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Sex-Related Adaptation to Disuse-Induced Skeletal Muscle Wasting

Toshinori Yoshihara* and Hisashi Naito

Graduate School of Health and Sports Science, Juntendo University, Japan

***Corresponding author:** Toshinori Yoshihara, Graduate School of Health and Sports Science, Juntendo University, 1-1 Hirakagakuendai, Inzai, Chiba 270-1695, Japan

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ABSTRACT

Males and females have some key different physiologies and hormonal profiles. These differences sometimes impact on muscle adaptation to various extracellular stimuli, including muscle disuse. For example, some investigators reported that muscles in women had a greater response to disuse than men. This suggests that disuse-induced skeletal muscle loss may be sex-specific; however, current evidence is limited and the underlying mechanisms responsible for this difference remain unclear. Nonetheless, growing evidences from human and animal studies are showing that there are sex-related differences in adaptation to muscle disuse, and the FoxO3a signaling pathway may be associated with this phenomenon. Moreover, sex may affect unloading-induced functional neuromuscular adaptations during disuse. This review summarizes sex-specific differential responses to muscle disuse in humans and provides potential mechanisms for such differences in the response to disuse-induced skeletal muscle wasting.

Introduction

Sex-related differences are well known in body composition [1], hormone concentrations [2], muscle fiber type composition [3], and substrate utilization [4]. These differences could affect muscle responses and adaptations to various extracellular stimuli such as exercise [5]. Importantly, some investigators reported that muscles in women have a greater response to disuse [6,7].

The goals of this review are:

a) to summarize sex-specific differences in responses to muscle disuse in humans, and

b) to discuss the underlying mechanisms responsible for sex-related differences in skeletal muscular wasting.

Sex-Specific Differences to Muscle Disuse in Humans

Information on sex-specific differences in muscle adaptation to disuse is still limited. However, some investigators report that women have a greater response to muscle disuse than men. For example, Shackelford et al. [7] demonstrated that 17 weeks of horizontal bed rest induced a greater reduction in whole muscle volume in women (-17.3%) as compared to men (-10.7%) subjects. Moreover, in a side-by-side comparison, women showed a greater decline in thigh muscle size than men, even after shorter periods of bed rest (-21% in 60 days in women vs. -17% in 84 days in men) [8-11]. In contrast, Yasuda et al. [12] demonstrated that immobilization-induced loss of knee extensor muscle strength was greater after 14 days of unilateral leg immobilization in women than in men despite a similar extent of atrophy at the myofiber and whole muscle levels. Moreover, after seven days of unloading by unilateral lower limb suspension, women experienced a greater strength decline during maximal isometric contractions, but not muscle mass, than men [13]. In addition, another study showed that the recovery of muscle strength from unloading was slower for women than for men [14]. These data indicate that the reduction in muscle strength and recovery period after disuse are greater in women regardless of the unloading period. However, sex differences are minimal in terms of a reduction in muscle size (2–4%) in the first two weeks of unloading. Collectively, unloading (disuse)-induced skeletal muscle loss and weakness may be sex-specific. However, there is limited

evidence supporting this possibility and it depends on the duration of disuse and the method of unloading in human skeletal muscle.

Potential Mechanisms for Sex-Specific Differences in Muscular Wasting

To date, the mechanisms responsible for sex-related differences in muscle wasting remain unclear, although some potential molecular changes have been identified that may explain the differences. A previous study demonstrated that women express higher levels of FoxO3 mRNA than men [15]. FoxO3a transcription factors have been associated with two main catabolic systems: the ubiquitin-proteasome and autophagy-lysosome systems [16]. This suggests that differential FoxO3 signaling in response to unloading is responsible for the higher degree of skeletal muscle loss during disuse in females. Moreover, FoxO3 upstream molecules, such as Akt, heat shock protein (Hsp) 72, and myostatin, also exhibit sex-specific abundances or responses to several extracellular stimuli in human and rat skeletal muscles [17-19]. Indeed, our recent results indicate that seven days of hindlimb unloading induces a greater reduction in relative soleus muscle weight and fiber cross-sectional area in female than in male rats and is associated with a differential response to the FoxO3a/ubiquitin-proteasome pathway after hindlimb unloading [20].

Moreover, differential activation of the FoxO3a/ubiquitin-proteasome pathway during hindlimb unloading may be associated with decreased Hsp72 expression and greater activation of myostatin signaling in female rat soleus muscle. Hsp72 inhibits FoxO3a nuclear localization during muscle atrophy and, therefore, contributes to the maintenance of phosphorylated FoxO3a expression [21]. Thus, female animals tend to reduce Hsp levels during unloading, whereas males do not during short term (5-8 days) unloading. Because overexpression of Hsp72 in skeletal muscle prevents hindlimb unloading- and immobilization-induced atrophy in rodents [21,22], the higher levels of Hsp72 in male rats may be a positive regulator of skeletal muscle mass that downregulate FoxO3a-mediated protein degradation pathways. Our data also demonstrated sex-related differences in myostatin signaling following hindlimb unloading in rats [20]. Specifically, female rats exhibited a slight increase in myostatin expression with greater activation of downstream Smad2/3 signaling, compared to a non-significant decline in muscles from male rats following unloading. Myostatin is known as growth differentiation factor 8 and is a member of the transforming growth factor-β (TGF-β) superfamily that acts as a negative regulator of muscle mass [23]. Therefore, a greater response of myostatin signaling to various cellular stresses may have a negative effect on the maintenance of muscle mass during hindlimb unloading. In contrast, Maher et al. [24] suggested that there were no significant differences in myostatin mRNA and protein contents between healthy men and women subjects, at least during the resting condition. Nonetheless, recent evidence suggests that women show greater increases in TGF-β signaling in response to acute resistance exercise [17]. Thus, the increased response of myostatin signaling to various cellular stressors in females may negatively affect the maintenance of muscle mass during disuse, as well as following resistance training.

Little is known about the physiological mechanisms related to sex-specific differences in the reduction of muscle strength. Deschenes et al. [13,25] have previously reported that women suffer more severe unloading-induced decrements in neuromuscular function than men. These may be due to the disparities in the capacity of the nervous system to activate contracting muscle and a greater diminution in the neural drive from the central nervous system in a woman. Moreover, in isolated rat soleus muscle, they also indicated that sex affected unloading-induced functional neuromuscular adaptations [26]. This suggested that the greater strength of male muscles was due to neuromuscular transmission efficiency as well as greater muscle mass. Additional studies are necessary to discover the potential mechanisms that cause a sex-specific reduction in muscle strength during disuse-induced skeletal muscle wasting.

Summary and Conclusion

In summary, growing evidence indicates that there are sex-related differences in response to muscle disuse both in humans and animal models. However, the response depends on the duration and the method of unloading, at least in human skeletal muscle. Moreover, the precise mechanisms associated with sex-specific differences in disuse-induced muscle atrophy and weakness remain debatable. Therefore, additional research is required to clarify the mechanisms that cause sex-specific differences in response to disuse-induced skeletal muscle wasting. A better understanding of sex-specific changes in intracellular signaling that occur during muscle disuse would offer novel insights into the mechanisms that underlie sex-dependent differences in muscle wasting and may help develop treatments to minimize such wasting.

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