The Exercise-Induced Growth Hormone Response in Athletes

Richard J. Godfrey,[1] *Zahra Madgwick*[2] and *Gregory P. Whyte*[3]

1 Brunel University, Uxbridge, Middlesex, UK
2 Paediatric Department, John Radcliffe Hospital, Oxford University, Oxford, UK
3 British Olympic Medical Centre, Northwick Park Hospital, Harrow, Middlesex, UK

Contents

Abstract

Human growth hormone (hGH) is secreted in a pulsatile fashion, generally following a circadian rhythm. A number of physiological stimuli can initiate hGH secretion, the most powerful, non-pharmacological of which are sleep and exercise. hGH has many varied roles throughout life, from growth itself, including the turnover of muscle, bone and collagen, to the regulation of selective aspects of metabolic function including increased fat metabolism and the maintenance of a healthier body composition in later life.

The exercise-induced growth hormone response (EIGR) is well recognised and although the exact mechanisms remain elusive, a number of candidates have been implicated. These include neural input, direct stimulation by catecholamines, lactate and or nitric oxide, and changes in acid-base balance. Of these, the best candidates appear to be afferent stimulation, nitric oxide and lactate.

Resistance training results in a significant EIGR. Evidence suggests that load and frequency are determining factors in the regulation of hGH secretion. Despite the significant EIGR induced by resistance training, much of the stimulus for protein synthesis has been attributed to insulin-like growth factor-1 with modest contributions from the hGH-GH receptor interaction on the cell membrane.

The EIGR to endurance exercise is associated with the intensity, duration, frequency and mode of endurance exercise. A number of studies have suggested an intensity 'threshold' exists for EIGR. An exercise intensity above lactate threshold and for a minimum of 10 minutes appears to elicit the greatest stimulus to the secretion of hGH. Exercise training above the lactate threshold may amplify the pulsatile release of hGH at rest, increasing 24-hour hGH secretion

The impact of chronic exercise training on the EIGR remains equivocal. Recent evidence suggests that endurance training results in decreased resting hGH and a blunted EIGR, which may be linked to an increased tissue sensitivity to hGH.

Whilst the potential ergogenic effects of exogenous GH administration are attractive to some athletes, the abuse of GH has been associated with a number of pathologies. Identification of a training programme that will optimise the EIGR may present a viable alternative.

Ageing is often associated with a progressive decrease in the volume and, especially, the intensity of exercise. A growing body of evidence suggests that higher intensity exercise is effective in eliciting beneficial health, well-being and training outcomes. In a great many cases, the impact of some of the deleterious effects of ageing could be reduced if exercise focused on promoting the EIGR.

This review examines the current knowledge and proposed mechanisms for the EIGR, the physiological consequences of endurance, strength and power training on the EIGR and its potential effects in elderly populations, including the aged athlete.

Growth hormone (GH) in health and disease has been the focus of attention for a number of reviews.[1-3] Limited reviews exist, however, examining the exercise-induced growth hormone response (EIGR). That is, the effect of exercise on GH secretion and its subsequent effects.

Human growth hormone (hGH), a peptide hormone, is one of seven hormones produced by the anterior lobe of the pituitary gland. hGH is produced throughout life, with its highest values being measured during puberty. Whilst it was believed for centuries that hGH played no part in the regulation of growth, or any other aspect of human physiology after puberty, recent evidence suggests that hGH has many varied roles throughout life.[3-5] In general, hGH secretion follows a circadian rhythm and is secreted in 6–12 discreet pulses per day with the largest pulse being observed around 1 hour after the onset of night-time sleep (i.e. midnight in the majority of cases). A number of stimuli can initiate hGH secretion, the most powerful, non-pharmacological, of which are sleep and exercise.

The fact that exercise stimulates GH secretion is well known and although the exact mechanisms remain elusive, a number of candidates have been implicated. These include neural stimulation, feedback from release of insulin-like growth factors (IGFs), direct stimulation by catecholamines, lactate and or nitric oxide (NO), and changes in acid-base balance. Exercise stimulates the release of GH into the general circulation, thereby stimulating other growth factors in different tissues around the body.

For example, it has been suggested that muscle hypertrophy is one of the outcomes that may be mediated by GH as a response to exercise. In addition to the recognised effects on growth, hGH is also believed to affect substrate utilisation during exercise. The positive impact of administration of exogenous GH, upon body composition, muscle mass and metabolic function widens the potential for its abuse from explosive to endurance athletes looking for illicit ways to improve performance in sport. However, in all likelihood, the same adaptations that are beneficial to performance can be accomplished by the application of appropriate specific physical training which will promote hGH release during exercise and at rest.

The reported potential for limiting ageing, or at least some of the believed physiological consequences of ageing, has been suggested for exogenous administration of GH[6,7] as it has for aspects of 'fitness' maintenance and improvement.[8] Indeed, exercise may slow ageing via hGH secretion.[9]

The EIGR has a positive role to play, from optimising training adaptation in elite athletes, and reducing the incidence of GH abuse in sport, to improving the quality of life in an ageing population. Further studies are needed to identify the optimal training programme to elicit the greatest EIGR.

1. Physiological Consequences of Human Growth Hormone (hGH) Secretion

hGH affects the action of a number of tissues and organs throughout the body, often initiating a cascade of reactions throughout many physiological systems. The use of exogenous administration of GH for anything other than linear growth (e.g. for treating short stature in dwarfism) is an area that is still expanding. Sacca et al.[10] demonstrated that supplemental GH has beneficial effects on the exercise capacity of patients with dilated cardiomyopathy. More recently, Hütler et al.[11] have shown that GH treatment improves exercise tolerance in children with cystic fibrosis.

1.1 Physiological and Biochemical Actions

In the plasma, the majority of hGH is bound to a carrier protein known as GH-binding protein and is then taken up by specific GH receptors which are located on target cells.

hGH is essential for postnatal and pubertal growth, and for normal carbohydrate, lipid, nitrogen and mineral metabolism. The growth-related effects of hGH are primarily mediated by IGF-1 and to a lesser extent IGF-2, both members of the insulin-like gene family. Production of IGF-1 is generally mediated by hepatic GH receptors.

1.2 Growth Hormone and Growth Regulation

The currently accepted hypothesis on growth involving GH is known as the Somatomedin Hypothesis.[12] This hypothesis states that in the liver and other target cells, through interaction with its receptor, hGH induces the production of somatomedins, or IGFs (IGF-1 and IGF-2). IGFs are produced by most tissues of the body, although IGF-1 is predominantly produced by the liver, and they are found in plasma bound to a family of proteins called IGF-binding proteins. Being so widely distributed it is understandable that IGFs have the potential to act via endocrine, autocrine and paracrine mechanisms.

IGF-1 released from the liver in response to hGH is involved in two negative feedback loops. One directly affects the somatotrope cells of the anterior pituitary, itself inhibiting further release of hGH, whilst the other affects GH releasing hormone and somatostatin release from the hypothalamus to reduce the secretion of hGH. However, during exercise, Kanaley et al.[13] demonstrated that the exercise stimulus counteracts most other negative feedback to ensure that hGH secretion continues to occur. They found that repeated bouts of exercise resulted in an exercise-induced hGH response to each acute exercise episode, thereby increasing the 24-hour secretion of hGH. Thus, it would appear that exercise counters negative feedback and so hGH secretion is maintained or increased.

Although most of the anabolic actions of hGH are mediated by the somatomedins (IGFs), some actions

are mediated in individual cells by pathways initiated by direct activation by hGH via the GH receptor interacting with 'JAK2', a tyrosine kinase. This complex initiates the growth processes of that cell via an intracellular cascade of growth and transcription factors.[14]

Studies administering recombinant hGH (rhGH) and exogenous IGF-1 in combination to healthy human subjects[15] or to AIDS patients with muscle wasting[5] have demonstrated far greater anabolic effects than the administration of rhGH or exogenous IGF-1 in isolation. Findings of this type could form the basis for the suggestion that some sports people are abusing a 'cocktail' of hGH in combination with IGF-1.

1.3 Growth Hormone and Metabolism

1.3.1 Protein Synthesis

Brahm et al.[16] demonstrated that GH is taken up by human skeletal muscle during dynamic exercise. In this study, the arteriovenous hGH concentration difference was examined in exercising thigh muscle and a significant uptake (3.1 mU/min, or 1.21 μg/min) found during exercise with a release of IGF-1 at the cessation of exercise. A number of studies by Fryburg and various coworkers[17-19] have shown that GH acutely stimulates muscle protein synthesis in healthy human adults.

1.3.2 Carbohydrate Metabolism

hGH generally antagonises the effects of insulin. The administration of rhGH results in hyperglycaemia as the combined result of decreased peripheral utilisation of glucose and increased hepatic production via gluconeogenesis.[3] In the liver, hGH increases liver glycogen derived from amino acids.[3] Impairment of glycolysis may occur at a number of steps, and the mobilisation of free fatty acids from triacylglycerol stores may also contribute to the inhibition of glycolysis in muscle. The mechanisms responsible for the effect of hGH on carbohydrate metabolism remain to be fully elucidated; however, it is clear that IGF-1 is not involved.[20] Consistent with the somatomedin hypothesis, the

main actions of IGF-1 seem to concern protein synthesis.[21]

1.3.3 Lipid Metabolism

hGH promotes the release of free fatty acids and glycerol from the adipose tissue, increases circulating free fatty acids and their oxidation in the liver.[22] A number of studies have also demonstrated that free fatty acids can, in turn, physiologically regulate hGH release via a negative feedback.[23-28]

Of the known metabolic functions of hGH, it has been suggested that the most important of these is its stimulation of lipolysis in adipose tissue.[29] Although fatty acid mobilisation from adipose tissue is known to be under nervous control, certain lipolytic hormones also increase the activity of triacylglycerol lipase and hence the release of free fatty acids. GH does this in the presence of glucocorticoids.[29] The mechanism by which a peptide hormone initiates changes in lipolysis is as a result of the hormone binding to β-receptors on the outer surface of the adipose tissue cell. These hormones either activate (lypolytic hormones) or inhibit (antilipolytic hormones) adenylate cyclase to alter the intracellular concentration of cyclic AMP and hence Ca^{2+} concentration, which in turn affects the activity of the triacylglycerol lipase enzyme.[30]

1.3.4 Mineral Metabolism

hGH and IGF-1 promote a positive calcium, magnesium and phosphate balance and cause the retention of sodium, potassium and chloride ions. The effect on calcium, magnesium and phosphate probably relates directly to the hGH action in bone, where it promotes the growth of long bones at the epiphysial plates in growing children and appositional or acral growth in adults.[22]

2. Proposed Stimuli for Increased hGH Secretion in Exercise

The exact mechanism for the increased secretion of hGH in response to exercise is unknown and it is unlikely that any one factor acts as the exercise-related stimulus, although a number of candidates have been suggested. These include: direct neural input to the anterior pituitary, facilitation via secre-

tion of NO, the increase in circulating catecholamines and lactate, and decrease in pH, that routinely accompany exercise at or beyond lactate threshold. Although ingestion of amino acids has been suggested to promote hGH secretion in athletes, this is beyond the scope of the present review. For a recent review in this area refer to Chromiak and Antonio.[31]

2.1 Neural Stimuli

Thompson et al.[32] studied the effects of a cholinergic agonist and an opioid receptor antagonist on hGH secretion during and after a moderate-intensity exercise bout. They found that resting serum hGH concentrations in response to both drugs was not significantly different from the baseline values. During exercise, and during recovery from exercise, the opioid antagonist did not significantly affect hGH concentration. In contrast, the cholinergic agonist caused a significant increase in the hGH concentration during and post-exercise, but did not affect the peak hGH concentration. They concluded that the enhanced cholinergic tone potentiates the hGH response to moderate-intensity exercise as seen by enhanced integrated and mean hGH concentrations during the exercise and recovery periods. Opioids appear to have only a minor role in hGH release; however, further investigation is indicated.

A number of papers examining the role of afferent input in hGH secretion have found that the neural response appears to be related, in particular, to bioassayable subfractions of hGH (BhGH) that are not detectable by immunoassay. These subfractions are typically 60–80kD in size and have been found in a number of human studies.[33,34] A number of papers[35-37] have suggested a heterogeneity of hGH fragments appearing in the circulation and a growing number of researchers are examining the role of BhGH.[34,38-40]

Gosselink et al.[40] demonstrated that, in rats, regulation of the release of bioassayable GH can be differentially mediated through low-threshold afferent inputs from fast or slow twitch skeletal muscle motor units. These appeared to be from type I and II afferent fibres suggesting inputs were of proprioceptive origin from muscle spindles and/or Golgi tendon organs. This may imply a role for increased muscle fibre tension, causing greater muscle spindle activity resulting in greater afferent traffic to the CNS and ultimately stimulating increased secretion of hGH.

The greater effect here would appear to be from afferents originating in fast twitch motor units. In a previous study Gosselink et al.[38] reported that 15-minute bouts of electrical stimulation of the proximal ends of severed nerves innervating predominantly fast twitch muscle fibres increased the bioassayable GH release in anaesthetised rats.

McCall et al.[39] examined the effect of microgravity (spaceflight) on the release of hGH in response to the same standardised exercise test that they had applied at normal gravity.[34] They found that the BhGH response to exercise was suppressed during spaceflight indicating that some minimum level of chronic neuromuscular activity and/or loading is necessary to maintain a normal exercise-induced BhGH release. These findings appear to support the hypothesis that there is a muscle afferent-pituitary axis that modulates BhGH release during exercise. A more recent study by McCall et al.[41] provides convincing evidence for afferent regulation of BhGH in humans. This study applied 10 minutes of vibration at 100Hz to intact muscle in situ. Tibialis anterior (TA) and Soleus (Sol) were vibrated on different days in random order. Vibration of these muscles at 100Hz resulted in a 94% increase in plasma BhGH from TA and a 22% decrease resulting from Sol vibration. Since both comprise predominantly slow twitch muscle fibres, the authors speculate that the differential regulation of BhGH must be due to the flexor versus extensor functions of the muscles. Immunoassay hGH were similar for both TA and Sol. The authors concluded that a muscle afferent-pituitary axis modulates the release of BhGH but not immunoassayable hGH in humans, and further that the release of BhGH is muscle specific.

In contrast, one study failed to show an exercise-induced BhGH response. Hymer et al.[42] examined the effects of an acute heavy resistance exercise

protocol on the molecular nature of secreted hGH in women. Blood samples were fractionated into >60kD (fraction A), 30–60kD (fraction B) and <30kD (fraction C). However, although large (2- to 4-fold) increases in circulating immunoassayable hGH were observed (in fractions B and C), these were reported as non-significant. The differences seen between the findings of McCall et al.[41] and Hymer et al.[42] could be due to sex differences but this is speculation that is yet to be confirmed.

2.2 Nitric Oxide

NO has been shown to enhance glucose transport in the skeletal muscle of rats[43] and has been identified as an important intra- and intercellular transmitter involved in the control of the hypothalamic-pituitary axis. This has been supported by the discovery of NO synthase in pituitary cells.[44,45] The role of NO in the modulation of GH secretion remains unclear; however, Pinilla et al.[46] were able to show that NO stimulates GH secretion *in vitro* and further, that this occurred through a specific calcium-cGMP-independent mechanism.

A number of studies have examined the role of NO during exercise. At the onset of exercise there is a huge (30-fold) increase in blood flow to working muscle. This requires massive vasodilatation in the arteries and arterioles leading to muscle capillary beds to allow the attendant substantial increase in muscle blood perfusion. The secretion of NO from the tunica intima of the vascular wall has a key role in the observed vasodilation.

Kusnar and Kaminski[47] found that NO synthase is concentrated at the skeletal muscle endplate. They suggest that NO may help facilitate the excitability of the sarcolemma as a result of incoming acetylcholine from the motor endplate. The presence of NO has also been shown to enhance the decrease in heart rate associated with vagus nerve stimulation.[48] This facilitatory role for NO has also been suggested as a mechanism for the release of hormones into the general circulation.[49,50]

Whilst the majority of studies examining the role of NO have employed animal models, Jungersten et al.[51] examined the effects of physical fitness and

acute exercise on the regulation of NO formation in healthy humans. They determined the relationship between peak work rate and resting levels of nitrate (a stable metabolite of NO) in plasma and urine of individuals of differing levels of physical fitness. Plasma nitrate was found to be higher in the resting samples of athletic individuals compared with a non-athletic control group, demonstrating a greater turnover of NO and suggesting a greater general 'readiness' for the huge hyperaemia observed at the onset of exercise. They also reported that those with a lower work capacity (i.e. less physically 'fit') have a lower correlation between 'fitness' and excretion of nitrate at rest, further suggesting a training effect on NO and that acute physical exercise increases plasma nitrate levels in both athletic and non-athletic individuals.

The suggestion that NO is involved in the EIGR is a highly attractive proposition and many studies have reported a diverse range of roles for NO in areas that are quite obviously related to exercise. NO has also recently been proposed to be involved in the post-tetanic relaxation process in skeletal muscle[52] and so is perhaps antagonistic to the lactate ion's interference with post-tetanic relaxation,[53] which is discussed later.

Whilst NO may not act as the primary stimulus for the EIGR, it may have a role in facilitating hGH secretion. However, this facilitatory role is likely to operate under all conditions for hGH secretion and is unlikely to be limited to exercise.

2.3 Catecholamines

The relationship between catecholamines and EIGR has received limited attention. Kinderman et al.[54] examined the catecholamine, hGH, cortisol, insulin and sex hormone response to aerobic versus anaerobic exercise. Plasma hGH concentration was significantly higher in the aerobic test whilst adrenaline and noradrenaline were significantly higher in the anaerobic test. The difference in the exercise duration between the two conditions may account for the observed difference in EIGR making direct comparisons difficult. However, these results sug-

gest little or no likely contribution of catecholamines in the EIGR.

In contrast, Chwalbinska-Moneta et al.[55] employed a progressive multistage exercise protocol on a cycle ergometer with endurance-trained study participants (marathon runners). Stages were a duration of 3 minutes with a 50W increment until volitional exhaustion. The investigators described a threshold rise in plasma hGH concentration which followed the patterns of plasma catecholamines and blood lactate concentration.

2.4 Acid-Base Balance and Lactate

It has been suggested that the abrupt decrease in blood pH, together with the increasing catecholamine concentrations during exercise act as humoral signals for a nonlinear increase in hGH secretion during exercise.[55]

Gordon et al.[56] examined the impact of bicarbonate ingestion on the hGH response to 90 seconds of maximal effort exercise. They found that whole blood pH was significantly lower in the control group compared with the bicarbonate group at all time points except baseline. Serum hGH concentrations were significantly increased above baseline at 10, 15, 20 and 30 minutes post-exercise in the control group but only at 20 and 30 minutes in the bicarbonate group. The authors proposed that an increase in the hydrogen ion concentration may be partly responsible for the hGH response to high-intensity, predominantly anaerobic, exercise.

In contrast, however, Elias et al.,[57] concluded that the pH reduction with exercise may not be the mechanism for changes in serum hGH. The authors used both pre-exercise ingestion and continuous infusion of bicarbonate during a progressive incremental cycle test and found no significant difference in the peak hGH concentration between treatments.

A number of studies have reported a high correlation between lactate threshold and what has been suggested as an hGH threshold in response to progressive incremental exercise.[55] A stimulatory effect of lactate on hGH secretion was first suggested by Sutton et al.[58] Since that time, a number of studies have supported this observation. Kozlowski

et al.[13] have reported a high correlation between blood hGH and blood lactate concentrations, in agreement with the previously cited work of Chwalbinska-Moneta et al.[55]

There appears to be a paucity of studies demonstrating any causal relationship between circulating lactate concentration and exercise-induced hGH secretion, further work is warranted.

2.5 Summary of Factors Affecting hGH Secretion During Exercise

There are perhaps a number of areas of overlap and or interaction between many of the proposed stimuli for the EIGR. Of these, three stand out: NO, afferent stimulation and lactate.

NO, whilst the most recently identified candidate, remains equivocal in the light of limited study. Currently, its role in EIGR seems limited to facilitation of hGH secretion. The use of bioassay has revealed the existence of what appear to be larger 'fragments' of GH with strong evidence suggesting this results from afferent stimulation. Blood lactate is the one stimulus which has been suggested, fallen out of favour and returned as a popular candidate more than once in the last 30 years. Clearly, further research is necessary to fully elucidate the role of these candidates in the EIGR. Table I lists the candidates suggested for the EIGR, summarises their proposed roles and lists relevant researchers.

3. hGH in Sport and Exercise

Since exercise itself is a powerful stimulus of endogenous hGH secretion, specific training regimens may also elicit training adaptation mediated by hGH. Whilst the potential ergogenic effects of rhGH administration are attractive to athletes who wish to gain an unfair advantage, the abuse of GH has been associated with an increased incidence of arthralgia, arthritis, cardiomegaly, muscle weakness, hyperlipidaemia, impaired glucose regulation, and the risk of type 1 diabetes mellitus and impotence.[59] Identification of a training programme that will optimise the EIGR reducing/eliminating the presentation of clinical complications in those who might otherwise abuse rhGH presents a viable alternative. However,

Table I. The main candidates proposed for mediation of exercise-induced human growth hormone secretion, the proposed role and major associated studies for each

Main candidates for EIGR	Proposed role	Prominent research studies
Neural stimulation	Direct afferent stimulation (e.g. from muscle spindles) of the pituitary resulting from muscle contraction has been suggested to result in the EIGR	Ellis et al.,[33] McCall et al.,[34] Gosselink et al.,[38] McCall et al.,[39] Gosselink et al.[40]
Nitric oxide	Discovery of nitric oxide in pituitary cells and evidence for the mechanism by which nitric oxide could be directly involved in secretion at the gland suggest a role in the EIGR	Brann et al.,[44] Nelson et al.,[45] Pinilla et al.[46]
Catecholamines	A correlation has been noted between the rise in catecholamines and the rise in hGH concentration with increasing exercise intensity suggesting that circulating catecholamines may directly result in the EIGR	Kinderman et al.,[54] Chwalbinska-Moneta et al.[55]
Acid-base changes	Changes in the pH as a result of exercise and associated with muscle, blood and cerebrospinal fluid may directly effect the EIGR	Gordon et al., [56] Chwalbinska-Moneta et al.,[55] Elias et al.[57]
Lactate	A strong correlation has been observed between the rise in blood lactate and blood hGH concentration during incremental exercise suggesting a role for lactate in the EIGR	Sutton et al.,[58] Kozlowski et al.,[13] Chwalbinska-Moneta et al.[55]

EIGR = exercise-induced growth hormone response; **hGH** = human growth hormone.

this issue is best reviewed in the light of the EIGR in strength and power, endurance and high-intensity exercise.

3.1 Muscle Mass, Resistance Exercise, Strength and Power

The role of GH in strength has been the focus for scientists since the late nineteenth century. In 1889, Brown-Séquard[60] recorded that the strength of his forearm flexor muscles had decreased with increasing age. Following auto-injection of anterior pituitary extract, he reported a significant increase in strength.

Since that time, resistance training has been commonly and successfully used to elicit muscle hypertrophy and to increase strength. A systematic, progressive programme of weight training results first in improvements of strength, independent of muscle hypertrophy, through improvements in neuromuscular facilitation.[61] After several weeks of progressive stimuli, muscle hypertrophy is observed[61] and this response is similar in men and women.[62,63] In general, males have a larger muscle mass due to the increased secretion of androgens at puberty and for this reason adult males are 40–50% stronger in most

muscle groups compared with adult females. Examination of power differences between male and female Olympic weight-lifters have shown a 33% greater power per kilogram in males.[64] These strength and power differences appearing post-puberty initially led to speculation that the sex hormones, the male androgens, in particular testosterone, were involved. A number of studies[65-69] have also examined the suggestion that hGH may play a role in the muscle hypertrophy that attends the later stages of increased strength development.

Kraemer et al.[66] demonstrated that heavy resistance training, i.e. high volume (49kJ and 59kJ per resistance training session) and high intensity, utilising large muscle groups, resulted in a significant EIGR. Vanhelder et al.[65] reported a similar response using a low volume (28kJ per resistance training session) resistance programme. These results suggested that the load and frequency of an exercise are determinant factors in the regulation of plasma hGH concentration. Both of these studies further conclude that in comparative training sessions, with total work constant, it is the greater demand on anaerobic glycolysis that stimulates serum hGH elevations. Kraemer et al.[66,67] observed acute increases in hGH, following heavy resistance

exercise, but the pattern of response of IGF-1 did not consistently follow that of hGH. This finding suggests that the greatest stimulus to hypertrophy and improvement in muscle strength and power occurs via local production of IGF-1, i.e. in skeletal muscle. In other words, IGF-1 secretion can be stimulated by both muscle contraction *per se*, i.e. locally, or by hGH stimulating IGF-1 secretion, from the liver. In a more recent study, Kraemer et al.[68] found that a high-intensity, high-load bout of resistance exercise increased circulating hGH, without affecting IGF-1 concentrations during the subsequent 24-hour recovery period in moderately strength-trained young males. These studies perhaps indicate that exercise of the appropriate modality, intensity and duration, can stimulate increased release of IGF-1 in a way that has a parallel in muscle contraction *per se*, facilitating the uptake of glucose into muscle independently of insulin.[70,71]

Much of the stimulus for protein synthesis seems to occur through IGF-1 with just modest contributions from GH-GH receptor interaction on the cell membrane leading to increased intracellular protein synthesis. This must raise doubts over the ability of exogenous GH alone to maintain muscle mass in older individuals (as has been suggested in the popular press) and to increase muscle mass in younger elite athletes. A 1994 review by Yarasheski[72] confirms that it is doubtful that the nitrogen retention associated with daily hGH administration results in an increase in contractile protein, improved muscle function, strength and athletic performance. More recently, in agreement with previous work, Zachwieja and Yarasheski[73] have suggested that the evidence for hGH alone to increase human skeletal muscle protein and maximum voluntary force is weak. Even when administration of hGH was added to a progressive resistance exercise programme, no further enhancement of training-induced adaptations were seen.[74]

A number of studies using a rat model have shown that GH is not essential for exercise-induced muscle hypertrophy or an improved cardiorespiratory response to training;[75-77] however, this does not mean that GH has no role to play. It may be that GH

and IGF-1 in combination produce the greatest responses, as previously suggested in work with AIDS patients, where treatment with a combination of rhGH and exogenous IGF-1 helped to minimise muscle wastage.[5,15] To date, no data exist examining this hypothesis regarding exercise in humans. In rats, however, it has been demonstrated that GH or exercise in isolation have a minimal effect in maintaining muscle mass of unloaded muscle but GH and exercise together exert a strong positive effect of maintenance of muscle mass.[78] Similarly, Grossman et al.[79] demonstrated that the phenotype of rat medial gastrocnemius muscle was only minimally affected by GH, IGF-1 or exercise. The combination, however, of GH or IGF-1 plus exercise resulted in an increase in the size of all fibre types present.

3.2 Endurance Exercise

It appears to be a combination of the intensity,[80] duration,[81] frequency[82] and mode[54] of exercise that determines the EIGR. A number of studies have examined the effect of exercise intensity and duration on the EIGR. Felsing et al.[81] noted that there was a non-significant elevation in hGH above baseline (an elevation of 1.5 ± 2.0 µg/L) after 10 minutes of low intensity (below lactate threshold) exercise. With high intensity exercise (above lactate threshold) significant elevation in hGH was only observed after 10 minutes of exercise (mean increase above baseline of 7.7 ± 2.4 µg/L, $p < 0.05$). Thus, an exercise intensity above threshold and for a minimum duration of 10 minutes would seem to be a significant stimulus to the secretion of hGH.

Cappon et al.[83] examined the effect of exercising for 10 minutes at 50% of the difference between lactate threshold and maximum oxygen consumption ($\dot{V}O_{2max}$). They reported small increases in circulating IGF-1 which were independent of circulating hGH. In discussing their findings, the authors note that there is considerable discrepancy between various studies in the statistical significance of GH and IGF-1 appearance (i.e. the magnitude of the rise above baseline). Their view is that this discrepancy arises from two main factors. Firstly, the intensity of exercise is often determined from a percentage of

$\dot{V}O_{2max}$, this often being extrapolated from constant-power tests rather than a measured value. This can lead to a sample population in which some individuals exercise above lactate threshold and others exercise below it. This is a point well made as hormonal and metabolic responses to exercise are often not related to exercise intensity in a simple linear manner. Secondly, as reported in their own study and supported by the work of Bang et al.[84] it appears that the IGF-1 response is rapid, peaking about 10 minutes after the onset of exercise. Therefore, the IGF-1 response may not be detectable with a longer sampling interval. In the study by Cappon et al.,[83] many of these areas of potential discrepancy appear to have been well controlled hence their findings of no link between GH and IGF-1 appears sound. They argue that a GH-dependant mechanism for an increase in IGF-1 with exercise might require GH-stimulated synthesis of IGF-1 and its subsequent transport to the circulation. The time required for synthesis would, however, be greater than the 10 minutes reported for the appearance of IGF-1 and this reaffirms the suggestion that appearance of IGF-1 is independent of GH.

Some studies have suggested an intensity 'threshold' exits for EIGR. Pooled data from 29 studies suggest that the threshold for hGH secretion occurs on average above 40% $\dot{V}O_{2max}$.[85] The majority of authors, however, suggest that for a consistent EIGR, an exercise intensity above 60% $\dot{V}O_{2max}$ is required.[86-88] It has been suggested that the threshold for the exercise-induced hGH surge is consistent with lactate threshold. The differences in the percentage of $\dot{V}O_{2max}$ at which the EIGR has been observed to occur may reflect the heterogeneity in the percentage of $\dot{V}O_{2max}$ at which lactate (anaerobic) threshold generally occurs in any exercising population. According to Wasserman et al.,[89] the point at which metabolic acidosis becomes evident can range from 40–80% of $\dot{V}O_{2max}$ in normal individuals. Accordingly, in hormonal studies in general, and those that examine hGH in particular, it may not be appropriate to use percentage of $\dot{V}O_{2max}$ as the index of relative exercise intensity. Rather, lactate threshold itself may be a more appropriate and consistent measure of exercise intensity when associated with the hGH surge.

One study, however, contradicts the suggestion of an exercise intensity-related threshold with respect to circulating hGH concentration. Pritzlaff et al.[90] examined five different exercise intensities corresponding to 25, 75, 100, 125 and 175% of the exercise intensity associated with lactate threshold (*viz.* 26, 47, 62, 76 and 90% of $\dot{V}O_{2max}$). Their findings suggested that serum hGH increases linearly with exercise intensity expressed either as a percentage of lactate threshold or as a percentage of $\dot{V}O_{2max}$. This evidence, however, fails to address the fact that significant hGH elevations above baseline are observed only above lactate threshold.

Exercise may also affect hGH release at rest. Weltman et al.[91] showed that exercise training above the lactate threshold amplified the pulsatile release of hGH at rest, while exercise below the lactate threshold didn't. Training in this study was for a duration of 1 year with training volume gradually increasing each week. Training at lactate threshold was compared with training above lactate threshold. Training above lactate threshold was reported to be the more effective for increasing the total volume of hGH secreted in 24 hours.

In addition to intensity-mediated differences, frequency of exercise appears to play a role in the pulsatile secretion of hGH. Repeated bouts of aerobic exercise on the same day (three 30-minute bouts at 70% $\dot{V}O_{2max}$) appear to significantly increase the daytime integrated hGH concentration without significant change in nocturnal concentrations compared with control conditions. The increase in hGH secretion with repeated bouts was related to an increase in hGH pulse amplitude and the mass of hGH secreted per pulse.[82] The authors conclude that high-intensity aerobic exercise is a potent stimulus of hGH secretion that is able to overcome hGH auto-negative feedback. Therefore, repeated bouts of exercise on the same day are able to consistently stimulate hGH secretion without attenuation of the hGH response. Thus, this type of exercise regimen may suit both increases in muscle mass and metabolic adaptations that could aid improvements in

endurance performance. The pulsatile release of hGH is more effective than continuous administration in inducing certain specific tissue responses to hGH in muscle, bone and liver.[92,93] Therefore, if the aim is to optimise hGH secretion, training should occur a number of times per day with each exercise session being of a duration greater than 10 minutes at an intensity above lactate threshold.[82,94]

The literature expresses a mixed view regarding the effect of chronic exercise training. Those studies that have examined training suggested that training blunts,[95,96] increases,[97] or does not affect[98] the hGH response to acute exercise. Weltman et al.[94] demonstrated that 3 and 6 weeks of endurance training resulted in a reduced hGH response to a 20-minute, high-intensity, constant load exercise test. These findings reinforce those of studies that have reported a blunted hGH response to acute exercise after a number of weeks of training. Chronic exercise training may blunt the acute hGH response to exercise for a number of reasons. Chronic exercise may induce an increased sensitivity to hGH in a similar way as the increased sensitivity to insulin which occurs with several weeks of training resulting in an increase in one of the glucose transport proteins regulated by insulin.[99,100] Alternatively, the chronic increase in hGH seen with a few weeks of increased exercise will continually feed back to the pituitary and hypothalamus, which may cause an adaptation such that a reduced hGH surge is seen in response to a given exercise stimulus.

3.3 High Intensity, Brief and Sprint Exercise

Limited data are available examining the EIGR to high intensity activity. Nevill et al.[80] examined the EIGR to treadmill sprinting in endurance-trained and sprint-trained subjects. Results demonstrated serum hGH was higher in the sprint-trained group, with 82% of the variation in the serum peak hGH concentration between the two groups explained by peak power and peak blood lactate response. The authors suggested that training at higher intensities (close to, or at maximum) will result in the greatest peak in EIGR, although no data were presented on 24-hour hGH secretion.

4. Exercise and the Ageing Athlete

Many believe that one of the natural consequences of ageing is that males lose muscle mass and tone and deposit more visceral and subcutaneous fat. In short, older males tend to have a body composition that is similar to that of young women. Since hGH has been found to decrease body fat, increase muscle mass and reverse the reduction in skin thickness in the elderly[101] it has been suggested that administration of rhGH may help to limit the impact of ageing generally. Neely and Rosenfield[102] reported a 7% rise in lean body mass, a 14% reduction in fat mass and a 7% increase in fasting blood glucose concentration following hGH administration. However, they also reported severe disturbances in glucose homeostasis indicative of a preclinical diabetic state.[102]

Ageing is often associated with a progressive decrease in the volume of exercise and very often associated with a decrease in the intensity of exercise. The evidence for beneficial health adaptations resulting from modest levels of low- to moderate-intensity exercise are now overwhelming and form the basis of many exercise guidelines for improving health.[103,104] However, a growing body of evidence suggests that higher intensity exercise, than was previously believed to be efficacious, may be more effective in eliciting beneficial health, well-being and training outcomes. This has been shown in insulin sensitivity,[105-107] and in positive effects on mood state and analgesia associated increases in circulating beta-endorphin which is seen after exercise above 60% $\dot{V}O_{2max}$.[108-112] In addition, it has been demonstrated that individuals in their nineties can improve muscle strength and size by a similar relative percentage as those individuals in their twenties.[113]

Häkkinen and Pakarinen[114] examined the hGH response to heavy resistance exercise in men and women in three age categories: 'young' (23–29 years), 'middle-aged' (44–51 years) and 'elderly' (65–71 years). They found that at the same relative workload, plasma GH concentrations were greatly reduced with increasing age in both men and women. Nicklas et al.[115] examined a group of 55- to

70-year-old men performing 14 different resistance exercises, three times per week on a number of machines, encompassing most muscle groups, carried out for 16 weeks. The training programme resulted in a 37% increase in upper body strength and a 39% increase in lower body strength. An 18-fold increase in hGH was observed in response to a single bout of resistance training but 24-hour hGH secretion was unaffected by the 16-week training programme. These studies demonstrate that the acute response to heavy resistance exercise is reduced with ageing but that a chronic resistance exercise programme can cause increases in the acute EIGR alongside increases in strength. This EIGR may contribute to the beneficial responses to exercise seen across the whole population with particular importance in the maintenance of quality of life in the elderly.

In a great many cases, the impact of some of the deleterious effects of ageing could be significantly reduced if individuals remained active, promoting the EIGR. Often this will require exercise at a higher intensity than is currently common in elderly populations.

5. Conclusions

hGH is a peptide hormone which is synthesised, stored and released in a pulsatile manner in response to a number of stimuli, from the anterior pituitary. The most potent physiological stimuli for hGH secretion are sleep and exercise. GH has been found to have a plethora of roles, from growth itself, including the turnover of muscle, bone and collagen throughout life, to regulation of selective aspects of metabolic function including increased fat metabolism and the maintenance of a more healthy body composition in later life.

The exact stimuli and mechanisms responsible for the hGH surge are still largely unknown but several candidates have emerged as potential stimuli. These factors include neural input, either from muscle afferents and/or centrally from the motor cortex, feedback from release of IGFs, direct stimulation by catecholamines, lactate and or NO and changes in acid-base balance. The best candidates

appear to be afferent stimulation, NO and lactate, and further work should aim to identify any individual or combined role that they play in the EIGR.

Exercise-induced hGH secretion has been widely studied, particularly in response to resistance exercise. The exact roles of, and relationship between hGH and the other candidate for increased protein synthesis resulting from strength training, IGF-1, remains unclear. Further work is warranted examining the combined effects of hGH and IGF-1 in the EIGR upon alterations in muscle mass.

The EIGR to endurance exercise has received less attention; however, interest in this area is growing. In general, scientific findings suggest that exercise duration of more than 10 minutes at an intensity above threshold results in a significant elevation in hGH secretion from baseline. Several discreet training sessions per day will significantly increase the 24-hour secretion of hGH with exercise overriding the normal circadian rhythm with respect to hGH release. Future work should focus on the impact of intensity, duration and frequency of exercise on the EIGR.

The EIGR has a positive role to play in optimising training adaptation in elite athletes, and reducing the incidence of rhGH abuse in sport, to improving the quality of life in an ageing population. In order to identify the optimal training programme to elicit the greatest EIGR, further work is indicated. Further longitudinal studies are indicated to examine the effects of training on the acute EIGR, resting hGH and the relationship between EIGR and training adaptations.

Acknowledgements

References

1. Jenkins PJ. Growth hormone and exercise: physiology, use and abuse. Growth Horm IGF Res 2001; 11 Suppl. A: S71-7
2. Caloa A, Marzullo P, Di Somma C, et al. Growth hormone and the heart. Clin Endocrinol (Oxf) 2001; 54 (2): 137-54

3. Murray RD, Shalet SM. Growth hormone: current and future therapeutic applications. Expert Opin Pharmacother 2000; 1 (5): 975-90

4. Baxter RC, Martin JL. Binding proteins for insulin-like growth factors: structure, regulation and function. Prog Growth Factor Res 1989; 1: 49-68

5. Waters D, Danska J, Hardy K, et al. Recombinant human growth hormone, insulin-like growth factor 1 and combination therapy in AIDS-associated wasting. Ann Intern Med 1996; 125: 865-72

6. Hoffman AR, Ceda GP. Should we treat the somatopause? J Endocrinol Invest 1999; 22 (10 Suppl.): 4-6

7. Morley JE, Unterman TG. Hormonal fountains of youth. J Lab Clin Med 2000; 135 (5): 364-6

8. Wannenberg T, Khan AS, Sane DC, et al. Growth hormone reverses age-related cardiac myofilament dysfunction in rats. Am J Physiol Heart Circ Physiol 2001; 281 (2): H915-22

9. Holt RI, Webb E, Pentecost C, et al. Aging and physical fitness are more important than obesity in determining exercise-induced generation of GH. J Clin Endocrinol Metab 2001; 86 (12): 5715-20

10. Sacca L, Cittadini A, Fazio S. Growth hormone and the heart. Endocr Rev 1994; 15 (5): 555-73

11. Hütler M, Schnabel D, Staab D, et al. Effect of growth hormone on exercise tolerance in children with cystic fibrosis. Med Sci Sports Exerc 2002; 34 (4): 567-72

12. Cohen P, Rosenfeld RG. Growth regulation. In: Griffin JE, Ojeda SR, editors. Textbook of endocrine physiology. 3rd ed. New York: Oxford University Press, 1996

13. Kozlowski S, Chwalbinska-Moneta J, Vigas M, et al. Greater serum GH response to arm than leg exercise performed at equivalent oxygen uptake. Eur J Appl Physiol 1983; 52: 131-5

14. Argetsinger LS, Campbell GS, Yang X, et al. Identification of JAK2 as a growth hormone receptor-associated tyrosine kinase. Cell 1993; 74: 237-44

15. Kupfer SR, Underwood LE, Baxter RC, et al. Enhancement of the anabolic effects of growth hormone and insulin-like growth factor I by use of both agents simultaneously. J Clin Invest 1993; 91: 391-6

16. Brahm H, Piehl-Aulhin K, Saltin B, et al. Net fluxes over working thigh of hormones, growth factors and biomarkers of bone metabolism during short lasting dynamic exercise. Calcif Tissue Int 1997; 60 (2): 175-80

17. Fryburg DA, Gelfand RA, Barrett EJ. Growth hormone acutely stimulates forearm muscle protein synthesis in normal humans. Am J Physiol 1991; 260: E499-504

18. Fryburg DA, Louard RJ, Gerow KE, et al. Growth hormone stimulates skeletal muscle protein synthesis and antagonizes insulin's antiproteolytic action in humans. Diabetes 1992; 41 (4): 424-9

19. Fryburg DA, Barrett EJ. Growth hormone acutely stimulates skeletal muscle but not whole-body protein synthesis in humans. Metabolism 1993; 42 (9): 1223-7

20. Fujiwara TM, Morgan K, Bichet DG. Molecular biology of diabetes insipidus. Annu Rev Med 1995; 46: 331-43

21. Lammers R, Gray A, Schlessinger J, et al. Differential signalling potential of insulin and IGF-1 receptor cytoplasmic domains. EMBO J 1989; 8: 1369-75

22. Granner DK. Pituitary and hypothalamic hormones. In: Murray RK, Granner DK, Mayes PA, et al., editors. Harper's Biochemistry. 25th ed. Stamford (CT): Appleton and Lange, 2000

23. Quabbe HJ, Bratzke HJ, Siegers U, et al. Studies on the relationship between plasma free fatty acids and growth hormone secretion in man. J Clin Invest 1993; 51: 2388-98

24. Pontiroli AE, Lanzi R, Monti LD, et al. Effect of acipomox, a lipid lowering drug, on growth hormone (GH) response to GH-releasing hormone in normal subjects. J Endocrinol Invest 1990; 13: 539-42

25. Pontiroli AE, Lanzi R, Monti LD, et al. Growth hormone (GH) autofeedback on GH response to GH-releasing hormone: role of free fatty acids and somatostatin in normal subjects. J Clin Endocrinol Metab 1991; 72: 492-5

26. Blackward WG, Hull EW, Lopez-S A. Effects of lipids on growth hormone secretion in humans. J Clin Invest 1971; 50: 1439-43

27. Casanueva F, Villanueva L, Penalva A, et al. Free fatty acids inhibition of exercise-induced growth hormone secretion. Horm Metab Res 1981; 13: 348-50

28. Imaki T, Shibasaki T, Masuda A, et al. The effect of free fatty acids on growth hormone (GH)-releasing hormone-mediated GH secretion in man. J Clin Endocrinol Metab 1985; 60: 290-3

29. Newsholme EA, Leech AR. Biochemistry for the medical sciences. Chichester: John Wiley and Sons Ltd, 1983

30. Hales EN, Luzio LP, Siddle K, et al. Hormonal control of adipose tissue lipolysis. Biochem Soc Symp 1978; 43: 97-135

31. Chromiak JA, Antonio J. Use of amino acids as growth hormone-releasing agents by athletes. Nutrition 2002; 18 (7-8): 657-61

32. Thompson DL, Weltman JY, Rogol AD, et al. Cholinergic and opiod involvement in release of growth hormone during exercise and recovery. J Appl Physiol 1993; 75 (2): 870-8

33. Ellis S, Vodian MA, Grindeland RE. Studies on the bioassayable growth hormone-like activity of plasma. Recent Prog Horm Res 1978; 34: 213-38

34. McCall GE, Goulet RE, Grindeland JA, et al. Bed rest supresses bioassayable growth hormone release in response to muscle activity. J Appl Physiol 1997; 83: 2086-90

35. Dimond RC, Wartofsky L, Rosen SW. Heterogeneity of circulating growth hormone in acromegaly. J Clin Endocrinol Metab 1974; 39 (6): 1133-7

36. Baumann G, Stolar MW, Amburn K. Molecular forms of circulating growth hormone during spontaneous secretory episodes and in the basal state. J Clin Endocrinol Metab 1985; 60 (6): 1216-20

37. Baumann G. Growth hormone heterogeneity in human pituitary and plasma. Horm Res 1999; 51 Suppl. 1: 2-6

38. Gosselink KL, Grindeland RE, Roy RR, et al. Skeletal muscle afferent regulation of bioassayable growth hormone in the rat pituitary. J Appl Physiol 1998; 84: 1425-30

39. McCall GE, Goulet RE, Roy RR, et al. Spaceflight supresses exercise-induced release of bioassayable growth hormone. J Appl Physiol 1999; 87 (3): 1207-12

40. Gosselink KL, Grindeland RE, Roy RR, et al. Afferent input from rat slow skeletal muscle inhibits bioassayable growth hormone release. J Appl Physiol 2000; 88: 142-8

41. McCall GE, Grindeland RE, Roy RR, et al. Muscle afferent activity modulates bioassayable growth hormone in human plasma. J Appl Physiol 2000; 89 (3): 1137-41

42. Hymer WC, Kraemer WJ, Nindl BC, et al. Characteristics of circulating growth hormone in women after acute heavy resistance exercise. Am J Physiol Endocrinol Metab 2001; 281 (4): E878-87

43. Balon TW, Nadler JL. Evidence that nitric oxide increases glucose transport in skeletal muscle. J Appl Physiol 1997; 81 (1): 359-63

44. Brann DW, Bhat GK, Lamar CHA, et al. Gaseous transmitters and neuroendocrine regulation. Neuroendocrinology 1997; 65: 385-95

45. Nelson RJ, Kriegsfeld LJ, Dawson VL, et al. Effects of nitric oxide on neuroendocrine function and behaviour. Front Neuroendocrinol 1997; 65: 385-95

46. Pinilla L, Tena-Sempere M, Aguilar E. Nitric oxide stimulates growth hormone secretion in vitro through a calcium- and cyclic guanosine monophosphate-independent mechanism. Horm Res 1999; 51: 242-7

47. Kusnar LL, Kaminski HJ. Nitric oxide synthase is concentrated at the skeletal muscle endplate. Brain Res 1996; 730: 238-42

48. Sears CE, Choate KJ, Paterson DJ. NO-cGMP pathway accentu- ates the decrease in heart rate caused by cardiac vagal nerve stimulation. J Appl Physiol 1999; 86 (2): 510-6

49. Bilski J, Konturek SJ, Bielanski W. Role of endogenous nitric oxide in the control of exocrine and endocrine pancreatic secretion. J Physiol Pharmacol 1995; 46 (4): 447-62

50. Laffranchi R, Gogvadze V, Richter C, et al. Nitric oxide stimulates insulin secretion by inducing calcium release from mitochondria. Biochem Biophys Res Commun 1995; 217 (2): 584-91

51. Jungersten L, Ambring A, Wall B, et al. Both physical fitness and acute exercise regulate nitric oxide formation in healthy humans. J Appl Physiol 1997; 82 (3): 760-4

52. Kobzik L, Reid MB, Bredt DS, et al. Nitric oxide in skeletal muscle. Nature 1994; 372: 546-8

53. Favero TG, Zable AC, Colter D, et al. Lactate inhibits Ca^{2+}- activated Ca^{2+}-channel activity from skeletal muscle sarcoplasmic reticulum. J Appl Physiol 1997; 82: 447-52

54. Kinderman W, Schnabel A, Schmitt WM, et al. Catecho- lamines, growth hormone, cortisol, insulin and sex hormones in anaerobic and aerobic exercise. Eur J Appl Physiol 1982; 49: 389-99

55. Chwalbinska-Moneta J, Krysztofiak F, Ziemba A, et al. Thres- hold increases in plasma growth hormone in relation to plasma catecholamine and blood lactate concentration during progres- sive exercise in endurance-trained athletes. Eur J Appl Physiol Occup Physiol 1996; 73: 117-20

56. Gordon SE, Kraemer WJ, Vos NH, et al. Effect of the acid-base balance on the growth hormone response to acute high-intensi- ty cycle exercise. J Appl Physiol 1994; 76 (2): 821-9

57. Elias AN, Wilson AF, Naqvi S, et al. 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 1997; 214: 156-60

58. Sutton JR, Young JD, Lazarus L, et al. The hormonal response to physical exercise. Australas Ann Med 1969; 18: 84-90

59. Kicman AT, Cowan DA. Peptide hormones and sport: misuse and detection. Br Med Bull 1992; 48: 496-517

60. Brown-Séquard C-E. A history of growth hormone research. Horm Res 1996; 46 (4-5): 236-47

61. Sale DG. Neural adaptation to resistance training. Med Sci Sports Exerc 1988; 20 (5 Suppl.): S135-45

62. Cureton KJ, Collins MA, Hill DW, et al. Muscle hypertrophy in men and women. Med Sci Sports Exerc 1988; 20 (4): 338-44

63. Häkkinen K, Pakarinen A, Kallinen M. Neuromuscular adapta- tions and serum hormones in women during short-term inten- sive strength training. Eur J Appl Physiol Occup Physiol 1992; 64 (2): 106-11

64. Garhammer J. Power production by Olympic weightlifters. Med Sci Sports Exerc 1980; 12 (1): 54-60

65. Vanhelder WP, Radomski MW, Goode RC. Growth hormone responses during intermittent weight lifting exercise in men. Eur J Appl Physiol 1984; 53: 31-4

66. Kraemer WJ, Marchitelli L, Gordon SE, et al. Hormonal and growth factor responses to heavy resistance exercise protocols. J Appl Physiol 1990; 69 (4): 1442-50

67. Kraemer WJ. Hormonal mechanisms related to the expression of muscular strength and power. In: Komi PV, editor. Strength and power in sport. Oxford: Blackwell Scientific Publications, 1991

68. Kraemer WJ, Aguilera BA, Terada M, et al. Responses of IGF-I to endogenous increases in growth hormone after heavy-resis- tance exercise. J Appl Physiol 1995; 79 (4): 1310-5

69. Kraemer WJ, Patton JF, Gordon SE, et al. Compatibility of high intensity strength and endurance training on hormonal and skeletal muscle adaptations. J Appl Physiol 1995; 78 (3): 976-89

70. Ivy JL. The insulin-like effect of muscle contraction. Exerc Sport Sci Rev 1987; 15: 29-51

71. Constable SH, Favier RJ, Cartee GD, et al. Muscle glucose transport: interactions of in vitro contractions, insulin and exercise. J Appl Physiol 1988; 64 (4): 2329-32

72. Yarasheski KE. Growth hormone effects on metabolism, body composition, muscle mass and strength. Exerc Sport Sci Rev 1994; 22: 285-312

73. Zachwieja JJ, Yarasheski KE. Does growth hormone therapy in conjunction with resistance exercise increase muscle force production and muscle mass in men and women aged 60 years or older? Phys Ther 1999; 79 (1): 76-82

74. Yarasheski KE, Zachwieja JJ, Campbell JA, et al. Effect of growth hormone and resistance exercise on muscle growth and strength in older men. Am J Physiol 1995; 268: E268-76

75. Cooper DM, Moromisato DY, Zanconato S, et al. Effect of growth hormone suppression on exercise training and growth responses in young rats. Pediatr Res 1994; 35: 223-7

76. Goldberg AL. Work-induced growth of skeletal muscle in nor- mal and hypophysectomised rats. Am J Physiol 1967; 213: 1193-8

77. Gollnick PD, Ianuzzo CD. Hormonal deficiencies and the meta- bolic adaptations of rats to training. Am J Physiol 1972; 223: 278-82

78. Grindeland RE, Roy RR, Edgerton VR, et al. Interactive effects of growth hormone and exercise on muscle mass in suspended rats. Am J Physiol 1994; 267 (1 Pt 2): R316-22

79. Grossman EJ, Grindeland RE, Roy RR, et al. Growth hormone, IGF-1, and exercise effects on non-weight-bearing fast mus- cles of hypophysectomized rats. J Appl Physiol 1997; 83 (5): 1522-30

80. Nevill ME, Holmyard DJ, Hall GM, et al. Growth hormone responses to treadmill sprinting in sprint- and endurance- trained athletes. Eur J Appl Physiol 1996; 72: 460-7

81. Felsing N, Brasel JA, Cooper DM. Effect of low and high intensity exercise on circulating growth hormone in men. J Clin Endocrinol Metab 1992; 75: 157-62

82. Kanaley JA, Weltman J, Veldhuis JD, et al. Human growth hormone response to repeated bouts of aerobic exercise. J Appl Physiol 1997; 83 (5): 1756-61

83. Cappon J, Brasel JA, Mohan S, et al. Effect of brief exercise on circulating insulin-like growth factor 1. J Appl Physiol 1994; 76 (6): 2490-6

84. Bang P, Brandt J, Degerblad M, et al. Exercise-induced changes in insulin-like growth factors and their low molecular weight binding protein in healthy subjects and patients with growth hormone deficiency. Eur J Clin Invest 1990; 20: 285-92

85. Cuneo RC, Wallace JD. Growth hormone, insulin-like growth factors and sport. Endocrinol Metab 1994; 1: 3-13

86. Luger A, Watschinger B, Deuster P, et al. Plasma growth hormone and prolactin responses to graded levels of acute exercise and to lactate infusion. Neuroendocrinology 1992; 56: 112-7

87. Farrell PA, Grathwaite TL, Gustafson AB. Plasma adrenocorticotropin and cortisol responses to submaximal and exhaustive exercise. J Appl Physiol 1983; 55: 1441-4

88. Naveri H. Blood hormone and metabolite levels during graded cycle ergometer exercise. Scand J Clin Lab Invest 1985; 45: 599-603

89. Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation. Philadelphia (PA): Lea and Febiger, 1987

90. Pritzlaff CJ, Wideman L, Weltman JY, et al. Impact of acute exercise intensity on pulsatile growth hormone release in men. J Appl Physiol 1999; 87 (2): 498-504

91. Weltman A, Weltman J, Schurrer R, et al. Endurance training amplifies the pulsatile release of growth hormone: effects of training intensity. J Appl Physiol 1992; 76 (6): 2188-96

92. Isgaard J, Carlsson L, Isaksson OGP, et al. Pulsatile intravenous growth hormone (GH) infusion to hypophysectomised rats increases insulin-like growth factor 1 messenger RNA in skeletal tissues more effectively than continuous GH infusion. Endocrinology 1988; 123: 2605-10

93. Jansson JO, Ekberg S, Hoath SB, et al. Growth hormone enhances hepatic epidermal growth factor receptor concentration in mice. J Clin Invest 1988; 82: 1871-6

94. Weltman A, Weltman J, Womack CJ, et al. Exercise training decreases the growth hormone (GH) response to acute constant-load exercise. Med Sci Sports Exerc 1997; 29 (5): 669-76

95. Hartley LH. Growth hormone and catecholamine response to exercise in relation to physical training. Med Sci Sports Exerc 1975; 7: 34-6

96. Koivisto V, Hendler R, Nagel E, et al. Influence of physical training on the fuel-hormone response to prolonged low intensity exercise. Metabolism 1982; 31: 192-7

97. Bunt JC. Sex and training differences in human growth hormone levels during prolonged exercise. J Appl Physiol 1986; 61: 1796-801,

98. Kjaer M, Bangsbo J, Lortie G, et al. Hormonal response to exercise in humans: influence of hypoxia and physical training. Am J Physiol 1998; 254: R197-203

99. Houmard JA, Egan PC, Neufer PD, et al. Elevated glucose transporter levels in exercise-trained middle-aged men. Am J Physiol 1991; 261 (24): E437-43

100. Houmard JA, Shinebarger MH, Dolan PL, et al. Exercise training increases GLUT-4 protein concentration in previously sedentary middle-aged men. Am J Physiol 1993; 264 (6 Pt 1): E896-901

101. Jorgensen JOL, Christiansen JS. Brave new senescence: HGH in adults. Lancet 1993; 341: 1241-8

102. Neely EK, Rosenfield RG. Use and abuse of human growth hormone. Annu Rev Med 1994; 45: 407-20

103. Phillips WT, Pruitt LA, King AC. Lifestyle activity: current recommendations. Sports Med 1996; 22: 1-7

104. American College of Sports Medicine. Position stand: the recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc 1998; 30: 975-91

105. Kang J, Robertson RJ, Hagberg JM. Effect of exercise intensity on glucose and insulin metabolism in obese individuals and obese NIDDM patients. Diabetes Care 1996; 19: 341-9

106. Romijn JA, Coyle EF, Siddossis LS, et al. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity duration. Am J Physiol 1993; 265: E280-391

107. Richter EA, Garetto LP, Goodman MN, et al. Muscle glucose metabolism following exercise in the rat: increased sensitivity to insulin. J Clin Invest 1993; 69: 785-93

108. DeMeirleir K, Naaktegeboren N, VanSteirteghem A, et al. Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. Eur J Appl Physiol Occup Physiol 1986; 55: 5-8

109. Goldfarb AH, Hatfield BD, Armstrong D, et al. Plasma beta-endorphin concentration: response to intensity and duration of exercise. Med Sci Sports Exerc 1990; 22: 241-4

110. Goldfarb AH, Hatfield BD, Potts J, et al. Beta-endorphin time course response to intensity of exercise: effect of training status. Med Sci Sports Exerc 1991; 12 (3): 264-8

111. McMurray RG, Forsythe WA, Mar MH, et al. Exercise intensity-related responses of beta-endorphin and catecholamines. Med Sci Sports Exerc 1987; 19 (6): 570-4

112. Rahkila P, Hakala E, Alen M, et al. Beta-endorphin and corticotropin release is dependent on a threshold intensity of running exercise in male endurance athletes. Life Sci 1988; 43 (6): 551-8

113. Fitarone MA, Marks EC, Ryan ND, et al. High-intensity strength training in nonagenarians: effects on skeletal muscle. JAMA 1990; 263 (22): 3029-34

114. Häkkinen K, Pakarinen A. Acute hormonal responses to heavy resistance exercise in men and women at different ages. Int J Sports Med 1995; 16: 507-13

115. Nicklas BJ, Ryan AJ, Treuth MM, et al. Testosterone, growth hormone and IGF-I responses to acute and chronic resistive exercise in men aged 55-70 years. Int J Sports Med 1995; 16: 445-50

Correspondence and offprints: *Richard J. Godfrey*, Department of Sport Sciences, Brunel University, Uxbridge, Middlesex, UB8 3PH, UK.