise in man, Biomedicine 19 (1973) 193–197.
[43] M.C. Cross, M.W. Radomski, W.P. VanHelder, S.G. Rhind, R.J. Shephard, Endurance exercise with and without thermal clamp: effects on leukocytes and leukocyte subsets, J. Appl. Physiol. 81 (1996) 822–829.
[44] M.W. Radomski, M. Cross, A. Buguet, Exercise-induced hyperthermia and hormonal responses to exercise, Can. J. Physiol. Pharmacol. 76 (1998) 547–552.
[45] H.C.M. Maas, W.R. de Vries, I. Maitimu, E. Bol, C.Y. Bowers, H.P.F. Koppenschaar, Growth hormone responses during strenuous exercise: the role of GH-releasing hormone and GH-releasing peptide-2, Med. Sci. Sports Exerc. 32 (2000) 1226–1236.
[46] L. Di Luigi, F.G. Conti, A. Casini, et al., Growth hormone and insulin-like growth factor I responses to moderate submaximal acute physical exercise in man: effects of octreocide, a somatostatin analogue, administration, Int. J. Sports Med. 18 (1997) 257–263.
[47] T.J. Marcell, R.A. Wiswell, S.A. Hawkins, K.M. Tarpenning, Age-related blunting of growth hormone secretion during exercise may not be solely due to increased somatostatin tone, Metabolism 48 (1999) 665–670.
[48] W.R. De Vries, S.A. Abdesselam, T.J. Schers, et al., Complete inhibition of hypothalamic somatostatin activity is only partially responsible for the growth hormone response to strenuous activity, Metabolism 51 (2002) 1093–1096.
[49] L. Wideman, J.Y. Weltman, J.T. Patire, et al., Synergy of L-arginine and GHRP-2 stimulation of growth hormone in men and women: modulation by exercise, Am. J. Physiol. 279 (2000) R1467–R1477.
[50] F. Camanni, E. Ghigo, E. Arvat, Growth hormone-releasing peptides and their analogs, Front. Neuroendocrinol. 19 (1998) 47–72.
[51] M. Kojima, H. Hosoda, Y. Date, M. Nakazato, H. Matsuo, K. Kangawa, Ghrelin is a growth-hormone-releasing acylated peptide from stomach, Nature 402 (1999) 656–660.
[52] R. Dall, J. Kanaley, T.K. Hansen, et al., Plasma ghrelin levels during exercise in healthy subjects and in growth hormone-deficient patients, Eur. J. Endocrinol. 147 (2002) 65–70.
[53] L. Wideman, J.Y. Weltman, N. Shah, S. Story, J.D. Veldhuis, A. Weltman, Effects of gender on exercise-induced growth hormone release, J. Appl. Physiol. 87 (1999) 1154–1162.
[54] T. Raastad, T. Bjoro, J. Hallen, Hormonal responses to high- and moderate-intensity strength exercise, Eur. J. Appl. Physiol. 82 (2000) 121–128.
[55] K. Stokes, M. Nevill, G. Hall, H. Lakomy, Reliability of the growth hormone response to a single 30-s cycle ergometer sprint, in: Proceedings of the 12th Commonwealth International Sport Conference, July 19–23, 2002, Manchester, UK (Abstract).
[56] J.O. Jansson, S. Eden, O. Isaksson, Sexual dimorphism in the control of growth hormone secretion, Endocr. Rev. 6 (1985) 128–150.
[57] J.-.C. Painson, G.S. Tannenbaum, Sexual dimorphism of somatostatin and growth hormone-releasing factor signalling in the control of pulsatile growth hormone secretion in the rat, Endocrinology 128 (1991) 2858–2866.
[58] B.E. Engstrom, F.A. Karlsson, L. Wide, Gender differences in diurnal growth hormone and epinephrine values in young adults during ambulation, Clin. Chem. 45 (1999) 1235–1239.
[59] K.Y. Ho, W.S. Evans, R.M. Blizzard, et al., Effects of sex and age on the 24-h profile of growth hormone secretion in man: importance of endogenous estradiol concentrations, J. Clin. Endocrinol. Metab. 64 (1987) 51–58.
[60] S.M. Pincus, E.F. Gevers, I.C.A.F. Robinson, et al., Females secrete growth hormone with more process irregularity than males in both humans and rats, Am. J. Physiol. 270 (1996) E107–E115.
[61] C.A. Jaffe, B. Ocampo-Lim, W. Guo, et al., Regulatory mechanisms of growth hormone are sexually dimorphic, J. Clin. Invest. 102 (1998) 153–164.
[62] E.E. Muller, V. Locatelli, D. Cocchi, Neuroendocrine control of growth hormone secretion, Physiol. Rev. 79 (1999) 511–607.
[63] C.A. Jaffe, D.K. Turgeon, K. Lown, R. Demott-Friberg, P.B. Watkins, Growth hormone secretion pattern is an independent regulator of growth hormone actions in humans, Am. J. Physiol. 283 (2002) E1008–E1015.
[64] C.J. Pritzlaff-Roy, L. Wideman, J.Y. Weltman, et al., Gender governs the relationship between exercise intensity and growth hormone release in young adults, J. Appl. Physiol. 92 (2002) 2053–2060.
[65] A. Iranmanesh, G. Lizarralde, J.D. Veldhuis, Age and relative adiposity are specific negative determinants of the frequency and magnitude of growth hormone (GH) sectretory bursts and the half-life of endogenous GH in healthy men, J. Clin. Endocrinol. Metab. 73 (1991) 1081–1088.
[66] J.D. Veldhuis, A.Y. Liem, S. South, et al., Differential impact of age, sex steroid hormones, and obesity on basal versus pulsatile growth hormone secretion in men as assessed in an ultrasensitive chemiluminescence assay, J. Clin. Endocrinol. Metab. 80 (1995) 3209–3222.
[67] N. Vahl, N. Moller, T. Lauritzen, J.S. Christiansen, J.O.L. Jorgensen, Metabolic effects and pharmacokinetics of a growth hormone pulse in healthy adults: relation to age, sex, and body composition, J. Clin. Endocrinol. Metab. 82 (1997) 3612–3618.
[68] T.K. Hansen, Pharmacokinetics and acute lipolytic actions of growth hormone: impact of age, body composition, binding proteins and other hormones, Growth Horm. IGF Res. 12 (2002) 342–358.
[69] G. Pyka, R.A. Wiswell, R. Marcus, Age-dependent effect of resistance exercise on growth hormone secretion in people, J. Clin. Endocrinol. Metab. 75 (1992) 404–407.
[70] N. Vahl, J.O.L. Jorgensen, C. Skjaerbaek, J.D. Veldhuis, H. Orskov, J.S. Christiansen, Abdominal adiposity rather than age and sex predicts mass and regularity of GH secretion in healthy adults, Am. J. Physiol. 272 (1997) E1108–E1116.
[71] J.L. Clasey, A. Weltman, J. Patrie, et al., Abdominal visceral fat and fasting insulin are important predictors of 24-hour GH release independent of age, gender, and other physiological factors, J. Clin. Endocrinol. Metab. 86 (2001) 3845–3852.

[72] N. Vahl, J.O.L. Jorgensen, A. Jurik, J.S. Christiansen, Abdominal adiposity and physical fitness are major determinants of the age-associated decline in stimulated GH secretion in healthy adults, J. Clin. Endocrinol. Metab. 81 (1996) 2209–2215.
[73] J.A. Kanaley, M.M. Weatherdrupp-Dentes, E.B. Jaynes, M.L. Hartman, Obesity attenuates the growth hormone response to exercise, J. Clin. Endocrinol. Metab. 84 (1999) 3156–3161.
[74] E.A. Galliven, A. Singh, D. Michelson, S. Bina, P.W. Gold, P.A. Deuster, Hormonal and metabolic responses to exercise across time of day and menstrual cycle phase, J. Appl. Physiol. 83 (1997) 1822–1831.
[75] R.S. Nathan, E.J. Sachar, G. Langer, M.A. Tabrizi, F.S. Halpern, Diurnal variations in the response of plasma prolactin, cortisol and growth hormone to insulin-induced hypoglycemia in normal men, J. Clin. Endocrinol. Metab. 49 (1979) 231–235.
[76] J.A. Kanaley, J.Y. Weltman, K.S. Pieper, A. Weltman, M.L. Hartman, Cortisol and growth hormone responses to exercise at different times of day, J. Clin. Endocrinol. Metab. 86 (2001) 2881–2889.
[77] W. Kern, B. Perras, R. Wodick, H.L. Fehm, J. Born, Hormonal secretion during nighttime sleep indicating stress of daytime exercise, J. Appl. Physiol. 79 (1995) 1461–1468.
[78] R. Lanzi, G.S. Tannenbaum, Time course and mechanism of growth hormone's negative feedback effect on its own spontaneous release, Endocrinology 130 (1992) 780–788.
[79] R. Lanzi, G.S. Tannenbaum, Time-dependent reduction and potentiation of growth hormone (GH) responsiveness to GH-releasing factor induced by exogenous GH: a role for somatostatin, Endocrinology 130 (1992) 1822–1828.
[80] K.A. Burton, D.K. Clifton, R.A. Steiner, Growth hormone receptor messenger RNA is colocalized in somatostatin neurons in the male rat hypothalamus, in: 21st Annual Meeting of the Society for Neuroscience (Abstract), New Orleans LA, 1991, p. 432.
[81] E. Ghigo, E. Arvat, F. Valente, et al., Arginine reinstates the somatotrope responsiveness to intermittent growth hormone-releasing hormone administration in normal adults, Neuroendocrinology 54 (1991) 291–294.
[82] J.A. Kanaley, J.Y. Weltman, J.D. Veldhuis, A.D. Rogol, M.L. Hartman, A. Weltman, Human growth hormone response to repeated bouts of aerobic exercise, J. Appl. Physiol. 83 (1997) 1756–1761.
[83] C.A. Jaffe, R. DeMott-Friberg, A.L. Barkan, Suppression of growth hormone (GH) secretion by a selective GH-releasing hormone (GHRH) antagonist, J. Clin. Invest. 92 (1993) 695–701.
[84] O. Ronson, E. Haug, B.K. Pedersen, R. Bahr, Increased neuroendocrine response to a repeated bout of endurance exercise.
[85] J. Cappon, J.A. Brasel, S. Mohan, D.M. Cooper, Effect of brief exercise on insulin-like growth factor I, J. Appl. Physiol. 76 (1994) 2490–2496.
[86] M. Berelowitz, M. Szabo, L.A. Frohman, S. Firestone, L. Chu, Somatomedin-C mediates growth hormone negative feedback by effects on both the hypothalamus and the pituitary, Science 212 (1981) 1279–1281.
[87] T.P. Fletcher, G.B. Thomas, F.R. Dunshea, L.G. Moore, I.J. Clarke, IGF feedback effects on growth hormone secretion in ewes: evidence for action at the pituitary but not the hypothalamic level, J. Endocrinol. 144 (1995) 323–331.
[88] F.F. Casanueva, L. Villanueva, C. Dieguez, et al., Free fatty acids block growth hormone (GH) releasing hormone-stimulated GH secretion in man directly at the pituitary, J. Clin. Endocrinol. Metab. 65 (1987) 634–642.
[89] A.E. Pontiroli, R. Lanzi, L.D. Monti, E. Sandoli, G. Pozza, Growth hormone (GH) autofeedback on GH response to GH-releasing hormone. Role of free fatty acids and somatostatin, J. Clin. Endocrinol. Metab. 72 (1991) 492–495.
[90] K.A. Stokes, M.E. Nevill, G.M. Hall, H.K.A. Lakomy, Effect of recovery period on human growth hormone responses to repeated sprint cycling, Med. Sci. Sports Exerc. 34 (2002) S72.
[91] S.R. Bloom, R.H. Johnson, D.M. Park, M.J. Rennie, W.R. Sulaiman, Differences in the metabolic and hormonal response to exercise between racing cyclists and untrained individuals, J. Physiol. 258 (1976) 1–18.
[92] K.J. Mikines, M. Kjaer, C. Hagen, B. Sonne, E.A. Richter, H. Galbo, The effect of training on responses of β-endorphin and other pituitary hormones to insulin-induced hypoglycemia, Eur. J. Appl. Physiol. 54 (1985) 476–479.
[93] J.C. Bunt, R.A. Boileau, J.M. Bahr, R.A. Nelson, Sex and training differences in human growth hormone levels during prolonged exercise, J. Appl. Physiol. 61 (1986) 1796–1801.
[94] T. Barreca, E. Reggiani, R. Franceschini, et al., Serum prolactin, growth hormone and cortisol in athletes an sedentary subjects after submaximal and exhaustive exercises, J. Sports Med. 28 (1988) 89–92.
[95] M. Bonifazi, E. Bela, C. Lupo, G. Martelli, B. Zhu, G. Carli, Influence of training on the to exercise of adrenocorticotropin and growth hormone plasma concentrations in human swimmers, Eur. J. Appl. Physiol. 78 (1998) 394–397.
[96] A. Weltman, J.Y. Weltman, C.J. Womack, et al., Exercise training decreases the growth hormone (GH) response to acute constant-load exercise, Med. Sci. Sports Exerc. 29 (1997) 669–676.
[97] K.A. Stokes, M.E. Nevill, P.W. Cherry, G.M. Hall, H.K.A. Lakomy, The effect of 6 weeks of sprint training on the growth hormone response to repeated maximal cycle ergometer exercise, J. Physiol. 528 (2000) 51P.
[98] D.L. Thompson, J.Y. Weltmen, A.D. Rogol, D.L. Metzger, J.D. Veldhuis, A. Weltman, Cholinergic and opioid involvement in release of growth hormone during exercise and recovery, J. Appl. Physiol. 75 (1993) 870–878.