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REVIEW ARTICLE

Small Bowel Review
Normal Physiology Part 1

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In the past year there have been many advances in the area of small bowel physiology and pathology and therapy. In preparation for this review, over 1500 papers were assessed. The focus is on presenting clinically useful information for the practising gastroenterologist. Selected important clinical learning points include the following: (1) glucose absorption mediated by SGLT1 is controlled by mRNA abundance, as well as by posttranscriptional processes including protein trafficking; (2) inducers of cytochrome P-450 decrease glucose and fructose absorption and increase glucose consumption in the intestine; (3) the regulated release of nutrients from the stomach into the upper intestine ensures that the modest intestinal transport reserve capacity is not exceeded; (4) hepatocyte growth factor and short-chain fatty acids may enhance intestinal adaptation and prevent the atrophy seen when total parenteral nutrition is infused; (5) inhibitors of pancreatic lipase and phospholipase H_2 may be useful clinically to reduce absorption as part of a treatment program for obesity and hyperlipidemia; (6) several membrane-bound and cytosolic proteins have been identified in the enterocyte as well as in the hepatocyte and may be the target for the future therapeutic manipulation of bile acid metabolism and control of hyperlipidemia; (7) suspect bile acid malabsorption in the patient with otherwise unexplained chronic diarrhea; (8) a proportion of lipid absorption is protein-mediated, and this opens the way to targeting these proteins and thereby therapeutically modifying lipid absorption; (9) a high protein diet may be useful to increase the intestinal absorption of drugs transported by the H^+/dipeptide cotransporter; (10) a metal transporter DCT1 has been identified, and this may open the way to a better understanding of disorders of, for example, iron and zinc metabolism; (11) the nutrient transporters such as SGLT1 are responsible for a portion of the intestinal absorption of water; (12) the influence of nitric oxide on intestinal water absorption and secretion depends on its concentration; (13) a trial of bile acid-sequestering agent may prove useful in the treatment of the patient who experiences diarrhea while taking an enteral diet; (14) a proteolytic extract from pineapple stems may prove to be useful to treat diarrhea, although the mechanism of this effect remains to be established; and (15) the antisecretory effect of the new peptide, sorbin, needs to be tested in a clinical situation on patients with diarrhea. Other new and promising antidiarrheal agents include bromelain, an extract from pineapple stems, and igmesine, a final sigma ligand.

KEY WORDS: small bowel; physiology; pathology; therapy; absorption; metabolism.

ABSORPTION

Carbohydrate

The intestinal brush border membrane enzyme lactase-phlorizin hydrolase digests lactose, the main carbohydrate in milk. Lactose is an important constituent of the diet of human children and adults. In people living in many parts of the world, lactase-phylorizin hydrolase activity declines in early life. However, in descendants of northern European ancestry, enzyme activity may persist into adult life. The persistence of lactase-phylorizin hydrolase activity is dominant to non-persistence. The genetic difference responsible for the persistence/nonpersistence polymorphism, which determines high or low lactase-phylorizin hydrolase mRNA expression, respectively, is *cis*-acting to the lactase gene. Using retrospective analysis of enzyme activity and prospective study for lactase–phylorizin hydrolase mRNA analysis, it was

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determined that the genetically programmed down-regulation of the lactase gene is detectable in children from the second year of life (1).

Enzymes that which are highly expressed in the brush border membrane at birth such as lactase-phylorizin hydrolase decline, while others, which are low or undetectable in the first two postnatal weeks, such as sucrase-isomaltase, show increases beginning early in the third week and then reach adult levels. These enzymatic changes coincide with weaning and enable the switch from a milk to a solid diet. The changes are not cued by the dietary change, but instead are initiated by an intrinsic timing program that is modulated by changing the hormonal mileu in the postnatal period. Glucocorticoid hormones and thyroxin act synergistically to elicit a precocious increase of sucrase-isomaltase activity that is paralleled by increased sucrase-isomaltase mRNA The synergism between these hormones is due to greater accumulation of sucrase-isomaltase per epithelial cell (2). Feeding a high-starch diet causes an elevation on sucrase–isomaltase mRNA in rat jejunum within 12 h of a sucrose load, and perfusion of the intestine with fructose results in increased sucrase-isomaltase activity and mRNA levels as well as the mRNA for the fructose transporter in the brush border membrane, GLUT5 (3). The premature increases in sucrase–isomaltase activity and mRNA as well as maltase activity in response to insulin are dose-dependent and are associated with increases of the intracellular polyamines spermine and spermidine (4).

The mRNAs for brush border membrane lactase–phylorizin hydrolase and sucrase–isomaltase are localized in the brush border membrane of the villus enterocytes, whereas the mRNAs for intestinal alkaline phosphatase and for β-actin are detected both apically and basally relative to the nucleus (5). Lactase–phylorizin hydrolase carries two hydrolytic sites, and there is multistep proteolytic processing of prolactase–phylorizin hydrolase to mature brush border membrane lactase–phylorizin hydrolase (6). Females with lactose malabsorption may have signs of the irritable bowel syndrome, premenstrual syndrome, and mental depression (7).

The gene expression of lactase–phylorizin hydrolase and sucrase–isomaltase has been studied extensively. These enzymes are anchored in the brush border membrane of the enterocyte, and are crucial in the digestion of dietary carbohydrates. Lactase–phylorizin hydrolase hydrolyzes lactose from milk, which is the primary energy source for newborn children. Sucrase–isomaltase is essential in the final hydrolysis of starch and becomes more important in later life when starch has become the predominant carbohydrate source in the diet. The precursor form of the sucrase–isomaltase complex is synthesized as a single polypeptide, which is transferred to the brush border membrane where it is cleaved into sucrase and isomaltase subunits for maturation by the action of pancreatic proteases such as trypsin and elastase. In the senescence-prone mouse the sucrase–isomaltase complex may be unstable against pancreatic proteases (8). Both lactase-phylorizin hydrolase and sucrase–isomaltase protein levels correlate with their respective mRNA levels and are thus transcriptionally regulated. Aging from one to eighteen years does not result in significant changes in mRNA or protein levels of either lactase–phylorizin hydrolase or sucrase-isomaltase (9).

Glucocorticosteroids play a role in the rise in sucrase–isomaltase activity at the time of weaning. A decline in lactase–phylorizin hydrolase activity and the accelerated appearance of sucrase–isomaltase in suckling rat pups may be associated with orogastrically administered insulin-like growth factor (IGF)-1 (10). The liver is the main source of circulating IGF-1, and there may be an altered profile of IGF-1 binding protein in hepatic cirrhosis. In cirrhotic rats, D-galactose absorption is reduced, and IGF-1 may correct these changes by modulating the cytoskeletal organization in the enterocyte (11). Sucrase–isomaltase activity is increased in diabetic patient. Insulin also reduces the mRNA level of the sucrase–isomaltase complex in intestinal explants (12). Keratinocyte growth factor is a fibroblast-derived member of the fibroblast growth factor family that down regulates sucrase–isomaltase mRNA and protein expression in Caco-2 cells (13).

The 3′-untranslated region of all sorted mRNAs studied thus far contain *cis*-acting sequences that are responsible for the localization and sorting of specific mRNAs to distinct cytoplasmic regions, and are a mechanism of protein localization. The expression of lactase–phlorizin hydrolase mRNA in humans with adult-type hypolactasia is patchy, whereas this patchiness does not occur in individuals who are lactase-sufficient. Some homologies between human lactase–phylorizin hydrolase and sucrase–isomaltase 3′-untranslated regions have been identified. It remains unclear whether these sequences play a role in the intracellular localization of these mRNAs.

A method has been developed for assaying intestinal brush border membrane sucrase–isomaltase in an intact intestinal preparation (14). The topic of human

glucose transporters has been reviewed (15). The mRNA for human sodium-dependent glucose transporter in brush border membrane (SGLT1) is localized to the apical region of the enterocyte (16). The octyl-glucosides are specific inhibitors of SGLT1 (17). SGLT1 may act as a molecular pump for water, and can account for almost half the daily re-uptake of water from the small intestine (18).

The satiety factor leptin decreases the maximal transport rate (V_{max}) for glucose transport in the rat small intestine (19). Leptin, a 167-amino acid protein transcribed from the *ob* gene, is strongly correlated with the body fat mass. Leptin acts on the hypothalamus to regulate body weight by decreasing food intake and by increasing physical activity and energy expenditure. Leptin is produced in fat cells as well as in skeletal muscle. Leptin has been described in the stomach, where it may be involved in early cholecystokinin-mediated effects activated by food intake (20). Leptin activates STAT3, the signal transducer and activator of transcription 3 in the hypothalamus, mediating increased satiety and increased energy expenditure. A leptin receptor has been described in the jejunum of the mouse. Intravenous injection of leptin rapidly induces nuclear STAT5 DNA binding activity in the jejunum of *ob*/*ob* mice, but has no effect in the diabetic *db*/*db* mouse that lacks the leptin receptor isoform (21). Leptin also induces the immediate-early gene *c-fos* in the jejunum and causes a twofold reduction in the apolipoprotein (apo) A-IV transcript level in the jejunum 90 min after a fat load. This suggests that the jejunum is a direct target for the action of leptin.

The intake of food is suppressed in a dose-responsive fashion by nutrients in the intestine. This suppression varies with the load (amount per minute) of nutrient entering the intestine, independent of the nature of the nutrients themselves. In rats, the secretion of apo A-IV is a putative signal of hypothalamic satiety. Calorie-dependent inhibition of food intake depends on feedback from sensors in the proximal and distal bowel contacted after high intakes of nutrients (22). When rats are ingesting food, infusion of fat rather than sucrose suppresses their continued intake of fat (23).

The apical uptake of α-methyl-D-glucoside, a non-metabolizable glucose analogue, falls with aging (24). The α-1,4-glucose linkages of dietary starch are efficiently hydrolyzed by luminal α-amylase and by brush border membrane α-glucosidase in the upper small intestine. The released glucose is absorbed by the brush border membrane-independent glucose transporter, SGLT1, and by a facilitated sodium-independent glucose transporter, GLUT2, at the basolateral membrane. The structure–function relationship of SGLT1 has been studied in COS-7 cells in culture. The replacement of an alanine residue by an α-cysteine residue at position 166 decreases transporter turnover rate, possibly because the mutation alters the movement of sodium with the transporter (25). Dextran, an α-1,6-linked glucose polymer, is not normally present in the diet. It is resistant to α-amylase, but there is some residual activity of mucosal isomaltase towards α-1,6-glucose linkages. Feeding dextran increases SGLT1-mediated glucose uptake after short-or long-term exposure to luminal dextran or to a hydrolytic product (26).

The topic of regulation of intestinal sugar transport has been reviewed elsewhere (27, 28). Messenger RNA sorting in polarized cells exists in human enterocytes. The mRNA for villin (a microvillus cytoskeletal protein) sorts to the basal region of the enterocyte, the mRNA for SGLT1 is localized to the apical region, and the mRNA for the liver form of the fatty-acid-binding protein (L-FABP) is distributed diffusely thoughout the cytoplasm (29).

There is increased SGLT1 expression in obese II (non-insulin-dependent) diabetic rats, which may be partially associated with postprandial hyperglycemia (30). In cirrhotic rats there is a reduced V_{max} of glucose uptake, which can be corrected by giving IGF-1 (11). Enteric glucagon-37 (also called oxyntomodulin), but not pancreatic glucagon-29, potently stimulate intestinal glucose absorption by SGLT1 (31). Vascular infusion of gastric inhibitory polypeptide (GIP) or glucagon like peptide (GLP-2) increases glucose uptake (32).

The activity of SGLT1 is increased within 30 min of infusion of GLP-2 when studied using isolate brush border membrane (33). This stimulation by GLP-2 is the result of an increase in the value of the V_{max} of SGLT1 and is associated with an increased abundance of the SGLT1 protein. This effect of GLP-2 is blocked by luminal brefeldin A or by wortmannin. This suggests that the trafficking of SGLT1 from an intracellular pool to the brush border membrane may be altered rapidly and involves phosphoinositol 3-kinase in the intracellular signaling pathway.

Clinical Learning Point: Glucose absorption mediated by SGLT1 is controlled by mRNA abundance, as well as by post-transcriptional processes including protein trafficking.

When administered in a vascular perfusion system in rats, cholecystokinin octapeptide reduces the rate

of glucose and of 3-*O*-methyl-D-glucose absorption. Cholecystokinin octapeptide also diminishes the SGLT1 protein abundance (34). This suggests that cholecystokinin octapeptide, in addition to delaying gastric emptying, may directly regulate the rate of glucose absorption across the small intestine.

The facilitated diffusion of glucose through the plasma membrane of mammalian cells is mediated by members of the GLUT glucose transporter family of proteins, and six isoforms have been described. The GLUT protein crosses the plasma membrane 12 times, and the transmembrane stretches show highly conserved primary amino acid sequences between the various isoforms. By introducing single amino acid mutations, it has been shown that certain portions of the transmembrane stretches are important for binding. The domains responsible for the fructose specificity of GLUT5 have been investigated by creating chimeras of GLUT5 with the selective glucose transporter GLUT2. The GLUT5 domain from the amino terminus of the third transmembrane domain and between the fifth and eleventh transmembrane stretches are necessary for fructose uptake (35).

The turnover of GLUT5 protein is diurnally influenced (36). The rat intestine up-regulates the hexose transporters prior to the onset of feeding, and this diurnal pattern of expression is hard-wired because GLUT5 is up-regulated in the absence of dietary fructose. The phenomenon of diurnality has been linked to the daily differentiation process whereby crypt cells migrate past the crypt–villus junction of mature enterocytes. The crypts are thought to be the initial site for the reception of dietary signals.

Inducers of cytochrome P-450 1A1 (CYP1A1) result in an increased rate of glucose consumption, as well as the modification at the protein and mRNA abundance level of the expression of a number of differentiation-associated proteins involved in the uptake, transport, and metabolism of glucose. These include decreased expression of sucrase–isomaltase, SGLT1, GLUT2, and GLUT5, without modifications of the morphological differentiation of the cells or the expression of other differentiation-associated proteins such as villin. In Caco-2 cells inducers of CYP1A1 also decrease the activity of γ-glutamyltranspeptidase (γ-GTP) activity and mRNA (37, 38). It is unclear whether the CYP1A1 inducers or the signal transduction system, which controls CYP1A1, is involved in the regulation of the expression of γ-GTP through a mechanism involving glucose metabolism. The authors suggest that there may be a physiological interpretation of the signal-transduction pathway responsible for CYP1A1 induction.

Clinical Learning Point: Inducers of cytochrome P-450 decrease glucose and fructose absorption and increase glucose consumption in the intestine.

In humans, fructose is transported across the brush border membrane by GLUT5-facilitated diffusion as well as paracellularly via glucose-activated solvent drag. GLUT5 contains a transmembrane domain that is responsible for fructose transport (35). GLUT5 mRNA protein levels are increased within 4 hr of fructose exposure, an effect that occurs in the mature enterocytes. The protein synthesis inhibitor cycloheximide blunts the diurnal and fructose-driven increase in GLUT5 mRNA expression in the morning but not in the evening (36). This suggests there may be two mechanisms of regulation. When the dietary nutrient load and intestinal capacity are varied in mice in studies involving intestinal resection, there is an increase in food intake, digestive efficiency, and glucose uptake. This allows for better survival of the animal, but greater degrees of resection are not necessarily associated with survival, possibly because the intestinal reserve uptake capacity has been exhausted (39).

The V_{max} of glucose and amino acid transport exceeds daily intakes by a factor of about 2. Gastric emptying is regulated by feedback control by the small intestine, in which nutrients enter the duodenum and jejunum and inhibit gastric emptying. The degree of this inhibition depends on the concentration of nutrients and the length of intestine exposed to nutrients, ie, the intestinal load of nutrients. In addition, the presence of nutrients in the ileum slows gastric emptying (the "ileal brake"). This feedback control of gastric emptying provides an additional reserve capacity for absorption (40).

Clinical Learning Point: The regulated release of nutrients from the stomach into the upper intestine ensures that the modest intestinal transport reserve capacity is not exceeded.

"Safety factors" are defined in engineering terms as the ratio of a component's designed strength or capacity to the maximum load that it is designed to bear. The safety factors of enzymes and transporters are defined as the ratio of the maximal reaction rates at high substrate concentrations (V_{max}) to the reaction rate under actual physiological conditions. Capacities both of sucrase–isomaltase and of SGLT1 increase with sucrose load and remain approximately matched to each other except when animals are on a carbohydrate-free diet (41). Neither sucrase–isomaltase nor

SGLT1 is the rate-limiting step for sucrose digestion; both steps are equally limiting.

After an 80% resection of the small bowel in rats, a 14-day infusion of hepatocyte growth factor upregulates SGLT1 mRNA and GLUT5 mRNA (42). It is unknown whether hepatocyte growth factor-enhanced gene expression of carbohydrate transporters may be useful for patients with short bowel syndrome. Short-chain fatty acids are the by-products of dietary fiber fermentation in the colon. Acetate, propionate, and butyrate account for about 85% of these short-chain fatty acids and are produced intraluminally in a nearly constant molar ratio of 60:25:15. One week of short-chain fatty acid supplementation retards total parenteral nutrition-associated intestinal atrophy in rats with intact bowels and as early as three days after an 80% intestinal resection. Short-chain fatty acids lead to rapid changes in ileal proglucagon mRNA abundance after 24 h of total parenteral nutrition plus short-chain fatty acid infusion, and as well increase GLUT2 mRNA and protein but not GLUT5 and SGLT1 (43).

Clinical Learning Point: Hepatocyte growth factor and short chain fatty acids may enhance intestinal adaptation, and prevent the atrophy seen when total parenteral nutrition is infused.

Epidermal growth factor (EGF) is a 53-amino acid peptide derived from numerous sources in the gastrointestinal tract including saliva, bile, Paneth cells, and Brunner's glands. It is a mitogen that promotes DNA synthesis and transcription of RNA, leading to protein synthesis. EGF increases intestinal nutrient and ion absorption by the recruitment of a pool of preformed brush border membrane. EGF increases glucose absorption by enhancing the insertion of preformed membrane and SGLT1 into the brush border membrane through a mechanism involving the polymerization of actin (44). Milk contains a number of peptide growth factors such as EGF, growth factors IGF, and somatostatin. Milk EGF is usually degraded in the intestinal lumen. The defatted and decaseinated supernatant of bovine milk prevents the degradation of EGF in both gastric and duodenal luminal fluids. Dietary derived protease inhibitors, such as soya bean trypsin, also prevent EGF degradation in the duodenal lumen (45).

Interleukin-1β, known to be a hypoglycemic cytokine, is produced by activated macrophages, B lymphocytes, and endothelial cells. The administration of interleukin-1 (IL-1) to normal or diabetic mice induces hypoglycemia without hyperinsulinemia, possibly by inhibiting the mucosal uptake of glucose by inhibiting the Na^+, $-K^+-$ATPase in the basolateral membrane (46). Atrial natriuretic peptide binds to specific receptors along cell surfaces, and the signalling of two of these receptors is coupled to guanylate cyclase. Atrial natriuretic peptide inhibits sodium, water, and glucose absorption in the intestine by increasing the value of the affinity constant (K_m) without modifying the V_{max} (47).

The topic of glucose–galactose malabsorption has been reviewed (48). Denervation of the canine jejunoileum decreases the *in vivo* and *in vitro* uptake of glutamine, alanine, leucine, and glucose (49). Microvillus inclusion disease is a congenital disorder characterized by severe fluid and electrolyte losses from the gastrointestinal tract. There is villous atrophy, loss of microvilli, and internalized inclusions of microvilli within the cytoplasm of the enterocytes. It is not known if this contributes to the clinical features of the disease. These patients have reduced brush border membrane expression of the sodium/hydrogen exchangers (NHE2, NHE3) and SGLT1 (50).

In the rabbit model of chronic ileal inflammation, there is inhibition of coupled NaCl absorption due to a reduction of Cl^-/HCO_3^- but not of Na^+/H^+ exchange; inhibition of SGLT1 via decreasing the number of contransporter; a decrease in Na^+–amino acid cotransporter affinity; and reduced Na^+–bile acid cotransport as a result of a decrease both in the affinity and the number of cotransporters. The glucocorticoid methylprednisolone has no effect on SGLT1 in normal rabbit ileum, but in the presence of chronic ileal inflammation methylprednisolone reverses the reduction in SGLT1 in villus cells seen with inflammation and also reverses the decrease in Na^+, K^+-ATPase (51). The thyroid hormone T3 stimulates SGLT1 cotransport activity in Caco-2 cells by involving both transcriptional and translational levels of regulation (52). Two interrelated levels of regulation may coexist: a differentiation-related control due to the induction in the crypt cells of SGLT1, and modulation of SGLT1 protein and mRNA abundance in already mature enterocytes.

Fat

The topic of the intestinal absorption of fatty acids has been reviewed previously (53). The lipid content of the intestinal brush border membrane changes with fasting: there are decreased ratios of cholesterol/phospholipid, sphingomyelin/phosphatidylcholine, protein/lipid, decreased oleic and linoleic acids, and increased brush border membrane total phospholipid, double-bond index, as well as an increased percentage

of stearic and arachidonic acids (54). These changes alter the physicochemical properties of the brush border membrane and may modify its transport properties.

The diffusion of cholesterol from the lipid-rich phases of the intestinal contents across the unstirred water layer to the brush border membrane is dependent on its emulsification and micellar solubilization by biliary lipids and by the detergent by-products of dietary lipid glycolysis. Phosphatidylcholine is an emulsifier of dietary cholesterol. Biliary cholesterol, the major portion of cholesterol entering the intestine, cannot be effectively solubilized in bile without biliary phosphatidylcholine. Although phosphatidylcholine solubilizes cholesterol, it suppresses cholesterol absorption by a phosphatidylcholine-dependent shift of the lipid–water partitioning of cholesterol towards the micellar phase. Inhibition with phosphatidylcholine-containing micelles results in reductions in the absorption, esterification, and secretion of cholesterol, without any influence on the absorption of oleic acid, its conversion to acylated lipids, or triacylglycerol secretion (55). Pancreatic phospholipase A_2 ($pPLA_2$) enhances cholesterol absorption from phosphatidylcholine-containing micelles, suggesting that inhibitors of $pPLA_2$ may be useful to reduce cholesterol absorption. Orilistat is an inhibitor of pancreatic and other lipases. It is used in the treatment of obesity by inhibiting intestinal fat absorption (56, 57).

Clinical Learning Point: Inhibitors of pancreatic lipase and phospholipase A_2 may be useful clinically to reduce absorption as part of a treatment program for obesity and hyperlipidemia.

Bile acids are synthesized from cholesterol in the liver and are secreted with bile into the small intestine. In the terminal ileum the luminal bile acids are actively reabsorbed by enterocytes and are returned to the liver via the portal circulation. This process is known as the enterohepatic circulation. About 95% of bile acids are conserved in each cycle as a result of the presence of high-affinity transporters located at the brush border membrance of the enterocyte and at the sinusoidal membrane of the hepatocyte.

A small fraction of the more lipophylic conjugates of bile acids is absorbed passively in protonated form in the acid pH of the duodenum. Conjugated bile acids are absorbed in the jejunum by anionic exchange and by an antiport transport mechanism (58). The ileal Na^+-dependent bile acid transporter has been cloned and has homology to the Na^+-dependent transporter for conjugated bile acids that is present in the basolateral membrane of the hepatocyte.

The topic of the physiology and molecular basis of the intestinal absorption of bile acids has been reviewed elsewhere (59). Photoaffinity labeling techniques have identified many putative proteins involved in the ileal bile acid transport system. After the Na^+-coupled 99-kDa protein-mediated uptake, bile acids are transported by actin (43 kDa) or by cytosolic proteins (14 and 35 kDa), either to the microsomal 20-kDa protein or directly to the basolateral membrane. Here the bile acid leaves the cell by an anionic exchange process mediated by a 54-kDa integral basolateral protein, and exit is possibly preceded by the binding of bile acid to a 59-kDa basolateral associated protein. The cDNAs encoding rat ileal apical Na^+-dependent bile acid transporter have been cloned. The apical Na^+-dependent bile acid transporter contains a glycosylation site, and a novel apical sorting signal is localized to the cytoplasmic tail of the apical Na^+-dependent bile acid transporter (60).

A 14- to 15-kDa cytosolic binding protein, the intestinal bile acid-binding protein, belongs to a family of hydrophobic ligand-binding proteins, the fatty acid-binding proteins. In Caco-2 cells incubated with bile acid, there is a 7.5-fold increase in intestinal bile acid-binding protein mRNA levels occurring in a time- and dose-dependent manner, and this mRNA increase is associated with enhanced abundance of cytosolic intestinal bile acid-binding protein protein (61). This implies transcriptional regulation. This stimulatory effect of bile acids is prevented by the pretreatment of Caco-2 cells with actinomycin D or cycloheximide. The binding of bile acids to ileal lipid-binding protein (ILBP) increases the affinity of ILBP for bile acids (62). This may be a substrate-load modification of transport activity and a positive-feedback regulation for active uptake of bile acids in the ileum. The ileal bile acid transporter (IBAT) is up-regulated by administration of glucocorticosteroids, and the enhanced V_{max} corresponds to an increase in both IBAT mRNA and protein (63). Inhibition of IBAT inhibits the development of hypercholesterolemia in rabbits in a manner similar to bile acid sequestrants (64).

Clinical Learning Point: Several membrane-bound and cytosolic proteins have been identified in the enterocyte as well as in the hepatocyte and may be the target for the future therapeutic manipulation of bile acid metabolism and control of hyperlipidemia.

Common bile duct ligation or feeding a bile acid-binding compound may be used to reduce ileal brush

border membrane bile acid uptake. Bile acid pool expansion or depletion results in an increased or decreased bile salt transport capacity of the liver, respectively. A reduction in the presentation of bile salts to the brush border membrane does not modulate the expression of the genes involved in their transport (65).

During chronic ileal inflammation in rabbits, Na^+-glucose cotransport is inhibited by a decrease in the cotransporter numbers and Na^+-amino acid cotransport is inhibited by a decrease in the affinity for amino acid, whereas Na^+-bile acid cotransport is inhibited by both a decrease in the affinity as well as a decrease in the V_{max} of the uptake of bile acid, associated with reduction in transporter protein and mRNA (66).

The topic of ideopathic bile acid malabsorption has been reviewed by Bai (67). This malabsorption may occur in about one sixth of patients with otherwise unexplained chronic diarrhea (68). The patient usually has a symptomatic response with the use of a bile acid sequestrant such as cholestyramine. While the pathogenesis of idiopathic bile acid malabsorption is unknown, there may be morphological changes in the patient's ileal biopsies or abnormalities in their uptake of bile acids. The mechanism of diarrhea does not depend on an enrichment of the bile acid pool with dihydroxy bile acids (69).

Clinical Learning Point: Suspect bile acid malabsorption in the patient with otherwise unexplained chronic diarrhea.

The absorption of ursodeoxycholic acid occurs in the proximal intestine by nonionic diffusion, and this is impaired in patients with Crohn's disease (70).

Fatty acid-binding proteins are a group of homologous, 14- to 16-kDa soluble proteins in the enterocyte cytosol that noncovalently bind long-chain fatty acids (LCFA) with affinities in the nanomolar range. Intestinal fatty acid-binding protein is specific to the intestine, whereas the liver fatty acid-binding protein (L-FABP) is present in the intestine as well as in the liver. Intestinal fatty acid-binding protein (I-FABP) binds a single molecule of LCFA in an interior cavity surrounded by two five-stranded antiparallel β-sheets. Intestinal fatty acid-binding protein is important for the intracellular trafficking and processing of dietary fatty acids. The α-helical region of acid bindin protein I-FABP is involved in membrane interactions, and plays a critical role in the collision mechanism of fatty acid transfer from I-FABP to phospholipid membranes (71). Intestinal fatty acid-binding protein is a monomeric, cytoplasmic protein that binds long-chain fatty acids such as palmitic acid. Intestinal fatty acid-binding protein is regulated by collagen in Caco-2 cells (72); and it may target dietary fatty acids to triglyceride synthesis pathways, while L-FABP liver fatty acid-binding protein may target fatty acids to oxidation and phospholipid synthesis. However, factors in addition to I-FABP play a role in determining the metabolic fate of LCFA in small intestinal epithelial cells (73). These binding proteins facilitate the cytoplasmic movement of fatty acids (74).

Most of the interindividual variation in the plasma lipoprotein response to dietary fiber can be attributed to the polymorphism in the gene which encodes I-FABP (75). Feeding sunflower oil increases L-but not I-FABP mRNA and protein levels in the intestine (76). Liver fatty acid-binding protein gene expression is usually silent in the distal ileum but can be induced by feeding fatty acids, and fatty acids may up-regulate gene expression in many tissues such as the intestine but down-regulate gene expression in the liver (77). Only L-FABP expression increases fatty acid uptake in fibroblasts (78). Intestinal fatty acid-binding protein does not affect fatty acid incorporation into cytosolic triglyceride (73). It is not known what importance these fatty acid-binding protein have in the control of lipid absorption.

The membrane-bound fatty acid-binding protein is a 40-kDa protein postulated to mediate fatty acid uptake through an active sodium-dependent process in the intestine. The regulation of this protein is unknown, since it has not yet been cloned. The fatty acid translocate (FAT) protein is a 88-kDa membrane protein which has been cloned. FAT RNA abundance is higher in the jejunum than in the ileum, is present in the upper two thirds of the intestinal villi, and the FAT protein is limited to the brush border membrane (76).

Cholesterol is thought to be absorbed by passive diffusion in the intestine, but a receptor mediating the absorption of dietary cholesterol has been identified. Sterol carrier proteins mediate the intracellular transfer and metabolism of cholesterol and are encoded by a single gene with two initiation sites. Sterol carrier protein-2 is involved in the uptake and intracellular fatty acid trafficking in L-cell fibroblasts (79).

Dietary unsaturated fatty acids increase cellular retinol-binding protein type II (CRBP II) mRNA and protein levels in rat jejunum, but CRBP II gene expression in rat jejunum is not regulated by dietary retinoids (80). CRBP II-retinal and -retinol complexes serve as substrate for the conversion of retinal into retinol catalyzed by retinal reductase, but also for the conversion of retinol into retinyl esters. The *trans-*

acting factors such as peroxisone proliferator-activated receptors (PPARs) may mediate gene transcription, and dietary fatty acids may lead to induction of CRBP II transcription through increases in PPAR-α as well as its ligand levels (80).

Clinical Learning Point: A proportion of lipid absorption is protein-mediated, and this opens the way to targeting these proteins and thereby therapeutically modifying lipid absorption.

Short-chain fatty acids are produced by bacterial degradation of complex carbohydrates and proteins entering the colon. Short-chain fatty acids are avidly absorbed. The absorption of medium-chain fatty acids (C_7-C_{12} fatty acids) are absorbed at the same rate as short-chain fatty acids in the human rectum (81). Short-chain fatty acids stimulate electroneutral sodium absorption via the activation of apical Na^+/H^+ exchange, which results from the short-chain fatty acids changing the intracellular pH gradients (82). NHE2 and NHE3 are expressed in the brush border membrane. NHE3 is involved in the transepithelial Na^+ absorption, and during ontogeny NHE3 is likely regulated at the transcriptional as well as the post-transcriptional levels. NHE2 functional protein levels are lowest in 2-week-old rats and are highest in 6-week-old animals, although NHE2 mRNA levels in the jejunum are unchanged. However, nuclear run-on analyses show a higher NHE2 transcription rate in the 6-week-old as compared with the 2-week-old animals, suggesting that the increases in NHE2 expression upon weaning are mediated by increased gene transcription (83).

Cholesterol esterase (bile salt-dependent lipase) is activated by the primary bile salts (cholic and chonic acids) and catalyzes the hydrolysis of a wide range of substrates. These include the hydrolysis of cholesterol esters into free cholesterol and fatty acids, and bile salt-dependent lipase participates in the intestinal free cholesterol absorption as a cholesterol transfer protein. Bile salt-dependent lipase is present in brush border membrane and in the endosomal compartment of enterocytes, but curiously bile salt-dependent lipase mRNA is not expressed by the intestinal mucosa (84).

The intracellular formation of cholesteryl esters is catalyzed by the action of the enzyme acyl-CoA (coenzyme A): cholesterol acyltransferase. Acyl-CoA:cholesterol acyltransferase attaches a fatty acid to the free hydroxyl group of cholesterol, thereby limiting the solubility of the esterified cholesterol in the lipids of the cell membrane and influencing the regulation of cholesterol signaling. The majority of cholesterol absorbed from the intestinal lumen by the mucosal cell is esterified by acyl-CoA:cholesterol acyltransferase and is incorporated into chylomicron particles.

Acyl-CoA:cholesterol acyltransferase may have the primary function of the secretion of cholesteryl esters into apoB-containing lipoproteins (85). The β apolipoproteins (apoB48 and apoB100) are important in the formation of triglyceride-rich lipoproteins. ApoB48 is essential for the assembly of chylomicrons in the intestine, and apoB100 is essential for the formation of very low density lipoprotein (VLDL) in the liver. The expression of the human apoB gene in the intestine is dependent on DNA sequences located at great distances from the structural gene (86).

The surface component of the chylomicron is comprised primarily of apolipoproteins ($apoB_{48}$, A-I, apoA-IV, and apoC), cholesterol, and phospholipids. The intestine responds to a requirement for increased triacylglycerol transport by producing chylomicrons of increased size rather than by increasing their numbers, thereby conserving their surface components. When the circulation is entered from the thoracic lymph duct, the surface components of the chylomicrons change, with the surface predominantly gaining apoE and losing apoA-I and apoA-IV.

Apolipoprotein A-IV is a major glycoprotein component of intestinally synthesized and secreted triglyceride-rich lipoproteins. Dietary fat stimulates the expression, synthesis, and secretion of intestinal apoA-IV. Peptide tyrosine-tyrosine stimulates the synthesis and lymphatic secretion of apoA-IV, but has no effect on mucosal apo AIV mRNA levels (87).

Lipid absorption stimulates apoA-IV synthesis and secretion by the jejunum. Lipid absorption in the distal small intestine stimulates the synthesis and release of apoA-IV by the jejunum, probably as a result of release of peptide tyrosine–tyrosine. Both apoB-IVA and apoB100 are important in the formation of triglyceride-rich lipoproteins. ApoB-IVA is essential for the assembly for chylomicrons in the intestine, and apoB100 is essential for the formation of VLDL in the liver. Chylomicron formation may involve the synthesis of apoB-free triglyceride-rich particles within the endoplasmic reticulum lumen. Transport of these lipid particles out of the endoplasmic reticulum to the Golgi apparatus and to the interstitium is facilitated by the acquisition of apoB (53).

Triacylglycerol is resynthesized at the level of the endoplasmic reticulum where triacylglycerol "flips" across the inner membrane of the endoplasmic reticulum. The triacylglycerol is then transported to the

growing chylomicron by the microsomal transport protein (MTP). MTP rescues apoB from intracellular degradation during early lipidation of the protein (88). It is unknown how the triacylglycerol goes from the endoplasmic reticulum to the Golgi. Brefeldin A is a fungal metabolite that causes disruption of the Golgi. This process may be sensitive to brefeldin A and is time-, ATP-, temperature- and cytosol-dependent (89).

The intestine can vary its triacylglycerol output rate depending on different physiological conditions. The rate-limiting step in the complex process from fatty acid and monoacylglycerol entry to triacylglycerol export may involve a protein for the transport of triacylglycerol from the endoplasmic reticulum to the Golgi complex (90). This transport particle has been isolated and characterized: electron microscopy shows a 200-nm vesicle containing immunoidentifiable apoB48 and apoA-IV, but very little apo A-I (91). The surface of the chylomicron contains both exchangeable apo A-I, apo A-IV, apo C, and apoE and nonexchangeable apoB48.

Postprandial lipidemia is determined by the contribution of chylomicrons containing triacylglycerol from dietary sources as well as that of VLDLs that carry liver-derived triacylglycerols. Various dietary fatty acids have specific effects on plasma triacylglycerol concentrations. Trans fatty acids, derived from partly hydrogenated vegetable oils and associated with a risk of developing coronary heart disease, increase triacylglycerol secretion and apoB48 and apoB100 secretion from Caco-2 cells (88).

Intestinal sensors for specific nutrients signal reductions of food intake, and these sensors are arrayed along the entire intestine. The timing and degrees of satiety do not correlate with the timing and extent of gastric distension, but rather correlate with the timing and extent of the spread of lipolytic products along the length of the small intestine (22).

The topic of the malabsorption syndromes has been reviewed previously (67). Steatorrhea and a decrease in the coefficient of fat absorption occur in a reversible manner in approximately half of patients with Grave's disease (92). The mechanism of the steatorrhea does not appear to be associated with pancreatic exocrine dysfunction. In the presence of biliary obstruction, vitamin A absorption is impaired, but the absorption of electrolytes and glucose is unchanged (93). In patients with nephrotic syndrome, hypercholesterolemia is common. The mechanism of this hypercholesterolemia is unknown, but it is not due to enhanced absorption of cholesterol (94).

Most cystic fibrosis patients malabsorb dietary fat because of pancreatic insufficiency, which leads to impaired lypolysis. Pancreatic enzyme replacement therapy frequently fails to correct intestinal fat malabsorption in cystic fibrosis patients, partially because of incomplete intraluminal solublization of long-chain fatty acids as well as reduced mucosal uptake (95).

Gymnemic acid, a mixture of triterpene glycosides extracted from the leaves of *Gymnema sylvestre*, inhibits the intestinal absorption of glucose as well as oleic acid (96). The therapeutic implication of this finding remains to be established.

Amino Acids and Protein

Two different protein families of amino acid transporters, designated CAT and BAT (broad-specificity amino acid transporters), mediate the plasma membrane transport of cationic amino acids. The isolation and functional expression of BAT has been described for this y^+L basolateral membrane transport in the intestine, kidney, and placenta (97).

The topic of the role of glutamine and nucleotide metabolism within enterocytes has been reviewed (98). Glutamine is the preferred substrate for the small intestine, and this amino acid is released by proteolysis during catabolic states. The intestinal uptake of glutamine is diminished in septic patients and is increased during surgical stress. After sepsis both growth hormone and IGF-I increase glutamine uptake (99).

Fluoxetine, a selective serotonin reuptake inhibitor, may cause diarrhea. One of the mechanisms by which this drug may cause is by reduction of the brush border and basolateral transport of the neutral, essential amino acid, L-leucine (100).

The absorption of dipolar amino acids by the intestine is mediated by multiple pathways, including several Na^+-dependent and Na^+-independent mechanisms. For example, in the chicken intestine L-methionine is transported by four transport systems (101). The brush border membrane uptake of L-glutamate is Cl^--independent and Na^+-dependent, and L-glutamate and D-aspartate share a common transport system in the rabbit small intestine (102). L-Carnitine is a γ-amino acid that serves as an essential cofactor for the transfer of long-chain fatty acids across the mitochondrial inner membrane in which β-oxidation occurs.

The intestinal absorption of L-carnitine is saturable (103). Serotonin is contained in the enterochromatin cells of the intestinal mucosal epithelium as well as in the enteric nervous system. Mucosal crypt epithelial

cells of the rat intestine express mRNA encoding the serotonin transporter, and the epithelial reuptake of serotonin is responsible for terminating the mucosal actions of serotonin (104).

Vasoactive intestinal peptide (VIP) inhibits alanine absorption through the capsaicin-sensitive primary afferents and the myenteric plexus, by a process that may involve cholinergic muscarinic mechanisms (105). The acute stimulation of the vagal capsaicin-sensitive primary afferent fibers decreases the jejunal absorption of alanine, whereas chronic blockade of these fibers results in an increase in the absorption of this amino acid.

The uptake of di- and tripeptides by the small intestine is mediated by the proton-coupled peptide transporter, PepT1. PepT1 is unaffected by 5-fluorouracil, whereas glucose transport is diminished by this agent (106). The abundance PepT1 and its mRNA can be increased in response to the exposure of Caco-2 cells to glycyl-L-glutamine (107). Delta-aminolevulinic acid is a photosensitizer and a precursor for cellular porphyrin synthesis. Aminolevulinic acid uptake is by PepT1 in the intestine, and by PepT2 in the kidney (108). A cDNA encoding a human intestinal peptide transporter has been cloned and has a high degree of similarity and homology with the rabbit intestinal peptide transporter. A computer model has been used to elucidate the transmembrane protein structure of this dipeptide transporter (109).

The mucosal-to-serosal transport of acyclovir, an agent used to treat herpes virus infection, is increased by conjugation with L-valine. This is likely the result of uptake occurring by the oligopeptide transporter, followed by intracellular hydrolysis. The distance between the N-terminal amino group and the C-terminal hydroxyl group is important for the interaction with the apical oligopeptide transporter in Caco-2 cells (110). The tyrosine 167 in transmembrane domain 5 contributes to the function of this protein-coupled peptide transporter (111).

Valacyclovir is a prodrug of the antiviral agent acyclovir and is a substrate for these peptide transporters (112). The membrane transport of valacyclovir is also by the PepT1 H^+ dipeptide cotransporter (113). The presence of a dipeptide in the culture medium of Caco-2 cells stimulates the uptake of dipeptide by PepT1 (114). The authors suggest that if the bioavailability of orally administered peptidomimetic drugs is limited, then patients may be tried on a high-protein diet to enhance their absorption of the medication.

Clinical Learning Point: A high protein diet may be useful to increase the intestinal absorption of drugs transported by the H^+ dipeptide cotransporter.

The lamina propria contains various immunocytes such as mast cells and lymphocytes. Their numbers increase during inflammation by reacting nonspecifically to certain bacterial products, or by reacting specifically to foreign protein antigens. During stress in a susceptible strain of rats, there is increased transport of the macromolecule horseradish peroxidase (115). The authors speculate that immune reactions to foreign proteins may initiate or exacerbate inflammation.

Peptide-derived drugs, such as α-amino-β-lactam antibiotics, angiotensin-converting enzyme inhibitors, or renin inhibitors are taken up in the small intestine by a saturable H^+-dependent active transport system. This is a 127-kDa microheterogeneous glycoprotein which is closely associated with the sucrase–isomaltase complex in the enterocyte brush border membrane (116).

The small intestine is an important component of whole-body protein metabolism, accounting for up to 10% of total protein synthesized. A luminal flooding dose method has been developed to study the effect of the luminal osmolarity of jejunal mucosal protein synthesis (117). In humans, duodenal protein synthesis is unaffected by feeding (118).

Enterocytes may play a role in antigen transport as well as in antigen presentation to the underlying lymphocytes. This process may lead to oral tolerance, which is the down-regulation of the systemic immune response to orally administered antigens via the generation of active cellular suppression or clonal anergy. In antigen-presenting cells, exogenous proteins are taken up by endocytosis; and then are processed by cathepsins into peptides that bind to MHC class II molecules. The MHC II/peptide complex is translocated to the external membrane for direct presentation to lymphocytes. Interferon-γ secreted by lymphocytes in the intestinal mucosa up-regulates MHC class II molecule expression and epithelial permeability. Intestinal cells process proteins such as horseradish peroxidase into peptides that are potentially capable of stimulating the immune system, and thereby increase the antigenic load in the intestinal mucosa (119).

Antibodies against food antigens are usually produced in healthy people. This hormonal response can be detected both in serum and secretions. Specific IgG levels are highest in serum, and the local IgA-producing population is functionally different in the various tissues of healthy people (120).

Minerals and Vitamins

Iron and Other Metals. The topic of hemochromatosis and iron absorption has been reviewed by Bacon et al. (121). Iron balance in humans and animals is maintained by modifications of the intestinal absorptive process. A positional cloning strategy has been used to identify a candidate murine iron transporter gene (122, 123). In the rat this metal-ion transporter, DCT1, has a broad range of substrates including Fe^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Cd^{2+}, Cu^{2+}, Ni^{2+}, and Pb^{2+} (123). This DCT1 mediates active transport that is proton-coupled, is ubiquitously expressed in the proximal small intestine, and is up-regulated by dietary iron deficiency. Perhaps this explains why nickel absorption is increased in iron-deficient rats, and the transport and accumulation of nickel in Caco-2 cells is depressed in iron-loaded monolayers (124).

The sex-linked anemia (SLA) mouse has an anemia that results from an inherited defect of intestinal iron absorption. Mapping of the SLA locus was an important first step into identifying the gene itself (125). Iron deficiency in rats influences lipid metabolism, resulting in reduced serum lipoproteins; increased hepatic phosphatidylcholine and phosphatidylethanolamine concentrations; lower activities of glucose-6-phosphate dehydrogenase, malic enzyme, and fatty acid synthase; and higher triacylglycerol concentrations in serum lipoproteins (126). The basis for this phenomenon is unknown.

Clinical Learning Point: A metal transporter, DCT_1, has been identified, and this may open the way to a better understanding of disorders of, for example, iron and zinc metabolism.

The Caco-2 cell monolayer may be used to assess food iron availability (127). A variety of ligands are known to inhibit iron absorption including phytates, tannates, phosphates, oxylates, and carbonates. Regular tea inhibits the intestinal absorption of nonheme iron and reduces the frequency of phlebotomies required in the management of patients with hemochromatosis (128). Unbound iron can generate free radicals, and the intestine of iron-deficient rats is more susceptible to peroxidative damage during iron supplementation (129).

Most of the approximately 110 mg of copper in the adult body is functional, acting as cofactors of enzymes catalyzing oxidation–reduction reactions. Newly absorbed copper is transported to bodytissues by plasma proteins, including albumin and ceruloplasmin (130). The cytosolic protein metallothionein participates in the regulation of zinc metabolism. Studies with transgenic and knockout mice suggest that metallothionein may reduce the efficiency of zinc absorption (131). Copper and zinc absorption are dependent on transmucosal fluid movement (132).

Calcium. Intestinal calcium (Ca^{2+}) absorption involves two processes, a transcellular metabolically driven transport process, and a passive paracellular process (133). The major part of the transcellular component of Ca^{2+} transport takes place in the duodenum, whereas the paracellular pathway takes place throughout the small intestine. Calcium absorption is stimulated by a low-Ca^{2+} diet (134). The Ca^{2+}-sensing receptor (CaR) is expressed in the intestine (135). The upper small intestine is the major site for active Ca^{2+} absorption, and this absorption is stimulated by calcitriol, which is mediated in part by vitamin D receptor-mediated genomic actions. This process results in an increased production of calbindin-$D_{9\ k}$, a cytosolic Ca^{2+}-binding protein that has been proposed to facilitate the movement of Ca^{2+} across the cytosol from the brush border membrane to the basolateral side of the enterocyte. Calbindin D also modulates the activity of an intestinal ATP-dependent calcium pump on the basolateral membrane of the enterocyte. Ca^{2+} absorption during early postnatal life of pigs involves a calcitriol-independent mechanism that may include intact microtubule actions (136).

Dietary carbohydrates such as inulin, resistant starch, and guar gum hydrosylate increase Ca^{2+} absorption. Fructooligosaccharides are low-molecular-weight indigestible carbohydrates that increase Ca^{2+} absorption and balance (137). Circulating 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D$], the hormonal form of vitamin D_3, is the prime hormonal regulator of intestinal Ca^{2+} absorption. Estradiol stimulates intestinal Ca^{2+}, absorption by a direct effect on the intestine, rather than by an effect on circulating 1,25-dihydroxyvitamin D or by reduced intestinal responsiveness to 1,25-dihydroxyvitamin D (138). The cellular action of $1,25(OH)_2D$ is mediated by an intracellular vitamin D receptor protein that binds to promoter regions in specific genes and regulates the transcription of these vitamin D-responsive genes.

Senescence in humans and animals is associated with a functional decline in a variety of physiological systems, including the efficiency of intestinal Ca^{2+} absorption. In old animals there are reduced circulating levels of $1,25(OH)_2D$, as well as a relative intestinal resistance to the action of this hormonal form of vitamin D_3 (139). It has been suggested that osteoporosis is as common in men as in women and that there

is an age-related decline in intestinal Ca^{2+} absorption and serum $1,25(OH)_2$-D_3 in healthy males (140).

Prolactin enhances the Ca^{2+} flux in the duodenum by a sodium-dependent mechanism, whereas in the proximal jejunum the mechanism of the prolactin-stimulation of plasma-to-lumen Ca^{2+} flux is unknown (141). Dietary phytate inhibits the absorption of a number of minerals such as Ca^{2+} and iron by forming insoluble phytate-mineral complexes. Certain inositol phosphate break-down compounds chelate and increase the solubility of minerals, and may be used as absorption enhancers (142).

Vitamin B_{12}. Vitamin B_{12} (cobalamin) binds to a plasma transporter, transcobalamin II, and is taken to tissues by receptor-mediated endocytosis via a transcobalamin II receptor. Brefeldin A reduces the cholesterol but not the phospholipid levels of the basolateral membrane of Caco-2 cells, and brefeldinA treatment also results in complete loss of transcobalamin II receptor activity and protein level in the basolateral membrane (143).

Water and Electrolytes

Sodium enters the enterocyte with cotransported substrates such as glucose or amino acids or by way of an exchanger in the brush border membrane. Human duodenal enterocytes contain at least three acid/base transporters: the Na^+/H^+ exchanger extrudes acid, the $Na^+HCO_3^-$ cotransporter acts as a base loader, and Cl^-/HCO_3^- exchanger operates as a base extruder (144). Brush border membrane Na^+/H^+ exchange (NHE) activity is inhibited by the activation of the protein kinase C pathway. There are several isoforms of the exchanger NHE:NHE1 is on the basolateral membrane of villous and crypt cells, and NHE2 and NHE3 are on the brush border membrane of villous cells. NHE1 is the "housekeeper isoform," regulating intracellular pH and volume, while NHE3 mediates sodium absorption. The role of NHE2 is uncertain. Na^+/H^+ exchange contributes to the electroneutral absorption of NaCl and to the regulation of luminal pH.

The activity of NHE3 decreases from the proximal to the distal small intestine (145). Homozygous mutant mice lacking NHE3 function develop mild diarrhea and acidosis (146). NHE3 exchanges extracellular Na^+ for intracellular H^+, with a stoichiometry of 1:1. Physiological regulation and function of epithelial-specific NHEs are dependent on tissue-specific factors and/or conditional requirements (147). Short-term regulation of NHE1 is by protein kinases (148), which alter the affinity for intracellular H^+. NHE1 on the basolateral membrane does not change in rat intestine between week 2 and adulthood (149). Short-term regulation and prolonged transcriptional regulation on NHE2 and NHE3 include changes in the values of their maximal transport velocity (V_{max}). Glucocorticosteroids stimulate intestinal water and NaCl absorption, increase Na^+/H^+ exchange, enhance NHE3 mRNA abundance, and also increase the NHE3 turnover number (150). X-ray microanalysis has shown that the Na^+ concentration of the villous cells is higher than in the crypts, whereas the concentration of potassium and chloride is less (151).

The intestinal absorption of water appears to occur by way of cotransporters such as the intestinal Na^+/glucose cotransporter (SGLT1), which act as a molecular water "pump." For each one molecule of sugar absorbed by SGLT1, two molecules of sodium and 225 molecules of water are transported. This coupling between sugar and water transport is constant, independent of sodium, sugar, voltage, temperature, and osmolarity (18, 152).

Clinical Learning Point: The nutrient transporters such as SLGT1 are responsible for a portion of the intestinal absorption of water.

The absorption of ingested water and most solutes occurs in the proximal small intestine, where the creation of suitable osmotic gradients promotes the uptake of water. Thus, the rate of gastric emptying and therefore the absorption of nutrients is an important factor in determining the rate of water absorption. Dilute hypotonic glucose–sodium solutions are effective oral rehydration solutions, and the inclusion of a small amount of glucose or amino acid assists in the overall rehydration process (153). Low osmolarity of a nutrient solution decreases intraluminal water flow rates in the upper intestine of healthy volunteers, without affecting the absorption rates of total nitrogen and carbohydrate. This may lower the water loss in patients with extensive small bowel intestinal resection (154). Total fluid absorption of a 6% carbohydrate–electrolyte beverage from the upper gastrointestinal tract of humans during exercise is no different from the absorption that occurs with water (155).

Nitric oxide is a modulator of intestinal water and electrolyte transport (156). Nitric oxide is a lipid-soluble gas, with a very short half-life under aerobic conditions. Nitric oxide and L-citrulline are formed from the oxidation of L-arginine. When its concentration is low, nitric oxide has a proabsorptive effect on water and electrolyte transport. This process involves the enteric nervous system, the suppression of pros-

taglandin formation, and the opening of basolateral membrane K^+ channels. When nitric oxide levels are high, net secretion may occur.

Clinical Learning Point: The influence of nitric oxide on intestinal water absorption and secretion depends on its concentration.

Both cholera toxin and *Escherichia coli* heat-labile enterotoxin increase the intracellular adenosine 3′, 5′-cyclic monophosphate concentration, but only cholera toxin-induced secretion is accompanied by 5-hydroxytryptamine (serotonin) release (157). Substance P is a member of the tachykinin family of neuropeptides, and is found in enteric neurons and some endocrine cells in mammalian small intestine. Several endogenous secretagogues such as substance P, serotonin, and IL-1β may release nitric oxide, thereby contributing to the secretory condition (156).

The cystic fibrosis transmembrane conductance regulator (CFTR) is an adenosine 3′, 5′-cyclic monophosphate (cAMP) regulated Cl^- channel that is activated by phosphorylation with protein kinase A. The CFTR gene is tightly regulated, both developmentally and in a tissue-specific manner. In human and rat gastrointestinal tracts, a decreasing gradient of CFTR mRNA and protein is observed along the proximal-distal axis and along the crypt-villus axis. The transcriptional regulation of the CFTR gene involves the combination of multiple regulatory elements, and a 6.6-kb region in rat CFTR derives specific expression of a reporter gene in cultured mouse intestinal cells with a crypt phenotype (158). The regulation of CFTR-mediated Cl^- permeability is achieved by phosphorylation of multiple serines in the regulatory domain of CFTR, followed by binding and hydrolysis of ATP at the nucleotide-binding folds. Protein kinase A is an holoenzyme consisting of a regulatory subunit dimer and two catalytic subunits. Protein kinase A exists as types I and II, which are defined by the type of regulatory subunit present in the holoenzyme, RI and RII, respectively. The type-II-selective analogs activate larger increases in CFTR-mediated current than do the type-I-selective analogs. This indicates that the differential activation of protein kinase A in cellular compartments is important in CFTR regulation (159). Guanylin is a 15-amino-acid peptide that activates CFTR and elevates the intracellular cGMP levels by activating guanylate cyclase C. The intravenous injection of guanylin induces mucous secretion from goblet cells in rat duodenal crypts (160).

Oxyntomodulin and glicentin are hormones present in the L cells of the ileum and colon. In these L cells, proglucagon processing gives rise to oxyntomodulin and glicentin. When active secretion in the ileum is induced by an electrogenic challenge, oxyntomodulin reduces hydromineral transport, the amplitude of which depends upon the integrity of the tetrodotoxin-sensitive neurons (161).

The etiology of enteral feeding-induced diarrhea is unknown, but it may be caused in part by antibiotic therapy, bacterial overgrowth in the intestine, bacterial contamination of the enteral formulas, hyperosmolarity of the formula, interaction with other mediators, or the production of choleretic diarrhea (162).

Clinical Learning Point: A trial of bile acid-sequestering agent may prove useful in the treatment of the patient who experiences diarrhea while taking an enteral diet.

Enterotoxigenic *Escherichia coli* (ETEC) that possess the $K88^+$, pilus are commonly associated with diarrheal diseases in young piglets. Bromelain, a proteolytic extract obtained from pineapple stems, protects piglets against diarrhea by temporarily inhibiting the $K88^+$. ETEC receptor activity (163). Most currently used anti-diarrheal drugs such as opiate derivatives, alter intestinal motility and secretion. The role of bromelain in the treatment of humans with diarrhea remains to be established.

Clinical Learning Point: A proteolytic extract from pineapple stems may prove to be useful to treat diarrhea, although the mechanism of this effect remains to be established.

The topic of the peptidergic regulation of intestinal ion transport has been reviewed (164). The endocrine and neural peptide tyrosine–tyrosine and neural peptide Y also have intestinal antisecretory activity, and this neurally-mediated effect is through the σ receptors. These are different from opiate, phencyclidine, or glutamate receptors and are present in high density in the wall of the intestine. In healthy volunteers, igmesine, a σ ligand, inhibits intestinal secretion and diarrhea induced by PGE_2 (165).

In patients with high fecal output (above 2.5 kg/day) from the short bowel syndrome, the proton pump inhibitor omeprazole (40 mg twice daily) increases water absorption (166). Serotonin (5-hydroxytryptamine$_3$) may contribute to the diarrhea of patients with carcinoid syndrome and in cholera toxin-induced secretion in man. The serotonin receptor antagonist, ondansetron, reverses the impaired jejunal fluid absorption observed in rats treated with the antineoplastic drug cisplatin (167), but it does not have a significant effect on the median diarrhea score,

stool weight, loparamide use, and overall colonic transit in patients with carcinoid diarrhea (168).

The sensory nerves, when stimulated by electrical field or capsaicin, cause Cl^- secretion but do not affect net absorption (or secretion) in the human jejunal mucosa (169).

The latex agglutination test for fecal lactoferrin may prove to be a highly sensitive, specific, and simple means for detection of fecal neutrophils, and thereby may be useful in the evaluation of patients presenting with chronic diarrhea (170).

The jejunum absorbs bicarbonate by a Cl^-/HCO_3^- exchanger on the basolateral membrane of the enterocyte. The presence of Na^+ positively affects the rate of anion antiport, but Na^+ itself is not transported. The jejunal enterocyte lacks a mechanism to counteract cellular alkalinization (171). The authors suggest that the main purpose of pH homeostasis might be to hinder acidification of the cytosol due to the influx of proteins and the production of acid by metabolism.

Congenital chloride diarrhea is a recessively inherited disorder characterized by massive loss of Cl^- in acidic stools, resulting from a defect in Cl^-/HCO_3^- exchange. The congenital chloride diarrhea locus has been mapped by linkage analysis to chromosome 7q31, adjacent to the CFTR gene, and is 4 chromosomal bands away from the Cl^-/HCO_3^- exchanger. *DRA* (down-regulated in adenoma) is the gene that is mutated in congenital chloride diarrhea, and DRA encodes an intestine-specific sulfate transporter. *DRA* also has a Cl^- transporter, which is defective in congenital chloride diarrhea (172, 173). DRA is also down-regulated in patients with ulcerative colitis, possibly contributing to the pathogenesis of diarrhea in this condition (174).

In most cell types volume regulatory mechanisms involve the activation of ionic pathways in order to restore the original volume of the cells. For example, in response to a hypoosmotic external solution, the cell will activate pathways that will result in the net efflux of K^+ and Cl^-. The anionic pathway is primarily activated by cell swelling (175). The Na^+-K^+-(2)Cl^- cotransporter participates in the homeostatic control of transmembrane ion gradients and cell volume. Activation of apical Cl^- channels is generally viewed as the primary regulatory event of cAMP-elicited Cl^- secretion. Basolateral Na^+-K^+-Cl^- cotransport must also increase in order to maintain cell electrolyte composition. The factors responsible for "cross-talk" between apical and basolateral transport events involve a complex interrelationship among intracellular Cl^- activity, cell volume, and the actin cytoskeleton in the regulation of epithelial Cl^- transport (176).

The stimulation of transepithelial Cl^- secretion increases the osmotic impetus for fluid secretion. After colonization of the small intestine by *Vibrio cholerae*, binding of the cholera enterotoxin to the intestinal enterocyte leads to ADP-ribosylation of the α-subunit of a stimulatory G protein, which then activates adenylate cyclase. The novel plant-derived inhibitor of cAMP-mediated fluid and Cl^- secretion has been identified (177). Its role as an antidiarrheal agent is unknown.

Sorbin is a new peptide localized in enterochromatin endocrine cells located in the enteric nervous system from the stomach to colon. Sorbin increases intestinal absorption in basal conditions, and decreases stimulated intestinal secretion. Synthetic sorbin derivatives inhibit the cholera-induced stimulation of the influx of water, Na^+, and K^+ (178). The COOH-terminal heptapeptide of sorbin stimulates neutral NaCl absorption, and inhibits electrogenic Cl^- in rat and human intestinal epithelium (179).

Clinical Learning Point: The antisecretory effect of the new peptide, sorbin, needs to be tested in a clinical situation on patients with diarrhea. Other new and promising antidiarrheal agents include bromelain, an extract from pineapple stems, and igmesine, a final sigma ligand.

Angiotensin II stimulates fluid absorption at low doses, but inhibits absorption at high doses. Angiotensin receptors involving cGMP are involved in the jejunal sodium and water absorption. Angiotensin II inhibits absorption via the AT_1 receptor by a mechanism that is negatively coupled to cAMP, and increases jejunal PGE_2 production (180). Substance P and neurokinin A are members of the tachykinin family, and are important in regulating intestinal function through the release of prostaglandin and enteric neurotransmitters (181).

Tolcapone (a catechol-*O*-methyl transferase inhibitor) is used in the treatment of Parkinson's disease. The development of diarrhea in patients on this novel drug may be the result of the intestinal secretion of fluid and electrolytes (182).

During the consumption of a high-salt diet, young animals experience a decrease in sodium absorption with a parallel increase in tissue levels of dopamine, and in 20-day-old but not in 40-day-old rats Na^+, -K^+-ATPase is reduced during a high-salt diet (183).

Surreptitious laxative abuse is a syndrome in which the patient secretly ingests laxatives to fabricate a

chronic diarrheal syndrome. The key to the diagnosis is the chemical detection of the laxative substance in stool. Diagnosing surreptitious use of phosphate laxatives has been helped with the establishment of upper limits of normal for stool soluble fecal phosphate concentration and output at 33 mmol/liter and 15 mmol/day, respectively (184).

Drugs

Passage of drugs from the intestinal lumen into the blood requires transport either through (transcellular) or between the enterocytes (paracellular). The Ussing chamber is useful to study the properties of the human intestinal mucosa *in vitro* (185). Predicting the extent of *in vivo* drug transport in humans has been achieved from indirect *in vitro* permeability data using intestinal epithelial preparations from rat or rabbits or from human Caco-2 or HT29-18 cell culture monolayers. In these monolayers, the mucosal surface area and the cross-sectional area are similar, but in the intestinal tissue the villi and the microvilli greatly amplify the surface area. For example, the amplification of the mucosal-to-serosal surface area is approximately 4.7 in the jejunum and 2.7 in the ileum. The mass of drug absorbed from the intestine is also influenced by its solubility, dissolution rate, luminal complexation, degradation, transit time, metabolism, and the physicochemical properties of the drug. Hydrophilic drugs are transported by the paracellular route across the tight junctions, whereas hydrophobic compounds are dissolved more easily in the lipid phase of the membrane and consequently generally have a higher intestinal permeability. Whereas the permeability coefficients determined for the human Caco-2 monolayer correlate with human absorption *in vivo*, the rat may not be a suitable choice for oral bioavailability studies of ester prodrugs (186).

The molecular basis for multidrug resistance is the action of P-glycoprotein (Pgp), as well as other efflux proteins such as multidrug resistance-associated protein. Pgp is expressed in the gastrointestinal tract as well as in other tissues such as the liver, kidney, and capillary endothelial cells of the brain. Pgp is an ATP-dependent efflux pump that increases the outward transport of these drugs from tissues. Many drugs such as the HIV-1 protease inhibitors are substrates of Pgp. Humans have one Pgp and Pgp contributes to the elimination of drugs by mediating their direct secretion from the blood into the intestinal lumen. In addition, Pgp may limit oral drug absorption. Caco-2 cells are a suitable cell line model for Pgp-mediated studies (187). Pgp causes multidrug resistance with cancer chemotherapy agents such as vinblastine, actinomycin D, and daunomycin. Pgp is also a substrate for several β-blockers and for quinidine (188). The calcium-channel blocker, verapamil, is affected by saturable efflux P-glycoproteins in the human intestine (189).

Intestinal cytochromes P-450 are involved in the biotransformation of dietary nutrients as well as orally ingested toxicants, procarcinogens, and other xenobiotics. This system plays a major role in the intestinal microsomal metabolism of retinal to retinoic acid (190).

With passage along the length of the small intestine, there is a decrease in the permeability to hydrophilic drugs and an increase in the permeability for hydrophobic drugs (191). Drugs with poor membrane permeability characteristics may be designed as lipophilic drug esters in an effort to enhance their oral delivery. The absorption of the lipophilic polyene antibiotic amphotericin-B may be enhanced by the use of bile salt mixed micelles (192). Biosurfactants such as unsaturated fatty acids, bile salt–fatty acid mixed micelles, milk fat globule membranes, and fatty acid sucrose esters have been used to enhance intestinal absorption of drugs with a low oral bioavailability. For example, fatty acid sucrose esters enhance the absorption of ciftibuten transport by rat brush border membrane vesicles, a property related to the dispersion parameter of these pharmaceutical adjuvants (193).

The clinical bioavailability of 5-fluorouracil following its oral administration to humans is low and erratic, probably due to first-pass metabolism of the drug in the intestinal mucosa as well as in the liver (194).

Guidelines for methods to determine efficacy and safety of drugs acting on the gastrointestinal tract have been published (195).

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