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Protein Intake: Effect of Timing

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summary

Differences in protein requirements for athletes and nonathletes, and different types of athletes (i.e., endurance vs. strength/power) are well acknowledged. This has led many athletes to use protein supplements as a means of achieving required protein intakes. Recent research has begun to examine the importance of protein timing. Specifically, does it make a difference when the protein is ingested in regards to augmenting the acute physiological response to a training session or in enhancing recovery from exercise. This review focuses on the timing of protein intake and its effects on skeletal muscle remodeling.

Introduction

Dietary supplement use among the adult population in the United States is widespread. Recent reports have suggested that more than half of the American adult and adolescent population use some form of nutritional supplement, with vitamin and mineral supplementation being the most widely reported (10). Thus, it comes as no surprise that nutritional supplementation use among athletes appears to be at record rates. Nearly 90% of collegiate athletes are currently using or have used nutritional supplements (18). However, whether nutritional supplementation by such a large segment of the athletic population is necessary could be cause for debate, especially considering that many collegiate athletes are not meeting their nutritional needs regarding both energy and protein intake (12, 20). Although a need exists to help athletes determine whether dietary supplementation is necessary, the primary focus for much of the research on nutritional supplementation has been on demonstrating the efficacy of various supplements or supplement combinations in regard to athletic performance improvements, muscle hypertrophy, and body mass changes. However, recent research has begun to examine the importance of nutrient timing. If an athlete is using a dietary supplement, does it make a difference when that supplement is consumed with regard to augmenting the acute physiological response to that training session or to enhancing recovery from exercise? This review focuses on the timing of protein intake and its effects on skeletal muscle remodeling.

Protein Timing and Muscle Anabolic Response to Resistance Exercise

The importance of both resistance exercise and protein intake has been well established with regard to increasing net protein balance (4, 33, 44). Resistance exercise has been shown to be a potent stimulator of muscle protein synthesis and results in a greater protein accretion than protein degradation (4, 33). Figure 1 compares muscle protein fractional synthesis rate and muscle protein fractional breakdown rate after resistance exercise in a fasted state. Muscle protein fractional synthesis rate increased 112% from rest at 3 hours post exercise, while muscle protein fractional breakdown rate was elevated 31% from resting levels by 3 hours post exercise. Although protein synthesis and breakdown increased simultaneously, protein synthesis increased to a greater extent than breakdown. Phillips and colleagues (33) also demonstrated a strong correlation (r = 0.88) between muscle protein fractional synthesis rate and fractional breakdown rate, suggesting that in the fasted state, amino acid uptake from the circulation via protein degradation provides the necessary amino acids for protein synthesis.

When amino acids are ingested or infused after resistance exercise, muscle protein synthesis is enhanced to a greater extent than that seen after resistance exercise in a fasted state, resulting in a positive protein balance and a more anabolic state (5, 42). Figure 2 shows the effect of resistance training, amino acid infusion, and the combination of the two on muscle protein synthesis. After a resistance training session, protein synthesis is seen to increase by about 100% from resting levels (4). If amino acids are infused during rest, protein synthesis increases to approximately 150%, and when amino acids are infused to subjects who are also performing resistance exercise, muscle protein synthesis may be elevated more than 200% from rest (5). Other investigators have reported that the combination of oral ingestion of amino acids and resistance exercise session may produce an even greater increase (3.5 fold) in muscle protein synthesis (32). Although resistance exercise and protein intake can increase muscle protein synthesis, the combination of the two is clearly superior in eliciting significant gains in protein synthesis.

The need for protein appears to be greater for the strength/power athlete than for the endurance-trained athlete or the sedentary population (27, 39). The higher protein pool is thought to enhance the recovery and remodeling processes of muscle fibers that have been damaged or disrupted during resistance exercise (41). Recent studies have shown decreases in muscle damage, attenuation of force decrements, and an enhanced recovery from resistance exercise in individuals using protein supplements (26, 36). The importance of protein intake for the strength/power athlete has led major sports medicine and dietetic associations to jointly release a position stand detailing this greater need (1). Considering that elevated protein intake requirements have become accepted for strength/power athletes, the focus area for many exercise scientists in the field has become the timing of protein consumption with regard to the workout.

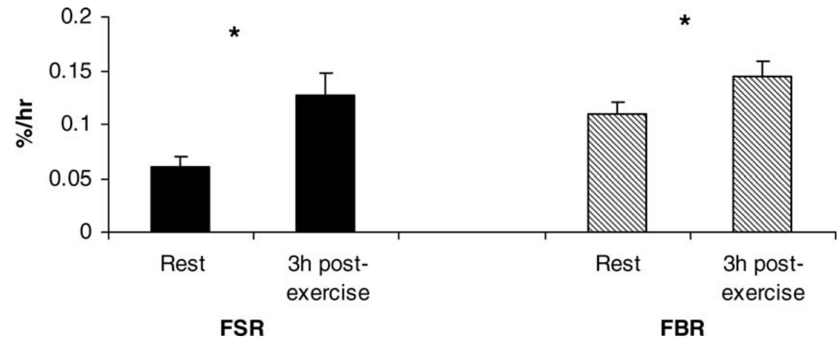

Figure 1. Fractional synthetic rate (FSR) and fractional breakdown rate (FBR) 3 hours after resistance exercise in a fasted state. * Significantly different from rest. Data are adapted from Phillips et al. (33).

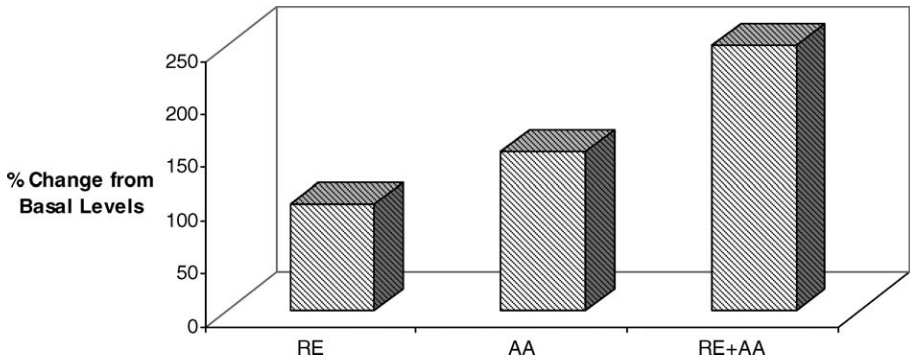

Figure 2. Rates of protein synthesis after resistance exercise (RE), amino acid infusion (AA), and resistance exercise plus amino acid infusion, expressed as a percent change from basal. Data adapted from Biolo et al. (4, 5).

Acute Protein Intake Before and/or After Resistance Exercise

The timing of protein ingestion appears to be critical in maximizing the anabolic response from resistance exercise (2, 14, 17, 44). However, many of the early studies demonstrating the benefits of postexercise amino acid uptake on elevated muscle protein synthesis primarily used an intravenous delivery of amino acids (5, 34). Although these results were quite impressive, this method of delivery was generally not practical for competitive or recreational athletes using such supplements. Initial studies used an intravenous method of delivery due to concern about the effectiveness of consuming amino acids orally. Previous studies have suggested that between 20% and 90% of the amino acids are removed from the circulation as they initially pass through the liver (13, 29, 30) and that perhaps more are removed during exercise (19, 45). However, later examination showed comparable changes in net muscle protein balance (synthesis

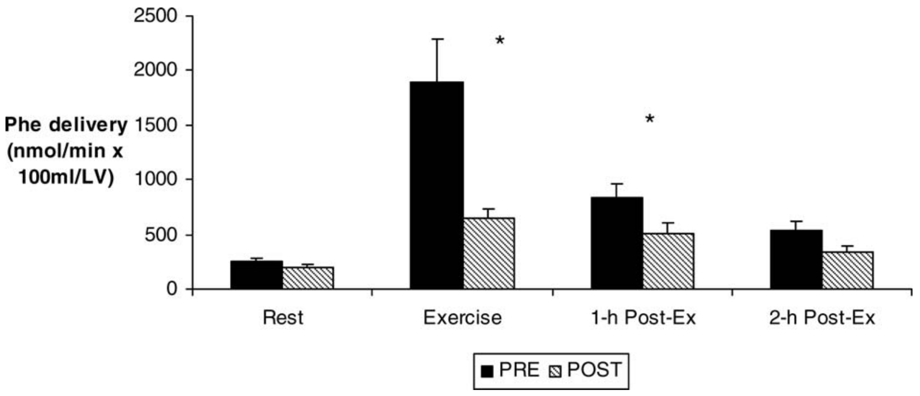

Figure 3. Mean delivery of phenylalanine to the leg for protein supplementation provided before (PRE) and immediately after (POST) exercise. Phe = phenylalanine; LV = leg volume; Post-Ex = post exercise. * Significant difference between PRE and POST. Data adapted from Tipton et al. (44).

– degradation) from both oral and infused ingestion of essential amino acids after resistance exercise (42), indicating that the oral consumption of protein, typically employed by most individuals ingesting protein supplements, is efficacious in enhancing the anabolic response to resistance exercise.

A major focus for research in nutrient timing has been directed at when the protein supplement is provided after a resistance exercise session. Rasmussen and colleagues (35) showed that when 6 g of essential amino acids (0.65 g histidine, 0.60 g isoleucine, 1.12 g leucine, 0.93 g lysine, 0.19 g methionine, 0.93 g phenylalanine, 0.88 g threonine, and 0.70 g valine) were provided with 35 g of sucrose to untrained subjects, a similar increase in net muscle protein synthesis was seen, whether the supplement was consumed at 1 or 3 hours after resistance exercise. However, when this same essential amino acid and carbohydrate supplement combination was given immediately prior to exercise, the increase in muscle protein synthesis was significantly greater than when given immediately after exercise (42). Tipton and colleagues (42) demonstrated that when amino acids were provided immediately before exercise, the amino acid concentration within skeletal muscle increased 46% by the end of exercise and was elevated further (86% above rest) an hour after exercise. These values were significantly greater than those seen in subjects consuming the supplement after exercise. By 3 hours after exercise, muscle amino acid concentrations still remained 65% above rest in subjects who were given supplements before exercise.

The benefit of amino acid ingestion prior to exercise is also seen in the increased rate of delivery and subsequent uptake by skeletal muscle during exercise. Figure 3 describes a 2.6-fold greater increase in the rate of phenylalanine delivery to skeletal muscle when essential amino acids are consumed before resistance exercise compared with the same supplement provided after exercise (44). This difference continued for at least 1 hour after exercise. In addition, the amino acid uptake by skeletal muscle in subjects consuming the supplement immediately before the onset of exercise was 160% greater for the total 3-hour period (rest, exercise, and postexercise period) compared with those subjects consuming the supplement immediately after exercise. The greater amino acid uptake is assumed to correspond to a greater synthesis of muscle protein. Thus, ingestion of amino acids combined with carbohydrates before the onset of exercise appears to be a potent stimulator of amino acid delivery via an increased blood flow to exercising muscle and subsequent muscle uptake, resulting in greater protein synthesis than consuming this supplement after exercise. Although Figure 3 illustrates the response of phenylalanine, similar responses have also been reported in other essential amino acids (42).

The composition of the amino acid mixture used in many of these studies was based upon the availability of each of these essential amino acids in proportion to their requirement for the synthesis of muscle protein (9). Previous research had determined that only essential amino acids were necessary for stimulation of protein synthesis (42, 43). When subjects were given 40 g (21.4 g essential and 18.6 g nonessential) of amino acids, the contribution to the increase in muscle protein synthesis was in proportion to a 40-g ingestion of only essential amino acids (43). An additional study compared 6 g of mixed amino acid (3 g essential and 3 g nonessential) with 6 g of essential amino acid supplement and again showed a dose response effect, suggesting that the greater the amount of essential amino acid in the supplement, the greater the muscle protein synthesis (9). Considering the effective reutilization of endogenously produced nonessential amino acids, it does not appear to be necessary to include these amino acids as part of any nutritional supplement.

Interestingly, the goal of proportional increases in the availability of all of the essential amino acids from ingestion of a supplement with a similar amino acid composition of muscle does not truly occur (9). It is possible that differences in clearance rates of individual amino acids after ingestion result in a differential uptake by muscle that differs from the ingested mixture (9). Leucine and isoleucine appear to increase to a greater extent than other amino acids, suggesting that these specific essential amino acids have a more potent effect on muscle protein synthesis. A subsequent study has shown that when leucine was added to a whole protein (whey) and carbohydrate supplement, whole body net protein balance was significantly greater than that seen after protein and carbohydrate supplement or carbohydrate supplement alone (24).

Differences in Whey and Casein Protein Ingestion on Protein Accretion

Casein and whey are 2 whole proteins from bovine milk that have different digestive properties. Casein, which is the predominant milk protein, exists in the form of a micelle, which is a large colloidal particle. The casein micelle forms a gel or clot in the stomach that makes it slow to digest. As a result, casein provides a sustained but slow release of amino acids into the blood stream, sometimes lasting for several hours (6). This provides better nitrogen retention and utilization by the body. Whey protein accounts for 20% of bovine milk (casein accounting for the remainder) that contains high levels of the essential and branched chain amino acids (21). Whey protein is the translucent liquid part of milk that remains after the process (coagulation and curd removal) of cheese manufacturing; as a result it is absorbed into the body much quicker than casein.

In a comparison between casein and whey protein supplementation, Boirie and colleagues (6) demonstrated that a 30-g feeding of casein versus whey had significantly different effects on postprandial protein gain. They showed that after whey protein ingestion, the plasma appearance of amino acids is fast, high, and transient. In contrast, casein is absorbed more slowly, producing a much less dramatic rise in plasma amino acid concentrations. Whey protein ingestion stimulated protein synthesis by 68%, while casein ingestion stimulated protein synthesis by 31%. When the investigators compared postprandial leucine balance 7 hours after ingestion, casein consumption resulted in a significantly higher leucine balance, whereas no change from baseline was seen 7 hours after whey consumption. These results suggest that whey protein stimulates a rapid synthesis of protein but a large part of this protein is oxidized (used as fuel), whereas casein may result in a greater protein accretion over a longer duration. A subsequent study showed that repeated ingestions of whey protein (an equal amount of protein but consumed over a prolonged period [4 hours] compared with a single ingestion) produced a greater net leucine oxidation than a single meal of casein or whey (15). Interestingly, both casein and whey are complete proteins, but their amino acid composition is different. Specifically, leucine content, which has an important role in muscle protein metabolism, is higher in whey than in casein. Thus, the digestion rate of the protein may be more important than the amino acid composition of the protein. These results were supported by Tipton and colleagues (41), who also reported that the differences in digestive properties between whey and casein do result in a fast and slow increase in muscle protein synthesis, respectively. However, the net muscle protein synthesis over a 5-hour period of examination was not different between these whole proteins when ingestion (20 g of each protein) occurred 1 hour after resistance exercise. It does appear that the whole proteins casein and whey are effective in stimulating muscle protein synthesis. Differences in digestive properties of the proteins, though, do result in a different pattern of protein synthesis, with whey ingestion resulting in a greater acute response compared with a more gradual rise in protein synthesis seen after casein intake. Although the total net muscle protein synthesis appears to be similar between the proteins, it is not clear whether the acute elevation seen after whey ingestion represents a greater window of opportunity after exercise for enhancing the recovery and remodeling of skeletal muscle.

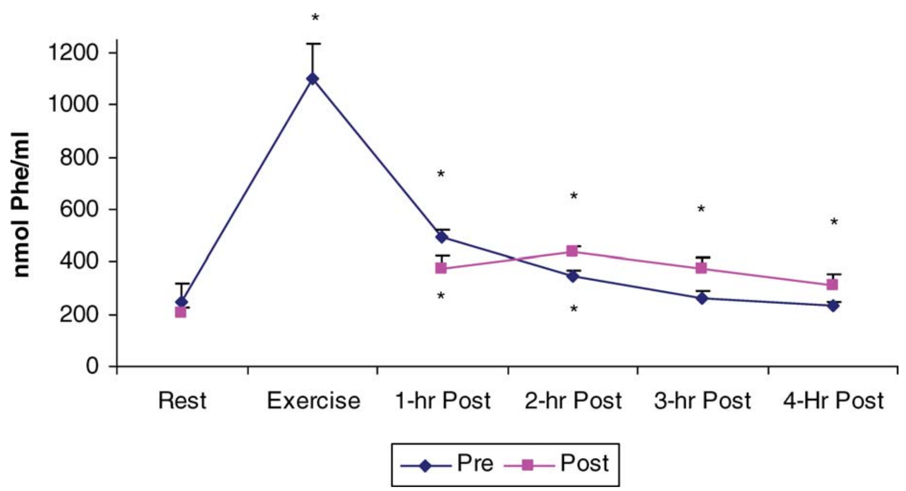

Figure 4. Phenylalanine concentrations in arterial blood to the leg before, during, and after resistance exercise. * Significantly different from rest. Data adapted from Tipton et al. (40).

Is There a Difference Between Amino Acid and Whole Protein Ingestion on Muscle Protein Synthesis?

Recent studies have been clear in demonstrating that ingestion of both amino acids and whole proteins, such as whey and casein, can increase muscle protein synthesis. The question, then, is whether one type stimulates muscle protein synthesis after resistance exercise to a greater degree than the other. What is known is that essential amino acid ingestion prior to resistance exercise stimulates greater muscle protein synthesis than essential amino acids consumed immediately after

(44), or 1 or 3 hours after exercise (35). However, when comparing protein timing of whole protein ingestion on differences in muscle protein synthesis, a recent study suggests that when whey protein is ingested immediately before or 1 hour after exercise, no significant difference in the anabolic response to such supplementation is seen (40). Figure 4 shows that when whey protein was ingested immediately before exercise, phenylalanine (amino acid often used to indicate changes in rate of protein synthesis) measured in the leg (determined by arterial phenylalanine concentrations × blood flow) significantly increased during exercise and returned to baseline levels by hour 3 post exercise. When whey protein was consumed within an hour after exercise, phenylalanine delivery increased and remained elevated throughout the 5-hour recovery period. However, no significant differences were seen between ingestion before or after exercise in net phenylalanine delivery to the muscle, suggesting that no benefit is apparent from consuming whey protein before exercise compared with immediately after exercise.

Previous studies showing the benefit of pre-exercise protein ingestion used an amino acid supplement. It appears that the same benefit is not seen with whole proteins. These differences are not well understood, but it has been speculated that differences in delivery of essential amino acids to the exercising muscle may be responsible (40). Increases in arterial amino acid concentrations is approximately 100% higher than resting levels after ingestion of essential amino acids but only 30% after whey protein ingestion (40). In addition, the delivery of phenylalanine to active muscle during exercise increases approximately 7.5 fold after essential amino acid ingestion but only 4.4-fold higher for whey protein (40). It is possible that the inclusion of carbohydrates in the amino acid supplement (no carbohydrate was included in the whey protein) influenced the response of muscle to amino acid ingestion by stimulating a greater insulin response, resulting in a greater amino acid uptake by muscle.

The addition of whey protein (17.5 g) to an amino acid (4.9 g) and carbohydrate (77.4 g) drink consumed 1 hour after resistance exercise does appear to enhance muscle protein net balance by extending the anabolic response (7). One of the benefits of including whey protein in a supplement could be to increase the palatability of a supplement compared with an amino acid and carbohydrate alone. Whether such a combination ingested before exercise provides any further ergogenic effect is not clear.

Elliot and colleagues (16) recently examined the effect of a food source on muscle protein balance after resistance exercise. They demonstrated that milk ingestion stimulated a net uptake of phenylalanine and threonine, indicating an increase in net muscle protein synthesis. Whole milk appears to be more beneficial than fat-free milk, unless the quantity of fat-free milk consumed was similar in caloric value as the whole milk. Whole milk and isocaloric fat-free milk ingested 1 hour after resistance exercise stimulated significant elevations in phenylalanine uptake that was 80% and 85%, respectively, greater than fat-free milk. Threonine uptake was 2.8-fold greater ($p < 0.05$) after whole milk than fat-free milk ingestion. No other differences were seen. These results demonstrate that a food source such as milk appears to be suitable for ingestion during recovery from resistance exercise and may be a cheaper and effective alternative to protein supplements.

Importance of Carbohydrate and Protein Combinations for Muscle Protein Synthesis

The inclusion of carbohydrates to a protein supplement is based upon a desire to stimulate insulin secretion. Insulin is critical for regulating glucose uptake by tissue. Interestingly, exercise serves to enhance skeletal muscle responsiveness to glucose by causing a greater sensitivity of muscle to the effects of insulin (31, 37). The importance of this, with regard to muscle remodeling and protein synthesis, is that insulin can also stimulate the uptake of amino acids (3). Although carbohydrates alone provide only a minor effect on improvements in muscle protein balance after exercise (8, 38), the combination of carbohydrate with protein or amino acids in a supplement may contribute to a more effective protein uptake and enhanced synthesis rate of muscle protein. Recently, investigators compared carbohydrate only with carbohydrate and protein, and carbohydrate, protein, and leucine combinations on muscle protein synthesis rate after resistance exercise (24). Results showed that the combination of carbohydrates and protein was superior to carbohydrates only in stimulating whole body protein balance. Furthermore, the inclusion of the essential amino acid leucine to the carbohydrate protein combination provided an even greater stimulus to muscle protein synthesis rate compared with the carbohydrate and protein mixture alone. The added benefit of leucine is likely related to its function as a nutritional signal for enhancing protein synthesis rate by potentiating the signaling process at the translational level (23).

Studies examining the timing of carbohydrate and protein supplement ingestion are equivocal. Although there are only limited data available, variability does appear to be related to whether the supplement is a whole protein or amino acids. No differences were seen in muscle protein synthesis when a carbohydrate (35 g of sucrose) and amino acid (6 g) supplement was provided at 1 or 3 hours after resistance exercise (35). However, when a supplement consisting of 10 g of protein (primarily casein), 8 g of carbohydrate (sucrose), and 3 g of lipid (milk fat) was provided immediately after exercise, a significant difference in muscle protein synthesis was seen compared with the same supplement provided 3 hours after exercise (28). In this latter study, plasma glucose, insulin, and amino acid concentrations were similar between the 2 supplement periods; however, glucose and amino acid uptake by exercising skeletal muscle was greater when the supplement was provided immediately after exercise. Thus, the period of time that skeletal muscle shows the highest responsiveness and potential for greatest adaptation may exist in the relatively short time (within 1 hour) after exercise.

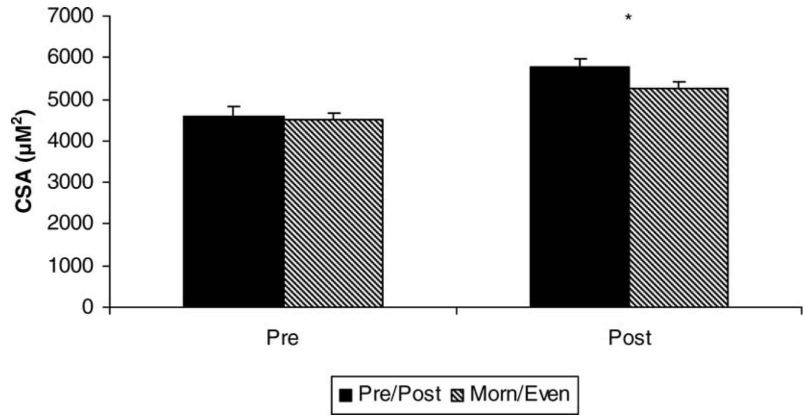

Figure 5. Cross-sectional area of type IIa fibers. * Significant difference between pre/post and morning/evening. Data adapted from Cribb and Hayes (14).

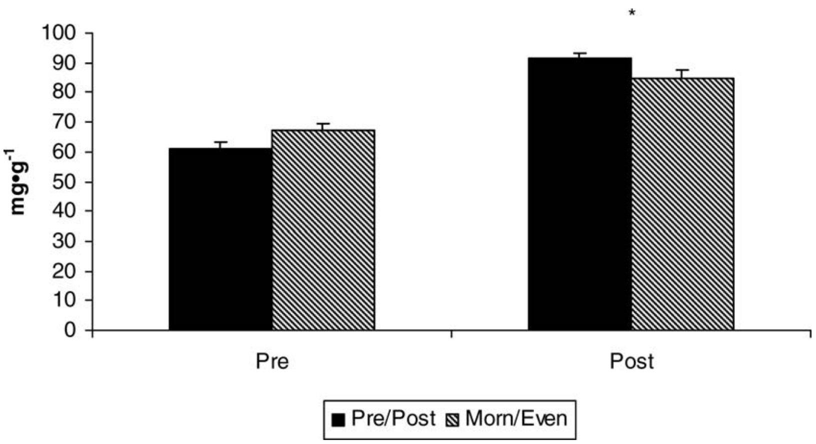

Figure 6. Contractile protein content. * Significant difference between pre/post and morning/evening. Data adapted from Cribb and Hayes (14).

Protein Timing and Training Studies

Studies examining the acute effect of protein ingestion have clearly demonstrated that ingestion occurring close to the workout (e.g., immediately before or within an hour after exercise) significantly enhances muscle protein synthesis rate and muscle protein accretion compared with when ingestion is delayed for longer periods. These results suggest that protein supplement timing may be critical in stimulating muscle adaptations that occur during prolonged training. However, there are only a limited number of studies that have examined the effect of protein timing in prolonged training studies.

Recently, several training studies have shown that protein ingestion occurring before and immediately after resistance exercise is a potent stimulus for muscle size and performance gains compared with carbohydrate-only supplements in young (19–23 years) and previously trained (22) and untrained individuals (2, 46). However, when examining the effect of protein supplementation in untrained elderly men, Candow and colleagues (11) reported no change in muscle mass or strength after 12 weeks of protein supplementation and resistance training, despite ingestion occurring immediately before and after exercise. The differences between these studies are not clear but may be attributed to differences in the endocrine response to resistance exercise between young and older men (25).

In the limited studies comparing various protein timing strategies, the importance of when the protein supplement is ingested has been demonstrated. One of the initial examinations on the effect of protein timing and muscle hypertrophy was performed in elderly subjects (74.1 ± 1 years) initiating a resistance training program (17). Subjects consumed a liquid protein supplement (10 g protein, 7 g carbohydrate, and 3 g fat) immediately after or 2 hours after each resistance training session (3 times per week) for 12 weeks. Results showed that muscle cross-sectional area and individual muscle fiber area increased significantly in the subjects who consumed the supplement immediately after exercise but did not change in those subjects consuming the supplement 2 hours after each training session. Cribb and Hayes (14) examined the effect of a protein (40 g of whey isolate) carbohydrate (43 g of glucose) supplement in young (21–24 years) recreationally trained male bodybuilders consumed immediately before and after resistance training sessions or consumed in the morning and evening. The group consuming the supplement immediately before and after the workouts experienced significantly greater gains in lean body mass, increases in the cross-sectional area of type II fibers (Figure 5) and contractile protein content (Figure 6), and increases in strength compared with the group consuming protein in the morning and evening.

Practical Applications

The majority of acute studies examining protein timing have used untrained or recreationally trained subjects. Although evidence does support the importance of timing as it relates to an amino acid supplement or whole protein intake, it should be acknowledged that training status may have an important role in the results. Still, based upon available studies, evidence strongly indicates that the proper timing of protein ingestion provides a distinct advantage in stimulating muscle protein synthesis rates and subsequent muscle adaptations. It appears that a whole protein and carbohydrate supplement should be consumed immediately after or within an hour of an exercise session. Whey protein may provide the greater immediate increase in the rate of protein synthesis. However, a combination of whey and casein protein may be an effective supplement that will generate immediate and prolonged elevations in protein synthesis rates. Amino acids are also effective in increasing muscle protein synthesis but appear to be more effective when consumed immediately before, rather than after, the workout. ♦

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