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The effects of testosterone and insulin-like growth factor 1 on motor system form and function

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Abstract

In this perspective article, we review the effects of selected anabolic hormones on the motoric system and speculate on the role these hormones may have on influencing muscle and physical function via their impact on the nervous system. Both muscle strength and anabolic hormone levels decline around middle age into old age over a similar time period, and several animal and human studies indicate that exogenously increasing anabolic hormones (e.g., testosterone and insulin-like growth factor-1 (IGF-1)) in aged subjects is positively associated with improved muscle strength. While most studies in humans have focused on the effects of anabolic hormones on muscle growth, few have considered the impact these hormones have on the motoric system. However, data from animals demonstrate that administering either testosterone or IGF-1 to cells of the central and peripheral motor system can increase cell excitability, attenuate atrophic changes, and improve regenerative capacity of motor neurons. While these studies do not directly indicate that changes in anabolic hormones contribute to reduced human performance in the elderly (e.g., muscle weakness and physical limitations), they do suggest that additional research is warranted along these lines.

Keywords

Testosterone; Insulin-like growth factor 1; Aging; Muscle strength; Motor system

1. Introduction

Forty-two percent of the 37.3 million older adults in the United States report having one or more physical limitations performing daily tasks that are essential for maintaining independent living (Seeman et al., 2010). By 2030, this age group is expected to increase to approximately 71.5 million, representing 20% of the U.S. population (CDC, 2008).With the

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increase in the aging population, weakness and associated conditions (e.g., sarcopenia, dynapenia and frailty) in the elderly are a growing concern. For instance, a loss of voluntary muscle strength predisposes elders to a 4-fold increase in functional limitations and a 2-fold increase in mortality (Manini et al., 2007).While most studies examining weakness with aging have examined the role of skeletal muscle atrophy (Visser et al., 2005, Newman et al., 2006, Manini et al., 2007), other findings suggest that alterations in the aging nervous system also underlie loss or inconsistencies in muscle function (e.g., strength & power) (Laidlaw et al., 2000, Kido et al., 2004, Christie and Kamen, 2006, Clark and Taylor, 2011, Manini and Clark, 2012). In phase with the declines in neuromuscular function is the decline in hormone levels with aging, particularly several circulating factors thought to have anabolic effects (e.g., steroid hormones, growth hormone, and IGF-1). While a majority of studies in humans have independently examined age-related changes in endocrine and nervous system functions, *few have integrated these separate concepts to identify possible neuroendocrine changes associated with aging that influence the motoric system (defined herein as the central and peripheral components of the nervous system specific to muscle force generation and control), which could conceptually serve as a mechanistic underpinning of the reduced muscle function, and arguably physical function, observed with advancing age*. Human studies examining increased muscle strength and physical function with elevated endogenous hormone levels or exogenous hormone replacement have examined muscle function, but to our knowledge, none have placed particular emphasis on endocrine actions on components of the motoric system. Conversely, most human studies examining the effects of steroids on the nervous system have mostly examined cognitive outcomes without particular emphasis on the motor system or physical function and/or strength. Thus, a gap exists in the literature for human studies examining the role of anabolic hormones (testosterone and insulin-like growth factor 1) on the motor system with respect to declining muscle and physical function with aging. Herein, we present a perspective article on the effects of selected anabolic hormones on the motoric system form and function to raise awareness, and increase discussion, of the potential role that anabolic hormones may have on influencing muscle and physical function via their impact on the human nervous system. Although not heavily examined in humans, we review the few studies in the human literature that have examined the role of anabolic hormones on the motoric system. We also cite relevant studies from the robust body of non-human animal work that have examined the neuroprotective and/or neuroregenerative roles of testosterone and insulin-like growth factor 1 (IGF-1) on the motoric system, and the translational implications from animals to humans will be discussed.

2. The potential role of hormones in the aging motoric system

It is widely accepted that nervous system functions decline in humans with aging, particularly in the cognitive domains, which are reviewed elsewhere (Jagust, 2013, Samson and Barnes, 2013). Separate studies have also indicated age-related functional declines in the human motor system at the levels of the cortex, spinal cord, and motor neurons (Wagman and Lesse, 1952, Kido et al., 2004, McGinley et al., 2010, Kaya et al., 2013, Yao et al., 2014). In the cortex, a cross-sectional study of magnetic resonance brain images of living individuals ranging in age from 18 to 93 years suggests that cortical thinning occurs

by middle age with areas near the primary motor cortex showing prominent atrophy (Salat et al., 2004), and a cross-sectional analysis of human cadavers who died without neurological signs found a 43% volumetric reduction in the premotor cortex neuron perikaryon size in individuals over 65 years of age in comparison to adults younger than 45 years (Haug and Eggers, 1991). In addition to anatomical and morphometric changes to the cortex, functional measures are also altered with aging. We have observed that motor cortical excitability is reduced in older adults when compared to young adults (McGinley et al., 2010), and recently reported that weaker seniors have reduced motor cortical excitability (specifically, higher levels of long-interval intracortical inhibition, which is classically believed to be mediated by $GABA_B$-mediated inhibition) when compared to their stronger counterparts (Clark et al., 2014, Abstract proceeding from International Conference on Frailty and Sarcopenia, Barcelona, Spain). Differences in brain region activation with motor tasks have also been observed in older adults, when compared to young adults, as fMRI measurements indicate that there is less lateralization of activated brain regions (Mattay et al., 2002), and this change is evident during both concentric and eccentric contractions (Yao et al., 2014). Functional decreases in spinal excitability, assessed via the H-reflex, have been reported with advancing age in humans (Kido et al., 2004). Additionally, declines in peripheral motor neuron anatomy and physiology have been observed. More specifically, nerve conduction velocity decreases in humans around the 5th decade (Wagman and Lesse, 1952), while motor neuron loss starts around the 6th decade (Tomlinson and Irving, 1977), arguing for a possible neural mechanism of weakness in the elderly although it should be noted that the results from Tomlinson and Irving have not been replicated in animals due to their use of non-stereological techniques (Tomlinson and Irving, 1977). Power declines are apparent in the upper and lower extremities by age 40 years, and strength declines occur between 50 and 60 years with a much more rapid rate of loss occurring after 60 years (Deschenes, 2004), which is in line with the observations of decreased nerve conduction and motor neuron loss. Our recent findings also suggest an interrelationship between functioning motor unit number and muscle strength in older adults with a reduced number of estimated functioning motor units being related to muscle weakness (Kaya et al., 2013). Thus, it is clear that with advancing age there is a plethora of form and function changes in the motoric system, and it is likely that these changes are linked to impairments in physical performance.

In addition to the age-related motoric system changes, decreases in hormone production occur in a similar time frame with studies indicating low testosterone levels correlating to higher rates of sarcopenia or fall risks in men (Szulc et al., 2004, Orwoll et al., 2006). Do the declines in hormones/circulating factors mediate declines in the motor system? Evidence from animal parabiosis studies suggest that linking the circulatory systems of young mice and old mice enhances skeletal muscle regenerative capacity in old mice with no detectable negative effects in young mice (Conboy et al., 2005). The evidence for circulating factors has also been replicated as blood from young mice injected into old mice improves motor performance (Sinha et al., 2014). In addition to possible influences on muscle tissue, recent evidence has emerged indicating that circulating factors also have a profound influence on the nervous system, as Villeda et al. observed improved cognitive function in old mice injected with serum from young mice, while Ruckh et al. observed remyelination is enhanced in older mice via parabiosis with young mice (Ruckh et al., 2012, Villeda et al.,

2014). Taken together, the data suggest the decline of circulating factors with aging may be a critical mechanism driving age-related alterations in the motor system. These data also raise the question of "Which hormone(s) (or other circulating factors) exert effects on the motor system?" In the following sections, we review the current literature with a critical eye on whether testosterone and/or insulin-like growth factor 1 (IGF-1) impact motor system form and function. Although growth hormone (GH) levels have a positive relationship with IGF-1 levels, discussion of GH function on the motoric system will not be specifically discussed herein due to the relatively limited number of investigations examining the effects of GH on the motoric system.

3. Testosterone Synthesis and Actions on the Motoric System

With advancing age in men, free and total testosterone begin to decrease between the third to fifth decade of life, and this decline continues progressively thereafter (Harman et al., 2001). Additionally, endogenous testosterone release pulses are lower in frequency and amplitude at night in middle-aged men compared to young men (Luboshitzky et al., 2003). Because animal and human research has suggested that testosterone is neuroprotective and exerts effects at a variety of the motoric segmental levels (i.e., the brain, spinal cord and motor neurons, etc.) (Bialek et al., 2004, Fargo et al., 2009), it is likely that age-related testosterone decline may lead to declines in strength and physical performance via the motoric system. The interpretation of the data in women is preliminary because of the limitations of total and free testosterone assays. A task force appointed by the Endocrine Society published a position statement emphasizing that T values across the lifespan in women are not accurate (Rosner et al., 2007). However, a study using a validated liquid chromatography-tandem mass spectrometry (LC–MS/MS) method for measuring T reported T levels were 1.8 times higher in pre-menopausal women with an average age of 35 years compared to post menopausal women with an average age of 59 years (Rothman et al., 2011).

In animals, the effects of testosterone on the neuromuscular system have been studied, perhaps most extensively, in the spinal nucleus of the bulbocavernosus (SNB) (Breedlove and Arnold, 1980). In male rats, the SNB is a pool of around 200 motor neurons that innervate the bulbocavernosus (BC), levator ani, and the external anal sphincter (Breedlove and Arnold, 1980, 1981, Schroder, 1980, McKenna and Nadelhaft, 1986). In female rats, the perineal musculature is greatly reduced, and the SNB contains around a third of the motor neurons in males that primarily innervate the external anal sphincter (Breedlove and Arnold, 1981, McKenna and Nadelhaft, 1986, Ueyama et al., 1987). Testosterone establishes the sex difference early by preventing normal cell death as prenatal block of androgen receptors (AR) with the anti-androgen flutamide in males results in the loss of the motor neuron pool (Breedlove and Arnold, 1983a) while perinatal testosterone propionate treatment of females preserves the nucleus (Breedlove and Arnold, 1983b, Nordeen et al., 1985, Sengelaub and Arnold, 1986). The early regulation of SNB motor neuron number is thought to be due to testosterone action on the target musculature as the motor neurons, themselves, lack AR expression in newborn rats and do not express AR until P10 (Fishman et al., 1990, Jordan, 1997). In adulthood, testosterone manipulation affects the size of the cells in the motor neuron pool rather than the numbers. In males rats, castration at 60–80 days of age decreases

soma size while testosterone treatment of females increases soma size, but not to the extent seen in males (Breedlove and Arnold, 1981). By this time, AR is expressed on SNB motor neurons (Jordan, 1997) and may directly regulate soma size (Watson et al., 2001). An important observation in the SNB is that normal aging in rodents leads to a decline in testosterone and AR expression on the motor neurons (Matsumoto and Prins, 1998), likely underlying in the shift towards decreased motor neuron soma size within the nucleus from 9 to 22 months of age (Fargo et al., 2007) and the decrease in sexual behavior with age (Larsson, 1958). However, the changes are reversible as testosterone treatment of aged animals restores the SNB motor neuron size distribution observed in young rats (Fargo et al., 2007). There is also evidence that testosterone treatment initiates electromyogram (EMG) burst activities in the BC muscle within minutes of injection into castrated male rats (n = 6/8; aged 8–10 months; castrated at 3 months), a physiological response that the authors attributed to steroid-sensitive neuronal membrane receptors (Sachs and Leipheimer, 1988). Taken together, the motor neuron is a likely site of action for testosterone in the adult androgen-sensitive rodent neuromuscular system and suggests that such androgen responses could occur in motor neurons innervating human muscles. Furthermore, aging could result in a decline of the neuroprotective properties of testosterone in motor neurons.

The SNB findings in rodents are specific to motor neurons whose survival in early development is mediated by AR. However, ARs are found in all spinal motor neurons of adult male and female rats (Sar and Stumpf, 1977, MacLusky et al., 1987, Lumbroso et al., 1996), which confer other important androgen-mediated properties to motor neurons. Cranial nerves contain androgen receptor mRNA and protein (Yu and McGinnis, 1986, Drengler et al., 1996) and are another well-studied model of androgenic neuroprotection on rodent motor neurons. Unlike the SNB, there seems to be no sexual dimorphism in adult neuron numbers in spite of 50% lower AR binding in female rats relative to males (Yu and McGinnis, 2001). However, gonadectomy in male hamsters decreases AR mRNA levels by approximately 50%whereas gonadectomy has no effects on females (Drengler et al., 1996). Additionally, AR binding decreases with age in the facial motor neurons, and the hypoglossal nuclei, in particular, exhibits a decrease in neuron number in 20 month old male rats compared to 4 month old male rats (McGinnis and Yu, 1995). Accordingly, studies in rodent facial nerves may be a useful translational model for age-related issues with strength and motor performance in humans. In the injury paradigm, the neuroprotective role of testosterone is indicated by data showing the regenerative speed of facial motor neurons following injury are significantly faster in young adult male rats in comparison to females and castrated males (Yu, 1982). This study also suggested it is testosterone, and not estradiol, that likely mediates the neuroprotective effects in the nerves. Subsequent studies have confirmed testosterone propionate administration to crushed motor neurons can accelerate facial nerve crush recovery (measured as mm outgrowth per day) in male golden hamsters, and a similar effect was also observed in female hamsters in the same study (Kujawa et al., 1991). With facial nerve crush, animals display unilateral facial paralysis with drooping of one corner of the mouth, flattened and paralyzed vibrissae, and loss of eyeblink reflex, but testosterone treatment in these rodents results in a return of movement during a 2–3 week postoperative period, indicating a functional recovery with the androgen-mediated neuroregeneration (Jones, 1994).

In motor neurons innervating the lower limb, androgen-mediated neuroprotection is observed in the sciatic nerve of rodents as it also expresses AR protein and mRNA (Jordan et al., 2002), and neuroregeneration is observed in the motor neuron axons (Kujawa et al., 1993, Brown et al., 1999) and soma (Tehranipour and Moghimi, 2010). After sciatic nerve crush in male rats, testosterone propionate administration slightly enhances the rate of regeneration and the outgrowth distance of the leading axons after 11 days of postoperative observation (Kujawa et al., 1993). Data from rodent studies examining motor neurons innervating the quadriceps muscles also suggest testosterone has a neuroprotective role in the L2 spinal segment. In the presence of the neurotoxin saporin, which results in motor neuron death and somal and dendritic atrophy of nearby surviving motor neurons, testosterone has also been shown to attenuate dendritic atrophy of the quadriceps motor neuron by 65% compared to groups not treated with testosterone (Little et al., 2009). Furthermore, compared to normal untreated specimens, saporin causes 63% dendrite morphology reduction in quadriceps motor neurons of treated female rats. However, testosterone treatment prevents the dendrite atrophy due to saporin such that only 8% of quadriceps motor neuron dendrites are lost, suggesting neuroprotective effects of testosterone are present in female mammals (Wilson et al., 2009). Although these injury models are not a perfect representation of normal aging, they suggest that testosterone exerts a neurotrophic/neuroprotective effect in androgen-responsive motor neurons and may affect motor neuron recovery. In normal aging of rats, changes in lower limb muscles have been examined in the medial gastrocnemius where there is an increase in slow motor units and a decrease in fast fatigue-resistant motor units. With aging, there is also evidence for motor unit denervation/reinnervation and declines in motor nerve conduction velocity (Kanda and Hashizume, 1989). Another anatomic study in rats indicate there is a ~29% decrease in the number of spinal motor units with age in the rat soleus, which results in longer contraction times (Edstrom and Larsson, 1987). These alterations are somewhat similar to the pattern observed in human anatomy and physiology. There is evidence that a process of denervation and reinnervation with aging occurs, resulting in fiber type grouping and a preferential atrophy of type 2 motor units (Doherty et al., 1993, Vandervoort, 2002), and much of the changes in type 2 muscle fibers occur in the lower body but not in the upper body (Grimby et al., 1982). Additionally, aging in men and women is associated with increased cortical threshold for relaxed motor-evoked potentials (MEPs), decreased MEP amplitudes, and delays in central motor conduction times in the foot, but not hand, muscles (Rossini et al., 1992, Tobimatsu et al., 1998). This finding was interpreted as in vivo evidence for different age-related effects on cervical and lumbar motor neurons in humans (Rossini et al., 1992, Tobimatsu et al., 1998). From a conceptual basis, it is plausible that testosterone decreases, particularly for men, may mediate these changes as the fraction of men who have hypogonadal testosterone increases during a similar time frame (Harman et al., 2001).

Further relevance of the animal work to human work is apparent in a few studies. In humans, Bonifazi et al. reported that exogenous administration of human chorionic gonadotropin in healthy males increased testosterone levels and reduced the ‘motor threshold’ (Bonifazi et al., 2004), which represents the amount of brain stimulation (delivered using transcranial magnetic stimulation) required to elicit a response. A reduction in motor threshold is generally interpreted as indicative of an acute increase in the

membrane excitability of pyramidal neurons (Maeda and Pascual-Leone, 2003, Ziemann, 2004). Testosterone also improved motor nerve CV after 9 weeks of treatment in an XXYY patient with peripheral neuropathy and low serum testosterone levels (125 mg treatment once a week for 4 weeks, once every 2 weeks for 4 weeks, and once every 3 weeks thereafter) (Izumi and Tsubahara, 2000). It should be noted that these studies were done in young individuals and one with a genetic syndrome, and it is uncertain what the findings would be in healthy, older adults. However, the decade between 50–60 years of age is when declines in motor nerve conduction velocity CV increase (Wagman and Lesse, 1952), and it is possible that the decline in testosterone levels may mediate this process. To our knowledge, no study has examined the effects of testosterone and age on CV. Thus, while findings of this nature are very limited, it does provide some basic proof of concept that testosterone may alter motoric system excitability and function.

With aging, it is generally accepted that motor units (motor neurons and their innervated muscles) are lost during sarcopenia with aging (Drey et al., 2013, 2014). Although correlational, low apparent free testosterone concentration and total free testosterone index has been observed in sarcopenic men (Szulc et al., 2004), and the loss of muscle strength far outweighs the loss of muscle mass with accompanying deterioration of neuromuscular coordination (Hughes et al., 2001). In summary, the evidence indicates that testosterone may exert a neurotrophic effect on androgen-responsive elements of the motor system and warrants further investigation in the aging human population.

4. IGF-1 synthesis and actions on the motoric system

Another anabolic hormone that could have effects on the motoric system is insulin-like growth factor 1 (IGF-1, also known as somatomedin C). Although the neuroprotective properties of IGF-1 are well known in some rodent models of disease (Kaspar et al., 2003, Palazzolo et al., 2009), we will primarily focus on the effects of IGF-1 in aging and injury of the motoric system components. A study in mice suggests a majority (an estimated 75%) of IGF-1 is produced in the liver (Liu et al., 2000), while data from the human population indicates hepatic IGF-1 production is correlated with growth hormone secretion (Rudman et al., 1981). The remaining IGF-1 in the body is extrahepatic, and a study in mouse cell lines suggests IGF-1 is produced locally in tissues to have autocrine/paracrine actions (Tollefsen et al., 1989). With advancing age, cross-sectional studies in men and women indicate serum IGF-1 levels peak in the middle to late teenage years, decreasing sharply shortly thereafter, and decline at a more gradual rate each year starting around the third decade (Brabant and Wallaschofski, 2007), and continues to decline to very low levels until ≥60 years of age in a process known as ‘somatopause’ (Junnila et al., 2013). In the nervous system, IGF-1 is an anti-apoptotic factor during development (Hodge et al., 2007) and also serves as a neuroprotective factor in adulthood by reducing neuronal loss in the nervous system when administered in rats before spinal cord injury (Sharma et al., 1998) and after hypoxic and/or ischemic injury in brain (Guan et al., 1993, Liu et al., 2001).With age-related decline of IGF-1, it is believed that the nervous system and the motoric system lose some regenerative capacity (Apel et al., 2010), potentially leading to a decline in muscle or physical function.

In the cortex, IGF-1 targets high voltage-activated Ca^{2+} channels to regulate membrane excitability (Shan et al., 2003), and IGF-1 treatment enhances Ca^{2+} current in motor cortex neurons in senescent rats (Shan et al., 2003). However, the above-referenced study also demonstrated that the Ca^{2+} channel currents of the neurons from senescent rats have similar voltage dependence and amplitude as those in young adult rats, and it was uncertain from this study whether IGF-1 at the cortical level affected muscle strength or motor unit recruitment. A series of studies in rodents have also documented the neurotrophic effects of IGF-1 on the motoric system (Gao et al., 1999, Ozdinler and Macklis, 2006, Apel et al., 2010). IGF-1 enhances axon outgrowth length of corticospinal motor neurons (CSMN) (Ozdinler and Macklis, 2006). The enhancement results in 2.5–3 times the length observed in vehicle- and brain derived neurotrophic factor (BDNF)-treated CSMNs. Although blockade of IGF-1 reduced axon outgrowth, the CSMNs were still viable, suggesting cell death and axon morphology were dissociated. Data suggest two active isoforms of IGF-1 confer neuroprotection: IGF-1Ea, which is the hepatic or systemic IGF-1, and mechano growth factor (MGF), which is expressed in response to mechanical overload/tissue injury (Yamaguchi et al., 2006). In a rat facial nerve avulsion model, IGF-1Ea- and MGF-preserves 37% and 88% more motor neurons when treated a week before injury compared to the untreated nerve avulsion group, respectively (Aperghis et al., 2004).

At the spinal level, motor neurons express IGF-1 receptors and are protected from glutamate toxicity with IGF-1 treatment in motor neurons from E15 rat embryos (Vincent et al., 2004), although the timing of the treatment is important to recovery (Vincent et al., 2004). In peripheral nerves, IGF-1 staining increases in regenerating nerves of female rats after transection (Hansson et al., 1986), and this effect has been localized to motor neurons of young rats (Hammarberg et al., 1998). Locally delivering IGF-1 in transected tibial nerve of old and young rats results in increased axons per nerve, axon density, and axon diameter (Apel et al., 2010). Furthermore, myelin is also thicker in old and young rats treated with IGF-1 (Apel et al., 2010). This would suggest greater nerve CV is a possibility with higher IGF-1 levels, and this has been demonstrated in an earlier study by examining IGF-1 knockout mice (Gao et al., 1999). Homozygous IGF-1 knockout mice exhibit about half the motor nerve CV seen in wild type mice with normal IGF-1 levels, and heterozygous mice with intermediate levels of IGF-1 have intermediate CV compared to the other two groups. Furthermore, treating IGF-1 knockout mice with IGF-1 increases CV up to wild type levels (Gao et al., 1999). Thus, it may be reasonable to expect that a decline in IGF-1 levels with age in humans may contribute to the slowing in motor nerve CV observed in older adults, but delaying the decline in IGF-1may attenuate the observed decline in motor nerve CV. Similar to the effects of testosterone described above, IGF-1 also allows functional recovery with the attenuation of cell death (Nakao et al., 2001). In a rabbits with spinal cord ischemia, intravenous IGF-1 preserves motor neuron number and terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate-biotin nick-end labeling (TUNEL — a marker for cell apoptosis) levels are comparable to sham but less than cells in vehicle- and insulin-treated rabbits (Nakao et al., 2001). Furthermore, hindlimb function after 48 h is maintained in IGF-1 treated animals, which is not observed with vehicle or insulin (Nakao et al., 2001).

Some of the action of IGF-1 on motor neuron survival seems to be mediated by contacting cells. While IGF-1 has muscle-specific actions, such as promoting muscle growth by preventing myofibrillar protein breakdown (Sacheck et al., 2004) and preventing age-related muscle atrophy in older animals (Musaro et al., 2001), some of the actions of IGF-1 are likely due to paracrine effects of muscular IGF-1 on peripheral motor neuron axons to preserve the function of the motoric system as IGF-1 treatment on gluteal muscles of adult mice induces motor neuron axon sprouting (Caroni and Grandes, 1990). IGF-1 overexpression in skeletal muscle prevents age-related loss of specific force (Gonzalez et al., 2003), and muscle-specific IGF-1 also enhances peripheral nerve regeneration after injury (Rabinovsky et al., 2003), indicating a paracrine or target-derived trophic effect of IGF-1. Furthermore, muscle fiber specific force is increased where IGF-1 injected into skeletal muscles is specifically targeted to motor neurons and retrogradely transported by the motor axons back to the motor neuron soma as visualized by immunocytochemistry (Payne et al., 2006). In cases where IGF-1 was not targeted to the motor neurons, no increase in specific force was observed. Cell cultures of newborn mouse motor neurons also suggest that astrocytes can mediate IGF-1 effects on cell survival (Ang et al., 1992). Thus, several pieces of evidence suggest IGF-1 regulates function of the motoric system elements by enhancing regeneration or increasing cell excitability by upregulating Ca^{2+} channels. Some studies examining muscle function also suggest muscle strength is increased with IGF-1 due to target-derived or paracrine trophic actions from neighboring non-neuronal cells onto the nervous system in mice (Rabinovsky et al., 2003, Payne et al., 2006). Thus, collectively, these findings suggest that IGF-1 may prevent the loss of strength accompanying aging by acting at different levels and by several separate mechanisms in the motoric system.

5. Conclusions

While only a limited number of human studies have examined the effects of steroids on the motor system, there is growing evidence, from animal studies in particular, that certain anabolic hormones, such as testosterone and IGF-1, exert effects on regenerative ability and anti-apoptotic effects on the central and peripheral tissues of the motoric system. The age-related decline of these hormones have not received significant attention as it relates to whether they mediate age-related changes in the human motor system and how these changes impact the loss of muscle strength and physical function commonly observed in the elderly. However, there is growing evidence for selected anabolic hormones to influence the form and function of the motoric system, and, as such, there is a need for increased research in this area.

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References

Ang LC, Bhaumick B, Munoz DG, Sass J, Juurlink BH. Effects of astrocytes, insulin and insulin-like growth factor I on the survival of motoneurons in vitro. J. Neurol. Sci. 1992; 109:168–172. [PubMed: 1634898]

Apel PJ, Ma J, Callahan M, Northam CN, Alton TB, Sonntag WE, Li Z. Effect of locally delivered IGF-1 on nerve regeneration during aging: an experimental study in rats. Muscle Nerve. 2010; 41:335–341. [PubMed: 19802878]

Aperghis M, Johnson IP, Cannon J, Yang SY, Goldspink G. Different levels of neuroprotection by two insulin-like growth factor-I splice variants. Brain Res. 2004; 1009:213–218. [PubMed: 15120599]

Bialek M, Zaremba P, Borowicz KK, Czuczwar SJ. Neuroprotective role of testosterone in the nervous system. Pol. J. Pharmacol. 2004; 56:509–518. [PubMed: 15591638]

Bonifazi M, Ginanneschi F, della Volpe R, Rossi A. Effects of gonadal steroids on the input–output relationship of the corticospinal pathway in humans. Brain Res. 2004; 1011:187–194. [PubMed: 15157805]

Brabant G, Wallaschofski H. Normal levels of serum IGF-I: determinants and validity of current reference ranges. Pituitary. 2007; 10:129–133. [PubMed: 17487588]

Breedlove SM, Arnold AP. Hormone accumulation in a sexually dimorphic motor nucleus of the rat spinal cord. Science. 1980; 210:564–566. [PubMed: 7423210]

Breedlove SM, Arnold AP. Sexually dimorphic motor nucleus in the rat lumbar spinal cord: response to adult hormone manipulation, absence in androgen-insensitive rats. Brain Res. 1981; 225:297–307. [PubMed: 7306791]

Breedlove SM, Arnold AP. Hormonal control of a developing neuromuscular system. I. Complete demasculinization of the male rat spinal nucleus of the bulbocavernosus using the anti-androgen flutamide. J. Neuroscie. 1983a; 3:417–423.

Breedlove SM, Arnold AP. Hormonal control of a developing neuromuscular system. II. Sensitive periods for the androgen-induced masculinization of the rat spinal nucleus of the bulbocavernosus. J. Neurosci. 1983b; 3:424–432. [PubMed: 6822871]

Brown TJ, Khan T, Jones KJ. Androgen induced acceleration of functional recovery after rat sciatic nerve injury. Restor. Neurol. Neurosci. 1999; 15:289–295. [PubMed: 12671219]

Caroni P, Grandes P. Nerve sprouting in innervated adult skeletal muscle induced by exposure to elevated levels of insulin-like growth factors. J. Cell Biol. 1990; 110:1307–1317. [PubMed: 2157718]

Centers for Disease Control and Prevention, Older Americans. Key Indicators of Well-Being. 2008. http://www.agingstats.gov/Main_Site/Data/2008_Documents/OA_2008.pdf

Christie A, Kamen G. Doublet discharges in motoneurons of young and older adults. J. Neurophysiol. 2006; 95:2787–2795. [PubMed: 16452261]

Clark BC, Taylor JL. Age-related changes in motor cortical properties and voluntary activation of skeletal muscle. Curr. Aging Sci. 2011; 4:192–199. [PubMed: 21529329]

Clark, BC.; Law, TD.; Hoffman, RL.; Gau, JT.; Russ, DW. Neurophysiological determinants of muscle weakness in aging. Presentation at the 2014 International Conference on Frailty and Sarcopenia Research; Barcelona, Spain. 2014.

Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature. 2005; 433:760–764. [PubMed: 15716955]

Deschenes MR. Effects of aging on muscle fibre type and size. Sports Med. 2004; 34:809–824. [PubMed: 15462613]

Doherty TJ, Vandervoort AA, Brown WF. Effects of ageing on the motor unit: a brief review. Can. J. Appl. Physiol. Rev. Can. Physiol. Appl. 1993; 18:331–358.

Drengler SM, Handa RJ, Jones KJ. Sex differences in androgen receptor mRNA levels and regulation in hamster facial motoneurons. Brain Res. Mol. Brain Res. 1996; 35:131–138. [PubMed: 8717348]

Drey M, Grosch C, Neuwirth C, Bauer JM, Sieber CC. The Motor Unit Number Index (MUNIX) in sarcopenic patients. Exp. Gerontol. 2013; 48:381–384. [PubMed: 23376626]

Drey M, Krieger B, Sieber CC, Bauer JM, Hettwer S, Bertsch T, Group DS. Motoneuron loss is associated with sarcopenia. J. Am. Med. Dir. Assoc. 2014; 15:435–439. [PubMed: 24656689]

Edstrom L, Larsson L. Effects of age on contractile and enzyme-histochemical properties of fast- and slow-twitch single motor units in the rat. J. Physiol. 1987; 392:129–145. [PubMed: 2965761]

Fargo KN, Iwema CL, Clark-Phelps MC, Sengelaub DR. Exogenous testosterone reverses age-related atrophy in a spinal neuromuscular system. Horm. Behav. 2007; 51:20–30. [PubMed: 16952361]

Fargo KN, Foecking EM, Jones KJ, Sengelaub DR. Neuroprotective actions of androgens on motoneurons. Front. Neuroendocrinol. 2009; 30:130–141. [PubMed: 19393684]

Fishman RB, Chism L, Firestone GL, Breedlove SM. Evidence for androgen receptors in sexually dimorphic perineal muscles of neonatal male rats. Absence of androgen accumulation by the perineal motoneurons. J. Neurobiol. 1990; 21:694–704. [PubMed: 2394986]

Gao WQ, Shinsky N, Ingle G, Beck K, Elias KA, Powell-Braxton L. IGF-I deficient mice show reduced peripheral nerve conduction velocities and decreased axonal diameters and respond to exogenous IGF-I treatment. J. Neurobiol. 1999; 39:142–152. [PubMed: 10213459]

Gonzalez E, Messi ML, Zheng Z, Delbono O. Insulin-like growth factor-1 prevents age-related decrease in specific force and intracellular Ca2+ in single intact muscle fibres from transgenic mice. J. Physiol. 2003; 552:833–844. [PubMed: 12937290]

Grimby G, Danneskiold-Samsoe B, Hvid K, Saltin B. Morphology and enzymatic capacity in arm and leg muscles in 78–81 year old men and women. Acta Physiol. Scand. 1982; 115:125–134. [PubMed: 7136797]

Guan J, Williams C, Gunning M, Mallard C, Gluckman P. The effects of IGF-1 treatment after hypoxic-ischemic brain injury in adult rats. J. Cereb. Blood Flow Metab. 1993; 13:609–616. [PubMed: 8314914]

Hammarberg H, Risling M, Hokfelt T, Cullheim S, Piehl F. Expression of insulin-like growth factors and corresponding binding proteins (IGFBP 1–6) in rat spinal cord and peripheral nerve after axonal injuries. J. Comp. Neurol. 1998; 400:57–72. [PubMed: 9762866]

Hansson HA, Dahlin LB, Danielsen N, Fryklund L, Nachemson AK, Polleryd P, Rozell B, Skottner A, Stemme S, Lundborg G. Evidence indicating trophic importance of IGF-I in regenerating peripheral nerves. Acta Physiol. Scand. 1986; 126:609–614. [PubMed: 3521205]

Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Baltimore Longitudinal Study of A. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J. Clin. Endocrinol. Metab. 2001; 86:724–731. [PubMed: 11158037]

Haug H, Eggers R. Morphometry of the human cortex cerebri and corpus striatum during aging. Neurobiol. Aging. 1991; 12:336–338. (discussion 352–335). [PubMed: 1961364]

Hodge RD, D'Ercole AJ, O'Kusky JR. Insulin-like growth factor-I (IGF-I) inhibits neuronal apoptosis in the developing cerebral cortex in vivo. Int. J. Dev. Neurosci. 2007; 25:233–241. [PubMed: 17459648]

Hughes VA, Frontera WR, Wood M, Evans WJ, Dallal GE, Roubenoff R, Fiatarone Singh MA. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. J. Gerontol. A: Biol. Med. Sci. 2001; 56:B209–B217.

Izumi S, Tsubahara A. Improvement of peripheral neuropathy by testosterone in a patient with 48, XXYY syndrome. Tokai J. Exp. Clin. Med. 2000; 25:39–44. [PubMed: 11127505]

Jagust W. Vulnerable neural systems and the borderland of brain aging and neurodegeneration. Neuron. 2013; 77:219–234. [PubMed: 23352159]

Jones KJ. Androgenic enhancement of motor neuron regeneration. Ann. N. Y. Acad. Sci. 1994; 743:141–161. (discussion 161–144). [PubMed: 7802411]

Jordan C. Androgen receptor (AR) immunoreactivity in rat pudendal motoneurons: implications for accessory proteins. Horm. Behav. 1997; 32:1–10. [PubMed: 9344686]

Jordan CL, Price RH Jr, Handa RJ. Androgen receptor messenger RNA and protein in adult rat sciatic nerve: implications for site of androgen action. J. Neurosci. Res. 2002; 69:509–518. [PubMed: 12210844]

Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. Nat. Rev. Endocrinol. 2013; 9:366–376. [PubMed: 23591370]

Kanda K, Hashizume K. Changes in properties of the medial gastrocnemius motor units in aging rats. J. Neurophysiol. 1989; 61:737–746. [PubMed: 2656932]

Kaspar BK, Llado J, Sherkat N, Rothstein JD, Gage FH. Retrograde viral delivery of IGF-1 prolongs survival in a mouse ALS model. Science. 2003; 301:839–842. [PubMed: 12907804]

Kaya RD, Nakazawa M, Hoffman RL, Clark BC. Interrelationship between muscle strength, motor units, and aging. Exp. Gerontol. 2013; 48:920–925. [PubMed: 23832080]

Kido A, Tanaka N, Stein RB. Spinal excitation and inhibition decrease as humans age. Can. J. Physiol. Pharmacol. 2004; 82:238–248. [PubMed: 15181462]

Kujawa KA, Emeric E, Jones KJ. Testosterone differentially regulates the regenerative properties of injured hamster facial motoneurons. J. Neurosci. 1991; 11:3898–3906. [PubMed: 1744696]

Kujawa KA, Jacob JM, Jones KJ. Testosterone regulation of the regenerative properties of injured rat sciatic motor neurons. J. Neurosci. Res. 1993; 35:268–273. [PubMed: 8350388]

Laidlaw DH, Bilodeau M, Enoka RM. Steadiness is reduced and motor unit discharge is more variable in old adults. Muscle Nerve. 2000; 23:600–612. [PubMed: 10716772]

Larsson K. Sexual activity in senile male rats. J. Gerontol. 1958; 13:136–139. [PubMed: 13549712]

Little CM, Coons KD, Sengelaub DR. Neuroprotective effects of testosterone on the morphology and function of somatic motoneurons following the death of neighboring motoneurons. J. Comp. Neurol. 2009; 512:359–372. [PubMed: 19003970]

Liu JL, Yakar S, LeRoith D. Conditional knockout of mouse insulin-like growth factor-1 gene using the Cre/loxP system. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine. 2000; 223:344–351.

Liu XF, Fawcett JR, Thorne RG, DeFor TA, Frey WH 2nd. Intranasal administration of insulin-like growth factor-I bypasses the blood–brain barrier and protects against focal cerebral ischemic damage. J. Neurol. Sci. 2001; 187:91–97. [PubMed: 11440750]

Luboshitzky R, Shen-Orr Z, Herer P. Middle-aged men secrete less testosterone at night than young healthy men. J. Clin. Endocrinol. Metab. 2003; 88:3160–3166. [PubMed: 12843160]

Lumbroso S, Sandillon F, Georget V, Lobaccaro JM, Brinkmann AO, Privat A, Sultan C. Immunohistochemical localization and immunoblotting of androgen receptor in spinal neurons of male and female rats. Eur. J. Endocrinol. 1996; 134:626–632. [PubMed: 8664984]

MacLusky NJ, Clark CR, Shanabrough M, Naftolin F. Metabolism and binding of androgens in the spinal cord of the rat. Brain Res. 1987; 422:83–91. [PubMed: 3499956]

Maeda F, Pascual-Leone A. Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders. Psychopharmacology. 2003; 168:359–376. [PubMed: 12830365]

Manini TM, Clark BC. Dynapenia and aging: an update. J. Gerontol. A: Biol. Med. Sci. 2012; 67:28–40.

Manini TM, Visser M, Won-Park S, Patel KV, Strotmeyer ES, Chen H, Goodpaster B, De Rekeneire N, Newman AB, Simonsick EM, Kritchevsky SB, Ryder K, Schwartz AV, Harris TB. Knee extension strength cutpoints for maintaining mobility. J. Am. Geriatr. Soc. 2007; 55:451–457. [PubMed: 17341251]

Matsumoto A, Prins GS. Age-dependent changes in androgen receptor immuno-reactivity in motoneurons of the spinal nucleus of the bulbocavernosus of male rats. Neurosci. Lett. 1998; 243:29–32. [PubMed: 9535105]

Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, Weinberger DR. Neurophysiological correlates of age-related changes in human motor function. Neurology. 2002; 58:630–635. [PubMed: 11865144]

McGinley M, Hoffman RL, Russ DW, Thomas JS, Clark BC. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. Exp. Gerontol. 2010; 45:671–678. [PubMed: 20417265]

McGinnis MY, Yu WH. Age-related changes in androgen receptor levels in cranial nerve nuclei of male rats. Brain Res. Bull. 1995; 36:581–585. [PubMed: 7757493]

McKenna KE, Nadelhaft I. The organization of the pudendal nerve in the male and female rat. J. Comp. Neurol. 1986; 248:532–549. [PubMed: 3722467]

Musaro A, McCullagh K, Paul A, Houghton L, Dobrowolny G, Molinaro M, Barton ER, Sweeney HL, Rosenthal N. Localized IGF-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. Nat. Genet. 2001; 27:195–200. [PubMed: 11175789]

Nakao Y, Otani H, Yamamura T, Hattori R, Osako M, Imamura H. Insulin-like growth factor 1 prevents neuronal cell death and paraplegia in the rabbit model of spinal cord ischemia. J. Thorac. Cardiovasc. Surg. 2001; 122:136–143. [PubMed: 11436046]

Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J. Gerontol. A: Biol. Med. Sci. 2006; 61:72–77.

Nordeen EJ, Nordeen KW, Sengelaub DR, Arnold AP. Androgens prevent normally occurring cell death in a sexually dimorphic spinal nucleus. Science. 1985; 229:671–673. [PubMed: 4023706]

Orwoll E, Lambert LC, Marshall LM, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings SR. Osteoporotic Fractures in Men Study G. Endogenous testosterone levels, physical performance, and fall risk in older men. Arch. Intern. Med. 2006; 166:2124–2131. [PubMed: 17060543]

Ozdinler PH, Macklis JD. IGF-I specifically enhances axon outgrowth of corticospinal motor neurons. Nat. Neurosci. 2006; 9:1371–1381. [PubMed: 17057708]

Palazzolo I, Stack C, Kong L, Musaro A, Adachi H, Katsuno M, Sobue G, Taylor JP, Sumner CJ, Fischbeck KH, Pennuto M. Overexpression of IGF-1 in muscle attenuates disease in a mouse model of spinal and bulbar muscular atrophy. Neuron. 2009; 63:316–328. [PubMed: 19679072]

Payne AM, Zheng Z, Messi ML, Milligan CE, Gonzalez E, Delbono O. Motor neurone targeting of IGF-1 prevents specific force decline in ageing mouse muscle. J. Physiol. 2006; 570:283–294. [PubMed: 16293644]

Rabinovsky ED, Gelir E, Gelir S, Lui H, Kattash M, DeMayo FJ, Shenaq SM, Schwartz RJ. Targeted expression of IGF-1 transgene to skeletal muscle accelerates muscle and motor neuron regeneration. FASEB J. 2003; 17:53–55. [PubMed: 12424223]

Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J. Clin. Endocrinol. Metab. 2007; 92:405–413. [PubMed: 17090633]

Rossini PM, Desiato MT, Caramia MD. Age-related changes of motor evoked potentials in healthy humans: non-invasive evaluation of central and peripheral motor tracts excitability and conductivity. Brain Res. 1992; 593:14–19. [PubMed: 1458317]

Rothman MS, Carlson NE, Xu M, Wang C, Swerdloff R, Lee P, Goh VH, Ridgway EC, Wierman ME. Reexamination of testosterone, dihydrotestosterone, estradiol and estrone levels across the menstrual cycle and in postmenopausal women measured by liquid chromatography-tandem mass spectrometry. Steroids. 2011; 76:177–182. [PubMed: 21070796]

Ruckh JM, Zhao JW, Shadrach JL, van Wijngaarden P, Rao TN, Wagers AJ, Franklin RJ. Rejuvenation of regeneration in the aging central nervous system. Cell Stem Cell. 2012; 10:96–103. [PubMed: 22226359]

Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP. Impaired growth hormone secretion in the adult population: relation to age and adiposity. J. Clin. Invest. 1981; 67:1361–1369. [PubMed: 7194884]

Sacheck JM, Ohtsuka A, McLary SC, Goldberg AL. IGF-I stimulates muscle growth by suppressing protein breakdown and expression of atrophy-related ubiquitin ligases, atrogin-1 and MuRF1. Am. J. Physiol. Endocrinol. Metab. 2004; 287:E591–E601. [PubMed: 15100091]

Sachs BD, Leipheimer RE. Rapid effect of testosterone on striated muscle activity in rats. Neuroendocrinology. 1988; 48:453–458. [PubMed: 3244402]

Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B. Thinning of the cerebral cortex in aging. Cereb. Cortex. 2004; 14:721–730. [PubMed: 15054051]

Samson RD, Barnes CA. Impact of aging brain circuits on cognition. Eur. J. Neurosci. 2013; 37:1903–1915. [PubMed: 23773059]

Sar M, Stumpf WE. Androgen concentration in motor neurons of cranial nerves and spinal cord. Science. 1977; 197:77–79. [PubMed: 867053]

Schroder HD. Organization of the motoneurons innervating the pelvic muscles of the male rat. J. Comp. Neurol. 1980; 192:567–587. [PubMed: 7419745]

Seeman TE, Merkin SS, Crimmins EM, Karlamangla AS. Disability trends among older Americans: national health and nutrition examination surveys, 1988–1994 and 1999–2004. Am. J. Public Health. 2010; 100:100–107. [PubMed: 19910350]

Sengelaub DR, Arnold AP. Development and loss of early projections in a sexually dimorphic rat spinal nucleus. J. Neurosci. 1986; 6:1613–1620. [PubMed: 3711999]

Shan H, Messi ML, Zheng Z, Wang ZM, Delbono O. Preservation of motor neuron Ca2+ channel sensitivity to insulin-like growth factor-1 in brain motor cortex from senescent rat. J. Physiol. 2003; 553:49–63. [PubMed: 12963799]

Sharma HS, Nyberg F, Westman J, Alm P, Gordh T, Lindholm D. Brain derived neurotrophic factor and insulin like growth factor-1 attenuate upregulation of nitric oxide synthase and cell injury following trauma to the spinal cord. An immunohistochemical study in the rat. Amino Acids. 1998; 14:121–129. [PubMed: 9871451]

Sinha M, Jang YC, Oh J, Khong D, Wu EY, Manohar R, Miller C, Regalado SG, Loffredo FS, Pancoast JR, Hirshman MF, Lebowitz J, Shadrach JL, Cerletti M, Kim MJ, Serwold T, Goodyear LJ, Rosner B, Lee RT, Wagers AJ. Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. Science. 2014; 344:649–652. [PubMed: 24797481]

Szulc P, Duboeuf F, Marchand F, Delmas PD. Hormonal and lifestyle determinants of appendicular skeletal muscle mass in men: the MINOS study. Am. J. Clin. Nutr. 2004; 80:496–503. [PubMed: 15277176]

Tehranipour M, Moghimi A. Neuroprotective effects of testosterone on regenerating spinal cord motoneurons in rats. J. Mot. Behav. 2010; 42:151–155. [PubMed: 20363715]

Tobimatsu S, Sun SJ, Fukui R, Kato M. Effects of sex, height and age on motor evoked potentials with magnetic stimulation. J. Neurol. 1998; 245:256–261. [PubMed: 9617705]

Tollefsen SE, Lajara R, McCusker RH, Clemmons DR, Rotwein P. Insulin-like growth factors (IGF) in muscle development. Expression of IGF-I, the IGF-I receptor, and an IGF binding protein during myoblast differentiation. J. Biol. Chem. 1989; 264:13810–13817. [PubMed: 2474537]

Tomlinson BE, Irving D. The numbers of limb motor neurons in the human lumbosacral cord throughout life. J. Neurol. Sci. 1977; 34:213–219. [PubMed: 925710]

Ueyama T, Arakawa H, Mizuno N. Central distribution of efferent and afferent components of the pudendal nerve in rat. Anat. Embryol. 1987; 177:37–49. [PubMed: 3439636]

Vandervoort AA. Aging of the human neuromuscular system. Muscle Nerve. 2002; 25:17–25. [PubMed: 11754180]

Villeda SA, Plambeck KE, Middeldorp J, Castellano JM, Mosher KI, Luo J, Smith LK, Bieri G, Lin K, Berdnik D, Wabl R, Udeochu J, Wheatley EG, Zou B, Simmons DA, Xie XS, Longo FM, Wyss-Coray T. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat. Med. 2014; 20:659–663. [PubMed: 24793238]

Vincent AM, Mobley BC, Hiller A, Feldman EL. IGF-I prevents glutamate-induced motor neuron programmed cell death. Neurobiol. Dis. 2004; 16:407–416. [PubMed: 15193297]

Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, Simonsick EM, Harris TB. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J. Gerontol. A: Biol. Med. Sci. 2005; 60:324–333.

Wagman IH, Lesse H. Maximum conduction velocities of motor fibers of ulnar nerve in human subjects of various ages and sizes. J. Neurophysiol. 1952; 15:235–244. [PubMed: 14946571]

Watson NV, Freeman LM, Breedlove SM. Neuronal size in the spinal nucleus of the bulbocavernosus: direct modulation by androgen in rats with mosaic androgen insensitivity. J. Neurosci. 2001; 21:1062–1066. [PubMed: 11157092]

Wilson RE, Coons KD, Sengelaub DR. Neuroprotective effects of testosterone on dendritic morphology following partial motoneuron depletion: efficacy in female rats. Neurosci. Lett. 2009; 465:123–127. [PubMed: 19735695]

Yamaguchi A, Fujikawa T, Shimada S, Kanbayashi I, Tateoka M, Soya H, Takeda H, Morita I, Matsubara K, Hirai T. Muscle IGF-I Ea, MGF, and myostatin mRNA expressions after compensatory overload in hypophysectomized rats. Pflügers Arch. Eur. J. Physiol. 2006; 453:203–210. [PubMed: 16941139]

Yao WX, Li J, Jiang Z, Gao JH, Franklin CG, Huang Y, Lancaster JL, Yue GH. Aging interferes central control mechanism for eccentric muscle contraction. Front. Aging Neurosci. 2014; 6:86. [PubMed: 24847261]

Yu WH. Sex difference in the regeneration of the hypoglossal nerve in rats. Brain Res. 1982; 238:404–406. [PubMed: 7093660]

Yu WH, McGinnis MY. Androgen receptor levels in cranial nerve nuclei and tongue muscles in rats. J. Neurosci. 1986; 6:1302–1307. [PubMed: 3486947]

Yu WH, McGinnis MY. Androgen receptors in cranial nerve motor nuclei of male and female rats. J. Neurobiol. 2001; 46:1–10. [PubMed: 11108611]

Ziemann U. TMS and drugs. Clin. Neurophysiol. 2004; 115:1717–1729. [PubMed: 15261850]