Relation between food structure and induced satiety, macronutrient uptake and health

A structured literature study for DuPont Nutrition Biosciences Aps
Academic report from Department of Food Science

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Louise Margrethe Arildsen Jakobsen

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Data

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Introduction

Overweight (BMI ≥ 25 kg/m^2) and obesity (BMI ≥30 kg/m^2), are major risk factors of type-2-diabetes, cardiovascular disease, musculoskeletal disorders and some cancers (WHO, 2015). Obesity is a result of an imbalance in energy consumption (increased consumption of foods with high energy density and fat content) and energy expenditure (increasingly sedentary lifestyle) (WHO, 2015). Even a small excess of energy (<25 kcal/day) over a prolonged period of time can result in significant weigh gain (Wansink, 2007). Conversely, a sustained reduction in daily calorie consumption could prevent or reduce this long-term weight gain. In this respect, one approach is producing healthier, more satiating food products, whilst not compromising on palatability. This requires advanced research into the complex structure of foods, detailed knowledge about the processes occurring in the human digestive tract as well as how these factors influence the appetite response.

Several reviews have been published within the last ten years focusing on the effect of food structure in different aspects of nutrition. This includes micronutrient and polyphenol bioavailability (Palafox-Carlos et al., 2011; Parada and Aguilera, 2007; Sensoy, 2014) and macronutrient properties (Turgeon and Rioux, 2011), as well as more specifically, carbohydrates and glycemic response (Parada and Aguilera, 2011) and protein and colloidal aspects of digestion (Mackie and Macierzanka, 2010). At the same time, increasing research is performed on designing microstructures for health, including improved bioavailability of nutraceuticals (McClements and Xiao, 2014), microstructures for replacement of fat, sugar or salt (Norton et al., 2007) as well as targeted functionality in the upper gastrointestinal tract (Kaufmann and Palzer, 2011; Norton et al., 2014; Zúñiga and Troncoso, 2012). In this respect, emulsions have received great attention, since they can aid in controlling stability, digestion and absorption of lipophilic compounds (Golding and Wooster, 2010; McClements et al., 2008; van Aken, 2010). However, only two reviews have specifically focused on strategies to develop microstructures that enhance control of appetite or enhance satiety (Halford and Harrold, 2012; Lundin et al., 2008).

Culinary preparation of food for consumption such as boiling, frying or baking render the structure of whole foods either positively or negatively (Sensoy, 2014). Heating of proteins lead to unfolding of the structure, which increases access for proteolytic enzymes, protein digestion, bioavailability of amino acids and possible formation of bioactive peptides (Silva and Malcata, 2005). In addition, boiling, high pressure homogenization or grinding of plant tissue increases bioavailability of carotenoids, which are otherwise trapped within the chloroplasts and chromoplasts in the plant cells (Svelander et al., 2011; Tumuhimbise et al., 2009; Tydeman et al., 2010). On the other hand, heating can also damage the nutrients and bioactives in foods, such as minerals (Galan and Drago, 2014) or polyphenols (Parada and Aguilera, 2007; Sensoy, 2014).

In order to achieve successful innovation of more satiating products through changes in the food structure, one needs to obtain information about the processes involved in appetite regulation, which methods are available to measure the response and finally what knowledge is already available with regard to food structure and appetite. This is the aim of the current report, where a structured literature search was conducted in relevant databases (Web of Science and PubMed) to discover scientific publications within the abovementioned areas. The focus was on processes occurring in the upper gastrointestinal tract (oral cavity, oesophagus, and stomach, small intestine, including the duodenum, jejunum, and ileum).

The first chapter of this report will define key concepts related to appetite. The second chapter gives an overview of the different methodologies used to measure appetite responses, presented in tables in order to facilitate quick overview. The third chapter provides a presentation of the nutrikinetic approach for measuring responses to bioactive food components. Then, in chapter four the emphasis is on the microstructural differences within the different macronutrients that affect the satiating response. In chapter five, bioactive compounds with appetite altering effects are presented. Finally, a conclusion and thoughts for future work is presented in chapter six.

1.0 Appetite

In respect to the time-dependent regulation of food intake, two concepts are important to define: satiation and satiety (Benelam, 2009; de Graaf et al., 2004; Halford and Harrold, 2012):

- **Satiation** is the process that leads to the termination of eating, which may be accompanied by a feeling of satisfaction
- **Satiety** is the feeling of fullness that persists after eating, potentially suppressing further energy intake until hunger returns

The sensation of appetite is a complex process interlinking physical (gastric distension), peripheral (hormones, circulating metabolites), and psychological (sensory-specific-satiety, fullness) processes (de Graaf et al., 2004), illustrated in Figure 1.

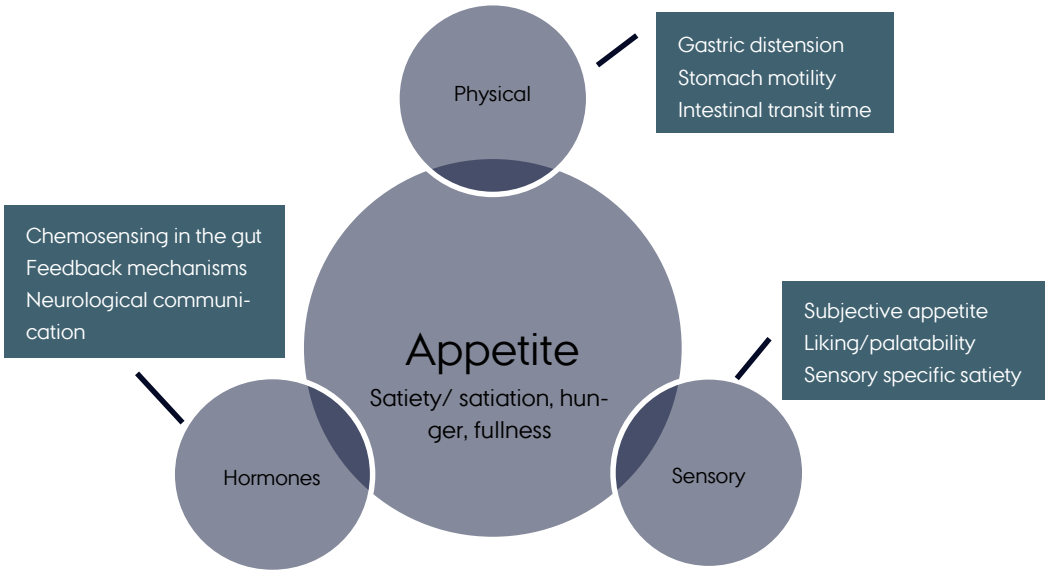

Figure 1 The interrelated components of appetite regulation.

The taste, palatability, texture and macronutrient content are all factors related to the food product that impact on appetite and hence the amount of food ingested in one sitting (satiation) and duration until the next meal (satiety). For example, decreasing the viscosity of a food product has been shown to increase food intake, probably through lower orosensory exposure and/or a shorter transit time within the oral cavity (Zijlstra et al., 2008). On the other hand, the effects of food viscosity on appetite hormones seem to be minor (Zijlstra et al., 2009).

Palatability (De Graaf et al., 1999; Yeomans, 1998) and sensory-specific satiety (satiation towards specific foods, textures, flavors or tastes) (De Graaf et al., 2004) have been found to decrease and increase satiety, respectively but also expected satiety (McCrickerd et al., 2014, 2012; Morell et al., 2014; Viskaal-van Dongen et al., 2011). However, in the current project, the focus is on the physical and hormonal factors that are involved in appetite regulation.

1.1/ Physicochemical conditions throughout the upper gastro-intestinal tract

When designing food products with targeted release or influence on specific mechanisms responsible for appetite, knowledge about the conditions in the gastrointestinal tract can be

helpful. Therefore, provided below, is a table overview of the conditions in each of the compartments of the upper digestive system.

*Table 1 Overview of the different relevant parameters in the compartments of the upper gastrointestinal tract. *site of action. References* (Allegancy Nutrition, 2008; Gropper et al., 2009; McClements et al., 2008)

			Small intestine	
	Mouth	Stomach	Duodenum	Jejunum/ileum
Enzymes*	α-amylase Proteases	Pepsin Lipases	Lipases Peptidases Esterases Trypsin/chymotrypsin Elastase/collagenase	Glycosidases α-amylase Alkaline phosphatase Retinyl ester hydrolase
Biofluids (composition)	Saliva (water, electrolytes, mucus, antibacterial and antiviral compounds)	Gastric juice (HCl, minerals, surface-active compounds)	Bile (bicarbonate, bile salts, phospholipids)	
pH	6.5-7.5	1.5-4.0	7.0-8.5	4.0-7.0
Duration food spends in location	Up to 1 minute	30 minutes – 3 hours	30-60 minutes	1-5 hours
Mechanisms related to satiety	Chewing/swallowing Psychological response to food	Distension of stomach Gastric motility Stomach emptying	Duodenal brake Emulsification	Ileal brake Uptake of nutrients

1.2/ Physiological appetite response

The interplay between nutrients in the gut and excreted hormones are particularly interesting, since some of the hormones are involved in negative feedback mechanisms, hereby regulating stomach motility and emptying, or glucose levels in circulation. This is referred to as chemosensing and include G-protein coupled receptors expressed in the intestinal mucosa, which are similar to those present in taste buds on the tongue. These receptors will not be covered in this report, but comprehensive reviews have been published by Reimann et al. (2012) and Janssen & Depoortere (2013). Several physiological biomarkers of satiation and satiety has been identified and reviewed by (De Graaf et al., 2004; Norton et al., 2014). In the following section, some of these appetite hormones that origin from tissue in the gastrointestinal tract will be presented. An overview of the hormones involved in appetite-regulation is presented in Figure 2.

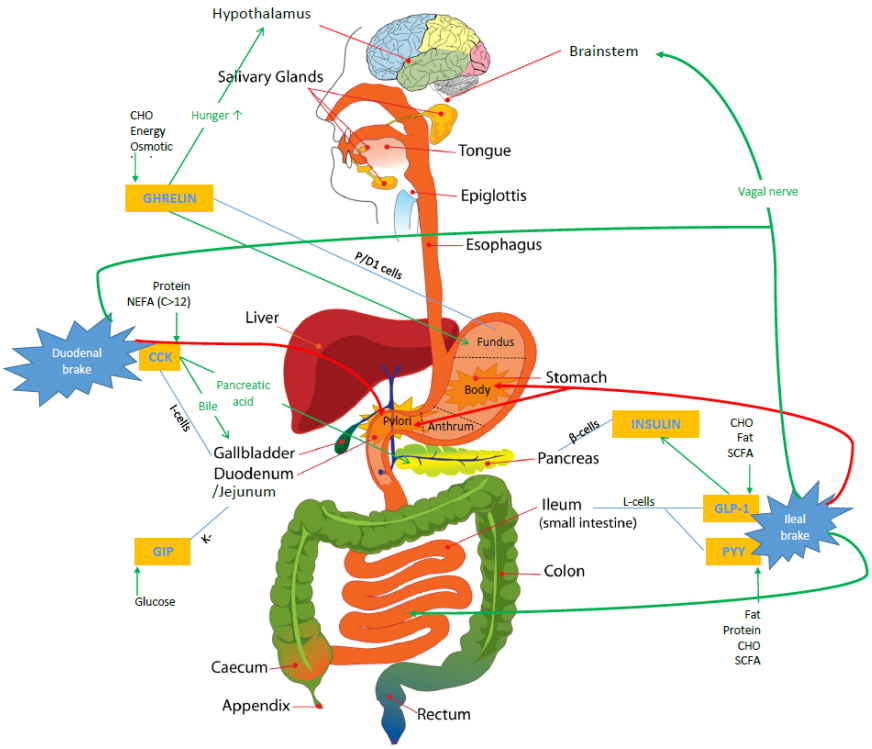

Figure 2 Appetite-regulating hormones: secretion and affection sites. Generated from reviews by (de Graaf et al., 2004; Halford and Harrold, 2012). CHO: carbohydrate, SCFA: short-chain fatty acids.

1.2.1/ Stomach

Starting in the stomach, ghrelin is excreted by P/D1 and other cells in the gastric fundus during fasting, leading to increased hunger and stomach motility. The circulating level decrease readily in response to ingestion of food due to stomach distension and nutrient sensing. Ghrelin is regarded as an excellent biomarker of satiety (low levels indicating satiety) (de Graaf et al., 2004).

1.2.2/ Duodenum and jejunum (duodenal/jejunal brake)

The duodenal brake is a feedback mechanism, where the presence of specific nutrients in the duodenum (very first part of the small intestine) result in the release of satiety hormones, which signals to the stomach to reduce gastric emptying.

GIP is secreted by duodenal and jejunal K-cells upon release of nutrient to the small intestine (energy in the form of glucose or fat). Although there is no convincing evidence that glucose-dependent-insulinotrophic polypeptide (GIP) is a biomarker of appetite, it is involved in the duodenal break mechanism, thus representing one of the feedback mechanism from the small intestine to the stomach. Furthermore, GIP acts insulinotrophic, when high amounts of glucose is present in the duodenum.

Another hormone that is secreted in response to nutrients (long chain fatty acids and amino acids) in the duodenum is cholecystokinin (CCK) from the duodenal I-cells. CCK is a biomarker of satiation, but in order to exert the appetite-suppressing effect, a full stomach (4-500 mL) is a necessity. The amino acid sequence of the CCK is very similar to gastrin, thus representing a problem with cross-reactivity with antibodies during quantitative assessment.

1.2.3/ Ileum (ileal brake)

In the distal small intestine, another feedback mechanism exist, specifically the ileal brake, which has been suggested to be more potent in regulating intestinal transit compared to the duodenal/jejunal brake (Van Citters and Lin, 2006). The ileal brake slows down gastric emptying and duodeno-jejunal motility, but might only rarely be activated following a meal due to nutrients not reaching the distal location, but rather being absorbed in the proximal intestine (Shin et al., 2013).

One of the best markers of satiation is glucagon-like-peptide 1 (GLP-1), which is secreted by ileal L-cells in response to presence of nutrients (especially carbohydrates or fat) in the ileum. GLP-1 is an incretin hormone, meaning the release is glucose dependent and stimulates secretion of insulin by the pancreatic β-cells ultimately lowering blood glucose levels (de Graaf et al., 2004). The biologically active form is GLP-$1_{(7\text{-}36)}$, however this is rapidly degraded by the enzyme dipeptidyl peptidase IV to the inactive GLP-$1_{(9\text{-}36\ amide)}$.

Peptide YY (PYY) is another hormone that is secreted by the L-cells in ileum and colon in response to carbohydrates (glucose), fat and protein. The active form of PYY is $PYY_{(3\text{-}36}$, which acts directly on the Y2 receptor in the hypothalamus, hereby inhibiting the secretion of neuropeptide Y, which normally stimulates appetite. As such, it is a causal agent in the satiety cascade, but data in this area is still scarce (de Graaf et al., 2004).

The ileal brake was identified by ileal perfusion with lipids, which seem to have the strongest impact on the response, but carbohydrates and protein are also effective (Maljaards et al., 2010; Van Citters and Lin, 2006). Although Shin et al. (Shin et al., 2013) stated that there is limited evidence of a causal relationship between ileal brake activation and reduced food intake, a recent study showed exactly this. Activation of the ileal brake in response to ileal perfusion of lipid (safflower oil), carbohydrate (sucrose) and protein (casein) reduced food intake and increased CCK and PYY and was correlated to delays in gastric emptying and intestinal transit (although the latter was statistically non-significant) (van Avesaat et al., 2014). However, unexpectedly, no differences in GLP-1 was found (van Avesaat et al., 2014).

2.0 Methodologies in appetite studies

Food consumption leads to stomach distension, resulting in a sensation of fullness. The effect of a food component on appetite is often assessed in a preload study by measuring subjectively rated appetite sensations and energy intake at an *ad libitum* meal. Furthermore, some studies include blood samples to assess changes in hormone levels that regulate stomach emptying. Novel methods for assessing the effect of food products is gaining impact, including brain imaging (de Graaf et al., 2004), metabolomics (Stanstrup et al., 2014) and nutrikinetics (Motilva et al., 2015; van Duynhoven et al., 2012). In the following section, examples of measurements used to assess different aspects of satiation and satiety are presented.

2.1/ Human measures of appetite

Methods have been developed to assess the subjective feelings of appetite. However, when asked, subjects are forced to think about feelings that normally function subconsciously, which probably affects the answer. Food intake, on the other hand, might give a more objective measure of appetite, if detection of amount and choice, are blinded to the test subjects.

Name of method ***(Reference)***	**Description**	**Outcome variables**	**Variable construction**
Visual analog scales (VAS) *(Flint et al., 2000)*	10 cm line scale Extremes anchored at each end	Subjective appetite Satiety Fullness Hunger Prospective consumption Desire to eat sweet/ savory etc.	Time-dependent development Incremental area under curve Composite appetite score
Ad libitum meal *(De Graaf et al., 2004)* *(Halford and Harrold, 2012)*	Buffet-type menu or standardized food item	Food intake Weight of food Time until meal request	Energy intake Macronutrient composition Food choice
Body temperature *(de Graaf et al., 2004)*	Infrared scanning of temperature near liver as a measure of kinetic activity	Temperature (°C)	Changes in temperature
Diet-induced thermogenesis *(de Graaf et al., 2004)*	Indirect calorimetry (respiration chambers or ventilated hoods).	A higher temperature is related to lower hunger ratings.	-
Self-reported food intake *(Halford and Harrold, 2012)*	Different approaches: food diaries, short-term recalls or food frequency questionnaires	Food intake Energy intake Food choice	Requires large population because it lacks precision. Underreporting is an issue.

2.2/ Small metabolite release

Small molecules can induce a satiation response, e.g. through actions on insulin secretion. In addition, the kinetics of release give information about the time the food component is present in the stomach and intestine as well as the rate of digestion. In general, a fast rise in plasma concentrations of nutrients might indicate short-term satiety effects, whilst slower release might be related to a more prolonged feeling of satiety.

Name of method *(Reference)*	**Description**	**Relation to appetite regulation**
Glycemic index *(De Graaf et al., 2004)* (Parada and Aguilera, 2011)	Glycemic index = postprandial glucose response after consumption of a standard amount of carbohydrate from a test food in comparison with the postprandial responses after consumption of a control food (glucose or white bread. Parameters: AUC, peak glucose concentration, and time	Decline in glucose is a marker of satiety (meal initiation). Related to insulin and incretin peptides and transient declines in blood glucose and meal requests Slightly, but not consistent, lower hunger levels have been reported with higher glucose concentrations.
Protein digestibility corrected amino acid score *(Kannan et al., 2001)*	True protein digestibility (TPD): nitrogen excreted in feces subtracted from amount ingested, expressed as percentage of nitrogen intake Amino acid ratio: mg of essential AA in 1 g of test product protein per mg of the same amino acid in 1 g of reference protein. Score is based on amount of the most limiting AA (requirements). Protein digestibility-corrected amino acids score (PDCAAS): obtained by multiplying TPD by most limiting AA.	Fast digestion of protein releases AA to plasma, affecting satiation inducing hormones.
Short-chain fatty acids *(Reimer et al., 2012)*	Short-chain fatty acids (SCFA) are produced in the colon as a product of fermentation of dietary fiber. They can be identified using NMR metabolomics techniques.	SCFA are indirect measures of satiety, as they might stimulate expression of PYY and GLP-1. More data on this relation are needed.
Breath hydrogen *Mentioned in (Smith et al., 2012)*	Marker of fermentation of dietary fiber in gut.	SCFA from microflora fermentation has been found to affect BG response to meals + GLP-1.

2.3/ Measures of gastric and intestinal transit/distension

Stomach distension contributes to satiation and satiety. Studies have shown that a distension of the stomach by >400 mL reduces food intake (de Graaf et al., 2004), leading to satiation. Furthermore, a reduced stomach capacity has been observed in obese subjects in response to a restricted diet (Geliebter, 2001). Slowing of gastric emptying prolongs this period and hence is a useful indirect measure of satiety. In addition, intestinal transit time might be interesting considering the feedback mechanisms on gastric emptying occurring in response to chemosensing of nutrients in the gut. Other methods that have been proposed, but have not been applied in such a wide extent is videofluourography and ultrasound for measuring oral processing of food (Norton et al., 2014).

Name of method ***(Reference)***	**Description**	**Advantages/limitations**	**Relation to appetite regulation**
Gastric balloon *(De Graaf et al., 2004)* *(Geliebter, 2001)*	Gastric balloon inserted into stomach and filled with saline solution (100 mL/min, 1 min pauses) Subjective measure: abdominal discomfort on 1-10 scale Objective measure: volume required to produce a 5 cm rise in water pressure	Accurate determination of stomach capacity/Uncomfortable for test subject	Indirect measure of gastric distension
Magnetic resonance imaging (MRI) *(De Graaf et al., 2004)* *(Norton et al., 2014)*	Gamma radiation camera measures of radioactive isotopes in the stomach or intestine of radioactive isotopes mixed with ingested food	Qualitative output of transit through stomach and intestine/Expensive + supine position during measurement	Indirect measure of gastric distension, direct measure of gastric emptying
Paracetamol absorption test *Mentioned in (Georg Jensen et al., 2012) and (Zhu et al., 2013)*	Paracetamol is not absorbed in the stomach, but from the small intestine where it passes to the bloodstream. Parameters of absorption: peak plasma conc. (C_{max}), time to reach C_{max} (t_{max}), area under the time vs conc. curve (AUC_t).	Easy administration (can be incorporated into food or given as tablet)/not an optimal measure of gastric emptying, as it might bind to gel matrix in stomach or alter gastric distension	Indirect measure of gastric emptying rate

2.4/ Neuroimaging techniques

Neuroimaging techniques are used to investigate the brain responses to food intake. Information on the relation between blood flow in specific areas of the brain and appetite sensations can be interesting, but limitations include the fact that measurements are not easily carried out and the techniques is expensive and not widely available. Finally, the unnatural position of the subject might influence the results.

Name of method ***(Reference)***	**Description**	**Advantages/Limitations**	**Relation to appetite**
Positron-emitting tomography (PET) *(De Graaf et al., 2004)*	Radioisotope ^{15}O incorporated into water molecules, administered intravenously, follow the cerebral blood flow (CBF). PET scan image Subtraction of an experiment image from a baseline image yields an image of the changes in regional CBF (rCBF).	Neural correlates of the pleasantness of foods and changes in rated pleasantness of foods during meal consumption can be reliably detected in the brain/expensive methods and resolution is not yet optimal to follow processes detailed	Sensory-specific satiety Food intake → hypothalamus Meal initiation/satiety → prefrontal cortex Hunger, extreme fullness, sensory-specific satiety, Liking → amygdala + medial orbifrontal cortex Aversion → lateral orbifrontal cortex, left amygdala
Functional magnetic resonance imaging (fMRI) *(De Graaf et al., 2004) Mentioned in* (Douglas et al., 2015; Leidy et al., 2015)	Strong magnetic field, magnetizes the tissue, radiofrequency pulses excite the protons. Blood oxygen level-dependent signal (BOLD) used to measure deoxygenated hemoglobin. Increased blood flow at the site of activation leads to decreased concentration of oxygenated hemoglobin.		

2.5/ Hormones in gastric and intestinal transit/distension

Several hormones regulate appetite sensations following a meal and they can be used to indicate the impact of food on satiation/satiety. The concentration of hormones in the blood can be followed as fixed-time measures (max concentration or time to reach max) or area under the time-concentration curve (AUC). Some hormones released from duodenum and ileum delay gastric emptying through regulation of pyloric pressure, stomach motility, or stomach muscle relaxation. The so-called duodenal or ileal brakes hereby ensure a constant, manageable influx of nutrients from stomach to the gut (Van Citters and Lin, 2006). De Graaf states that PYY is CCK is likely to have effects in the physiological range, hereby representing a better indicator of satiation when compared to GLP-1 and PYY, which show effects at supra-physiological ranges, potentially complicating interpretation of the relation to satiation (Mars et al., 2012).

Hormone ***(Reference)***	**Active/inactive forms + measurement issues**	**Within meal (satiation) or between meal biomarker (satiety)/Causality**
Ghrelin *(de Graaf et al., 2004)*	Increased 4.5 times in Praeder Willis syndrome (hyperphagia = overeating) compared to obese.	Excellent biomarker of **satiety**/ **causal** factor in appetite
Glucose-dependent-insulinotropic polypeptide (GIP) *(de Graaf et al., 2004)*	Too few studies on appetite and GIP.	Weak biomarker of satiety/**causal** factor in appetite
Glucagon-like-peptide 1 (GLP-1) *(de Graaf et al., 2004)*	Reduces appetite $GLP\text{-}1_{(7\text{-}36\ amide)}$: biologically active form $GLP\text{-}1_{(9\text{-}36\ amide)}$: inactive Rapidly degraded by enzyme (dipeptidyl peptidase IV) → continuous infusion prolongs appetite suppressing effects. $GLP\text{-}1_{total}$: active + inactive Consistenty effects on normal, obese, diabetic subjects	Feasible, valid, reproducible, sensitive and specific biomarker of **satiation/causal** factor in appetite
Cholecystokinin (CCK) *(de Graaf et al., 2004)*	Technical difficulty in quantitative assessment in blood. AA sequence similar to gastrin → cross-reactivity with antibodies	Biomarker of **satiation**/ **causal** factor in appetite
Gastrin-releasing peptide (GRP) *(de Graaf et al., 2004)*	Suppress appetite Limited research on humans Lower sensitivity of obese subjects than of lean subjects	Interesting biomarker of **satiation**/needs more studies to establish causality
Peptide YY (PYY) *(de Graaf et al., 2004)*	Active form $PYY_{(3\text{-}36)}$ PYY_{total} Total PYY lower in obese subjects (negatively correlated to BMI).	Interesting biomarker of **satiation**/needs more studies to establish causality

3.0 Nutrikinetics and nutridynamics

Assessing the impact of a bioactive compound in a food product on the human organism is a challenging task, because foods are complex and often the food matrix and interactions between other components of the diet influence the results and limit the establishment of an exposure-effect relationship (van Duynhoven et al., 2010). In addition, there is an increasing recognition of the role of the gut microbiome altering the metabolism of food components. Recently it was shown that the postprandial glycemic response is not only related to the carbohydrate (amount and type) of the food, but also varies according to parameters related to the individual (Zeevi et al., 2015). When evaluating the impact of a food containing functional compounds, it is important to consider the bioavailability and bioaccesibility of the compound. The food matrix influences these parameters – and as such to maximize the availability and accessibility of the compound, manipulation of the matrix by either degrading the natural matrix or constructing a matrix to protect the active ingredients might be good strategies. However, insight into effects of the food matrix on the fate of individual compounds is essential.

Nutrikinetics and nutridynamics represent promising approaches to studying these complexities. In general the approach has been recommended as a strategy for development of bioactive compounds (Gil et al., 2015). Examples of application of the nutrikinetic approach include investigation of the effects of polyphenols from tea (van Velzen et al., 2014, 2009) and administration of fish oil capsules with gastric acid resistant coating (Schneider et al., 2011). According to van Duynhoven et al. (2012), nutrikinetics is *an application area of pharmacokinetics that studies the absorption, distribution, metabolism and excretion (ADME) of food compounds or dietary supplements within the human superorganism, including the interaction between host metabolome and the gut microbiome.* On the other hand, nutridynamics is defined as *the study of how food acts on living organisms, including dose-effect responses of dietary interventions* (de Vos et al., 2006).The nutrikinetic approach originates from pharmacology, where pharmacokinetics explore the dose-exposure effect and pharmacodynamics explore the exposure-response effect (Motilva et al., 2015).

Kinetic models based on compartments are useful in order to get an overview of the processes occurring during metabolism of an isolated bioactive compound or a bioactive compound embedded within the food matrix (van Duynhoven et al., 2012). These models include the following stages: consumption, gut luminal events, absorption and distribution (Motilva et al., 2015; van Duynhoven et al., 2012). A very comprehensive model is presented in Figure 3.

Urine and blood are most commonly included in metabolic profiles for kinetic studies. Urine gives a wide variety of information e.g. 24 h collections give information about metabolites generated in small and large intestine (van Duynhoven et al., 2012). Blood drawn at different time-points can provide information about the kinetics of the bioactive compound, i.e. when it appears in the blood stream, in what concentrations, and the rate of clearance (metabolism or cellular uptake) (van Duynhoven et al., 2012). In addition, fecal samples contribute with information about the concentration of the bioactive that is not utilized, but simply excreted. Construction of nutrikinetic models are based on selected, relevant markers of intake, measured in blood or urine. The kinetics are adapted to account for dietary background baseline levels assessed in the placebo group, hereby overcoming potentially high baseline values.

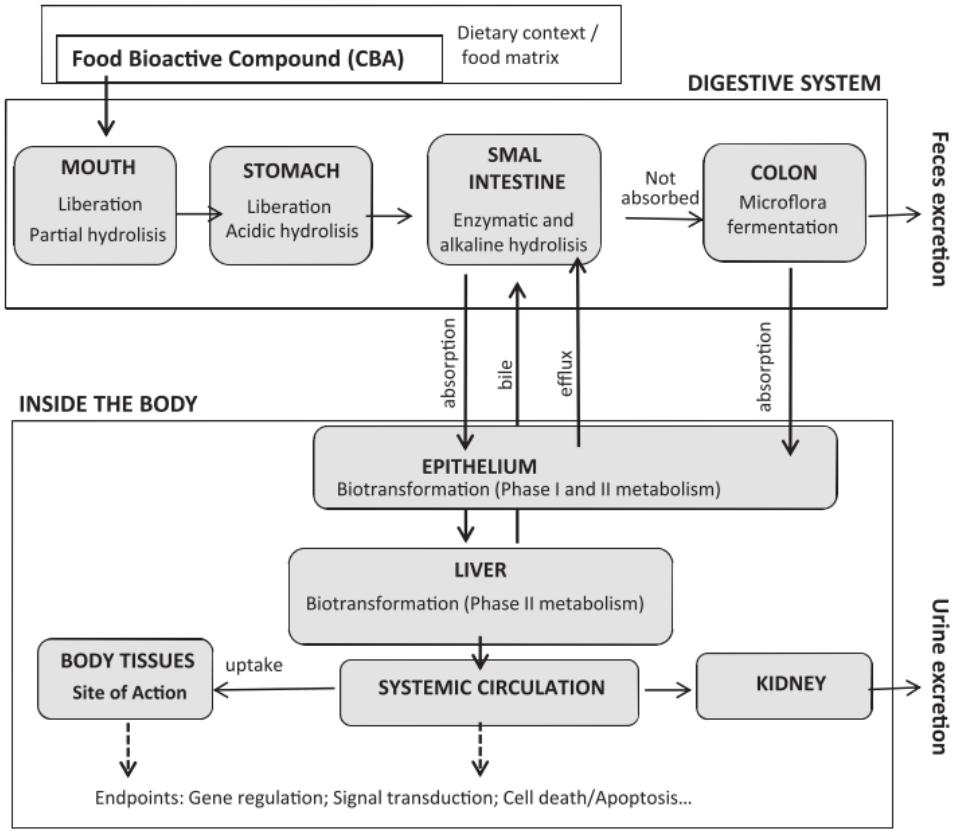

Figure 3 "The journey of food bioactive compounds from food through the human body" reprinted from Motilva et al. (2015)

The metabolic profiles are obtained using different instruments. High-field NMR is suitable for global metabolic profiling requiring only limited sample preparation (Want et al., 2005; Wishart, 2008). However, the method is relatively insensitive (Want et al., 2005; Wishart, 2008). Untargeted LC-MS is more sensitive, but identification of relevant metabolites is not comprehensive, although constantly improving (Want et al., 2005; Wishart, 2008).

Nutrikinetics can be applied in different stages of the development process of functional foods: in vitro test, preclinical animal testing and finally human clinical trials (Motilva et al., 2015). The method considers the compositional complexity of dietary ingredients, background diet and inter-individual variation and integrates study design, metabolic profiling and variable selection (van Duynhoven et al., 2012).

4.0 Macronutrient composition and impact on satiety and nutrient release

The overall content of carbohydrates, dietary fiber, protein and fat affect the satiating potential of food products. Dietary fiber and protein seem to represent the two most potent macronutrients with respect to inducing a satiety response.

Dietary fibers has been associated to a lower body weight (Clark and Slavin, 2013) and a decrease in short-term energy intake was found after consumption of a dextrin-enriched beverage (Monsivais et al., 2011) suggesting a role of dietary fiber intake and weight management. Furthermore, Ingerslev et al., (2014) found a diet containing the dietary fiber arabinoxylan to increase short-chain fatty acid (SCFA) absorption and reduce insulin secretion, when compared to a resistant starch and a low-fiber diet, suggesting a positive role of colonic arabinoxylan fermentation in healthy insulin economy.

Protein has also received a lot of attention in relation to inducing satiety, thus affecting weight reduction and management (Veldhorst et al., 2008). Specifically, energy from protein was found to be more satiating (subjectively measured appetite) than energy from carbohydrates (Benelam, 2009; Poppitt et al., 1998), fat (Benelam, 2009; Poppitt et al., 1998) and alcohol (Poppitt et al., 1998). A high protein diet also affected appetite hormones (GLP-1, PYY, ghrelin) more than carbohydrates (Belza et al., 2013). Furthermore, protein infusion in rats increased the inter-meal interval, and decreased the size of proceeding meal (Burton-Freeman et al., 1997). Finally, protein has beneficial impact on satiety, thermogenesis, maintenance or accretion of fat free mass (Paddon-Jones et al., 2008). A study by Smith et al. (2012), showed that the protein fraction, rather than the fiber fraction, of yellow peas is responsible for the suppression of food intake and decrease in the glycemic response observed after yellow pea consumption. However, discrepancies occur, as some studies give other results. For example, in a study on rats, a high fiber diet has shown to increase the plasma and intestinal mRNA levels of anorexigenic hormones PYY and GLP-1, compared to a high protein or control diet, possibly due to a higher production of short-chain fatty acids in the colon (Reimer et al., 2012). This was furthermore associated to a lower body weight and energy intake.

Therefore, individual macronutrients have very differing and complex microstructures, which also influences the properties of the macronutrient structure on satiation, satiety and nutrient response upon ingestion. The following section will review some of the microstructures of macronutrients with effects on satiety.

4.1/ Proteins – importance of amino acid composition and digestibility

Proteins are well-known for their satiating properties. However, there seems to be pronounced differences between proteins from different sources in the impact on satiety. This area is increasingly being studied and some of the relevant intervention studies are presented in Table 2 and discussed in the following.

Protein-induced satiety occurs when minimal protein requirements are met so that a positive protein balance is obtained by ingestion of the protein-containing meal or food product (Gilbert et al., 2011). The recommended unit for measuring protein intake is gram protein per kilogram body weight per day, rather than expressing it as energy percent (Gilbert et al., 2011). Recommendations for protein intake stretches from a minimal level of 0.8 g/kg per day and to an acceptable upper level of 2.5 g/kg per day (Gilbert et al., 2011).

Table 2 Human studies investigating the effect of consuming different protein sources and effect on ap-petite. VAS: visual analog scales. EI: energy intake, wk: week, d: day, E%: energy percentage, BW: body weight, BMI: body mass index, fMRI: functional magnetic resonance imaging, CCK: cholecystokinin, PYY: peptide YY, GIP: gastric inhibitory peptide, GLP-1: glucogen-like peptide 1. Table is continued on next page.

Author (year) ***Title***	Belza et al. (2013) *"Contribution of gastroenteropancreatic appetite hormones to protein-induced satiety"*	Douglas et al. (2015) *"Consuming beef vs. soy protein has little effect on appetite, satiety, and food intake in healthy adults"*
Study participants	25 young men Lean (n=13) BMI: 19.1-24.8, obese (n=12) BMI: 25.2-37	21 subjects Age: 23.1 ± 1 year BMI: 23.4 ± 0.6 kg/m^2
Active component	NP: normal protein (14 E%) MHP: medium-high protein (25 E%) HP: high protein (50 E%)	BEEF: lean ground meat (24g protein, 1g fiber) SOY: textured soy protein concentrate (14g protein, 5g fiber)
Food structure	Isocaloric protein meals (pork, rice and mushroom patés flavored with thyme)	1) Nutrient matched (24g protein, 2g fiber) pasta lunch meal , 2) Serving size matched lunch sandwich with patty of BEEF or SOY
Study design	3-way crossover, randomized, double-blind study, 4 wk washout, 3 separate occasions Morning (t=0): serving of test meal t=240 min: *ad libitum* lunch, pizza slices with ham and cheese	Randomized, double-blind, crossover design, acute study, 7-14 d washout, 2 testing days per lunch treatment Morning (t=0): breakfast Midday (11-13): lunch meals (400 kcal) Afternoon (t~250 min): *ad libitum* dinner served upon request
Outcome measures	VAS: hunger, satiety, prospective consumption, fullness, desire for something sweet/salty/fat/ meat and fish. Palatability, EI. Biochemical: insulin, glucose, GLP-1, GIP, glucagon, PYY, total ghrelin, CCK	1) VAS: hunger, fullness Blood: GLP-1, PYY. *Ad libitum* buffet: initiation, amount consumed, type of foods chosen. Dietary recall for evening energy intake 2) Food-cue stimulated fMRI brain scans
Results	Satiety: HP (+16%)>MHP (+ 7%)>NP Fullness: HP (+19 %)>MHP (+ 6 %)>NP Hunger: HP (+25 %)>MHP (+15 %)>NP Prospective consumption: HP (+26 %) >MHP (+13 %)>NP Composite appetite score: HP (+17 %)>MHP (8 %)>NP Desires for sweet, fat, salty or meat: HP<MHP=NP IE: not sign. Palatability: NP (23 %) >MHP=NP GLP-1: HP (+20 %)>MHP (+10 %)>NP PYY: HP (+14 %)>MHP (+7 %)>NP Glucagon: HP (+116%)>MHP (47 %)>NP No dose-dependent effect on: GIP, cholecystokinin, total ghrelin, insulin, glucose	Eating initiation: not sign. VAS: not sign. Hormonal responses: not sign. fMRI neural activation: No difference in nutrient matched lunches. Post-lunch brain activity in response to stimuli was greater in the anterior cingulate and insula after SOY (+7±9%, -7±10%) compared to BEEF (-22±6%, -30±6%) (serving size matched). EI: not sign

Table 2 continued Human studies investigating the effect of consuming different protein sources and effect on ap-petite. VAS: visual analog scales. EI: energy intake, wk: week, d: day, E%: energy percentage, BW: body weight, BMI: body mass index, fMRI: functional magnetic resonance imaging, CCK: cholecystokinin, PYY: peptide YY, GIP: gastric inhibitory peptide, GLP-1: glucogenlike peptide 1.

Author (year) ***Title***	Juvonen (2011) *"Structure modification of a milk protein-based model food affects postprandial intestinal peptide release and fullness in healthy young men"*	Tehavorgar et al. (2014) *"Whey protein preloads are more beneficial than soy protein preloads in regulating appetite, calorie intake, anthropometry, and body composition of overweight and obese men"*
Study participants	8 healthy male subjects Age: 24.0 ± 0.82 years BMI: 23.3 ± 0.5 kg/m^2	45 men (excl. 7 dropouts) Age: WPI: 39.4±6.9 years, SPI: 38.8±8.8 years BMI: WPI: 32.1±3.2 kg/m^2, SPI: BMI: 32.1 ±2.7 kg/m^2
Active component	Cas: casein (solution) → high viscious Cas-TG: transglutaminase cross-linked casein (gel) → rigid gel WH: whey (solution) → low viscious	WPI: whey protein concentrate, 67.5g SPI: soy protein isolate, 60g
Food structure	Milk protein-based test products (sweetener, aroma, water) with protein	Sachet with protein, strawberry flavor and sucralose to be dissolved in 500 mL water (final protein content in beverage: WPI~13% and SPI~12%).
Study design	Randomized, repeated-measures, cross-over design, 2d washout Morning (t=0): test product consumption + 400 mL water Blood and VAS recorded during next 240 min.	Randomized 12 wk intervention study, 7 visits in total (before intervention and every 2 wk after start) Daily: dissolve one sachet in 500 mL water and drink 30 min prior to afternoon meal
Outcome measures	VAS: hunger, satiety, desire to eat, fullness and thirst + pleasantness Biochemical: GLP-1, PYY, CCK, glucose, insulin	Dietary intake (24h dietary recall) Physical activity (international PA questionnaire) VAS BW, body fat (%), lean mass (kg), waist circumference (WC)
Results	Mean time of test product consumption: Cas = 6.0 ± 1.2 min, Cas-TG = 20.3 ± 2.9 min, WH = 2.5 ± 0.7 min Insulin: WH > Cas=Cas-TG (15 min). WH=Cas >Cas-TG (30 min) PYY: only small variations CCK: Cas=WH>Cas-TG GLP-1: not sign. Palatability: Cas-TG<Cas=WH Fullness: Cas-TG>Cas=WH	Nutrient intake not sign. Calorie, protein and CHO intake decreased in both groups as cons. of intervention, but not sign. different. Appetite: WPC<SPI EI: WPC<SPI BW: WPC<SPI BMI: WPC<SPI WC: WPC<SPI Body fat %: WPC<SPI Lean mass: WPC>SPI

One can distinguish between different sources of proteins, such as animal (meat and dairy) and vegetable proteins. These proteins are integral components embedded into the complex structures of whole foods. Besides these mixed structures, an increasing amount of studies include pure proteins to investigate their functionality. This includes whey, casein, soy protein isolate, wheat proteins (gluten), egg albumin and many more, as well as hydrolysates thereof.

Animal sources (milk, meat, egg) make up complete sources of proteins, as they provide all nine essential amino acids (valine, leucine, isoleucine, methionine, tryptophan, phenylalanine, threonine, lysine and histidine). On the other hand, plant proteins and gelatin are incomplete protein sources as they are deficient or low in specific essential amino acids. Plants especially lack lysine but also threonine, and sulphur-containing methionine and cysteine (Gilbert et al., 2011). However, an essential amino acid profile equivalent to, or greater than, animal proteins can be obtained by combining different sources of plant proteins, e.g. grains and legumes (Gilbert et al., 2011).

High protein diets have been shown to induce satiety to a higher degree than normal protein diets (Veldhorst et al., 2008). Different mechanisms trigger protein-induced satiety, including effects on hormones of satiety (GLP-1, CCK, PYY, insulin) or hunger (ghrelin), circulating amino acid levels, which contribute to postprandial satiety perception and finally gluconeogenesis that probably regulates food intake (Gilbert et al., 2011; Veldhorst et al., 2008). Additionally, proteins lead to an increased energy expenditure (24 h diet-induced energy expenditure), which might explain the relation between high protein consumption and improved weight management (Paddon-Jones et al., 2008; Veldhorst et al., 2008). These mechanisms are complex, but in general, the responses reflect the quality (digestion rate and amino acid composition) and quantity of the ingested protein (Gilbert et al., 2011; Veldhorst et al., 2008).

A more in-depth review of the details regarding protein consumption and satiety will be presented in the following sections.

4.1.1/ Effect of protein source on subjective satiety

In the studies included in the review by Gilbert et al. (2011), it seems that whey protein constitutes the most satiating protein source. This was supported by a 12-week intervention study on obese men, where a whey protein concentrate preload beverage resulted in significantly decreased appetite and calorie intake than a soy protein isolate beverage (Tahavorgar et al., 2014). Whey protein concentrate also had a stronger impact on reducing body weight, BMI, waist circumference, body fat and increasing lean body mass compared to a soy protein isolate beverage (Tahavorgar et al., 2014).

4.1.2/ Effect of protein source on satiety hormones

Protein in the gut affects the CCK secretion of duodenal I-cells as well as PYY secretion from ileal L-cells, leading to sensations of satiety and feedback mechanisms on gastric emptying and motility. Furthermore, circulating levels of amino acids affects insulin secretion, which also leads to satiation. However, very little data exists on the effect of specific protein sources on the hormonal response. Some studies indicate that milk (high in isoleucine and leucine) stimulate GLP-1 secretion, and furthermore, whey, soy and gluten have shown to extend the postprandial elevation of GLP-1. CCK seems to be does-dependently affected by protein intake in general, whilst the specific effect on PYY needs more investigation (Gilbert et al., 2011).

Meals consisting primarily of proteins as well as meals resulting in high plasma concentration of branched chain amino acids increase the postprandial insulin response. However, when proteins are ingested together with carbohydrate, the result is a synergistic insulin release (Gilbert et al., 2011). Dairy proteins, and especially whey, seems to result in higher insulin responses compared to other protein sources, such as beef, turkey, fish, egg and soy (Gilbert et al., 2011). However, a high insulin response is not necessarily desirable, since insulin promotes the stor-

age of fat as well as impeding fat oxidation. Hence, some researchers suggest, that insulinotrophic agents should be limited in order to improve body weight regulation (Gilbert et al., 2011). A recent study by Douglas et al. (2015) did not find differences in hormone levels (GLP-1 and PYY), subjective appetite, meal initiation or fMRI brain scans in response to macronutrient and fiber matched lunches differing only in the protein source (beef or soy). Serving size matched lunches of beef or soy (with differing protein and fiber content) could indicate, that consuming beef results in a lower GLP-1 and hunger response during the entire postprandial period, although not statistically significant. They hypothesize that this difference could be due to the synergistic effect of soy protein and fiber in the soy lunch to induce a similar satiety response as a protein meal.

4.1.3/ Amino acid composition

The impact of circulating amino acid concentrations on appetite regulation is described by Gilbert et al. (2011). Specifically, they mention the aminostatic appetite regulation hypothesis as the underlying reason for the higher satiating impact of some proteins. Interestingly, higher satiety response to ingesting incomplete as compared to complete proteins has been found e.g. in response to pea protein versus milk protein and gelatin versus casein (Gilbert et al., 2011). After ingestion, digestion and absorption, the amino acids are transported to the liver, where they take part in different reactions, depending on the body's need: transamination and recirculation, splanchnic protein synthesis or oxidation and elimination in urea (Gilbert et al., 2011). High quality protein, characterized by a sufficient amount of readily digestible essential amino acids, result in utilization of the amino acids for protein synthesis, and hereby an efficient removal of amino acids from the blood. On the other hand, non-essential amino acids disrupt the protein synthesis process and hereby, the concentration of circulating amino acids increase, mediating the satiety response (Gilbert et al., 2011). In addition, the group of branched-chain amino acids (valine, leucine and isoleucine) are released to the circulation in the same amount as ingested, whereas for other amino acids only about 50 % reach circulation (Gilbert et al., 2011). As mentioned previously, circulating levels of branched-chain amino acids can increase the postprandial insulin response and in this way induce satiety (Gilbert et al., 2011).

Individual amino acids also have the potential to modulate appetite sensations. In this respect, tryptophan is a precursor for the neurotransmitter serotonin (suppress appetite), tyrosine can be converted into dopamine and norepinephrine (increase appetite), histidine to histamine (suppress appetite) and finally leucine (high in whey) has a direct effect on the hypothalamus (suppress appetite) as well as stimulating leptin secretion (Gilbert et al., 2011). An overview of the amino acid composition of selected foods are presented in Table 3.

4.1.4/ Protein digestibility

Digestibility of proteins influence the postprandial amino acid bioavailability. Animal sources generally represent the highest digestibility, but also wheat protein, peanuts and soy protein isolate show high digestibility (Gilbert et al., 2011). On the other hand, digestibility of e.g. plant proteins is generally low, leading to a relatively low level of circulating amino acids (Gilbert et al., 2011). Observations such as a slower digestion rate for fish protein compared to beef and chicken and a faster digestion of soy proteins compared to milk proteins (Gilbert et al., 2011) indicate that the structure of proteins affects their digestion rate.

Table 3 Amino acid composition of selected protein sources. Specified in mg/100g. E: essential amino acid, B: branched chain amino acid. Reference database: www.foodcomp.dk.

Product	Casein	Whey	Soy beans	Lentils	Beef	Turkey	Tuna	Egg
Specification	*Sodium caseinate*	*Powder*	*Dried*	*Dried*	*Lean (<5% fat), raw*	*Raw*	*In water, canned*	*Whole, raw*
Isoleucine (E, B)	4100	710	1600	1100	1000	980	1300	750
Leucine (E,B)	6900	1200	2800	2000	1700	1500	1900	1100
Lysine (E)	5400	1000	2300	1900	1800	1900	2300	990
Methionine (E)	1100	240	450	210	560	560	730	440
Cysteine	1300	240	480	250	150	140	170	260
Phenylalanine (E)	4400	410	1800	1400	870	810	1000	710
Tyrosine	3500	370	1100	840	730	630	890	560
Threonine (E)	3500	810	1400	1000	940	880	1100	600
Tryptophan (E)	1300	200	460	250	230	220	280	180
Valine (E,B)	4300	690	1700	1300	1100	1200	1500	950
Arginine	6500	390	2600	2300	1300	1300	1400	830
Histidine (E)	2200	240	910	710	760	670	1300	320
Alanine	3600	610	1500	1100	1300	1200	1500	790
Asparagic acid	10100	1300	4200	3000	1900	1900	2300	1400
Glutamic acid	16300	2200	6700	4400	3100	2800	3200	1500
Glycine	3600	280	1500	1100	1100	1200	1100	460
Proline	4700	790	2000	1100	870	950	850	500
Serine	4100	630	1800	1400	870	840	970	990

Both the macro- and microstructure are important parameters influencing digestibility. Texture is a macrostructural property, and in this respect, proteins in solid structures are generally slower digestible than proteins in liquid form. Microstructure, as represented by differences in primary, secondary, tertiary and potentially quaternary structure of the proteins is more complex. However, one common example is the difference in the dairy protein fractions caseins and whey. In general, it seems that caseins are slowly digestible and give rise to a longer sensation of satiety, whilst whey is easily digestible, giving rise to a fast and more pronounced increase in plasma amino acids and short satiety sensations (Veldhorst et al., 2008). In this respect, the study by Juvonen et al. (2011) is quite interesting, because they investigate both the effect of macrostructure and microstructure of solutions of casein and whey, as well as transglutaminase cross-linked casein gel on subjective appetite and hormone response (GLP-1, PYY, CCK, insulin). They found a trend towards increased GLP-1 response after ingestion of the whey solution and suggested this to be mediated through inhibition of dipeptidyl peptidase IV, the enzyme responsible for degradation of GLP-1 (Juvonen et al., 2011). Cross-linking significantly attenuated insulin response and CCK release as well as ratings of fullness compared to the two liquid milk-protein solutions, which could be correlated to the rapid digestion and absorption of proteins from the liquid solutions (Juvonen et al., 2011).

Components of the diet can affect protein digestion rates. In a study investigating bioavailability of lacto-tripeptides with antihypertensive effects, increased systemic availability was found when incorporating the tripeptides into a protein matrix or a meal that contained casein hydrolyte (Ten Have et al., 2015). Furthermore, low protein quality and fiber in the meal increased

the systemic bioavailability of the tripeptides even more (Ten Have et al., 2015). However, previously carbohydrates, including fiber, and fat have been shown to delay absorption of peptides and amino acids (Gilbert et al., 2011).

Different approaches have been applied to dairy proteins in order to alter the digestibility. On one hand, hydrolysis of dairy (Stanstrup et al., 2014) or soy proteins (Hira et al., 2011) (hydrolysates) might improve digestibility, whilst on the other hand, cross-linking using transglutaminase (Buchert et al., 2010; Juvonen et al., 2011; Monogioudi et al., 2011) or tyrosinase (Monogioudi et al., 2011) increases the viscosity and possibly lowering digestibility. However, complete investigations accounting for the exact microstructural characteristics that lead to different properties with respect to digestibility are still lacking, especially on proteins other than those originating from milk.

4.1.5/ Energy expenditure

Protein induces strong thermogenic effects compared to the other macronutrients due to lack of effective storage for excess amino acids and an increase in the energy requiring processes occurring during the postprandial period to metabolize the protein (diet-induced thermogenesis). Amino acids differ in the efficacy of oxidation and hereby the heat production. This depends on the structure of the amino acids, e.g. amino groups, the removal of which requires 4 ATP's per group (Veldhorst et al., 2008). Gilbert et al. (2011) proposes that there is a difference in energy expenditure induced by different protein sources, and that this is related to the anabolic capacity (i.e. ability to induce protein synthesis). For example, a plant diet increased protein oxidation (measured by increase urinary nitrogen) and this was correlated to lower energy expenditure, whereas the opposite was the case for an animal protein diet. According to Veldhorst (2008) the effect of protein on energy expenditure seems to relate to a high protein diet rather than high protein meals and as such, long-term exposure to protein is needed in order to observe effects on weight management. Furthermore, resting energy expenditure is affected by muscle mass, which in turn affects the energy cost of protein turnover (Gilbert et al., 2011).

4.2/ **Carbohydrates – importance of digestibility and viscosity**

Carbohydrates can take very different forms and differences in the conformation of a single chemical bond is important with respect to the ability of hydrolytic enzymes to break down the structure. This is one of the main differences between starch and dietary fiber.

Viscosity is a texture parameter expressing the degree of thickening of a solution. It can be measured using a viscometer and is given in Pa s. Viscosity is dependent on structure, chemical composition and molecular weight (MW) of the thickening agent (Kristensen and Jensen, 2011). Furthermore, rate of hydration is an important property, since some fibers will increase in viscosity over time compared to right after mixing with water.

The following section will describe some of the differences in microstructure of carbohydrates that gives rise to viscosity changes as well as effects that are related to the appetite response.

4.2.1/ Starch – importance of crystallinity

Cereals (e.g. wheat, rice) and tubers (e.g. potatoes) are main sources of starch, a mixture of two polysaccharide structures that plants use for storage of energy: amylase and amylopectin. Amylase has a linear structure and is more resistant to digestion than the more branched amylopectin, due to a higher number of potential binding sites for the amylases (Parada and Aguilera, 2011)..

Several structural changes of starch are relevant to discuss in relation to altering the satiating potential of food products: gelatinization, crystallinity and dextrinization (Figure 4). These structures have importance for the digestibility of the starch as well as the glycemic response, i.e.

the macronutrient release and uptake. Native starch (i.e. in plants or legumes) is found as granules with varying degree of crystallinity (Figure 4 A). There are A and B crystalline polymorphic forms, with B crystallites being less digestible, i.e. more resistant to α-amylase (Parada and Aguilera, 2011) Usually, starch is processed before ingestion (e.g. by heating in the presence of water), whereby the granule swells in a process called gelatinization (Figure 4 B). This increases the digestibility and glucose availability, depending on whether the granule is partly of fully gelatinized (Parada and Aguilera, 2011). On the other hand, retrogradation (Figure 4 C) is a physicochemical, time- and temperature-dependent change occurring during storage of swollen starch matrices (especially amylose e.g. in bread), where the chains interact by hydrogen bonding, lose water and go through incomplete recrystallization, lowering the digestibility (Parada and Aguilera, 2011). Finally, one can subject the starch granules to dextrinization (Figure 4 D), which is a hydrolysis process occurring mainly during extrusion, resulting in a lower molecular weight and increasing the susceptibility to enzyme action (Parada and Aguilera, 2011).

A) Native starch B) Gelatinized starch C) Retrograded starch D) Dextrinized starch

Figure 4 Structural changes of starch. Illustrations obtained from (Wageningen University, n.d.)

Classification of starch according to digestibility occur in three categories: rapidly digestible starch, slowly digestible starch and resistant starch (Parada and Aguilera, 2011). Several researchers have investigated the effect of resistant starch on appetite as well as its potential actions on health. In a study of catherized pigs fed either a Western-style control diet, an arabinoxylan supplemented diet or a resistant starch diet, it was found that resistant starch had a different effect on net portal flux of insulin and glucose response than arabinoxylan. Furthermore, resistant starch resulted in an intermediate net portal flux of short-chain fatty acids (Ingerslev et al., 2014). In a study of different dietary fibers and their effects on human satiety response, resistant starch (together with corn bran) was found to have the greatest impact on satiety (Willis et al., 2009)

In the nutridynamics article by de Vos et al. (2006), he mentions factors, affecting insulin response to starch consumption. Examples are food structure (e.g. rye bread vs wheat bread), structure of matrix, structure of starch granules, starch source (oat, wheat, potato lower compared to rye bread and pasta based carbohydrate), processing (baking, cooking, frying) and food context (eaten with vinegar and peanuts reduces blood glucose response) (de Vos et al., 2006). More research is needed to elucidate the impact of each of these factors.

4.2.2/ Dietary fiber – importance of viscosity

The definition of dietary fiber has long been discussed, however in 2014, the Codex Alimentarius Commission stated a harmonized definition (short version): *"dietary fibers means carbohydrate polymers with 10 or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the small intestine of humans (…)"* (Jones, 2014). As can be deduced from this definition, the category of dietary fibers represent a very broad range of compounds, which have differing properties, depending on the number and type of molecular units, type of linkages between the molecular units and the presence of branches in the chain.

The content and composition of dietary fiber of e.g. cereals depend on different factors, including variety and species, maturation and degree of milling (Mejbom et al., 2008). In addition, there are great differences in the composition amongst the different fiber fractions of the grain:

cellulose and lignin are found in the bran, whereas arabinoxylans and β-glucans are found in the aleuron layer just below the bran. Even though the aleuron layer is part of the endosperm, it often ends up in the bran fraction during milling (Mejbom et al., 2008). Insoluble fibers are generally without branches and include cellulose, which is a D-glucose polymer with (1,4)-β-glucoside linkages. β-glucans are similar to cellulose, as they are composed of linear chains of D-glucose units with (1,4)-β-linkages, but in addition, they also contain (1,3)-β-branches, making the molecule soluble in water. Depending on degree of branching, arabinoxylans (chains of (1,4)-β-D-xylose and branches of α-L-arabinose bound to the OH-groups of xylose) are either insoluble or soluble in water (Glitsø and Bach Knudsen, 1999). Generally, arabinoxylans have a high water binding capacity and the water soluble arabinoxylans (low arabinose/xylan ratio) are able to form highly viscous solutions (Nyström et al., 2008).

There is increasing consensus that dietary fibers have beneficial effects on human health such as stimulating intestinal motility and prolonging satiety. Dietary fiber supplements have furthermore been found to have beneficial effects on obesity and metabolic syndrome and gastrointestinal functions (Papathanasopoulos and Camilleri, 2010). Furthermore, since dietary fibers are not digested in the small intestine, they will reach the colon, and undergo fermentation by the gut microorganisms, leading to a prebiotic effect (De Vrese and Schrezenmeir, 2008). Dietary fiber lowers the energy density of food products, and as such, less calories are ingested, as compared with the same amount of food from a similar product without dietary fibers.

Polydextrose (randomly cross-linked polymer of glucose) has received great attention as a sugar and fat replacer semi-liquid products such as yoghurt (King et al., 2005) or for beverages such as a smoothies (Ranawana et al., 2013) and drinking yoghurts (Hull et al., 2012). Some dietary fibers are included in the group of hydrocolloids as particularly healthy food structures (Gidley, 2013). When considering effects on appetite response, Kristensen and Jensen (2011) emphasize the role of viscosity in regulating appetite and food intake. This is supported in the systematic review by Wanders et al. (2011), who showed that more viscous fibers resulted in a greater reduction in appetite than less viscous fibers and that this was also the case for short-term energy intake. Viscosity is related to the ability of dietary fibers to thicken liquids or form gels (Dikeman and Fahey, 2006). Some soluble dietary fibers increase the viscosity of solutions through their ability to absorb water (Elleuch et al., 2011). Viscosity increases when increasing the chain length and molecular weight, but concentration, temperature and pH are also important factors (Tungland and Meyer, 2006). Viscosity can affect appetite through two mechanisms: increasing the sensory exposure of the oral cavity to the food by increasing the product viscosity or through gastric or intestinal distension and transit time by increasing the viscosity of the gastrointestinal digesta. The first option is related to the sensory signals leading to termination of a meal (e.g. sensory specific satiety) and the second is related to the sensation of fullness and contribute to satiety (postprandial effects). Furthermore, viscosity decrease absorption of some nutrients in the small intestine and increases the intestinal transit time, affecting the satiety signals, as the release of satiety hormones depend on the interaction between nutrients and intestinal epithelium (Kristensen and Jensen, 2011). In several studies a high viscosity was found to increase meal duration, fullness and the glucose response (AUC), whilst decreasing hunger, desire to eat, time for glucose peak concentration and gastric emptying rate (Zijlstra et al., 2009, 2008). In these studies, there were no effects on energy intake, however, studies like these give an indication that hydrocolloids that produce viscous food products not only affects eating rate due to higher oral processing, but they might also affect the rate of digestion due to the delayed stomach emptying. Table 4 is an overview of studies on dietary fiber and appetite.

Table 4 Human studies investigating the effect of consuming different dietary fibres and effect on appetite. VAS: visual analog scales, BMI: body mass index, EI: energy intake, CHO: carbohydrates. Table is continued on next page.

Author (year) ***Title***	Monsivais et al. (2011) *"Soluble fiber dextrin enhances the satiating power of beverages"*	Ranawana et al. (2013) *"Polydextrose: its impact on short-term food intake and subjective feelings of satiety in males—a randomized controlled cross-over study"*	King et al. (2005) *"Evaluation of the independent and combined effects of xylitol and polydextrose consumed as a snack on hunger and energy intake over 10 d"*
Study participants	36 subjects (14 males, 22 females, excl. 4 dropouts) Age: 25.0 ± 0.58 years BMI: 22.6 ± 0.42 kg/m^2	26 male subjects (excl. 2 dropouts) Age: 28 ± 7 years BMI: 24.1 ± 3.2 kg/m^2	16 subjects (8 female, 8 male) Age: 30.1 years BMI: 22.7 kg/m^2
Active component	20-24 g fiber in test foods RS: Resistant starch SFD: Soluble fiber dextrin P: Polydextrose SCF: Soluble corn fiber 70	P: Polydextrose (12 g)	X: xylitol (25 g/d) P: polydextrose (25 g/d) PX: xylitol (12.5 g/d) + polydextrose (12.5 g/d)
Food structure	155 mL lemon-flavored and sugar-sweetened beverage + solid snack Control1 (C1): no fiber in beverage Control2 (C2): no fiber, low energy content (aspartame sweetened)	400 g commercial peach and passion fruit smoothie (apples, peaches, banana, passion fruit, orange, lime) Control (C): smoothie	200 g strawberry flavored yoghurt Control (C): yoghurt + sucrose (25 g/d)
Study design	Double-blind crossover 6 testing days over 6 wk >1wk washout Morning (t=0): first preload t=100 min: second preload Lunch (t=140 min): mixed tray lunch	Repeated measures, single-blind randomized cross-over 2 occasions, 2 d washout Morning (t=0): breakfast Preload consumption Lunch (t=60 min): buffet lunch	4-way cross-over Preload consumed as snack during 10 days, 1 wk washout Test day (day 1 and 10): Morning (t=0): fixed breakfast t~180 min: preload Lunch (t~270 min): sandwich, crisps and fruit
Outcome measures	VAS: hunger, fullness, thirst, nausea, desire to eat Food and nutrient intake	VAS (change from baseline): hunger, fullness, desire to eat, prospective consumption Palatability of preload Energy/nutrient intake	VAS: hunger, fullness Palatability Bloatedness and nausea Energy and nutrient intake (EI test preload – EI control)
Results	Hunger: C2>RS=SFD=P=SCF Desire to eat: C2>RS=SFD=P=SCF Fullness: RS=SFD>C1=P=SCF>C2 Thirst/nausea: Not sign. EI: C2>SFD=SCF, C1> SFD Macronutrient intake: not sign.	Palatability: not sign. EI: P(-100 kcal=10 %)<C Nutrient intake (CHO, fiber, fat, not protein): C>P Hunger/fullness/desire to eat/prospective consumption: not sign.	Palatability: not sign. EI (suppression): X(11.9 %)>P(9.9 %)>XP (7.2 %)>C Tot EI (suppression): P>C, X>C=XP Hunger: not sign. Fullness: XP>C Relative satiety (rating before lunch/kJ): hunger (not sign), fullness (sign) → C<XP Discomfort: no differences

Table 4 continued Human studies investigating the effect of consuming different dietary fibres and effect on appetite. VAS: visual analog scales, BMI: body mass index, EI: energy intake, CHO: carbohydrates.

Author (year) ***Title***	Hull et al. (2012) *"Consuming polydextrose in a mid-morning snack increases acute satiety measurements and reduces subsequent energy intake at lunch in healthy human subjects"*	Zijlstra (2009b) *"Effect of viscosity on appetite and gasto-intestinal hormones"*
Study participants	34 subjects (24 female, 10 male) Age: 37 ± 1.9 years BMI: 22.9 ± 0.25 kg/m^2	32 subjects (12 male, 20 female) Age: 22±2.2 years BMI: 21.9kg/m^2
Active component	LP: low polydextrose (6.25 g) HP: high polydextrose (12.5 g)	Modified starch
Food structure	100 g strawberry flavored drinking yoghurt Control (C): glucose syrup to match energy to LP, no fiber	400g (female) or 500 g (male) milk-based products with chocolate flavor (served in cup w straw) 1) liquid ~ chocolate milk 2) semi-solid ~chocolate custard
Study design	Randomized, cross-over design, 3 test sessions, 1 wk washout Morning (t=0): breakfast t=180 min: preload Lunch (t=90 min): sandwich lunch Dinner (t=450 min): pasta with tomato and cheese sauce	Randomized cross-over study, 2 test sessions 2 d washout Morning: test product for breakfast meal t=90 min: *ad libitum* meal of chocolate cake
Outcome measures	VAS: desire to eat, hunger, fullness, satiety, prospective consumption, liking and feelings of discomfort Energy intake (lunch and dinner)	VAS: hunger, fullness, desire to eat, appetite for something sweet/savory, prospective consumption, thirst Pleasantness, sensory attributes of products Hormones: ghrelin, CCK-8, Total GLP-1
Results	EI (lunch): HP<C (+219 kJ), not sign for dinner and total EI Liking: not sign. Bloating: LP>HP, belching: LP<C, nausea: LP>control=HP Desire to eat: lunch: LP<C=HP, fullness: not sign., hunger: LP=HP<C, prosp. cons.: H <C, satiety: LP>C <u>Preload – dinner</u> Desire to eat: LP < C Fullness: LP < C / HP < control Hunger: no diff. Prosp. cons.: no diff. Satiety: HP < C	Semi-solid product decreased: desire to eat, appetite for something sweet and prospective consumption Increased: fullness Appetite AUC not sign. diff. Desacyl ghrelin: semi-solid ↑ Active ghrelin: no diff. CCK-8: no diff. Total GLP-1: no sign. diff. Hormone AUC not diff. EI: not sign. different

4.2.3/ Acid gels - self-structuring in human stomach

Some hydrocolloids (alginate and gellan gum) form gels in the presence of cations, such as protons, which are available in acidic environments such as in the stomach. Thus, they have the potential to increase gastric distension and delay gastric emptying upon consumption. The research in this area is still in its prime as only few studies are published to date. In addition, these few studies are quite heterogeneous, making it difficult to make any general assumptions on differences between the applied hydrocolloids. Therefore, the following will only include a brief introduction to some of the work performed in this area.

Alginate is an anionic polysaccharide from brown algae composed of linear chains of (1-4)-β-D-mannuronate and (1,4)- β-D glucoronate arranged in copolymers which are either homogenous (either mannuronic or glucuronic acid) or mixed (both mannuronic and glucuronic acid) (Belitz et al., 2009). Alginates have been investigated in two studies (Georg Jensen et al., 2012; Hoad et al., 2004) (see Table 5).

Hoad et al. (2004) performed a study investigating the effect of weak- or strong gelling alginates (low and high in glucuronic acids, respectively) or guar gum on stomach emptying time, when consumed as a part of a milk-based meal-replacing beverage. Guar gum consists of main chains of (1,4)-β-D-mannopyranosyl with (1,6)-α-D-galactopyranosyl branches at every second residue in the main chain (Belitz et al., 2009). It is not acid-sensitive, but can form highly viscous solutions that are shear rate dependent. The authors applied serial MRI for qualitative investigation on how the different beverages would structure inside the stomach, as well as to identify the time of gastric emptying. They found evidence that the alginate beverages formed lumps inside the stomach, and some of these where forming on the stomach wall (where the stomach acid is excreted). Guar gum did not form lumps, but rather a high viscosity homogenous emulsion, which prolonged the sensation of satiety. The strong-gelling alginate and guar gum beverages suppressed hunger the most, but were reported by the test subjects to be very unpleasant to drink. Conversely, the weak-gelling alginate did postpone the return of hunger levels to baseline compared to control with no hydrocolloid, and was rated comparably more palatable (Hoad et al., 2004). A limited dose-response effect of alginate load was found in a study by Georg Jensen et al. (2012) who applied the paracetamol absorption test in an investigation of the effect of alginate beverages on stomach emptying time and appetite. The consumption of alginate beverages of either low or high volume, before a fixed breakfast and again before an *ad libitum* lunch significantly reduced energy intake when compared to a placebo beverage. Furthermore, the high volume beverage increased satiety feelings, reduced hunger and the feeling of prospective consumption and reduced the gastric emptying time, when compared to placebo (Georg Jensen et al., 2012).

Table 5 Human intervention studies investigating the effect of consuming foods containing acid gels. VAS: visual analog scale, BMI: body mass index, MRI: magnetic resonance imaging, GER: gastric emptying rate.

Author (year) ***Title***	Georg-Jensen (2012) *"Acute Effect of Alginate-Based Preload on Satiety Feelings, Energy Intake, and Gastric Emptying Rate in Healthy Subjects"*	Hoad et al. (2004) *"In vivo imaging of intragastric gelation and its effect on satiety in humans"*
Study participants	19 subjects (10 men, 9 female) Age: men: 25.9 ± 3.4 years, women: 26.4 ±2.5 years BMI: men: 23.5 ±1.7 kg/m^2, women: 23.7 ± 2.1 kg/m^2)	12 subjects (3 men, 9 female) Age: 24 years (range: 19-29) BMI = 22 kg/m^2 (range: 19-25)
Active component	3% alginate LW: low volume (9.9 g alginate in 330 mL). HV: high volume (15 g alginate in 500 mL)	WGA: weak-gelling alginate (1%) SGA: strong-gelling alginate (1 %) VG: viscous guar (1%)
Food structure	330 or 500 mL orange flavored beverage (water, alginate, aspartame, β-carotene, natural orange flavor, maltodextrin). LV control: 330 mL. HV control: 500 mL	325 mL. meal-replacing milk beverage with hydrocolloid (sugar-sweetened, vanilla-flavored). Control: no hydrocolloid
Study design	Randomized, double-blind, placebo-controlled, four-way cross-over intervention, 3 wk washout, 4 test days Morning (t=0): first preload beverage + paracetamol (1,500 mg) t=30 min: breakfast (iso-caloric, bread, cheese, raspberry jam, yoghurt, water) t=210 min: second preload t=240 min: *ad libitum* lunch (pasta with meat sauce, water)	Crossover, placebo controlled intervention study, 4 test days Morning (t=0): consume test drink within 10 min. t=0-120 min: serial MRI t=120 min: drink 500 mL water (determine remaining solid components in stomach)
Outcome measures	VAS: satiety, hunger, fullness, prospective food consumption, thirst, well-being, desire to eat something fatty/sweet/salty/savory Biochemical: hemoglobin, blood glucose, insulin Blood pressure, heart rate Adverse effects (AE) GER (paracetamol method)	VAS: fullness, hunger, prospective consumption. MRI scans: gastric emptying (using special pulse sequence and calculation, relaxation rates (T_2^{-1} of the meal in vivo), gelation (in vivo multislice images, stereology → volume → lump classification)
Results	Satiety: HV>HV-control. HV>LV. Prosp. cons.: HV<HV-control. Hunger: HV<HV-control. Fullness: HV>HV-control. Sensory-specific satiety: not sign. EI: LV<LV-control Palatability: HV<HV-control. LV<LV-control GER: HV<HV-control Insulin, blood pressure, heart rate: not sign.	Fullness: WGA=SGA=VG>control. Hunger: viscosity of meal. Palatability: VG = SGA < WGA Control: liquid phase on top of solid phase (milk protein precipitate). WGA: heterog. in the stomach. Solid lumps (acid induced), stuck to stomach wall (more irregular than control), appeared within 2h. SGA: dark-centered and "halo" surrounded lumps. Larger tot. volume than WGA. VG: homogenous, no phase separation or lump-formation

A research team at Department of Chemical Engineering at Birmingham University have performed several experiments with acid-sensitive gels, including individual low-acyl gellan gum (Norton et al., 2011), but also mixed systems of high- and low-acyl gellan gum (Bradbeer et al., 2014) or low-methoxy–pectin and and low-acyl gellan gum (Spyropoulos et al., 2011). Gellan gum is an anionic polysaccharide like alginate, but consists of a linear chain of (1,3)-linked repeated elements of two D-glucose units, one L-rhamnose and one D-glucoronic acid. Two acyl subunits are present at each glucose units in the high-acyl variant, whilst in the low-acyl variant, some of these have been removed by deacylation, creating a hydrocolloid with higher elasticity (Bradbeer et al., 2014). Furthermore, the properties of gels formed with low-acyl gellan gum showed pH dependence, with maximal gel strength achieved at pH 3-4 (Norton et al., 2011)

Overall, the mixed systems allow for controlled the abilities of the gels to structure and destructure. Spyropoulus et al. (2011) conducted an in vitro study to investigate the properties of gels composed of hydrocolloid mixtures (low-methoxy pectin and low-acyl gellan gum) using the same total amount of hydrocolloid (3 wt%) but in different ratios. Pectin is a mixture of a homogalacturonan with (1,4)-linked α-D-galacturonic acid, a galacturonan with side chains of apiose, fucose, arabinose, and xylose and a rhamnogalacturonan with a backbone of (1,4)-linked α-D-galacturonic acid and (1,2)-linked α-L-rhamnose and linked to chains of arabinan and galactan (Belitz et al., 2009). The galacturonic residues can be esterified with methanol to varying degrees, resulting in high-methoxy or low-methoxy pectin, the former will gel in the presence of Ca^{2+} ions or at low pH in the absence of Ca^{2+} (Lootens et al., 2003). To assess the gel properties, Spyropoulus et al. (2011) studied the elasticity (Young's modulus), stiffness (bulk modulus) and total work of failure on the gels. To imitate the acidification by the stomach, they placed biopolymer solution in dialysis tubing and immersed into acid bath (pH=1) for 24 hours. The authors found that gellan gums creates stronger gels, but by including low-methoxy pectin in the hydrocolloid mixture one can obtain a more efficient acidification and avoid over structuring in the stomach. These studies on low- and high-acyl gellan gum and low methoxy pectin were limited to in vitro studies and the results does not translate into effects on human appetite. However, this represents and interesting area for future studies.

5.0 Bioactive compounds with effects on appetite

Adding or maximizing the content and intestinal release of bioactive compounds that act specifically to reduce digestion or absorption of the macronutrients (fat, carbohydrate and protein) or that modulate the secretion of hormones related to appetite is another approach to increasing the appetite-suppressing effect of foods.

Individual whey proteins have received attention with regard to satiety and weight management. In this respect, glycomacropeptide (GMP) (a whey protein originating from cleavage of κ-casein during cheese making) and β—lactoglobulin might be involved in reducing energy intake (Veldhorst et al., 2008), although some studies state that GMP alone is not critical in premeal whey-induced satiety (Chungchunlam et al., 2014). Furthermore, β-conglycinin from soy has been suggested as one of the isolated proteins responsible for the satiating effect of soy (Hira et al., 2011). The exact mechanism of these peptides in appetite suppression is still to be completely elucidated.

Normally, the release of opioids in response to food consumption stimulates food intake and their release is involved in food cravings (Mercer and Holder, 1997). Opioid peptides have been found in food products and might affect food intake, as it has been shown that blocking the opioid receptors (using opioid receptor antagonists) leads to decreased the orosensory reward value of food, thus reducing intake (Yeomans, 1998). Examples of opioid peptides have been found in milk (β-casomorphins, (Silva and Malcata, 2005)) as well as casein and soy (Pupovac and Anderson, 2002). The latter study also showed increase CCK release in response to ingestion of peptides from both soy and casein (Pupovac and Anderson, 2002).

Some food components can alter the digestibility of starch, e.g. tea polyphenols have shown to inhibit α-amylase in the digestion of rice amylopectin, hereby representing an approach to lowering the glycemic index of foods by lowering the release of glucose units from starch (Koh et al., 2011). One could speculate, whether this changes the taste of the food product, since the release of glucose units from starch hydrolysis in the mouth contributes to the sweet taste of starch-containing products. However, the approach of altering the activity of digestive enzymes seems interesting and further investigations might reveal other components of foods that affect the gastrointestinal enzymes.

With respect to gastrointestinal transit time, the alkaloid piperine (from black and long pepper) has been found to inhibit gastric emptying and the intestinal transit (Bajad et al., 2001). The study by Ripken et al. (2014) showed that ingestion of sodium caseinate or rebaudioside A (a sweet glucoside from the plant S*tevia rebaudiana* Bertoni) induced release of both GLP-1 and PYY in an in vitro study.

The compounds mentioned here only represent a small fraction of the potential appetite-suppressing compounds that can be found in food products. Investigations into the identification and isolation of other compounds with similar properties are needed. Furthermore, small molecules like the bioactive compounds mentioned in this section might have unpalatable tastes or smells. They might also be sucseptible to degradation and modulation during digestion processes, which alters their activity. In this regard, it might be very important to consider the food matrix and if possible design a microstructure to facilitate delivery of the active compound at the correct location and possibly disguise adverse flavors/smells, which could reduce intake.

6.0 Conclusion and future perspectives

The aim of the current report was to review scientific literature on the effect of food microstructure on satiety, macronutrient uptake and health. Overall, the result show that indeed, small differences in microstructure of protein and dietary fiber alters their satiating potential and physicochemical properties.

With regard to protein, the potential to increase the postprandial level of circulating amino acids is important. Higher circulating amino acid levels can be achieved by ingestion of easily digestible protein sources with high content of non-essential amino acids or branched chain amino acids (e.g. leucine that suppresses appetite through direct action on hypothalamus). On the other hand, low digestibility results in slower digestion and thus longer time within the gastrointestinal tract, which is a strategy for prolonging the satiety response. Furthermore, proteins increase the energy expenditure and this is different depending on the specific amino acid composition (e.g. more nitrogen groups require more ATP for oxidation). In addition, specific peptides from whey or soy might bind to receptors in the intestinal tract thus directly modifying the satiety response.

Satiating carbohydrates have the property in common that enzymatic hydrolysis is hindered either due to the physical conformation of carbohydrate chains that hinder enzymatic binding or the presence of bonds that are indigestible for the human enzymes. The first is the case for recrystallized starch (retrograded starch or resistant starch) and the second for dietary fibers. Dietary fibers that form viscous solutions increase the sensory exposure in the oral cavity or result in gastric or intestinal distention and increased transit time through the gastrointestinal tract. However, these carbohydrates often change the viscosity of a liquid or semi-liquid food product before consumption, potentially reducing palatability. Increased viscosity in the stomach after ingestion might be a favorable strategy. This can be obtained by means of acid sensitive gels that respond to the acidic environment in the stomach by increasing viscosity and forming gels. Small changes in the structure of such acid gels (alginate or gellan gum) contribute to control over the intragastric gelation, but need further investigation in humans to measure the effects on appetite.

The appetite-suppressing activity of some foods might be due to the content of bioactive compounds with specific effects. Investigations into this matter has revealed compounds with appetite-modulating effects through different mechanisms such as inhibiting digestive enzymes, binding to opioid receptors or activation of receptors leading to secretion of gastrointestinal hormones, which slows down gastric emptying and intestinal transit time.

In future studies, it could be interesting to investigate, if mixing of protein sources with different properties (high absorption and as slow digestion) could act synergistically and increase the satiety response. Furthermore, much of the research on satiating effects of proteins have been conducted on dairy proteins, but this does not exclude the potential of plant proteins to exert similar effects on the satiety. Therefore, increasing focus on obtaining protein from plant sources and studying their effects on satiety could be beneficial. For example, some canola peptides have shown to have ACE-inhibitory as well as anorexigenic effects, by reducing food intake and gastric emptying (Aachary and Thiyam, 2012). Other examples of plant protein powders available include rice, hemp, pea, soy, quinoa, millet, buckwheat, flaxseeds and many more, suggesting a good possibility of finding other peptides with specific effects on food intake.

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