The Digestive Tract: A Complex System

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1 Introduction

The digestive tract in humans and other mammals has evolved to maximise the nutrients and bioactive compounds extracted from the food we eat while at the same time protecting us from pathogens and toxins that may be contained within it. As a result, the gastrointestinal (GI) tract is highly complex with multiple layers of control involving four distinct compartments, namely the mouth, stomach, small intestine, and large intestine. The first of these compartments is the mouth or oral cavity where food is first admitted into the body. This is where the most significant sensory appraisal of the food takes place as rejection of the food is still possible. It is also where the first preliminary steps in digestion occur as solid food is chewed to reduce particle size and saliva containing amylase is added. The saliva also provides lubrication to allow the food to be swallowed and passed to the second compartment, the stomach. The stomach acts as a reservoir for the food until it can be passed into the intestine for further digestion. This is not to say that digestion does not occur in the stomach but certainly it is limited. During the gastric phase of digestion, hydrochloric acid is added along with protease (pepsin) and gastric lipase.

From the stomach food passes through the pyloric valve into the small intestine, where the pH is increased towards neutral. Pancreatic proteases, lipases, and amylase are added along with the endogenous surfactant bile and the whole system is well mixed. Chyme is passed along the whole length of the small intestine where most of the nutrients are absorbed. The small intestine comprises the duodenum, jejunum, and ileum and chyme passes from one to the other until it finally passes through the ileocaecal valve into the large intestine. In the large intestine, some of the remaining undigested food (dietary fibre) is fermented by bacteria into absorbable

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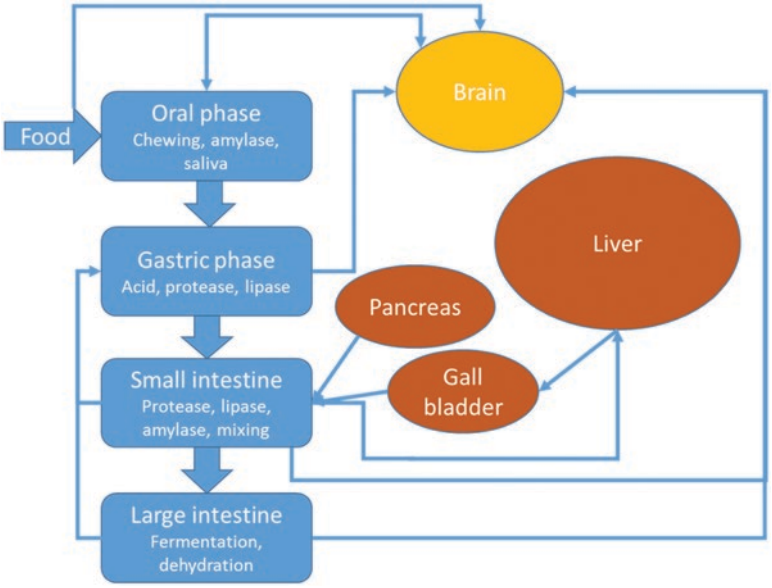

Fig. 1 A schematic diagram of the processes described in this chapter

compounds such as short chain fatty acids and most of the remaining water is removed before being excreted from the body. The basics of this complex system are illustrated in Fig. 1. In this chapter, the main processes controlling digestion and absorption in these different compartments will be described as well as how they are interlinked with one another and other organs in the body.

2 Oral Phase

Digestion is considered to start in the oral phase where food is chewed and mixed with saliva, allowing for sensory exploration of the oral contents in terms of taste, texture, and smell (Chen, 2009). The mouth represents not just the start of the digestive process by which the body gains nutrients but also the place where we gain pleasure from food. Because it is the pleasure aspect of food that drives the choice of which foods to consume, there has been significant research into factors such as texture perception (van Aken, 2010) and aroma release (Trelea et al., 2008). However, in this section only the features of oral processing that relate to digestion will be discussed although one of the confounding factors is the large variability between individuals and food types. For liquid food, the oral phase plays a very limited role in digestion but for solid food it can be critical.

After the initial bite, solid food is repeatedly chewed and manipulated between the tongue and palate until the particle size is reduced and the food has been hydrated

sufficiently to form a bolus. During this time a number of different stages can be identified depending on the food involved (Van Vliet, Van Aken, De Jongh, & Hamer, 2009):

- manipulation of the food before it is brought into the mouth
- ingestion/biting by the front scissors
- chewing of hard foods by the molars
- deforming of softer semi-solid foods between the tongue and palate
- wetting by saliva
- enzymatic breakdown
- manipulation of the food by the tongue to form a bolus at the back of the oral cavity
- swallowing

In order to complete all these stages particles should be smaller than ~2 mm although soft particles that are not liable to injure the upper digestive mucosae can be larger. This suggests the existence of a threshold for swallowing modulated in particular by food bolus consistency (Jalabert-Malbos, Mishellany-Dutour, Woda, & Peyron, 2007). In addition to lubrication, saliva also introduces amylase into the bolus and performs many other functions in the mouth. Salivary flow rate in healthy adults is ~0.3 mL/min unstimulated and 1–2 mL/min when stimulated (Sreebny, 2000) and the daily flow lies somewhere between 0.5 and 1.5 L in healthy individuals. The amylase content of the saliva is also variable but seems unaffected by stimulation and is normally ~45 U/mL (Neyraud, Palicki, Schwartz, Nicklaus, & Feron, 2012). Because of its multifunctional nature the overall composition of saliva is complex (Humphrey & Williamson, 2001). It contains a complex range of ions and also found in saliva are proteins including immunoglobulins, enzymes and mucins, and nitrogenous products, such as urea. These components function in the following general areas: (1) bicarbonates, phosphates, and urea modulate pH and the buffering capacity of saliva; (2) proteins and mucins serve to clean, aggregate, and/or attach oral microorganisms and contribute to dental plaque metabolism; (3) calcium phosphate and proteins work together to modulate dental demineralisation and remineralisation; and (4) immunoglobulins and enzymes provide antibacterial action.

The importance of oral processing has been highlighted in a number of studies showing the ability of cellular structures to retain nutrients if left intact. In particular, work on almonds (Grundy et al., 2015) has shown that following mastication, most of the almond cells remained intact with lipid encapsulated by cell walls. Thus, most of the lipid in masticated almonds is not immediately bioaccessible and remains unavailable for early stages of digestion. The lipid encapsulation mechanism provides a convincing explanation for why almonds have a low metabolisable energy content and an attenuated impact on postprandial lipaemia. Similar results have also been shown for other plant foods such as carrot (Tydeman et al., 2010). Carotene bioaccessibility was found to be greater from raw samples than heated samples of the same size. This is because heating increases the propensity for intact cells to separate, effectively encapsulating the carotene. Although the gross structure of the tissues was found to be relatively unaffected by in vitro digestion, at the

cellular level some cell-wall swelling and cell death were observed, particularly close to the surfaces of the tissue. This study suggests that cell-wall rupture prior to digestion is an absolute requirement for carotene bioaccessibility in the upper GI tract and that heating does not enhance carotene release from intact cells.

A related area of research is the issue of poor dentition in the elderly, which can also have an impact on nutrient release and digestion rate as well as food choice (Jauhiainen et al., 2017). In a study by Laguna et al., fracture mechanics of 15 commonly consumed food products of fruits, vegetables, and dairy origin were analysed using penetration test. Food score difficulty showed that high breaking forces of food products were related linearly with perceived difficulty ($r = 0.729$) and with higher oral processing time ($r = 0.816$). Other food breakdown characteristics such as the number of peaks and gradient of the penetration curves showed linear correlation with mastication time ($r = 0.830$, $r = 0.840$) and number of chew cycles ($r = 0.903$, $r = 0.914$) (Laguna, Barrowclough, Chen, & Sarkar, 2016). Regardless of the number of chewing cycles, once the bolus has been formed it is swallowed and passes down the oesophagus into the stomach.

3 Gastric Phase

The stomach is a food storage vessel where the process of food hydrolysis starts and acidic conditions start to kill bacteria present in the food. In general, in its rested state the stomach has a small volume (10–50 mL) and contains a limited volume of highly acidic secretions. The arrival of food into the stomach immediately stimulates the secretion of pepsinogen and gastric lipase by chief cells and hydrochloric acid by parietal cells. The pH sensitivity of all of the enzymes present in the stomach is key to what digestion occurs. Immediately after consumption of a meal the gastric pH is dominated by the pH and buffering capacity of the food. Thus, the pH can easily be above 6 initially and only gradually drop below 2 after several hours (Malagelada, Go, & Summerskill, 1979; Sams, Paume, Giallo, & Carriere, 2016). As the contents of the main body of the stomach is not well mixed there can be localised differences in pH that have the potential to affect the local rates of hydrolysis (Nyemb et al., 2016). There is a certain amount of evidence that gastric mixing, which relies on gastric muscle tone can decrease in the elderly. This is likely to affect not just gastric mixing but gastrointestinal motility more generally (Levi & Lesmes, 2014). In the presence of acid, pepsin is formed from the zymogen pepsinogen. Pepsin is active over a wide range of acid conditions between 1.5 and 5 with a maximum at pH 2 (Piper & Fenton, 1965). Pepsin is an aspartic protease that preferentially cleaves after the N-terminal of aromatic amino acids. However, hydrolysis depends on accessibility to the substrate and that depends on the secondary and tertiary structure of the protein as well as its aggregation state. Bovine milk contains proteins at both extremes of the pepsin susceptibility spectrum. The whey protein β-lactoglobulin has been shown to be largely pepsin resistant, while the

caseins are highly susceptible to pepsin hydrolysis under fixed conditions (Mandalari, Adel-Patient, et al., 2009). This difference is due to the differences in protein structure as β-lactoglobulin is a globular protein with its secondary structure held together by disulphide bonding while the caseins have little secondary structure and this is clearly a result of their biological functions (Sawyer & Holt, 1993). Thermal and other types of processing are known to alter protein structure, so it is not surprising that it can also alter susceptibility to proteolysis (Macierzanka et al., 2012). Heating can often lead to the irreversible unfolding of protein. However, this can also expose more hydrophobic regions that can lead to aggregation. Finally, it is worth mentioning in relation to these two groups of protein that despite the pepsin susceptibility mentioned above, casein is known for its slow digestion while whey is known as a fast digesting. This is because the combination of low pH and limited pepsin hydrolysis leads to the irreversible coagulation of the casein and subsequent slow gastric emptying (Boirie et al., 1997).

The other digestive enzyme secreted into the stomach is gastric lipase, which is active between pH 3 and 6 but has an optimum between 4 and 5. This acidic lipase preferentially cleaves triacylglycerides at the sn-3 position (Sams et al., 2016). Typically in healthy adults the lipolysis catalysed by gastric lipase reaches 10–20%. Although this limited gastric lipolysis may not be quantitatively important in healthy subjects, the action of gastric lipase may be qualitatively important by initiating fat digestion and facilitating some fat emulsification in the stomach and thereby facilitating the action of pancreatic lipase in the duodenum (Armand et al., 1995).

The final enzyme present in the gastric compartment is salivary amylase, much of which has already been intimately mixed with the food during oral processing and is indeed continuously added to the gastric content. The α-amylase in saliva, also known as ptyalin has a pH optimum between 6.7 and 7.0 but it can still be active in gastric conditions down to a pH of ~4 (Fried, Abramson, & Meyer, 1987). As has already been stated, the pH during initial stages of gastric digestion can often remain relatively high meaning that the amylase can be active for a prolonged period. It should also be noted that the loss of activity is a combination of degradation by pepsin and loss of conformation due to pH. In addition to hydrolysis, there is also some specific physical processing in the gastric antrum that can further decrease the size of particles and other structures (Marciani et al., 2000, 2012). However, in the main body of the stomach there is very little physical motion meaning that phase separation of different components in the food can occur. For example lipids, having a lower density than water, can float to the top of the stomach leaving a more aqueous phase below it, or denser particles can sediment to the bottom of the stomach (Mackie, Rafiee, Malcolm, Salt, & Van Aken, 2013; Marciani et al., 2009). Both of these possibilities can alter the composition of the chyme being emptied from the stomach at any given time.

Although there are no endogenous surfactants secreted into the gastric compartment as part of the digestion process, it is clear that both bile salts and phospholipids are likely to be present in the antrum at least. The bile is present as a result of reverse transport/retropulsion from the duodenum. An additional source of phospholipid is

from the cellular debris produced as a part of the normal turnover of the gastric epithelium. In both cases the concentrations are relatively low and highly variable but the presence of such surfactant may have an impact on protein hydrolysis by altering the accessibility of potential cleavage sites as shown in vitro (Mandalari, Mackie, Rigby, Wickham, & Mills, 2009).

In addition to the biochemical degradation of food, the stomach also erodes the food bolus and shears it into smaller particles. This process has been described in some detail using computational fluid dynamics (CFD) (Ferrua & Singh, 2010). Using this approach, the authors were able to show that in agreement with the classical description of gastric function, the strongest fluid motions were predicted in the antropyloric region. A significant degree of recirculation of gastric contents from the fundus towards the antrum was also identified. However, for a given motor response of the stomach, the viscosity of the gastric digesta significantly affected the local flow behaviour and pressure gradients that developed within the stomach. This runs somewhat counter to the idea of rapid and complete homogenisation of the meal. Indeed, gastric contents associated with high viscous meals seem to be poorly mixed. The diminution of food in the stomach is thought to involve two main flow patterns, the retropulsive jet-like motion and eddy structures where relatively high shear rates may be generated. However, this study found that increasing the viscosity of gastric contents significantly diminished the flow, while predicting a significant enhancement of the pressure field.

During the digestion of food there are two modes of gastric emptying. Firstly by eroding the solid bolus of food in the stomach from the outside, where the food has been most exposed to acid and enzymes. The chyme may then be squeezed through the pylorus into the duodenum if the particle size is sufficiently small (Marciani, Gowland, Fillery-Travis, et al., 2001; Marciani, Gowland, Spiller, et al., 2001). When the gastric contents are more fluid or semi-solid (e.g. soup or porridge), emptying occurs primarily during periods of quiescence in antral pressure activity and, by implication, in antral contractile activity (Indireshkumar et al., 2000) and thus may empty from the centre of the stomach, a zone that has not been subjected to significant pH change or exposed to gastric enzymes (Pal, Brasseur, & Abrahamsson, 2007). In the antrum, selective "sieving" permits the rapid passage of liquids and smaller food particles while the larger particles are retained for further processing, although this is effected by the viscosity of the gastric contents (Marciani et al., 2012). The size cut-off means that particles larger than about 3 mm (Kong & Singh, 2008) tend to be retained longer, although not indefinitely (Stotzer & Abrahamsson, 2000). The rate at which food is emptied from the stomach depends on a number of factors but one is the energy density of the food (Hunt, Cash, & Newland, 1975; Hunt & Stubbs, 1975). As far back as the 1970s it was shown that energy density has an inverse effect on gastric emptying. However, in addition, the rheological properties of the gastric content play an important role on gastric processing (Ferrua & Singh, 2010) and emptying rate. Although both are important, increasing the viscosity is considered less effective than increasing the energy density in slowing gastric emptying (Camps, Mars, De Graaf, & Smeets, 2016).

4 The Small Intestine

Once the chyme has been emptied into the small intestine from the stomach it undergoes an increase in pH and is mixed with pancreatic enzymes and bile. This opens a new round of hydrolysis in which salivary amylase and gastric lipase may also play a role, although pepsin will be inactivated. Pancreatic enzymes fall into three groups associated with different macronutrient substrates. The proteases present are primarily trypsin and chymotrypsin as well as elastase, carboxypeptidase, and other peptidases. Trypsin is a serine protease activated from the proenzyme trypsinogen. It is primarily active against the C-terminal side of the amino acids lysine and arginine. Chymotrypsin preferentially cleaves the C-terminal side of hydrophobic amino acids (e.g. tryptophan, tyrosine, and phenylalanine). It can also cleave other peptide bonds but at a lower rate.

Starch in the chyme is further hydrolysed by pancreatic amylase. Indeed, for the most part starch is hydrolysed in the small intestine by pancreatic amylase. There has been a significant amount of research into factors that affect rates of starch hydrolysis (Dona, Pages, Gilbert, & Kuchel, 2010; Lehmann & Robin, 2007). Starch is a complex polysaccharide comprising two different polymers, namely amylose and amylopectin that are both formed from linked glucose molecules. Amylose is a linear polymer, while amylopectin is branched and the ratio of the two has a significant effect on digestibility, with high amylose starches being less digestible. The degree of crystallinity and the extent of gelatinisation, both of which can be effected by the thermal history of the starch, can have a significant impact of digestibility. The role of resistant starch as a form of dietary fibre is still under investigation. Starch is divided into three fractions depending on digestibility and are defined as:

Rapidly digestible starch (RDS): amount of glucose released after 20 min,
Slowly digestible starch (SDS): amount of glucose released between 20 and 120 min hydrolysis, and
Resistant starch (RS): total starch minus amount of glucose released within 120 min hydrolysis

The final group of pancreatic macronutrient hydrolysing enzymes are the lipases. Although there is a limited amount of lipolysis in the gastric phase of digestion (10–20%) as indicated above, the majority takes place in the proximal small intestine. Lipolysis is a complex process because both the substrate and products involved are only sparingly soluble in an aqueous environment while the enzymes need to stay in that aqueous environment. This means that the hydrolysis occurs at the interface and is strongly affected by interfacial area and interfacial composition, both of which evolve with time. The only exception to this is with very short chain lipids such as tributyrin that are primarily hydrolysed from solution. This is why tributyrin is often used as a substrate for determining lipase activity. Non-polar lipids are generally present in food as triglycerides, which can be hydrolysed to monoglycerides and free fatty acids with diglycerides as an intermediate. Thus each molecule of

triglyceride will result in one molecule of monoglyceride and two molecules of free fatty acid. The specificity of pancreatic lipase is for the sn-1 and sn-3 positions of the triglyceride meaning that the monoglyceride is normally left at the sn-2 position. The rate of hydrolysis also tends to be faster for the shorter chain fatty acids than the long chain molecules. The hydrolysis also takes place in the presence of bile that has been secreted from the gall bladder as a result of cholecystokinin (CCK) mediated contraction along with the pancreatic secretions. Bile is important for the removal of lipid hydrolysis products from the triglyceride interface through the formation of mixed micelles (Maldonado-Valderrama, Wilde, Macierzanka, & Mackie, 2011). In the presence of bile, the interfacial tension is lowered sufficiently that the adsorption efficiency of the lipase is decreased. This is not an issue in the small intestine as the more amphipathic protein, co-lipase can still adsorb to the triglyceride interface. Once adsorbed, lipase can bind to the co-lipase, anchoring it to the substrate and allowing hydrolysis to continue. Phospholipids are also hydrolysed in the small intestine by pancreatic phospholipases such as phospholipase A1 (PLA1) that cleaves at the sn-1 position to release a fatty acid and a lysophospholipid (Carriere et al., 1998).

Bile contains a number of endogenous surfactants but is primarily composed of bile salts, phospholipids and cholesterol. The other major component in bile is bilirubin. Bile is a potent surfactant but has an unusual structure as it is a cholesterol derivative in which one side of the sterol is more hydrophobic than the other (Maldonado-Valderrama et al., 2011). Thus the aggregation behaviour with other more conventional surfactants such as phospholipids and fatty acids leads to the formation of rather disc-shaped mixed micelles. The composition of bile can vary between individuals as bile acids are recirculated and can be modified by exposure to bacterial enzymes. Bile is formed from cholesterol in the liver and is conjugated with the amino acids glycine or taurine. In humans, the main bile salts are cholate and chenodeoxycholate with the glyco-form being more widely present than the tauro-forms. These bile acids are different to those found in other animals often used to study digestion such as pigs or mice. About 95% of the bile secreted into the duodenum is reabsorbed in the distal ileum by the apical sodium-dependent bile acid transporter (ASBT). The bile is then secreted from the basolateral side of the enterocytes via the OST α/β transporters. The amino acid conjugated bile is largely deconjugated by bile salt hydrolase secreted by gut microbiota, primarily in the large intestine, where some may be absorbed.

Although bile is secreted into the duodenum from the gall bladder, it originates in the liver and is simply stored in the gall bladder ready for use. The multistep enzymatic conversion of cholesterol into bile acids confers surface active properties that are crucial for their physiological functions in hepatic bile formation and absorption of dietary lipids and fat-soluble vitamins from the small intestine. The immediate products of bile acid synthesis are referred to as primary bile acids. In humans these consist of cholic acid (3α,7α,12α-trihydroxy-5β-cholanoic acid) and chenodeoxycholic acid (3α,7α-dihydroxy-5β-cholanoic acid). Although both mice and pigs are often used as models for human digestion, murine and porcine bile compositions are very different to that of humans.

Transport of digestion products from the lumen to the epithelium of the small intestine does not rely on diffusion but on the efficient mixing of enzymes, bile and chyme. A simple calculation of the diffusion of for example, glucose will show that if we assume the intestinal diameter to be 1 cm, then the cross-sectional area of the intestine would be 7.8×10^{-5} m^2. The glucose molecule is about 1 nm in radius, the viscosity of the chyme at the very best case is equal to water but let us approximate that to 0.001 Pas and of course the temperature is 37 °C. From the area we can set the mean square displacement of the glucose at 7.8×10^{-5} m^2 and the diffusion coefficient is thus 2.27×10^{-10} m^2/s. From these values we can calculate the time taken for the glucose to diffuse from the centre of the lumen to the gut wall would be ~24 h. Because of this there is significant interest in factors that affect the efficiency of mixing such as the viscosity of the chyme or the presence of particulates (Gouseti et al., 2014; Lentle & de Loubens, 2015). The work of Gouseti et al. involved in vitro digestion studies using a dynamic duodenum model to simulate intestinal motility. The work illustrates the importance of mass transfer on simulated glucose absorption by using a range of food hydrocolloids. Addition of guar gum, CMC, and pectin showed a reduction in glucose bioaccessibility by up to 30% compared with aqueous solutions. The work suggests an explanation for the significant delay of in vivo postprandial blood glucose observed by the addition of hydrocolloids. Although there are indications that luminal viscosity can affect mass transfer, the luminal contents are often non-Newtonian in their rheological behaviour and shear regimes are poorly defined. Thus the effect of hydrocolloids or insoluble fibre on mixing in the small intestine is still poorly understood. The evidence presented by Lentle et al. suggests that the small intestine does not function to optimise mixing within a minimal length of small intestine or within a minimum time. Rather, it appears that postprandial contractile activity disperses chyme along the length of the small intestine and facilitates mixing within the bulk of the luminal space by kneading and folding. The resulting, relatively slow, rate of mixing within the bulk of the lumen allows for the slower rate of enzymatic diffusion into, and digestion of, nutrients within the complex milieu of the chyme. Establishing mixing throughout the lumen of the small intestine also maximises the surface area of mucosa that is available for absorption at a given time. Finally in addition to the mixing of material in the lumen, there is a boundary "unstirred" layer between the lumen and the intestinal epithelium that comprises for the most part intestinal mucus. Nutrients must diffuse through this layer before they are absorbed by the enterocytes.

An additional factor that effects transport and mixing is the architecture of the gut. There are significant differences in this between the proximal and distal ends of the small intestine. The highest rate of absorption is in the duodenum at the proximal end and this is where the surface area is maximised by the maximal length of the villi at this point. The villi then become progressively shorter towards the more distal parts of the small intestine. The impact of the villi on mixing has been investigated by Lentle et al. (Lentle & de Loubens, 2015; Lim, de Loubens, Love, Lentle, & Janssen, 2015) with the conclusion that laminar eddies at the edges of the groups of villi and augmented mass transfers in the radial direction between the inter-

villous space and the intestinal lumen improved the absorption of nutrients and mixing at the periphery of the lumen.

5 Large Intestine

The movement of material from the small intestine to the large intestine is controlled by the ileal-caecal valve. The large intestine comprises the ascending, transverse and descending parts of the colon followed by the sigmoid colon and the rectum. By the time that chyme reaches the large intestine, more than 90% of the nutrients have been removed leaving primarily dietary fibre. The colon has two main functions: Firstly, to convert as much as possible of that dietary fibre into energy for the body. This is done by the intestinal microbiota fermenting the fibre, primarily into short chain fatty acids (SCFA). Secondly to remove most of the water from the chyme in order to minimise water loss from the body. The colonic fermentation of dietary fibre into SCFA releases some 40–50% of the energy in the fibre. Thus in the distant past, when humans were hunter gatherers and their diet comprised significantly higher levels of fibre, a significant amount of the energy supplied by the diet could come from the fermentation of fibre but in the modern western diet this is very much less (Cummings & Macfarlane, 1997).

The interactions between gut microbiota, diet, and the host have been the subject of extensive research over the last 10 years. It is not the intention of this chapter to cover this research other than to highlight some key points of relevance to gut function. Almost independently of the type of substrate the colonic fermentation produces SCFAs. Butyrate is the major energy source for colonocytes, propionate is largely taken up by the liver, and acetate enters the peripheral circulation to be metabolised by peripheral tissues such as muscle. Specific SCFA may reduce the risk of developing gastrointestinal disorders, cancer, and cardiovascular disease. Butyrate has been studied for its role in nourishing the colonic mucosa and in the prevention of colon cancer by promoting cell differentiation, cell cycle arrest, and apoptosis of transformed colonocytes. Therefore an increase in SCFA production and potentially greater delivery of SCFA, specifically butyrate, to the distal colon may result in a protective effect. As a result, butyrate irrigation has also been suggested in the treatment of colitis.

6 The Gastrointestinal Mucosa

The intestinal mucosa is the site of nutrient absorption and indeed the site where digested food and other components in chyme really come into close contact with the body. Thus, the intestinal mucosa has developed to optimise nutrient absorption while minimising pathogen infection. The intestine is lined with crypts (intestinal glands) and villi (finger-like protrusions). Intestinal epithelial cells are produced in

the base of the crypts and migrate to the villus tips over a period of 3–5 days. During this migration the cells are differentiated into a number of different cell types including:

- Enterocytes—the normal absorptive cells
- Goblet cells—responsible for secreting mucin
- Endocrine cells—responsible for the detection of a range of nutrients and the secretion of gastrointestinal hormones

Mucus is secreted by goblet cells throughout the GI tract. However, the composition of the mucus layer varies significantly depending on the location. In the stomach, the primary secreted mucin is MUC5AC but MUC6 is also present while in the intestine it is MUC2 (Phillipson et al., 2008/10). The enterocytes are also protected by the membrane bound mucin MUC1 that has a role to play in regulation of the secreted mucins but does not affect their adherence to the underlying epithelium. The architecture of the mucosa has a significant effect on the properties of the mucus layer. In the stomach the layer has been shown to be striated (Ho et al., 2004) and this has also been extensively shown in the colon where the mucus forms two distinct regions, the tightly and loosely adherent layers (Johansson, Larsson, & Hansson, 2011). The tightly adherent mucus layer in healthy individuals is thought to be an effective barrier to bacterial penetration while the loosely adherent layer can provide an environment that is more conducive to bacterial growth (Johansson et al., 2008). In the small intestine there is still evidence of a tightly adherent layer but it is significantly reduced in thickness (Bajka, Rigby, Cross, Macierzanka, & Mackie, 2015) and the loosely adherent layer is more heterogeneous. Because of these differences, there are a number of other factors that contribute to the permeability of the small intestinal mucus layer to both bacteria and nutrients. Although bacteria are more easily able to penetrate the mucus layer in the small intestine, a number of antimicrobial components are co-secreted by the mucosa.

The permeability of the mucus layer to particulates clearly depends on the size, charge, and surface properties of the particles but also on the pore size of the network through which it needs to diffuse. In general the pore size of the network has been shown to be of the order of 100 nm (Mackie, Round, Rigby, & Macierzanka, 2012). However, in addition the free diffusion of particulates depends on them carrying sufficient negative charge and in the small intestine this can be imparted by bile salts adsorbing to the particle surface. In studies following the diffusion of 500 nm latex beads and also lipid digestion products, it was found that in the absence of bile the particles/lipids were unable to penetrate the mucus layer (Macierzanka et al., 2011).

The properties of the mucus layer have also been shown to be affected by other endogenous and exogenous polymers. The first of these is DNA that is woven into the mucus layer as a result of cell shedding from the tips of the villi. This is part of the normal cellular turnover and is done in a very controlled way but it does mean that cell debris including DNA is regularly added to the mucus layer around the villus tips and this can significantly increase the local viscosity of the mucus layer (Mackie, Bajka, & Rigby, 2016). Soluble dietary fibre has been shown to have the

same affect. The soluble fibre sodium alginate was shown to freely diffuse into the mucus and to have minimal effect on the bulk rheology when added at concentrations below 0.1% (Mackie, Macierzanka, et al., 2016). Despite this lack of interaction between the mucin and alginate, the addition of alginate had a marked effect on the diffusion of 500 nm probe particles, which decreased as a function of increasing alginate concentration. It was also shown that diffusion of a fluorescently labelled digested protein stabilised emulsion was decreased by the addition of 0.1% alginate to porcine intestinal mucus. This reduction may be sufficient to reduce problems associated with high rates of lipid absorption such as hyperlipidaemia. In a study using β-glucan as the soluble fibre, a preliminary study investigated the effect of doubling the β-glucan content of a porcine diet for 3 days and focussed on the properties of the intestinal mucus layer (Mackie, Rigby, Harvey, & Bajka, 2016). In vitro digestion of the enhanced β-glucan and control meals showed that over 90% of the β-glucan was released from the enhanced β-glucan diet in the simulated proximal small intestine, although this did not alter rates of nutrient hydrolysis. Measurements of the permeability of the porcine intestinal mucus showed that the diet decreased permeability to 100 nm latex beads and more importantly reduced permeability to lipid from the digested diet. The dietary fibre, β-glucan, has been shown to lower cholesterol by reducing bile recycling. The authors suggest that reducing mass transfer of bile and lipid through the intestinal mucus layer may be one way in which this decrease in bile reabsorption is enabled and that postprandial lipid absorption is prolonged.

7 Feedback and Control

In some of the previous sections, references have already been made to the complexity of the systems that control digestion. In this section, some more details of that control will be described. The sensing of food by G-protein couple receptors (GPCRs) starts but is by no means limited to the mouth. Although it is clear that oral processing and taste can affect digestion this has already been discussed. There are a number of sensors in the stomach and small intestine that allow the body to respond to the food that has been consumed. Ghrelin is an acylated 28-amino acid peptide hormone produced primarily by the stomach and to a lesser extent the small intestine. Ghrelin increases appetite and gastrointestinal motility but decreases insulin secretion (Karhunen, Juvonen, Huotari, Purhonen, & Herzig, 2008). It also decreases the response of gastric mechanosensors making them less sensitive to gastric distension. Another GI hormone that has a significant effect on gastric behaviour is CCK, which is secreted by I-cells in the proximal small intestine. CCK affects digestion by slowing down gastric emptying, increasing gall bladder contraction and increasing gastric mechanosensor sensitivity. Another hormone that is secreted by endocrine cells in the proximal small intestine is glucose-dependent insulinotropic peptide (GIP), which shares the insulinotropic effect with

glucagon-like peptide 1 (GLP-1). GIP is secreted by K-cells, which like I-cells are in high density in the proximal small intestine but decrease in density more distally. GLP-1, oxyntomodulin and peptide YY (PYY) are secreted by L-cells that are in low density in the duodenum and increase in density towards the ileum and are most widespread in the colon. PYY mediates the so called ileal and colonic brakes, mechanisms that ultimately slow gastric emptying and promote digestive activities to increase nutrient absorption and enhance satiety. GLP-1 is thought to play an important part in the ileal brake a mechanism regulating the flow of nutrients from the stomach into the small intestine. In addition, GLP-1 is an incretin hormone and increases glucose-dependent insulin release, inhibits glucagon secretion, and increases pancreatic ß-cell growth. These gastrointestinal hormones along with others not discussed here are responsible for controlling the passage of nutrients, energy metabolism, and satiation.

8 Psychology Versus Physiology

This chapter has described the body's physiological responses to food. However, it is well known that there is also a significant psychological component to our response to food. A well-known example is the Nobel Prize winning work of Pavlov on conditioning associated with salivation in dogs (Pavlov, 1927). The same behaviour is seen in humans when we see or even think about certain foods; but does this affect responses such as appetite and satiation?

Satiation signals arise from multiple sites in the GI tract. Ingested food evokes satiation by two primary effects, namely gastric distension and release of peptides from enteroendocrine cells. The hindbrain is the principal central site receiving input from fast-acting satiation signals transmitted both neurally and hormonally. Although the perception of fullness clearly involves conscious awareness, perception of GI feedback signals is not required for satiation. Therefore, gut-hindbrain communication is sufficient for satiation, although this normally interacts with higher cognitive centres to regulate feeding (Cummings & Overduin, 2007). The article by Cummings and Overduin, gives an excellent overview of the physiological mechanisms involved in the regulation of food intake.

Because of concerns about the high levels of obesity in developed countries, there has been significant research on eating behaviour and appetite showing that in addition to the satiety signals, environment can have a significant effect on energy intake (Chambers, McCrickerd, & Yeomans, 2015; Rolls, Hetherington, & Burley, 1988). These articles concluded that food can be manipulated in terms of structure and composition to enhance the consumer's experience of satiety but that a combination of factors will ultimately determine the foods effect on appetite control. The authors suggested that taking this integrated approach to satiety will lead to the more optimised development of high satiety foods. The psychology of eating and feeling of satiation is discussed in more detail in Chap. 10.

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