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No effect of anti-inflammatory medication on postprandial and postexercise muscle protein synthesis in elderly men with slightly elevated systemic inflammation

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ABSTRACT

Background: Based on circulating C-reactive protein (CRP) levels, some individuals develop slightly increased inflammation as they age. In elderly inflamed rats, the muscle response to protein feeding is impaired, whereas it can be maintained by treatment with non-steroidal anti-inflammatory drugs (NSAIDs). It is unknown whether this applies to elderly humans with increased inflammation. Thus, the muscle response to whey protein bolus ingestion with and without acute resistance exercise was compared between healthy elderly individuals and elderly individuals with slightly increased inflammation ± NSAID treatment.
Methods: Twenty-four elderly men (>60 years) were recruited. Of those, 14 displayed a slightly increased systemic inflammation (CRP > 2 mg/l) and were randomly assigned to NSAID (Ibuprofen 1800 mg/day) or placebo treatment for 1 week. The remaining 10 elderly individuals served as healthy controls (CRP < 1 mg/l). The muscle protein synthetic response was measured as the fractional synthetic rate (FSR) and p70S6K phosphorylation-to-total protein ratio.
Results: The basal myofibrillar FSR and the myofibrillar FSR responses to whey protein bolus ingestion with and without acute resistance exercise were maintained in inflamed elderly compared to healthy controls ($p > 0.05$) and so was p70S6K phosphorylation. Moreover, NSAID treatment did not significantly improve the myofibrillar and connective tissue FSR responses or reduce the plasma CRP level in inflamed, elderly individuals ($p > 0.05$).
Conclusion: A slight increase in systemic inflammation does not affect the basal myofibrillar FSR or the myofibrillar FSR responses, which suggests that elderly individuals with slightly increased inflammation can benefit from protein ingestion and resistance exercise to stimulate muscle protein anabolism. Moreover, the NSAID treatment did not significantly affect the myofibrillar or connective tissue FSR responses to protein ingestion and acute resistance exercise.

1. Introduction

Aging is characterized by a gradual loss of muscle mass (sarcopenia) and strength (dynapenia), which can ultimately lead to decreased mobility and disability. Even though the development of dynapenia may only partly be caused by sarcopenia (Clark and Manini, 2008; Newman et al., 2003), the present study focused mainly on the regulation of muscle mass through changes in muscle protein synthesis. Although ingestion of protein and muscular activities are important factors in daily life to maintain muscle mass, the muscle anabolic response to hyperaminoacidemia and exercise stimuli has been demonstrated to be somewhat reduced with advancing age (Fry et al., 2011; Katsanos et al., 2005; Katsanos et al., 2006). Moreover, this anabolic resistance has been suggested to contribute to the reduction in muscle mass and strength observed in elderly individuals (Fry et al., 2011; Haran et al., 2012; Katsanos et al., 2005). Thus, a further understanding of which age-dependent factors may contribute to the anabolic resistance is important for the development of interventions that can

Abbreviations: CRP, C-reactive protein; FSR, fractional synthetic rate; NSAID, non-steroidal anti-inflammatory drug; TNF-α, tumor necrosis factor α; IL-6, interleukin-6; OA, osteoarthritis; BMI, body mass index; ALM, appendicular lean mass; 1RM, one repetition maximum; DXA, dual-energy X-ray absorptiometry; LBM, lean body mass; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ELISA, enzyme-linked immunosorbent assay; CV, coefficient of variation; NAP, *N*-acetyl-n-propyl; GC-C-IRMS, gas chromatograph-combustion-isotope ratio mass spectrometer; p70S6K, ribosomal protein S6 kinase; ANOVA, analysis of variance.

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counteract the anabolic resistance and, therefore, potentially may slow down the sarcopenic process.

One of the suggested mechanisms behind anabolic resistance is a slight increase in systemic inflammation (Balage et al., 2010; Rieu et al., 2009). In human individuals, the C-reactive protein (CRP) is regarded as the most general and nonspecific inflammatory marker (Macy et al., 1997; Ridker, 2003; Vigushin et al., 1993). Moreover, the CRP production can be stimulated by the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) (Bruunsgaard and Pedersen, 2003). Based on the circulating levels of CRP and IL-6, some individuals experience a slight increase in systemic inflammation during aging, apparently without any clear state of pathology (Bruunsgaard and Pedersen, 2003; Donato et al., 2008; Ferrucci et al., 2005; Gurven et al., 2008; Miles et al., 2008; Schaap et al., 2006; Stowe et al., 2010). In addition to the increased inflammation, these elderly individuals are often characterized by increased body mass index (BMI) and adiposity (Festa et al., 2000; Hamer and Steptoe, 2009; Miles et al., 2012; Murton et al., 2015; Shanely et al., 2013), as well as diminished muscle mass and strength when compared to healthy (non-inflamed) elderly peers (Bautmans et al., 2005; Newman et al., 2003; Schaap et al., 2006; Schaap et al., 2009).

Recently, it was demonstrated that even in a very homogenous group of recreationally active elderly, the CRP level is negatively associated with skeletal muscle mass (Wåhlin-Larsson et al., 2014). Moreover, the prevalence of sarcopenia (classified by appendicular lean mass (ALM)/BMI ≤ 0.789 in elderly men (Cawthon et al., 2014; Prior et al., 2016)) was recently found to be strongly associated with CRP level (Batsis et al., 2016). Additionally, circulating levels of CRP and IL-6 were negatively correlated with the basal (resting, postabsorptive) mixed muscle fractional synthetic rate (FSR) in young and elderly humans (Toth et al., 2005). Furthermore, in elderly rats with low-grade inflammation, basal mixed muscle FSR was unaffected, whereas the postprandial stimulation of FSR was blunted compared to healthy, elderly rats (Balage et al., 2010). However, treatment with the non-steroidal anti-inflammatory drug (NSAID), ibuprofen, prevented the development of inflammation and maintained the anabolic response to food intake in elderly rats (Rieu et al., 2009). Recently, it was shown that the postprandial level of mixed muscle FSR was equal between healthy elderly (CRP < 1 mg/l) and elderly with slightly increased inflammation (CRP > 2 mg/l) (Buffière et al., 2015). However, in the study by Buffière et al. (2015), a continuous protein ingestion pattern was used, which is not fully representative for the normal protein bolus ingestion of the general population. Moreover, the continuous ingestion pattern did most likely only induce a slight increase in plasma amino acid concentrations (especially leucine) and a suboptimal stimulation of the postprandial FSR (Rieu et al., 2006). Indeed, a continuous protein ingestion pattern has been demonstrated to result in a lower FSR response compared to protein bolus ingestion (West et al., 2011). Furthermore, the 5-hour postprandial FSR measuring period in the study by Buffière et al. (2015)) may have resulted in dilution of the peak muscle FSR response because the FSR most likely peaks during the first hours after ingestion in resting muscles (Bohé et al., 2001). Thus, it remains an open question whether the postprandial FSR response is reduced in elderly individuals with slightly increased inflammation compared to healthy elderly individuals after ingestion of a protein bolus during the initial postprandial period with hyperaminoacidemia. Additionally, because the anabolic response only has been addressed in mixed muscle proteins, it is unknown if the FSR response differs between subfractions of structural muscle proteins (i.e., the myofibrillar and connective tissue proteins).

The muscle anabolic response to protein ingestion stimuli can be enhanced by muscular activity (Biolo et al., 1997), but it has not been investigated if, and to what degree, prior acute resistance exercise affects the anabolic response to protein bolus ingestion in elderly with slightly increased inflammation compared to healthy elderly individuals. Regarding the muscle anabolic response induced by acute exercise, it has been shown that ibuprofen diminishes the exercise-induced increase and mixed muscle FSR (Trappe et al., 2002) in young, healthy individuals. In elderly osteoarthritis (OA) patients, ibuprofen was found not to affect myofibrillar FSR at rest or after exercise compared to a placebo (Petersen et al., 2011b). In accordance, ibuprofen did not affect muscle hypertrophy after 12 weeks of resistance training in patients with knee OA, even though the CRP level only decreased significantly in the ibuprofen group (Petersen et al., 2011a). However, the maximal isometric strength increased more with ibuprofen compared to a placebo (Petersen et al., 2011a). Furthermore, it was shown that ibuprofen induced additional muscle hypertrophy and strength gains in healthy elderly individuals during 12 weeks of resistance training (Trappe et al., 2011). Interestingly, the non-trained hamstring muscles did not hypertrophy (Trappe et al., 2011), which indicates that the additional effect of ibuprofen was specific to the exercised muscles and was not related to systemic inflammation.

The primary objective of the present study was to determine whether the basal FSR and the FSR response to whey protein bolus ingestion were impaired in individuals with slightly increased inflammation and whether it could be affected by NSAID treatment. Secondly, the study aimed at investigating whether the FSR response to acute resistance exercise in combination with whey protein was affected in individuals with increased inflammation and whether NSAID treatment would influence this response. It was hypothesized that the myofibrillar FSR response to protein bolus ingestion would be reduced in inflamed, elderly individuals compared to healthy elderly individuals and that NSAID treatment would improve the FSR response to acute resistance exercise in inflamed, elderly individuals.

2. Methods

2.1. Intervention protocol

2.1.1. Subject recruitment

Twenty-four elderly individuals were included in the present study. Based on standard laboratory blood tests and by a health, exercise, and nutrition questionnaire, the individuals were considered suitable for inclusion. Inclusion criteria were the following: non-smokers, age ≥ 60 years, BMI ≥18.5 kg/m^2, Western diet (protein content >0.8 g/kg/day), moderately active but with no regular participation in heavy resistance exercise within the last 6 months, and absence of cancer, metabolic, cardiac, or neurological diseases. Finally, the individuals were instructed not to take any kind of analgesic medication at least 2 weeks prior to the study. Each individual was given written and oral information about the study design, purpose, and possible risks before submitting written consent to participate. The project adhered to the Helsinki declaration II and was approved by the Ethics Committee of Region Hovedstaden (H-4-2011-028).

2.1.2. Pre-experiment tests

In the present study, elderly individuals with slightly increased systemic inflammation (plasma CRP > 2 mg/l), but who otherwise appeared healthy, were included and compared to healthy elderly controls with a plasma CRP <1 mg/l. To locate elderly individuals with increased inflammation, a total of 100 elderly (≥60 years) males were screened by telephone. Of these, 56 individuals did comply with the study criteria and were prescreened for their CRP level by blood samples taken approximately 4 weeks before the experimental day. Based on the CRP concentration in that blood sample, the individuals were allocated to either the inflamed groups or the healthy control group. One week before the experimental day and again at the experimental day, blood samples were drawn in order to follow the CRP level. Of the 56 screened elderly, 14 individuals had a CRP level above 2 mg/l, which is considered to be high in relation to the normal, subclinical (CRP < 10 mg/l) range (Buffière et al., 2015). In other words, 25% of the screened elderly individuals had slightly increased systemic inflammation, which is in