

Is There an Optimal Time for Warfighters to Supplement with Protein?^{1,2}

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Abstract

Although nutritional requirements for warfighters will inevitably vary in accordance with job role and active-inactive duty cycling, somewhat generic recommendations do still apply. In considering aspects of “optimal” nutrient timing, it is important to outline singular and combinatorial relationships between protein intake and physical activity (e.g., exercise) in the context of the following: 1) skeletal muscle protein turnover, 2) functional recovery, and 3) adaptation to exercise. The essential amino acid (EAA) components of dietary protein are key macronutrients regulating muscle proteostasis, because they provide substrate to replenish muscle proteins lost during fasted periods. This occurs through a substantial, albeit short-lived (~2 h) EAA-induced stimulation of muscle protein synthesis (MPS) and via an insulin-mediated suppression of muscle protein breakdown (MPB) (via carbohydrate- and/or EAA-mediated insulin secretory effects). At rest, intake of protein (optimal range between 20 and 40 g of high-quality protein, equating to ~10–20 g EAAs) every ~4–5 h is advocated due to the refractoriness of MPS in response to continuous supply. Bouts of exercise also stimulate muscle protein turnover (increasing both MPS and MPB), but in the absence of protein intake net muscle protein balance remains negative such that exercise alone is catabolic. Intake of dietary protein redresses this balance through enhancing both the amplitude and duration of exercise-induced increases in MPS while concomitantly limiting MPB. These postexercise periods of positive net protein balance permit muscle adaptation and functional recovery. Finally, in relation to exercise, protein dosing (at a minimum of ~20 g) both in close proximity to exercise and thereafter every 4–5 h during waking hours (including before bedtime) is likely optimal for adaptation/functional recovery. J. Nutr. 143: 1848S–1851S, 2013.

Protein Nutrition for Warfighters

Whereas some warfighters³ have very high occupational demands (e.g., Special Forces) others have quite sedentary roles, and, of course, there is everything in between. In addition, physical

demands will vary according to deployment cycle. Regardless of this, protein serves a crucial role in the maintenance of muscle proteostasis and in supporting musculoskeletal remodeling and functional recovery from exercise under all conditions. To contextualize advice surrounding “optimal timing” of nutrition for a warfighter, it is first necessary to outline the temporal effects of nutrition and exercise on muscle protein metabolism as independent factors, before considering their interaction in the regulation of skeletal muscle adaptation and functional recovery.

Temporal Effect of Protein on Muscle Protein Turnover and Regulatory Mechanisms

The stability of skeletal muscle mass depends on a dynamic equilibrium whereupon muscle proteins lost during postabsorptive periods are replenished in postprandial periods. Dietary protein is most vital for maintaining this dynamic equilibrium (1,2)

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³ The term “warfighter” is used by the U.S. Department of Defense to refer to any member of the U.S. Armed Forces. Warfighter is intended to be neutral regarding military service or branch, sex, and service status and replaces previously used terminology including “soldier,” “service member,” and “military personnel.”

because essential amino acid (EAA)⁴ constituents, and leucine in particular (3), are the most crucial nutrients for muscle anabolism. Protein-mediated increases in muscle protein synthesis (MPS) are initiated after transport of EAAs into the muscle cell (4) where leucine, in particular (but not exclusively), activates mammalian target of rapamycin complex 1 (mTORC1), independently of proximal insulin signaling [phosphatidylinositol 3-kinase (PI3K)] pathways (5). Instead, at least in models of deprivation/reprovision, leucine signaling to mTORC1 occurs via leucyl tRNA (transfer RNA) synthetase signaling mechanisms (6,7). Subsequent downstream mTORC1 signaling enhances translational initiation via activating mTORC1 substrates such as ribosomal protein S6 kinase (p70S6K1) and 4E-binding protein 1 (4EBP1) (8), culminating in polyribosome formation and increased MPS. Increasing the plasma availability of EAAs by oral (9) or intravenous (10) supply or via oral protein intake (11) stimulates MPS. The amplitude of increase in MPS after protein/EAA intake ranges from 20% to 300% depending on dosing, “quality” (EAA/leucine content) (12), and technical aspects, such as measurement duration. The optimal dosing of protein to maximize MPS is between 20 and 40 g of high-quality protein (12) or between 10 and 20 g of EAAs (9), with “optimal” dosing within this bracket perhaps reflecting each individual’s whole-body muscle mass and perhaps training status and age (aspects beyond the scope of this review). At rest, providing higher doses of EAAs fails to have any further effect because muscles are receptive to the anabolic effects of EAAs for only a short period, equating to ~2 h (11). After this period of stimulation, MPS displays tachyphylaxis (10), termed “muscle-full” (13). To conclude, an effective meal in terms of the stimulation of MPS should include a minimum of 20 g of high-quality protein, and although the refractory period has yet to be defined in humans, it is likely that protein intake every 4–5 h (approximately double the acute “stimulation period”) would be somewhere near optimal. Finally, because the longest postabsorptive period of a diurnal cycle is overnight (~8 h), intake of protein before retiring for the night (and/or when waking during the night) may yield some benefit (14).

In addition to the stimulation of MPS, the intake of nutrients also triggers a second route for muscle anabolism via suppression of muscle protein breakdown (MPB). However, despite stimulating MPS, increasing EAA availability does not cause a suppression of MPB in the absence of increases in plasma insulin (15). Therefore, it is the release of insulin in response to nutrients that causes suppression of MPB (15,16) rather than being a direct effect of EAAs. On this basis it is important to note that carbohydrate intake is not a prerequisite for nutrition-mediated suppression of MPB. This is because the modest (i.e., in comparison with glucose) insulin secretagogue properties of EAAs, in particular leucine (17), increase plasma insulin concentrations. Because MPB is maximally suppressed (~50%) with small physiologic increases in plasma insulin (from ~5 to 15 $\mu\text{U} \cdot \text{mL}^{-1}$), intake of the recommended ≥ 20 g of protein alone is likely to achieve this.

Temporal Effects of Exercise on Muscle Protein Turnover and Regulatory Mechanisms

The mechanistic basis for exercise-induced anabolism is complex, because exercise triggers a host of mechanotransduction

and physicochemical (i.e., endocrine, auto/paracrine) mechanisms (18). Although it is well established that, as with nutrition, mTORC1 is a crucial signaling pathway regulating exercise-induced alterations in protein turnover (19), the proximal signals eliciting these effects remain poorly defined. Much of the early animal and cell (20) work pointed to a signaling pathway whereby increases in insulin-like growth factor (IGF) 1 stimulates IGF receptor-protein kinase B (AKT)-mTORC1 signaling. In a parallel exercise-activated pathway, the guanine exchange factor, eukaryotic initiation factor 2B (eIF2B) shuttles the initiator tRNA to the ribosome during formation of the 48S pre-initiation complex, thereby promoting MPS alongside mTORC1 signaling (21). However, there are now a number of lines of evidence arguing against a canonical IGF-1 receptor-AKT-mTORC1 pathway in regulating exercise-induced MPS. For example, West et al. (22, 23) reported that systemic concentrations of growth hormone (GH) and testosterone did not influence MPS (22) or strength/hypertrophy (23) adaptations. Also, despite increasing serum GH/IGF-1 and muscle IGF-1 mRNA expression, 14 d of GH administration had no effect on MPS (24). Finally, animal models in which the IGF-1 receptor was genetically ablated demonstrated normal muscle hypertrophy in response to overloading (25). Thus, it seems mechanotransduction and autocrine/paracrine factors rather than endocrine hormones drive loading-induced adaptation.

Irrespective of exercise mode (e.g., endurance vs. resistance), physical activity is “anabolic” in nature—even walking will increase MPS (26). However, the anabolic effects of exercise are not typically realized until after exercise because MPS is likely unchanged/depressed during most forms of exercise (27). This occurs because the ATP-contraction cost of exercise diverts ATP use away from energy-consuming processes (i.e., peptide bonding). After cessation of exercise, MPS “rebounds” to exceed postabsorptive rates (28). However, exercise-induced increases in MPS are limited to ~4 h (29) in the fasted state, with protein intake being an absolute requirement to extend the duration of the MPS response (30). The duration of the postexercise MPS response also depends on exercise mode, intensity, training status, and measurement details. For instance, in the trained state, the duration of MPS (31) is reduced in an “amplitude-duration trade-off.” Also, specific effects can occur in a muscle subfraction-dependent manner and in accordance with characterized exercise-specific adaptations [e.g., resistance exercise increases the selection (32) and duration (30) of myofibrillar MPS, whereas endurance exercise stimulates the preferential synthesis of mitochondrial proteins (32)]. As with increases in MPS, exercise is also synonymous with increasing MPB for remodeling purposes, and increased MPB can persist >24 h after exercise in the fasted state (33); only protein intake is able to temper this. To conclude, whereas net protein balance after exercise in the fasted state remains negative (34), intake of protein shifts net protein balance to positive, which outlines how crucial protein intake is to exercise recovery/adaptation.

Effect of Exercise and Protein on Muscle Protein Turnover and Regulatory Mechanisms

It is well established that postexercise protein intake represents an obligatory component of maximizing adaptation to (resistance) exercise, as was unequivocally summarized in a recent meta-analysis (35). After exercise, intake of protein acts to extend the “anabolic window” via augmenting the amplitude/duration of

⁴ Abbreviations used: AKT, protein kinase B; CK, creatine kinase; EAA, essential amino acid; eIF2B, eukaryotic initiation factor 2B; GH, growth hormone; IGF, insulin-like growth factor; MAPK, mitogen-activated protein kinase; MPB, muscle protein breakdown; MPS, muscle protein synthesis; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol 3-kinase; p70S6K1, ribosomal protein S6 kinase; 4EBP1, 4E-binding protein 1.

MPS over that seen in response to protein intake at rest. Mechanistically, this occurs at least in part due to the synergistic effects of exercise and EAA signals on the phosphorylation of proteins within the mTORC1 and mitogen-activated protein kinase (MAPK) pathways (36). Whereas the time course of this enhanced exercise-mediated sensitization to the anabolic effects of protein intake is poorly defined, Burd et al. (37) recently reported that this still occurs 24 h after a single exercise bout. Therefore, given the facts that 1) the additive effects of exercise on MPS responses to protein are sustained for ≥ 24 h due to “muscle memory of prior exercise” and 2) that between 20 and 40 g of protein are sufficient to maximize anabolic responses to exercise, pulse intakes of 20–40 g of protein (minimum of ~ 20 g) can be advocated to maximize the stimulatory effects of exercise. In support of this, a recent study demonstrated that intermittent feeding of 20 g of protein provided greater 24-h protein accretion after an exercise bout compared with an equal volume of protein consumed as small 10-g pulses or a large 80-g bolus (38). Finally, once again, nighttime feeding (14) could be useful to fill the void of the long catabolic overnight postabsorptive period with the goal of maximizing the beneficial effects of protein in the context of exercise.

Specific Issues over Timing of Protein Intake

Skeletal muscle metabolism/adaptation. There is a relative paucity of studies examining issues over optimal timing of nutritional intake in relation to exercise. As such, whether it is better to consume protein before, during, or after exercise remains a relatively poorly defined question. In 1 study, when participants consumed 6 g of EAAs and 35 g of sucrose 1 or 3 h after resistance exercise, the anabolic effects (on protein turnover) were identical (39). These data indicate that delaying nutritional intake for up to 3 h after exercise does not affect anabolic responses to resistance exercise. In a follow-up study, the authors set out to determine whether consumption of an oral EAA/carbohydrate supplement before exercise results in different anabolic responses compared with supplementation after exercise. These studies revealed that phenylalanine disappearance, an indicator of MPS, was greater when the nutrition was consumed immediately before resistance exercise, indicating nutritional intake before exercise as a best practice (40). Because this previous study involved free EAAs rather than protein supplements, a further study was carried out to determine whether this effect could be recapitulated with protein feeding. To achieve this, a solution of whey proteins was consumed either immediately before exercise or immediately after exercise (10 sets of 8 repetitions of leg-extension exercise). In contrast to when EAAs and carbohydrates were ingested (40), the results of this study showed that intake of the whey solution either before or after exercise yielded similar anabolic effects (41). Drawing a line through these 2 studies, it can be concluded that the timing of whey protein ingestion in proximity to the exercise bout (i.e., before vs. after) is less critical when compared with the combination of free EAAs and carbohydrate. Nonetheless, with so few studies on this topic these conclusions remain somewhat uncorroborated. Finally, in an exercise-training study in older-aged subjects, Esmarck et al. (42) determined the effects of oral protein provided immediately or 2 h after each training session. In response to training, fiber area and strength increased more when the protein-based supplement was consumed immediately after exercise, suggesting that early intake of protein is important

for hypertrophy, at least in old age. To conclude, although limited data exist, the evidence favors protein intake in close proximity to exercise as being beneficial; whether it is taken before or after exercise seems to be less important.

Muscle functional recovery. The additive anabolic effect of protein intake in the period after exercise is important to support muscle remodeling and successful adaptation. Moreover, it is perhaps intuitive that feeding strategies able to best improve muscle net protein balance in the period after exercise are those that also beneficially affect functional recovery [e.g., force or indices of muscle damage such as creatine kinase (CK)]. For example, White et al. (43) demonstrated that supplementation with protein + carbohydrate better preserved maximal voluntary contraction and reduced serum CK in the recovery period from eccentric exercise (6–96 h), independent of whether the supplement was consumed before or after exercise. In a second study, branched-chain amino acid supplementation demonstrated similar findings of reduced serum CK and better preservation of maximal voluntary contraction in the post-eccentric exercise recovery period (44). Finally, supply of 100 g of EAAs enhanced recovery of both force and power in the postexercise period while concomitantly limiting increases in serum CK (45). Collectively, these data point to the notion that recovery from exercise can be enhanced by consuming EAA-containing (protein) supplements in close proximity to exercise.

Conclusions and Possible Recommendations for the Warfighter

The intake of protein represents a key part of muscle proteostasis, with the best current advice for the warfighter being an intake of a minimum of 20 g (with each individual's own recommendation ranging from ~ 20 to 40 g) of EAA-enriched protein every ~ 4 –5 h during the daytime, including before bedtime (14,46). For the warfighter, the intake of protein also plays a key role in both exercise adaptation and in functional recovery from acute exercise bouts, and is subject to similar timing and quantity recommendations as the nonexercise state. Finally, the intake of protein in close proximity to exercise, whether just before or just after, is likely an optimal nutritional strategy for a warfighter to adopt.

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