Exercise-induced changes in protein metabolism

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ABSTRACT

Exercise has a profound acute effect on protein metabolism. Whereas reports on whole body responses to exercise have varied results, it is generally agreed leucine oxidation is increased during exercise, thus indicating increased net protein breakdown. Following endurance exercise, whole body protein breakdown is generally reduced from resting levels, while following eccentric exercise, both whole body protein breakdown and leucine oxidation are increased. Whole body protein synthesis, on the other hand, is either increased or unaltered. Much of the disagreement in the results of studies on the response of whole body protein metabolism to exercise may be attributed to the limitations of the available methods. Even if the methodology accurately reflects whole body metabolism, this may not reflect changes in the protein metabolism of muscle. Although endurance exercise has not been studied, muscle protein breakdown is increased following resistance exercise. There is a concomitant, and qualitatively greater, increase in muscle protein synthesis following resistance exercise, which may last for as long as 48 h. Increased muscle protein synthesis is linked to increased intramuscular availability of amino acids, and thus, to increased blood flow and increased amino acid delivery to the muscle, as well as increased amino acid transport. Administration of exogenous amino acids after exercise increases protein synthesis while ameliorating protein breakdown, thus improving net muscle protein balance. While it is clear that muscle protein synthesis and protein breakdown increase in a qualitatively similar manner following exercise, the mechanisms of stimulation have yet to be determined. However, we propose that the intracellular availability of amino acids is the link between these processes.

Keywords muscle, protein breakdown, protein synthesis, stable Isotopes.

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Exercise has a profound acute effect on protein metabolism. The available information on protein metabolism is not without some controversy. Much of the disagreement in the literature may be linked to the disparate methodology used in the studies. In this review we will summarize the results of studies on the acute response of in vivo protein metabolism in human subjects, primarily those using stable isotopic tracers, during and following exercise. We will then attempt to propose a scheme, based on this information, that might help explain how the metabolic processes in the various tissues are linked and how they operate in response to exercise.

The general nature of exercise can be classified as either resistance or endurance exercise. It is easy to separate these, as the responses to training in each are different. Endurance training results in increased aerobic capacity of muscle, whereas resistance training increases muscle size and ability to produce force. Unfortunately, with regard to acute responses to endurance and resistance exercise, there are few instances in which the response of protein metabolism to both endurance and resistance exercise has been characterized. As will be seen, in these situations, the responses are similar. Therefore, in our discussion we will generally not differentiate between endurance and resistance exercise.

WHOLE BODY PROTEIN METABOLISM

The responses of protein synthesis and protein breakdown have been reported to last from several minutes to as long as several days after exercise (Fielding et al. 1991). Since exercise generally lasts only a relatively short time (a few minutes to 3–4 h), it can be argued that the post-exercise responses may be fundamentally...
more important to the overall state of protein metabolism than changes that occur during exercise. Whereas the primary focus of this paper is on the responses of protein metabolism following exercise, we will also briefly discuss the responses during exercise in order to better understand the starting point for recovery.

**During exercise**

There does not seem to be good agreement between studies that have examined whole body responses of protein metabolism during and after exercise. Most of the information on this topic comes from whole body studies during endurance exercise, usually cycling or walking. The rate of leucine appearance in the plasma pool, as determined by the infusion of isotopically labelled leucine can be used as an indicator of whole body protein breakdown. Several studies have determined that whole body protein breakdown, as reflected by leucine appearance, is increased during endurance exercise in humans (Rennie et al. 1981, Wolfe et al. 1982, Phillips et al. 1993, Carraro et al. 1994) and dogs (Williams et al. 1996). On the other hand, others found protein breakdown to be unchanged (Stein et al. 1989, Carraro et al. 1990a). However, in all cases, leucine oxidation has been shown to increase during exercise (Rennie et al. 1981, Hagg et al. 1982, Wolfe et al. 1982), so there is apparently a net negative balance of leucine, which should correspond to increased net protein breakdown. The increase in whole body protein breakdown arises primarily from gut (Williams et al. 1996) and, perhaps, the muscle (Rennie et al. 1981).

**Post-exercise**

Following endurance exercise, whole body techniques indicate that protein breakdown is either unchanged (Devlin et al. 1990, Tipton et al. 1996b), or decreased (Rennie et al. 1981), from rest. Following resistance exercise (Tarnopolsky et al. 1991, Biolo et al. 1995c, Tipton et al. 1996b), or the combination of endurance and resistance exercise (Tipton et al. 1996b), whole body protein breakdown is unchanged from rest. Following cycling exercise, the rate of leucine oxidation was reported to be less than the rate at rest (Devlin et al. 1990). However, Fielding et al. (1991) reported that whole body protein breakdown and leucine oxidation were increased for up to 10 days following a bout of eccentric cycling exercise. Whole body protein synthesis has been reported to be decreased (Rennie et al. 1981, Wolfe et al. 1982) or unchanged (Carraro et al. 1990a, Phillips et al. 1993) during endurance exercise. Following endurance exercise, increased protein synthesis was reported (Rennie et al. 1981, Devlin et al. 1990), whereas following resistance exercise whole body protein synthesis was unchanged (Tarnopolsky et al. 1991).

**Leucine oxidation**

Although results of studies on protein breakdown, as indicated by whole body amino acid appearance, are not clear, it seems clear that leucine oxidation is increased, thus indicating an increase in net protein breakdown that may result from a need for amino acids to be oxidized for energy in the working muscles. Alternatively, increased protein breakdown may provide a source of amino N for later use for protein synthesis following exercise. While protein breakdown is increased in response to exercise, urea production does not appear to be elevated from rest either during (Wolfe et al. 1982, 1984, Carraro et al. 1993) or following exercise (Carraro et al. 1993). This would seem to be a contradiction, since urea production is generally considered to be a reflection of protein breakdown.

An increased rate of amino acid oxidation during exercise should increase the transfer of N to other amino acids, particularly alanine and glutamine. Since urea is the end product for the disposal of N, it might be expected that urea production would increase during or following exercise. Thus, the infusion of alanine into resting volunteers causes an immediate increase in urea production (Wolfe et al. 1987). However, this does not seem to be the case in exercise. The rate of appearance of alanine into plasma has been shown to increase during exercise (Williams et al. 1997), but as stated above, urea production is unaffected at low (Wolfe et al. 1982, 1984, Carraro et al. 1993) or high (Carraro et al. 1993) exercise intensities, both during and following exercise. It might be argued that the total N available to the liver during exercise might be diminished if glutamine production is reduced in favor of alanine synthesis. Thus, urea production would not have to be increased. However, work in our laboratory (Williams et al. 1998) has demonstrated that the rate of appearance of glutamine is unchanged during moderate aerobic exercise and, combined with a 2.5-fold increase in alanine rate of appearance, the total rate of appearance of N is increased.

A possible, partial explanation for the apparent discrepancy between increased protein breakdown and lack of change in urea production is that acute phase plasma protein synthesis is increased both during and following endurance exercise (Carraro et al. 1990a). The increased alanine, and thus N, flux seen during exercise may be accounted for, in part, by incorporation into these acute phase proteins (Carraro et al. 1990a), rather than urea (Wolfe et al. 1982, 1984, Carraro et al. 1993). Also, in another study, the recycling of urea N back into protein was shown to be accelerated both during and
following exercise (Carraro et al. 1993), thus providing another source of N for these acute phase proteins. Therefore, N from protein breakdown seems to be channelled to the acute phase proteins, rather than urea (Carraro et al. 1993). The acute phase proteins would then be available as an amino acid N source for protein synthesis following exercise. The disproportionate increase in leucine oxidation may simply reflect the fact that there is relatively more leucine in skeletal muscle than in acute phase proteins (Reeds et al. 1994).

The poor agreement between studies on the response of whole body protein metabolism to exercise probably reflects the limitations of the methodology. Whole body methods were designed for studying steady-state circumstances and may be inaccurate and/or too insensitive in the non-steady-state of exercise and recovery. Even if the methodology accurately reflects whole body metabolism, this may not reflect changes in the protein metabolism of muscle. For example, whereas muscle protein makes up about 50% of the protein in the body, it accounts for only about 25% of total protein synthesis at rest (Nair et al. 1988, Bennett et al. 1989). Therefore, an increase of 50% in muscle protein synthesis theoretically would result in an increase of 12.5% in whole body protein synthesis. Since only exercised muscles are likely to respond to the exercise (Devlin et al. 1990), much less than the theoretical 12.5% increase in whole body protein synthesis is likely. Further, responses in various tissues of the body other than muscle, e.g. splanchnic bed (Williams et al. 1996), may obscure changes in muscle when only whole body data are considered.

MUSCLE PROTEIN METABOLISM

Methods

Arteriovenous model. Due to limitations of the whole body approach, we developed a new approach to quantifying muscle protein and amino acid kinetics. The approach is a modification of the traditional arteriovenous (A-V) model that also includes data obtained by tissue biopsy (Biolo et al. 1992). Stable isotopic tracers of various amino acids are infused intravenously, and steady-state enrichments and concentrations are determined in the femoral artery, femoral vein, and in the intramuscular fluid. From these measurements, the model allows calculation of muscle protein synthesis, breakdown and also the rates of transmembrane amino acid transport. Because of the specificity of analysis of enrichment by gas chromatography-mass spectrometry, multiple amino acid tracers can be infused simultaneously. This is the first model developed to quantify, in vivo, either muscle protein breakdown or the transmembrane transport of naturally occurring amino acids.

The results from our A-V balance technique illustrate the limitations in whole body kinetic data when evaluating the responses to exercise. We measured leg protein breakdown following an intense resistance exercise bout in six untrained male volunteers, while simultaneously measuring whole body protein breakdown (Biolo et al. 1995c). Leg protein breakdown was increased by 50% after exercise, but only a slight (non-significant) increase in whole body protein breakdown was noted (Fig. 1).

The results shown in Figure 1 were the first direct evidence that there is an increase in muscle protein breakdown after exercise. Although some previous studies had derived this conclusion from an increase in the rate of excretion of 3-methylhistidine (Rennie et al. 1981, Dohm et al. 1982, 1985), others found no change (Plante & Houston 1984a,b, Carraro et al. 1990a), or decreased (Radha & Bessman 1983, Dohm et al. 1985, Mussini et al. 1985) excretion of 3-methylhistidine in response to exercise. Thus, using whole body and 3-methylhistidine techniques to measure protein breakdown gives a less than clear picture of the response of protein breakdown to exercise.

Figure 1 Comparison of the response of (a) whole body phenylalanine rate of appearance (Ra), a measure of whole body protein breakdown and (b) muscle protein synthesis (PS), muscle protein breakdown (PB) and net protein balance (NB) measured by the A-V/biopsy model. Both were determined at rest and 3–4 h following a heavy resistance exercise routine in untrained male volunteers. Values are mean ± SE. *, significant difference (P < 0.05) from corresponding resting value. (Adapted from Biolo et al. 1995c.)
Quantification of the rate of muscle protein breakdown is an important step forward in the understanding of the response to exercise, since any net change in muscle mass caused by exercise is the result of changes in not only protein synthesis, but also protein breakdown. Further, in a variety of studies we have performed using this model (Biolo et al. 1992, 1995c, Ferrando et al. 1996), we have consistently found a close relationship between muscle protein synthesis and breakdown (Fig. 2), and we propose (see below) a mechanistic link between the two processes. Consequently, assessment of protein metabolism after exercise is incomplete if both protein synthesis and breakdown are not quantified. We have also repeatedly noted a relationship between amino acid delivery to the muscle, blood flow, amino acid transport into the muscle and protein synthesis (Biolo et al. 1995a, c). All these factors appear to be linked, although it is yet unclear as to any cause and effect relationships between these aspects of muscle protein metabolism.

Whereas our A-V model was the first approach described to quantify muscle protein breakdown, the approach has some potential limitations. Most prominently, it is often not feasible to place the necessary catheters, especially in healthy and/or exercising volunteers. Additionally, the method requires the measurement of blood flow, and changes in blood flow may predominate in the calculation of changes in synthesis and breakdown. Finally, the leg balance is not determined entirely by muscle, but also reflects contributions from skin and bone, and we must assume that the biopsy data are representative of the muscle of the entire leg. These assumptions have been previously discussed in detail (Biolo et al. 1992). Despite these potential limitations, results from the A-V/biopsy model agree well with the more widely used direct incorporation method of measuring protein synthesis using the fractional synthetic rate (FSR). A comparison of FSR to protein synthesis determined by the A-V/biopsy model revealed a significant ($P = 0.0006$) correlation ($r = 0.88$) (Fig. 3), signifying good agreement between the model derived values and the direct approach (Biolo et al. 1995a). Additionally, we found that changes in both FSR and the model-derived value of protein synthesis were similar following resistance exercise (Biolo et al. 1995c), as well as during hyperaminoacidemia at rest and following resistance exercise (Biolo et al. 1997). Since different assumptions underlie each approach, the correspondence of the values derived from the two methods supports the validity of each approach.

**Fractional breakdown rate.** The A-V/biopsy model has some potential limitations and, therefore, may not be appropriate in all situations. For example, it might be valuable to examine protein breakdown and protein synthesis in particular muscles, including those that cannot be isolated by A-V sampling, e.g. deltoid muscle. Therefore, we have developed an alternative method of quantifying muscle protein breakdown (Zhang et al. 1996). This approach measures the fractional breakdown rate (FBR) of muscle protein and is analogous to the FSR, which is the traditional approach for determining synthesis. The general principle of the FBR is that the rate of entry of an essential amino acid into the muscle intracellular compartment is a function of the FBR and the rate of entry of that amino acid from the blood. The FBR is calculated by first infusing a tracer of an amino acid that is not produced de novo in the muscle, e.g. phenylalanine, until an isotopic equilibrium is achieved in the intramuscular pool. When the tracer infusion is then stopped, the intracellular en-
enrichment will decay as a function of the rate of entry of unlabelled and labelled phenylalanine from blood, and unlabelled phenylalanine from muscle breakdown. The derivation of the equation for this measurement is presented in Zhang et al. (1996). Thus the FBR can be determined at the same time and in the same tissue as the FSR, provided uniquely identifiable tracers of phenylalanine are used to calculate FSR and FBR, respectively. Since the direct approach of FSR and FBR and the A-V/biopsy model operate using different assumptions, both may be utilized simultaneously to measure protein synthesis and protein breakdown. We have compared the FBR, and FSR, with the A-V/biopsy model results and found good agreement between the two approaches (Zhang et al. 1996).

Post-exercise muscle protein kinetics

Using our new tracer decay technique to directly measure muscle FBR, we again demonstrated increased muscle protein degradation following resistance exercise (Phillips et al. 1997). We have also found that muscle protein synthesis was increased, using both the A-V model (Biolo et al. 1995c) and amino acid incorporation method (FSR) (Biolo et al. 1995c, Phillips et al. 1997). Using both approaches, the increase in protein synthesis was always greater than the increase in protein breakdown following exercise (Fig. 1); (Biolo et al. 1995c, 1997, Phillips et al. 1997). Similar findings, with regard to protein synthesis, have been reported by other investigators using the tracer incorporation technique (Chesley et al. 1992, Yarasheski et al. 1993, MacDougall et al. 1995). To date, protein breakdown has not been measured in exercised skeletal muscle during or following an endurance exercise bout in human subjects and only a few studies have measured protein synthesis directly. However, we have demonstrated that muscle protein synthesis was increased following both long-term endurance exercise in untrained volunteers (Carraro et al. 1990b) and, more recently, a combination of endurance and resistance exercise in trained female swimmers (Tipton et al. 1996b). On the other hand, there was no increase in FSR in the deltoid muscles of trained female swimmers following resistance exercise or swimming only (Tipton et al. 1996b).

Similarly, using the A-V model, we have shown that amino acid transport into the muscle and muscle blood flow are increased following resistance exercise (Biolo et al. 1995c). The increased blood flow is linked to the increased transport of amino acids into the muscle by increasing delivery of amino acids to the muscle. It follows that intracellular appearance of amino acids increases the amino acid availability and thus muscle protein synthesis (Fig. 4; Biolo et al. 1995b, c, 1997). We have repeatedly found that the changes in muscle protein synthesis and muscle protein are correlated (Fig. 2), but that protein synthesis shows a consistently greater increase in response to resistance exercise than does protein breakdown (Fig. 1; Biolo et al. 1995b, c, 1997, Phillips et al. 1997). We can only speculate as to whether protein synthesis or protein breakdown is initially stimulated by exercise and if changes in the other follow.

Practical implications

There are practical implications regarding the link between the intracellular availability of amino acids in muscle and the rate of protein synthesis. In one scenario, the availability of amino acids inside the muscle cell would be the limiting factor for protein synthesis. The exercise-induced stimulation of protein synthesis would cause a concomitant, transient decrease in the intracellular amino acid pool. Without an increase in
protein breakdown and/or amino acid transport, this pool would be depleted, thereby limiting protein synthesis. This suggests that the timing of protein intake following exercise may be critical for post-exercise recovery, because if more amino acids were available to the muscle in the post-exercise state, the muscle might be more responsive. Support for this notion is provided by a recent study from our laboratory. Muscle protein breakdown and synthesis were measured in six volunteers 3–4 h post-exercise (Biolo et al. 1997). An amino acid infusion elevated plasma amino acid concentrations, inward amino acid transport and muscle intracellular amino acid levels. The rate of protein synthesis following exercise was elevated by amino acid infusion to a greater extent than when amino acids were infused at rest. Further, there was not a concomitant increase in protein breakdown, as was seen without exogenous amino acids (Biolo et al. 1995c, Phillips et al. 1997). Providing amino acids to the intracellular pool following exercise allows protein synthesis rates to increase without the necessity for increasing protein degradation. The amelioration of the increase in protein breakdown after exercise by providing exogenous amino acids and increasing inward amino acid transport to the muscle (Biolo et al. 1997) would enable the high rate of protein synthesis post-exercise to be maintained. By maximizing protein synthesis and minimizing protein breakdown when both are at their peak in the first few hours following exercise, net protein balance, the difference between synthesis and breakdown that is necessary for muscle hypertrophy and remodelling, would then be optimized. We have demonstrated that providing exogenous amino acids, both through infusion (Biolo et al. 1997) and orally (Tipton et al. 1996a), in the first 4 h after resistance exercise maximizes protein synthesis and reduces protein breakdown, thus maximizing net protein balance. This may be an important addition to any strategy aimed at optimizing post-exercise recovery or for stimulating an anabolic response in muscle.

Resistance exercise exerts a prolonged effect on muscle protein metabolism. Muscle protein synthesis was reported to be increased for up to 24 h following resistance exercise (Chesley et al. 1992, MacDougall et al. 1995, Phillips et al. 1997). MacDougall et al. (1995) reported that the elevation of muscle protein synthesis lasts for 24 h in trained weight lifters, but returns to baseline by 36 h post-exercise. However, we recently found that the stimulation of muscle protein synthesis lasted for 48 h (Phillips et al. 1997) in untrained subjects. It is possible that the training status of the subjects played a role in the difference in duration of muscle protein synthesis stimulation between studies. Muscle protein breakdown, on the other hand, had returned to resting levels by 24 h post-exercise, resulting in improved (vs. rest) net protein balance for at least 48 h in our study (Phillips et al. 1997).

INITIATION OF MUSCLE PROTEIN SYNTHESIS AND BREAKDOWN

Muscle protein synthesis

Assuming the stimulation of protein synthesis precedes, and thus causes, elevated protein breakdown, we can only speculate on the factors responsible for increased protein synthesis following exercise. Mechanical factors, such as stretch, possibly mediated by prostaglandins (Vandenburgh et al. 1990), may be important. While we are aware of no in vivo data in humans, stretch has been demonstrated to initiate a twofold increase in protein synthesis in wing muscles of domestic fowl (Laurent et al. 1978). However, we do have indirect evidence in humans to support this particular scheme. We have demonstrated that the lack of mechanical activity decreases protein synthetic rates in human muscle. Two weeks of bed rest resulted in a 50% decrease in the FSR of muscle protein in human volunteers (Ferrando et al. 1996). More recently, we noted that when mechanical activity, in the form of light resistance exercise, was added to the bed rest every other day, there was no decrease in FSR (Ferrando et al. 1997).

Alternatively, increased blood flow from exercise may contribute to elevated protein synthesis following exercise. Post-exercise increases in blood flow will increase amino acid delivery to the muscle (Biolo et al. 1995c). Increased amino acid delivery is associated with increased transport of amino acids into muscle, thus increasing the intracellular availability of amino acids necessary for protein synthesis (Biolo et al. 1995c, 1997) and possibly initiating the elevation of muscle protein synthesis following exercise. Protein turnover in non-exercised muscle is decreased following exercise (Devlin et al. 1990), perhaps due to decreased blood flow to those muscles. Additionally, the decreased protein synthetic rate of non-exercised muscles would mean that more amino acids would be available for protein synthesis in previously exercised muscles. On the other hand, it has been demonstrated that an anabolic shift in protein metabolism due to hormonal stimulation is not dependent on increasing blood flow (Fryburg et al. 1995, Fryburg 1996). Further, increased blood flow is transient and only lasts for a relatively short time post-exercise (Hussain et al. 1996), while protein synthesis may last for up to 48 h post-exercise (Phillips et al. 1997).

Muscle protein breakdown

It is also possible that protein breakdown may be stimulated during exercise and remain elevated post-
exercise, thus stimulating protein synthesis by increasing the intracellular concentration of amino acids. Whereas it is somewhat uncertain if muscle protein breakdown is increased during exercise, we have clearly demonstrated that skeletal muscle proteolysis is elevated post-exercise (Biolo et al. 1995c, Phillips et al. 1997). If protein breakdown precedes protein synthesis, then we would expect increased muscle amino acid concentrations immediately post-exercise. Unfortunately, at present, the available data on intramuscular amino acid concentrations immediately following exercise are conflicting and do not help decipher this puzzle. Cycling at 75% \( V_{\text{O}_2 \text{max}} \) has been reported to both increase (MacLean et al. 1991) and decrease (Blomstrand et al. 1995) amino acid concentrations in the vastus lateralis immediately post-exercise, while 3 h of knee extension exercise did not change the amino acid concentrations (Graham et al. 1995). Moreover, muscle amino acid concentrations were not significantly changed from rest 45–90 min following a 30 or 42.2 km run (Blomstrand & Newsholme 1992). Thus the available data on post-exercise muscle amino acid concentrations do not help determine the temporal course of protein metabolism after exercise.

If an increase in protein breakdown is the primary response of muscle protein to exercise, factors that may be responsible for this response are not clear. Intense or prolonged exercise, especially eccentric exercise, may result in increased skeletal muscle damage (Friden et al. 1983, Newham et al. 1983, Fielding et al. 1991). A direct link between exercise-induced muscle damage and muscle protein breakdown has not been demonstrated. Fielding et al. (1991) reported that whole body muscle breakdown was increased and Cannon et al. (1991) reported increased urinary 3-methylhistidine excretion, an indirect marker of myofibrillar protein breakdown, following eccentric exercise. These authors concluded that the increased muscle damage was responsible for elevated muscle protein breakdown (Cannon et al. 1991, Fielding et al. 1991), possibly due to increased muscle levels of cytokines (Cannon et al. 1989, 1991, Fielding et al. 1993). Whereas these data do not directly support the link between the immediate elevation in post-exercise muscle proteolysis (Biolo et al. 1995c) and muscle damage, caution may be warranted in the interpretation of urinary 3-methylhistidine excretion data (Rennie & Millward 1983). Furthermore, muscle protein breakdown may be elevated after exercise in the absence of any morphological change in muscle. In a recent study, we found that, although muscle protein breakdown was increased immediately and for up to 24 h following a resistance exercise workout involving either eccentric or concentric exercise, there was no evidence of muscle damage immediately, or 24 and 48 h following the workout (Phillips et al. 1997). These data do not support the idea that muscle damage is necessary to induce muscle protein breakdown, and thus protein synthesis, although muscle damage could amplify the responses. Alternatively, calcium-activated proteases are stimulated by exercise and have been implicated in increasing post-exercise protein breakdown in vitro (Belcastro 1993).

The stimulus for increasing protein breakdown during exercise may be hormonally mediated. Endurance exercise causes a suppression in the release of insulin (Bloom et al. 1976, Galbo 1985) and an increase in the levels of glucocorticoids (Cumming et al. 1987, Davis et al. 1987, Kraemer et al. 1993). Several authors have shown that increased insulin levels caused a decrease in the rate of release of essential amino acids across both the forearm (Gelfand & Barrett 1987, Louard et al. 1992) and the leg (Denne et al. 1991), thus concluding that muscle protein breakdown was reduced. Hence, reduced insulin levels during exercise may contribute to increasing muscle protein breakdown. However, findings from our laboratory, using a tracer model that takes into account the re-utilization of amino acids from the intracellular pool, showed no decrease in muscle protein breakdown with hyperinsulinemia (Biolo et al. 1995b). Further, Balon et al. (1990) demonstrated that there was no effect of insulin on protein degradation in isolated rat hindquarters after exercise. Additionally, resistance exercise does not result in suppressed insulin (Jurimae et al. 1990, Chandler et al. 1994), but clearly results in increased protein breakdown (Biolo et al. 1995b, Phillips et al. 1997).

Glucocorticoids are known as potent stimulators of protein breakdown (Simmons et al. 1984, Louard et al. 1994, Garrel et al. 1995) and leucine oxidation (Garrel et al. 1995). Therefore, increases in glucocorticoid levels from exercise (Cumming et al. 1987, Davis et al. 1987, Kraemer et al. 1993) may contribute to stimulation of amino acid oxidation and protein breakdown. Additionally, it has been shown that insulin-mediated changes in protein metabolism are attenuated by glucocorticoids (Louard et al. 1994). On the other hand, since leucine oxidation is not elevated following exercise (Devlin et al. 1990) and net muscle synthesis is improved (Biolo et al. 1995c, 1997), it is unlikely glucocorticoids play a dominant role in controlling muscle protein kinetics after exercise.

**PROPOSED SCHEME**

Given the state of knowledge, we propose a working physiological scheme in which muscle protein synthesis is directly stimulated by yet to be determined factors, leading to decreasing levels of intracellular amino acids (Fig. 5). We propose that the transient fall in intrace-
lular amino acids, as a result of the increased protein synthesis, leads to increases in both protein breakdown and/or inward amino acid transport to maintain the intracellular amino acid pool. If protein breakdown or inward amino acid transport, or both, were not increased, then elevated levels of synthesis could not be maintained in the presence of diminished intracellular amino acid levels. Thus protein breakdown and amino acid transport would be 'pulled' by the original stimulation of protein synthesis. If this were the case, then synthetic mechanisms that were turned on by exercise would be limited by the intracellular availability of amino acids. This is supported by the fact that muscle protein synthesis can be increased without a simultaneous increase in protein breakdown as long as intracellular availability is maintained.

We recognize that, at this juncture, it is impossible to rule out other schemes. For example, it is possible that protein breakdown is initially stimulated by exercise, which in turn would drive an increase in protein synthesis. Alternatively, increased blood flow from exercise may cause an increased inward amino acid transport and subsequent stimulation of protein synthesis. We feel that the available data do not support these explanations as well as the scenario of an initial pull from protein synthesis. For example, it is difficult to imagine why a stimulation of protein breakdown would coincide with an increase in inward amino acid transport, since amino acid availability would already be increased by the increased protein degradation. On the other hand, why would protein breakdown be increased if inward transport were providing the push for protein synthesis? We have already shown that the infusion of exogenous amino acids prevents the rise in protein breakdown after exercise. Further, since the response of protein synthesis following exercise is always greater in magnitude than the response of protein breakdown, it is difficult to envision how, if protein breakdown is driving protein synthesis, protein breakdown could provide the amino acids necessary for the greater increase in protein synthesis.

Although, most studies of protein metabolism after exercise present data from a single point in time, it seems logical that the response to exercise is transient. We know that protein synthesis and protein breakdown change on the order of days following resistance exercise, but it is unknown how protein metabolism changes on the order of minutes to hours post-exercise. Therefore, studying only a given time point following exercise provides only a snapshot and hampers the interpretation of the available information. It is necessary to study the time course of the responses of protein synthesis, protein breakdown, inward amino acid transport and the intracellular amino acid pool to allow a complete delineation of the order of events and the precise nature of the controlling factors of post-exercise protein metabolism.

Finally we cannot rule out the possibility that all the central aspects of muscle protein metabolism (i.e. synthesis, breakdown and amino acid transport) are independently regulated and their coordinated response to exercise occurs by coincidence. However, the close correspondence of, and apparent coordination of, the responses of these factors suggests that they are linked.
Identification of the primary stimulus that initiates changes in muscle protein metabolism will help to clarify all aspects of the response to exercise. Additionally, exercise intensity and/or duration, as well as exercise mode (i.e. endurance or resistance exercise), may stimulate responses in protein metabolism that are not identical to each other. Therefore, determining the responses of muscle protein metabolism to different modes, intensities and durations of exercise would seem to be important to complete our knowledge of the changes induced by exercise.

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