Abstract
The synthesis of new protein is necessary for both strength and endurance adaptations. While the proteins that are made might differ, myofibrillar proteins following resistance exercise and mitochondrial proteins and metabolic enzymes following endurance exercise, the basic premise of shifting to a positive protein balance after training is thought to be the same. What is less clear is the contribution of nutrition to the adaptive process. Following resistance exercise, proteins rich in the amino acid leucine increase the activation of mTOR, the rate of muscle protein synthesis (MPS), and the rate of muscle mass and strength gains. However, an effect of protein consumption during acute post-exercise recovery on mitochondrial protein synthesis has yet to be demonstrated. Protein ingestion following endurance exercise does facilitate an increase in skeletal MPS, supporting muscle repair, growth and remodeling. However, whether this results in improved performance has yet to be demonstrated. The current literature suggests that a strength athlete will experience an increased sensitivity to protein feeding for at least 24 h after exercise, but immediate consumption of 0.25 g/kg bodyweight of rapidly absorbed protein will enhance MPS rates and drive the skeletal muscle hypertrophic response. At rest, ~0.25 g/kg bodyweight of dietary protein should be consumed every 4–5 h and another 0.25–0.5 g/kg bodyweight prior to sleep to facilitate the postprandial muscle protein synthetic response. In this way, consuming dietary protein can complement intense exercise training and facilitate the skeletal muscle adaptive response.

Introduction
Muscular adaptation to resistance (muscle hypertrophy) and endurance (mitochondrial biogenesis and angiogenesis) type exercise is dependent on the de novo synthesis of myofibrillar and mitochondrial proteins, respectively [1]. The
phenotype of bigger muscles in the strength athlete is the result of the rate of myofibrillar protein synthesis exceeding the rate of myofibrillar protein breakdown, whereas the endurance phenotype of more mitochondrial proteins occurs when this subset of proteins is synthesized faster than they are broken down. Therefore, protein balance (the sum of protein synthesis and breakdown) is key to determining the phenotypic adaptation to exercise training. Even though the rate of muscle protein breakdown increases following an acute bout of exercise [2], the corresponding increase in muscle protein synthesis (MPS) is 3- to 5-fold greater [2, 3]. Together with the methodological difficulties in measuring protein breakdown, this means that most research has focused on the regulation of protein synthesis after exercise.

In the fasted state, protein balance is negative. Resistance type exercise in the fasted state results in an increase in both protein synthesis and degradation [3]. Since the increase in synthesis is greater than the increase in degradation, net balance becomes less negative. However, in order for protein balance to become positive, an individual needs to consume a source of amino acids [4]. Tipton et al. [4] showed that when subjects consumed 40 g of either a mixed amino acid solution (containing both essential, EAAs, and non-essential amino acids) or an EAA solution (also containing arginine), MPS increased equally between supplemented groups and to a greater degree than in the fasted state, resulting in a positive protein balance. Therefore, resistance type exercise combined with provision of sufficient EAAs can shift net protein balance to positive. The effects of protein supplementation on mitochondrial protein synthesis have not been studied extensively. However, the early reports suggest that amino acid supplementation does not affect mitochondrial protein synthesis during the acute stages of post-exercise recovery [5]. This chapter will explore the mechanisms underlying the effects of amino acids on skeletal muscle adaptations and provides some practical suggestions based on these mechanisms in an effort to maximize the effects of training.

**Adaptations to Strength Exercise**

Resistance exercise, forcing a muscle to work close to or above its maximal isometric force to failure, results in an acute increase in MPS that can last more than 24 h [6, 7]. When repeated at a sufficient frequency, this transient increase in protein synthesis leads to an increase in muscle mass and strength. A number of cellular and molecular processes have been identified that transduce mechanical load into an increase in protein synthesis. Chief among these is the activation of the mTOR. In every model studied to date, loading results in the activation of
mTOR, and the acute activation of mTOR is predictive of the gain in muscle mass and strength following more prolonged exercise training [8, 9]. Further, inhibiting mTOR with the macrolide antibiotic rapamycin blocks the acute increase in protein synthesis in people [10] and the increase in muscle mass in rodents [11, 12], suggesting that mTOR activation is required for muscle hypertrophy. Interestingly, mTOR is initially activated by both resistance and endurance type exercise. However, only after resistance exercise is the activation of mTOR maintained for longer periods [1]. In fact, following resistance type exercise, mTOR can remain active for upwards of 18 h [13], suggesting that mTOR might drive the protein synthesis response to resistance type exercise.

mTOR

mTOR is a serine/threonine protein kinase with structural similarities to PI-3 kinase (phosphatidylinositol-3 kinase). On its own, mTOR has no catalytic activity. In order for mTOR to become a functional kinase, it has to form a complex with other proteins that stabilize its structure, move it to specific regions of the cell, and regulate its binding to target proteins [14]. There are two known complexes of mTOR (complex 1 and 2). Both of the complexes contain the G-protein β-subunit-like protein (GβL; also known as lS8) and the DEP domain-containing mTOR-interacting protein (DEPTOR) [15] that positively and negatively regulate mTOR, respectively. mTORC2 is targeted to membranes through its interaction with mammalian stress-activated map kinase-interacting protein 1 (mSIN1) [16], and is held together by protein observed with rictor (PROTOR) 1 or 2 [17]. The two mTOR complexes phosphorylate different proteins due to the presence of either the regulatory-associated protein of mTOR (raptor) or rapamycin-insensitive companion of mTOR (rictor) [18]. In mTORC1, raptor binds to proteins that contain a TOS (TOR signaling) motif such as eukaryotic initiation factor (eIF) 4E binding protein-1 (4E-BP1) [19], the 70-kDa ribosomal protein S6 kinase (S6K1) [20], hypoxia-inducible factor-1 (HIF-1) [21], and proline-rich Akt substrate of 40 kDa (PRAS40) [22, 23]. In contrast, rictor directs mTOR towards akt/PKB (protein kinase B), serum- and glucocorticoid-induced protein kinase (SGK), and protein kinase C (PKC) [24].

The most studied targets of mTOR are 4E-BP1 and S6K1. Phosphorylation of 4E-BP1 by mTOR changes its shape and prevents it from binding to eIF4E [25]. Free eIF4E can then bind to two other initiation factors, eIF4G and eIF4A, to form eIF4F and promote translation initiation. When S6K1 is activated by mTOR, it phosphorylates and turns on eIF4B [26] and phosphorylates and turns off eukaryotic elongation factor 2 kinase (eEF2K) [27]. Activation of eIF4B in-
creases the unwinding of secondary structure in mRNA so that they can be translated. This specifically increases the rate of translation of genes that are important in cell growth, such as fibroblast growth factor (bFGF) [28]. Inactivation of eEF2K prevents the phosphorylation of elongation factor 2 (eEF2), accelerating the elongation step and promoting protein synthesis. In this way, S6K1 contributes to the regulation of both translation initiation and elongation. Even though these are the most studied targets of mTOR, there is developing evidence that other targets of mTOR are more important for muscle hypertrophy [MacKenzie et al. unpubl. obs.]. To that end, the recent discovery of two novel kinases downstream of mTOR that lead to ribosome biogenesis and an increase in the capacity for protein synthesis is extremely exciting [29].

**Activation of mTOR**

mTOR activity is regulated by growth factors, nutrients, and mechanical loading [30]. Of particular importance to this review is the role of amino acids in regulating the activation of mTOR. Amino acids can directly stimulate mTOR activity in the absence of changes in metabolic stress, growth factors, or mechanical loading. Amino acids mediate this effect by uniting mTOR and its activator Rheb (ras homologue enriched in brain) within the cell. Over the last few years, the mechanism underlying this complex process has been elucidated, and a number of novel molecular actors have been identified including: the vacuolar protein sorting-34 [31], the leucyl tRNA synthase (LRS) [32], Rag proteins [33], and the ragulator [34]. Vps34 is one of the oldest kinases in our genome [31] and functions primarily to move vesicles around within the cell. Since the mTOR activator Rheb is located on the membrane of a vesicle, activating Vps34 moves Rheb and increases the likelihood of interacting with mTOR. LRS is the enzyme that ligates the amino acid leucine onto tRNAs containing the sequence TTA, TTG, CTT, CTC, CTA, or CTG and therefore is required for the synthesis of proteins containing the amino acid leucine. The Rag proteins are a family of four small G proteins that form heterodimers and control the location of mTOR within the cell. The ragulator is a trimer of MP1, p14, and p18 that binds to active Rag heterodimers and brings mTOR to its activator Rheb. As illustrated in figure 1, when leucine enters it binds to and activates the LRS. Han et al. [32] elegantly showed that the LRS serves as a GTPase activating protein (GAP) towards RagD. When RagD is bound to GTP, the Rag complex is inactive. When LRS acts as a GAP towards RagD, RagD hydrolyzes its GTP to GDP.

After RagD hydrolyzes its GTP, the ragulator makes RagB release its GDP and bind GTP and in so doing activates the Rag complex. Once active, the Rag
complex can bind to both raptor and the regulator. Since the regulator is located on the same vesicle as Rheb (the activator of mTOR), the net effect of leucine is to bring mTOR to its activator. If Rheb has been activated by either growth factors or mechanical loading, the result is an increase in mTOR activity and MPS. Interestingly, the other Rag heterodimer is not activated by the LRS [32], suggesting that there may be other amino acids or amino acid analogues that activate the RagA/RagC complex and by extension mTOR.

The Role of Leucine Uptake in Control of mTOR

As described above, leucine uptake is critical for activating mTOR via RagB/RagD and consequently increasing MPS. Following resistance type exercise in humans [3] and rats [13], the free leucine content of muscle is transiently increased, suggesting that the prolonged activation of mTOR could be mediated by a rise in intracellular leucine. From these data, it stands to logic that leucine entry into muscle could limit mTOR activation and the synergistic effect of resistance exercise and amino acid supplementation. The primary leucine trans-
porter in muscle is the L-type amino acid transporter 1 (LAT1/SLC7A5). LAT1 transports leucine (along with other EAAs) into muscle in exchange for glutamine [35]. Glutamine and the other neutral amino acids are transported into muscle through the system A amino acid transporters: sodium-coupled neutral amino acid transporter 1 and 2 (SNAT2/SLC1A5) [36]. These transporters work in unison in what has been termed tertiary active transport. Primary active transport, where movement of ions is directly coupled with ATP consumption, of sodium through the Na⁺/K⁺-ATPase sets up the low intramuscular sodium gradient used for secondary active transport of glutamine through SNAT2. The glutamine gradient generated by SNAT2 in turn drives leucine influx and glutamine efflux through LAT1. Experimentally, this is observed as an increase in LAT1 transport of leucine when SNAT2 is coexpressed or an increase in leucine uptake when cells are pre-loaded with glutamine [35]. In contrast, mTOR signaling and protein synthesis are simultaneously decreased when leucine uptake is reduced due to SNAT2 inhibition [37, 38]. The data suggest that LAT1 and SNAT2 are important for mTOR activation.

With the importance of LAT1 and SNAT2 in leucine uptake and the transient increase in intramuscular leucine after resistance exercise, it is not surprising that LAT1 protein increases in skeletal muscle of young individuals following resistance exercise. Interestingly, Drummond et al. [39] found LAT1 protein and mTOR activity (S6 phosphorylation) increased significantly 6 and 24 h after resistance exercise in younger subjects, whereas in older subjects LAT1 protein did not increase and the activity of mTOR returned to baseline by 6 h. These data suggest that an increase in LAT1 protein is required for the prolonged activation of mTOR following loading, and the inability to increase LAT1 could underlie the anabolic resistance seen in old individuals. In agreement with this hypothesis, we have found that mice lacking LAT1 in their muscles show a marked reduction in mTOR activity 3 h after resistance exercise compared with wild-type mice [Aguirre and Baar, unpubl.]. Like resistance exercise, LAT1 and SNAT2 mRNA and protein increase after consuming EAA, and this increase occurs concomitant with mTOR activation [40]. Together, these data suggest that the activation of mTOR and the increase in protein synthesis after resistance exercise or amino acid feeding is dependent on leucine uptake through LAT1.

Resistance exercise, when combined with EAAs (specifically leucine), results in the prolonged activation of mTOR. In the absence of LAT1, this increase in mTOR activity is largely lost, suggesting that the uptake of leucine is an important trigger for mTOR activation and protein synthesis. This so-called ‘leucine trigger’ through LAT1 and the LRS not only forms the molecular mechanism underlying the activation of mTOR and protein synthesis, but
also the practical consideration of which protein sources are more effective in facilitating the adaptive response in skeletal muscle in response to exercise training.

**Protein Supplementation and Endurance Adaptations**

The role of protein supplementation in the adaptation to endurance type exercise (i.e. the increase in mitochondrial protein synthesis) is far less studied than for resistance type exercise. From the limited studies performed to date, it does not appear that protein supplementation increases mitochondrial protein synthesis during the acute stages of post-exercise recovery. Specifically, Breen et al. [5] showed that adding 10 g of whey protein to a drink containing 25 g of carbohydrate had no effect on mitochondrial protein synthesis rates. With either drink, mitochondrial protein synthesis was increased from previously reported control levels [1]. However, the presence of whey protein after endurance type exercise did not affect mitochondrial protein synthesis rates, even though myofibrillar protein synthesis rates increased by ∼50%. It could be speculated that the inability of protein ingestion following endurance type exercise to stimulate mitochondrial protein synthesis rates is due to mTOR not regulating mitochondrial protein synthesis [41]. In fact, in cell culture, treatment with the mTOR-specific inhibitor rapamycin actually increases cytochrome oxidase (COX) activity, COX IV protein, and mitochondrial transcription factor A levels [41]. This suggests that mTOR is not necessary to increase mitochondrial proteins, and therefore amino acid supplementation would not have a direct effect on muscle mitochondrial protein synthesis. However, it is possible that the time line of post-exercise stimulation of protein synthesis rates differs substantially for mitochondrial and myofibrillar proteins, making a direct comparison challenging. Since providing exogenous amino acids modulates skeletal MPS both by activating signaling pathways and by providing substrate for de novo MPS, it will be of key importance to identify the factors(s) that limit myofibrillar as well as mitochondrial MPS rates in vivo during acute and more prolonged post-exercise recovery.

**Amino Acids Attenuate the Immunosuppression Response after Intense Exercise**

The absence of a protein-dependent increase in mitochondrial protein synthesis does not mean that protein supplementation would not be beneficial for endurance performance. Besides the capacity of exogenous amino acids to modu-
late post-exercise muscle protein synthetic and/or proteolytic signaling and provide precursors for MPS, there have been suggestions that amino acids may also be relevant for maintaining proper immune status during intense endurance type exercise training. Immediately following strenuous exercise, there is a transient suppression of the immune system that may lead to an ‘open window’ for infection [42]. This ‘window’ is proposed to last anywhere from 6 h to a week following exhaustive exercise, is directly related to the intensity and duration of exercise [43, 44], and can be exacerbated in an overtrained state [45]. One potential cause of this ‘open window’ may be a decline in glutamine bioavailability of more than 20% [43, 44, 46–49] likely due to accelerated glutamine metabolism by leukocytes [47–49]. Since glutamine is a metabolic substrate for many immune cells, including lymphocytes, macrophages and neutrophils, many experts hypothesize that the reduction in plasma glutamine and branched-chain amino acids (BCAA) after intense exercise promotes immunosuppression [42, 47–49]. Current evidence supports this hypothesis by linking lower plasma glutamine concentrations in middle-distance runners, marathoners, ultra-marathoners and elite rowers with impaired immune responses [43, 44, 46] and higher incidences of infection up to 7 days after intense training/competition (fig. 2) [43]. In these same experiments, supplementation with glutamine [43, 44] or BCAA [46] was effective at restoring circulating plasma glutamine to pre-exercise levels, as well as preventing immunosuppression and reducing athletes’ reported infections [43]. BCAA having the same effect as glutamine on immunosuppression is likely due to the conversion of BCAA into glutamate [50] and enhanced export of glutamine into the bloodstream in the presence of BCAA [35].

**Fig. 2.** Effect of glutamine (Gln) supplementation on plasma Gln (a) and incidence of infection (b) following an Olympic distance triathlon. Adapted from Castell and Newsholme [43] and Bassit et al. [46].

![Graph showing plasma Gln and incidence of infection before and after triathlon](image-url)
The mechanism by which glutamine opposes immunosuppression is not completely understood, but recent findings suggest that glutamine consumed in conjunction with whey protein isolate improves lymphocyte function [51]. As discussed above, glutamine exchange with leucine through LAT1 is important in the activation of mTOR. Consistent with a role of mTOR in lymphocyte function, Sinclair et al. [52] have shown that rapamycin can redirect activated T cells to secondary organs such as the spleen and lymph nodes resulting in premature termination of immune responses. Ingestion of sufficient glutamine and leucine is likely required to increase leucine uptake and mTOR activation in the lymphocytes, through SNAT2 and LAT1, and as such to maintain proper immune function. Glutamine supplementation also decreases neutrophil apoptosis after a bout of endurance type exercise in part by enhancing antiapoptotic gene expression of bcl-xL and inhibits proapoptotic genes such as bax, bal, p53 and caspase 3 [53, 54]. These data suggest that ingestion of ample glutamine and BCAA may be beneficial for limiting the ‘open window’ for infection following intense exercise or competition. However, several recent glutamine feeding intervention studies indicate that although the plasma glutamine concentration can be kept constant during and after prolonged strenuous exercise, specific glutamine supplementation does not seem to prevent post-exercise changes in various aspects of immune function [55]. Although glutamine is essential for lymphocyte proliferation, the plasma glutamine concentration does not seem to fall sufficiently low after exercise to compromise the rate of proliferation [55]. Therefore, whether glutamine/BCAA supplementation will improve immune function in endurance athletes has yet to be determined conclusively.

Practical Considerations regarding Protein Supplementation

For sedentary adults, the Institute of Medicine recommends consumption of 0.8 g·kg⁻¹·day⁻¹ protein [56]. However, this recommendation is based on nitrogen balance studies and is unlikely to support proper adaptation to intense exercise training in athletes. The American College of Sports Medicine’s (ACSM) position stand recommended protein intake ranges from 1.2 to 1.7 g·kg⁻¹·day⁻¹ for athletes [57]. In strength athletes, consuming protein near Institute of Medicine levels (0.86 g·kg⁻¹·day⁻¹) resulted in lower whole-body protein synthesis rates than a diet containing either 1.4 g·kg⁻¹·day⁻¹ or 2.4 g·kg⁻¹·day⁻¹ [58]. Interestingly, increasing dietary protein from 1.4 to 2.4 g·kg⁻¹·day⁻¹ did not further increase whole-body protein synthesis rates but stimulated amino acid oxidation. In endurance-trained athletes, 1.4 g·kg⁻¹·day⁻¹ has been recommended on the basis of nitrogen balance [59]. Overall, there does not seem to be any
advantage for athletes when consuming more than the upper boundary of recommended protein intake described in the ACSM position even during intense training cycles [57]. In addition, it should be noted that overall dietary protein intake in most athletes is generally well above requirements as the greater energy intake with a diet containing more than 15% energy derived from protein translates in a daily protein intake well in excess over 1.4 g protein/kg per day. However, this does not imply that dietary protein supplementation cannot be of benefit to optimize skeletal muscle adaptation to exercise training as provision of the proper type and amount of dietary protein with the right timing can be of great importance when trying to optimize muscle reconditioning following exercise training and competition.

**Protein Amount and the Adaptation to Exercise**

Dose-response analysis of the rate of protein synthesis either at rest [60] or following resistance type exercise [61] has demonstrated that ingestion of 8–10 g of EAAs, roughly 20–25 g of a high-quality protein, maximizes mixed MPS rates in healthy young volunteers. At rest, ingestion of 10 g of EAA has been shown to result in peak postprandial MPS rates in healthy young males [60]. Following resistance exercise, there is an increase in amino acid sensitivity that increases the muscle protein synthetic response to protein and/or amino acid provision [62]. Consuming 20 g of whole egg protein, approximately 8 g of EAA, after resistance type exercise maximizes MPS rates (fig. 3) [61]. Increasing the amount of protein consumed, up to 40 g, resulted in only a marginal increase in mixed

**Fig. 3.** Dose-response of MPS in relation to the amount of egg protein consumed after resistance exercise. Adapted from Moore et al. [61].
MPS (11%), whereas protein oxidation increased significantly [61]. These data suggest that post-exercise ingestion of more than 20–25 g dietary protein will not be of much benefit. However, the latter may be restricted to young adults as larger amounts of dietary protein need to be ingested to maximize postprandial MPS in older individuals [63, 64], indicating that our sensitivity to amino acids may decline with aging [39, 40].

Protein Timing and the Adaptation to Exercise

The dose-response experiments suggest that ingestion of 20–25 g of a high-quality protein will maximize mixed MPS rates. Consequently, this amount of protein should be consumed at various intervals throughout the day. However, the length of the intervals between protein meals remains to be fully determined. We know that prolonged exposure to elevated amino acid concentrations can induce insulin resistance through a feedback mechanism initiated by mTOR [65]. In fact, chronic elevation of plasma amino acids levels does not maintain elevated MPS rates [66], and is therefore unlikely to benefit skeletal muscle adaptation. In support of this concept, Moore et al. [67] demonstrated that after ingesting 25 g whey protein following myofibrillar protein synthesis returned to baseline levels after 5 h of postprandial recovery. Therefore, to optimize postprandial MPS, it is advised to provide 20–25 g dietary protein every 4–5 h.

Recent work suggests that it might also be of benefit to provide some protein prior to an overnight fast. Preventing muscle protein balance from becoming negative during sleep may facilitate the muscle protein synthetic response to exercise and improve muscle reconditioning. 40 g of casein consumed 30 min before going to sleep was shown to be properly digested and absorbed throughout the night, and more importantly this amount of protein strongly stimulated (∼22%) MPS [68, 69]. Together, these data suggest that athletes who are looking to increase lean mass should be consuming ∼25 g of protein every 4–5 h throughout the day and a further 25–40 g of protein prior to sleep.

For many athletes though, increasing lean body mass is not the goal. The goal for these athletes is to improve protein turnover in muscles that are important for performance but without overall changes in bodyweight. For these individuals, a more restrictive diet together with timed protein intake will be more effective. Rather than consuming protein throughout the day, these individuals should be advised to consume fewer calories throughout the day and then supplement their diet with protein in conjunction with their workouts. Taking a little protein or amino acids prior to and/or during resistance type exercise results in greater post-exercise MPS than taking the same supplement after the
exercise bout. This is likely attributed to a more rapid provision of dietary protein-derived amino acids that will be available directly after cessation of exercise [70]. Furthermore, there is evidence to suggest that protein and/or amino acid ingestion prior to exercise can already stimulate MPS during exercise, thereby contributing to the muscle protein synthetic response to exercise [71, 72].

Ingestion of EAA in the period immediately after resistance exercise increases mTOR activation and MPS more than EAA or resistance exercise alone [1, 70, 73–75]. The result is that consuming protein within the first 2 h after resistance type exercise results in greater muscle hypertrophy and strength gains than consuming the same protein later [76, 77]. A similar increase in intracellular leucine content, mTOR signaling and MPS is seen when EAA are taken during endurance exercise [78]. However, as discussed above, the increase in protein synthesis after endurance exercise likely reflects myofibrillar and not mitochondrial protein synthesis [5]. Overall, these data suggest that athletes maintain body-weight and muscle mass and promote protein turnover simply by consuming a calorie-neutral diet with supplemental protein timed for the first 30 min after a workout. This strategy can also be used to reduce lean body mass loss during periods of weight reduction [79].

Protein Quality and the Adaptation to Exercise

The data presented above suggest that consuming 20–25 g protein immediately following resistance exercise maximizes the mixed muscle protein synthetic response. However, the question remains which proteins are best for maximizing the response. Following ingestion, dietary protein is digested and absorbed [80]. Approximately 95% of amino acids are absorbed through the intestinal wall and released into the portal vein or used by the gut [81] with only ∼50–60% of the ingested dietary protein being released into the systemic circulation [64, 82–84]. Depending on the protein quality, amount and the macronutrients ingested with the protein, the digestion and absorption kinetics can be modulated, resulting in more or less amino acids derived from that dietary protein being released in the circulation [85].

The most obvious example of how protein absorption can alter the MPS after exercise is seen between the two protein fractions, the so-called ‘fast’ and ‘slow’ proteins, found in milk [86]. The ‘fast’ protein is the acid soluble whey fraction that is rapidly absorbed and results in a dramatic rise in amino acid levels [74, 87–89]. The ‘slow’ protein is the acid-insoluble fraction consisting primarily of casein. When casein is ingested, the acidic environment of the stomach causes the protein to clump, slowing its passage from the stomach and absorption from
the small intestine. The result is a modest, but prolonged increase in amino acids in the blood [74]. When consumed after a bout of resistance exercise, the rapidly absorbed whey stimulates protein synthesis to a greater degree than an isocaloric/isonitrogenous amount of the slower absorbed casein [74]. Hydrolyzing the casein to make it water soluble increases its absorption and the subsequent rate of MPS in response to an isonitrogenous amount of casein [90, 91], suggesting that the rate of absorption and uptake of amino acids results in different acute rates of protein synthesis [82]. However, the speed of absorption is not the only consideration. Soy protein, another acid-soluble ‘fast’ protein, does not stimulate MPS following resistance exercise to the same extent as whey [92], suggesting that the amount of leucine in the blood following ingestion may also play a role in stimulating MPS [93]. The latter is supported by the observation that even a more rapidly digested casein hydrolysate does not stimulate postprandial MPS to the extent as observed following the ingestion of whey protein [90]. The greater postprandial muscle protein synthetic response was significantly correlated with the postprandial rise in circulating plasma leucine concentrations. Therefore, the muscle protein synthetic response to dietary protein depends on the digestion and absorption kinetics as well as the amino acid composition of the protein.

Macronutrient Coingestion and Adaptation

Since the rate of amino acid appearance in the blood, with leucine in particular, is a key determinant of the MPS response, then a mixed meal of protein together with fat and carbohydrate may alter the postprandial muscle protein synthetic response. Consuming carbohydrates with protein slows amino acid uptake from the gut but also lowers liver amino acid uptake and gluconeogenesis [81, 94], suggesting a modest effect of carbohydrate on amino acid appearance in the blood. Even though fat consumption slows gastric emptying [95], coingestion of fat with protein does not seem to alter amino acid uptake kinetics [94]. In fact, when whole milk was directly compared with non-fat milk, the rate of amino acid uptake was found to be higher following resistance exercise in the presence of fat [96]. It remains to be determined how the postprandial muscle protein synthetic response can be modulated through the coingestion of other macronutrients. Besides the impact of fat and carbohydrate on protein digestion and absorption kinetics, the subsequent postprandial rise in circulating insulin may modulate muscle perfusion, thereby increasing amino acid delivery and/or amino acid uptake in skeletal muscle tissue. However, the effects of insulinogenic supplements (high in carbohydrate or arginine) have yet to be extensively tested.
Conclusion

Protein uptake, especially the amino acid leucine, into muscle results in the activation of mTOR and a subsequent increase in MPS. Following exercise, this results in an increase in the rate of myofibrillar protein synthesis and shifts muscle into a positive protein balance. However, it is important to note that protein consumption during acute post-exercise recovery does not seem to stimulate mitochondrial protein synthesis rates. Protein ingestion following exercise facilitates the increase in skeletal MPS rates following exercise, supporting muscle repair, growth and remodeling. For the strength athlete, exercise training increases the sensitivity to amino acids for at least 24 h after exercise, but immediate consumption of 20–25 g of rapidly absorbed protein will enhance MPS rates and drive the skeletal muscle hypertrophic response. At rest, 20–25 g of dietary protein should be consumed every 4–5 h and another 20–40 g prior to bedtime to facilitate the postprandial muscle protein synthetic response. In this way, consuming dietary protein can complement intense exercise training and facilitate the skeletal muscle adaptive response.

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