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# Hormonal Responses and Adaptations to Resistance Exercise and Training

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## Abstract

Resistance exercise has been shown to elicit a significant acute hormonal response. It appears that this acute response is more critical to tissue growth and remodelling than chronic changes in resting hormonal concentrations, as many studies have not shown a significant change during resistance training despite increases in muscle strength and hypertrophy. Anabolic hormones such as testosterone and the superfamily of growth hormones (GH) have been shown to be elevated during 15–30 minutes of post-resistance exercise providing an adequate stimulus is present. Protocols high in volume, moderate to high in intensity, using short rest intervals and stressing a large muscle mass, tend to produce the greatest acute hormonal elevations (e.g. testosterone, GH and the catabolic hormone cortisol) compared with low-volume, high-intensity protocols using long rest intervals. Other anabolic hormones such as insulin and insulin-like growth factor-1 (IGF-1) are critical to skeletal muscle growth. Insulin is regulated by blood glucose and amino acid levels. However, circulating IGF-1 elevations have been reported following resistance exercise presumably in response to GH-stimulated hepatic secretion. Recent evidence indicates that muscle isoforms of IGF-1 may play a substantial role in tissue remodelling via up-regulation by mechanical signalling (i.e. increased gene expression resulting from stretch and tension to the muscle cytoskeleton leading to greater protein synthesis rates). Acute elevations in catecholamines are critical to optimal force production and energy liberation during resistance exercise. More recent research has shown the importance of acute hormonal elevations and mechanical stimuli for subsequent up- and down-regulation of cytoplasmic steroid receptors needed to mediate the hormonal effects. Other factors such as nutrition, overtraining, detraining and circadian patterns of hormone secretion are critical to examining the hormonal responses and adaptations to resistance training.

Resistance exercise and/or training elicits a milieu of acute physiological responses and chronic adaptations that are critical for increasing muscular strength, power, hypertrophy and local muscular endurance.[1] Of primary importance to acute exercise performance and subsequent tissue remodelling is the role(s) played by the neuroendocrine system.[2] Hormonal elevations in response to resistance exercise take place in a unique physiological environment. Acute elevations in circulating blood hormone concentrations (i.e. resulting from either increased secretion, reduced hepatic clearance, plasma volume reductions, reduced degradation rates) present a greater likelihood of interaction with receptors on either the target tissue cell membrane (e.g. peptides) or with nuclear/cytoplasmic receptors located within the target tissue (e.g. steroid receptors). Coinciding with blood hormonal concentrations is the number of available receptors for binding and subsequent cellular changes. Interaction with the receptor initiates a milieu of events, ultimately leading to a specific response such as an increase in muscle protein synthesis.

Perhaps the most influential mediating factor in the acute responses and subsequent adaptations is the resistance exercise stimulus. Proper resistance exercise prescription and manipulation of the acute programme variables (e.g. intensity, volume, rest intervals, exercise selection and sequence, repetition velocity, frequency) ensures an optimal neuroendocrine response.[2,3] Programme design will incorporate three fundamental concepts of progression (e.g. progressive overload, variation and specificity) that attempt to maximise adaptations of the neuromuscular system.[1] For example, with progressive overload, motor unit recruitment will increase.[4] Recruitment of a greater number of muscle fibres enables greater hormone-tissue interaction within the realm of a larger percentage of the total muscle mass. Consequently, tissue activation is a precursor to anabolism. Therefore, the training programme as well as genetic predisposition, sex, fitness level and

the potential for adaptation all play significant roles in the hormonal response to resistance exercise.

Several hormones are discussed in this review. Emphasis is placed upon those anabolic and catabolic hormones most relevant to tissue remodelling. Tissue remodelling is a dual process in that catabolism initiates the process during resistance exercise and anabolism predominates in the recovery period leading to growth and repair. Thus, both catabolic and anabolic hormones play key roles in this process. Adaptations to resistance training entail four general classifications:

1. acute changes during and post-resistance exercise;
2. chronic changes in resting concentrations;
3. chronic changes in the acute response to a resistance exercise stimulus;
4. changes in receptor content.

Other factors such as nutritional intake, training experience, sex, age and/or maturity, interaction with other modalities of exercise and diurnal variations, as well as the resistance training programme, affect the endocrine responses and adaptations to resistance training are also discussed.

## 1. Testosterone

### 1.1 Acute Responses to Resistance Exercise

Resistance exercise has been shown to acutely increase total testosterone concentrations in most studies in men,[5-12] while in young women no change[8] or an elevation[13,14] may take place. These elevations have been attributed to plasma volume reductions, adrenergic stimulation,[15] lactate-stimulated secretion[16,17] and potential adaptations in testosterone synthesis and/or secretory capacity of the Leydig cells in the testes.[18] It appears that its role in augmentation of other hormonal mechanisms (e.g. growth hormone [GH], insulin-like growth factor-1 [IGF-1]) in anabolic processes,[19] as well as the effect of testosterone on the nervous system (i.e. testosterone can interact with receptors on neurons and increase the amount of neurotransmitters released, regenerate nerves, increase cell body size and dendrite length/diameter)[20,21] may be of primary interest when examining the potential benefits to enhancing acute force production.

It is the unbound fraction of testosterone that is biologically active and able to interact with androgen receptors (AR). The response of free testosterone has been shown to parallel total testosterone in some studies,[11,12,22] whereas a lack of response or reductions have been demonstrated in others.[23,24] Recently, Tremblay et al.[11] reported elevated free testosterone concentrations following resistance exercise. Interestingly, the acute elevation was greater in resistance-trained men than endurance-trained men, thereby indicating a beneficial chronic adaptation from resistance training. These data partially support Kraemer et al.[25] who reported significant elevations in serum free testosterone in both young and elderly men. However, the magnitude of elevation was greater after 10 weeks of periodised strength training compared with the pre-training response, thereby suggesting that a resistance training base may enhance the acute response to a workout. In addition, a significant elevation in resting serum free testosterone was observed in the young men. Free testosterone has been shown to be elevated by 25% in young women following acute resistance exercise (e.g. six sets of ten repetition maximum [RM] squats with 2-minute rest intervals);[14] however, no changes have been observed following resistance exercise in middle-aged and elderly women.[26]

Several factors appear to influence the acute serum total testosterone responses to resistance exercise. The magnitude of elevation during resistance exercise has been shown to be affected by the muscle mass involved (i.e. exercise selection),[27,28] intensity and volume,[29-36] nutritional intake,[9] training experience,[11,37] and is independent of the individual's absolute level of muscular strength.[37] Large muscle-mass exercises such as the Olympic lifts,[38] deadlift[39] and jump squats[27] have been shown to produce large elevations in testosterone compared with small muscle-mass exercises. These large muscle-mass exercises have been shown to be potent metabolic stressors[35,40] and a strong metabolic component may be a stimulus for testosterone release.[16] Based on these data, it appears that programmes designed to stimulate testosterone secretion should be structured around large muscle-mass exercises.

**Table I.** The effects of intensity and volume on the acute total testosterone response

| Study | Protocol | Results |
|---|---|---|
| Weiss et al.[7] | Three sets of four exercises to failure, 80% of 1RM with 2 min RI | Sig. ↑ in T |
| Ratamess et al.[35] | 1 × 10 squats, 80–85% 1RM<br>6 × 10 squats, 80–85% 1RM, 2 min RI | NC<br>Sig. ↑ in T |
| Raastad et al.[31] | 70% of 3–6RM vs 100% of 3–6RM | Sig. ↑ in T; 100% >70% |
| Schwab et al.[32] | 4 × 6 squats (90–95% of 6RM)<br>4 × 9–10 (60–65% of load used for high intensity) | 31% ↑ in T<br>27% ↑ in T |
| Bosco et al.[34] | 20 sets of 2–4 reps vs 10 sets of 2–3 reps of half squats | Sig. ↑ in T<br>NC |
| Häkkinen and Pakarinen[33] | 20 sets of 1RM squats<br>10 sets of 10 reps with 70% of 1RM | NC<br>Sig. ↑ in T |
| Gotshalk et al.[36] | One vs three sets of 10RM for eight exercises | Sig. ↑ in T; 3 > 1 |
| Kraemer et al.[29,30] | Eight exercises, 3–5 × 5RM vs 10RM with 1- and 3-min RI | Sig. ↑ in T; T ↓ as load ↓ and RI ↑ |

**NC** = no change; **reps** = repetitions; **RI** = rest interval; **RM** = repetition maximum; **sig.** = significant; **T** = testosterone; ↓ indicates decrease; ↑ indicates increase.

Little is known concerning the testosterone response to varying the sequence of exercises during resistance training. It has been suggested that large muscle-mass exercises be performed prior to small muscle-mass exercises.[1] The hypothesis is that performance of large muscle-mass exercises (i.e. squat, deadlift, power clean) early in the workout may produce significant elevations in testosterone, which potentially may expose smaller muscles to a greater response than that resulting from performance of small muscle-mass exercises only. This hypothesis was recently examined. Hansen et al.[28] measured muscle strength changes in the elbow flexor muscles following 9 weeks of resistance training. However, one group performed a workout consisting of elbow flexion exercises only and a second group performed lower-body exercises prior to the elbow flexion exercises. Performing elbow-flexion exercises only failed to acutely elevate testosterone significantly. However, testosterone was significantly elevated when lower-body exercises were performed first, and muscle strength increased to a greater extent as well when both lower- and upper-body exercises were performed. These data provide support for performing large muscle mass, multiple-joint exercises early in a workout and smaller muscle-mass exercises later in the workout when training to enhance muscle strength.

The intensity and volume of the resistance training programme has been shown to affect the acute testosterone response. Protocols of sufficient intensity and volume have been shown to produce substantial elevations in total testosterone (see table I). Schwab et al.[32] reported significant elevations in testosterone during two squat protocols. However, testosterone did not significantly increase until after the fourth set was completed. When resistance is held constant, the larger acute testosterone response is observed in the protocol consisting of a higher number of sets.[34-36] Similarly, if repetitions are held constant then the protocol with higher loading tends to produce the greatest acute testosterone response.[31] However, Ahtiainen et al.[12] recently reported no differences in the acute testosterone response between two protocols of similar repetition number, but intensity was slightly greater in one protocol that incorporated forced repetitions. The interaction between these variables has yielded interesting results favouring those programmes with a higher glycolytic component (e.g. moderate intensity, high volume, relatively short rest intervals). Guezennec et al.[41] reported minor elevations in testosterone during conventional strength training (i.e. 3–4 sets of 3–10 repetitions at 70–95% of 1RM, 2.5-minute rest periods). However, when load was increased further and repetitions decreased to three, a limited testosterone response was observed. Kraemer et al.[42] reported significant elevations in testosterone following five sets of 15–20 repetitions of the squat, despite using loads of 50% of 1RM. Kraemer et al.[29,30] reported that a bodybuilding programme (moderate load, high volume) with short rest periods produced greater testosterone responses than high-

load, low-volume training with long (3-minute) rest periods.

The effect of training frequency on the acute testosterone response has not been adequately addressed. Häkkinen et al.[24] reported a greater testosterone response during afternoon sessions compared with morning sessions in elite weightlifters during multiple training sessions per day. However, it is difficult to interpret hormonal data at different times of day as diurnal variations are very influential. In addition, total training volume is influential as serum testosterone concentrations returned to normal when training frequency was reduced to one workout per day.[43]

The acute response of testosterone has been shown to be influenced by the age, training experience of the individuals, sex, as well as baseline values. College-aged men typically display a significant acute response, whereas the response may be limited in younger high-school aged men.[39] Junior weightlifters (14–18 years of age) with >2 years of lifting experience have been shown to produce a greater acute testosterone response than those with <2 years of experience.[38] The response in adults has been less pronounced such that no changes in the acute response have been observed with additional training experience.[44] This was recently demonstrated by Ahtiainen et al.[45] who reported no differences in the acute response between strength-trained and non-strength-trained men before and after 21 weeks of training. Older individuals have been shown to produce significant elevations of testosterone; however, the absolute concentrations are significantly lower than that of younger individuals.[25] The acute testosterone response in women appears limited[8,34,46,47] as only few studies have shown significant elevations.[13,14] In direct comparison, men have shown acute elevations in testosterone but not women immediately following the same protocol.[7,8] Rather, it appears other anabolic hormones such as GH may be more influential for promoting muscle hypertrophy in women.

The acute testosterone response to resistance exercise appears to be influenced by nutritional supplementation. Carbohydrate/protein supplementation has been shown to limit the testosterone response to resistance exercise.[9] The rationale is unclear but a previous study reported reduced circulating concentrations of testosterone in response to low dietary fat intake and a diet with a high protein/carbohydrate ratio.[27] Elevations in insulin concentrations have coincided with decreased testosterone in another study examining protein/carbohydrate supplementation.[6] Thus, a possible interaction between insulin and testosterone warrants further study.

### 1.2 Chronic Changes in Resting Concentrations of Testosterone

Changes in resting testosterone concentrations during resistance training have been inconsistent or non-existent in men and women,[48-51] although significant elevations have been reported in both prepubertal and pubertal boys.[52] In fact, similar resting concentrations between untrained women and national-level elite female weightlifters have been reported.[47] Rather, it appears that resting concentrations reflect the current state of muscle tissue such that elevations or reductions may occur at various stages depending on substantial changes in the volume and intensity of training,[45,53] although no changes have also been observed during periodised resistance training.[49] Elevated resting testosterone concentrations have been reported in some studies,[25,45,53-55] whereas several studies have shown no differences[5,23,26,48,56-58] or reductions.[45] Examination of elite Olympic weightlifters has shown no significant differences occurring over a 1-year period;[23] however, elevations were reported following a second year of training.[53] Recently, Ahtiainen et al.[45] reported significantly higher free and total testosterone concentrations during a 7-week high-volume training phase compared with pre-training values. However, reductions were observed when volume was reduced and intensity was increased over a subsequent 7-week training period. We have reported similar findings where no changes in resting testosterone concentrations were observed during 2 weeks of high-volume overreaching but reductions were observed during a subsequent 2-week high-intensity, lower-volume phase (unpublished observation). In addition, Raastad et al.[59] reported a 12% reduction in resting testosterone concentrations during a heavy training phase. Thus, substantial changes in volume and intensity may elicit transient changes in resting testosterone concentrations; how-

ever, values may return to baseline when the individual returns to 'normal' training.

### 1.3 Modification of Androgen Receptor Content

The presence of AR in tissues has been shown to correlate highly with the known functions of androgens. The AR concentration in rat skeletal muscle depends on several factors including muscle fibre type, contractile activity and the concentrations of testosterone.[60,61] Resistance training or exercise in general, has been shown to modulate AR content.[62,63] In rats, resistance training elicits a significant increase in androgen binding capacity in the extensor digitorum longus muscle but reduces androgen binding capacity in the soleus, thereby demonstrating a fibre-type specific effect of training.[64] Electrical stimulation of the rat gastrocnemius increased AR content by 25% within 3 days (with a concomitant increase in muscle mass) but plateaued at 5 days when the stimulation remained the same.[65] However, administration of an AR antagonist in rats (i.e. oxendolone) during 2 weeks of electrical stimulation attenuated 70% of the stimulation-induced hypertrophy observed compared with a vehicle control group.[66] Collectively, these data demonstrate the importance of the androgen-AR interaction during training to maximise hypertrophy.

Resistance training has been shown to up-regulate AR content following resistance exercise in humans. Bamman et al.[67] reported that AR messenger RNA (mRNA) in the vastus lateralis increased 63% and 102%, respectively, 48 hours following eight sets of eight repetitions of either eccentric (~110% of 1RM) or concentric (~85% of 1RM) squats. Kadi et al.[68] cross-sectionally examined 17 power lifters, nine of whom were cycling anabolic steroids and reported that power lifters had a higher percentage of AR-positive myonuclei in the trapezium muscles compared with untrained controls. Power lifters administering anabolic steroids had a greater percentage of AR-positive myonuclei than drug-free power lifters. Interestingly, no differences were observed between power lifters and controls for percentage of AR-positive myonuclei in the vastus lateralis muscle during baseline measurements. We have recently shown significant correlations between baseline AR content in the vastus lateralis and 1RM squat, thereby suggesting that AR content, in part, assists in mediating strength changes during resistance training.[35]

The resistance exercise stimulus appears to mediate the magnitude of acute AR modifications. The effect of resistance exercise volume on AR content was recently examined. Ratamess et al.[35] compared two protocols (one vs six sets of ten repetitions) consisting of the squat exercise to examine potential acute modifications in AR content 1 hour post-exercise. No differences were observed in AR content following the single set protocol. However, the higher-volume protocol elicited significant down-regulation of AR content. Considering that ARs are protein molecules and protein catabolism increases during resistance exercise,[69] our data demonstrated that when sufficient volume is reached, AR protein content may initially down-regulate (despite large elevations in circulating testosterone) prior to the up-regulation that has been observed in other studies.[67] The relationship between the magnitude of initial down-regulation and the subsequent compensatory up-regulation that occurs several hours later warrants further investigation. However, we have also discovered that ingestion of a protein/carbohydrate supplement before and after the workout attenuates the AR down-regulation with higher-volume resistance exercise observed 1 hour post-exercise (unpublished observation). Thus, nutritional intervention plays a critical role in AR modification post-resistance exercise.

### 1.4 Response of Luteinising Hormone

Luteinising hormone (LH) is a protein hormone secreted from the basophilic cells of the anterior pituitary, which is the primary regulator of testosterone secretion from the Leydig cells of the testes.[18] Blood concentrations of LH are positively related to the intensity and volume of resistance training.[23,70] Resting concentrations of LH did not change significantly in men and women during 16–24 weeks of strength and power training[50,56] but slight elevations have been shown in strength athletes during intense training periods[71] and in resistance-trained men compared with endurance-trained men.[11] Busso et al.[70] compared a 4-week intensive training programme in elite weightlifters with a 2-week re-

duced training period and reported a reduction in testosterone concentrations with a concurrent elevation in LH during the intense training phase. It was hypothesised that the decrease in testosterone contributed to the elevation in LH. An acute bout of resistance exercise does not induce LH secretion,[43] although a delayed response has been demonstrated later into the recovery period;[11] therefore suggesting that acute elevations in serum testosterone concentrations during resistance exercise are due to other regulatory mechanisms (e.g. reduced clearance, plasma volume shifts).

### 1.5 Testosterone Precursors

The biosynthetic pathway of testosterone contains many steps. Theoretically, supplementation with such testosterone precursors may enhance testosterone concentrations (by reducing the number of conversion steps) and subsequent acute resistance exercise performance. Some of these precursor molecules that have been investigated include dehydroepiandrosterone (DHEA) [prasterone], 4-androstendione, 4-androstenediol, 5-androstenediol, 19-norandrostenediol, 19-norandrostenedione and 1-androstene-3β-17β-diol.[72,73] Studies have shown that low doses (50–100 mg/day) of these prohormones do not increase circulating testosterone concentrations in young, healthy men[74-78] although elevations of DHEA, androstenedione and LH have been observed in addition to less desirable responses such as elevations in estrone, estradiol, and reductions in high-density lipoproteins (HDLs). In fact, the magnitude of estradiol elevation has been shown to be dose-dependent.[78] It has been suggested that this range of administration was too low considering that young, healthy men have much higher resting testosterone concentrations than women and older men.[72]

Interestingly, low-dose supplementation of androstenedione has been shown to elevate testosterone in post-menopausal women[79] and higher doses (~300mg) have been shown to elevate free testosterone by 37% in middle-aged men.[80] However, in young men, supplementation with 200–300 mg/day of 4-androstenediol, 4-androstenedione and/or supplements consisting of multiple prohormones (i.e. 300mg of androstenedione plus 150mg of DHEA, as well as other ingredients) has shown variable responses. Both acute elevations[78,81] and a lack of acute elevation in testosterone have been reported.[82]

Leder et al.[83] have shown that during small (i.e. 100mg) and large (i.e. 300mg) administered doses of oral androstenedione, the majority of androstenedione undergoes hepatic metabolism to testosterone and then to testosterone metabolites prior to release into systemic circulation. The net effect is a large production of testosterone metabolites despite only small or no elevations in testosterone. Further support for these data were provided by Brown et al.[84] who examined a low dose of sublingual androstenediol administration (60mg) and reported significant elevations of both total and free testosterone (that were not observed during oral administration) for 180 minutes (with a peak occurring at 60 minutes) post-administration. These data indicate that small to moderate oral doses of prohormones produce minimal, if any, elevations in testosterone in young men. However, the subsequent elevations in testosterone metabolites, estradiol, estrone, and reductions in HDLs potentially pose health risks that need to be considered prior to prohormone use.

Long-term studies have shown no further improvement in muscle strength or hypertrophy with DHEA/androstenedione/androstenediol supplementation (150–300 mg/day) over 8–12 weeks of resistance training.[74,77,82,85-87] Baseline testosterone values measured during this time did not change significantly, although significant elevations in androstenedione/androstenediol, DHEA sulfate (PB 008), estrone and estradiol were reported.[85] In addition, 5 days of oral androstenedione supplementation (100 mg/day) did not elevate protein synthesis.[88] Therefore, the potential ergogenic effects of precursor hormones remain to be seen and require further examination particularly since many individuals consume higher than the recommended dose.

Adrenal androgens may play a greater role in women considering the low levels of testosterone present. Women tend to have a slightly larger conversion percentage of circulating DHEA and its precursor DHEA sulfate to androstenedione and testosterone at the tissue level[89] and typically have higher baseline concentrations of androstenedione than men.[7] However, androstenedione is significantly less potent than testosterone. Few studies

have examined the acute response to resistance exercise. Weiss et al.[7] reported 8–11% elevations in circulating androstenedione in both men and women following a programme consisting of four exercises for three sets to failure with 80% of 1RM and 2-minute rest intervals. Tremblay et al.[11] reported elevations in DHEA sulfate during resistance exercise and this response was greater in resistance-trained men than endurance-trained men. No changes[26] and reductions[48] in baseline concentrations of androstenedione, DHEA and DHEA sulfate have been reported during 24 weeks of resistance training. However, baseline concentrations of DHEA sulfate were elevated after 8 weeks of resistance training in young women and this elevation correlated significantly to increases in lean body mass.[90] The impact of acute and chronic changes in the concentrations of testosterone precursors warrants further investigation.

### 1.6 Sex Hormone-Binding Globulin

Circulating androgens are predominately bound to the transport protein sex hormone-binding globulin (SHBG). A change in SHBG concentrations may influence the binding capacity of testosterone and the magnitude of free testosterone available for diffusion across the cell membrane to interact with membrane-bound steroid receptors. Recent studies have identified SHBG receptors on cell membranes and a possible receptor-mediated role for SHBG in mediating androgen actions through a cyclic adenosine monophosphate mechanism.[91] Differential responses have been observed during resistance training. Acute elevations have been reported[35,37] in some but not all studies,[24] whereas reductions[23] and no changes in resting SHBG concentrations have been reported following 3–24 weeks of resistance training,[26,50,51,56,58] following 1 week of intensive Olympic weightlifting[43] and over a 2-year period in elite Olympic weightlifters.[53]

## 2. Growth Hormone (GH) Super Family

The acidophilic cells of the anterior pituitary secrete molecules that make up the family of GH polypeptides. The most commonly studied GH isoform, the 22kD molecule, consists of 191 amino acids.[18] Other biologically active spliced fragments are also released such as a 20kD isoform missing residues 32–46, a 5kD isoform consisting of residues 1-43 and a 17kD isoform consisting of residues 44–191.[92] In addition, other monomeric, dimeric, protein-bound GH and aggregates of GH have been identified, which are included this GH superfamily.[92] The physiological roles of these variants are now under investigation but appear to function similarly to the 22kD molecule in promoting tissue anabolism.

### 2.1 Acute Response to Resistance Exercise

The 22kD GH molecule has been the focus of most resistance exercise studies. Exercise,[93-95] especially resistance exercise,[96] has been shown to acutely elevate many of the GH variants. Recently, Hymer et al.[97] examined a common protocol used in our laboratory (e.g. six sets of ten repetitions of the squat with 75% of 1RM with 2-minute rest intervals) and reported significant elevations in GH variants <30kD and 30–60kD in size in women. In addition, Kraemer et al.[98] using the same protocol in women reported differential acute responses in GH variants based on muscular strength. A subgroup of the ten strongest women showed the highest resting concentrations of all GH fractions, although the ten weakest women displayed the highest concentrations of the <30kD fractions. Similar acute responses were observed in strong and weak women in >30kD fractions although the weaker women showed a greater <30kD response. These results indicate that other molecular weight variants of GH appear responsive to resistance exercise; however, further research is warranted in order to elucidate the impact of these elevations. The remainder of this section will focus on the often-studied 22kD GH molecule.

Resistance exercise has been shown to elevate the concentrations of human GH through 30 minutes post-exercise similarly in men and women, although the resting concentrations of GH are significantly higher in women.[46] The magnitude appears dependent upon exercise selection and subsequent amount of muscle mass recruited,[28,38] muscle actions used (i.e. greater response during concentric than eccentric muscle actions),[22] intensity,[12,99,100] volume,[36,101] rest intervals between sets[29,30] and training status (e.g. greater acute elevations based on

individual strength and the magnitude of total work performed).[45,102,103] The importance of total work has been demonstrated as multiple-set protocols have elicited greater GH responses than single-set protocols.[36,104,105] It appears that the acute GH response to resistance exercise is highly influenced by the metabolic properties (total work) of the protocol. That is, protocols eliciting high blood lactate values (e.g. those programmes that are moderate to high in intensity, high in volume, stress large muscle mass, and use relative short rest intervals) tend to produce the most substantial GH responses.[29,30,36,42,101] High correlations between blood lactate and serum GH concentrations have been reported[33] and it has been proposed that $H^+$ accumulation produced by lactic acidosis may be the primary factor influencing GH release.[46] This finding was supported by an attenuated GH response following induced alkalosis during high-intensity cycling.[106] Hypoxia, breath holding, acid-base shifts and protein catabolism have been reported to influence GH release.[46] Thus, resistance exercise is a potent stimulus for elevating GH so long as the threshold of volume and intensity are met.[99]

Several investigations have given support to the association between acidosis resulting from resistance exercise, total work and the acute GH response. Moderate- to high-intensity, high-volume programmes using short rest periods have shown the greatest acute GH response compared with conventional strength or power training using high loads, low repetitions and long rest intervals in men.[29,30] Häkkinen and Pakarinen[33] reported that 20 sets of 1RM in the squat only produced a slight increase in GH, whereas a substantial increase in GH was observed following ten sets of ten repetitions with 70% of 1RM. Hoffman et al.[101] compared a low-intensity, higher volume protocol (15 repetitions of the squat with 60% of 1RM) to a high-intensity, low-volume protocol (four repetitions of the squat with 90% of 1RM) and reported a significantly higher GH response with the higher-volume protocol.

Zafeiridis et al.[107] compared a strength protocol (i.e. four sets of five repetitions using 88% of 1RM with 3-minute rest intervals), hypertrophy protocol (i.e. four sets of ten repetitions using 75% of 1RM with 2-minute rest intervals) and an endurance protocol (i.e. four sets of 15 repetitions using 60% of 1RM with 1-minute rest intervals) all consisting of four exercises and reported the acute GH response matched total work such that the most substantial response was observed in the endurance protocol. Using a similar protocol, Smilios et al.[108] reported that the acute GH response was greater following four sets versus two sets of resistance exercise (no additional elevation was observed using six sets) targeting hypertrophy and local muscular endurance. The hypertrophy protocol produced a significant elevation but less compared with the endurance protocol. The strength protocol yielded only a small elevation.

Ahtiainen et al.[12] compared two programmes of similar format with the exception that one group used 12RM loading and the other group used forced repetitions in order to perform 12 repetitions with a heavier load and reported a more substantial GH response when using forced repetitions. Williams et al.[109] compared three protocols of high ($3 \times 10$RM, 1-minute rest intervals, eight exercises), moderate (15 sets of ten repetitions for the leg extension, 1-minute rest intervals), and low ($3 \times 10$RM for the leg extension, 1-minute rest interval) volumes, and reported that only the high-volume protocol elicited a significant rise in GH. Goto et al.[110] examined a strength protocol (five sets using 90% of 1RM with 3-minute rest intervals) and reported a low GH response. However, the addition of a single set of high repetitions with 50% of 1RM to the end of the strength protocol elicited a much higher GH response. These data indicate that the hormonal response to a strength protocol may be maximised by inclusion of high volume set(s) and the end of the workout.

It has been shown that the acute GH response is somewhat limited in older individuals.[25,44,100] In general, GH concentrations decline with age (e.g. somatopenia) and these reductions correspond to periods of muscle atrophy (sarcopenia) in the elderly. Considering the impact of these findings, attempts to restore GH to some extent appear warranted to increase muscle strength and hypertrophy. It has been suggested that a major factor contributing to the limited GH response (other than age) maybe the magnitude of exertion displayed. Pyka et al.[100] reported lower blood lactates in the elderly during resistance exercise, thereby supporting the

hypothesis that maximal effort is necessary for optimising the exercise-induced secretion of GH. Interestingly, resistance training over 12 weeks in the elderly has been shown to promote greater acute GH response to a resistance exercise protocol,[44] possibly suggesting the greater response was due to an increased ability to exert oneself.

The specificity of muscle action selection during resistance training may affect the acute GH response to resistance exercise. Kraemer et al.[111] trained subjects for 19 weeks performing either all concentric repetitions, concentric repetitions with double the volume, or concentric and eccentric repetitions and the acute response to a resistance exercise protocol consisting of either concentric or eccentric muscle actions was measured pre- and post-exercise. The GH response was high for the concentric training groups during the concentric protocol; however, the acute response was greater for the eccentric protocol for the concentric/eccentric training group. These data indicate that GH secretion may be sensitive to the muscle actions used during resistance training. It has been shown that the anterior pituitary may be directly innervated by nerve fibres mostly with synapses on corticotroph and somatotroph cells.[112] It has also been suggested that 'neural-humoral' regulation of GH secretion may take place such that a rapid neural response is observed during the initial stress with the humoral phase subsequently occurring.[112] If such is the case then it may be possible for higher brain centres, e.g. motor cortex, to play an active role in regulating GH secretion during resistance exercise and this regulatory mechanism may be sensitive to specific muscle actions used during resistance training.

### 2.2 Chronic Changes in Resting GH Concentrations

Traditional resistance training does not appear to affect resting concentrations of GH. No changes in resting GH concentrations have been observed in men and women of various ages.[25,26,55,58] This contention is also supported by data demonstrating similar resting concentrations of GH in elite Olympic weightlifters[53] and strength athletes (i.e. body builders, power lifters, weightlifters)[45] compared with lesser-trained individuals. These findings are consistent with dynamic feedback mechanisms of GH and its roles in the homeostatic control of other variables, e.g. glucose. In addition, these findings suggest that the acute response of GH to resistance exercise may be most prominent for tissue remodelling. The exercise-induced increase has been highly correlated with the magnitude of type I and type II muscle fibre hypertrophy ($r = 0.62–0.74$).[58] These relationships could be indicative of a role for repeated acute resistance exercise-induced GH elevations on cellular adaptations in trained muscle. Changes in receptor sensitivity, differences in feedback mechanisms, IGF-1 potentiation and diurnal variations may also play significant roles.

### 2.3 GH Binding Protein

Circulating GH is complexed to mostly high-affinity GH-specific binding proteins (GHBPs) that greatly extend its half-life and enhance the overall biological effects of GH. It is now known that the human high-affinity GHBP arises from proteolytic cleavage of the extracellular domain of the GH receptor.[113] This process is thought to occur principally at the liver, which is the most GH receptor-rich tissue, but could occur wherever the GH receptor exists. Little is known concerning GHBP and resistance exercise. Rubin et al.[103] recently reported that acute resistance exercise (six sets of squats with 80–85% of 1RM for ten repetitions with 2-minute rest intervals) resulted in significant elevations of GHBP; however, no differences were observed between resistance-trained and untrained individuals suggesting that chronic resistance training does not alter circulating GHBP or change GH receptor expression.

## 3. Cortisol

Glucocorticoids are released from the adrenal cortex in response to the stress of exercise. Of these, cortisol accounts for approximately 95% of all glucocorticoid activity. Cortisol has catabolic functions that have greater effects in type II muscle fibres.[2] About 10% of circulating cortisol is free, while ~15% is bound to albumin and 75% is bound to corticosteroid-binding globulin. In peripheral tissues, cortisol stimulates lipolysis in adipose cells and increases protein degradation and decreases protein synthesis in muscle cells resulting in greater

release of lipids and amino acids into circulation, respectively. Because of its major role in tissue remodelling, acute and chronic changes of cortisol during resistance training is often examined.

### 3.1 Acute Response to Resistance Exercise

Studies have shown significant elevations in cortisol and adrenocorticotropic hormone (ACTH, a pituitary hormone that stimulates cortisol release from the adrenal cortex) during an acute bout of resistance exercise[10,24,25,38,41,46] with the response similar between men and women[46] although one study reported an increase in cortisol in men but not women who performed the same protocol.[8] The acute cortisol response appears to be independent of training status at least in adolescent weightlifters,[38] although a recent study has shown less of a response in endurance athletes compared with resistance-trained men performing the same resistance exercise protocol.[11] Some hormonal elevations have been attributed to plasma volume reductions; however, when corrected for plasma volume changes cortisol concentrations still remain elevated.[58] In addition, it has been reported that the acute increase in cortisol secretion during resistance exercise may be attenuated by anabolic steroid use.[114]

Programmes that elicit the greatest cortisol response also elicit the greatest acute GH and lactate response. Significant correlations between blood lactate and serum cortisol have been reported.[35,115] In addition, acute elevations in serum cortisol have been highly correlated to 24-hour post-exercise serum creatine kinase concentrations.[116] Metabolically demanding protocols high in total work, i.e. high volume, moderate to high intensity with short rest periods, have elicited the greatest acute lactate and cortisol response with little change during conventional strength/power training.[33,46,117] In fact, some strength protocols have failed to elicit a significant cortisol response whereas hypertrophy and endurance protocols performed by the same group of subjects elicited more substantial acute elevations through 30 minutes post-exercise.[107,108] The number of sets per exercise and/or volume appears to influence the acute cortisol response in most studies but not all.[109] Smilios et al.[108] have shown that four to six sets of resistance exercise elicited a significantly larger cortisol response than two sets. We have recently demonstrated that six sets of ~10RM squats with 2-minute rest intervals increased serum cortisol concentrations substantially, whereas performance of only one set did not elicit any response.[35] Increasing total volume by the inclusion of higher intensity sets using forced repetitions has been shown to elicit a larger cortisol response than the same protocol performed with less loading and no forced repetitions.[12] It addition, the rest interval length affects the acute cortisol response.[46,117] Kraemer et al.[118] reported that performing eight sets of 10RM leg press exercises with 1-minute rest intervals elicited a significantly greater acute cortisol response than the same protocol using 3-minute rest periods. Thus, while chronic high levels of cortisol have adverse effects, acute elevations may be part of a larger remodelling process in muscle tissue.

The effect of carbohydrate supplementation on the subsequent acute cortisol response to resistance exercise has been studied. Tarpenning et al.[119] reported that the acute cortisol response was limited with a 6% carbohydrate solution during resistance exercise, and that a carbohydrate-supplemented group experienced greater gains in hypertrophy over 12 weeks of resistance training. Kraemer et al.[9] reported a blunted cortisol response during 3 days of carbohydrate supplementation and resistance training. However, not all studies have shown an attenuation of the acute cortisol response to resistance exercise with carbohydrate supplementation.[109] It has been suggested that carbohydrate supplementation during resistance exercise reduces the demand for gluconeogenesis, thereby reducing the need for cortisol.[120] Although further research is warranted, some evidence exists supporting carbohydrate supplementation during resistance exercise for limiting the acute cortisol response.

### 3.2 Chronic Adaptations in Resting Cortisol Concentrations

Resting cortisol concentrations generally reflect a long-term training stress. Chronic resistance training does not appear to produce consistent patterns of cortisol secretion as no change,[23,26,45,49-51,53,121] reductions[37,48,55,56,58] and elevations[71] have been reported during normal strength and power training in men and women, and during short-term overreach-

ing. In animals, cortisol concentrations have explained a substantial amount of the variance observed in muscle mass changes.[122] Thus, it appears that the acute cortisol response may reflect metabolic stress whereas the chronic changes (or lack of change) may be involved with tissue homeostasis involving protein metabolism.

### 3.3 Testosterone/Cortisol Ratio

The testosterone/cortisol (T/C) ratio and/or free testosterone/cortisol ratio have been suggested to be indicators of the anabolic/catabolic status of skeletal muscle during resistance training.[123] Either an increase in testosterone, a decrease in cortisol, or both would indicate potential state of anabolism. However, this appears to be an oversimplification and is at best only an indirect measure of the anabolic/catabolic properties of skeletal muscle.[18] Some studies have shown changes in the T/C ratio during strength and power training, and this ratio has been positively related to performance improvements,[48,56] whereas other studies have shown no change.[45] Stressful training (overreaching) in elite weightlifters has been shown to decrease the T/C ratio.[23] Periodised, higher-volume programmes have been shown to produce a significantly greater increase in the T/C ratio than a low-volume, single-set programme.[55] However, in an animal study where the T/C ratio was manipulated to investigate muscle hypertrophy, it was reported that the T/C ratio was not a useful indicator of tissue anabolism.[122] Thus, the use of the T/C ratio remains questionable.

### 3.4 The Glucocorticoid Receptor and Resistance Training

The catabolic effects of cortisol are mediated through interaction with glucocorticoid receptors. Consequently, cortisol and possibly androgen concentrations appear to be critical to determining the level of up- or down-regulation of glucocorticoid receptors. For many years it has been suggested that anabolic steroids may also be anti-catabolic in nature because of competitive inhibition of binding between androgens and cortisol for the glucocorticoid receptor.[124] Although evidence does support this contention,[125] further research is warranted to examine the anti-catabolic nature of androgen administration on the glucocorticoid receptor. It appears that with consistent resistance training experience, down-regulation of the glucocorticoid receptor may occur, thereby reducing the catabolic influence on skeletal muscle tissue.

Eccentric resistance exercise has been shown to up-regulate glucocorticoid receptor content and myofibrillar proteolysis.[126] Recently, Willoughby et al.[126] examined glucocorticoid receptor content and mRNA 6 and 24 hours following two eccentric resistance exercise protocols (both consisting of seven sets of ten repetitions of knee extensions with 150% of 1RM) and reported significant up-regulation at 6 and 24 hours post-exercise (with a much more substantial increase at 24 hours) following the first bout. However, the up-regulation was significantly attenuated following the second bout, thereby indicating a protective training effect with exposure to eccentric exercise. In addition, these changes paralleled elevations in serum cortisol (i.e. larger elevations were observed immediately after, 6, 24, and 48 hours following bout 1 than bout 2). The attenuated up-regulation in glucocorticoid receptor content and mRNA following bout 2 also coincided with attenuated up-regulation of factors of the ATP-dependent ubiquitin proteolytic pathway. These data indicate that chronic exposure to eccentric resistance exercise does provide a protective effect in limiting tissue catabolism and reducing some of the magnitude of associated muscle damage through modifications of glucocorticoid receptor content.

## 4. Insulin-Like Growth Factors (IGFs)

IGFs are structurally related to insulin and mediate many of the actions of GH. IGFs are small polypeptide hormones (70 and 67 amino acid residues for IGF-1 and IGF-2, respectively) that are secreted as they are produced by the liver in response to GH-stimulated DNA synthesis.[91] IGFs increase protein synthesis during resistance training and enhance muscle hypertrophy.[91] The importance of these hormones, in particular IGF-1, has been recently shown as immunisation to IGF-1 in diabetic rats prevented protein synthesis following resistance exercise.[127] Of the two, IGF-1 has been extensively studied and will be discussed from here on.

### 4.1 Acute IGF-1 Response to Resistance Exercise

The acute response of IGF-1 to resistance exercise remains unclear. Most studies have shown no change in IGF-1 during or immediately following an acute bout of resistance exercise,[6,9,128] whereas a few studies have shown acute elevations during and following resistance exercise.[29,30,103] The lack of change has been attributed to delayed secretion of IGF-1, i.e. 3–9 hours, following GH-stimulated mRNA synthesis,[46] as peak values may not be reached until 16–28 hours post-stimulated GH release.[6] Therefore, it appears that IGF-1 elevation following an acute bout of resistance exercise may be delayed until GH-stimulated synthesis and secretion from the liver can take place.

### 4.2 Chronic Circulating IGF-1 Adaptations to Resistance Training

No change in resting concentrations of IGF-1 have been reported during normal short-term resistance training[25,58] and overreaching (unpublished observation), unless concurrent with carbohydrate/protein supplementation.[9] Resistance-trained men have been shown to have higher resting IGF-1 concentrations than untrained men.[103] However, long-term studies in women have shown elevations in resting IGF-1, particularly during high volume training.[55,129] Borst et al.[130] reported significant elevations in resting serum IGF-1 following only 13 weeks of a 25-week training programme. The elevations reported by Borst et al.[130] were similar between single-set and multiple-set training groups despite a significantly greater strength increase observed in the multiple-set group. Marx et al.[55] reported significant elevations in resting IGF-1 concentrations in previously untrained women following 6 months of training. In addition, the magnitude was greater when a high-volume, multiple-set programme was used. Reductions in IGF-1 (~11%) have also been reported during high volume and intensity overreaching, but have returned to baseline once the overreaching phase subsided.[59,131] Thus, it appears that the volume and intensity of training are important for chronic IGF-1 adaptations.

### 4.3 Muscle Isoforms of IGF-1 and Adaptations to Resistance Training

IGF-1 has been shown to have autocrine/paracrine functions within muscle cells.[132,133] Two isoforms in skeletal muscle have been identified each functioning independently.[134] One isoform is similar to the circulating hepatic IGF-1 called IGF-1Ea and the second muscle-specific isoform of IGF-1 is mechano growth factor (MGF).[133,134] The second isoform only differs from the liver isoform by the presence of the first 49 base pairs from exon 5.[134] Overloaded muscle and subsequent mechanical damage, e.g. resistance training, appear to be prominent stimuli for these isoforms.[67,133] It appears both isoforms increase protein synthesis and promote satellite cell activation.[134] Bamman et al.[67] reported significant elevations in muscle IGF-1 mRNA following resistance exercise, particularly during eccentric resistance exercise. Hameed et al.[134] examined muscle content 2.5 hours following a lower-body workout (e.g. ten sets of six repetitions using 80% of 1RM with 2-minute rest intervals) and reported that in young men MGF mRNA increased substantially (however, no increase was observed in older men), whereas IGF-1Ea mRNA did not significantly change in young or older men. Brahm et al.[135] have shown that arterial concentrations of IGF-1 remained constant during intensive exercise. However, venous concentrations of IGF-1 increased, which may suggest that a circulating elevation may be accounted for by greater release from the muscles (i.e. via cell disruption and greater blood flow). Nevertheless, it does appear that the muscle isoforms of IGF-1 play a prominent role during tissue remodelling.

### 4.4 IGF Binding Proteins

Nearly all circulating IGFs are bound to IGF binding proteins (IGFBPs). These regulate IGF availability and prolong IGF circulation.[91] The most common is IGFBP-3. Acute resistance exercise has been shown to elevate IGFBP-3[42,136] and this response was greater following L-carnitine L-tartrate supplementation.[42] Nindl et al.[136] have shown that an acute bout of resistance exercise did not influence IGF-1 specifically but affected the manner in which IGF-1 was partitioned among its

family of binding proteins. IGFBP-3 was elevated for the first hour following resistance exercise but did not differ overnight whereas IGFBP-2 was elevated overnight.[136] Less is known concerning chronic circulating concentrations of IGFBP-3. Borst et al.[130] have reported a significant decline in IGFBP-3 between weeks 13 and 25 of a resistance training programme. The impact of changes in IGFBPs requires further study.

## 5. Insulin

Insulin has been shown to significantly affect muscle protein synthesis when adequate amino acid concentrations are available, especially by reducing protein catabolism.[137,138] Serum insulin concentrations parallel changes in blood glucose, and the response is enhanced when protein/carbohydrates are ingested prior to, during, or following the workout.[6,9,137-140] Without supplementation, serum insulin concentrations have been shown to decrease during an acute bout of resistance exercise.[31] We have reported depressed fasted insulin values during 4 weeks of resistance training overreaching.[141] Although a potent anabolic hormone when in its normal range of physiological concentrations, insulin appears to be mostly affected by blood glucose concentrations and/or dietary intake. Therefore, ingestion of carbohydrates, amino acids, or combinations of both prior to, during, and/or immediately after the resistance exercise protocol is recommended for maximising insulin's effects on tissue anabolism. Supplementation prior to or during resistance exercise is especially beneficial for maximising protein synthesis because it takes advantage of the large increase in muscular blood flow and subsequent amino acid delivery.

## 6. Catecholamines

Catecholamines reflect the acute demands of the resistance exercise protocol and are important for increasing force production, muscle contraction rate, energy availability, as well as several other functions including the augmentations of hormones such as testosterone.[2] An acute bout of resistance exercise has been shown to increase plasma concentrations of epinephrine,[10,41,117,142] norepinephrine[10,41,117] and dopamine.[10,117] The magnitude may be dependent upon the force of muscle contraction, amount of muscle stimulated, volume of resistance exercise and rest intervals.[117,142] Prior to intense exercise, a significant elevation in plasma epinephrine and norepinephrine has been observed,[10,30] thereby demonstrating an 'anticipatory rise'. This anticipatory rise may be part of the body's psychophysiological adjustment for preparing to maximally perform during resistance exercise. Chronic adaptations remain unclear, although it has been suggested that training reduces the catecholamine response to resistance exercise.[41] However, alterations in the acute response may reflect the demands of the programme such that systematic variation and progressive overload may obviate any subsequent decrease.

## 7. Other Hormones

### 7.1 β-Endorphins

Less is known concerning the role of β-endorphins during resistance training. Elevations have been reported during resistance exercise in men and women.[38,143,144] However, no changes[145,146] and post-exercise reductions[147] have also been reported. Although a threshold of intensity and volume is necessary for acute elevations to occur during aerobic exercise (i.e. at least 70% of maximum oxygen consumption [$\dot{V}O_{2max}$]),[148] a similar scenario may also be observed during resistance exercise as protocols that have shown no acute elevation in β-endorphins have also failed to result in acute elevations of cortisol.[145] The acute elevation has been attributed to the magnitude of muscle mass used, rest interval length, intensity and volume of the resistance exercise programme,[38,116] has correlated highly with blood lactate concentrations in those studies that reported elevations,[115,116] and does not appear related to training experience or muscle strength.[38] In addition, the response is greater and longer in duration when resistance exercise is performed by individuals in negative energy balance.[144] Body building type workouts (high volume, moderate load, short rest periods) elicit the most substantial elevations in plasma β-endorphin concentrations compared with traditional strength training (high load,

low repetitions, long rest periods).[116] Thus, acute elevations may occur during resistance exercise; however, further research is needed to elucidate the role(s) of β-endorphins during resistance training.

### 7.2 Thyroid Hormones

The role of thyroid hormones during resistance training remains unclear but may be permissive in its interaction with other hormones. In animals, the interaction of liothyronine ($T_3$) with its receptor has been shown to up-regulate AR mRNA with this effect potentiated by higher androgen concentrations.[149] In moderately trained men and highly trained rowers, significant resting reductions in thyroxine ($T_4$),[150] free $T_4$,[150] free $T_3$,[151] and thyroid stimulating hormone (TSH)[151] were reported, whereas no changes in $T_3$[150] or $T_4$[151] have also been reported. Pakarinen et al.[152] reported significant reductions in TSH, $T_3$ and $T_4$ during one intensive week of resistance training (two workouts per day) in elite weightlifters. However, over the course of 1 year of training in elite weightlifters, no changes were observed for any thyroid hormone until the pre-competition period, i.e. lower volume of training, where significant increases in free $T_4$ and $T_3$ were reported.[153] These hormonal changes returned to baseline when the intensity increased during the next training phase. It appears that resistance training may alter thyroid function; however, the impact of these alterations remains speculative at the present time. Due to the tight homeostatic control of thyroid hormones, elevations during resistance training are not expected.

### 7.3 Fluid Regulatory Hormones

Fluid homeostasis is critical to acute exercise performance in general, although the majority of the literature has examined aerobic modalities of exercises. Fluid regulatory hormones such as arginine vasopressin, atrial peptide, renin, aldosterone and angiotensin II have been shown to increase in response to exercise with the magnitude dependent on exercise intensity, duration and hydration status.[154,155] Resistance exercise has been shown to reduce plasma volume[35,156] comparable to changes elicited by running and/or cycling at 80–95% of $\dot{V}O_{2max}$.[157] Kraemer et al.[10] had competitive power lifters perform one set of the leg press exercise to exhaustion using 80% of their 1RM. Immediately post-exercise into 5 minutes of recovery plasma osmolality, atrial peptide, renin activity and angiotensin II were elevated. These data were the first to demonstrate that fluid balance and the subsequent hormonal response may be affected in as little as the first set of a resistance exercise workout.

### 7.4 Leptin

Leptin, a product of the *ob* gene arising from adipose tissue, is a protein hormone thought to relay satiety signal to the hypothalamus to regulate energy balance and appetite.[158] Leptin concentrations are highly correlated to body fat mass such that obese humans have on average four times more serum leptin than lean individuals.[159] Serum leptin concentrations may be influenced by sex, metabolic hormones (e.g. stimulated by insulin and cortisol and inhibited by β-adrenergic agonists) and current energy requirements.[160] In middle-aged and elderly obese hypogonadal men, testosterone and anabolic steroid administration have been shown to reduce age-associated increases in fat mass, percentage body fat and body mass index (BMI),[161,162] and has been shown to reduce concentrations of leptin in a dose-dependent manner.[163]

Many studies have shown no direct impact of exercise on leptin concentrations independent of its effect on adipose tissue,[160] although high levels of energy expenditure may lead to a delayed reduction. Gippini et al.[164] reported that leptin did not correlate with BMI in body builders and that resistance training did not influence leptin production independently of changes in body composition. Simsch et al.[151] reported reductions in resting leptin concentrations following high-intensity resistance training in highly trained rowers. Zafeiridis et al.[107] compared three types of resistance exercise protocols: (i) strength; (ii) hypertrophy; and (iii) muscular endurance, and reported significant reductions in leptin through 30 minutes of recovery. However, similar reductions were observed in non-exercising, control subjects, thereby demonstrating that resistance exercise did not result in the reduction. Rather, fasting and/or diurnal variation appeared to be critical factors. We have reported similar findings after resistance exercise in fasted subjects.[103] Nindl et al.[165]

had subjects perform a high-volume protocol (i.e. 50 total sets) and reported no acute changes in leptin concentrations. However, a delayed reduction (9–13 hours) was observed and this was accompanied by a 12% increase in resting energy expenditure, thereby demonstrating that a large disruption in metabolic homeostasis (e.g. >800 kcals of exercise) could elicit reductions in leptin independent of changes in fat mass. These data indicate that the resistance exercise stimulus (i.e. interaction of volume, intensity, rest intervals, total work, etc.) does not influence the acute leptin response; however, if a protocol high enough in volume is performed then a delayed response may be observed.

Leptin is a critical mediator of several endocrine pathways pertinent to resistance training. One such pathway regulated by leptin is testicular steroidogenesis. Leptin has been shown to directly reduce steroidogenesis by reducing enzymatic conversion to 17-OH progesterone and through inhibition of steroidogenic acute regulatory protein, cytochrome P450 cholesterol side-chain cleavage enzyme, and steroidogenic factor 1,[166] while only having small negative effects on LH and follicle stimulating hormone pulse amplitude.[167] Men who are considered obese (i.e. with high serum concentrations of leptin) have been shown to have low concentrations of total and free testosterone (i.e. 22–45%), SHBG, and SHBG binding capacity with the magnitude directly related to the level of body fat.[167,168] Thus, high levels of leptin may be associated with reduced androgen production. The impact of reduced steroidogenesis on subsequent adaptations to resistance training requires further study but does appear to be a potential limiting factor.

### 7.5 Peptide F

Peptide F is a proenkephalin fragment secreted from chromaffin cells of the adrenal medulla along with epinephrine.[18] Although the physiological function of peptide is not entirely known, it has been shown that it improves the B cell helper function of T lymphocytes.[169] Exercise has been shown to increase concentrations of peptide F.[170] Little is known concerning resistance training. High-intensity resistance exercise-induced overtraining does not change circulating peptide F concentrations at rest or after exercise;[171] however, acute heavy resistance exercise has been shown to depress peptide F 4 hours into the recovery period.[142] Interestingly, changes in the ratio of peptide F to epinephrine were observed suggesting that overtraining may alter the secretory patterns of chromaffin cells.[171]

### 7.6 Estrogens

Estrogens are steroids synthesised and secreted primarily by the ovaries (and adrenals to a lesser extent) in women, but are also produced from aromatisation of testicular and adrenal androgens in men. Estrogens perform many functions in the human body. In particular, estrogens have been shown to reduce bone resorption[172] and muscle damage,[173] which may have important ramifications for musculoskeletal adaptations to resistance training. Of the estrogens, estradiol is the most active and has been studied most often during resistance training. Very little is known concerning the acute responses and chronic adaptations of estradiol synthesis and secretion in response to resistance training. Critical to examining estradiol concentrations in women, is proper delineation of the menstrual cycle. Studies that have examined muscle strength, endurance and power performance in women during various phases of the menstrual cycle (e.g. menstruation, follicular, ovulation/mid-cycle or luteal) have shown conflicting results where performance enhancement during menstruation[174] and ovulation[175] were reported; however, several studies have shown no differences.[176-178] Thus, a lack of significant difference indicates that acute muscular performance is not affected by elevated concentrations of estrogens. In women, acute elevations following resistance exercise have been reported,[144,179] especially when women are in a hypocaloric state.[144] Chronically, Häkkinen et al.[50] reported no significant changes in resting estradiol concentrations following 16 weeks of power training. Thus, the role of estrogens in mediating the acute and chronic effects of resistance training is unclear at the present time and warrants further investigation.

## 8. Overtraining and Detraining

Overtraining is defined as any increase in training volume and/or intensity resulting in long-term

performance decrements.[18] In contrast, overreaching is a short-term increase in volume and/or intensity, which is often planned in resistance training programmes thought to increase performance through a 'rebound effect' when used correctly.[121,141] Repeated overreaching may lead to overtraining and subsequent performance decrements in addition to neuroendocrine changes. One and two weeks of overreaching have been shown to reduce resting concentrations of testosterone and IGF-1.[43,59] These decreases were significantly correlated to strength decrements.[59] We have reported that 4 weeks of overreaching with and without amino acid supplementation did not alter resting concentrations of IGF-1 and cortisol (unpublished observation), although a significant elevation in cortisol was observed in a group supplementing with creatine after 1 week of high-volume overreaching.[141] However, the free androgen index (total testosterone/SHBG) was reduced and this effect was more notable in the placebo group (unpublished observation). In addition, short-term overreaching may not result in elevated resting cortisol and may augment the acute testosterone response to resistance exercise when the individual has at least 1 year of weightlifting training and previous exposure to the overreaching stimulus.[121] Thus, overreaching may either not change or reduce the resting concentrations of some anabolic hormones, not change or increase cortisol concentrations, and the magnitude may depend on the volume/intensity of the training stimulus as well as nutritional supplementation.

Overtraining, resulting from a chronic large increase in volume, has been shown to result in elevated cortisol and reductions in resting LH, total and free testosterone concentrations with the free pool of testosterone most sensitive to the overtraining stimuli.[18,71] In addition, the exercise-induced elevation in total testosterone is attenuated during volume-related overtraining.[23] Intensity-related overtraining does not appear to alter resting concentrations of hormones thus demonstrating a differential response in comparison to large increases in training volume.[18] Fry et al.[171] reported no changes in circulating total or free testosterone, cortisol, GH, or peptide F concentrations during high-intensity overtraining (e.g. ten 1RM lifts of the squat everyday for 2 weeks). In a similar study, Fry et al.[180] reported no change in resting concentrations of epinephrine or norepinephrine. However, the acute catecholamine response to resistance exercise was greater in overtrained men. Therefore, it appears that intensity-related overtraining does not alter resting hormonal concentrations significantly with a corresponding decrease in performance, whereas volume-related overtraining does appear to significantly alter circulating hormone concentrations.

Detraining is the cessation of resistance training or significant reduction of training volume, intensity, or frequency resulting in reduced performance (e.g. reduced muscle strength, power, hypertrophy, local muscle endurance).[2] Alterations in hormonal activity may occur, in addition to changes in neural and muscle function. It appears that the duration of the detraining period is important for the magnitude of change as well as the training status of the individual. Hortobagyi et al.[181] reported significant elevations in resting concentrations of GH, testosterone, and the T/C ratio with a significant reduction in cortisol following 2 weeks of detraining in highly trained power lifters and football players. It was hypothesised that this elevation in anabolic hormone concentrations was related to the body's ability to combat the catabolic processes associated with detraining and suggested that short-term detraining may represent an augmented stimulus for tissue remodelling and repair. However, these increases have only been shown during short-term detraining. We have recently reported no significant changes in testosterone, GH, LH, SHBG, cortisol or ACTH following 6 weeks of detraining in recreationally trained men.[182] No changes have been observed for cortisol, SHBG and LH following 8 weeks of detraining in women.[50] Detraining periods >8 weeks have shown significant reductions in the T/C ratio, which correlated highly to strength decrements[48,56] and elevations in $T_4$.[150] These hormonal changes coincide with periods of muscle atrophy[181] and indicate a hormonal role in muscle size and strength reductions observed during periods of detraining.

## 9. Circadian Patterns

Several hormones are secreted in various pulses throughout the day in a circadian pattern. Salivary testosterone secretion has been shown to be secreted in a circadian manner with the greatest elevations

observed early in the morning with less throughout the rest of the waking day.[183] Because of circadian patterns, it is essential that researchers examining resistance exercise measure hormonal concentrations at the same time of day or use control, non-exercised subjects for multiple sampling periods throughout the day for circadian control. Considering that resistance exercise stimulates acute hormonal elevations, it is of interest to examine whether or not resistance exercise alters circadian patterns. Kraemer et al.[183] reported that resistance exercise did not affect circadian patterns of testosterone secretion over a 16-hour waking period in resistance-trained men. It has been shown that afternoon resistance exercise-induced elevations in testosterone are sometimes greater than that observed in the morning,[71] thus reflective of diurnal variations. It appears that regulatory mechanisms are quickly re-engaged after a resistance exercise workout such that homeostasis is maintained within 1 hour post-exercise.

The nocturnal hormonal response following resistance exercise may differ. McMurray et al.[184] had trained individuals perform three sets of six exercises to exhaustion at 1900–2000 hours and sampled blood prior to, and at 20-minute intervals following from 2100 to 0700 hours. Resistance exercise did not alter nocturnal patterns of GH and cortisol secretion. However, testosterone secretion was greater between 0500 and 0700 hours in the resistance exercise group and nocturnal secretion of $T_4$ decreased. However, Nindl et al.[185] examined GH pulsatility at 10-minute intervals (i.e. shorter intervals than McMurray et al.[184]) following high-volume resistance exercise and reported that a differential pattern during sleep such that GH was lower the first half of sleep and higher during the last half of sleep. In addition, total and free IGF-1 did not differ overnight. However, IGFBP-2 was elevated, thereby suggesting that heavy resistance exercise may alter the partitioning of IGF-1 to its binding proteins overnight.[136] The circulating IGF-1 response beyond the overnight period remains to be elucidated but would be of interest to study due to the late pulsatile bursts of GH observed the day of heavy resistance exercise. Thus, nocturnal changes in these hormones may have implications for tissue anabolism.

## 10. Concurrent Strength and Endurance Training

Several studies have indicated that there is an incompatibility between simultaneous high-intensity strength and endurance training such that maximal strength and power appear to be limited.[186,187] In addition, the neuroendocrine system may or may not be altered. Bell et al.[187] reported no changes in resting concentrations of testosterone, GH, or SHBG following 12 weeks of combined strength and endurance training. However, greater urinary cortisol was observed in women.[187] Kraemer et al.[186] had subjects perform a total-body, high-volume resistance training programme 4 days per week along with 4 days per week of endurance training for 12 weeks and reported a substantial increase in exercise-induced cortisol concentrations. These data indicate that the incompatibility may also be the result of overtraining which in itself may produce a catabolic hormonal environment.

## 11. Conclusion

Resistance exercise elicits a milieu of hormonal responses critical to acute muscular force and power production as well as subsequent tissue growth and remodelling. In general, the acute response is dependent upon the stimulus (e.g. intensity, volume, muscle mass involvement, rest intervals, frequency) and may be the most critical element to tissue remodelling. Long-term adaptations in neuroendocrine function appear minimal but may be related to the current intensity/volume of the training stimulus.

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