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Review Article

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Making muscles "stronger": Exercise, nutrition, drugs

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Abstract

As described in this review, maximal muscle strength is strongly influenced by resistive-types of exercise, which induce adaptive changes in both neuromuscular function and muscle morphology. Further, timed intake of protein in conjunction with resistance training elicit[5] greater strength and muscle size gains than resistance training alone. Creatine supplementation amplifies the hypertrophic response to resistance training, although some individuals may not respond positively. Locally produced muscle growth factors are upregulated during creatine supplementation, which contributes to increase the responsiveness of muscle cells to intensive training stimuli. Usage of anabolic steroids boosts muscle hypertrophy beyond inherent genetical limits, not only by increasing the DNA transcription rate for myofibrillar proteins but also by increasing the nucleus-to-cytoplasm ratio due to accelerated activation of myogenic satellite cells. However, severe tissue damaging effects exist with anabolic steroids, some of which are irreversible.

Keywords: Resistance Training, Neural Adaptation, Muscle Adaptation, Ergogenic Supplementation

Introduction

Maximum strength capacity of skeletal muscle is influenced by a multitude of factors, many of which interact in a synergistic manner. The most influential factor is resistance training, which effectively increases maximal isometric and dynamic muscle contraction strength. The training-induced increase in maximal contractile muscle strength is brought about by changes in both neural system function and muscle morphology as consistently demonstrated in young and elderly individuals (Figure 1). Accelerated muscle strength gains are observed when resistance exercise is accompanied by timed intake of nutritional or ergogenic supplements (i.e. protein, creatine). Further, various banned substances and drugs may boost the build-up of muscle mass, leading to amplified gains in maximal muscle strength with training.

The author has no conflict of interest.

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Adaptive changes in maximal muscle strength, power and rate of force development

Resistance training results in increased maximal isometric and dynamic muscle strength[1-5], increased muscle power[6], elevated contractile Rate of Force Development (RFD)[2,7,8], and increased eccentric contraction strength[1,4,9]. In addition, neural drive to the muscle fibers is increased during maximal muscle contraction[1-3,7-9] due to neural adaptation at both spinal and supraspinal levels[3], while adaptive changes in muscle morphology and structure also contribute to the increase in maximal muscle strength (discussed below).

Adaptive changes in neural function

Electromyography amplitude

Concurrent increases in maximum contraction muscle strength and electromyography (EMG) amplitude have been observed during maximal isometric, concentric and eccentric muscle contraction[5] in response to resistance training, which indicate an elevated neural drive to the muscle fibres[1,2,7-15] (Figure 1). Increases in EMG have also been observed in highly trained strength athletes during periodized training regimes[16] indicating that neural plasticity also exists in subjects with highly optimized neural function.

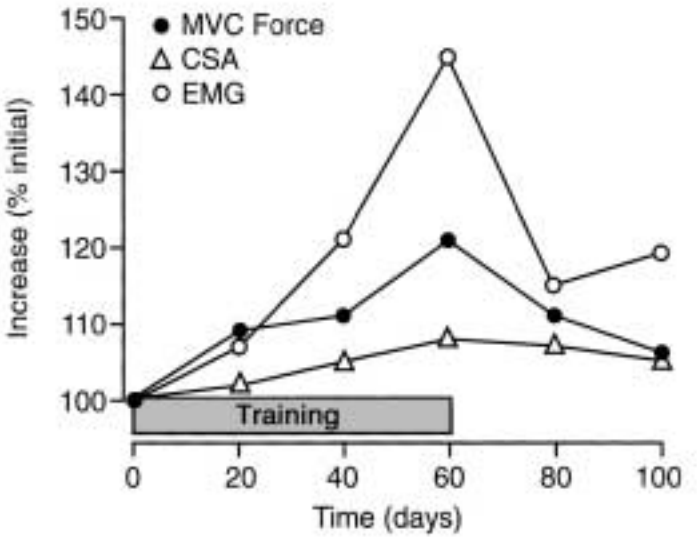

Figure 1. Changes in maximal isometric quadriceps contraction strength (MVC), anatomical muscle cross-sectional area (CSA) and neuromuscular activation (EMG) in response to resistance training and detraining. Data adapted from Narici et al.[13] (graph adapted from RM Enoka: Neuromechanics of human movement 2002; Human Kinetics, Champaign, IL).

The amplitude of the compound surface EMG signal is substantially affected by the degree of out-of-phase summation of the single motor unit action potentials (MUAPs)[17,18]. Consequently, the increase in surface EMG amplitude observed with resistance training reflects changes not only in motor unit (MU) recruitment and/or MU firing frequency but also in MUAP synchronization.

Rapid muscle contraction: rate of force development

The rate of muscle force rise (i.e. contractile Rate of Force development: RFD= ΔForce/Δtime) in the initial 0-200 ms of contraction sets a limit for the maximal force and power that can be generated during rapid, forceful movements[2]. Notably, a high RFD is equally vital to the explosive-type athlete as to the elderly individual who needs to control postural balance.

Parallel increases in RFD, EMG amplitude and rate of EMG rise have been observed in the initial 0-500 ms of muscle contraction following resistance training[2,7,8,10,11,14,15] (Figure 2). The specific neural adaptation mechanisms appear to include increases in maximal motoneuron firing frequency and an elevated incidence of doublet discharge firing[15]. In addition, resistance training induces[5] increases in muscle fiber area and fiber pennation angle[19] that also contribute to the increase in RFD.

While the sedentary elderly show reduced maximal MU firing frequency compared to young subjects[20-23], this difference appears to disappear in response to resistance training[22], which is accompanied by an increased maximal MU firing frequency both in young[15,22,23] and elderly[22,23] subjects. This adaptation likely contributes to the increase in RFD observed following resistance training in elderly subjects[7,8].

Maximal eccentric muscle contraction

During maximal voluntary eccentric contraction, the EMG recorded in the quadriceps femoris muscle is markedly reduced compared to that of maximal concentric contraction[1,24,25] suggesting that a neural regulatory pathway exists during maximal eccentric muscle contraction that limits MU recruitment and/or MU discharge rate. Notably, the inhibition in motoneuron activation during maximal eccentric contraction is removed by resistance training[1], explaining the marked increase in maximal eccentric muscle strength typically seen with heavy-resistance training[1,4,9,12].

The specific neural pathways responsible for the suppression in muscle activation during maximal eccentric contraction remain unidentified. During maximal voluntary muscle contraction, efferent motoneuronal output is influenced by (i) central descending pathways, (ii) afferent inflow from group Ib Golgi organ afferents, (iii) group Ia and II muscle spindle afferents, (iv) group III muscle afferents and (v) recurrent Renshaw inhibition. All of these pathways may exhibit adaptive plasticity with training[26].

It has been suggested that the marked increase in eccentric muscle strength seen with resistance training is due to downregulated activity in spinal inhibitory Ib interneurons activated by Golgi organ Ib afferents[27]. Furthermore, the finding of reduced H-reflex excitability during passive muscle lengthening compared to shortening[28] suggests that substantial presynaptic inhibition of Ia afferents may be present during eccentric muscle contraction. It is possible, therefore, that pre-synaptic inhibition is downregulated with resistance

training, hence increasing Ia afferent excitatory inflow to spinal motoneurons during eccentric muscle contraction, in turn increasing maximum eccentric force generation.

Evoked spinal motoneuron responses

When measured during maximal muscle contraction (i.e. at MVC) evoked motoneuron responses can be utilized to quantify the change in spinal motoneuronal output, motoneuron excitability and/or pre-synaptic inhibition with training[27]. Elevated H-reflex and V-wave responses have been observed during maximal muscle contraction following resistance training[3,29], reflecting enhanced neural drive in descending cortico-spinal pathways, and elevated excitability and/or reduced pre-synaptic or post-synaptic inhibition of spinal motoneurons (Figure 3). In contrast, when recorded during resting conditions the H-reflex response appears to remain unchanged with resistance training[3,30] which suggests that the adaptive mechanisms not so much involve changes in neuro-morphology (i.e. changes in size or number of synapses) but rather comprise dynamic adjustments of the spinal circuitry by means of pre-synaptic gating and/or post-synaptic facilitation or inhibition via descending pathways.

Adaptive changes in muscle morphology, fiber type and architecture

Anatomical muscle CSA and volume

Anatomical muscle cross-sectional area (CSA) measured by MRI, CT or ultrasonograhy imaging techniques have been reported to increase following resistance training both in young[9,13,19] and elderly subjects[31-34] (Figure 4). Consequently, total muscle volume is found to increase in response to resistance training[13,19] (Figure 4).

Single muscle fiber area

Resistance training is effective in producing hypertrophy of type I and II muscle fibers of both young and aging subjects[8,33,35,36] although selective or more marked hypertrophy typically is seen for the type II fibers[5,19,31,37,38]. The accelerated hypertrophy of the type II muscle fibers represents a beneficial type of adaptation both for the power athlete and the elderly individual since the type II fibers have greater contractile RFD[39] and elevated power production[40] compared to type I fibers. The relative increase in single muscle fiber CSA typically exceeds the increase in whole muscle CSA (Figure 4), since muscle architecture may change in a manner that allows physiological CSA to increase more than anatomical CSA (discussed in detailw below). The result is the increase in maximal contractile muscle force exceeds the increase in whole muscle CSA[19].

Muscle fiber type composition

While resistance training or detraining induce significant shifts in the fast myosin isoform composition of skeletal muscle, i.e. MHC IIA→IX or MHC IIX←IIA, respectively[5,37,38,41-44] no or only minor shifts seem to occur between the slow (MHC I) vs. fast (MHC II) myosin isoforms[39,45,46] (Figure 5). Notably, recent data suggest that detraining from long-term resistance training can evoke a boosting in the proportion of MHC IIX

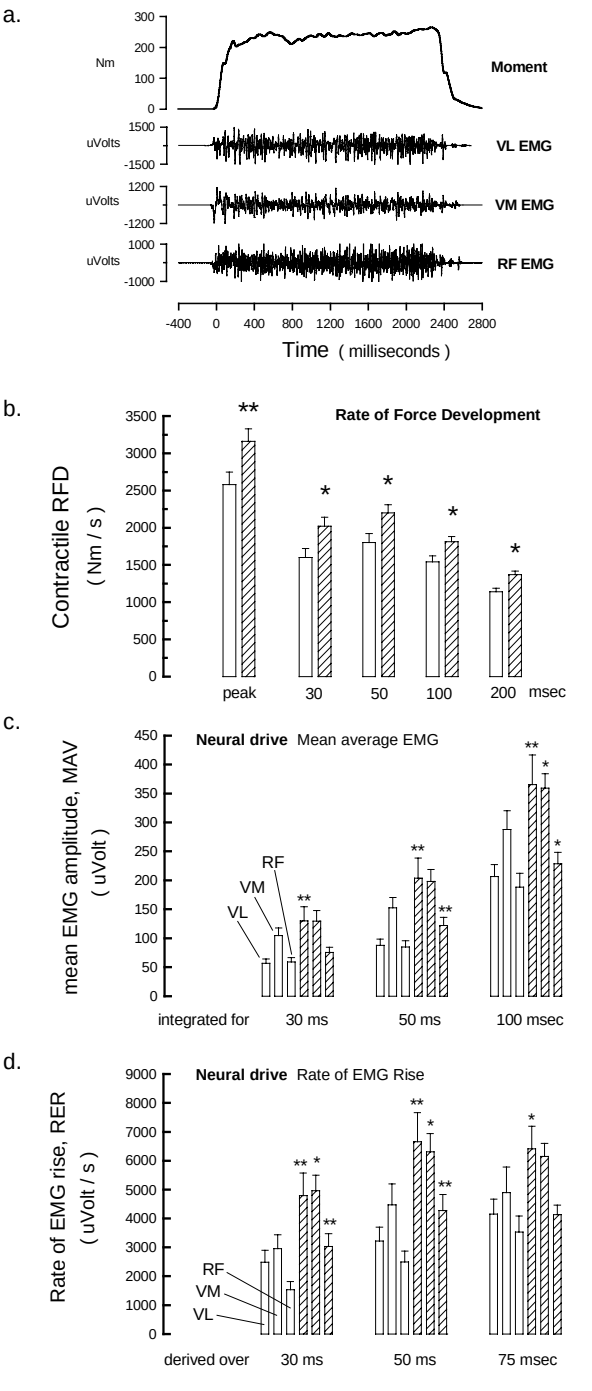

Figure 2. (a) Knee extensor moment and raw EMG signals recorded during maximal isometric quadriceps contraction. Rate of force development (RFD), (b) mean average EMG voltage, (c) and rate of EMG rise (RER), (d) before and after (hatched bars) 14 weeks of resistance training. Data adapted from Aagaard et al.[2].

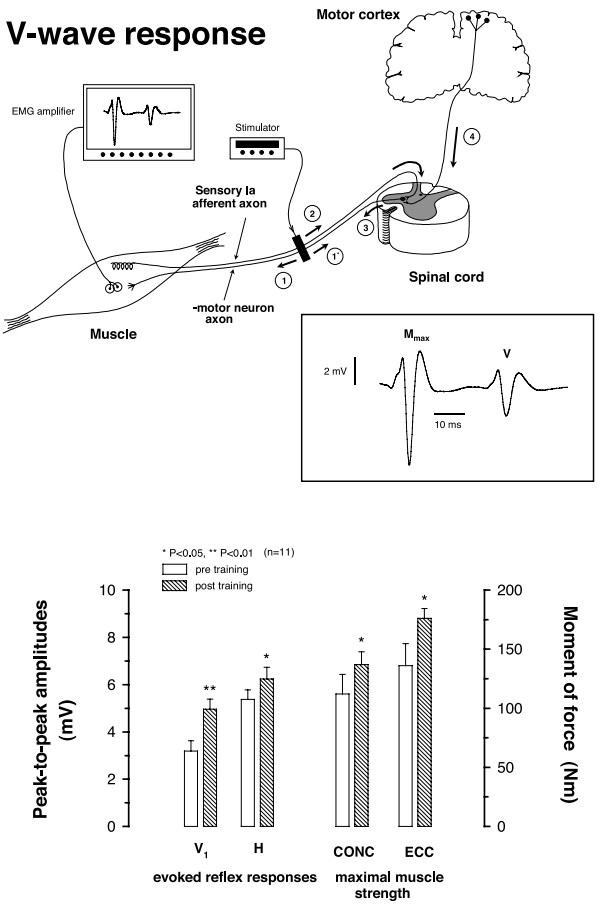

Figure 3. Evoked spinal motoneuron responses recorded in the human soleus muscle. H-reflex and V-wave responses (3) are elicited by electrical stimulation of Ia afferent axons in the peripheral nerve (1). All H-reflex and V-wave responses were recorded during maximal muscle contraction. Increased H-reflex and V-wave amplitudes were observed along with increases in maximal concentric and eccentric plantarflexor strength following 14 weeks of heavy-resistance strength training, indicating neural adaptative changes at spinal and/or supraspinal levels. Data adapted from Aagaard et al.[3].

myosin, which may transiently increase 1-2 fold[37] (Figure 5).

Long-term spinal cord injured subjects demonstrate an unusually high proportion of MHC IIA and IIX isoforms (>99%) compared to age-matched healthy subjects (~50%) suggesting that the MHC IIX isoform represents a default gene expression[43]. Interestingly, a dramatic decrease in MHC IIX was observed in the SCI subjects along with a corresponding increase in type I MHC following long-term cycle training (6 months) using functional electrical stimulation[43].

Muscle architecture

In pennate skeletal muscle, physiological fiber CSA and thereby maximal contractile muscle force progressively increases with increase in muscle fiber pennation angle. Recent studies have shown that resistance training can induce increases in fiber pennation angle both in young[19,47] (Figure 5) and elderly subjects[48], which *per se* contributes to the training s increase in maximal muscle force. Importantly, the increase in fiber pennation angle theoretically allows single muscle fiber CSA (i.e. physiological CSA) to increase disproportionally more than whole-muscle CSA (i.e. anatomical CSA)[19]. In support of this notion, single muscle fiber CSA has been found to increase more than whole-muscle CSA following resistance training[8,19,31,33] (Figure 4). Consequently, data on muscle CSA or volume obtained by MRI or CT may not readily replace the information obtained by measurements of single muscle fiber area by biopsy sampling, or vice versa.

Adaptive changes in gene expression

Gene transcription factors

Muscle resistance exercise gives rise to acute changes in gene expression that are accelerated by activation of various gene encoding transcription factors, i.e. MyoD, myogenin, Myf-5, MRF4[49]. Recent data indicate that MyoD and myogenin produced by myonuclei, satellite cells and other myogenic cells play an essential role in the exercise-induced hypertrophy of skeletal muscle[50]. Furthermore, the hypertrophic response to resistance training is modulated by activation of intracellular kinases that control the rate of RNA transcription/translation and thereby regulates muscle protein synthesis rate. For example, a strong positive relationship between activation of the $p70^{S6k}$ kinase and the long-term increase in muscle mass with resistance training was recently observed in the rat[51].

Post-transcriptional mechanisms

Increased mRNA translation, rather than increased mRNA content, may play a key role in the initiation of the hypertrophic response to resistance training[52]. Thus, data obtained in humans showed no increase in mRNA content along with a rise in translational efficiency following acute bouts of resistance exercise, indicating an increased synthesis rate per unit RNA[53].

Adaptive changes in local growth factors

IGF-1 and satellite cell activation

Animal experiments have indicated an increased autocrine production of insulin-like growth factor IGF-1 by the muscle itself in response to chronic muscle loading[54,55]. While circulating IGF-1 and GH do not seem important for muscle hypertrophy or to maintain muscle mass during adulthood[56], locally produced IGF-1 may play an important role in the hypertrophic process both in young and aging individuals[57]. Locally produced IGF-1 isoforms (IGF-1Ea and IGF-1Ec (MGF)) stimulate the proliferation and differentiation of myogenic satellite cells into myoblasts, which subsequently fuse with myofibers and provide new nuclei to the

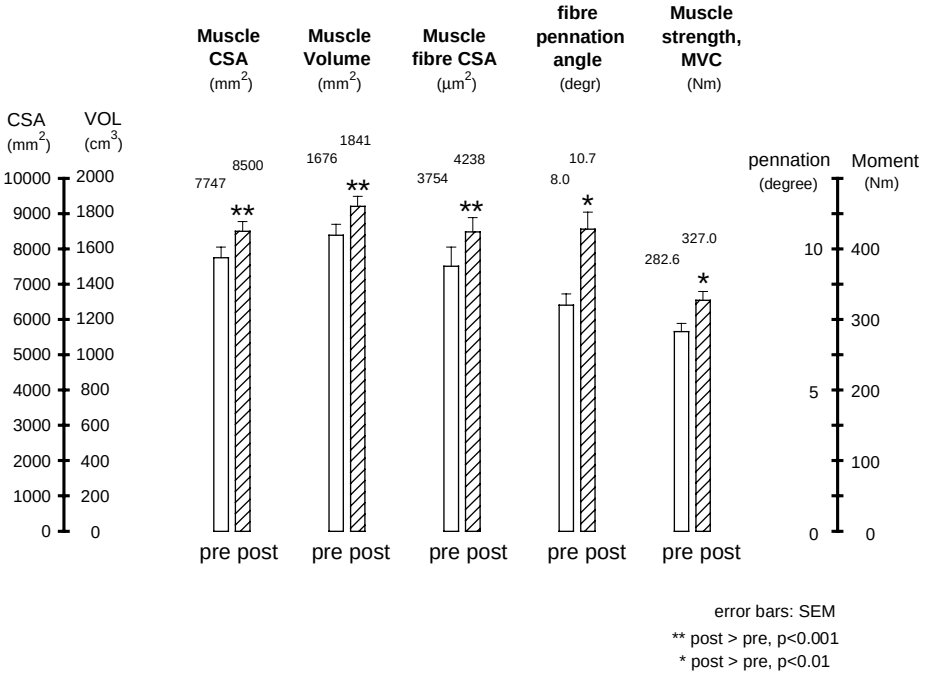

Figure 4. Anatomical muscle CSA and volume obtained by MRI, single muscle fiber CSA obtained by muscle biopsy sampling, muscle fiber pennation angle obtained by ultrasonography and maximal isometric muscle contraction strength (MVC) pre- and post- resistance training. Notice the greater relative increase in muscle fiber CSA and MVC (~15-17%) compared to anatomical muscle CSA and volume (~10%), which was possible due to the increase in muscle fiber pennation angle[19]. Data adapted from Aagaard et al.[19].

muscle cell[56-59]. It has been proposed that this process helps to maintain the nuclei (i.e. DNA) to cell volume ratio in the hypertrophying muscle fibers[56,92] to expand the range of cellular growth.

IGF-1 and eccentric resistance exercise

Locally produced IGF-I is found to increase with no increase in circulating IGF-1 following eccentric resistance training, while more variable and statistically non-significant changes were seen with concentric resistance training[60,61]. These findings help to explain the observation that eccentric resistance training can elicit more pronounced[9,12] and long-lasting[5] hypertrophy than concentric training.

Influence of nutrition

There is a growing interest for optimal nutrition in combination with resistance exercise, and recent studies suggest that the timed intake of protein may effectively enhance the hypertrophic response to training.

Muscle Protein Synthesis and Breakdown

Muscle protein metabolism can be stimulated by resistance exercise *per se*[62-65]. Similarly, an elevated level of circulating amino acids cause muscle protein synthesis to accelerate[63,66,67]. The increase in muscle protein synthesis is further elevated when amino acids is ingested in combination with resistance exercise[63,68], indicating that resistance exercise and amino acid supplementation have complementary effects on muscle protein synthesis. However, in the absence of pre or post exercise nutritional intake muscle protein breakdown may exceed protein synthesis, causing net protein balance to remain negative and thereby inducing a catabolic state[62,64].

Timed Intake of Protein

As suggested by the above data it seems important to ingest protein in conjunction with resistance training when muscular hypertrophy or optimal restitution is the goal. Somewhat surprising, however, several studies have not been able to demonstrate an additive effect of post-exercise amino acid plus carbohydrate supplementation compared to placebo on gains in maximal muscle strength in young or aging individuals[32,69]. The explanation for this apparent paradox may be that it is the *timed* intake of pre or post exercise protein that provides the effective stimulus, whereas protein ingested at delayed time points exerts no major cumulative effect on muscle protein synthesis. In support of this notion, immediate intake of amino acids post-exercise was found to

enhance the acute exercise-induced increase in muscle protein synthesis[70] and to result in long-term hypertrophic effects compared to a delayed intake[31].

Pre- versus post-exercise protein intake

Recent data indicate that net muscle protein synthesis is increased more when essential amino acids plus carbohydrate are ingested prior to the training bout rather than after[72]. This effect could be caused by an increased availability of amino acids due to the increased muscle blood flow during exercise.

Carbohydrate intake

Post-exercise carbohydrate ingestion also seems beneficial to increase muscle protein accumulation, which mainly occurs through a decreased rate of muscle protein breakdown[72] likely due to an elevated level of insulin. Thus, insulin appears to decrease breakdown while not stimulating synthesis of myofibrillar proteins, although also playing a permissive role in protein synthesis[73,74].

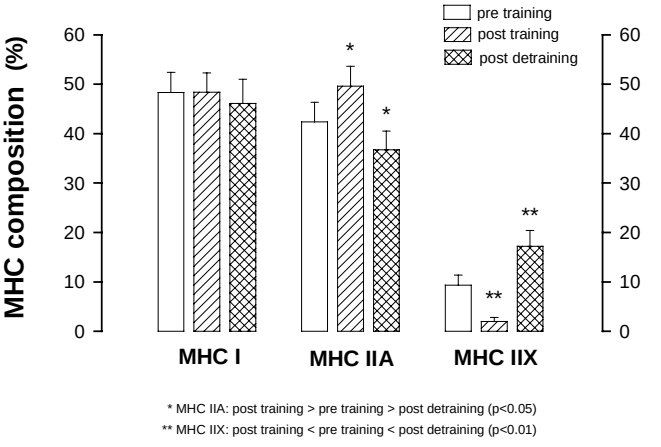

Figure 5. Changes in myosin heavy chain (MHC) isoform composition in the quadriceps muscle (VL) in response to 14 weeks of heavy-resistance strength training followed by 12 weeks of detraining. Notice the boosting of the fastest MHC isoform (IIX) with detraining. Data adapted from Andersen and Aagaard[37].

Ergogenic supplements

The alleged performance-enhancing effect of various ergogenic supplements such as caffeine, antioxidants, HMB, and pyruvate has been addressed in previous reviews[75]. No other sports supplement has been studied as intensively as creatine, and positive strength-enhancing effects have been consistently demonstrated for creatine in combination with resistance training.

Creatine

Creatine supplementation amplifies the adaptive response to resistance training both in female and male subjects[76], resulting in greater increases in maximal muscle strength and fat free mass[77-79] in parallel with greater increases in muscle cross-sectional area[80,81] compared to placebo intake. Notably, not all subjects respond with elevated muscle cell creatine content following creatine loading (~10%), particularly not individuals with initially high muscle creatine concentration[82,83].

Creatine loading initially gives rise to an increased retention of water in the body, along with fluid shifts into the muscle fibers due to elevated osmotic gradients caused by the increase in intracellular creatine concentration[84,85]. Data exist to suggest that this initial osmotic-induced increase in muscle fiber volume provide a stimulus *per se* for increased cellular protein synthesis[86].

Creatine and myogenic growth factors

To explain the elevated hypertrophic response with combined resistance training and creatine supplementation, an increased production of myogenic growth factors seems to occur in the muscle tissue itself. Thus, increased mRNA and protein levels of various myogenic regulatory factors (MyoD, myogenin, MRF4) have been observed following combined training and creatine intake[87]. Although resistance training *per se* results in increased mRNA and protein content of MyoD, myogenin and MRF4, this increase is substantially accelerated when training is combined with creatine intake[87,88]. A rise in myogenic regulatory factors with creatine supplementation may not *per se* elicit an enhanced hypertrophic response, rather it increases the sensitivity of the muscle cell to the resistance training stimulus, which in turn contributes to the accelerated hypertrophy.

Creatine and satellite cell activation

Animal experiments have shown that creatine supplementation may result in enhanced satellite cell activity[89]. Given the fact that locally produced IGF-1 exerts similar effects[56,58], it is possible that combined creatine intake and resistance training leads to elevated satellite cell activation compared to resistance training alone, which amplifies the hypertrophic response.

Effects of drugs

Anabolic steroids

Anabolic steroids are synthetically-derived molecules that mimic the signalling actions of the androgen hormone testosterone, causing increased DNA transcription for the myofibrillar proteins. Anabolic steroids are highly effective in boosting the rate of muscle protein synthesis beyond its normal physiological limits[75]. However, severe adverse affects exist, some of which are irreversible[75]. Moreover, anabolic steroids are banned by the IOC and prohibited in numerous countries by means of criminal legislation.

Anabolic steroids increase muscle mass and maximal muscle strength by increasing the rate of muscle protein synthesis[90]. Further, anabolic steroids stimulate the proliferation and differentiation of muscle satellite cells[59].

Power lifters with a history of long-term steroid use demonstrate increased muscle fiber areas for both type I and II fibers along with an increased number of myonuclei when compared to power lifters not using steroids[91]. Power lifters using steroids also showed an elevated number of myonuclei containing androgen-receptors in the trapezius muscle compared to non-using power lifters[92]. Consequently, it was proposed that the incorporation of matured satellite cells into pre-existing muscle fibers to maintain a constant nuclear-to-cytoplasmic ratio represents a fundamental mechanism for muscle growth and that this process is enhanced by intake of anabolic steroids[91].

Human growth hormone

Growth hormone secreted by the anterior pituitary gland stimulates synthesis of the anabolic hormone IGF-1 in the liver, hence influencing the level of circulating IGF-1. The systemic release of GH and IGF-1 is important for developmental growth. In contrast, when growth hormone administration was combined with resistance training in young[93] and old subjects[94], muscle protein synthesis was not elevated compared to resistance training alone. Consequently, similar changes in muscle mass and maximal muscle strength was observed in aging subjects when resistance training was performed with or without intake of growth hormone[95].

Conclusions

Maximal muscle strength is strongly influenced by resistive-types of exercise, which induce adaptive changes in both neuromuscular function and muscle morphology. Further, timed intake of protein in conjunction with resistance training elicits greater strength and muscle size gains than resistance training alone. Likewise, creatine supplementation amplifies the hypertrophic response to training, although some individuals (~10%) may not respond positively. Locally produced muscle growth factors are upregulated during creatine supplementation, which contributes to increase muscle cell responsiveness to intensive training stimuli. Usage of anabolic steroids boosts muscle hypertrophy beyond inherent genetical limits, not only by increasing the DNA transcription rate for myofibrillar proteins but also by increasing the nucleus-to-cytoplasm ratio due to accelerated activation of myogenic satellite cells. However, severe tissue damaging effects exist with anabolic steroids, some of which are irreversible.

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