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Influence of obesity on skeletal muscle contractile dysfunction in aging

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Abstract Obesity and aging reduce skeletal muscle contractile function, which represents a reduction in muscle quality. Dysfunction of muscle contraction may contribute to a greater risk for diabetes, cardiovascular diseases, and cancer; therefore, the synergistic effects of obesity and aging on muscle function may exacerbate morbidity and mortality. However, evidence directly examining the synergistic effects of obesity and aging on muscle contractile function is lacking and controversial. We recently demonstrated that diet-induced obesity significantly exacerbates contractile dysfunction in aged skeletal muscle. The focus of this review is the effects of obesity on muscle contractile dysfunction in skeletal muscle, particularly during aging.

Keywords : obesity, skeletal muscle, contraction, calcium, sarcoplasmic reticulum, high-fat diet

Introduction

Skeletal muscle is the most abundant tissue in the human body and is important for maintaining a healthy body composition, physical function, and locomotion. In particular, skeletal muscle contractile function depends on muscle mass and is closely related to physical performance. However, physical function declines with age, and it was shown that decreased muscle strength, but not reduced muscle mass, was associated with increased mortality^{1,2}. On the other hand, obesity due to overeating and lack of exercise causes major health problems worldwide^{3,4}. A previous study has demonstrated that decreased muscle strength is observed in obese young adults⁵. These studies suggest that obesity accelerates muscle weakness in the elderly population and causes various aging-related diseases.

We recently demonstrated that diet-induced obesity impaired contractile force during *ex vivo* muscle contraction independently of muscle mass loss⁶. Furthermore, the observed muscle contractile dysfunction in metabolic disease may be induced by impaired contraction-relaxation cycling, which depends on the capacity for Ca^{2+} release and reuptake by the sarcoplasmic reticulum (SR)⁷. This review considers the influence of obesity on skeletal muscle contractile function during aging. Furthermore, this review discusses the mechanisms underlying diet- and age-induced muscle contractile dysregulation, focusing on SR Ca^{2+} cycling.

Effect of obesity on skeletal muscle contraction

The influence of obesity on impaired muscle strength

caused by aging is an important issue, but it remains unclear how obesity affects muscle quality (force/power normalized to muscle mass) because it is difficult to examine *in vivo*⁸⁻¹⁰. Thus, isolated muscle contraction force *ex vivo* is measured by electrical stimulation, which can provide information about contractile function normalized to muscle mass, i.e., assessment of muscle quality^{11,12}. A previous study showed that diet-induced obesity results in not only muscle loss, but also muscle weakness¹³. Furthermore, previous studies demonstrated that muscle strength normalized to fiber size is decreased in obese humans¹⁴, and diet-induced obesity impaired muscle contractile force per muscle mass in a rodent model⁶. These results suggest that obesity can lead to lower muscle quality, which might lead to reduced physical performance.

As shown in Fig. 1, we recently demonstrated that long-term, but not short-term, high-fat diet (HFD)-induced obesity causes decreased muscle tetanic contractile force independently of muscle mass in fast-twitch dominant muscle in mice, suggesting that the main factor in reducing the contractile force is metabolic impairment depending on feeding duration⁶. Consistent with our data, HFD consumption for a period shorter than 8 weeks has little effect on muscle contractile force^{15,16}. On the other hand, Tallis and colleagues showed that body fat accumulation is associated with reduced contractile force and independent of the feeding duration in obese female mice¹⁷. Furthermore, another study showed that obese female mice fed a 16-week HFD did not show any influence on contractile force in skeletal muscle¹⁸. Thus, the effect of obesity on contractile function might be influenced by the duration of HFD and gender, and further investigations are required to clarify these effects.

Effect of obesity on muscle contractile dysfunction in aging

Age-induced loss of muscle mass and function (sarcopenia) is a highly significant and prevalent problem and an unmet medical need. In particular, the mechanism by which muscle contractile force is significantly reduced in aged muscle and in the context of obesity has received little attention¹⁹⁻²³. It has been reported that muscle force production normalized to muscle mass is substantially lower in aged mice²⁰. Consistent with this, many studies have demonstrated skeletal muscle contractile dysfunction in mice with HFD-induced obesity^{24,25}, but it remains unclear whether obesity further exaggerates impaired

muscle contractile force induced by aging. A previous study demonstrated that 14-month-old mice that consumed a HFD for 5 months exhibited decreased skeletal muscle strength compared to mice fed a low-fat diet²⁶. Another study showed that the contractile force was lower in 50-week-old mice that had consumed a HFD for 30 weeks than in mice fed a normal diet²⁴. Taken together, these studies suggest that the synergistic effects of obesity and aging may exacerbate muscle contractile dysfunction.

As shown in Fig. 2, we recently demonstrated that chronic high-fat feeding (20 months) significantly reduced contractile force in fast-twitch dominant muscles, but not slow-twitch dominant muscle in aged skeletal muscle²⁷. Consistent with this finding, impairment of

Fig. 1 A long-term high-fat diet (HFD), but not a short-term HFD, impairs contractile force in fast-twitch muscle. Isometric tension at several frequencies (force-frequency relationship) was determined in the extensor digitorum longus muscles from control (CONT) mice and mice fed a 4-week HFD (A) or 12-week HFD (B). *Significant difference between the CONT and HFD groups ($P < 0.05$). Values shown are the means $\pm$ SEs. From Eshima et al⁶.

Fig. 2 Chronic high-fat feeding (20 months) accelerates muscle weakness in fast-twitch dominant muscles, but not slow-twitch dominant muscle, in aged mice. Specific force-frequency relationship in the extensor digitorum longus (EDL) muscle (A) and in the soleus (SOL) muscle (B). The specific force was calculated from the absolute force, muscle weight and muscle length. LFD: low-fat diet, HFD: high-fat diet. * $p < 0.05$ vs. 4-month LFD. † $p < 0.05$ vs. 4-month HFD and 20-month LFD. Values shown are the means $\pm$ SEs. From Eshima et al²⁷.

contractile function in obese and aging skeletal muscle might be fiber type-specific. For instance, in terms of the fiber type that is affected by HFD, recent studies that include our own research, have shown that only fast-twitch muscle, not slow-twitch muscle, exhibits a reduction in specific force in mice with HFD-induced obesity^{6,18}. This phenomenon also occurs in skinned fibers from aged humans, where the contractile force was reduced in fast-twitch dominant muscle (Type II) from aged humans compared to those from young humans²⁸. In contrast, aged mice fed a high-fat diet for 9 weeks did not exhibit an alteration in contractile force in fast-twitch dominant muscles compared to lean aged mice²⁹. Similarly, a previous study using single muscle fibers reported that the specific force was also substantially lower in slow-twitch dominant muscle (Type I) from obese adults than that of normal-weight adults¹⁴. Therefore, fundamental questions for understanding muscle weakness associated with aging and/or obesity remain to be more fully addressed.

Mechanism of contractile dysfunction in obesity and aging

The molecular basis of contractile apparatus dysfunction that occurs with age and obesity is uncertain. One putative mechanism for functional alterations in skeletal muscle relates to impairments of Ca^{2+} -dependent processes known as excitation-contraction coupling, as may be the case in cardiac muscle^{11,30}. In fact, impair-

ment of Ca^{2+} release from the SR has been reported in aged skeletal muscle^{20,31}. In particular, ryanodine receptor (RyR) from aged mice was oxidized and depleted of the channel-stabilizing subunit calstabin1, causing $[\text{Ca}^{2+}]$ leakage in skeletal muscle²¹. Consistent with this finding, a previous study demonstrated impaired Ca^{2+} release during muscle contraction in ob/ob mice, which are a model of obesity³². Furthermore, the db/db mouse, a model of obesity associated with type 2 diabetes, demonstrates contractile dysfunction and reduced SR Ca^{2+} -ATPase (SERCA) content in skeletal muscle³³. Indeed, we also observed impairment of muscle contractile force and Ca^{2+} regulation in male db/db mice⁷. These results suggest that dysfunctional Ca^{2+} flux may contribute to skeletal muscle contractile dysfunction in obesity and aging. However, to our knowledge, there is no direct evidence showing whether obesity further exaggerates the impaired SR Ca^{2+} cycling induced by aging.

We investigated the effects of HFD-induced obesity and aging on impaired SR Ca^{2+} cycling in skeletal muscle. Consistent with contractile force (Fig. 2), electrically stimulated Ca^{2+} peak levels were also reduced by aging and HFD feeding, with additive effects in aged HFD-fed mice. Experiments with RyR agonists (4-chloro-m-cresol, and caffeine) also support this notion (Fig. 3). Furthermore, we found a consistent reduction in sarcalumenin, which is a Ca^{2+} -binding protein localized in the SR of the intracellular Ca^{2+} store³⁴⁻³⁶, in the skeletal muscles of aged mice. Our data suggest that impairment of the contractile

Fig. 3 Electrically and pharmacologically RyR-stimulated Ca^{2+} peak levels were reduced by aging and high-fat diet (HFD) feeding, with additive effects in aged HFD-fed mice. Average peak Ca^{2+} responses (fluoro-4 fluorescence) during twitch and tetanus stimulation (A). Average peak Ca^{2+} responses (fura-2 fluorescence) during 4-chloro-m-cresol (4-CmC) with or without 30 mM MgCl_2 stimulation (B). Average peak Ca^{2+} responses (fura-2 fluorescence) in the presence of low and high concentrations of caffeine (C). The peak fluorescence intensity (F or R; ratiometric images) during stimulation was measured, and the quantified data are shown in the graph as changes from the prestimulation level (F_0 or R_0). $[\text{Ca}^{2+}]_i$ is expressed as the delta ratio (delta F/F_0 or delta R/R_0). LFD: low-fat diet, HFD: high-fat diet. $[\text{Ca}^{2+}]_i$ measurement was performed in intact flexor digitorum brevis muscles. Values shown are the means $\pm$ SEs. * $p < 0.05$ vs. 4-month LFD. # $p < 0.05$ vs. 4-month HFD. † $p < 0.05$ vs. 4-month HFD and 20-month LFD. From Eshima et al²⁷.

Fig. 4 Schematic diagram of the working hypothesis. Obesity and aging reduce skeletal muscle contractile function, which may be due at least in part to dysfunction in intracellular Ca^{2+} release from the sarcoplasmic reticulum. On the other hand, exercise is generally assumed to be effective for the prevention of obesity and sarcopenia. We proposed that efficient exercise might ameliorate muscle weakness in these patients due to the improvement of dysfunction in Ca^{2+} cycling.

force in aged muscle is aggravated by HFD-induced obesity, which may be due at least in part to dysfunction of intracellular Ca^{2+} release from the SR.

A previous study showed that exercise training elevated proteins involved in skeletal muscle Ca^{2+} cycling in mice³⁷⁾. Our group and other groups demonstrated increased protein expression of sarcalumenin in the muscle during aging³⁸⁾ and in type 2 diabetes⁷⁾. In addition, a previous study suggested that sarcalumenin is involved in exercise ability after endurance exercise training³⁹⁾. Collectively, it is expected that exercise intervention may increase the Ca^{2+} store content and improve calcium handling and contractile dysfunction in the muscle. Because exercise interventions are beneficial for improving obesity⁴⁰⁾ and sarcopenia^{41,42)}, we propose that exercise might attenuate muscle weakness through improved SR Ca^{2+} cycling (Fig. 4).

Conclusion

The present review provides evidence that diet plays an important role in the maintenance of skeletal muscle contractile properties. We propose that these diet-dependent effects are equally relevant to aging. This phenomenon might be involved in dysfunctional SR Ca^{2+} cycling. Further studies should examine whether combinations of exercise and nutrition might enable the amelioration of skeletal muscle weakness in obesity and aging.

Conflict of Interests

No conflict of interests, financial or otherwise, are declared by the author.

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