Experimental Gerontology 106 (2018) 145–153

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Plasticity in central neural drive with short-term disuse and recovery - effects on muscle strength and influence of aging

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ARTICLE INFO

Keywords:
Disuse
Mechanical muscle function
Voluntary muscle activation
Central neural drive
Muscle contractile properties

ABSTRACT

While short-term disuse negatively affects mechanical muscle function (e.g. isometric muscle strength) little is known of the relative contribution of adaptions in central neural drive and peripheral muscle contractility. The present study investigated the relative contribution of adaptations in central neural drive and peripheral muscle contractility on changes in isometric muscle strength following short-term unilateral disuse (4 days, knee brace) and subsequent active recovery (7 days, one session of resistance training) in young ($n = 11$, 24 yrs) and old healthy men (n = 11, 67 yrs). Maximal isometric knee extensor strength (MVC) (*isokinetic dynamometer*), voluntary muscle activation (*superimposed twitch technique*), and electrically evoked muscle twitch force (*single and doublet twitch stimulation*) were assessed prior to and after disuse, and after recovery. Following disuse, relative decreases in MVC did not differ statistically between old (16.4 ± 3.7%, $p < 0.05$) and young (−9.7 ± 2.9%, $p < 0.05$) (mean ± SE), whereas voluntary muscle activation decreased more ($p < 0.05$) in old (−8.4 ± 3.5%, $p < 0.05$) compared to young (−1.1 ± 1.0%, ns) as did peak single (−25.8 ± 6.6%, $p < 0.05$ vs −7.6 ± 3.3%, $p < 0.05$) and doublet twitch force (−23.2 ± 5.5%, $p < 0.05$ vs −2.0 ± 2.6%, ns). All parameters were restored in young following 7 days recovery, whereas MVC and peak twitch force remained suppressed in old. Regression analysis revealed that disuse-induced changes in MVC relied more on changes in single twitch force in young ($p < 0.05$) and more on changes in voluntary muscle activation in old ($p < 0.05$), whereas recovery-induced changes in MVC mainly were explained by gains in voluntary muscle activation in both young and old. Altogether, the present data demonstrate that plasticity in voluntary muscle activation (~central neural drive) is a dominant mechanism affecting short-term disuse- and recovery-induced changes in muscle strength in older adults.

1. Introduction

Periods of short-term disuse (~acute physical inactivity) occur frequently in older individuals (> 65 years) due to disease or injury that involve hospitalization and/or bed rest (Brown et al., 2009; Engberg et al., 2009; Gill et al., 2009; Isaia et al., 2010; Pedersen et al., 2013). During clinical admission, length of hospital stay (LOS) often span 4–6 days in older individuals depending on the causes of hospitalization (Cookson and Laudicella, 2011; Lippuner et al., 2011; Saczynski et al., 2010; Traissac et al., 2011), and generally introduce a marked reduction in weight-bearing activities (Brown et al., 2009; Pedersen et al., 2013). Studies that have examined the influence of short-term disuse (lasting 4–14 days) on parameters of lower limb mechanical muscle function (e.g. strength, power, rate of force development (RFD)) in healthy old individuals (range of mean age in these studies = 66–73 years) have consistently reported marked decrements (Boesen et al., 2014;Deschenes et al., 2008; Deutz et al., 2013; Hvid et al., 2010; Hvid et al., 2014; Kortebein et al., 2008; Pisot et al., 2016; Reidy et al., 2017; Suetta et al., 2009; Tanner et al., 2015; Wall et al. 2014), which in turn increases the risk of limitations in physical function, loss of independency and elevated mortality (Cesari et al., 2009; Covinsky et al., 2003; Gill et al., 2009; Isaia et al., 2010; Newman et al., 2006). These impairments in mechanical muscle function appear to occur very rapidly following onset of disuse, and demonstrate a greater overall rate of decline in the initial phase of disuse (days) in old compared to young individuals (Deschenes et al., 2008; Hvid et al., 2010;

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https://doi.org/10.1016/j.exger.2018.02.019
Received 11 July 2017; Received in revised form 17 February 2018; Accepted 19 February 2018
Available online 21 February 2018
0531-5565/

Hvid et al., 2014; Pisot et al., 2016; Reidy et al., 2017; Suetta et al., 2012; Tanner et al., 2015) that is followed by an attenuated rate of decline over the subsequent course of time (weeks) (Hvid et al., 2014; Suetta et al., 2012). Moreover, older individuals tend to demonstrate a reduced rate of recovery in parameters of mechanical muscle function following post-disuse rehabilitation (typically including progressive resistance training) compared to younger individuals, particularly during the initial phase of recovery (days-to-weeks) (Hvid et al., 2014; Pisot et al., 2016; Sarabon and Rosker, 2013). Altogether, these age-related trends are of strong relevance given the fact that even prior to disuse, healthy older individuals demonstrate lower levels of muscle strength, power and RFD compared to their younger counterparts (Aagaard et al., 2010).

While changes in muscle mass indisputable is a main peripheral mechanism contributing to disuse- and recovery-induced adaptations in mechanical muscle function (Wall et al., 2013), which has been emphasized in many of the aforementioned studies (Hvid et al., 2010; Hvid et al., 2014; Pisot et al., 2016; Reidy et al., 2017; Suetta et al., 2009; Tanner et al., 2015; Wall et al., 2013), so far only two studies have examined the effects of short-term disuse on other potential central and peripheral mechanistic factors in older individuals (Deschenes et al., 2008; Suetta et al., 2009), with none of them studying disuse periods < 7 days. From a scientific point of view, this is quite surprising for two reasons. First, previous short-term disuse studies involving older individuals have consistently reported a disproportionally greater decline in mechanical muscle function (e.g. isometric muscle strength) compared to that of muscle mass (Boesen et al., 2014; Dirks et al., 2014; Kortebein et al., 2008; Pisot et al., 2016; Reidy et al., 2017; Suetta et al., 2009; Tanner et al., 2015) which suggest that alterations in central and peripheral factors - apart from muscle mass - are also likely to contribute to the disuse- and recovery-induced adaptations in mechanical muscle function at old age. Second, as a well-established hallmark within the area of exercise physiology, central factors (i.e. neural adaptations) has predominantly been used to explain “early phase” (days-to-weeks) adaptations in mechanical muscle function induced by physical training (Del Balso and Cafarelli, 2007; Kamen and Knight, 2004) whereas muscle hypertrophy has predominantly been used to explain “late phase” (weeks-to-months) adaptations (Wall et al., 2013). Yet the former aspect has not previously been examined in older individuals undergoing short-term disuse. Interestingly, by applying the superimposed twitch technique our research group previously observed age-dependent changes in voluntary muscle activation (~proxy of central neural drive) obtained during maximal isometric knee extension following 14 days of lower limb disuse and subsequent 28 days of active recovery (reloading), with much larger effects observed for this parameter in older versus younger individuals (Suetta et al., 2009). This observation is supported by observations from Deschenes and colleagues demonstrating a greater decrease in muscle EMG activity during maximal isometric knee extension in old versus young individuals following 7 days of disuse (Deschenes et al., 2008). These findings altogether indicate that aging may amplify the reduction in central neural drive following short-term disuse, potentially constituting a dominant mechanistic factor parallel to that of muscle atrophy. Further emphasizing the plasticity in central neural drive associated with disuse or use (loading/reloading), physical training have been shown effective in improving voluntary muscle activation in older individuals (Arnold and Bautmans, 2014), and importantly to be positively associated with concurrent improvements in maximal walking speed in mobility-limited older individuals (Hvid et al., 2016).

Peripheral factors such as intrinsic muscle contractility may also undergo marked changes in response to both short-term disuse and recovery. To assess muscle contractility independently of central neural drive, electrically evoked muscle twitch properties following disuse and recovery have been examined in both animal (Witzmann et al., 1982a; Witzmann et al., 1982b) and human studies (Gondin et al., 2004; Suetta et al., 2009). However, to our best knowledge electrically evoked muscle twitch properties were only examined in older individuals in one of the two previous human studies (Suetta et al., 2009) (discussed above), revealing disuse- and recovery-induced changes in evoked single twitch properties that were of similar magnitude in young and old individuals (Suetta et al., 2009).

As outlined above, experimental data on the underlying potential mechanisms involved in the central and peripheral adaptations elicited by short-term disuse and subsequent recovery in older adults are sparse. The purpose of the present study, therefore, was (1) to investigate the effect of 4 days lower limb disuse followed by 7 days active recovery on maximal knee extensor isometric muscle strength, voluntary muscle activation, and electrically evoked muscle twitch properties in young and old healthy individuals, and (2) to investigate to what extent alterations in maximal knee extensor isometric muscle strength might be attributed to changes in central neural drive versus changes in peripheral muscle contractile properties. It was hypothesized that more pronounced alterations in voluntary muscle activation would be observed in old versus young participants in response to short-term disuse and subsequent recovery (reloading).

2. Material and methods

2.1. Subjects

While the present study focused on the relative contribution of adaptations in central neural drive and peripheral muscle contractility on changes in isometric muscle strength following short-term disuse and subsequent active recovery in young and old individuals, detailed information on the study design and additional data have been published previously (Hvid et al., 2014; Hvid et al., 2013; Suetta et al., 2012).

Responding to advertisement in local newspapers, 23 healthy men volunteered to participate in the study, however one subject failed to adhere to the disuse protocol and consequently data from this subject was omitted. Thus, 11 old (67.2 ± 1.0 yrs. (range 60–72 yrs), 178.8 ± 1.7 cm, 87.7 ± 3.0 kg) and 11 young subjects (24.3 ± 0.9 yrs. (range 20–30 yrs), 180.4 ± 2.7 cm, 74.3 ± 2.4 kg) completed the study protocol. Body weight differed between young and old ($p < 0.05$), and remained unaffected during the study period. All subjects were healthy and had no history of illness or intake of medicine that could potentially affect skeletal muscle anatomy, physiology or function. None of the included subjects had previously performed resistance training on a regular basis. Using questionnaire assessment (Saltin and Grimby, 1968), both young and old were moderate-to-vigorously physically active in terms of their participation in occupational and recreational activities corresponding to 4.3 ± 0.6 vs 4.4 ± 0.6 h·wk^{-1}, respectively (time spent in vigorous activities: 1.8 ± 0.2 vs 1.7 ± 0.3 h·wk^{-1}, respectively). All subjects were informed of the risks associated with the investigation and provided written informed consent. The study (KF01-322606) was approved by the local Ethics Committee of Copenhagen and adhered to the Helsinki declaration.

2.2. Experimental procedures

Subjects underwent 4 days of unilateral lower limb disuse followed by 7 days of active recovery which included one session of high-intense resistance training. The length of the disuse period was chosen to experimentally resemble the short duration(s) of disuse typically encountered in real-life settings (hospital length of stay (LOS) corresponding to an average of 4–6 days in older individuals, depending on the causes of hospitalization) (Cookson and Laudicella, 2011; Lippuner et al., 2011; Saczynski et al., 2010; Traissac et al., 2011), while the length of the active recovery period was chosen to be approximately twice as long based on previous study reports (Hortobagyi et al., 2000; Hvid et al., 2010; Labarque et al., 2002). The contra-lateral (non-