What is the relationship between acute changes in muscle protein synthesis response and changes in muscle mass?

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Rates of synthesis of skeletal muscle protein pools (myofibrillar, mitochondrial, sarcoplasmic) are often directly measured through determination of the fractional synthetic rate (FSR) using stable isotope tracer labelled amino acids. This is accomplished by measuring the incorporation of tracer amino acid into muscle protein (bound enrichment), determining the enrichment of the precursor pool, and dividing the incorporation of amino acid tracer over a given period of time by the precursor enrichment yielding a rate in % per unit time (3, 22). Measures of muscle protein FSR, often referred to as muscle protein synthesis (MPS), have been routinely employed to examine the acute effects (i.e., several hours to 24 hours) of various exercise and nutritional stimuli. This begs the question as to whether acute early changes in MPS, particularly following resistance exercise (RE), relate to the magnitude of muscle hypertrophy in longer-term training studies? It has been proposed that chronic adaptation (i.e., muscle hypertrophy) with resistance training (RT) occur as a result of summed periods of repeated acute exercise-induced positive protein balance where MPS exceeds muscle protein breakdown (MPB) (20). In such a scenario, one thesis is that the clearly established heterogeneity of the hypertrophic response to resistance training (8, 14, 15) may be explained, to some degree, by divergent responses of MPS to acute exercise stimuli; but is this the case? It is possible the variations in MPB are also important for the regulation of muscle hypertrophy however, the measurement of MPB is hampered by methodological limitations and thus is reported infrequently. The magnitude of regulation of MBP is much smaller than MPS (7). Additional resistance exercise appears to regulate MPB and MPS in a concomitant manner (21). We believe that although it would be ideal to measure the balance between MPS and MPB that MPS is likely to have a greater relationship with hypertrophy than MPB.

To date, only a single study has reported the within-subject association between acute MPS rates after RE and skeletal muscle hypertrophy following prolonged RT (15). Another
study attempted to correlated MPS measured 24h after the first training session with muscle hypertrophy (14). In neither study was a linear correlation between MPS and hypertrophy observed (14, 15). The lack of a correlation between pre training measures of MPS and muscle hypertrophy after prolonged training may lead one to question the value of acute measurements of MPS to yield insight into phenotypic adaptations following RT. Nonetheless, while acute MPS response is not always quantitatively related to muscle hypertrophy, there are a number of examples where MPS response following an acute intervention (nutrition and/or exercise) is aligned with changes in muscle hypertrophy in different subject cohorts. Multiple studies from our laboratory (2, 3, 8, 16, 27, 28, 31), and others (9, 10) have demonstrated that patterns of change in acute (i.e. over several hours) of MPS response following a single session RE were aligned with the adaptive hypertrophic response following repeated exposure (i.e. for several weeks) to a similar dietary/exercise intervention. For example, the acute MPS response following post-RE consumption of milk versus a soy beverage (31) was qualitatively aligned with changes in lean body mass obtained following 12 weeks of RT and the same protein supplementation (8). In addition, the response of MPS following RE employing lower load contractions (3) and RE bouts employing greater volumes of work (three sets versus one set) (2), were congruent with the hypertrophic response following a period of RT employing these training protocols (16). However, the magnitude of the acute response of MPS and the subsequent hypertrophy with the same stimuli in RT is highly variable between individuals. The source of such hypertrophic variability is likely due to an individual’s inherited genetic predisposition, epigenetic influence, and transcriptional plasticity, all of which are likely further impacted by factors such as age, habitual physical activity, and training status. For example, multiple set training has been demonstrated to elicit a greater acute response of MPS (2) and training mediated muscle hypertrophy (12, 16) than single set training, however a ‘hypertrophic
A responder to resistance exercise may demonstrate a greater response both acutely (i.e. MPS), and in response to RT (i.e. muscle hypertrophy), following single set training, than a ‘non-responder’ to multi-set RT. We propose that the response heterogeneity to RT (8, 14) is often overlooked but it is inherently hard to modify and highlights the importance of adequate sample size to detect differences in the hypertrophic response to various exercise/nutritional stimuli.

In comparison to younger persons older persons have a lower MPS rates in response to protein feeding and exercise (5, 13, 17), a condition termed ‘anabolic resistance’ (5). Reductions in loading/physical activity very quickly lead to reductions in anabolic sensitivity to feeding (1, 6, 26). Conversely, even relatively short-duration moderate intensity aerobic exercise performed 15 hours earlier improves the MPS response to meal feeding (25). We hypothesize that physical activity in the hours, possibly days, before measurement of MPS, as well as habitual levels of physical activity and training status, can have a significant impact on magnitude of the MPS response to feeding (25) and possibly exercise. To date, only a few studies have measured MPS in both the trained and untrained state within the same individuals (11, 24, 29). These studies have shown that RT generally reduces the duration of the acute MPS response to a session of RE preformed at the same relative intensity (11, 24); however, we do not know when in a RT program this change occurs. It is known, however, that the transcriptional response following the first exercise session is reflective of muscle damage and differs substantially from a second RE bout performed 48 h later (18). In addition, integrated daily MPS rates were shown to be lower after only two workouts during an 8 day resistance training period (29). Thus, it appears that very little ‘training’ is required to modify the acute transcriptional (18) and protein synthetic (11, 24, 29) responses to a bout of RE, at least of the same relative intensity. These observations (11, 18, 24, 29) suggest that acute measurement of the response of MPS to RE is not going to be useful in predicting
longer-term capacity for adaptation to RT within individuals because it does not represent a ‘typical’ response over a RT program comprised of multiple training sessions (3-4 per week).

Indeed, we reported that following the first training session the acute MPS response is not correlated with muscle hypertrophy after RT in the same individuals (15). There are multiple factors that might explain this observation (15): the short duration of the FSR measurement, subtle differences in proteolysis (7), or inherent variation in the measurement (23); however, we theorize that the most likely explanation for the discordance is that the magnitude and duration of the MPS response to acute RE is highly variable between individuals and can change considerably (11, 24, 29, 30) as RT progresses.

It is important to point out that in addition the physiological variability methodological variability and test retest reliability could obscure any relationship between acute MPS and hypertrophy. Muscle hypertrophy can be measured in a number of different ways including fibre area from histological section, lean mass from DXA and cross sectional area of volume from MRI or CT scans. In our previous study (15) hypertrophy was measured by MRI derived muscle because in our experience and that of others (19) variability is ~1%. Much less is known about reproducibility of MPS measure in the same subject and it is conceivable variability inherent in the MPS methodology could obscure any potential relationship.

Acute measurements of MPS response can provide important insight into the mechanistic underpinnings of divergent exercise and nutritional manipulations (3, 4, 10, 24, 31). Such measures have shown the ability to discriminate between gross differences in muscle contraction volume (2) and relative fatigue (3, 10) as well as differences in protein quality and amino acid composition (4, 31). Nonetheless, at an individual level a divergent acute response in MPS may be necessary but is not sufficient to conclude that a divergent muscle hypertrophic response will follow and similarly so for RT plus nutrition-induced
changes in hypertrophy (14, 15). It is likely that a high degree of intra-individual variation in various factors with repeated exposure to the exercise stimulus. In conclusion, results from acute measures of MPS should continue to be regarded important indicators of the gross-level potential of a given exercise/nutritional intervention; however long term studies are necessary to elucidate the capacity to which an individual will respond in terms of altered phenotype (i.e. increased muscle mass) in response to chronic exposure to a given exercise/nutritional intervention.


