Overview

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Anatomy and Physiology of the Gastrointestinal Tract

The gastrointestinal tract (GIT) is divided into distinct subunits, with morphological and functional differences: mouth including teeth, esophagus, stomach, pancreas and biliary tract, liver, duodenum, jejunum, ileum, colon, and anus. The different functions are reflected in macroscopic and microscopic anatomy. Macroscopically the stomach, for instance, has longitudinal, oblique, and circular muscle layers to mix and churn food and so aid digestion. Microscopically, the cells lining the stomach include specialized H cells that produce hydrochloric acid (see below).

In contrast, the ileum is an approximately 3 m long tube-like structure, with circular and smooth muscle optimized for peristalsis, and microscopically, the predominant cell type is the enterocyte, specialized for absorption of nutrients. The surface area of the ileum is increased by internal folds covered with projecting villi. These in turn are microscopically covered with microvilli, which project from the luminal surface of the epithelial cells.

The colon is specialized for extracting water, solidifying waste into feces before excretion. Bacteria in the colon aid metabolism by producing short chain fatty acids (SCFAs) such as butyrate, which is a source of energy for colonic epithelial cells. In this chapter we review important functions of the gastrointestinal tract, particularly the stomach, ileum, and colon, emphasizing nutritional and metabolic implications.

Gastrointestinal Tract-Specific Metabolic/Molecular Pathways and Processes

The Stomach

The stomach expands to accommodate food after a meal, initiates the release of hormones that coordinate subsequent events, and secretes hydrochloric acid (HCl), which converts pepsinogen into functional pepsin. Pepsin digests dietary proteins and peptides into smaller peptides that are further digested and absorbed as oligo- and dipeptides in the duodenum, jejunum, and ileum.

HCl creates an environment that is inhospitable to most microorganisms. Epithelial cells are protected from the effects of HCl by a number of mechanisms including gastric mucus. Additionally, gastric acid favors the reduction of iron from ferrous to ferric (Fe^{2+} to Fe^{3+}), which promotes its absorption in the proximal duodenum. In addition, intrinsic factor (IF) secreted by

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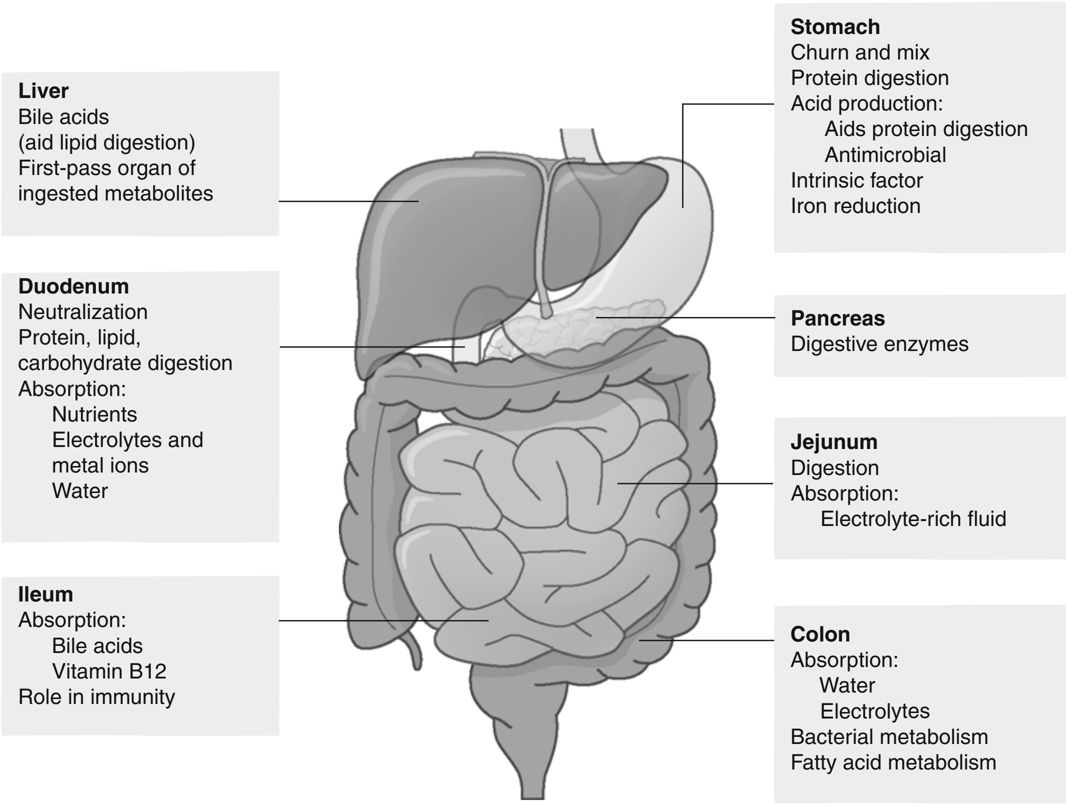

Fig. 1 Overview of the gut with summary of main functions demonstrating absorption of water and electrolytes, carbohydrate, lipid, proteins, vitamins, and minerals. Gut physiology is determined by the specialized cells lining the epithelium with absorption of different molecules in different parts of the gut

the gastric mucosa binds to dietary cobalamin, protecting it from digestion and enabling absorption in the terminal ileum (Fig. 1).

The Small Intestine: Duodenum, Jejunum, and Ileum

The small intestine is differentiated along its length, with distinct functions occurring in duodenum, jejunum, and ileum. Acidic chyme from stomach is released gradually into the duodenum, where it is mixed with alkaline bile and pancreatic secretions rich in HCO_3^-. The duodenal mucosa is specialized for absorption.

The pancreas produces the bulk of digestive enzymes for carbohydrates, lipids, and proteins, and bile acids contribute to the formation of mixed micelles of lipid, aiding their digestion. Intestinal epithelial cells contribute to digestion by secreting enzymes such as lactase (see chapter "Lactose intolerance") that are bound to their surface and express in their cell membranes protein transporters that enable nutrients to pass from the lumen of the intestine into the epithelial cell and then out of the cell and into the lymphatic and vascular circulation (lipophilic and hydrophilic substances, respectively). In addition, epithelial cells absorb electrolytes and metallic trace elements such as Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, Cu^{2+}, and water. Paracellular movement of water and electrolytes also occurs, and the direction, either into or out of the lumen, depends on osmotic and ionic gradients. Tight junctions between epithelial cells are more effective distally, and paracellular transport in the healthy intestine plays only a minor role.

Digestion and absorption continue in the jejunum, where much of the electrolyte-rich fluid that is secreted by the stomach, pancreas, and duodenum is reabsorbed. Without this reabsorption, total body water, Na^+, K^+, and Mg^{2+} are rapidly depleted, presenting a clinical problem for patients who undergo intestinal resection leaving them with a jejunostomy or proximal ileostomy.

The terminal ileum is particularly important for the absorption of bile acids and Vitamin B_{12}. As a consequence, disease of the ileum can cause vitamin B_{12} deficiency and diarrhea caused by loss of the enterohepatic circulation of bile salts (see chapter "Overview" under part "Liver"), with consequent excess of these in the colon, where they cause secretion of water and electrolytes [1]. The ileum also acts as a barrier between the large and small intestine, with effects on bacterial populations, and intestinal motility. Finally, the ileum plays a prominent role for the immune system (see below) [2].

Absorption of carbohydrates requires digestion of complex carbohydrates into monosaccharides, as polysaccharides and disaccharides cannot be absorbed. Lactose, a disaccharide of galactose and glucose, is the main sugar in bovine and human milk and is digested by lactase, which is produced by intestinal epithelial cells. Lack of lactase causes lactose intolerance, in which colonic bacteria digest lactose to produce fermentation by-products, which, with the lactose, increases the osmotic gradient and results in diarrhea (see chapter "Lactose intolerance"). Furthermore, excess lactose may alter colonic bacteria. Avoiding dietary dairy can lead to Ca^+ deficiency and potentially osteomalacia (Fig. 2).

The Large Intestine: Cecum, Colon, and Rectum

The main function of the specialized colonic epithelium is to reabsorb H_2O from the 3–6 l/day of fluid that enters the cecum, so that approximately 200 ml is excreted as fecal waste. Reabsorbed water is accompanied by electrolytes, particularly Na^+, K^+, and Mg^{2+}. Colonic bacteria metabolize fats and contribute to the provision of essential fatty acids. Tight junctions between colonic epithelial cells prevent salt and water loss from the interstitial tissue space and limit the translocation of bacteria and toxins from the colonic lumen into the circulation.

The practical importance of reabsorption is illustrated by patients who have undergone extensive resection of the small intestine. When they have a proximal jejunostomy or ileostomy, loss of salt and water means that they require regular intravenous supplementation, even when absorption of dietary carbohydrate, fat, and protein is sufficient. In such cases, anastomosis of the small intestine to the colon typically reverses dependence on intravenous fluids.

Colonic bacteria contribute metabolically to the host. Food residue in the colon is fermented, yielding gases such as methane (CH_4), H_2, and CO_2 and short chain fatty acids (SCFAs), such as acetate, butyrate, and propionate. However, fermentation can also produce toxic metabolites (see below). Butyrate is a major energy source for colonic epithelial cells and its absence can result in inflammation (see also chapter "Colorectal cancer").

Moreover, the mix of colonic bacterial species, termed the microbiome, varies between individuals. This variation may be associated with diseases including obesity and autoimmunity [3].

Inside-In: Metabolites of the Gastrointestinal Tract Affecting Itself

Regulation of digestive processes involves structures in the hypothalamus (see chapters "Overview" under part "Brain", "Diabetes mellitus", and "Overview" under part "Brain"), yet it also occurs to a major part within the gastrointestinal tract, starting with the amount of food intake sensed by chewing and stomach filling. Most importantly, the stomach releases hormones, such as gastrin, cholecystokinin (CCK), and secretin, which in turn promote the release of HCl, stimulate contraction of the gallbladder, and promote secretion from the pancreatobiliary system, while enhancing intestinal propulsion.

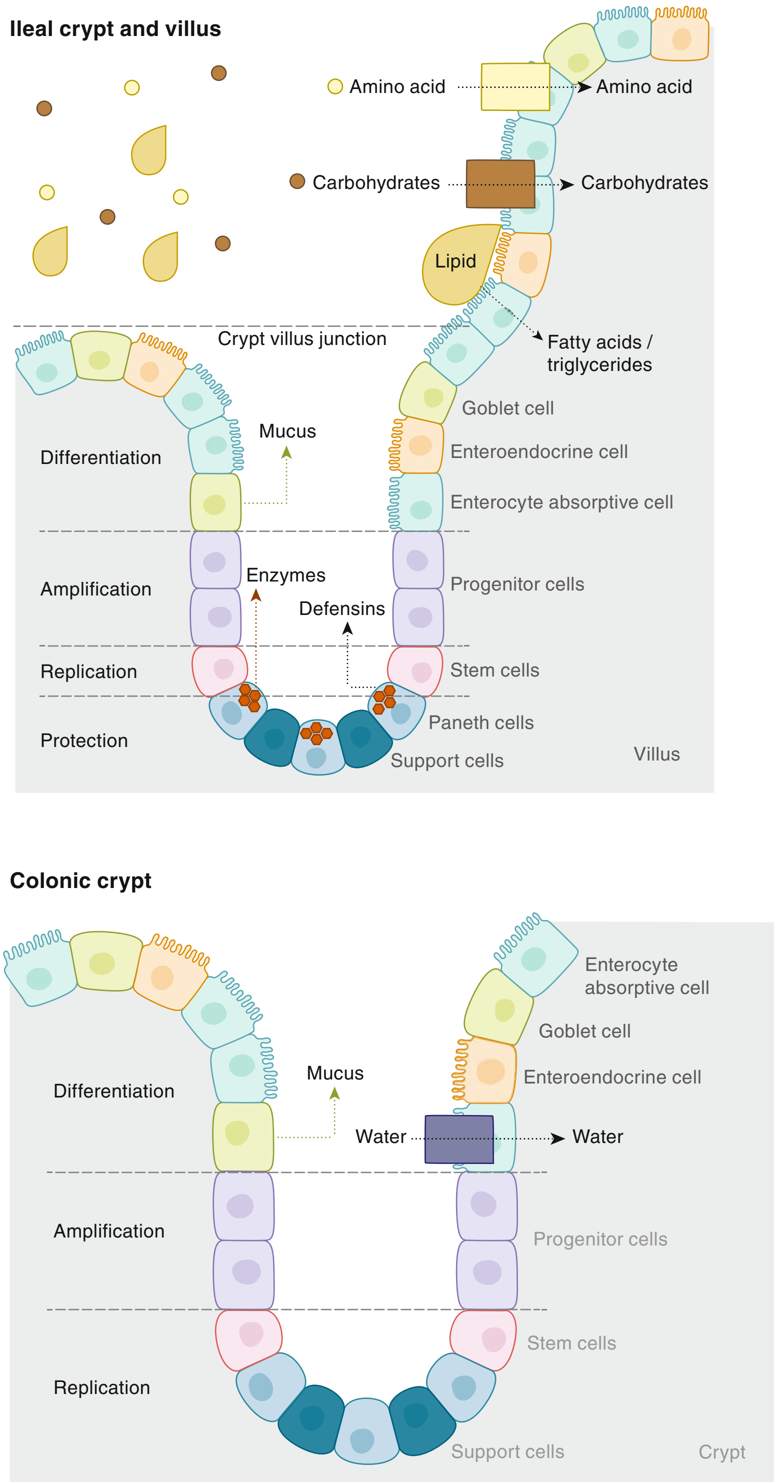

Fig. 2 Diagram of the microscopic appearance of a stylized crypt-villus unit and colonic crypt, showing specialized cells, enzymes, absorption, secretion, and immune functions

Outside-In: Metabolites of Other Tissues and External Factors Affecting the Gastrointestinal Tract

Stomach

Helicobacter pylori (*H. pylori*) is an infectious bacterial strain that has adapted to gastric acid by secreting a urease that generates NH_4^+ from urea, thus raising the local pH. As a consequence, *H. pylori* infection is widespread and is associated with a number of diseases including gastritis, peptic ulcer (see chapter "Peptic ulcer disease"), and gastric cancer.

Consequently, *H. pylori* can cause metabolic and nutritional problems, with hypochlorhydia, reduced IF production, and gastritis leading to bleeding.

Small Intestine

There are several examples how circulating hormones and neural signals can regulate intestinal absorption [4]. However, a detailed discussion is not within the scope of this chapter.

Iron transporters particularly are concentrated proximally, where the majority of iron is absorbed. As an example, iron absorption is inhibited by the circulating hormone hepcidin, levels of which are increased by infection and inflammation contributing to the anemia seen in many chronic diseases.

The small intestine is also highly relevant to the interaction with endogenous material and antigens. Thus, intestinal lymphoid tissue is concentrated in the ileum, with many prominent Peyer's patches, and specialized cells that form part of the innate immune system (see chapter "Overview" under part "Immune system"), such as Paneth cells, are most abundant in the ileum [2]. Paneth cells and goblet cells, among others, produce many antibacterial proteins such as α and β defensins, regenerating (REG) proteins, and cathelicidins. Innate and adaptive immune mechanisms, as well the effects of constant propulsion along the intestinal tract, and chemical and mechanical barrier functions of glycosaminoglycan-rich mucus maintain near sterility of the small intestine, with approximately 10^5–10^7 bacteria/ml of luminal content, compared to 10^{11}–10^{12}/ml in the colon. Commensal bacteria in the intestine probably have a symbiotic relationship with the host, preventing colonization by pathogens by competing for the ecological niche and contributing partly to the production of nutrients such as vitamin K.

Inside-Out: Metabolites of the Gastrointestinal Tract Affecting Other Tissues

Obviously, the main function of the gastrointestinal tract is to supply the whole body with nutrients, electrolytes, and trace elements required for regular metabolism and homeostasis.

Small Intestine

Additionally, the gastrointestinal tract, more specifically the small intestine, can act as an endocrine organ secreting incretins, which act on pancreatic β-cells causing an increase in insulin secretion even before blood glucose is elevated or delay gastric emptying (see chapters "Overview" under part "Pancreas" and "Diabetes mellitus").

Colon

Fermentation by colonic bacteria can produce toxic metabolites that can be absorbed into the circulation to exert systemic effects (see chapter "Cirrhosis"). There is therefore now a concerted research effort aimed at understanding how the microbiome interacts with the intestine and the whole body in health and disease.

Typical Pathology of the Gastrointestinal Tract

Stomach and Small Intestine

Vomiting causes loss of acid. This loss results in concomitant K^+ loss in the urine to favor retention of hydrogen (H^+) ions (see chapter "Overview" under part “Kidney”). The loss of K^+ can be exacerbated by diarrhea, which also causes loss of Mg^{2+} and Ca^{2+}. The absorption of vitamins and minerals can also be affected by intestinal transit time and absorptive capacity. Acute illnesses, such as gastroenteritis (see chapter “Gastroenteritis”), do not typically cause nutritional deficiencies. However, in chronic disease, water-soluble vitamins, e.g., thiamine (B1), riboflavin (B2), pyridoxine (B6), niacin, folate, B12, and ascorbic acid (C), initially, and later fat-soluble vitamins (vitamins A, D, E, and K) may become deficient. Essential minerals, such as Zn^{2+}, Cu^{2+}, selenium, and phosphate, are also typically depleted in chronic malabsorptive states [5].

Colon

The capacity of the colon to reabsorb water and electrolytes is reduced by inflammation, including infection, ulcerative colitis, and microscopic colitis. Bile acid diarrhea results from colonic secretion stimulated by bile acids that are not reabsorbed in the ileum, when they enter the colon. Laxatives and microbial toxins can also stimulate secretion and cause diarrhea. An example is the heat stable enterotoxin of E. coli, STa, which binds to a guanylate cyclase-linked receptor expressed on the surface of colonic epithelial cells, causing secretion of Cl^- and water secondary to increased intracellular cGMP.

Colorectal cancer (CRC, see chapter “Colorectal cancer”) is a major cause of morbidity and mortality. The interaction of diet and the microbiome may provide a mechanistic link for these observations. Chronic inflammation of the colon, including longstanding ulcerative colitis increases the risk of CRC [5].

Final Remarks

The intestine is critically important for nutrition and metabolism and has to meet major challenges posed by the ingestion of food containing potential toxins and pathogens. Specialized structures at the macroscopic and microscopic level contribute to the function of the gastrointestinal tract and are altered in disease. A symbiotic relationship with commensal intestinal microorganisms is only now being understood in more detail, and alterations in this relationship may be a major determinant of health and disease. This introductory chapter is followed by more detailed chapters on important and common intestinal diseases, i.e., *H. pylori* infection (see chapter “Peptic ulcer disease”), gastroenteritis (see chapter “Gastroenteritis”), lactose intolerance (see chapter “Lactose intolerance”), and colorectal cancer (see chapter “Colorectal cancer”). For further information, the reader is referred to more extensive textbooks of gastroenterology [5, 6].

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