

Hormones as Stimuli for Muscle Growth

Olga Rutherford

CIB, Biomedical Sciences, Imperial College School of Medicine, South Kensington, London, UK

Abstract

Skeletal muscle is affected by many hormones and growth factors, both catabolic and anabolic in nature. Our understanding of the synthesis, release, transport and tissue sensitivities of these hormones has increased greatly in recent years. Despite this knowledge we still do not know the link between hormonal/growth factor release, training and muscle hypertrophy.

The hormonal response to high resistance exercise involves an acute increase in cortisol, GH, testosterone, and catecholamines and a decrease or no change in insulin and thyroid status. In the longer term there may also be changes in muscle sensitivity.

Much attention has focused on the anabolic effects of androgens. The evidence that exogenous derivatives of testosterone are anabolic in eugonadal men is still controversial. In supraphysiological doses, and combined with training, there is some evidence for their anabolic effects. This needs to be weighed against their potentially harmful side-effects. Studies on GH replacement in GH-deficiency strongly indicated an important role for GH in the maintenance of lean tissue mass. Despite its role in clinical situations, the controlled trials have failed to demonstrate a clear anabolic role for GH in either the healthy younger or older person.

A likely candidate for causing muscle hypertrophy as a result of resistance training, is IGF-1. This would appear to be independent of GH release and act in an autocrine/paracrine fashion. A splice variant of IGF-1 has been identified and is expressed locally in muscle during repair and overload. This mechano growth factor (MGF) may be an important factor linking a mechanical stimulus and growth.

More recently there has been renewed interest in searching for an "anabolic hormone" due to the increasing numbers of elderly people within populations and the associated frailty common in this group. Reduced physical activity levels and a shifting anabolic/catabolic ratio all contribute to this problem.

Key words: anabolic hormones, growth factors, muscle hypertrophy, steroids.

Basic Appl. Myol. 9 (6): 285-288, 1999

Mechanical overload of skeletal muscle leads to fibre and muscle hypertrophy. Such changes can result from strength training regimes in humans or stretch and compensatory overload models in animals. As yet we do not know the hypertrophic link between the overload and muscle growth. Skeletal muscle is affected by many hormones and growth factors which can have both anabolic and catabolic effects. There has been a long-term interest in identifying which of these is involved in the growth of muscle in the adult. Many hormones are released in response to an exercise stimulus (see table). The difficulty has been that many of these are released systemically, yet the growth response is isolated to the

muscle/s undergoing the overload. Recently attention has shifted away from the endocrine hormones and has concentrated on growth factors which are synthesised *in situ*.

Studying the effects of strength training on the endocrine system is complicated by a variety of factors related to both the exercise challenge itself and the accurate measurements of hormones. Exercise variables include the amount of muscle mass involved, the loads lifted, the number of sets and repetitions, and the length of rest periods between sets [9].

The measurement of hormonal changes is further complicated by the manner in which they are released,

Hormones as stimuli for muscle growth

Table 1. Hormonal changes and resistance training.

Increase	Decrease / Stay same
GH/IGF-1	Insulin
Testosterone	T3/T4
Cortisol	
Catecholamines	
β -Endorphins	

transported and interact with the target tissue. Many hormones are released in a pulsatile manner with superimposed diurnal, monthly, and seasonal rhythms. They often exist in different molecular weight fractions and are frequently transported in a bound form; both factors affecting the bioactivity. The metabolism and clearance of the hormone by different tissues is often complex and the interaction with the target tissue is affected by such factors as receptor density and sensitivity. For these, and other reasons, a single blood sample may not reflect the true physiological significance of the underlying hormonal change. As we gain greater knowledge of these processes and the assays improve, there should be considerable developments in our understanding.

Anabolic Steroids

The first hormones to receive considerable attention from scientists, the pharmaceutical industry and athletes, were the anabolic steroids, most notably derivatives of testosterone. These substances have been widely abused by athletes and bodybuilders because of the perception that they increase muscle mass and strength. The evidence that this is the case remains somewhat controversial and there are considerable methodological problems with many of the studies. Some are not randomised, some include exercise and others do not, and protein and energy intake are rarely controlled. Testosterone replacement can increase fat-free mass in castrated animals and hypogonadal men. A review of the better studies in 1991 concluded that "Anabolic steroids may slightly enhance muscle strength in previously trained athletes.....results for the low steroid dosages studied in the published reports cannot be generalised to steroid-using athletes taking megadose regimes" [4]. A more recent report, studied the effects of supraphysiological doses of testosterone on muscle size and strength in normal men with previous weight-lifting experience who were on standardised diets [1]. The men were randomly assigned to one of four groups: placebo with no exercise, placebo with exercise, testosterone with no exercise and testosterone with exercise. The exercise was a supervised strength training regime. They found that testosterone, especially when combined with exercise, increased fat-free mass, muscle size and strength to a greater degree than either the testosterone

or exercise intervention alone. The authors did however stress that these doses, if taken for longer periods of time, could have serious side effects.

Payne [12] examined the efficacy of anabolic steroids for improving performance by plotting the world records from the 1960's in events where drug taking is thought to be most common. It was around this time that steroids were introduced to the athletic world. If they were having a significant effect, a clear improvement in performances should be observed. Examination of the data reveals no clear upturn in the records over this period, suggesting that any effects of the steroids were small.

It is often noted by observers, and the athletes themselves, that those individuals abusing such drugs have a much greater resistance to fatigue during training. This led Hervey [6] to propose a non-anabolic mechanism of action for these steroids in which the major effect is for testosterone to block the catabolic effect of cortisol on muscle, but raise the systemic levels which helps counteract fatigue. In this way the intensity of training is enhanced. They demonstrated that blood levels of cortisol did increase following steroid administration. This hypothesis could explain why the testosterone effect is only observed when coupled with strength training.

Catecholamines

Catecholamines and their derivatives can have short-term effects on muscle force production. In animal studies, B-adrenergic agonists have potent anabolic effects on some muscle groups and particularly effect the Type II fibre population. The effect is rapid but not sustained with continued administration. Prolonged administration appears to result in a down-regulation of receptor density resulting in a cessation of the anabolic effect. There are few equivalent human trials and the potential side-effects of these compounds would strongly argue against their use [8].

Growth Hormone

More recently, attention has focused on role of the somatotrophic axis (growth hormone and IGF-1) on muscle growth. It has been shown that hypopituitary patients, discontinuing growth hormone (GH) treatment after puberty, lose muscle mass and strength [15]. GH replacement in the hypopituitary adult can cause significant improvements in muscle mass, muscle strength and endurance capacity in many patients [2, 14]. GH is released following a bout of strength training, if the intensity is high enough. In one strength training study, the increase in fibre area was significantly related to the increase in GH levels which occurred as a result of the exercise [11]. A number of trials have investigated the use of GH supplementation, with and without exercise, in healthy adults, but with little, or no, effect on muscle [18]. Recombinant technology has meant the human GH

is fairly accessible and as a result this is now a widely abused drug which is difficult, if not impossible, to detect. As with many hormones, supplementation at high doses could have quite serious side-effects including hyperglycaemia, water retention, acromegaly and tumour stimulation.

IGF-1

Animal work has clearly demonstrated that IGF-1, the anabolic mediator of GH, can be synthesised in muscle, independent of GH release [3]. This occurs following stretch, damage and mechanical overload [17] and appears closely linked to protein synthesis and repair. A splice variant of IGF-1 has also been identified in human and animal muscle and has been termed muscle growth factor (MGF) [5]. It is thought that this acts in an autocrine/paracrine fashion to cause muscle hypertrophy in response to a mechanical stimulus. MGF is currently the most likely "hormone" to be involved in muscle growth in response to strength training. It could provide the link between exercise of an isolated muscle and growth of that muscle alone. It has also been demonstrated that IGF-1 receptors are up-regulated as a result of training [16]. Recombinant IGF-1 is now available but there are also considerable health risks associated with its administration including hypoglycaemia and tumour growth. Despite this, it is known to be abused in groups such as body-builders.

Ageing

Ageing is associated with an atrophy of the musculoskeletal system. There are a number of hormonal changes accompanying ageing which may, in part, be responsible for this change [10]. Two of the clinically most important changes in endocrine activity with ageing are an increase in insulin resistance and thyroid dysfunction. There are four other endocrine stages associated with ageing which have often been considered more physiological and therefore often untreated [10]. These stages can be classified as:

- Menopause: the loss of ovarian function and accompanying decline in the female sex steroids, particularly oestradiol;
- Adrenopause: the decline in output of the adrenal androgens, particularly dehydroepiandrosterone and its sulphate;
- Somatopause: the fall in growth hormone (GH) and the insulin-like growth factors (IGF's);
- Andropause: the decline in total and free testosterone levels in men.

Hormonal changes in themselves are not the simple explanation for all of the changes associated with ageing. However, together with reduced physical activity, they may play an important role in the frailty of the older person.

One particularly striking alteration is the decrease in GH/IGF-1 release [7]. Trials of GH supplementation have been carried out in older people. Yarasheski et al [19] examined whether GH administration could augment the effects of 16 weeks of strength training on body composition in 64-75 year-old men. They found that the changes in lean tissue mass and muscle strength were similar, regardless of GH administration during the training period. They discussed the possibility that the GH may have to be given in a manner more closely resembling the normal physiological pulsatility. Alternatively GH administration may not be able to further enhance muscle growth above that stimulated by strength training alone.

Other studies have suggested a more positive effect [13]. Although the results are contradictory, the consensus appears to suggest that in the relatively healthy older person, any marginal benefits outweigh the costs and risks [18]. This may not be the same for a particularly frail or "at risk" group, such as people recovering from a hip fracture or prolonged periods of immobilisation.

Conclusions

There are a number of hormones which are released during strength training exercise and have the potential for causing muscle growth. Currently the muscle variant of IGF-1 is considered an important growth factor and is synthesised during mechanical loading and muscle damage. Many of these hormones are abused by athletes and there is concern about the long-term (and in some cases short term) health implications of the high doses used. Replacement therapy is being considered for frail elderly groups in which muscle atrophy and weakness is a considerable problem.

Address correspondence to:

CIB, Biomedical Sciences, Imperial College School of Medicine, South Kensington, London SW7 2AZ, UK, phone 020 7594 3170, fax 020 7594 3169, Email .

References

- [1] Bhasin S, Storer TW, Berman N, et al: The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *NEJM* 1996; 335: 1-7.
- [2] Cuneo RC, Salomon F, Wiles CM, et al: Growth hormone treatment in growth hormone-deficient adults. 1. Effects on muscle mass and strength. *J Appl Physiol* 1991; 70: 688-694.
- [3] DeVol DL, Rotwein P, Levis Sadow J, et al. Activation of insulin-like growth factor gene expression during work-induced skeletal muscle growth. *Am J Physiol* 1990; 259: E89-95.

Hormones as stimuli for muscle growth

- [4]Elashoff JD, Jacknow AD, Shain SG, et al: Effects of anabolic-androgenic steroids on muscular strength. *Ann Int Med* 1991; 115: 387-393.
- [5]Goldspink G: Changes in muscle mass and phenotype and the expression of autocrine and systemic growth factors by muscle in response to stretch and overload. *J Anat* 1999; 194: 323-334.
- [6]Hervey GR: What are the effects of anabolic steroids? in Davies B, Thomas G (eds): *Science and sporting performance*. Clarendon Press, Oxford, 1992, pp 120-136.
- [7]Ho KY, Evans WS, Blizzard RM, et al: Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. *J Clin Endocrinol Metab* 1987; 64: 51-58.
- [8]Kim YS, Sainz RD: B-adrenergic agonists and hypertrophy of skeletal muscles. *Life Sci* 1992; 50: 397-407.
- [9]Kraemer WJ: Endocrine responses and adaptations to strength training, in PV Komi (ed): *Strength and power in sport*. Publ. Blackwell Scientific, 1992, pp 291-304.
- [10]Lamberts SW, van den Beld AW, van der Lely A: The endocrinology of aging. *Science* 1997; 278: 419-424.
- [11]McCall GE, Byrnes WC, Fleck SJ, et al: Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. *Can J Appl Physiol* 1999; 24: 96-107.
- [12]Payne AH: Anabolic steroids in athletics. *Br J Sports Med* 1975; 9: 83-88.
- [13]Rudman D, Feller AG, Nagraj HS, et al: Effects of human growth hormone in men over 60 years old. *NEJM* 1990; 323: 1-6.
- [14]Rutherford OM, Beshyah SA, Johnston DG: Quadriceps strength before and after growth hormone replacement in hypopituitary adults: relationship to changes in lean body mass and IGF-1. *Endocrinol Metab* 1994; 1: 41-47.
- [15]Rutherford OM, Jones DA, Round JM, et al: Changes in skeletal muscle and body composition after discontinuation of growth hormone treatment in growth hormone deficient young adults. *Clin Endocrinol* 1991; 34: 469-475.
- [16]Willis PE, Chadan SG, Baracos V, et al: Restoration of insulin-like growth factor 1 action in skeletal muscle of old mice. *Am J Physiol* 1998; 275: E525-530.
- [17]Yang S, Alnaqeeb M, Simpson H, et al: Changes in fibre type, muscle mass and IGF-1 gene expression in rabbit skeletal muscle subjected to stretch. *J Anat* 1997; 190: 613-622.
- [18]Yarasheski KE: Growth hormone effects on metabolism, body composition, muscle mass, and strength. *Med Sci Sports Rev* 1994; 22: 285-312.
- [19]Yarasheski KE, Campbell JA, Kohrt WM: Effect of resistance exercise and growth hormone on bone density in older men. *Clin Endo* 1997; 47: 223-229.