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Commentary

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.

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 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

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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

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