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Mechanisms of resistance exercise-induced muscle hypertrophy: 'You can't make an omelette without breaking eggs'

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It is well established that resistance exercise (RE) is a potent stimulus for skeletal muscle hypertrophy. As a result, a plethora of research has been directed towards unravelling the complexity of mechanisms driving these muscular changes in order to establish how RE training variables might best be manipulated to optimize phenotypic adaptations, with important implications for athletic performance and prevention of a myriad of negative health complications (e.g. sarcopenia, metabolic diseases and rheumatoid- and osteoarthritis).

Major breakthroughs in the field have arisen from studies utilizing the muscle biopsy technique and arteriovenous catheterization in conjunction with the infusion of one or multiple stable amino acid (AA) isotope tracers. Measuring the rate of appearance and/or disappearance of isotopic tracer(s) in various skeletal muscle protein sub-fractions (predominantly myofibrillar or sarcoplasmic) or across the artery–vein has demonstrated that skeletal muscle mass is regulated via temporal fluctuations in muscle protein synthesis (MPS) and muscle protein breakdown (MPB) (Atherton & Smith, 2012). Individuals undertaking RE in the post-absorptive state mount a robust increase in the acute MPS response alongside elevated MPB rates, such that net protein balance (NPB) remains negative. However, when an adequate amount of high-quality protein is consumed in close proximity to the RE bout, the MPS response is potentiated and a positive NPB is achieved. Over time, the accumulation of periods of positive NPB leads to skeletal muscle protein accretion, manifested as increased muscle fibre cross-sectional area and an increased muscle mass.

Although we are slowly beginning to understand the principle molecular and metabolic mechanisms underpinning muscle hypertrophy, a lot is yet to be discovered. Acute stable AA isotope infusion trials to assess MPS and MPB have proven extremely insightful; however, this method is not without limitations. First, it is extremely difficult to measure the true precursor (labelled tRNA) when using the precursor–product approach to calculate fractional synthesis rate. Second, and perhaps more importantly, this approach does not offer the opportunity to assess MPS in a free-living environment over an extended period (e.g. over the course of a training regimen) as extended AA isotope infusions lead to participant discomfort and are extremely costly. These limitations are important as it has been reported that a discord exists between the MPS response to an acute bout of RE (at the onset of training) and the chronic muscle remodelling that occurs over the course of prolonged RE training, thought to be due to the limited window in which exercise-induced MPS rates can be captured using stable AA isotope tracer infusions (Mitchell *et al.* 2014). Circumventing these issues to increase RE research validity is critical in order to understand the complex relationship between temporal fluctuations in MPS and long-term muscle remodelling, and might be accomplished by incorporating the use of deuterium oxide (D_2O), an isotopic tracer that has seen a resurgence in recent years.

A recent article published in *The Journal of Physiology* by Damas and colleagues (2016) attempted to address one of the major limitations in isotopic tracer research, investigating long-term rates of MPS in a free-living environment over the course of RE training. In an elegantly designed study, 10 young, previously untrained males underwent a 10 week, twice per week, lower-limb RE training programme. Each RE session comprised three sets of 9–12 repetitions until volitional fatigue. Rates of myofibrillar protein synthesis (MyoPS) were measured over a 48 h period after the first, the fifth and the final RE training session using oral D_2O consumption. Furthermore, muscle damage was assessed directly by Z-band streaming and indirectly via plasma creatine kinase (CK), subjective soreness, and maximal knee extensor strength. Hypertrophy was assessed via change in fibre and vastus lateralis cross sectional area (fCSA and VL CSA).

As expected, the authors demonstrated that MyoPS was elevated at 24 and 48 h following the first training bout, although this response became somewhat attenuated after the fifth and final training bout. These observations provide support for the refinement in exercise-induced rates of MPS over the course of continuous RE training. Indirect muscle damage markers followed an expected pattern, with CK and subjective soreness increasing and knee extensor strength decreasing after the first training bout, whereas only soreness increased after the fifth and final training bouts. Moreover, muscle damage (Z-band streaming) was significantly greater than pre-training basal levels after the first training bout, gradually decreasing thereafter. Thus, RE-induced MyoPS rates and indices of muscle damage appear to subside over the course of long-term training. Intriguingly, a significant correlation was found between the increase in VL, fCSA and integrated MyoPS rates after the fifth and final training bouts. However, when corrected for muscle damage, the integrated MyoPS response did not differ over time, which although not definitive, lends support to the notion that elevated MyoPS rates in the early phase of RE training are largely directed towards muscle repair, whilst elevations in the later phase of RE training are more likely to support muscular hypertrophy. Interestingly, the idea that MPS may be directed towards repairing muscle damage at the onset of training might explain the discord between RE-induced MPS at the onset of training and long-term muscle hypertrophy observed by others (Mitchell *et al.* 2014) in previously untrained individuals.

The novel insights provided by Damas and colleagues are particularly interesting when compared with the recent findings of Brook and colleagues (2015). In this study, participants underwent a 6 week, 3 times per week, unilateral moderate-intensity RE training model consisting of six sets of eight repetitions. RE sessions were followed by bilateral muscle biopsies 60–90 min post-RE in the first, third and sixth week of training using D_2O to calculate integrated MyoPS

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rates. The authors observed elevated MyoPS rates in the initial RE phase (0–3 weeks) in the trained compared with the untrained control leg, whereas MyoPS rates did not differ between legs during the later phase of training (3–6 weeks). These findings were supported by a dampened anabolic signalling response in the mTORC1 pathway and a suppressed increase in muscle thickness, fibre pennation angle and length beyond the first 3 weeks of training. Combined, the findings of Brook and colleagues suggest that muscle hypertrophy predominates during the early phase of a RE training regime.

At first, the findings of Brook and colleagues appear to contradict those of Damas and colleagues in that hypertrophy appears to dominate the early stages of RE training in the former study and later stages in the latter study. This discrepancy could be attributed to the fact that Damas and colleagues measured integrated MyoPS rates over a 48 h post-exercise period, which is more likely to result in greater MyoPS rates compared to when MyoPS rates are measured in the order of weeks, as was the case in the study of Brook and colleagues (thereby incorporating multiple sinusoidal patterns of MPS responsiveness).

Although not immediately apparent, both studies (Brook *et al.* 2015; Damas *et al.* 2016) demonstrate similar findings in that a robust increase in MyoPS to an initial RE bout is observed, and that there is an attenuation of MyoPS with continued exposure to a RE stimulus.

The novel findings by Damas *et al.* (i.e. correlating MyoPS with direct markers of muscle damage over time) have provided us with another important step forward in understanding the mechanisms through which resistance exercise-induced muscle hypertrophy is regulated. Translating these exciting results into a practical message would lead us to conclude that one has to train with a novel stimulus for at least 3 weeks before rewards can be reaped. Thus, it seems that a number of eggs need to be broken (or muscles damaged) before the 'hypertrophy omelette' can be cooked. The recent revival of D_2O tracer has proven to be an invaluable, affordable tool for the assessment of MyoPS and will open doors for future research investigating RE-induced regulation of muscle hypertrophy in a free-living environment. However, the adoption of D_2O tracer methodology should not necessarily lead to the expulsion of stable AA isotope tracers. On the contrary, both tracer techniques can complement one another and can be combined to inform us on both the more acute (0–24 h) and long-term effects (days–weeks–months) of stimuli leading to muscle hypertrophy. Nevertheless, the use of acute stable AA isotope infusions might yield more valuable findings in trained individuals, for whom the bulk of any early training damage symptoms would be expected to have subsided. Alas, it is important to remember also that an omelette has two sides that require cooking, and the continued pursuit of accurate and specific measures of muscle protein breakdown (specifically, myofibrillar) will provide greater insight into RE-induced regulation of muscle mass.

Nonetheless, Damas and colleagues are to be commended for their novel insights into the temporal regulation of RE-induced muscle hypertrophy by shedding light on the contribution of acute muscle damage to the long-term remodelling response. By attacking the complex question from a novel angle (i.e. correlating skeletal muscle damage to MyoPS rates), Damas and colleagues have added an important piece to the puzzle.

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Additional information

Competing interests

None declared.

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