British Journal of Nutrition (2002), **88**, Suppl. 2, S159–S163
DOI: 10.1079/BJN2002681

Gastrointestinal physiology and functions

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While the health benefit of a functional food may be a metabolic response that lowers risk for disease, the actual target for the food or food component may be on the functioning of the gastrointestinal tract (GIT). For example, slowing absorption from the intestine, as measured by examining the appearance of the nutrient or food component in the blood, the hormone response associated with absorption of the compound or excretion of the compound, may provide a health benefit. However, the food component may slow absorption by delaying gastric emptying, altering the mixing within the intestinal contents or decreasing the availability of digestive enzymes in the intestine. These measures of GIT function provide validation of the mechanisms by which the functional food or food components affect metabolism. Bioavailability of physiologically active compounds from foods will be determined by the digestibility of foods that contain these compounds, their subsequent absorption and utilization by tissues. The physical structure of foods contributes to the functional effects of foods as well as to the availability of compounds from foods. For example, recent studies have demonstrated that changing the viscosity of the gut contents alters absorption and GIT response. Additionally, food structures such as the plant cell wall change the availability of absorbable compounds along the gastrointestinal contents. The areas of probiotics and prebiotics have highlighted the potential importance of gut microflora in health. While evidence suggests biological activity relevant to disease risk reduction, the long-term implications of the microbial activity have yet to be established.

Gastrointestinal tract: Health benefit: Absorption: Digestibility: Pro-/prebiotics

Introduction

The gastrointestinal tract (GIT) serves as an interface between the body and the external environment. The GIT is a highly specialized organ system that allows man to consume food in discrete meals as well as a very diverse array of foodstuffs to meet nutrient needs. In the GIT food is converted to compounds that can be absorbed into the body. The organs of the GIT include the mouth, oesophagus, stomach, small intestine and large intestine; in addition, the pancreas and liver secrete into the small intestine. The system is connected to the vascular, lymphatic and nervous systems to facilitate regulation of the digestive response, delivery of absorbed compounds to organs of the body and the regulation of food intake. Johnson (1997) provides an excellent overview of the gastrointestinal system. A primary function of the GIT is to extract nutrients from the complex mixture of foods as consumed. Foods contain more than essential nutrients, and the GIT has a role in metabolizing and eliminating non-nutrient and toxic compounds as well.

Functional foods include the categories of food products that are consumed for a specific health benefit or as part of a dietary plan to lower risk for chronic disease. As such, the components of these foods may exert their effects through a direct action on the GIT or become available to other target organs in the body after absorption from the GIT. In this context, three perspectives are useful to examine the importance of GIT physiology and functions in mediating the effects of functional foods: (1) meal-induced responses in the GIT caused by factors in foods, which may result in longer-term adaptive changes; (2) the ability of foods or mixtures of foods to alter the digestive and absorptive functions of the GIT in a manner that influences metabolism; and (3) the impact that the GIT, through its adaptation to diet, has on risk factors for disease. Examples are used below to illustrate each of these perspectives regarding the physiology and function of the GIT.

Meal-induced responses

Regulation of the gastrointestinal response to a meal involves a complex set of hormone and neural interactions.

Abbreviations: CCK, cholecystokinin; GIT, gastrointestinal tract; SCFA, short-chain fatty acids.

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The sensory, macronutrient composition and physical properties of the diet modulate the response to a meal during the cephalic, gastric and intestinal phases of digestion. In the cephalic phase the sight, smell and taste of foods stimulate the secretion of digestive juices into the mouth, stomach and intestine, essentially preparing these organs to digest the foods to be consumed. Experiments, in which animals are sham-fed so that food consumed does not actually enter the stomach or intestine, demonstrate that the cephalic phase accounts for about 20 % or more of the secretion into the gut. The gastric and intestinal phases occur when food and its components are in direct contact with the stomach or intestine, respectively. During these phases the distension of the organs with food, as well as the specific composition of the food, can stimulate a GIT response. The GIT is the richest endocrine organ in the body, containing a large array of peptides; however, the exact physiological function of each of these compounds has not yet been established. Five peptides, gastrin, cholecystokinin (CCK), secretin, gastric inhibitory peptide and motilin, are established as regulatory hormones in the GIT and several factors affect their release and subsequent actions. Among the established gastrointestinal peptides, secretin stimulates secretion of fluid and bicarbonate from the pancreas, gastrin stimulates secretion in the stomach, gastric inhibitory peptide inhibits gastric acid secretion and stimulates insulin release, and motilin stimulates the motility of the upper GIT (Bloom, 1983). In addition to the various factors causing release of these hormones and the response to them, physiologists are also interested in the interactions among hormones, as well as with the nervous system, since the response to a meal involves release of many factors. Of these established hormones, CCK provides a useful example to examine some implications of meal-induced responses.

CCK is released from cells of the upper small intestine into the blood. Dietary protein and fat stimulate its release from the intestine, while digestible carbohydrates have no effect on release of the hormone. Gastric acid inhibits CCK secretion. Once released CCK can inhibit gastric emptying, stimulate secretion of acid in the stomach and pancreatic juice into the small intestine, and stimulate contraction of the gallbladder, which releases bile into the intestine. In addition, it stimulates motility and growth in the GIT. Newer identified functions of CCK include inhibition of food intake and stimulation of insulin release. Thus CCK is a hormone that prepares the GIT to digest food by stimulating secretion, regulates the rate of digestion and absorption by controlling gastric emptying, helps signal the termination of eating once food is in the intestine, and helps facilitate the storage of energy consumed in the meal. Only recently have reliable immunoassays become available for CCK that allow investigation of typical meal-stimulated CCK responses. Test meals that provide about 25 % energy from fat stimulate a peak increase in CCK concentration of about 3–6 pmol/l (Bourdon *et al.* 1999, 2001). Increasing the amount of fat in an infusion into the intestine of rats increases peak CCK response as well as the length of time that plasma CCK concentrations are elevated above baseline. Including a source of β-glucan, a viscous polysaccharide, in a test meal does not change the peak concentration of CCK released after a meal but prolongs the time that CCK is significantly elevated above baseline (Bourdon *et al.* 1999). When cooked dry beans are included in the test meals, the CCK response is doubled compared with a test meal that is low in fibre-rich foods (Bourdon *et al.* 2001). This effect of dry beans to enhance CCK release may be related to their fibre content and to the presence of trypsin inhibitor (Schwartz *et al.* 1994). In a subsequent study we demonstrated in women that addition of fat or fibre to a test meal that is relatively low in fat or fibre will significantly ($P < 0.05$) increase the CCK response to a test meal (Burton-Freeman *et al.* 2002). Thus while protein and fat are the primary macronutrients that stimulate the release of CCK, the presence of non-digestible polysaccharides appears to modulate the pattern of CCK release. This meal-induced response of CCK has implications for understanding the potential effects of fibre on insulin release and/or satiety (Holt *et al.* 1992; Rushakoff *et al.* 1993; Burton-Freeman, 2000). The subjective measures of satiety recorded by subjects after consuming test meals were correlated with the CCK response. Thus meals that elicit the highest CCK response are perceived by human subjects as the most filling.

This example illustrates that the meal-induced response causes secretion of digestive juices essential for the digestion of food components; however, the response also influences other metabolic responses to the meal. The GIT is one of the richest endocrine organs in the body, and CCK is just one example of a variety of hormones released during the response to a meal (Bloom, 1983; Johnson, 1997). These hormones have metabolic effects beyond the GIT. The system is simultaneously preparing the GIT to digest and absorb the meal that has been consumed in an efficient manner and also is signalling short-term satiety so that feeding is terminated at an appropriate point.

Digestive and absorptive functions of the gastrointestinal tract

The GIT breaks down food into absorbable compounds through mechanical and biochemical processes. Chewing breaks food into smaller particles that can mix more readily with the GIT secretions. In the mouth saliva lubricates the food bolus so that it passes readily through the oesophagus to the stomach. The sensory aspects of food stimulate the flow of saliva, which not only lubricates the bolus of food but also is protective and contains digestive enzymes. Swallowing is regulated by sphincter actions to move the bolus of food into the stomach. The motility of the stomach continues the process of mixing food with the digestive secretions, now including gastric juice, which contains acid and some digestive enzymes. The action of the stomach continues to break down food into smaller particles prior to passage to the intestine. The stomach, which after a meal may contain over a litre of material, regulates the rate of digestion by metering chyme into the small intestine over several hours. Several factors can slow the rate of gastric emptying; for example, solids take longer to empty than liquids, mixtures relatively

high in lipid take longer to empty, and viscous or thick mixtures take longer to empty than watery, liquid contents.

Once digesta is in the small intestine, peristaltic motor activity propels it along the length of the intestine and segmentation allows mixing with digestive juices in the intestine, which include pancreatic enzymes, bile acids and sloughed intestinal cells. Digestion of macronutrients, which began in the mouth, continues in the small intestine primarily through the action of enzymes. Each of the macronutrients has a unique set of enzymes that break the macromolecules into sub-units that can be taken up by the absorptive systems in the intestinal cells. The phytochemicals that have been investigated for lowering risk of chronic disease are part of the cell matrix in plant foods and depend on the mechanical and biochemical disruption of the food matrix to become available for absorption from the GIT. Thus factors that alter the rate and site of digestion and absorption will alter their bioavailability as well. To illustrate how the GIT functions of digestion and absorption are important for bioavailability and subsequent metabolism, a useful example is to consider some of the factors that affect carbohydrate digestion and utilization.

Carbohydrates are categorized as digestible or non-digestible. Digestible carbohydrates are the various sugar-containing molecules that can be digested by amylase or the saccharidases of the small intestine to sugars that can be absorbed from the intestine. The predominant digestible carbohydrates in foods are starch, sucrose, lactose (milk sugar) and maltose. Foods may also contain simple sugars such as glucose or fructose that do not need to be digested before absorption from the gut. α-Amylase, which hydrolyses the α(1–4) linkages in starch, is secreted in the mouth from salivary glands and from the pancreas into the small intestine. The action of amylase produces smaller carbohydrate segments that can be hydrolysed further to sugars by enzymes at the brush border of the intestinal cells. This hydrolysis step is closely linked with absorption of sugars into the intestinal cells.

The glucose absorbed from digestible carbohydrate stimulates the release of insulin. In healthy, normal-weight individuals, the postprandial increase in blood insulin concentration is correlated with the intake of carbohydrate (Lee & Wolever, 1998; Lu *et al.* 2000). Insulin is important for regulation of energy metabolism in the body and its release after a meal promotes energy storage. Thus, in healthy individuals, the postprandial release of insulin results in glucose and amino acid uptake by cells and stimulates glycolysis and synthesis of glycogen, protein and fatty acids. The rate and pattern of carbohydrate digestion and absorption will influence the appearance of glucose in blood and stimulation of insulin secretion. Consequently there is considerable interest in how factors that influence carbohydrate digestion and absorption might affect energy metabolism during the postprandial period. Slowing gastric emptying, which slows entry of digestible carbohydrate into the small intestine, blunts the glycaemic and insulinaemic response to a meal. The hormone CCK, discussed above, also modulates the release of insulin. In healthy individuals dietary factors that enhance CCK reduce insulin and glucose response (Liddle *et al.* 1988; Rushakoff *et al.* 1993; Liddle, 2000). CCK may function by stimulating an early release of insulin before plasma glucose begins to increase. This priming of the system results in an overall lower glycaemic and insulinaemic response to a meal (Bloom, 1983). In certain types of obesity, cells become insulin-resistant, which results in elevated plasma levels of insulin, leading to non-insulin dependent diabetes mellitus. To help manage this condition, dietary factors such as viscous polysaccharides or α-amylase inhibitors that can blunt the postprandial rise in glucose have been investigated.

Non-digestible carbohydrates cannot be digested by the enzymes in the small intestine and are the primary component of dietary fibre. Most of these non-starch polysaccharides are part of the plant cell wall. The most abundant polysaccharide in plant tissue is cellulose, which is a glucose polymer with β(1–4) links between the sugars. Amylase, the starch-digesting enzyme of the small intestine, can hydrolyse only α linkages. The non-digestible carbohydrates also include hemicelluloses, pectins, gums, oligofructose and inulin. While non-digestible, they do affect the digestive process because they provide bulk in the intestinal contents, hold water, can become viscous or thick in the intestinal contents, and delay gastric emptying. Viscosity is correlated with the ability of polysaccharides to lower plasma cholesterol levels (Gallaher & Hassel, 1995; Carr *et al.* 1996; Gallaher *et al.* 2000). Slowing gastric emptying is associated with blunting of the glucose and insulin response to a meal as well as enhancing feelings of satiety. In addition, non-starch polysaccharides are the primary substrate for growth of the micro-organisms in the large intestine and contribute to stool formation and laxation. Products of microbial action include ammonia, gas and short-chain fatty acids (SCFA). SCFA are used by cells in the large intestine for energy and some appear in the circulation and can be used by other cells in the body for energy as well. Thus, while dietary fibre is classified as non-digestible carbohydrate, the eventual digestion of these polysaccharides by microbes does provide energy to the body. Current research is focused on the potential effect of SCFA on the health of the intestine and their possible role in the prevention of gastrointestinal diseases.

In summary, the rate at which macromolecules in food are digested and absorbed influences metabolism in the body. Additionally, physical properties of foods such as viscosity will influence the bioavailability and utilization of nutrients and other compounds in foods by the body.

The potential impact of the gastrointestinal tract on health

The examples above illustrate that the GIT modulates metabolic responses through meal-induced responses to diet properties and composition, and through the rate of digestion and absorption. These examples indicate that the physiology and function of the GIT can influence risk factors for non-communicable diseases and thus the GIT has an important role in maintaining health. Research on dietary fibre has illustrated that actions within the GIT modify risk factors for non-communicable diseases since

fibre is non-digestible and exerts its effects on metabolism during its transit through the GIT. For example, the ability of certain fibres to reduce plasma cholesterol is associated with an increase in viscosity of digesta (Carr *et al.* 1996) and with increased excretion of bile acids due to binding or adsorption by fibre fractions (Buhman *et al.* 2000). Non-starch polysaccharides are the primary substrates for microflora in the large intestine.

The fact that fibre is utilized by the GIT microflora has stimulated research on the potential impact of the metabolism of this microflora on reducing the risk of disease and promoting health. Fermentable carbohydrates increase the microbial mass in the large intestine, which contributes to stool bulk and aids laxation (Cummings *et al.* 1992; Chen *et al.* 1998). Fermentation also produces SCFA, which provide energy from highly fermented polysaccharides. SCFA are utilized by the intestinal epithelial cells, liver and muscle and have a trophic effect on the intestinal epithelium. Of considerable research interest is the potential role of butyrate in protecting the colon from developing cancer because of its role in cell differentiation and growth (Salminen *et al.* 1998). Cummings *et al.* (2001) have summarized the effects of various substrates, including inulin, oligofructose, resistant starch, polydextrose, pectin and arabinogalactan, on SCFA production. While each of these substrates can be fermented by the microflora from the large intestine, it is more difficult to change markedly the molar ratio of SCFA produced. The fermentability of carbohydrates may also be associated with metabolic enzymes, including cell signal transduction pathways in colonic mucosal cells (Pajari *et al.* 2000) and the enzymes associated with microbial metabolism of mutagenic compounds (Cummings *et al.* 2001).

Approximately 10^{12} micro-organisms reside in the GIT, most of which are in the large intestine. Some of these microbes are considered harmful and have been associated with intestinal diseases, while others are considered beneficial and have been associated with decreasing risk for chronic disease as well as the synthesis of vitamins, facilitating mineral absorption and immune stimulation. The microflora of the intestine is complex and diverse and attempts to modify the composition by dietary means have not been very effective. However, feeding cultured products that contain certain strains of *Bifidobacterium* or *Lactobacillus* have been reported to have metabolic effects that impact health. Typically, the response is seen only while the product containing a live culture is fed, suggesting that the bacteria do not colonize the GIT permanently but remain metabolically active during their transit thorough the GIT. At the simplest level these cultures are reported to improve lactose digestion in lactose-intolerant individuals and, at a more complex level, stimulate several facets of immune response (Salminen *et al.* 1998; Gill *et al.* 2000). The functional significance and sustainability of the immuno-stimulation have not been reported. However, certain live cultures have been reported to help ameliorate symptoms of diarrhoea. The emerging research in this area suggests that we still have a poor understanding of the significance of the microbial population in the GIT and its role in promoting health and reducing risk for disease.

Conclusions and need for future research

While the health benefit of a functional food may be a metabolic response that lowers risk for disease, the actual target for the food or food component may be on the functioning of the GIT. This situation raises interesting challenges for assessing the response to functional foods and the validation of health claims. For example, there may be a health benefit from slowing absorption from the intestine; slower absorption might be measured by examining the time course for appearance of the nutrient or food component in the blood, measuring the hormone response associated with absorption of the compound, or measuring parameters related to excretion of the compound. However, the food component may slow absorption by delaying gastric emptying, altering the mixing within the intestinal contents or decreasing the availability of digestive enzymes in the intestine. These measures of GIT function provide validation of the mechanisms by which the functional food or food component affects metabolism. Such validation is essential to demonstrate that the food or food component has a specific effect on health or risk for disease. For example, health claims for sources of dietary fibre and reduced risk of cardiovascular disease are strengthened by demonstrating the mechanisms by which fibre lowers plasma cholesterol levels. Research is needed to validate the links between various aspects of gastrointestinal function and subsequent health effects of functional foods.

Understanding the GIT response to foods and meals is critical to understanding the metabolic effects of functional foods. Three important research needs are evident from a review of the function and physiology of the GIT in relation to foods. A primary need is to determine the bioavailability of physiologically active compounds from foods. Bioavailability will be determined by the digestibility of foods that contain these compounds, their subsequent absorption and their utilization by tissues. For certain compounds their mode of action will be in the GIT and the focus will be on interaction with organs of the GIT; however, in other cases, absorptive mechanisms will be important in determining the metabolic effects of functional foods. The physical structure of foods has often been overlooked in understanding the metabolic response to diet. However, this structure contributes to the functional effects of foods as well as to the availability of compounds from foods. For example, recent studies have demonstrated that changing the viscosity of the gut contents alters absorption and GIT response. The implications of these studies need to be investigated further. Additionally, food structures such as the plant cell wall change the availability of absorbable compounds along the gastrointestinal contents and raise interesting research questions about the importance of plant cell walls beyond their content of dietary fibre. A third area of research with emerging importance relative to the GIT concerns the function of microflora along the intestines. Studies on probiotics and prebiotics suggest that this microflora is responsive to dietary influences. Understanding the influence of the GIT microflora on health promotion and

disease prevention is a complex but important research agenda.

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