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# Eat the meat or feed the meat: protein turnover in remodeling muscle

Matthijs K.C. Hesselink[a], Ronnie Minnaard[a] and Patrick Schrauwen[b]

**Purpose of review**

The present review outlines the role of muscle protein turnover in muscle remodeling, with emphasis on the effects of nutrition and exercise.

**Recent findings**

Progress in our understanding of the pathways signaling and regulating protein synthesis and degradation, and thus protein turnover, in skeletal muscle has been substantial over the past decade. Protein synthesis and degradation jointly allow the active remodeling of skeletal muscle to adapt to changes in mechanical and metabolic demand. Nutrition and exercise are potent ways to stimulate protein turnover. This occurs in an amino acid and exercise-type (resistance versus endurance) and mode (lengthening and shortening)-specific manner.

**Summary**

For optimal muscle remodeling, the timing and type of feeding and exercise appear to be crucial.

**Keywords**

exercise, nutrition, protein degradation, protein synthesis

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**Abbreviations**

| | |
|---|---|
| **Akt/PKB–mTOR** | Akt/protein kinase B–mammalian target of rapamycin |
| **AMPK** | adenosine monophosphate kinase |

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## Introduction

In healthy humans, skeletal muscle comprises approximately 50% of total body mass. Skeletal muscle is essential for gait and posture, and is fueled by multiple metabolic processes residing within the muscle. Skeletal muscle accounts for almost 80% of the basal metabolic rate [1]; in addition, skeletal muscle is responsible for approximately 80% of postprandial glucose uptake [2]. Skeletal muscle is obviously an important organ for locomotory and metabolic control. Muscular proteins are continuously subjected to (changes in) mechanical and metabolic demand, resulting in the remodeling of muscle. This requires a continuous tuned degradation and (re)synthesis of muscular proteins, myofibrillar contractile as well as sarcoplasmic metabolic proteins under a wide variety of conditions. In muscle remodeling the modulation of protein turnover is therefore crucial to maintain muscle mass and function.

The level and 'quality' of myofibrillar and sarcoplasmic proteins present at any given time reflects the net balance of protein degradation ('eat the meat') and protein synthesis ('feed the meat'). For protein synthesis to occur the ability to incorporate exogenous (dietary) or endogenous amino acids into the protein pool is essential. During protein degradation, the activation of proteolytic machinery results in the release of amino acids from the muscles.

Both protein synthesis and protein degradation are affected by (mal)nutrition, physical (in)activity and mechanical (un)loading and the hormonal changes that parallel these processes. Here we aim to review briefly the role of muscle protein turnover in muscle remodeling, with a focus on the role of nutrition and exercise.

## Dietary modulation of muscle protein turnover

It has been shown in humans that over 50% of the whole body protein synthesis rate was accounted for by skeletal muscle protein synthesis [3]. In the same study it was shown that muscle protein synthesis was doubled in the fed compared with the fasted state [3]. Similar observations (35% increase in protein synthesis) have been made while infusing a mixed amino acid solution in humans after 4 h of fasting [4]. This clearly identifies amino acids as the main food component responsible for the increased rate of protein synthesis after meal



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ingestion. The stimulatory effect of individual amino acids on protein synthesis, however, appears to be amino acid-specific. Administration of the essential amino acids, phenylalanine or threonine, significantly increases muscle protein synthesis, whereas administration of non-essential amino acids, arginine, glycine, or serine, failed to do so [5]. Large doses of individual essential amino acids thus stimulate the muscle protein synthesis rate.

### Nutritional effects on muscle protein synthesis

Whereas a dose–response relationship between supplemented amino acids and the stimulation of protein synthesis was anticipated, things have turned out to be more complex. The administration of modest doses of leucine resulted in increased muscular protein synthesis, with a simultaneous drop in intramuscular amino acid levels, suggesting the incorporation of these amino acids into the muscular protein pool [6]. It could thus be hypothesized that a transient extracellular increase in leucine upon infusion somehow results in the increased incorporation of intracellular amino acids into the protein pool. It has recently been shown that the infusion of incremental amounts of an amino acid mixture resulted in increased plasma levels of the essential amino acids infused. In turn, these plasma levels were related in a hyperbolic fashion to muscle protein synthesis rates, with similar increases in myofibrillar, sarcoplasmic and mitochondrial proteins. Strikingly, a modest drop in free intracellular essential amino acid levels was observed upon the infusion of amino acids [7]. These observations point towards a yet to be determined extracellular amino acid (most likely leucine) sensor, which signals to incorporate intracellular free amino acids into the muscular protein pool [8].

In healthy individuals, meal ingestion results in the secretion of insulin, a hormone with recognized anabolic effects in rodents and in in-vitro assays [9]. *In vivo* in humans it has been shown that the addition of protein hydrolysates or amino acids to carbohydrate solutions potentiates insulin secretion in an amino acid-specific manner [10]. Combined with observations of a stimulated protein synthesis rate under physiological hyperinsulinemia [11], the administration of insulinogenic amino acid solutions may thus be advocated to augment muscle protein synthesis.

Again, however, things appear to be more complicated. Studies in which the pancreatic response to insulinogenic substances was blunted by the administration of octreotide have shown that exogenous amino acids stimulate the muscle protein synthesis rate to a similar extent under both basal and hyperinsulinemic conditions [12••]. Therefore, it appears premature to attribute the potentiating effect of amino acids on protein synthesis directly to insulin.

Clearly, increasing the amino acid intake stimulates the muscle protein synthesis rate and results in muscle hypertrophy and increased muscle mass. The bulk of muscular proteins are myofibrillar proteins, involved in force generation. The supply of energy needed to generate force, however, relies on metabolic processes accounted for by sarcoplasmic proteins such as glycolytic enzymes and mitochondrial proteins facilitating aerobic processes. It would thus be of relevance to examine whether increased amino acid intake specifically affects myofibrillar, sarcoplasmic or mitochondrial protein synthesis. This however, does not appear to be the case [8,13,14].

In summary, it seems safe to state that amino acids are capable of stimulating protein synthesis in an amino acid-specific manner, with essential amino acids being the most potent. Enhancing protein synthesis rates by the administration of amino acids does not occur in a dose-specific manner. The sensing of exogenous amino acids (mainly leucine) may signal to the pool of endogenously (intracellularly) available amino acids, which then are incorporated into muscular proteins. Therefore, rather than the absolute level of exogenously available amino acids, the pool of intracellularly available amino acids appears to be of importance. The role of insulin with respect to the protein synthesis rate is equivocal but may rely on indirect rather than direct effects.

### Nutritional effects on muscle protein degradation

Selective protein degradation in eukaryotic cells occurs mainly via the ubiquitin–proteasome pathway [15]. In brief, this pathway selectively recognizes damaged, redundant and misfolded proteins that are tagged by the polypeptide ubiquitin in a process catalysed by E1 (ubiquitin-activating), E2 (ubiquitin-conjugating) and E3 (ubiquitin-ligating) enzymes. Polyubiquitinated proteins are targeted to the 26S proteasome, comprising a 19S regulatory domain that recognizes polyubiquitinated proteins and a 20S proteolytic domain, which hydrolyzes proteins to peptides of typically 4–25 amino acids [16].

An examination of muscle protein degradation in humans and *in vivo* is complicated by limitations in the validity or sensitivity of the methodology available. Classic markers for muscle proteolysis such as the urinary excretion of 3-methyl histidine are biased by the high turnover of, for example, gastrointestinal smooth muscle cells, and in-vivo measures of endogenous leucine release in the circulation also reflect whole-body protein degradation rather than (skeletal) muscle-specific proteolysis. Therefore, the majority of the data available are derived from animal and in-vitro studies. These studies clearly point towards increased muscular protein degradation by the ubiquitin–proteasome pathway during long-term fasting [17], with increased rates of ubiquitination

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and the induction of gene expression and increased protein levels of the major components involved [18,19]. The routes resulting in activation of the ubiquitin–proteasome pathway in muscle during fasting, however, remain largely unknown. Under conditions of nutrient restriction it has been shown that increased proteasomal activity serves to provide amino acids to maintain protein synthesis and thus cell survival of vital organs [20••]. During feeding, when the net protein balance is positive, a modest reduction of approximately 12% in protein degradation has been reported after amino acid infusion [4], whereas protein synthesis rates may double [8]. Although quantitatively the contribution of protein degradation to net protein balance in the fed state may be minor, it is of importance to realize that protein synthesis is paralleled by increased levels of polypeptides that never attained native structure owing to errors in translation or posttranslational processes. These polypeptides are degraded by the ubiquitin–proteasome pathway [21]. This underscores the importance of maintaining a certain level of regulated, selective and targeted proteolytic activity to preserve muscle 'quality'.

Therefore, although data on nutritional effects on protein degradation are limited compared with the effects on protein synthesis, it is obvious that starvation triggers muscle proteolysis in a ubiquitin–proteasome-dependent fashion, which may serve to maintain amino acid availability to vital organs. Feeding, on the contrary, blunts muscular protein degradation possibly via indirect antiproteolytic effects of insulin. The precise routes along which (insulin-induced) inhibition of the proteolytic system occurs remain to be elucidated.

## Physical (in)activity and muscle protein turnover

Physical exercise and the concomitant metabolic changes are potent ways to enhance protein synthesis rates resulting in muscle hypertrophy. Insulin, amino acid and exercise-responsive signal transduction pathways in skeletal muscle have now been identified contributing to exercise-induced muscle hypertrophy. The Akt/protein kinase B–mammalian target of rapamycin (Akt/PKB–mTOR) signaling pathway is the common denominator in these pathways. Activation of the Akt/PKB–mTOR signal transduction pathway results in both the acute (within minutes to hours) and long-term (hours up to days) upregulation of protein synthesis through modulation of multiple steps involved in mediating the initiation of messenger RNA translation and ribosome biogenesis, respectively [22].

Mechanical loading associated with exercise contributes to muscle hypertrophy. Transsarcolemmal proteins physically connecting the extracellular matrix to sarcomeric protein muscle allow sensing of external load. For example, the giant sarcomere-spanning protein, titin, connected to the extracellular matrix via costamere structures and integrins, was found to possess kinase activity upon passive stretching, resulting in increased protein synthesis [23••].

### Effects of activity on muscle protein synthesis

Muscle growth after physical activity is more prominent after resistance exercise, whereas after endurance exercise changes towards slower more oxidative myofibrillar proteins and increased mitochondrial biogenesis are most striking. In an ex-vivo model of high-frequency stimulation to mimic resistance exercise, myofibrillar and sarcoplasmic protein synthesis increased by 5.3 and 2.7%, respectively, within 3 h. Low-frequency stimulation to mimic endurance exercise failed to affect the protein synthesis rate within the same time span, but did increase the activity of adenosine monophosphate kinase (AMPK) and gene expression of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC 1-α) [24••], a key transcriptional co-factor in mitochondrial biogenesis. High-frequency stimulation acutely activated Akt/PKB and its downstream targets, resulting in prolonged activation of the translational regulators p70-S6k, 4E-BP1, eIF-2B, and eEF2 without affecting the AMPK–PGC-1α signaling pathway. AMPK–PGC-1α signaling thus seems to mediate adaptive responses to endurance training, whereas activating the Akt/PKB–mTOR pathway may underlie increased protein synthesis after resistance exercise. A human study examining the effect of training history (resistance versus endurance exercise) on signaling selectivity revealed that 3 h postexercise AMPK activity increased after cycling in resistance exercise-adapted but not endurance-trained individuals. Conversely, the activation of AMPK increased after resistance exercise in endurance but not strength-trained individuals. One hour of cycling increased Akt/PKB–mTOR signaling in endurance-trained, but not strength-trained individuals after cycling, but was unchanged in either group after resistance exercise [25••]. Exercise-type selective activation of distinct signaling cascades involved in protein synthesis have thus been observed in a training history-specific manner.

In-vitro data in mechanically stretched muscle cell activation revealed that specific types of mechanical stretch activate distinct signaling pathways [26•]. In this respect, it has been hypothesized that differences in the direction and level of mechanical load of shortening versus lengthening contractions results in the activation of distinct signaling pathways. In a human model of short-term (12 min) stepping exercise, resulting in lengthening contraction in one leg and shortening contractions in the contralateral leg, protein synthesis rates were comparable across legs; however, differences in the signaling pathway could be not detected [27•]. In a more sophisticated

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model, the same researchers again observed comparable increases in muscle protein synthesis during the 8.5 h period after shortening and lengthening exercise. The increased protein synthesis rate, however, peaked earlier following lengthening exercise [28•]. This suggests that muscle protein synthesis can be further augmented by timed repetitive lengthening contractions. The anabolic power of lengthening exercise is further substantiated by the notion that activation of the anabolic signaling protein, p70-S6k, has been observed after a single session of maximal lengthening, even in the absence of a nutritional intake [29•].

In conclusion, both the types of exercise (resistance exercise versus endurance exercise) and the mode of exercise (lengthening versus shortening) differentially affect the level of protein synthesis as well as the signaling routes involved.

### Effects of activity on muscle protein degradation

As with protein synthesis, changes in muscular activity also affect protein degradation in a duration, intensity and mode of exercise-specific fashion. Two weeks of human limb casting followed by 6 weeks of exercise rehabilitation resulted in increases in gene expression of the 20S proteasome and the muscle-specific proteolytic transcription factors, MAFbx and MuRF1 [30]. In rats, the induction of the same genes was observed within 5 days of limb casting, resulting in a significant loss of muscle mass [31]. Disuse atrophy in this model was rescued by the administration of a specific proteasome inhibitor indicating that the remodeling of immobilized skeletal muscle during atrophy is regulated by the ubiquitin–proteasome pathway [31]. The induction of proteasome-specific genes by immobilization was suppressed upon rehabilitation exercise, allowing the instigation of muscle hypertrophy and remodeling [30].

The importance of the ubiquitin–proteasome pathway in muscle remodeling upon exercise under non-atrophying conditions is less prominent. Although it seems plausible to hypothesize that during endurance training, which results in a shift towards more oxidative and less glycolytic myofibrillar proteins, the glycolytic isoforms are selectively targeted and degraded in a ubiquitin–proteasome-dependent fashion, no studies are available that firmly underpin this hypothesis. For acetyl co-enzyme A carboxylase, a key enzyme regulating fat oxidation, selective targeting of ubiquitin in a ubiquitin ligase E3-specific manner to acetyl co-enzyme A carboxylase has recently been shown in adipose tissue [32••]. This unmasks a novel proteasome-dependent route co-regulating lipid metabolism along with the more classic routes of kinase-dependent phosphorylation. Whether similar routes are present in muscle, whether they are affected by exercise, and whether they also exist for other 'metabolic master switches' is an intriguing, yet unanswered, question.

For protein degradation apparent differences have also been observed between shortening and lengthening exercise. Many studies have observed the involvement of the ubiquitin–proteasome pathway in postexercise remodeling after lengthening exercise, including increased ubiquitin-conjugated protein content [33], as well as increased gene and protein expression of the ubiquitin ligase E3 and the 20S proteasome [34]. Interestingly, in a second session of lengthening exercise, the increase in proteolytic proteins was blunted, possibly reflecting a rapid and adaptive remodeling response to lengthening exercise [34]. A rapid and adaptive response to lengthening exercise is not restricted to myofibrillar proteins, but also includes remodeling of extracellular matrix [28•,35••,36] and the intermediate filament lattice.

In summary, increased muscle protein degradation in a ubiquitin–proteasome-dependent fashion is of particular importance under unloading conditions. The vast majority of studies reporting exercise-induced blunting in protein degradation do so in models with negative net protein synthesis at the onset of exercise (limb casting, Duchenne muscle dystrophy, muscle damage, etc.). The few studies that examined the effect of exercise (either lengthening or shortening) on protein degradation in healthy individuals report no (shortening exercise) or less robust (lengthening exercise) effects on exercise-induced protein degradation. Importantly, recent data indicate that the targeted degradation of proteins involved in fuel selection may also serve to regulate substrate metabolism.

## Conclusion

The maintenance of muscle mass and its ability to adapt to changes in metabolic demand is a tightly regulated process requiring simultaneous but tuned activity of protein synthesis and degradation. Both nutritional interventions [with essential (insulinogenic) amino acids as key components] and physical exercise stimulate net protein synthesis. These effects are mostly accounted for by the direct or indirect activation of protein synthesis, and to a lesser extent by the inhibition of protein degradation. Nevertheless, to maintain muscle quality and not solely muscle quantity, selective protein degradation is essential for the removal of redundant, damaged and misfolded proteins. Distinct signaling pathways have now been identified for endurance versus resistance exercise, possibly explaining the differential phenotypical effects of these types of exercise. For the mode of exercise (lengthening or shortening) distinct signaling pathways have been identified in cultured muscle cells, which so far could not be confirmed in humans.

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Exercise-induced blunting effects on protein degradation have mainly been examined in models in which exercise was superimposed in states when net protein synthesis was negative. Exercise-induced effects on protein degradation in situations of protein balance are equivocal.

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