



Revisiting the role of protein-induced satiation and satiety



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ABSTRACT

‘Satiation’ and ‘satiety’ are key terms that have come to be widely used to help understand processes involved in appetite control. Satiation is considered to be the signals or processes that bring a meal to an end, whereas satiety is the signals or processes, following the end of a meal, that inhibit eating before hunger returns. Protein is the most effective food macronutrient providing a satiating effect. Thus, formulating foods with increased protein contents can help to modulate food intake, promoting body weight loss and body weight maintenance thereafter. Mechanisms explaining protein-induced satiety are primarily nutrient-specific, but they are of course not mathematically related to satiety. Different proteins cause different nutrient-related responses of anorexigenic hormones. Glucagon-like peptide-1 (GLP-1) release evoked by a high protein meal is stimulated by the carbohydrate content. Also, cholecystokinin (CCK) and peptide YY (PYY) release is stimulated by a high-protein meal. Sensory, cognitive, post-ingestive and post-absorptive signals will determine jointly the feeling of satiation and satiety. Oral perception cues also contribute increased expectations of satiating capacity when the oral residence time and in-mouth handling are longer and more laborious. In the present review, the authors want to obtain an overview of the satiating ability of dietary protein and its role in satiation and satiety. This could be really significant in showing the food industry the path for developing protein-rich satiating foods in response to consumer demand.

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1. Introduction

The global obesity epidemic is an issue that commands the resources of many public health organizations and demands the input of health professionals and scientists to develop new approaches to prevent and treat it. It also invites researchers to revisit some previously accepted effects of macronutrients, specifically that of protein on energy balance, to determine if greater than expected benefits might be obtained from diet manipulations (Arentson-Lantz, Clairmont, Paddon-Jones, Tremblay, & Elango, 2015).

Many studies have investigated the effects of protein on satiety (Fig. 1) and satiation, and most but not all have found that, at sufficiently high levels, protein has a stronger effect than equivalent quantities of energy from either carbohydrate or fat (Blundell, Lawton, Cotton, & Macdiarmid, 1996; Holt, Brand Miller, Petocz, & Farmakalidis, 1995; Veldhorst et al., 2008; Veldhorst et al., 2009b, 2009c, 2009a; Weigle et al., 2005). Introducing the concepts of

satiation, satiety, and the factors that influence them through the “satiety cascade” lie outside the scope of the present review. Protein has taken centre stage as the highest satiety food constituent because of considerable research indicating that increasing the protein composition of the diet without changing the net energy load can lead to enhanced feelings of satiety (Paddon-Jones et al., 2008).

Protein is an indispensable nutrient; its ingestion as a source of amino acids is necessary for almost all biological processes. Accordingly, food intake is sensitive to protein and the response to the protein content of meals and diets is controlled at different levels, from peripheral organs to the brain. Protein intake induces complex signals including neuropeptides secreted in the gut, metabolic hormones and blood amino acids, as well as derived metabolites released in the blood (Journel, Chaumontet, Darcel, Fromentin, & Tomé, 2012). The mechanisms described for protein-induced satiety are 1) increases in concentrations of ‘satiety’ hormones, 2) increases in energy expenditure, 3) increases in concentrations of amino acids, and 4) the process of gluconeogenesis (Veldhorst et al., 2008).

Knowing why to select the food constituents, what they contribute to the food’s physical and sensory properties and how

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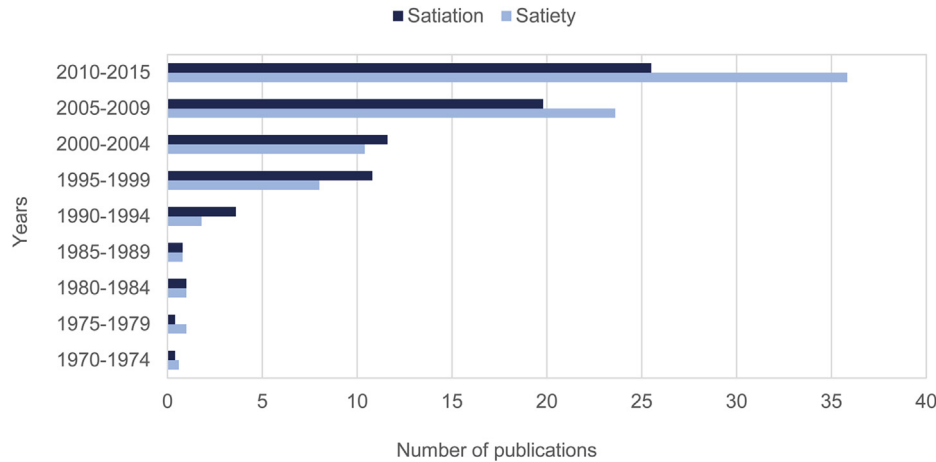


Fig. 1. Evolution of the number of publications with satiation “in the abstract, title or key words” since 1970 (data from Scopus).

they are integrated into the food matrix will provide suitable tools for designing high-protein satiating foods (Morell, Hernando, Llorca, & Fizman, 2015a). An additional value is that this design would have direct implications for the consumer's satisfaction and the perception of satiety. It is difficult to reformulate food products to enhance their satiating capacities because the constituents can themselves influence energy density, palatability, texture and a number of other factors involved in feeding behaviour (Fizman & Varela, 2013). Some of the effects overlap, to an uncertain degree, emphasizing the need for integrative multidisciplinary research. In recent years the food market has seen a rise in the sale of enhanced satiety products (categorically different to reduced-energy diet foods), which claim to be effective in staving off hunger and seem to be well received by the public (Bilman, van Kleef, Mela, Hulshof, & van Trijp, 2012; Chambers, McCrickerd, & Yeomans, 2015; Hetherington & Havermans, 2013).

Human eating is a complex and varied behaviour (Harrold, Dovey, Blundell, & Halford, 2012). A radical change in diet cannot and should not be recommended, but a feasible lifestyle adaptation to a moderately higher-protein, higher-fibre, controlled energy diet should be possible (Hill, 2006).

2. Physiological aspects of protein satiating ability

2.1. Protein-related hormones

Both short- and long-term signals of appetite control act directly through receptors in the brain or indirectly via the nervous system on areas of the brain involved in appetite control pathways (Hillebrand, De Wied, & Adan, 2002; Morris & Hansen, 2009). The pathways can broadly be divided into anorexigenic (inhibit feeding) and orexigenic (stimulate feeding) pathways. Each pathway can be both stimulated and inhibited by signals from the gut, pancreas and adipose tissue.

Protein-induced satiety coincides with a relatively high increase in concentrations of anorexigenic hormones or a larger decrease in orexigenic hormones (Batterham et al., 2006; Hall, Millward, Long, & Morgan, 2003; Lejeune, Westerterp, Adam, Luscombe-Marsh, & Westerterp-Plantenga, 2006; Smeets, Soenen, Luscombe-Marsh, Ueland, & Westerterp-Plantenga, 2008; Veldhorst et al., 2008).

Satiating involves gastric distension and gut hormones such as cholecystokinin (CCK) and GLP-1 (De Graaf, Blom, Smeets, Stafleu, & Hendriks, 2004). A study conducted by Geliebter (1988) showed the effects of various levels of gastric distension – a balloon filled with different volumes of water inserted into

subjects' stomach – on spontaneous meal intake before consumption of a lunch meal. As the balloon volume increased, food intake decreased. Stomach distension is sensed by mechanoreceptor neurons in the stomach and relayed to the hindbrain via vagal afferent and spinal sensory nerves (Ritter, 2004).

GLP-1 is a potential biomarker for satiety that can be measured from blood samples and can be seen to rise for 2 h after a meal (De Graaf et al., 2004). There is some evidence that a high protein meal in combination with carbohydrate stimulates GLP-1 release (Smeets et al., 2008), yet this also depends on the carbohydrate content. Batterham et al. (2003) observed significantly higher plasma PYY responses to a high protein meal, reaching a plateau after 1–2 h and remaining high for approximately 6 h. Similarly to CCK, GLP-1 also acts as a short-term regulator of feeding behaviour. The endogenous release of GLP-1 after a meal has been shown to reduce meal size and also to increase the time to the next meal, thus affecting both satiation and satiety (Williams, Baskin, & Schwartz, 2009). Leptin has also been suggested as a biomarker for satiety (De Graaf et al., 2004). However, since high leptin levels do not appear to increase satiety reliably it cannot be assumed that changes in leptin will cause a related change in appetite.

The physiological systems underlying the control of satiation and satiety involve associations between peripheral physiology (stomach emptying and gastrointestinal peptides) and metabolism (glucose homeostasis and adiposity), which in turn are linked to various brain processes (Blundell & Bellisle, 2013).

2.2. Energy expenditure via protein-induced thermogenesis

One of the mechanisms that classically have been suggested to explain the satiating power of protein is energy expenditure. Daily energy expenditure consists of three components: basal metabolic rate, diet-induced thermogenesis and the energy cost of physical activity (Westerterp-Plantenga, 2004). A relationship between energy expenditure and protein-induced satiety has mainly appeared in relation to a high protein diet, and to a lesser extent after a single high protein meal. The theoretical basis of this relationship may be that increased energy expenditure at rest implies increased oxygen consumption and an increase in body temperature that may lead to feeling deprived of oxygen and thus promote satiety (Westerterp-Plantenga, Lemmens, & Westerterp, 2012; Westerterp-Plantenga, Rolland, Wilson, & Westerterp, 1999).

It has been known for many years that the ingestion of dietary proteins stimulates energy expenditure in the postprandial period immediately after meal ingestion.

The thermic effect of a food is the increase in energy expenditure above baseline following consumption. It can be defined further as the energy required for digestion, absorption, and disposal of ingested nutrients (Halton & Hu, 2004). Certainly, the typical thermic effect of protein is 20%–35% of energy consumed, while for carbohydrate it is usually between 5% and 15% less (Westerterp-Plantenga et al., 1999). These values have found support and been confirmed for protein and carbohydrate/glucose in several human clinical trials (Acheson et al., 2011). Protein not only increases energy expenditure (Halton & Hu, 2004; Johnstone et al., 2002) but also decreases energy intake through mechanisms that influence appetite control (Anderson, Tecimer, Shah, & Zafar, 2004b; Lejeune, Kovacs, & Westerterp-Plantenga, 2005; Nickols-Richardson, Coleman, Volpe, & Hosig, 2005; Schoeller & Buchholz, 2005; Weigle et al., 2005). Westerterp-Plantenga et al. (2012) stated that from combining the studies on protein intake, it can be concluded that protein intake causes an acute increase in diet-induced energy expenditure and, when sustained over three days, results in an increase in the sleeping metabolic rate.

An interesting theory concerning thermogenesis as it relates to protein intake is the Stock Hypothesis (Stock, 1999). This author cited 12 human overfeeding studies to support the view that diets high in protein increase thermogenesis in an effort to homeostatically waste energy when fed an unbalanced diet. This would make sense from an evolutionary perspective, in that such an increase in thermogenesis would help ensure an adequate supply of nutrients while avoiding the risks to survival associated with excess weight gain. An area of research worth mentioning concerns the theory that the obese have a blunted thermic effect in general and in relation to fat in particular (Granata & Brandon, 2002).

In fifteen studies concerning thermogenesis reviewed by Halton and Hu (2004), the thermic effect of food was measured in a variety of ways. The results suggested that high-protein diets exert a greater effect on energy expenditure than low-protein ones. One limitation was that the numbers might be underestimated, as most studies were conducted for a period of only 6–7 h and many believe that the thermic effect of protein continues for longer.

One important reason for the difference in the thermic effects of food may be the fact that the body has no protein storage capacity, so it requires immediate metabolic processing. Protein synthesis, the high ATP cost of peptide bond synthesis and the high cost of urea production and gluconeogenesis are often cited as reasons for the higher thermic effect of protein (Mikkelsen, Toubro, & Astrup, 2000). Energy expenditure is not clearly dependent on the protein source, although there is some evidence that animal proteins produce higher energy expenditure than vegetable proteins, resulting in reduced appetite (Westerterp-Plantenga, 2003).

2.3. Amino acids

Dietary protein and amino acids, including glutamate, generate signals involved in the control of gastric and intestinal motility, pancreatic secretion, and food intake. The signals include postprandial meal-induced visceral and metabolic signals and associated nutrients, gut neuropeptides, and hormonal signals. Protein reduces gastric motility and stimulates pancreatic secretions (Blundell & Bellisle, 2013).

The amino acid composition of the protein is a determinant of the metabolic efficacy of protein oxidation (hence, heat production) because there are large differences in the efficacy with which amino acids are oxidized. This is due to the wide variety of carbon chains and co-factors that result from amino acid catabolism (Boirie et al., 1997; Dangin et al., 2001; Dangin, Boirie, Guillet, & Beaufère, 2002; Van Milgen, 2002).

Both the quality and type of protein appear to be involved in

hunger suppression. Protein quality is mainly determined by the amino acid composition. Some proteins are considered 'incomplete' or 'lower quality' proteins because they are lacking one or more essential amino acids or have an inadequate balance of them. High protein diets with proteins that predominantly consist of ketogenic amino acids may result in increased plasma ketone body concentrations, which in turn contribute to increased satiety (there are seven ketogenic and glucogenic amino acids: tyrosine, threonine, isoleucine, phenylalanine, tryptophan, leucine and lysine, although the last two are exclusively ketogenic; Westerterp-Plantenga et al., 2012).

Metabolites, including certain amino acids, contribute to the perception of postprandial satiety. As early as in 1956, Mellinkoff suggested a relationship between serum amino acid concentration and fluctuations in appetite. This theory is termed the aminostatic hypothesis. Whether induced by feeding protein or amino acids, or by infusing amino acid mixtures, a rise in the serum amino acid concentration appeared to be accompanied by a waning of appetite. The subsequent increase in appetite was accompanied by a fall in the amino acid concentration. This author has also suggested that a high concentration of blood or plasma amino acids that cannot be channelled into protein synthesis may serve as a satiety signal for a food intake regulating mechanism and thereby result in depressed food intake. More recently, it has been proposed that protein- and amino acid-induced satiety could be associated with the branch-chain amino acids found in complete proteins, which could be involved in the regulation of amino acid oxidation and gluconeogenesis (Aldrich et al., 2011). In addition, the good balance of indispensable amino acids usually obtained from dietary protein is sensed by the protein synthesizing machinery in specialized cells in the brain (Fromentin et al., 2012; Gietzen & Aja, 2012) which influences subsequent feeding-related responses.

Until now hardly any clear differences in satiating properties between different protein types have been shown, mainly due to the design of the studies, which have not used just one single protein. An important issue that should also be taken into account is timing, due to marked differences in protein metabolism kinetics. In their review on whey proteins in the regulation of food intake and satiety, Luhovyy, Akhavan, and Anderson (2007) showed that the satiating power of a high protein meal may be used optimally when the timing of the meal interval synchronizes with timing of the amino acid profiles. The speed of absorption of dietary amino acids by the gut varies according to the type of dietary protein ingested, and since amino acids are potent modulators of protein synthesis, breakdown and oxidation, different patterns of postprandial aminoacidemia might well be found to influence satiety or satiation. Dietary carbohydrates are commonly classified as slow or fast because it is now well recognized that their structure affects their speed of absorption, which in turn has a major impact on the metabolic and hormonal response to a meal. However, less is known about how postprandial protein kinetics could be affected by the speed of absorption of dietary amino acids. The latter is very variable, depending on gastric and intestinal motility, luminal digestion, and finally mucosal absorption. This concept of slow and fast proteins could be applied to distinguishing different kinetic types of proteins (Boirie et al., 1997).

2.4. Gluconeogenesis

Finally, the mechanism of gluconeogenesis has been mentioned as contributing to satiety in relation to protein, or better, to food intake regulation, at least in the animal model.

Azzout-Marniche et al. (2007) suggested that hepatic gluconeogenesis is stimulated by a high-protein diet in rats. As glucoreceptors are able to send a satiety signal to the brain via the

vagal nerve, stimulation of gluconeogenesis could be involved in the satiating effect of protein through the modulation of glucose signalling to the brain (Melanson, Westerterp-Plantenga, Saris, Smith, & Campfield, 1999; Westerterp-Plantenga, Lejeune, Smeets, & Luscombe-Marsh, 2009). The study by Azzout-Marniche et al. (2007) also showed that a diet with a high protein content and without any carbohydrates did not stimulate gluconeogenesis sufficiently to signal satiety. Therefore, mechanisms other than amino acid-induced gluconeogenesis are involved in protein-induced satiety.

Duraffourd et al. (2012) showed that μ -opioid receptors present in nerves in the portal vein walls respond to peptides to regulate a gut-brain neural circuit that controls intestinal gluconeogenesis and satiety in rats. Moreover, transient blood glucose declines have been shown to be related to the signal of meal initiation (Melanson et al., 1999). Thus, an amino acid-induced gluconeogenesis may prevent a decrease in glycaemia and thereby contribute to satiety. Gluconeogenesis was increased and appetite was lower when healthy human subjects consumed a high-protein diet in comparison with the consumption of a normal-protein diet. Although appetite was strongly suppressed by the high-protein diet, there was no correlation between gluconeogenesis and appetite ratings. Gluconeogenesis in humans is thought to remain relatively stable in varying metabolic conditions (Nuttall, Ngo, & Gannon, 2008).

Veldhorst, Westerterp, Van Vught, and Westerterp-Plantenga (2010) showed that increased concentrations of β -hydroxybutyrate and increased dietary fat oxidation contribute to the appetite suppression effect of a high-protein diet. Several studies have shown increased concentrations of β -hydroxybutyrate coinciding with reduced appetite in human subjects (Johnstone, Horgan, Murison, Bremner, & Lobley, 2008; Veldhorst, Westerterp, & Westerterp-Plantenga, 2012), thus potentially contributing to appetite suppression.

Although the exact mechanistic basis of protein-induced satiety is still unknown, it is likely to involve several complementary routes (Fig. 2) that can be altered by diet composition; the challenge will be to identify which conditions promote satiety (Johnstone, 2013).

3. High protein diets

There is currently no formal definition of 'high protein' as a percentage of energy in a meal or diet. The composition of the diet can be determined as the absolute amount of protein (grams), the % of total energy as protein or the amount of protein ingested per kg body weight (Johnstone, Gonzalez, & Harrold, 2012).

In a review of the safety and efficacy of high protein diets, Eisenstein, Roberts, Dallal, and Saltzman (2002) suggested that protein intakes higher than 25% energy should be defined as 'high' and over 35% energy as 'extremely high' based on the US dietary recommended intakes which give 10–35% as the acceptable range of protein intake. In the context of research on prevention and treatment of overweight and obesity, relatively high-protein diets have come into focus as having the potential to act on the different metabolic targets regulating body weight (Westerterp-Plantenga et al., 2006) and thereby providing the required conditions for successful weight maintenance after weight loss (Veldhorst et al., 2008). High-protein diets reported in weight loss studies often include ~30% of energy intake as protein. In general, protein as a percentage of energy is doubled from 15% to 30% (Halton & Hu, 2010). There are many variants, such as the Dukan diet (Dukan, 2004), the Zone diet (Gardner et al., 2007) and the CSIRO diet (Wyld, Harrison, & Noakes, 2010). Both the safety (St. Jeor et al., 2001) and efficacy of high protein diets have been questioned, particularly in combination with low-carbohydrate advice (Astrup,

2005). Low-carbohydrate diets are described as ketogenic diets since ketone bodies such as β -hydroxybutyrate and acetoacetate are produced by the liver, replacing glucose as an energy source for the brain. One example of such a low-carbohydrate diet is the Atkins' diet (Johnstone et al., 2012).

The consumption of a high protein diet induces an immediate strong depression in food intake followed by a progressive but incomplete return to the level of energy intake of the control diet in animals (Fromentin et al., 2012; Jean et al., 2001).

The commonly poor palatability of high-protein diets has been documented (McArthur, Kelly, Gietzen, & Rogers, 1993), but with respect to protein intake its relative importance remains unclear. It is possible that the appetite-suppressing effect of dietary protein is partially induced by poor palatability. Taken together, experiments indicate that the overall behavioural response more probably originated in an initial lower palatability of the food combined with an enhanced satiety effect of the high-protein diet and a delay required for metabolic adaptation (Fromentin et al., 2012).

In the laboratory, the satiating effects of high protein foods or meals have been compared to iso-energetic lower protein counterparts, typically using a "preload" methodology where the measure of satiety is subjective post-consumption ratings of appetite and/or food intake. The majority of these types of studies indicate that high protein foods deliver better satiety than energy-matched foods with lower levels of protein (e.g. Astbury, Stevenson, Morris, Taylor, & MacDonald, 2010; Bertenshaw, Lluch, & Yeomans, 2009; Booth, Chase, & Campbell, 1970; Fischer, Colombani, & Wenk, 2004; Hill & Blundell, 1986; Rolls, Hetherington, & Burley, 1988; Teff, Young, & Blundell, 1989), though this is not always reported (de Graaf, Hulshof, Weststrate, & Jas, 1992; Vozzo et al., 2003).

It is widely accepted that a reduced-carbohydrate, high-protein diet is associated with better fat loss and relatively less lean mass loss.

4. Designing protein-rich satiating food

4.1. Effect of type and amount of protein

A large number of behavioural studies indicate that both the quantity and quality of dietary protein can influence food intake and metabolism markedly, and that dietary protein intake may be prioritized over energy intake (Morrison & Laeger, 2015).

Different proteins appear to involve different satiety mechanisms and the different mechanisms appear to be related mainly to different food components (Anderson, Tecimer, Shah, & Zafar, 2004b; Diepvens, Häberer, & Westerterp-Plantenga, 2008; Veldhorst et al., 2008).

4.1.1. Short-term studies

A number of studies have investigated the short-term effects of different protein sources on satiety. Twelve years ago Halton and Hu (2004) reviewed the literature on the effects of high protein foods and diets on satiety. At least in the short-term, they found convincing evidence that high-protein meals are more satiating than lower protein meals and stated that the mechanisms remain elusive. Later, in a meta-regression approach, Krieger, Sitren, Daniels, and Langkamp-Henken (2006) examined 87 short-term studies and found that protein intakes of >1.05 g/kg of actual (rather than desirable) body weight were associated with 0.6 kg better retention of lean mass; in studies of more than 12 weeks' duration, this increased to 1.2 kg.

Veldhorst et al. (2009a, 2009b, 2009c) have published many preloading studies that have suggested that in iso-energetic amounts, high-protein diets are more satiating than normal protein meals. In short, the evidence supports the conclusion that

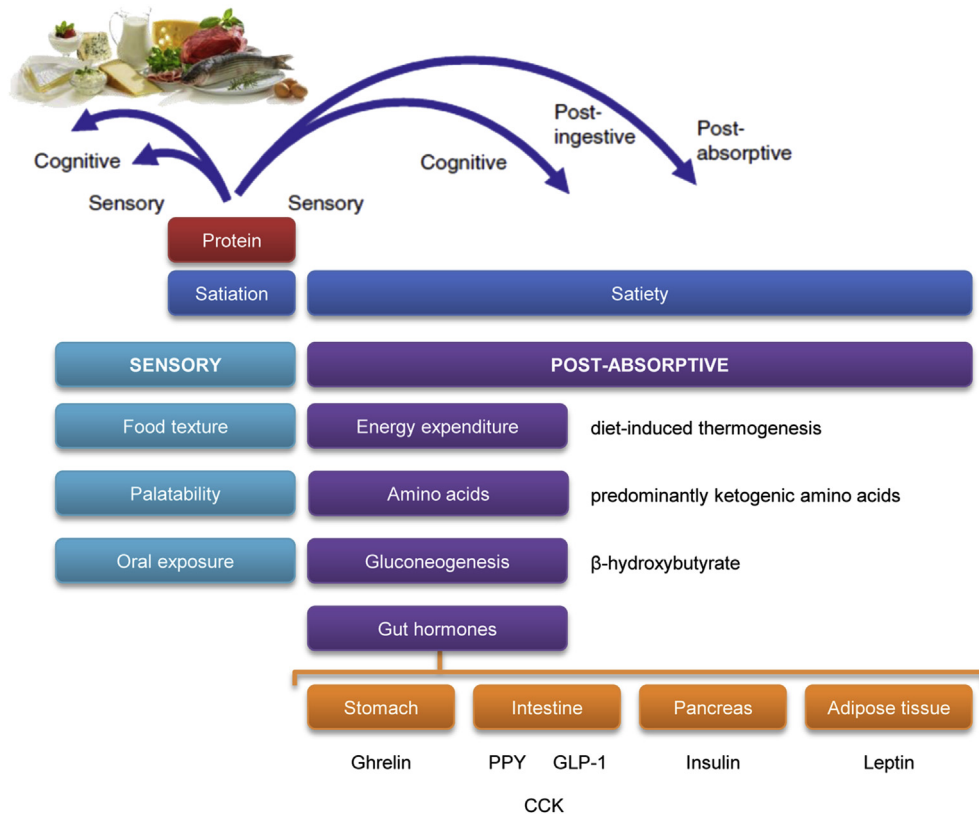


Fig. 2. Schematic view of factors related to protein influence on satiation and satiety. PPY: peptide YY; GLP-1: glucagon-like peptide-1; CCK: cholecystokinin.

higher-protein meals tend to increase satiety when compared to lower-protein ones, at least in the short term.

Fish and meat proteins. Uhe, Collier, and O'Dea (1992) measured the relative satiating effects of protein in beef, chicken and fish over a period of 3 h. Visual analogue scale (VAS) measurements of satiety were found to be significantly higher after the subjects consumed fish than after beef or chicken; subsequent energy intake was not measured. Borzoei, Neovius, Barkeling, Teixeira-Pinto, and Rössner (2006) looked at the satiating effects of beef and fish. With fish they found a non-significant increase in satiety by appetite ratings and a significant decrease in energy intake at a subsequent meal. However, both studies were relatively small (6 and 23 subjects, respectively) and the participants only included lean men. The authors hypothesized that these results might be due to differences in amino acid content or the slower rate of digestion of fish proteins, and also suggested serotonergic factors as a possible explanation of extended observations of fish protein enhanced satiety.

A series of seminal papers have addressed the satiating effect of dietary compounds introduced by duodenal infusion in rats, where glucose, fatty acids, and meat protein hydrolysates clearly affected the release of CCK and resulted in lower dietary intake due to smaller and less frequent meals (Young et al., 2013). Johnstone et al. (2008) indicated that high-protein (30% protein) meat-based weight-loss diets are highly satiating and reduce *ad libitum* food intake over a 4-week period.

Cudennec, Fouchereau-Peron, Ferry, Duclos, and Ravallec (2012) and Nobile et al. (2016) showed that hydrolysates produced from blue whiting muscle reduced short-term food intake, which was correlated to an increase in the CCK and GLP-1 plasma levels. Moreover, they demonstrated that their chronic administration led to a decrease in body weight gain.

Milk proteins. The fact that different proteins may affect satiety differently has been studied especially with respect to whey and casein protein. Hall et al. (2003) found an increased satiety response to whey compared with casein, involving post-absorptive increases in plasma amino acids together with some hormones or peptides as potential mediators of that response. These authors compared the effects of drinks containing very large amounts of whey or casein and found that compared with the casein preload, the whey reduced the energy intake by 19% at a subsequent meal. However, the buffet meal was offered 90 min after the preloads, which is probably too soon to be a realistic sensitive time frame. Anderson and Moore (2004a) considered that this difference between casein and whey proteins could be attributed to clotting of the casein (unlike the soluble whey) in the acidic media of the stomach, giving it a longer gastric emptying effect and longer exposure to gastric peptic hydrolysis. Since whey contains high concentrations of branched chain amino acids (leucine, isoleucine and valine), it has been suggested that these perform a unique metabolic role, enhancing satiety due to the extra-hepatic metabolism and interactions with insulin-signalling pathways (Diepvens et al., 2008). In addition, other nutrients such as vitamin D and fatty acids might also have a role in the impact of dairy supplementation.

Other recent studies have shown that dairy protein supplements favourably influence appetite sensations and time of request of meal (Douglas, Ortinau, Hoertel, & Leidy, 2013), as well as subsequent energy compensation (Akhavan, Luhovyy, Brown, Cho, & Anderson, 2010).

Anderson et al. (2004b) compared the effects on subsequent energy intake of liquid preloads containing 45–50 g of whey protein, soy protein, egg albumen or sucrose and a control (water). Whey and soy protein suppressed energy intake at a meal provided

1 h later, but egg albumen and sucrose did not, resulting in a greater energy intake overall (preload plus meal). Whey was more effective than soy. In Akhavan et al. (2010), the ingestion of a preload supplemented with whey protein resulted in a subsequent decrease in energy intake that was larger than the energy content of the supplement.

Bowen, Noakes, Trenerry, and Clifton (2006) compared energy intake, ghrelin, and CCK after different carbohydrate and protein preloads in overweight men. Although they did not find different effects from different proteins (casein and whey), they observed that the protein preloads induced a larger satiating effect than the carbohydrate ones. In addition, they referred to differences in appetite-regulatory hormone responses by body mass index status.

The satiating properties of caseinomacropptide have been considered to involve an increased release of CCK and inhibition of gastric secretions. However, most human studies conducted to date with caseinomacropptide appeared to have failed to demonstrate a clear satiating effect followed by a reduction in food intake (Nongonierma & FitzGerald, 2015).

Mycoprotein. Mycoprotein, a high-protein food produced from a fungal source, has also been tested for its effects on satiety. Burley, Paul, and Blundell (1993) and Turnbull, Walton, and Leeds (1993) compared the effects on satiety of a mycoprotein-based meal and a chicken-based one with the same protein content. In both studies, subsequent energy intake was lower after the mycoprotein than after the chicken meal. Although the meals were matched for energy and protein, it should be noted that the mycoprotein meal was higher in fibre, which may have affected the satiety response. It is therefore not possible to draw conclusions about the specific effects of protein on satiety in this case (Benelam, 2009). Williamson et al. (2006) compared the effects on satiety of mycoprotein, chicken and tofu preloads with matched protein contents. The energy intake at the test lunch was lower after both the tofu and mycoprotein preloads than after the chicken preload, while there was no significant difference in appetite ratings.

Egg, soy, and other protein sources. Different types of isolated protein added to meals have also been investigated for their potential effects on satiety. Lang et al. (1998) looked at the effects of egg albumen, casein, gelatine, soy protein, pea protein, and wheat gluten on satiety, using a preload design, and found no significant differences in their effects on appetite ratings.

In a separate experiment, the effect of soy protein was compared with a combination of soy protein and carbohydrates (either glucose or amylose) on energy intake at a meal 1 h later. Soy protein alone caused a significant reduction in energy intake, but when the protein content was reduced and carbohydrate added, there was no significant reduction in the energy intake (Anderson et al., 2004b). Overall, the evidence suggests that the source of protein itself, at levels feasible in foods, does not have a large and consistent effect on subsequent appetite and food intake. Neacsu, Fyfe, Horgan, and Johnstone (2014) concluded that appetite control and weight loss were similar for vegetarian and meat-based diets. The gut hormone profile was similar for both, which suggest that vegetarian diets can be as effective as meat-based diets for appetite control during weight loss.

Some studies have shown that eggs eaten at breakfast are more satiating than cereals in normal weight subjects (Fallaize, Wilson, Gray, Morgan, & Griffin, 2013) and are also more satiating than bagels in overweight (Ratliff et al., 2010) and obese subjects (Vander Wal, Marth, Khosla, Jen, & Dhurandhar, 2005). Despite a similar energy density and macronutrient composition, consuming an egg-based breakfast compared to a cereal-based breakfast significantly reduced short-term, but not long-term, energy intake, influencing the fullness rating (Bayham, Greenway, Johnson, & Dhurandhar, 2014). This was also so in children (Kral, Bannon,

Chittams, & Moore, 2016). In these studies, the satiating effect of eggs was demonstrated not only by decreased feelings of hunger, but also by a lower energy intake.

Marsset-Baglieri et al. (2015) concluded that despite important differences in protein kinetics and their subsequent effects on hormone secretion, eggs and cottage cheese had a similar satiating power. This strongly suggested that with a dose of proteins that is compatible with supplement strategies, i.e. 20–30 g, a modulation of protein kinetics is ineffective in increasing satiety.

In conclusion, protein intake enhances satiety, but there is not clear evidence to indicate whether there is a difference in the effect size dependent on the source of the protein, i.e. animal- or plant-based.

4.1.2. Long-term studies

Boirie et al. (1997) studied the effect of two milk proteins – casein and whey protein – on postprandial whole-body protein metabolism. They combined oral and intravenous administration of proteins. According to the speed at which amino acids appeared in the bloodstream, the authors classified whey as a fast protein and casein as a slow protein. The postprandial amino acid levels differ a lot depending on the mode of administration of the dietary protein: a single protein meal results in an acute but transient peak of amino acids whereas the same amount of the same protein given in a continuous manner, which mimics slow absorption, induces a smaller but prolonged increase (Boirie et al., 1997; Wolever, 1994). The slowly absorbed casein promotes postprandial protein deposition by an inhibition of protein breakdown without an excessive increase in amino acid concentration, whereas a fast dietary protein stimulates not only protein synthesis but also oxidation.

Halton and Hu (2004) stated that in long-term studies conducted over a few days, higher post-absorptive satiety and thermogenesis are sustained irrespective of the protein source. There is no clear consensus that one type of protein is more satiating than another. Weigle et al. (2005) looked at the effects of both iso-caloric and *ad libitum* high-protein diets. Their subjects were given a diet that provided either 15% or 30% of the energy from protein (carbohydrate was kept constant at 50% of energy and fat varied from 35% to 20% of energy). For the first four weeks, when the high- and low-protein diets were isocaloric, the subjects reported significantly higher satiety ratings on the high-protein diet. For the following 12 weeks the macronutrient proportions of the diet remained constant but the subjects were allowed to eat *ad libitum* from the foods provided. This resulted in a spontaneous reduction in energy intake among those on the high-protein diet, and weight loss at the end of the study. The reduction in energy intake did not appear to cause a reduction in satiety, according to self-reported appetite ratings.

Lejeune et al. (2006) conducted a study on protein and satiety in respiration chambers, allowing energy expenditure to be assessed. For four days, subjects were fed either an adequate-protein diet (10% of energy from protein) or a high-protein diet (30% of energy from protein), which were iso-caloric. VAS measurements showed that satiety was significantly higher and hunger was significantly lower on the high-protein diet, despite the energy intake being the same. Sleeping metabolic rate and diet-induced thermogenesis were significantly higher on the high-protein than on the adequate-protein diet. These results confirmed those of similar studies performed by the same research group in 1999 (Westerterp-Plantenga et al., 1999).

Skov, Toubro, Rønn, Holm, and Astrup (1999) showed large weight loss benefits at 6 months on a high-protein weight loss regime. According to Clifton (2006a, 2006b), groups consuming a high-protein, moderate-carbohydrate diet have an increased likelihood of maintaining weight loss at 12 months and beyond, with

minimal risk of side effects. In addition, high-protein diets provide a potential benefit of improved compliance during weight loss attempts: in a 12-month study, [Due, Toubro, Skov, and Astrup \(2004\)](#) reported substantially greater compliance in subjects consuming a higher protein diet (25% of energy from protein).

4.2. Satiety implications of increasing oral exposure by adding protein

Satiety is a complex object which needs to be studied from both a metabolic and a behavioural point of view ([Allirot et al., 2014](#)). Oral exposure is affected by a number of food characteristics ([de Wijk, Zijlstra, Mars, de Graaf, & Prinz, 2008](#); [Hutchings et al., 2009](#)), such as food viscosity ([de Wijk et al., 2008](#); [Viskaal-van Dongen, Kok, & de Graaf, 2011](#)), bite size, oral processing time, or chewing frequency ([Bolhuis, Lakemond, de Wijk, Luning, & de Graaf, 2011](#); [Morell, Fiszman, Varela, & Hernando, 2014](#); [Zijlstra et al., 2009](#)), among others. [Morell et al. \(2015a\)](#) showed that adding whey protein to yogurts raised the expectations of their satiating ability significantly in a consumer test ($n = 121$) and attributed this effect to the higher viscosity of these yogurts in comparison to the control samples (no extra protein added). This suggested that an increased time or intensity of the orosensory exposure (i.e. food present in the oral cavity) would contribute to controlling further energy intake.

A review by [Hogenkamp and Schiöth \(2013\)](#) found that satiety and satiation are modified not only by cognitive processes but also by sensory exposure to food. Years before, [French and Cecil \(2001\)](#) showed that satiety was greater when a food was consumed orally than when the same food was infused into the gastro-intestinal tract. It has also been observed that because of their fluid nature, beverages require less oral processing time than semi-solid and solid caloric equivalents, minimizing oro-sensory exposure ([de Wijk et al., 2008](#); [Morell et al., 2014](#); [Tieken et al., 2007](#); [Zijlstra et al., 2009](#)). A number of studies have indicated that “liquid” energy fails to suppress subjective appetite ([Leidy, Apolzan, Mattes, & Campbell, 2010](#); [McCrickerd, Chambers, Brunstrom, & Yeomans, 2012](#)), eliciting weaker suppressive appetite responses than “more solid” iso-caloric versions of the same food product ([Bertenshaw et al., 2009](#); [Mattes & Rothacker, 2001](#); [Zijlstra, Mars, Stafleu, & de Graaf, 2010](#)). According to [McCrickerd et al. \(2012\)](#), the possible reason is that longer oro-sensory exposures contribute to the development of satiety through triggering anticipatory responses related to learned associations between the sensory characteristics of a food and its caloric value post-consumption ([Yeomans, Weinberg, & James, 2005](#)). These associations are likely to influence explicit expectations about the effect a food will have on appetite ([Blundell et al., 2010](#); [Brunstrom, Shakeshaft, & Scott-Samuel, 2008](#)). In line with this, [Morell, Ramírez-López, Vélez-Ruiz, and Fiszman \(2015c\)](#), using food photograph visual scales, reported that a milk-based dessert with added HPMC and protein and a thick, dense texture elicited the perception of having a high satiating capacity. The taste, smell and texture of a food all contribute to the representation of its flavour, but food texture (or form) has been isolated as a sensory component of food that plays a key role in satiety ([Chambers et al., 2015](#); [McCrickerd & Forde, 2016](#)). Food texture, therefore, may serve as a reliable predictive cue for further sensations of satiety ([Davidson & Swithers, 2005](#)). Creamy texture cues have been associated with nutrient-rich foods ([Bertenshaw, Lluch, & Yeomans, 2008](#); [Bertenshaw et al., 2009](#); [Bertenshaw, Lluch, & Yeomans, 2013](#)) and satiety-relevant sensory cues can be used to estimate the satiating power of foods. This would support the view that oro-sensory sensations such as taste and texture cues act as nutrient sensors ([Woods, 2009](#)), directing eating behaviour to ensure the efficient consumption of nutrient-

rich or nutrient-lacking foods ([McCrickerd, Lensing, & Yeomans, 2015](#)).

Textured foods require mastication, which will slow down consumption rates and enhance orosensory exposure times ([Zijlstra, Mars, de Wijk, Westerterp-Plantenga, & de Graaf, 2008](#)). The mechanical processing of food in the mouth might be one way in which the nutrient content of a food is estimated. Indeed, chewing has been associated with satiety-related cognition ([Forde, van Kuijk, Thaler, de Graaf, & Martin, 2013](#)), preparatory cephalic phase responses and appetite peptide release ([Li et al., 2011](#)), but relationships with satiety signals have not always been reported ([Mattes & Considine, 2013](#); [Teff, 2010](#)).

Differences in *ad libitum* intake after treatment with either liquid yogurt consumed with a straw, or liquid yogurt or semi-solid yogurt both consumed with a spoon, have been explained by eating rate, which was faster with a straw and led to reduced oral processing time ([Hogenkamp, Mars, Stafleu, & de Graaf, 2010](#)). The daily energy intake increased with decreasing viscosity ([Juvonen et al., 2009](#)), while the *ad libitum* intake increased by 30% in the beverage group compared to the semi-solid group in another study ([Zijlstra et al., 2008](#)). Controlling for the effort involved in consuming the test load did not influence intake, but the eating rate, measured as the volume consumed per minute, was positively associated with intake, whereas there were no differences between any of the treatments in the ratings for hunger, fullness, and a desire to eat ([Zijlstra et al., 2008](#)). The subjects consumed greater quantities of a beverage test load compared to a semi-solid test load, although these differences were eliminated after standardizing the duration of oral processing ([de Wijk et al., 2008](#)).

More solid products require more labour and time in the mouth, causing longer oro-sensory exposure, which in turn may result in a greater timespan to allow satiety signals to induce meal termination or evoke satiety ([Hogenkamp & Schiöth, 2013](#)). An increase in proxies of orosensory exposure may result in an increase in nutrient-energy-sensing, and a longer timespan for satiety signals to reach the brain.

Increasing the food texture complexity could also be an interesting strategy for prolonging oral exposure ([Marcano, Morales, Vélez-Ruiz, & Fiszman, 2015](#)). A few examples of added-protein milk-based desserts with enhanced satiating capacity have recently been published ([Morell et al., 2015a](#); [Morell, Piqueras-Fiszman, Hernando, & Fiszman, 2015b](#)). Literature on the development of novel food items with enhanced satiating capacity is still scarce. [Marcano, Varela, and Fiszman \(2015\)](#) selected a system that was basically made of fresh cheese, eggs, sugar, milk, and starch as a model for designing a satiating dairy pie with increased protein content.

Long-term intervention studies have reported that slowing down the normal eating rate may alter the physiological responses to food beneficially ([Galhardo et al., 2011](#)) and may be a useful therapy to include in programs that aim to reduce obesity ([Ford et al., 2010](#)). This suggests that aspects of oral processing and eating rate can make a beneficial contribution to controlling our energy balance and meal size.

The physical properties of solids may require increased energy expenditure to break them down and their incomplete degradation may promote inefficient energy and nutrient absorption ([Conley et al., 2011](#)). Stomach distention and retention of stomach contents produce feelings of fullness ([Cuomo et al., 2011](#)). Rapid gastric emptying could result in faster gastrointestinal transit, which, in turn, could result in decreased absorption and blunted nutrient-based feedback signalling (e.g., CCK or GLP-1 release) ([Moukarzel & Sabri, 1996](#)). Nutrient sensing in the proximal and distal gastrointestinal tract can trigger physiological responses that slow transit time, e.g., CCK ([Schwartz & Moran, 1998](#)) and GLP-1 secretion ([Flint,](#)

Raben, Ersbøll, Holst, & Astrup, 2001).

There is considerable evidence on the relationship between endocrine status, appetite, and ingestive behaviour, but it is very mixed (Apolzan, Leidy, Mattes, & Campbell, 2011; Cassady, Considine, & Mattes, 2012; Juvonen et al., 2009; Leidy et al., 2010; Tieken et al., 2007; Zijlstra et al., 2009), leading to questions about whether the relationships are associative or causal under physiological conditions. It may be that measurable circulating concentrations of endocrine factors are poor predictors of the more important influence of central effects (Havel, 2001; Ionut, Huckling, Liberty, & Bergman, 2005). Taken together, the evidence suggests that different food states lead to different patterns and magnitudes of endocrine responses and, in consequence, to different effects on feeding.

Food scientists could take advantage of this knowledge about food texture and food form as sensory aspects that play basic roles in satiety. Proteins have a number of techno functional properties (emulsifying, gelling, foaming, etc.) that could be used to build structures in foods. Since the length of orosensory exposure influences satiety and satiation, researchers have to take into account that in order to attain the proper design of really worthwhile enhanced-satiety products, adding protein to food will modify characteristics, such as oral processing time or chewing frequency.

5. New protein-rich food development

A new product development process should involve the following critical stages: idea generation, concept development, product development, launch and post-market monitoring. New ideas have been derived from human biology and physiology, nutritional epidemiology, food technology, consumer learning and consumer psychology in choice and consumption contexts. A crucial challenge in new product development is to determine the extent to which the physical product can actually live up to its expectations in enhancing feelings of satiety and satiation. Once the product is ready for its market launch it will be successful both in terms of its commercial and public health ambitions, but satiety-enhancing product features need to be convincingly and responsibly communicated to consumers (Van Kleef, Van Trijp, Van Den Borne, & Zondervan, 2012).

A number of satiety/satiation-related patents have taken out over the past ten years. One of the principal approaches has consisted in adding a number of proteins such as whey proteins, caseinmacropeptide, glycomacropeptides, whey protein hydrolysate, lactalbumin, sodium caseinate, intact pea and wheat protein, hydrolysed yeast proteins, codfish, egg, or egg hydrolysate to foods. There are patents that mention the protein formulation's potential for stimulating hunger-control related neurotransmitters or enzymes. Others use the fact that certain proteins have an unfolding transition in the stomach's pH range, as is the case for some cross-linked globular proteins that can form hydrogels.

From the food development point of view, it is important to note that the pleasantness of eating fish, for example, is not the same as that of eating meat, and that the type and quality of the fats or oils of the fish or meat consumed influence the feeding response. Also, the versatility of milk proteins is greater than that of other types of protein from several points of view, such as predisposition and times when they are consumed. Similarly, many other factors influence a particular choice (Paddon-Jones et al., 2008).

High protein food products invariably contain other energy-yielding nutrients, usually both carbohydrates and fats. Therefore, in order to optimize high satiety products the carbohydrate-to-fat ratio should also be considered (Chambers et al., 2015).

Processing is another factor to be taken into account, since proteins normally require optimal pH control, protein

concentration, heat treatment and evaluation of the risks from other ingredients (gums, minerals) in order to prevent flocculation, turbidity or sedimentation. In spite of this, proteins are a wide ranging group, some of which are highly functional and have been developed and optimized by the industry for different food systems.

Reformulating foods to increase their protein content can also affect the sensory properties of the final system. An understanding the mechanism of texture perception is essential when developing food products to both meet nutritional needs and maintain an acceptable level of sensory quality (Çakır et al., 2012). The appearance of unpleasant flavours and texture features has been reported in high-protein satiating yogurts formulated with whey proteins (Morell et al., 2015a) and in high-protein satiating bars (Little, Gregory, & Robinson, 2009).

Finally, in the development of satiety-enhancing food products it is crucial to be aware that they require an integrated multidisciplinary perspective of the problem (Allirot et al., 2014), in relation to both public health governance and corporate ambitions and in relation to nutritional, food technology, communication and consumer sciences. The efforts of various segments of the food industry to provide foods with a lower energy density in response to recommendations from nutrition experts and insistent demands from consumers, in spite of the technical difficulty, deserves a little more attention (Bellisle & Tremblay, 2011). The consumer and health benefits of satiety-enhancing products need to be better defined. It is not clear what the consumer understands by satiety (Fiszman, Varela, Diaz, Linares, & Garrido, 2014) or whether consumers know how satiety products should be incorporated into their daily diet (Halford & Harrold, 2012).

Products designed to incorporate and claim high amounts of protein or meet a specific preferred ratio of protein/other macronutrients, are one of the most interesting potential ways to market satiety-related food items. Although bars and shakes are currently the most common novel formulations, other high-protein foods and meals seem to be promising.

5.1. Conclusion and future trends

As general conclusions, according to Johnstone (2013), there is some evidence to suggest that enhanced protein-induced satiety effects are likely to be amplified, particularly in cases where negative energy balance is induced. The optimal amount of protein, the type, the timing of protein intake, and the interactions with other interventions (e.g., exercise) is still unclear.

Energy from protein, in a sufficient dose, has a greater effect on satiety than an equivalent amount of energy from carbohydrate or fat in the short-term. The literature reviewed indicates that increasing the protein content of a food is an effective way to deliver enhanced satiety.

On the other hand, it should be taken into account that manipulating the macronutrient content of a food while keeping its energy level constant makes it difficult to be certain whether the effects are caused by the superior satiating effect of protein, reduction of the less satiating nutrients (carbohydrate and fat), or a combination of the two.

When *ad libitum* high-protein diets (often include ~30% of energy intake as protein) are compared with lower-protein diets, larger weight losses appear with the former in longer-term studies. This may be a result of the higher satiating effect of protein, although appetite measurements are often not taken in these studies. Differences in study designs make it difficult to pinpoint the optimum dose or percentage of energy needed to observe significant effects of protein on satiety. It is generally accepted that at least 50 g of protein in a food or meal is necessary to see a

significant effect on satiety, but that currently there is not sufficient information to describe a dose–response relationship. The protein content of food, and its source, is a solid determinant of short-term satiety and of how much food is eaten. However, the role of protein in the regulation of long-term food intake and body weight is less clear, but several lines of evidence suggest that further research to define its role is merited.

All in all, the development of protein-rich food with enhanced texture and good sensory properties seems to be a good strategy for designing satiating food.

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