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RIEVIEW ARTICLE

Phenotypic regulation of animal skeletal muscle protein metabolism

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This review highlights the current state of phenotypic mechanisms of regulation of muscle protein metabolism in animals. Since the skeletal muscle represents 40–50% of body mass in mammals it is a critical regulator of overall metabolism. Therefore, an understanding of the processes involved in the postnatal increase in muscle mass, with associated accumulation of protein, is fundamental. Throughout life, a delicate balance exists between protein synthesis and degradation that is essential for growth and normal health of humans and animals. Signaling pathways coordinate muscle protein balance. Anabolic and catabolic stimuli are integrated through the PKB/Akt-mTORC1 signaling to regulate mechanisms that control muscle protein synthesis and breakdown. At an early periods of intensive growth, muscle mass is stimulated by an increase in protein synthesis at the level of mRNA translation. Throughout the life, proteolytic processes including autophagy lysosomal system, ubiquitin proteasome pathway, calcium-dependent calpains and cysteine protease caspase enzyme cascade influence the growth of muscle mass. Several signal transmission networks direct and coordinate these processes along with quality control mechanisms to maintain protein homeostasis (proteostasis). Genetic factors, hormones, amino acids, phytoecdysteroids, and rhodanines affect the protein metabolism via signaling pathways, changing the ability and / or efficiency of muscle growth.
Keywords: autophagy; proteasomes; muscle protein metabolism; proteomics; metabolomics; phytoecdysteroids; amino acids; rhodanine derivative

Introduction

Worldwide population growth has increased global demand for adequate protein nutrition. Novel strategies to increase meat production are needed while minimizing the adverse effects on the environment. Genetic approaches to increase production of animal products through selective breeding are successful but also result in economic, environmental and ethical complications. Overall, efforts to meet the world's protein needs against a backdrop of environmental stress (i.e., physical, chemical and biological constraints on the productivity of the species) are creating greater pressures on animal agriculture than ever before. For these reasons, a deep understanding of the fundamental control points in determining muscle protein balance is relevant to animal agriculture sustainability (Anthony, 2016; Post, 2012; Bassett, 2009; Zuo et al., 2015).

Over the past two decades, advances in genomics allowed for selective breeding to be more informed and thus targeted. Recent developments in technology have further bolstered if not replaced the genomic age with an age of proteomics and metabolomics. These technologies allow to solve more sophisticated questions, moving from monitoring of genotype to phenotype. A deeper understanding of the phenotypic mechanisms that regulate muscle mass will in turn provide new insight concerning addressing the environmental challenges towards animal growth and improving overall health of livestock (Anthony, 2016; Boggess et al., 2013).

Thus, the problem of protein biosynthesis, which has theoretical and practical significance, remains relevant for many decades and forms the basis of most research areas in animal biology. Despite certain successes, the laws of synthesis and renewal of body proteins, the mechanisms that regulate these processes in the body of productive animals are extremely poorly understood. Knowledge of metabolic mechanisms and protein synthesis pathways opens up the prospect of regulating this process within the biological capabilities of the animal body.

Protein turnover in animals

It is known that proteins in animal cells undergo constant update or turnover. In addition, this protein circuit is a homeostatic mechanism that is required for the normal physiological functioning of the body. The formation of protein pools in organs and tissues of the body is determined by the ongoing processes of synthesis and breakdown of proteins. Most of the quantitative characteristics of these processes are carried out by isotopic methods. Quantitatively, the processes of protein renewal are characterized not in all species of growing animals and not in all tissues, and also when regulated by various factors (Erimbetov et al., 2005).

Considering that the amount of free amino acids does not exceed 0.5% of their total pool in the animal's body, protein turnover is the unique mechanism of the constant redistribution of amino acids for the synthesis of proteins needed by the body at one time or another (Swick, 1982). The quantitative characteristics of protein turnover are usually 5 times greater than the daily requirement for an animal. For example, a typical daily intake of human dietary protein is 50-100 g, while protein synthesis exceeds 300 g / day (Clugston & Garlick, 1982). The corresponding values for young rapidly growing pigs are 250 g per day of digestible protein and 500 g of synthesized protein per day (Reeds et al., 1980). These daily synthesis rates represent 2–8% of the total body protein, so the equivalent protein mass is updated in animals every 8 and 30 days for young pigs and adults, respectively. Decay values also typically exceed daily protein intake, i.e. 300 and 350 g for humans and pigs. Thus, at least 60-70% of the amino acids released during protein decomposition are recycled (Millward et al., 1973; Kalnitsky & Kalashnikov, 2006). In this regard, food protein is used in the body only to compensate for the loss of amino acids during growth, oxidation or export. This is an important adaptive property, since it facilitates the maintenance of free amino acids in blood plasma and in tissue fluids within certain limits, even if consumption (absorption) is zero.
The main biological factors controlling the total protein fund in the body of mammals, according to H. Munro (1974) include the intake of amino acids, regulators that determine the functioning of the cell during growth, anabolic and catabolic hormones.
Of particular interest is the metabolism of proteins in muscle tissue in the context of their constant renewal and research on the formation of meat productivity in growing animals. Skeletal muscle is the largest tissue in mammals.

Regulation of the protein synthesizing system of skeletal muscle

For constitutive proteins, including muscle proteins, net deposition reflects the balance between synthesis and degradation, so changes in one or both of the constituent processes can increase (or decrease) the amount of growth. Although it is known that a large number of factors, including nutrition factors (Seve & Ponter, 1997; Lobley, 1998) and hormones (Davis et al., 2003) stimulate protein synthesis in muscles, degradation can also be controlled. Thus, rapid muscle growth in certain genotypes (for example, in sheep carrying callipyge muscle hypertrophy gene) can be ensured by suppression of protein degradation (Lorenzen et al., 2000).
Muscle protein synthesis is controlled at the level of mRNA translation. Studies in rodents and pigs show that postnatal skeletal muscle growth occurs via increases in muscle protein synthesis that are controlled at the initiation step of mRNA translation (Davis et al., 2008; Jefferson, Kimball, 2001). Two events in translation initiation are identified as contributing factors in the regulation of muscle mass: 1) the creation of a ternary initiation complex, which consists of methionyl-tRNA, eukaryotic initiation factor 2 (eIF2) and guanosine triphosphate (GTP); and 2) formation of the eIF4-initiated ribosomal complex. Both of these cellular events are regulated by phosphorylation of specific eIFs that can be monitored using immunoblotting techniques and then used as biomarkers of muscle protein synthesis in response to environmental factors. Among various environmental factors, nutritional factors are of primary importance. Feeding increases muscle protein synthesis, via enhanced formation of the eIF4 complex (Kimball et al., 2000; Wilson et al., 2009) whereas fasting and low protein reduces muscle protein synthesis in concert with reduced eIF4 formation (Liu et al., 2015). Stimulation of muscle protein synthesis by feeding is developmentally regulated, with the capacity of the translational machinery reducing with age (Davis et al., 2008). Furthermore, recent evidence points to bolus feeding as more effective in stimulating muscle protein synthesis than continuous feeding in neonates (Davis et al., 2015). Catabolic stimuli such as infection, inflammation, disuse and aging blunt or block feeding-induced stimulations in muscle protein synthesis at the level of translation initiation and correspond with reductions in the formation of the ternary initiation complex and/or the eIF4 complex (Goodman et al., 2011; Laufenberg et al., 2014; You et al., 2015).
Among nutritional strategies examined in recent years, dietary amino acid supply and composition have been a focus (Duan et al., 2016; Erimbetov & Obvintseva, 2011). Some of this work began with the seminal observations that the branched chain amino acids and especially leucine stimulated MPS independent of insulin or energy intake (Anthony et al., 2001; Columbus et al., 2015; Sheybak, 2014). Efforts that are more recent have further identified a potentially important role for the leucine metabolite, beta-hydroxy-beta-methylbutyrate (Duan et al., 2015; Qiao et al., 2013; Wheatley et al., 2014). Other related research efforts have studied the impact of dose and timing of amino acid intake on maximizing muscle protein synthesis over time, particularly in relation to physical activity and aging (Gazzaneo et al., 2011; Mitchell et al., 2015; Pasiakos et al., 2015; Layman et al., 2015). The logic behind these studies is clear: maximize MPS with each meal and over time muscle mass will increase. Many examples are to be found in the literature showing impressive increases in muscle protein synthesis in response to feeding protein or leucine more frequently and / or in greater amounts (Gazzaneo et al., 2011; Arnal et al., 2002). Nonetheless, long term studies examining the impact of protein or amino acid supplementation on lean mass gains are inconsistent or equivocal (Columbus et al., 2015; Pasiakos & McClung, 2011) with significant differences between breeds and among phases of growth evident (Goodband et al., 2014; Otten et al., 2013). Thus, it is difficult to assign a single conclusion about the effect of supplementing dietary protein or specific amino acids on skeletal muscle growth; sometimes a reduction rather than an increase in dietary protein or amino acids improves quality of finished product (Madeira et al., 13). The use of dietary protein and amino acids must therefore be utilized according to the biological goal in mind alongside an appreciation for the underlying genetic and hormonal background (Anthony, 2016).

Regulation of protein degrading system in skeletal muscle

The opposite of the synthesis process is protein catabolism. Considering the problem of decay, it should be emphasized that the magnitude and speed of the increase in muscle mass depends on the balance of the rates of protein synthesis and catabolism in cells. The protein accumulated during the growth process represents only a small fraction of the total amount of protein synthesized during this period. Thus, a change in the average rate of degradation of muscle protein can affect changes in tissue mass, and this is confirmed by some evidence that the concentration and level of specific enzymes in cells can be determined by changes in the rate of protein breakdown. In addition, the rate of protein degradation is controlled by substrate hormonal factors and can vary independently of its synthesis (Larbaud et al., 2001; Combaret et al., 2001; Davis et al., 2010).
Skeletal muscle cell mass is influenced by protein turnover/degradation in all phases of life. Enhanced degradation not only reduces muscle mass but also alters muscle fiber type composition. How the different proteolytic systems regulate the capacity and efficiency of growth in the different muscle fiber types, particularly during environmental stress, are important research questions without clearly defined answers. The difficulty in answering these questions lies in the complexity of proteolysis. The stability or half-life of any single protein is modulated by the activity of assorted, overlapping degradative systems in the body. The main proteolytic processes influencing skeletal muscle mass are the 1) autophagy lysosomal system, 2) ubiquitin proteasome pathway, 3) calcium-dependent

calpains and 4) cysteine protease caspase enzyme cascade. The relative contribution of these processes in determining muscle mass fluctuates according to genetics, life stage, hormones and environmental stimuli. Furthermore, these catabolic processes interact through associated quality-control signaling networks and gene expression events that modulate one another. As such, a deeper understanding of the regulatory processes guiding activation of each of these modes of proteolysis is a subject of intense investigation (Anthony, 2016; Pasiakos & Carbone, 2014; Milan et al., 2015).

The ubiquitin-proteasome system (UPS) and autophagy-lysosome system are major pathways that are involved in the regulation of protein degradation in skeletal muscle. The autophagy-lysosome system plays a significant role in bulk proteolysis while the UPS is responsible for the control of the degradation of specific proteins. UPS-dependent protein degradation is highly regulated. In this system, lysyl residues of the target proteins are serially attached by ubiquitin (a 76-amino acid protein) which marks them for protein degradation in the proteasome. It is known that two major muscle-specific E3 ubiquitin ligases, MuRF1 (muscle RING-finger protein-1) and atrogin-1/MAFbx), are important components of the UPS (Suryawan & Davis, 2014).

It has become increasingly evident that autophagy and the UPS are needed for normal muscle development (Bonaldo & Sandri, 2013). Although in both systems free amino acids can be generated, only the autophagy system appears to be physiologically regulated by amino acids (Kadowaki & Kanazawa, 2003). Autophagy is a tightly regulated process that involves the degradation of cell components including proteins through the lysosomal machinery. In normal physiological conditions, autophagy is active and plays an important role in several biological processes including cell development (Cecconi & Levine, 2008). Autophagy is crucial for the survival of neonatal animals under starvation conditions (Kuma et al., 2004) and is induced by early weaning in the piglet model (Zhang, 2011). In the lysosomal degradation pathway, there are two major processes: macroautophagy and chaperone-mediated autophagy (CMA). While the microtubule-associated protein 1 light chain 3 (LC3) is an important component or a marker for macroautophagy, lysosome-associated membrane protein-2 (lamp-2) is crucial for CMA processes (Rajawat et al., 2009). mTOR plays a crucial role in the regulation of autophagy via unc51-like kinase 1 (UKL1), an upstream component of LC3 (Bach et al., 2011). When the activation of mTOR (mammalian target of rapamycin) is high, such as under nutrient sufficiency, mTOR prevents the activation of ULK1 by phosphorylating ULK1 at Ser757 resulting in the suppression of autophagy (Neel et al., 2013; Suryawan & Davis, 2014).

Studies show that both insulin/IGF-I (insulin-like growth factor-I) and amino acids regulate protein synthesis (Clemmons, 2009) and protein breakdown (Kadowaki & Kanazawa, 2003; Banerjee & Guttridge, 2012), however, the role of amino acids on the latter process is not well understood. In vivo and in vitro studies have shown that the branched-chain amino acids, especially leucine, attenuate muscle protein degradation. However, the detailed molecular aspects of the amino acid-induced reduction of proteolysis in skeletal muscle through UPS and autophagy have not been elucidated (Kadowaki & Kanazawa, 2003; Suryawan, Davis, 2014).

Signaling pathways regulating the synthesis and breakdown of muscle proteins

Intracellular signaling events are initiated by a variety of chemical signals that reflect nutrition and hormonal status (e.g., insulin/IGF-I), energy state and activity (e.g., AMP kinase, phosphatidic acid), and other mediators of environmental stress (e.g., glucocorticoids, cytokines). A key point of integration in muscle growth and development is the protein kinase B/Akt kinase. The insulin/IGF-I- Akt pathway increases muscle protein synthesis via inhibiting glycogen synthase kinase 3β (an inhibitor of eIF2 ternary complex formation) and activating mechanistic target of rapamycin complex 1 (mTORC1) signaling. Akt also reduces MPB via phosphorylation of the Forkhead box class O (FOXO) transcription factors (Glass, 2010; Schiaffino & Mammucari, 2011; Sanchez et al., 2014; Milan et al., 2015; Anthony, 2016).

Signaling pathways coordinate muscle protein balance. Anabolic and catabolic stimuli are integrated through the PKB/Akt-mTORC1 signaling to regulate mechanisms that control muscle protein synthesis and breakdown (Anthony, 2016). In general, anabolic stimuli (e.g., growth hormone, insulin/IGF-I, amino acids, testosterone, β-agonist) activates the mTORC1 signaling pathway whereas catabolic stimuli (e.g., inflammatory cytokines, glucocorticoids, myostatin, fasting, low protein) represses mTORC1 signaling (Bonaldo, Sandri, 2003; Braun, Marks, 2015). Nutrients, especially the branched chain amino acids, are potent activators of mTORC1 in muscle independent of insulin-like growth factor-I (IGF-I)-Akt (Duan et al., 2016; Columbus et al., 2015). Likewise, growth factors can stimulate mTORC1 signaling in skeletal muscle independent of amino acid nutrition (O'Connor et al., 2003).

A variety of plant steroid compounds called phytoecdysteroids are found to increase protein synthesis and activate Akt signaling similarly to IGF-I in cultured myocytes (Gorelick-Feldman et al., 2008; Gorelick-Feldman et al., 2010). In experiments on pigs, an increase in protein synthesis with the introduction of 20-hydroxyecdysone into the diet was found (Kratky et al., 1997). Feeding these and other phytoecdysteroids produce an anti-obesity effect in mice (Kizelsztein et al., 2009).

Nonetheless, recent feeding trials are unable to identify an acute impact of 20-hydroxyecdysone on Akt or mTORC1 signaling in skeletal muscle suggesting that phytoecdysteroids may require other factors for activity and/or regulate longer-term transcriptional changes in muscle protein breakdown versus signaling mechanisms that regulate muscle protein synthesis (Anthony et al., 2015; Anthony, 2016).

It was found that the 3- (2-phenylethyl) -2-thioxo-1,3 thiazolidin-4-one rhodanine derivative can increase muscle protein synthesis through inhibition of glycogen synthine kinase 3β (an inhibitor of the formation of the eIF2 triple complex) and activation of the mechanistic target signal transduction of the rapamycin 1 complex (mTORC1). Its inhibitory activity, expressed as IC_{50}, is 35 μM (Martinez et al., 2002, 2005).

The control of gene expression through key transcription factors plays a major role in regulating muscle mass. Many of these proteins such as the FOXO family promotes muscle atrophy through increased expression of both E3 ubiquitin ligases as well as inducing autophagosome membrane components. These discoveries are revealing how the ubiquitin proteasome and autophagy lysosome pathways often work together versus separate from each other. Furthermore, hormones and other growth factors can alter the activities and function of both mTORC1 and transcription factors. For example, insulin/IGF-I treatment promotes increases Akt signaling, which promotes mTORC1 complex assembly and MPS but also inhibits MPB via reduced proteolytic gene expression under control of the FOXO transcription factors. Myostatin treatment blocks Akt, which reduces MPS via mTORC1 complex assembly and increases MPB by activating the FOXO transcription factors (Bonaldo & Sandri, 2003; Schakman et al., 2013; Milan et al., 2015; Anthony, 2016).

Conclusion

The dynamics of the synthesis and breakdown of proteins is important for maintaining temperature homeostasis, which allows animals to respond to physiological stimuli and environmental changes quickly and efficiently. As part of normal function, digestion and immune defense mechanisms are likely to be costly and their functioning is accompanied by catabolism and loss of proteins and amino acids. These losses can be reduced, but not eliminated due to the rational organization of the technology, and the possibility that these processes determine certain amino acid needs will need to be taken into account in the future when preparing diets. The latest data indicate that the obligate catabolism of amino acids in the liver is relatively low, and the oxidation of amino acids in the liver is more likely to reflect the extraction of the amount that is excessive in relation to the need for peripheral tissues than the regulated provision of productive processes. Therefore, research efforts should be aimed at understanding the mechanisms of protein deposition in productive tissues. Except in some special situations, the anabolic response in peripheral tissues is not limited by either the influx of amino acids or the transport into the cells. Reactions are regulated by intracellular events that change the relationship between protein synthesis and breakdown. These relationships probably include interactions of nutrient substrates and hormones (Lobley, 2003).
Understanding how protein synthesis and protein degradation are regulated during the neonatal period is crucial for the development of new nutritional strategies that can support maximum growth of neonates.

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