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Opinion paper

Is there a maximal anabolic response to protein intake with a meal?

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SUMMARY

Several recent publications indicate that the maximum stimulation of muscle protein fractional synthetic rate occurs with intake of 20–30 g protein. This finding has led to the concept that there is a maximal anabolic response to protein intake with a meal, and that the normal amount of protein eaten with dinner will generally exceed the maximally-effective intake of protein.

However, protein breakdown has not been taken into account when evaluating the anabolic response to protein intake. Protein anabolism occurs only when protein synthesis exceeds protein breakdown.

Higher protein intakes when protein synthesis is maximized is characterized by suppressed protein breakdown and *via* that mechanism leads to a greater anabolic response. This explains why when net protein synthesis is measured, the relationship between amino acid availability and net gain remains linear, without any apparent plateau of effect at higher levels of availability.

We conclude that there is no practical upper limit to the anabolic response to protein or amino acid intake in the context of a meal.

1. Introduction

The principal nutritional goal of a protein-rich meal is to induce an anabolic state in which muscle protein synthesis exceeds the rate of breakdown. Several recent publications, including our own,[1] indicate that the maximum stimulation of muscle protein fractional synthetic rate (FSR) occurs with intake of 20–30 g protein. This finding has led to the concept that there is a maximal anabolic response to protein intake with a meal, and that the normal amount of protein eaten with dinner will generally exceed the maximally-effective intake of protein.[2] However, the extent of muscle protein anabolism (the anabolic response) is not simply the response of muscle protein FSR, but rather the net balance between the response of FSR and the rate of protein breakdown. Account has generally not been taken of protein breakdown when evaluating the anabolic response to protein intake. It is also important that many previous protein dose–response studies have considered the response to ingestion of pure amino acids, an isolated protein, or protein occurring in a particular food source (e.g. meat or milk) rather than in the context of a complete meal. We will review the anabolic response to protein or amino acid intake in isolation and in the context of a complete meal in order to address the question of whether there is a maximal anabolic response to protein intake with a meal.

2. Measurement of the anabolic response

When specific amino acid isotopes are infused as tracers in plasma or consumed with a meal, all proteins in the body will incorporate the labeled amino acids at rates that reflect the fractional synthetic rate (FSR) of the protein. The amount of tracer incorporated in a measured amount of time, corrected for the enrichment of the tracer in the precursor pool, enables calculation of the FSR for the protein in the tissue sampled. In the case of muscle, specific proteins (e.g. myofibrillar protein) may be isolated from the tissue and the synthesis rate calculated separately.

Muscle FSR only identifies the synthesis rate of muscle protein. All proteins in the body are in a constant state of turnover, meaning that there is simultaneous synthesis and breakdown. The net gain in muscle protein over time, or the anabolic response, is calculated as the difference between the rate of synthesis and the rate of protein breakdown. Although it is possible to measure the muscle fractional protein degradation rate (muscle FBR), this is not a very common measurement as it requires a more complicated experimental protocol, additional blood sampling, and complicated calculations,[3] especially during feeding. An alternative approach to

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calculating muscle protein synthesis and breakdown is to measure the balance of specific amino acids across the leg or arm. This approach requires arterial and venous catheterization and measurement of tissue blood flow, and consequently over recent years has been used infrequently in human subjects. Furthermore, the reliability of this method to measure protein breakdown is limited in the non-steady state that exists after ingestion of amino acids or a protein meal.[4] A three pool arterial–venous (a–v) model that also includes a tissue biopsy improves accuracy and enables an estimation of protein breakdown in the non-steady state.[5]

Whole body protein synthesis and breakdown can also be measured in response to protein meals. This approach uses the addition of isotopes to the meal and the infusion of isotopes into the blood stream and collection of blood and/or exhaled CO_2. Commonly used approaches are the addition of phenylalanine/leucine to the meal (taking into account absorption kinetics, either as a free amino acid or within a labeled protein), infusion of labeled tyrosine and phenylalanine and collection of blood or the infusion of labeled leucine and collection of blood and exhaled air. Although the measurement of whole body protein synthesis and breakdown is theoretically limited by the fact that all of the tissues are included in the measurement of net protein synthesis, during feeding it is often assumed that muscle protein synthesis and breakdown comprise a large portion of the whole body response above the basal value. There are technical advantages to determining whole body protein synthesis and breakdown, because no muscle biopsies are required and frequent blood sampling enables reasonable calculation of both synthesis and breakdown during amino acid or protein absorption.

Measurement of muscle FSR is technically and theoretically the most straight forward technique with which to assess the response of muscle protein synthesis to a protein meal, but it is limited because it gives us only half of the information needed to determine the anabolic response to a protein meal. The anabolic response can only be determined when synthesis and breakdown are measured simultaneously.

2.1. Which approach provides the best measure of the anabolic response?

The anabolic response is traditionally equated with muscle anabolism, so the measurement of protein synthesis and breakdown directly in muscle is obviously important in determining the nature and magnitude of the anabolic response. However, measurement of protein synthesis and breakdown at the whole body level is also of value when evaluating the anabolic response. The principal factor differentiating the responses to different types or amounts of protein is the resulting change in amino acid concentrations and profiles in the blood. However, not all of the amino acids absorbed from the digestion of protein appear directly in peripheral blood. Following ingestion of intact protein some of the digested amino acids are retained in the splanchnic area (splanchnic extraction). This retention mainly takes place in the gut,[6] which can function as a labile protein pool that the body uses as a temporarily storage pool of essential amino acids.[7] The gut has a high protein turnover rate and is therefore capable of rapidly retaining amino acids for protein synthesis, then releasing those amino acids over time for eventual incorporation into protein in other tissues, in particular muscle. Measurement of the acute response of muscle protein metabolism to intake of protein may therefore underestimate the total anabolic response over time. The total anabolic response from a nutritional standpoint is determined by the total gain of body protein, and for this reason, the determination of the whole body response is important. The ideal scenario is to measure both the whole body and muscle protein synthesis and breakdown, thereby enabling the determination of the anabolic response both at the whole body level and in muscle.

2.2. What is the mechanism of net anabolism?

The net balance between muscle protein synthesis and breakdown distinguishes the catabolic state (breakdown exceeds synthesis) from the anabolic state (synthesis exceeds breakdown). The relationship between muscle protein turnover and plasma and intracellular essential amino acids is shown schematically in Fig. 1. The synthesis of new protein is derived from the intracellular pool of amino acids.[8] The intracellular pool of essential amino acids (amino acids not produced in significant quantities in the body) is the most important determinant of protein synthesis as the non-essential amino acids are readily available.[9] These amino acids are derived from protein breakdown and inward flux from plasma. An anabolic response requires that the inward flux of amino acids exceeds the rate of oxidation or transamination of those amino acids within the muscle. In the post-absorptive state there is a net efflux of amino acids from the muscle into the blood. The absorption of digested protein causes an increase in plasma amino acid concentrations that result in an accelerated inward flux into muscle. The increased availability of intracellular essential amino acids stimulates the synthesis of new protein, as reflected by the measurement of muscle protein FSR.

The schematic representation in Fig. 1 illustrates that changes in breakdown alone can never induce a shift from the catabolic state to the anabolic state, since some of the amino acids released from protein breakdown are oxidized or transaminated and therefore not available for reincorporation into protein. On the other hand, the rate of protein breakdown will always be linked to some extent to the rate of synthesis because of the contribution of amino acids from breakdown to the intracellular pool of amino acids. In fact under most conditions, the majority of the intracellular pool of amino acids is derived from protein breakdown rather than inward flux from plasma. Thus, when considering the role of amino acid availability in regulating the rate of muscle protein synthesis it is necessary to take account of not only the amino acids from plasma, but also the amino acids that appear in the intracellular pool as a consequence of protein breakdown. In a wide variety of circumstances we have found a direct linear relationship between the total

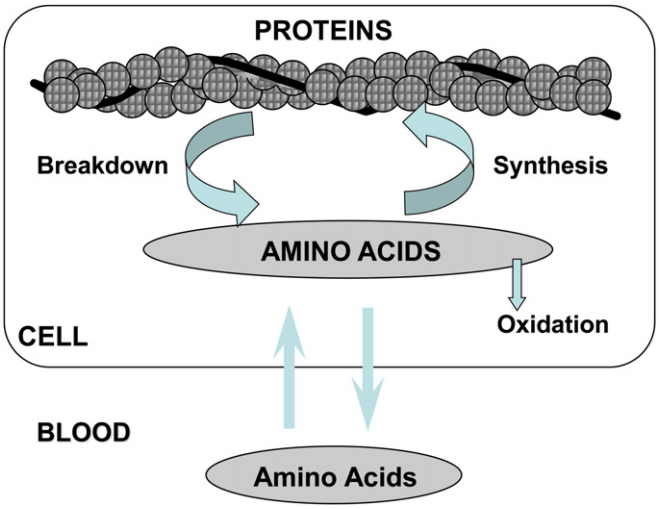

Fig. 1. The intracellular pool of amino acids is the precursor pool for muscle protein synthesis. These amino acids can be derived from either protein breakdown or inward transport of amino acids from plasma. In addition to being incorporated into protein, intracellular amino acids can be oxidized or released into plasma.