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The muscle protein synthetic response to food ingestion

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ABSTRACT

Preservation of skeletal muscle mass is of great importance for maintaining both metabolic health and functional capacity. Muscle mass maintenance is regulated by the balance between muscle protein breakdown and synthesis rates. Both muscle protein breakdown and synthesis rates have been shown to be highly responsive to physical activity and food intake. Food intake, and protein ingestion in particular, directly stimulates muscle protein synthesis rates. The postprandial muscle protein synthetic response to feeding is regulated on a number of levels, including dietary protein digestion and amino acid absorption, splanchnic amino acid retention, postprandial insulin release, skeletal muscle tissue perfusion, amino acid uptake by muscle, and intramyocellular signaling. The postprandial muscle protein synthetic response to feeding is blunted in many conditions characterized by skeletal muscle loss, such as aging and muscle disuse. Therefore, it is important to define the characteristics that modulate postprandial muscle protein synthesis. Previous work has shown that the muscle protein synthetic response to feeding can be modulated by changing the amount of protein ingested, the source of dietary protein, as well as the timing of protein consumption. Most of this work has studied the postprandial response to the ingestion of isolated protein sources. Only few studies have investigated the postprandial muscle protein synthetic response to the ingestion of protein dense foods, such as dairy and meat. The current review will focus on the capacity of proteins and protein dense food products to stimulate postprandial muscle protein synthesis and identifies food characteristics that may modulate the anabolic properties.
1 INTRODUCTION

Muscle mass maintenance is achieved through sinusoidal fluctuations in muscle protein synthesis and breakdown rates that are eventually counterbalanced such that net muscle protein balance remains zero by the end of each day (Burd et al., 2009). However, aging, muscle disuse, and chronic metabolic diseases are characterized by a decline in skeletal muscle mass. This decline in muscle mass must be attributed to an imbalance between protein breakdown and synthesis rates, resulting in a negative net muscle protein balance. Since basal muscle protein synthesis rates do not seem to differ between healthy young and older men (Volpi et al., 2001), researchers have been assessing whether derangements in the muscle protein synthetic response to the main anabolic stimuli, physical activity and food intake, underpin the loss of skeletal muscle mass. Several studies have shown that muscle protein synthesis rates are not increased to the same extent in older when compared with young individuals following ingestion of amino acids (Cuthbertson et al., 2005; Katsanos et al., 2005; Volpi et al., 2000). This phenomenon has been referred to as ‘anabolic resistance’ (Burd et al., 2013; Rennie, 2009). Optimizing food intake to allow for maximal stimulation of postprandial muscle protein synthesis rates may yield valuable information that can be used to develop more effective strategies to attenuate the loss of skeletal muscle mass in various clinical settings.
2 POSTPRANDIAL MUSCLE PROTEIN SYNTHESIS

Food intake, and protein ingestion in particular, has been shown to stimulate muscle protein synthesis. The postprandial muscle protein synthetic response to protein ingestion is regulated on a number of levels (Burd et al., 2013). Protein digestion and amino acid absorption kinetics have a major impact on the postprandial anabolic response. Rapidly digestible proteins (such as whey) may stimulate protein synthesis to a greater extent and for a shorter time period, whereas slowly digestible proteins (such as casein) may stimulate protein synthesis for a longer time period (Boirie et al., 1997a). Modulating protein digestion and amino acid absorption kinetics by ingesting whey in repeated small boluses (simulating digestion and absorption kinetics of a slowly digestible protein) or by ingesting hydrolyzed casein (rapidly digestible) affects the postprandial muscle protein synthetic response (Dangin et al., 2001; Koopman et al., 2009a; Pennings et al., 2011a; West et al., 2011). Moreover, splanchnic retention of dietary protein-derived amino acids (which includes amino acid uptake by gut and liver tissue) may modulate postprandial muscle protein synthesis by affecting the postprandial availability of circulating amino acids (Boirie et al., 1997b; Gorissen et al., 2014; Volpi et al., 1999). Furthermore, the postprandial rise in insulin concentrations can modulate the muscle protein synthetic response through its vasodilatory properties, i.e. stimulating endothelial nitric oxide synthase (eNOS), resulting in greater capillary recruitment, increased microvascular volume and nutritive blood flow to skeletal muscle tissue (Timmerman et al., 2010a; Timmerman et al., 2010b). It could be speculated that the postprandial increase in muscle tissue perfusion will increase the exposure of muscle tissue to nutrients and growth factors and, as such, stimulate muscle protein synthesis rates. The stimulation of muscle protein synthesis has been shown to be blunted in insulin resistant subjects under hyperinsulinemic-euglycemic conditions (Fujita et al., 2009; Rasmussen
et al., 2006), further emphasizing the proposed role of insulin in the postprandial stimulation of muscle protein synthesis. Finally, the postprandial increase in muscle protein synthesis may also be regulated through amino acid uptake by amino acid transporters located on the cell membrane of muscle cells (Drummond et al., 2010) and subsequent intramyocellular mTORC1 signaling towards protein synthesis (Cuthbertson et al., 2005; Guillet et al., 2004). One or more of these processes may be compromised in conditions that are characterized by skeletal muscle loss such as aging, disuse, or chronic metabolic diseases. Several protein (intake) characteristics may influence the postprandial muscle protein synthetic response and may need consideration when trying to develop more effective dietary strategies to prevent or attenuate the loss of skeletal muscle mass.

2.1 Protein source

Various studies have reported improved net protein balance and/or increased muscle protein synthesis rates following the ingestion of isolated protein sources such as whey (Pennings et al., 2012), casein (Koopman et al., 2009b), casein hydrolysate (Koopman et al., 2009a; Pennings et al., 2011a), soy (Fouillet et al., 2002; Tang et al., 2009; Yang et al., 2012), and egg protein (Moore et al., 2009). Even though all of these protein sources have the capacity to stimulate muscle protein anabolism, postprandial muscle protein fractional synthetic rates can vary substantially following the ingestion of these different protein sources. The question arises what protein characteristics may influence the postprandial muscle protein synthetic response. It has previously been suggested that the consumption of more rapidly digestible proteins results in a greater stimulation of postprandial muscle protein synthesis when compared with slowly digestible proteins. This concept has been developed by measuring dietary protein digestion and
absorption kinetics and subsequent postprandial protein accretion following whey compared with casein protein (Boirie et al., 1997a; Dangin et al., 2001). However, these proteins differ not only in their digestion and absorption kinetics (Mahe et al., 1996), but also in their amino acid composition. Even when casein was hydrolyzed prior to ingestion it was still unable to stimulate postprandial muscle protein synthesis rates to the same extent as the ingestion of whey protein (Pennings et al., 2011a). This suggests that the amino acid composition, and leucine content in particular, represents another key determinant of the postprandial muscle protein synthetic response following protein ingestion. In agreement, addition of free leucine to a bolus of amino acids, protein, or a meal has been shown to further enhance postprandial muscle protein synthesis rates (Katsanos et al., 2006; Rieu et al., 2006; Wall et al., 2013).

2.2 Amount of protein

Though it has been well established that dietary protein effectively stimulates muscle protein synthesis, less information is available on the amount of protein that should be ingested to maximize the postprandial muscle protein synthetic response. It has been shown that graded intakes of essential amino acids (EAA) up to 10 g (equivalent to ~25 g of a high quality protein) stimulates myofibrillar protein synthesis rates in a dose-dependent manner (Cuthbertson et al., 2005). However, this response is lower in older individuals, and higher intakes of EAA (20 and 40 g) failed to promote a greater muscle protein anabolic response (Cuthbertson et al., 2005). Recently, postprandial muscle protein synthesis rates following the ingestion of increasing amounts of whey protein (i.e., 10, 20, and 40 g) have been assessed in both young (Witard et al., 2014) and older individuals (Yang et al., 2012). In both age groups, 20 g of whey protein was required to significantly stimulate muscle protein synthesis rates, and ingesting a higher dose of
40 g had no additive effect (Witard et al., 2014; Yang et al., 2012). However, greater amounts of protein may result in prolonged hyperaminoacidemia (rather than higher peak values) and, as such, stimulate muscle protein synthesis for a more prolonged time period following protein ingestion. Therefore, future dose-response studies should include an assessment of muscle protein synthesis rates over an appropriate postprandial period.

2.3 Timing of protein ingestion

Daily protein intake is mainly consumed at breakfast, lunch, and dinner (Tieland et al., 2012). Some researchers suggest that the distribution of protein intake throughout the day affects net protein balance over a longer period (Areta et al., 2013; Arnal et al., 2000a; Arnal et al., 1999; Bouillanne et al., 2013; Bouillanne et al., 2014; Mamerow et al., 2014; Moore et al., 2012), while others did not observe an effect of protein feeding pattern (Adechian et al., 2012; Arnal et al., 2000b; Kim et al., 2015). Despite the ongoing debate on the impact of protein intake pattern throughout the day, it is generally accepted that at least 20 g of high-quality protein needs to be consumed per meal to maximize the postprandial muscle protein synthetic response and allow for muscle mass maintenance. As a consequence, it is speculated that increasing dietary protein intake with breakfast might represent an effective strategy for dietary interventions aiming to maintain skeletal muscle mass (Tieland et al., 2012). Furthermore, the night generally represents a relative long period during which net protein balance remains negative due to low levels of circulating amino acids. Ingesting a bolus of protein prior to sleep, enhancing aminoacidemia during the night, has been shown to stimulate overnight muscle protein synthesis, resulting in a more positive overnight net muscle protein balance (Groen et al., 2012; Res et al., 2012).
Physical activity sensitizes skeletal muscle tissue to the anabolic properties of amino acids, increasing the muscle protein synthetic response to protein ingestion (Pennings et al., 2011b). Furthermore, it was shown that more of the ingested protein was directed towards *de novo* muscle protein synthesis when physical activity was performed prior to food intake. The stimulatory properties of physical activity on the postprandial muscle protein synthetic response to protein ingestion can persist for up to 24 h following a single bout of exercise (Burd et al., 2011). Therefore, daily physical activity is of key relevance to maintain anabolic responsiveness to food ingestion and plays a key role in maintaining skeletal muscle mass.

### 2.4 Macronutrient composition

Most studies have investigated the muscle protein synthetic response to the ingestion of isolated protein sources. However, dietary protein is generally consumed as part of a product or meal, with carbohydrate and fat (and other nutritional factors) being co-ingested with protein. The presence of fat and/or carbohydrate may modulate dietary protein digestion and absorption kinetics and, as such, the postprandial amino acid availability for the stimulation of muscle protein synthesis. In support, amino acid uptake by the leg (indicative of muscle protein anabolism) has been shown to be higher following the ingestion of high fat when compared with skim milk in young males during recovery from resistance type exercise (Elliot et al., 2006). Furthermore, several studies have assessed postprandial muscle protein synthesis rates when carbohydrate is co-ingested with protein under both post-exercise (Glynn et al., 2010; Koopman et al., 2007; Staples et al., 2011) and resting conditions (Glynn et al., 2013; Gorissen et al., 2014; Hamer et al., 2013). It could be suggested that the higher insulin response following carbohydrate co-ingestion may enhance the muscle protein synthetic response (Fujita et al.,...
2009). However, circulating insulin may only be permissive, as opposed to stimulatory, to allow for a postprandial increase in muscle protein synthesis (Phillips, 2008) and a moderate rise in circulating insulin may already be sufficient to maximize postprandial muscle protein anabolism (Greenhaff et al., 2008). In our observations, co-ingesting carbohydrate with protein tends to slow down dietary protein digestion and absorption, blunting the postprandial rise in muscle protein synthesis conditions (Glynn et al., 2013; Gorissen et al., 2014; Hamer et al., 2013). However, this initial delay in protein digestion (likely caused by reduced gastric emptying rate) does not seem to modulate the postprandial muscle protein synthetic response when assessed over the entire 5 h postprandial period. It is obvious that the matrix in which protein is ingested can modulate the postprandial muscle protein synthetic response. Meal composition, other food products, as well as numerous nutritional components may modulate the postprandial muscle protein synthetic response on a variety of levels.
3  PROTEIN DENSE FOODS

3.1  Protein dense foods

The main protein dense food products that provide a large portion of daily protein intake within a Western diet include dairy and meat. Relatively few studies have examined the impact of ingesting protein dense foods on postprandial muscle protein synthesis rates. It has been shown that the ingestion of 113 g lean (90%) ground beef (containing 30 g protein, 10 g EAA, and 2 g leucine) stimulates muscle protein synthesis rates in both young and older individuals by ~50% when compared to post-absorptive muscle protein synthesis rates (Symons et al., 2007). Ingesting more meat (i.e., 340 g lean beef containing 90 g protein) does not seem to further increase postprandial muscle protein synthesis rates, suggesting that the ingestion of ~120 g lean beef maximizes postprandial muscle protein synthesis rates (Symons et al., 2009). In contrast, others assessed postprandial myofibrillar protein synthesis rates following ingestion of graded intakes of beef (57, 113, and 170 g beef corresponding with 12, 24, and 36 g protein, respectively) and observed a measurable increase in muscle protein synthesis rates following the ingestion of the higher dose only (Robinson et al., 2013). Similar observations were reported when beef was ingested during recovery from exercise (Robinson et al., 2013; Symons et al., 2011).

Besides meat, various studies have assessed the postprandial muscle protein synthetic response to the ingestion of dairy products. Milk ingestion has been shown to increase muscle protein anabolism (Elliot et al., 2006; Wilkinson et al., 2007). So far, few studies have compared the muscle protein synthetic responses to the ingestion of different protein dense foods. Recently, we observed similar increases in postprandial muscle protein synthesis rates following the ingestion
of milk or lean beef, both providing 30 g of protein (unpublished observations). Despite the fact that large differences were observed in the postprandial rise in plasma amino acid concentrations (and leucine in particular), no differences were observed in postprandial muscle protein synthesis rates following milk or beef ingestion (Figure 1).

3.2 Food texture and food preparation

It could be speculated that food texture can modulate postprandial muscle protein synthesis by affecting protein digestion and absorption kinetics. We have shown that the gelation of milk in dairy products, whatever the mode of coagulation, slows down the gastric emptying of milk proteins and the amino acid absorption, and attenuates the postprandial rise in circulating amino acid concentrations (Barbe et al., 2014; Barbe et al., 2013). For solid food such as meat, the speed of protein digestion can also be modulated by food preparation (i.e., cooking or mincing) through modifications at the macrostructural and microstructural levels, leading to products which architecture is more or less sensitive to digestion. For example, minced beef is more rapidly digested and absorbed when compared with the consumption of beef steak, resulting in a more rapid release of beef-derived amino acids in the systemic circulation, thereby creating a more positive postprandial protein balance in the elderly (Pennings et al., 2013). Similarly, in elderly subjects with impaired chewing efficiency, meat protein digestion rate and postprandial plasma amino acid concentrations as well as the subsequent utilization for protein synthesis is reduced (Remond et al., 2007). These two studies support the view that for solid food the characteristics of the swallowed bolus (i.e., granulometric distribution of particles and cohesiveness) are key determinants of the protein digestion efficiency. As a consequence, meat texture should be adapted to chewing efficiency of elderly in order to reach optimal kinetics of
amino acid absorption and postprandial protein synthesis. Furthermore, meat cooking temperature can also significantly impact on the speed of protein digestion and the kinetics of amino acid appearance in blood (Bax et al., 2013). This effect is not linear and seems to follow a bell-shaped curve, with the highest rate of digestion being observed for a cooking temperature of about 75°C. This could be explained by a gradual denaturation of proteins for cooking temperatures up to 75°C, followed by the formation of molecular aggregates at higher temperatures. These phenomena lead to an increase and then a decrease in the accessibility of digestive enzymes to their cleavage site within the proteins (Bax et al., 2012). Meat cooking not only relies on temperature, but also on cooking time. These studies showed that, besides mechanical processing such as mincing, cooking conditions constitute an interesting way to adapt meat preparation to the elderly population by modulating the speed of protein digestion, without affecting the protein digestibility in the small intestine (Bax et al., 2013). Indeed, we recently observed in elderly subjects that the assimilation of minced meat proteins is significantly different according to the cooking conditions (unpublished observations).
4 CONCLUSION

Adequate protein intake is a key factor for maintaining skeletal muscle mass by stimulating muscle protein synthesis. The protein source, amount of protein, and timing of protein ingestion can modulate the muscle protein synthetic response to protein ingestion. Within a normal diet, protein is generally not consumed as an isolated protein. Our diet provides dietary protein from a wide variety of plant-based as well as animal-derived protein sources. Dairy products and meat represent two of the main protein dense foods that provide a large portion of daily protein intake in a Western diet. The food matrix in which the protein is provided may also modulate protein digestion and amino acid absorption and can, as such, modify postprandial muscle protein synthesis rates. Food preparation such as heating, cooking, cutting, and mastication may also play a modulatory role in protein digestion and amino acid absorption kinetics as well the subsequent postprandial muscle protein synthetic response. Future research should focus on the metabolic fate of dietary protein-derived amino acids provided in protein dense foods and meals (rather than from isolated protein sources). Optimizing food intake to allow for maximal stimulation of postprandial muscle protein accretion may help us to develop more effective interventional strategies to support muscle mass maintenance in both health and disease.
REFERENCES


FIGURES AND LEGENDS

Figure 1. Mean (± SEM) myofibrillar protein synthesis rates expressed as fractional synthesis rates (FSR) before (Rest) and after 30 g milk (n=12) and beef (n=12) ingestion during recovery from exercise. Time × Treatment interaction $P=0.114$, Time effect $P<0.001$, Treatment effect $P=0.114$. 
Figure 1
Highlights

- Identification of dietary protein characteristics that modulate protein anabolism
- Capacity of meat protein to stimulate postprandial muscle protein synthesis
- Food texture and food preparation can modulate protein digestion and absorption