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Review

Update on maximal anabolic response to dietary protein

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SUMMARY

The anabolic response to dietary protein can be defined as the difference between protein synthesis and breakdown, or the net protein balance, in response to ingestion of protein alone or a mixed meal containing protein. Others have concluded that a maximal anabolic response can be achieved with ingestion of 20–35 g of a high quality protein, leading to the formulation of a popular concept that the maximal anabolic response can be achieved by distributing the total protein intake evenly throughout the day, rather than eating a majority of dietary protein with dinner. However, this concept was based entirely on the measurement of muscle protein synthesis and thus ignored the potential contributions of suppression of protein breakdown to the anabolic response, as well as the possibility that tissues and organs other than muscle may also play a role in the anabolic response. In this review we discuss the factors comprising the total anabolic response, discuss relevant methodological issues, derive a theoretical maximal anabolic response based on current literature values, and interpret recent papers addressing the issue of maximal anabolic response as well as meal distribution of dietary protein. We conclude that it is not likely that there is a practical limit to the maximal anabolic response to a single meal, and the most efficient way in which to maximize the total anabolic response over a 24-h period is to increase dietary protein at breakfast and lunch without reducing protein intake with dinner.

1. Introduction

Dietary protein intake serves many physiological roles, but the most prominent is the maintenance or gain of body protein stores. This is accomplished by stimulation of protein synthesis, the inhibition of protein breakdown, or a combination thereof. A net gain in protein balance (i.e., synthesis minus breakdown) is called an anabolic response, as opposed to a catabolic response caused by the rate of protein breakdown exceeding the rate of protein synthesis. An anabolic response usually refers to gain of muscle protein, but can involve the entire body. Optimal protein nutrition in an individual meal could be defined as the minimal amount of protein intake that results in the maximal anabolic response, as that will be the most likely approach to maintaining or increasing lean body mass (LBM) over time. Consumption of dietary protein in excess of the amount needed to elicit the maximal anabolic response could be considered excessive, since no further stimulation of the net gain of body protein can occur. Consequently, determining the amount of dietary protein needed to elicit the maximal anabolic response is directly relevant to defining the "optimal" amount of dietary protein in a meal. Determining the optimal amount of dietary protein in a meal involves quantification of the rates of protein synthesis, breakdown, and the balance between synthesis and breakdown in response to dietary protein in the context of a complete mixed meal. There is presumably a limit to the extent to which protein synthesis can be stimulated by dietary protein intake, and protein breakdown cannot be suppressed to less than zero. Therefore, there must be some level of protein intake beyond which no further gains in net balance can occur, which we will define as the maximal anabolic response.

It has been postulated that the maximal anabolic response can be elicited with intake of 20–35 g of high quality protein solely based on the stimulation of muscle protein synthesis (MPS) [1]. If true, this would mean that the typical, uneven distribution of dietary protein intake in the American diet results in considerable

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excessive protein consumption in the dinner meal, as the average protein intake at dinner may be as much as 40 g or more [2]. As a consequence, it has been proposed that the anabolic response to protein intake would be improved if the traditional pattern of the American diet in which approximately half of dietary protein is consumed at dinner were altered so that daily intake of protein is more evenly distributed throughout breakfast, lunch and dinner. In this paper we will examine the validity of this perspective within the practical range of protein intake (i.e., the Acceptable Macronutrient Distribution Range or AMDR, 10–35% of daily calorie intake). In that context we will discuss if the maximal anabolic response to dietary protein is important physiologically, the physiological determinants of the net anabolic response, and the methodologies that have been used to evaluate the "even distribution" hypothesis. We will discuss relevant experimental data from studies performed in human subjects, including consideration of the difference between the responses to pure protein intake as opposed to intake of a protein-containing mixed meal. Finally, we will conclude that, based on currently-available data, there is no practical limit to the anabolic response to dietary protein intake at least within the range of AMDR in a single meal. Further, we conclude that the total amount of dietary protein over the day is more relevant to the total anabolic response to dietary protein than the distribution of intake over the course of the day. From a practical standpoint this conclusion can most readily be incorporated into daily nutritional pattern by increasing the amount of dietary protein as part of breakfast and lunch without diminishing the amount of dietary protein eaten at dinner.

2. Is a maximal anabolic response important? Implications for health and disease

The anabolic response in the fed state affects protein mass in many tissues and organs, but prominently involves repletion of skeletal muscle proteins lost in the post-absorptive or fasting state. The issue is thus important in maintaining or increasing skeletal muscle mass. In the fasted state the net breakdown of muscle protein (i.e., protein breakdown exceeding protein synthesis) provides amino acids into the circulation. The transient increase in muscle protein breakdown (MPB) in the post-absorptive or fasting state is very effective in this process, as fasting amino acid levels remain constant for days and even weeks if muscle mass is adequate [3]. Many of the processes maintained by the supply of plasma amino acids in the fasted state involve protein synthesis in tissues such as skin and brain that have little protein reserve and therefore must maintain a balance between protein synthesis and breakdown, even in the fasted state. In addition to tissue protein synthesis, plasma amino acids are involved in maintaining other processes during fasting, such as synthesis of enzymes, neurotransmitters, and nitric oxide (important for regulation of blood flow and immune function) and gluconeogenesis. The importance of skeletal mass (reflected in LBM) are evident in many (patho) physiological circumstances such as starvation, cancer, obesity, osteoporosis, and sarcopenia [4]. In this regard, the fast turning-over gut tissue plays an important role for reducing the burden placed on muscle tissue to provide amino acids to the circulation for maintaining the processes mentioned above. This will be discussed later in this paper. Further, the basal rates of protein synthesis and breakdown of skeletal muscle constitute a significant component of total resting energy expenditure, so maintenance of muscle (protein) mass plays an important role in energy balance [4]. Finally, and perhaps most obviously, maintenance of muscle mass is central to physical strength and function. Since it is undeniable that maintaining or increasing skeletal muscle mass is important, and the anabolic response to protein intake at the muscle level is the principle metabolic basis to achieve this goal, it follows that maximizing the anabolic response to dietary protein over the entire day is an important nutritional goal.

3. The balance between protein synthesis and breakdown: the metabolic determinants of the anabolic responses

Changes in muscle protein mass are a consequence of net changes in anabolic or catabolic responses to factors including nutritional intake, hormonal milieu, physical exercise, starvation, inflammation, and more serious physiological stress such as sepsis or trauma. Changes in muscle mass are most conventionally considered the primary target of anabolic and catabolic responses, although imbalances between protein synthesis and breakdown can occur in many body tissues and organs to some extent. Thus, to determine the extent of net anabolism or catabolism it is necessary to quantify both rates of protein synthesis and breakdown not only at the muscle level but at the whole-body level. There is a relationship between protein turnover (i.e., protein synthesis and protein breakdown) and the availability of amino acids that can be incorporated into proteins. Intracellular amino acids are derived from the inward transport from plasma and from protein breakdown. The possible fates of intracellular amino acids are new protein synthesis, efflux back to plasma, or, in some cases, oxidation. In the post-absorptive state, the net efflux of amino acids from the muscle into the blood predominates. However, ingestion of a protein rich meal increases inward transport of plasma amino acids into muscle, which in turn increases intracellular amino acid availability and thus protein synthesis. Quantitatively, protein breakdown is the most important source of the intracellular amino acid pool and thus precursors for protein synthesis [5]. There is thus a close link between protein synthesis and breakdown that is evident even in various catabolic circumstances including type I diabetes, cancer cachexia, and burn injury. In these catabolic circumstances, the rate of protein synthesis is typically normal or often elevated even though there is net loss of muscle tissue over time [6]. The reason for this counterintuitive phenomenon of an elevated rate of protein synthesis in a catabolic state is that availability of intracellular amino acids (regardless of the source – in this case protein breakdown) is the main determinant of the rate of protein synthesis. In other words, acceleration of protein breakdown drives protein synthesis as a consequence of increased availability of amino acids. However, because some portion of intracellular amino acids are either oxidized or released from the cell into the plasma, protein synthesis will be stimulated less than the elevation in breakdown, leading to a net loss of muscle protein over time.

The extent to which the interplay between protein synthesis and breakdown determines if the body gains or loses protein underscores the importance of simultaneous determination of both protein synthesis and protein breakdown when assessing the maximal anabolic response to dietary protein. If only the stimulated protein synthesis in a seriously burned patient is measured, for example, one could erroneously conclude that the patient was in anabolic state, when the exact opposite was actually the case. This point is relevant to the quantification of the response to dietary protein intake, in that if only the synthetic response is measured the total net response is unknown.

4. Methodological considerations in determination of the anabolic response

There are various methods that estimate anabolic responses to dietary protein at the muscle and the whole body levels in response to a single meal or over the course of an entire day [5,7]. We will