Food and Symptom Generation in Functional Gastrointestinal Disorders: Physiological Aspects

Ricard Farré, PhD[1] and Jan Tack, MD, PhD[1]

The response of the gastrointestinal tract (GIT) to ingestion of food is a complex and closely controlled process, which allows optimization of propulsion, digestion, absorption of nutrients, and removal of indigestible remnants. This review summarizes current knowledge on the mechanisms that control the response of the GIT to food intake. During the cephalic phase, triggered by cortical food-related influences, the GIT prepares for receiving nutrients. The gastric phase is dominated by the mechanical effect of the meal volume. Accumulation of food in the stomach activates tension-sensitive mechanoreceptors, which in turn stimulate gastric accommodation and gastric acid secretion through the intrinsic and vago-vagal reflex pathways. After meal ingestion, the tightly controlled process of gastric emptying starts, with arrival of nutrients in the duodenum triggering negative feedback on emptying and stimulating secretion of digestive enzymes through the neural (mainly vago-vagal reflex, but also intrinsic) and endocrine (release of peptides from entero-endocrine cells) pathways. Several types of specialized receptors detect the presence of all main categories of nutrients. In addition, the gastrointestinal mucosa expresses receptors of the T1R and T2R families (taste receptors) and several members of the transient receptor potential channel family, all of which are putatively involved in the detection of specific tastants in the lumen. Activation of nutrient and taste sensors also activates the extrinsic and intrinsic neural, as well as entero-endocrine, pathways. During passage through the small bowel, nutrients are progressively extracted, and electrolyte-rich liquid intestinal content with non-digestible residue is delivered to the colon. The colon provides absorption of the water and electrolytes, storage of non-digestible remnants of food, aboral propulsion of contents, and finally evacuation through defecation.

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INTRODUCTION

The gastrointestinal tract (GIT) is the organ system that controls ingestion and transit of food while digestion, absorption of nutrients, and removal of indigestible remnants and waste products takes place (1). This function needs to be balanced with the need for protection and defense, as during food transit, the gut wall is constantly exposed to potentially noxious ingested elements and infectious agents such as bacteria (2). Proper regulation of intestinal propulsion, secretion, absorption, blood flow, and defense against pathogens requires a correct interplay of multiple cellular, humoral, and neural pathways. In this article, current views and understanding on the response of the GIT to food ingestion are summarized.

STRUCTURES INVOLVED IN THE RESPONSE TO NUTRIENT INGESTION

The contents of the intestinal lumen are monitored by different types of enteroendocrine cells, including enterochromaffin cells, which are scattered throughout the intestinal epithelium. The mucosa itself is actively involved in absorption of nutrients from the gastrointestinal lumen, as well as in secretion of water and electrolytes and digestive enzymes, although the latter occurs mainly through specialized glands or accessory organs. Intestinal transit occurs through relaxatory and contractile activity of the circular and longitudinal muscle layers, with interstitial cells of Cajal serving as pacemaker cells by generating rapidly rising, large potential changes that conduct into the intestinal smooth muscle syncytium (3).

To accurately coordinate all major gastrointestinal functions, such as absorption, secretion, blood flow, and motility, the GI tract receives extensive autonomic innervation. Both the submucosa and the smooth muscle layer contain ganglionated nerve plexi that constitute the enteric nervous system, an extensive neural network embedded in the wall of the gut that is able to control GI functions largely independent from the central nervous system (CNS) (4).

Besides these extensive intrinsic networks of enteric neurons, the nervous pathways that connect to the CNS also innervate the

[1]Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Leuven, Belgium. **Correspondence:** Jan Tack, MD, PhD, Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Herestraat 49, Leuven B-3000, Belgium.
E-mail: jan.tack@med.kuleuven.be
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bowel. This extrinsic innervation comprises a sympathetic and a parasympathetic component. Together with the enteric nervous system, these two components make up the autonomic nervous system. The extrinsic innervation of the GIT is predominantly an afferent nerve route, referred to as "the gut-brain axis", which conveys sensory information to the CNS. Visceral afferent nerves comprise vagal afferents, which have their cell bodies in the nodose and jugular ganglia and project to the nucleus tractus solitarius, and spinal afferents, which enter the CNS via the spinal cord. Spinal afferents can be subdivided in splanchnic and pelvic afferents, with their respective cell bodies in the thoracolumbar and lumbosacral dorsal root ganglia. Sensory information conveyed by visceral afferents is not only important for the integration of visceral sensation but also provides input for the coordination of gut reflex activity through efferent nerves (5).

UPPER GIT: FOOD INTAKE AND DIGESTION

Ingestion of nutrients induces profound changes in gastrointestinal motility, gastrointestinal and pancreatic secretion, and release of gastrointestinal hormones. These changes serve to coordinate the digestive process and to adapt it to the nature and composition of the ingested nutrients. The type of physiological processes and their controls depend on the phases of nutrient ingestion, the site of the GIT that is exposed to nutrients, and the physicochemical properties of the meal.

Phases of physiological events related to food intake

The behavior of the upper GIT with regards to food intake can be subdivided into three phases, depending on the level where nutrients are present: the cephalic phase, gastric phase, and intestinal phase. Each phase has its own specific physiological role and control mechanisms.

The *cephalic phase*, which consists of innate and learned physiological responses to sensory signals, precedes food ingestion, and prepares the GIT for receiving and processing the food that is about to be ingested. The cephalic phase is triggered by the sight, smell or thought of food, or any other signal that has been conditioned to be associated with food intake. Activation of secretion of saliva, gastric acid, and pancreatic secretion, as well as inhibition of phasic motility in the upper GIT, is induced through vagal efferents. In addition, the release of a number of peptide hormones, such as gastrin and ghrelin, is triggered during the cephalic phase (6).

The *gastric phase* is mainly triggered by the mechanical effect of the volume of food that is ingested and stored in the stomach. Arrival of food in the stomach activates mechanoreceptors, which in turn will stimulate gastric relaxation and gastric acid secretion through the intrinsic and vago-vagal reflex pathways (**Figure 1**). There is only a limited role for chemosensing of the presence of nutrients in the stomach. After food intake, when the stomach gradually empties, the role of gastric relaxation and distension diminishes and intestinal exposure of the nutrients will dominate physiological control mechanisms (1).

The *intestinal phase* is mainly triggered by chemoreceptor activation in the proximal small bowel, where the presence of oligopeptides stimulates the release of gastrin from duodenal G cells. Mechanical factors may still contribute to some extent, as distension of the duodenum also stimulates gastrin release. In contrast, acidification of the duodenum will stimulate the release of secretin, which inhibits gastric acid secretion and stimulates pancreatic bicarbonate secretion. The presence of lipids releases several peptides (cholecystokinin (CCK), glucose-dependent insulinotropic peptide (GIP), neurotensin, peptide YY (PYY), and somatostatin, among others) that synergistically contribute to inhibition of gastric acid secretion and stimulation of pancreatic enzyme secretion. The presence of lipids, with release of CCK, also stimulates gallbladder contraction. At the same time, negative feedback vago-vagal reflexes, in synergy with hormonal effects, will inhibit gastric contractility and will slow down gastric emptying in response to the presence of nutrients, low pH, or hyperosmolar contents in the small intestine (1,7).

The gastric and intestinal phases require the presence and detection of food in the upper GIT. A variety of sensory mechanisms are involved in nutrient sensing, which allows the coordination of these phases.

Nutrient sensing in the upper GIT

Sensory modalities in the upper GIT. The sensory repertoire of the GIT relies on three types of modalities: mechanosensitivity, chemosensitivity, and thermosensitivity, all of which can be activated by the ingestion of food. The arrival of food in the upper GIT triggers several physiological events, including direct actions on mucosal cells, changes in peptide hormone release, activation of local reflexes and long-distance (prevertebral) reflexes, and finally signaling to the brain, which may lead to perception.

Mechanoreceptors in the upper GIT. Perception of mechanical changes elicited by food ingestion requires the activation of mechanoreceptors. Observations in animal models suggest the existence of two conceptual types of mechanoreceptors. Mechanoreceptors arranged in a parallel fashion to intestinal smooth muscle respond to stimuli that elongate hollow viscera. Mechanoreceptors arranged in series respond to stimuli that increase the tension of the stomach wall. During distension of hollow viscera, activation of both elongation and tension mechanoreceptors is expected to occur (**Figure 2**) (8,9). Studies in healthy volunteers, which used indirect assessments of influences of elongation and contraction, support the hypothesis that visceral mechanosensitivity relies mainly on in-series mechanoreceptors that respond to increases in tension (10,11).

It has been suggested that the simplified law of Laplace can be used to estimate wall tension during distension of hollow viscera, and that this level of wall tension determines the level of perception (12). However, the use of Laplace's law has been criticized in several studies in which variance in sensation scores was not accounted for by changes in wall tension estimated by Laplace's law (13–16). The involvement of tension receptors in mediating responses to nutrient ingestion is important both from a pathophysiological and therapeutic perspective. Tension receptors are particularly sensitive to changes in tone of hollow viscera, and

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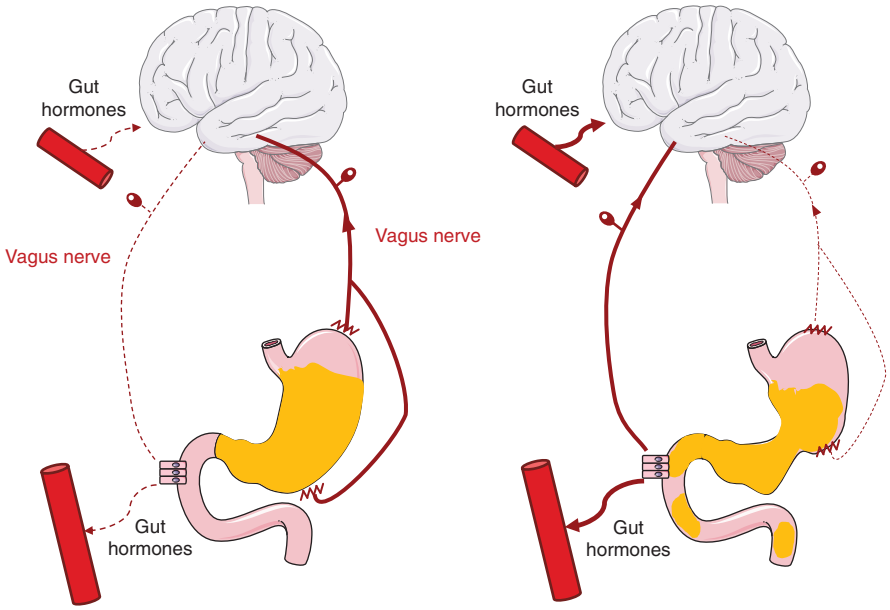

Figure 1. Signaling from the upper gastrointestinal tract (GIT) during and after food intake. Left: During and initially after food intake, gastric distension and gastric accommodation are major determinants of nutrient signaling. Signals are generated from gastric mechanosensitive receptors, which relay their information via vagal nerves to the brain. Right: After food intake, when the stomach gradually empties, the role of gastric distension in nutrient signaling decreases and the focus is shifted to signaling-related intestinal exposure to nutrients. The presence of various types of nutrients is mainly sensed by entero-endocrine cells in the mucosa of the small intestine that release a variety of peptides and small molecules. These can act locally, activate vagal nerves that signal to the brain, or enter the blood stream and act as hormones.

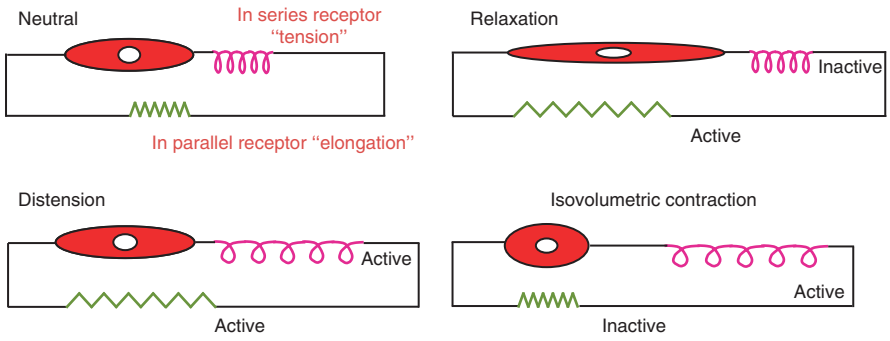

Figure 2. Schematic conceptual model of mechanoreceptors in the gastrointestinal tract (GIT), relative to the muscular compartment. The four panels represent the modeled behavior of in-series tension receptors and in-parallel elongation receptors under various physiological conditions. Top left panel: Neutral condition. Bottom left panel: During distension, both elongation and tension receptors are activated. Muscular contraction status is unchanged. Top right panel: During relaxation, elongation but not tension receptors are activated. The muscular component is lengthened. Bottom right panel: During isometric contraction, only tension receptors but not elongation receptors are activated. The muscular component is shortened.

manipulations of visceral tone therefore provide the pathways through which mechanical responses to nutrient ingestion can be inhibited or intensified. Animal studies have shown that activation of in-series mechanoreceptors occurs during distension and during contraction against a resistance; they are inactivated during relaxation (9).

Nutrient-sensing chemoreceptors in the upper GIT. A number of specialized receptors in the upper GIT are involved in detecting the presence of all main categories of nutrients in the lumen (**Figure 3**).

In L- and K-type entero-endocrine cells that release GLP-1 and GIP in response to luminal glucose, this is mediated through membrane depolarization, action potential discharge with Ca2+ entry, and hormone release. Based on cell-culture studies, glucose induces depolarization through activation of the sodium glucose co-transporter-1 or through closure of the ATP-sensitive potassium K^{ATP} in response to intracellular metabolization of glucose (17,18).

It is well established that intestinal lipid infusion induces a number of physiological events, including afferent signaling to the brain, but the candidate receptors involved in lipid sensing have

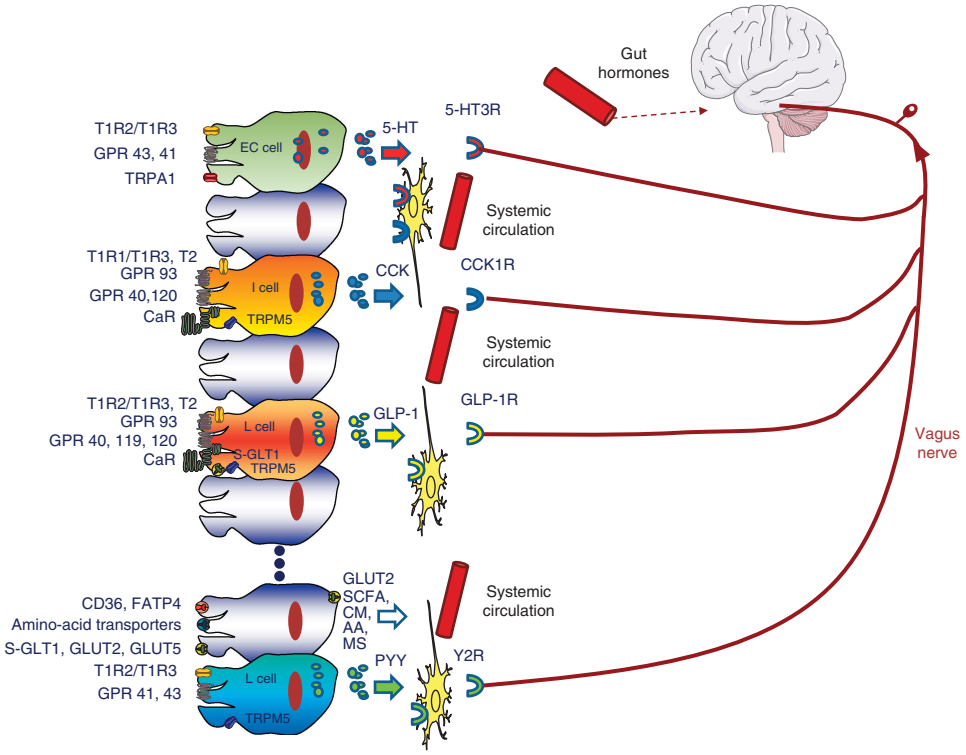

Figure 3. Small-intestinal nutrient sensing and transmission of signals to the brain. The presence of nutrients is mainly detected by specialized receptors on the apical side of entero-endocrine cells. Upon their activation, they will allow a rise in intracellular calcium and release of signaling molecules (e.g., 5-hydroxytryptamine) and gastrointestinal hormones (e.g., CCK, GLP1, and PYY). These peptides will act locally on nerves and epithelial cells, will signal to the brain via the vagus nerve, and may enter systemic circulation. Nutrient absorption occurs through carriers in the brush-border membrane of enterocytes. AA, amino acid; CaR, Ca-sensing receptor; CCK, cholecystokinin; CCK1R, CCK type 1 receptor; CM, chylomicron; EC cell, entero-endocrine cell; FATP4, fatty acid transport protein 4; GPR, G-protein-coupled receptor; GLP-1, glucagon peptide 1; GLP-1R, GLP-1 receptor; 5-HT, 5-hydroxytryptamine; 5-HT3R, 5-HT type 3 receptor; MS, monosaccharide; PYY, peptide tyrosine tyrosine; SCFA, short chain fatty acid; TRPA1, transient receptor potential channel ankyrin type 1; TRPM5, transient receptor potential channel melastatin type 5; Y2R, Y2 receptor.

only been identified more recently. Fatty acids are sensed by the G-protein-coupled receptors GPR40, GPR41, GPR43, and GPR120, depending on their aliphatic chain length (19). In addition, oleoylethanolamide, produced in the small intestine in response to fatty acid exposure, activates GPR119. GPR120 and GPR40, the receptors for long and medium chain fatty acids, have been implicated in fatty acid-induced CCK, GLP-1, and GIP secretion by I, L and K cells, respectively. In addition, short-chain fatty acids acting on GPR43 and GPR41 have been implicated in control of PYY and 5-hydroxytryptamine release (19,20). The fatty acid translocase CD36, expressed by taste bud cells in the oral cavity as well as enterocytes, mediates cellular uptake of very long-chain fatty acids, and has been implicated in lipid sensing and the feeding inhibitory effect of intestinal lipid infusions, at least in part mediated through synthesis of the endocannabinoid oleoylethanolamide (21).

Intestinal amino acid-sensing mechanisms have also been identified. The G-protein-coupled calcium-sensing receptor CaR is expressed in gastric, intestinal, and colonic epithelial cells and is able to detect aromatic and some aliphatic amino acids under stable calcium concentrations. Activation of this receptor in the stomach induces secretion of acid, pepsinogen, and mucus. CaR has also been implicated in the stimulation of CCK and GLP-1 secretion by amino acids. The G-protein-coupled receptor GPRC6A senses basic amino acids, is expressed in the stomach and the pancreas, and also stimulates gastric acid and pepsinogen secretion. In the small intestine, GPR93 is expressed on enterocytes and activated by protein hydrolysate. GPR93 has also been implicated in the stimulation of CCK and GLP-1 secretion by protein hydrolysate (19).

Taste receptors. The tongue expresses receptors or channels that are sensitive to the five basic tastes bitterness, saltiness, sourness, sweetness, and umami. Similar to taste cells present on the tongue, the gut mucosa has been shown to express taste receptors of the G-protein-coupled families T1R and T2R, which are sensitive to taste stimuli. In the T1R receptor family, T1R1/T1R3 and T1R2/T1R3 heterodimers sense umami and sweet taste, respectively. The T2R receptor family comprises approximately 30 receptors with sensitivities to different bitter agonists (22–24). Downstream effects of T1R and T2R receptor activation are mediated by the G proteins α-gustducin and α-transducin, which activate phospholipase Cβ2, formation of inositol 4,4,5-triphosphate, increase in intracellular Ca2+, and depolarization through transient receptor potential 5 (TRPM5) channels. Through this pathway,

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sweet sensing through T1R2/T1R3 heterodimer receptors are able to stimulate GLP-1 and PYY secretion, and bitter agonists are able to stimulate secretion of CCK and GLP-1 (17,19). T1R1/T1R3 receptors are sensitive to "umami"-tasting substances such as monosodium glutamate and certain amino acids. Activation of the receptor is enhanced by inosine or guanosine 5′-monophosphate, and the intracellular transduction pathway is also mediated through α-gustducin. In mouse small intestine, T1R1 is expressed on CCK-containing I cells. In a mouse entero-endocrine cell line, activation of this pathway by L-amino acids like phenylalanine and leucine was shown to stimulate CCK release (25).

In mice, activation of bitter receptors in the GIT after gavage of a mixture of bitter agonists has been shown to decrease food intake and delay gastric emptying (26). So far, no experiments in humans have been described that investigate the effect of bitter agonists on intestinal taste cells, and, hence, the functional role of the taste receptors of the stomach and duodenum in humans is presently unclear. A preliminary study reported increased satiation and inhibition of food intake after intragastric administration of the bitter agonist denatonium benzoate (27).

Transient receptor potential (TRP) channels. Another category of receptors involved in nutrient sensing belongs to the mammalian TRP superfamily, which comprises 28 TRP cation channels that can be subdivided into six main subfamilies: the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and the TRPA (ankyrin) channels (28). TRP channels can control cell functions by directly permitting Ca^{2+} influx into the cell in response to specific stimuli, or through depolarization of the membrane potential due to cation influx.

Known activators of TRP channels include specific agonists, such as menthol (TRPM8) and capsaicin (TRPV1), or physical stimuli, such as temperature (heat: TRPV1, 2, 3, 4, TRPM4, 5; cold: TRPM8, TRPA1), and mechanical or osmotic stress (TRPV4, TRPCs) (28).

Besides a location on extrinsic afferents, TRPV1 receptors expressed on esophageal epithelial cells have been implicated in the sensation of heartburn and sensitivity to ingested capsaicin. In the gastric mucosa, TRPV1 receptors may be involved in the regulation of gastric acid secretion, and perhaps also sensitivity to ingested capsaicin (28–30). TRPM5 channels are expressed on entero-endocrine cells and have been implicated in the release of several gut peptides including GLP-1, GIP, PYY, CCK, enkephalin, and uroguanylin (28). TRPM8 may be expressed on gastric mucosal cells, and may mediate sensitivity to cooling and to ingested menthol (31). TRPA1 is expressed on mucosal afferents and may mediate mechanosensitivity as well as sensitivity to a number of ingested agents including cinnamon, pungent compounds in mustard oil, wasabi and horseradish, and also menthol. TRPA1 is also expressed on entero-endocrine cell and may be involved in the control of release of 5-hydroxytryptamine (28).

Gastric responses to food intake

Sensory responses to gastric nutrients. Ingestion of a meal activates both the mechanosensitive and nutrient-sensing pathways, and both may induce perception. Gastric distension has been shown to trigger stretch- as well as tension-sensitive mechanoreceptors that in turn relay their information via vagal and splanchnic nerves to the brain stem and several other brain areas (32,33).

In humans, distension of the proximal stomach in low, physiological ranges induces a sensation of satiety, whereas higher-range distensions may induce discomfort, nausea, and pain (34,35). In line with these observations, postprandial hunger and satiety were correlated to postprandial gastric volumes, without a significant influence of the nutrient composition (lipids, carbohydrates, or proteins) of the meal (36). Studies using isobaric and isovolumetric balloon distension of the stomach suggest that tension-sensitive mechanoreceptors in the proximal stomach mediate the effect of intragastric pressure (IGP) on the occurrence of satiation (10,37). Hence, relaxation of the proximal stomach is likely to influence and increase volume tolerance, whereas contraction is expected to decrease nutrient volume tolerance (10).

Although these findings indicate a very limited role for gastric chemosensing in response to meal ingestion, the presence of nutrients does influence brain cortical responses to gastric distension: although gastric balloon distension activates key components of the visceral pain neuromatrix, distension by nutrient infusion deactivates the same areas (38). The difference between both types of distension may relate to induction of gastric accommodation or release of gut peptides, but is likely to be involved in the tolerance of normal meal volumes in health.

Gastric motor response to nutrients. Between meals, the proximal stomach maintains a high basal muscle tone, which is mainly driven by constant cholinergic input from the vagus nerve (39). Upon food intake, a vago-vagally-mediated reflex relaxation occurs, which decreases the tone of the proximal stomach through the release of nitric oxide from intrinsic nerves (39,40). Animal studies from the previous century reported that this process of gastric accommodation increases the storage capacity of the stomach and serves to prevent a rise in IGP during food intake (41).

Recent studies in man have established that nutrient ingestion is in fact associated with a rapid drop in IGP, which is mediated by nitric oxide release, and followed by a gradual recovery of IGP (42). The rise in IGP during nutrient ingestion is closely correlated with the occurrence of satiation, suggesting a role for IGP rise in determining meal-induced satiation. A role of IGP in the control of satiation was further confirmed in studies where increasing IGP through externally applied local pressure induced early satiation, or where inhibition of the drop in IGP through antagonism of endogenous opioid receptors decreased nutrient tolerance (43,44).

After the phase of food ingestion, tonic contractions of the proximal stomach propel gastric content distally, whereas peristaltic contractions emerging from the mid-corpus progress in the direction of the antrum. These repetitive contractions break down the food particles, mix them with gastric secretions, and form a second drive that pushes the food content distally. Together with tonic contractions of the proximal stomach and peristaltic contractions of the distal stomach, opening and closure of the pylorus controls

gastric emptying (45). The emptying speed of a meal is inversely correlated with its caloric content and also depends on the acidity, osmolarity, and viscosity of the meal (46–48). Most of these influences are controlled by duodeno-gastric negative-feedback mechanisms, which are discussed below. Emptying of a solid meal follows a biphasic pattern: during the lag phase, which can take up to 30–60 min, solids are redistributed in the stomach and broken down to smaller particles. Particles < 1 mm in diameter can pass through the pylorus during the emptying phase (49,50). So, although some initial gastric emptying may occur, especially for the liquid phase of a meal, most of the solid meal will remain in the stomach during food intake (51).

Upon food intake, the motor pattern of the stomach changes drastically: the proximal stomach relaxes and serves initially as a reservoir. After food intake, a tonic contraction of the proximal stomach pushes the food distally. By a powerful and regular peristaltic contraction pattern, the distal stomach is engaged in mixing and grinding of the food. This postprandial motor pattern of the stomach serves three major mechanical functions of the stomach: the proximal stomach acts as a reservoir without a major IGP increase; food digestion is started by antral contractions that mix and grind food to smaller particles; and tonic and peristaltic contractions assure a steady controlled flow of food to the duodenum (46–50).

When the meal is emptied from the stomach, the upper GIT exhibits interdigestive phase motility, characterized by a recurrent contraction pattern known as the migrating myoelectrical (or motor) complex (52).

Gastric secretory response to nutrients. Ingestion of a meal is accompanied by a pronounced activation of gastric acid secretion. Gastric distension by meal ingestion activates two neural pathways that stimulate gastric acid secretion: a vago-vagal reflex pathway and a local intrinsic pathway. Mechanical distension activates a local intrinsic pathway that releases acetylcholine to stimulate parietal cell acid secretion. Acetylcholine acts directly on the parietal cell and indirectly on gastric entero-endocrine cells to release histamine. Activation of the vagal pathway releases both acetylcholine and gastrin releasing peptide, the latter stimulating release of gastrin from G cells. Gastrin will in turn directly stimulate acid secretion through activation of CCK2 receptors on parietal cells and indirectly through enhanced release of histamine of entero-endocrine cells in the stomach (53). There is a limited role for chemosensing, as the presence of a low intragastric pH will inhibit gastric acid secretion through enhanced release of somatostatin from D cells, whereas the presence of amino acids and oligopeptides in the gastric lumen will enhance gastrin release and gastric acid secretion (53).

Secretion of gastric acid has a number of physiological roles, including direct and indirect (through activation of pepsin) involvement in digestion of food, anti-bacterial defense, and facilitated uptake of nutrients such as minerals and selected vitamins.

Intestinal responses to food intake

Sensory responses to intestinal nutrients. Ingestion of a meal is able to activate both the mechanosensitive and nutrient-sensing pathways in the small intestine. Although the intestine is sensitive to distension, duodenal balloon distension in physiological pressure range induces only limited amount of satiety; higher-range distension induces nausea discomfort and pain (54). Most authors therefore agree that sensation of intestinal contents is mainly based on mucosal recognition of luminal content. Entero-endocrine cells in the mucosa of the small intestine react to different properties of luminal content by releasing a variety of peptides (including CCK, GLP-1, oxyntomodulin, and PYY) and small molecules (such as serotonin (5-hydroxytryptamine)) that can act locally or enter the blood stream and work as hormones.

The presence of acid in the duodenum may generate perception of epigastric burning, pain, and nausea (55,56). Many of these actions are mimicked by the TRPV1 receptor agonist capsaicin (30). The presence of nutrients, especially lipids, induces sensations of satiety at low concentrations, and occurrence of nausea at higher concentrations (57,58). The latter are at least in part mediated through release of CCK induced by long-chain fatty acid and lipase activity (58–60). Duodenal infusions of lipids, carbohydrates, or proteins, as well as amino acids, induce a gastric relaxation and release of CCK, but the responses to protein are slower in onset and, unlike lipid and carbohydrates, are not associated with increased sensitivity to gastric distension (61–63).

In the small intestine, monosaccharides are absorbed by enterocytes through specific transporters (sodium glucose co-transporter-1 for glucose and galactose and GLUT2 and Glut5 for fructose) in the brush border and GLUT2 in the basolateral membrane (19). Amino acids and oligo-peptides are absorbed by a variety of specific brush-border transporters (referred to as system 1–5 transporters) (19). Absorption of lipids, mainly long-chain fatty acids, involves two carriers, the fatty acid translocase CD36 and the fatty acid transport protein 4. Uptake of shorter fatty acids may occur through diffusion, and the existence of transporters for short-chain fatty acids has been postulated (19). These processes are discussed in greater detail elsewhere (64–66).

Motor responses to intestinal nutrients. Nutrient ingestion disrupts the interdigestive migrating motor complex and converts motility to the seemingly irregular postprandial pattern. Postprandial motility patterns in the small bowel are poorly understood, and although meals induce different contractions according to solubility and viscosity, a clear influence of nutrient composition has not been reported (67–71).

In the upper GIT, duodenal exposure to nutrients governs a multitude of duodeno-gastric negative-feedback mechanisms. The aim of these negative-feedback mechanisms, which are mediated through vago-vagal reflexes and hormonal signals (GLP-1, PYY, and CCK, among others) is to delay the arrival of acidic, hyperosmotic, or calorie-rich gastric contents into the duodenum by inhibiting proximal gastric tone, gastric phasic contractions, and by stimulating closure of the pylorus (45–50).

Secretory response to intestinal nutrients. In the fasting state, duodenal and pancreatic secretion and biliary excretion follow the phases of the migrating motor complex, with maximal stimulation

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during the passage of phase 3. Neural control mechanisms, as well as release of motilin and, potentially, ghrelin, are thought to integrate this interdigestive secretomotor complex (71).

The arrival of nutrients in the duodenum triggers pancreatic secretion, which contains enzymes that are crucial to digestion of lipids, protein, and carbohydrates. Digestive activity of pancreatic enzymes requires a neutral pH and this is partially provided by the high bicarbonate content in pancreatic juice. Besides a vagal efferent stimulatory drive, pancreatic secretion is also stimulated by gastrointestinal peptides, such as CCK (released by the presence of lipids and peptones in the duodenum), gastrin, secretin (released by duodenal acidification), and bombesin, and by the short duodeno-pancreatic neural pathways (72).

Upon arrival of either food or acid in the duodenum, secretion of bicarbonate by the duodenal mucosa is also stimulated, and secretin is a key mediator of this response. This creates a pH that is closer to neutral in the duodenal lumen, which is crucial for the activity of pancreatic enzymes involved in digestion of lipids, protein, and carbohydrates (73,74).

Release of CCK from the duodenum in response to the presence of long-chain fatty acids induces contraction of the gallbladder and relaxation of the sphincter of Oddi, thereby allowing bile to mix with the nutrients emptied from the stomach. Bile acids will facilitate lipid digestion through emulsification and formation of micelles, which provide an interface between the hydrophilic lumen and the hydrophobic fat contents of nutrients, where lipid digestion and absorption can occur. In the ileum, bile acids are reabsorbed through an apical ileal bile acid transporter (75).

LOWER GIT: PROCESSING AND EVACUATION

The role of the lower GIT in nutrient handling is more limited, as the recognition, break-down, digestion, and absorption of nutrients all occur in the upper GIT. The role of the colon is absorption of water and electrolytes, storage of non-digestible remnants of food, aboral propulsion of contents, and finally evacuation through defecation. Because of its relative inaccessibility, knowledge of human colonic physiology, including motor activity, is relatively limited in comparison with other parts of the GIT. Whether ingested foods have specific effects in the lower GIT according to the nutrient type and composition has been less well studied.

In the cecum and the ascending colon, active reabsorption of water and electrolytes occurs. The pathways involved in colonic secretion and absorption have recently been reviewed (76). The right colon provides a net absorption of on average 1.5 l water per day, with osmotic pressure in the lumen being a limiting factor. The absorbed quantity is in reality much higher as the colon is also involved in secretion of water and electrolytes, including sodium and chloride. The ascending and transverse colon function as storage sites where prolonged stasis may occur, whereas the descending colon serves mainly as a conduit. Colonic transit times are closely associated with stool consistency, probably through the time that is allowed for fluid reabsorption in the right colon (77). In the colon and sigmoid, bacterial fermentation of unabsorbed complex carbohydrates generates short-chain fatty acids, which are absorbed by the colonic mucosa (78). This is addressed in more detail elsewhere (79). The colonic microflora is also involved in the production of vitamin K and a several amino acids, and contributes to transformation of bile acids in the colonic lumen (80). Furthermore, a methane-producing colonic microflora has been associated with the presence of constipation, possibly through effects on contractility and transit (81,82). The sigmoid and rectum act as a secondary storage site until defecation (83). Progressive distension of the descending colon induces sensations of fullness, which increase to discomfort or pain, and there is indirect evidence that this involves tension-sensitive mechanoreceptors (11).

Colonic propulsion occurs through a combination of increases in colonic tone and phasic propulsive contractions (84,85). Variations in tone and phasic contractility are determined by sleep (low contractile activity), awakening (induces highest activity), and meals (followed by transient increases in motor activity). Besides retrograde and non-propagated contractions, antegradely propagated contractions of low and high amplitude occur in the human colon (85). High-amplitude propagated contractions move colonic contents over large distances aborally. They occur most frequently after meals, often precede defecation, and are suppressed at night (85).

Arrival of colonic contents in the rectum generates sensations of fullness, which may increase to reach thresholds for desire to defecate and finally discomfort (86). Here again, there is evidence of involvement of tension-sensitive mechanoreceptors (87). Rectal filling can be accommodated through relaxation of the rectum, or when socially acceptable, can progress into defecation. Upon defecation, the puborectalis muscle and the anal sphincter relax, and content is expelled through contractions of the abdominal wall and the rectosigmoid (88).

Food ingestion is associated with stimulation of colonic motility, and this effect is slower in onset but more prolonged with a fatty meal compared with a carbohydrate meal (89). Ingestion of lipids stimulates mainly non-propulsive colonic motility and also enhances sensitivity to visceral distention (89,90). Non-absorbed nutrients in the colon may also alter gastrointestinal motor function. Nonabsorbable carbohydrates inhibit colonic water absorption and stimulate colonic transit (91). Infusion of lactulose in the colon inhibits gastric tone and increases the occurrence of transient lower esophageal sphincter relaxation, and these effects are mimicked by short-chain fatty acids and metabolites of lactulose fermentation (92,93). Infusion of oleic acid in the ascending colon induces high-amplitude colonic contractions, decreases storage capacity in the ascending colon, and accelerates colonic transit (94). Finally, fermentation of starch in the colon stimulates colonic propulsive activity (95).

CONCLUSIONS

Handling of ingested nutrients by the GIT is a complex process that is closely regulated by both humoral and neural mechanisms. Nutrient sensing, a prerequisite for the control of nutrient handling, is mainly based on mechanosensitivity in the stomach and chemosensitivity in the intestine. Recent discoveries of the

newly described nutrient sensing pathways and physiological principles have improved our understanding of the process but also have unraveled the complexity of the integrated gastrointestinal response to nutrients in health and the potential alterations in disease. Understanding of these pathways is likely to enhance insights into the pathophysiology of functional disorders and how they are modulated by nutrients.

CONFLICT OF INTEREST

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