Small bowel review: Part I

ABR Thomson MD PhD FRCPC FACG, G Wild MDCM PhD FRCPC FACP

ABR Thomson, G Wild. Small bowel review: Part I. Can J Gastroenterol 1997;11(6):515-531. Significant advances have been made in the study of the small bowel. Part I of this two-part review of the small bowel examines carbohydrates, including brush border membrane hydrolysis and sugar transport; amino acids, dipeptides, proteins and food allergy, with a focus on glutamine, peptides and macromolecules, and nucleosides, nucleotides and polyamines; salt and water absorption, and diarrhea, including antidiarrheal therapy and oral rehydration treatment; lipids (digestion and absorption, fatty acid binding proteins, intracellular metabolism, lipoproteins and bile acids); and metals (eg, iron) and vitamins.

Key Words: *Amino acids, Carbohydrates, Diarrhea, Lipids, Metals, Small bowel, Vitamins*

Progrès significatifs dans l'étude de l'intestin grêle : 1re partie

RÉSUMÉ : Cette première partie d'un article en deux volets sur l'intestin grêle portera sur les glucides, y compris sur l'hydrolyse de la membrane de la bordure en brosse, le transport du sucre, les acides aminés, sur les dipeptides, les protéines et les allergies alimentaires en insistant sur la glutamine, les peptides et les macromolécules, sur les nucléosides, les nucléotides et polyamines, sur le sel, l'absorption hydrique et la diarrhée, y compris le traitement antidiarrhéique et les traitements oraux de réhydratation, sur les lipides (digestion et absorption, protéines de liaison aux acides gras, métabolisme intracellulaire, lipoprotéines et acides biliaires) et sur les métaux (par exemple, le fer) et les vitamines.

Significant advances have been made in the study of the small bowel. Part I of this two-part review of the small bowel concentrates on carbohydrates, including brush border membrane (BBM) hydrolysis and sugar transport; amino acids, dipeptides, proteins and food allergy, with a focus on glutamine, peptides and macromolecules, and nucleosides, nucleotides and polyamines; salt and water absorption, and diarrhea, including antidiarrheal therapy and oral rehydration treatment; lipids (digestion and absorption, fatty acid binding proteins [FABP], intracellular metabolism, lipoproteins and bile acids); and metals (eg, iron) and vitamins.

CARBOHYDRATES

BBM hydrolysis: Various aspects pertaining to the structure, function and development of intestinal brush border glycohydrolases have been reviewed (1). Dietary carbohydrates are hydrolyzed to monosaccharides before the latter are taken up across the intestinal BBM. Disaccharides and some oligosaccharides are digested by BBM sucrase-isomaltase (SI), lactase-phlorizin hydrolase (LPH), maltase-glucomylase and trehalase. Lactase deficiency is common worldwide. SI deficiency is a rare congenital condition found mainly in Greenland, and similarly trehalose maldigestion is uncommon outside of Greenland (2).

There is an apical targeting mechanism that allows the specific delivery of protein and lipid constituents to either the BBM or basolateral membrane (BLM) surfaces. BBM enzymes are targeted directly from the trans-Golgi network towards this membrane surface (3). Small intestinal LPH is synthesized as a very large precursor (precursor to pro-LPH). In most mammals and humans, LPH activity declines at the time of weaning, a decline that is not related to an effect of pancreatic proteases on the proteolytic processing of LPH (4). A variety of cellular mechanisms are seen in adults with nonpersistent lactase activity, including a decline in lactase protein or mRNA levels. Curiously, in some individuals lac-

Nutrition and Metabolism Research Group, Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta; and Division of Gastroenterology, Department of Anatomy and Cell Biology, McGill University, Montreal, Quebec

Correspondence: Dr ABR Thomson, University of Alberta, 519 Robert Newton Research Building, Edmonton, Alberta T6G 2C2. Telephone 403-492-6490, fax 403-492-7964, e-mail alan.thomson@ualberta.ca

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tase mRNA levels increase (5). In persons with lactase persistence, polymorphism may be controlled at the level of lactase gene expression. Analysis of LPH gene expression on adjacent sections of human proximal jejunum in individuals with persistent lactase activity, as well as in those with hypolactasia, indicated that in hypolactasic tissues, lactase mRNA is detected only in some villus enterocytes; other villus enterocytes express both protein and LPH activity, whereas others do not (6).

Clinical learning point: Different mechanisms may control lactase expression in enterocytes on the same villus.

In adult rats, LPH activity is increased in the jejunum of animals fed a high carbohydrate diet compared with those fed a low carbohydrate, high fat diet. Carbohydrate intake increases LPH mRNA levels, whereas a low starch diet containing long chain triacylglycerol accelerates inactivation and/or degradation of lactase (7). Mild to moderate protein energy malnutrition also decreases the activity of lactase throughout the small intestine, and reduces the activity of other BBM hydrolases such as sucrase and maltase (8).

The distribution of LPH mRNA has been studied at the ultrastructural level in enterocytes. Distinct patterns of mRNA and protein occur along the villus during the continuous process of cell differentiation of the intestinal epithelium (9). Mucosal atrophy is characterized by high lactase and low intestinal alkaline phosphatase (IAP) mRNA levels. This pattern is reversed on restoration of epithelial growth (10).

Interestingly, the prevalence of abdominal pain, bloating, gas, flatulence, diarrhea and/or constipation is similar in children with and without lactose maldigestion (11). Children with lactose maldigestion have overall clinical improvement with a lactose-restricted diet, but clearly clinical evaluation alone cannot adequately predict the presence of lactose maldigestion in children. Thus, formal evaluation for lactose maldigestion using breath hydrogen testing methods should be considered in children with recurrent abdominal pain.

Clinical learning point: If a child is suspected of having lactose intolerance, an objective test for lactose maldigestion should be done.

Similarly, some adults who insist that even small quantities of milk cause them severe gastrointestinal symptoms may be mistaken. In a randomized, double-blind, crossover trial, gastrointestinal symptoms were evaluated in persons who reported severe lactose intolerance, saying that they consistently had symptoms after ingesting less than 240 mL of milk. In these self-reported lactose-intolerant individuals, gastrointestinal symptoms after ingesting milk were similar to symptoms after lactose-hydrolysed milk (12). Thus, persons who identify themselves as being severely lactose-intolerant may mistakenly attribute a variety of their abdominal symptoms to lactose intolerance. Yet, when intake is limited to the equivalent of 240 mL of milk or less a day, symptoms may be negligible and the use of lactose-digestive supplements is probably unnecessary.

The treatment of lactose intolerance has been reviewed (13). Control trials and studies of unselected lactose nonabsorbers have included subjects claiming severe lactose intolerance. In some subjects, symptoms from a cup of milk are no greater than symptoms from a lactose-hydrolysed control beverage. In those with true lactose malabsorption, the frequency of individuals experiencing symptoms increases as the lactose load is increased. Digestive aids, including prehydrolyzed milk and lactase preparations, may not be needed when the amount of milk ingested is small.

The cloning and expression of a full-length cDNA encoding human BBM SI has been reported (14). At weaning, adaptation to solid food requires functional maturation of the small intestine. Maturation includes closure of the epithelium to macromolecule absorption, the appearance of jejunoileal differences or gradients of gene expression, the onset of expression of several digestive enzymes such as SI, and the decline of other digestive enzymes such as LPH. The spontaneous and irreversible maturation of the small intestine at weaning depends primarily on the autonomous program that governs intestinal development. However, dietary changes and the modifications of the hormonal status of the animal also modulate this intrinsic program. Starvation of rats at postnatal day 12 causes a precocious expression of SI activity and its mRNA (15). The starvation-evoked appearance of SI is preceded by a transient burst of expression of the proto-oncogene c-*fos* without an obvious increase in epithelial cell proliferation or turnover. These observations suggest that the autogenic increase of glucocorticoids before weaning may participate in the onset of SI expression, but uncoupling of changes in epithelial cell turnover from the onset of SI expression can be achieved by starvation.

There is a temporal relationship between the developmental rise of alpha-glycosidase activities (maltase, isomaltase, sucrase and trehalase) and the dietary change from lactose (the major sugar during suckling) to maltose, trehalose, sucrose and starch (the major sugars after weaning). Exogenous glucocorticoids and endogenous corticosterone induce sucrase activity in the suckling rat, and a similar effect is observed on trehalase activity. In the intestine of 10- to 14-day-old rats, cortisol induces a coordinate increase in both trehalose activity and its mRNA, but between 14 to 16 days of age there is loss of trehalase mRNA responsiveness to glucocorticoids (16).

Clinical learning point: Steroids and reduced food intake increase the activity of sucrose-isomaltase at weaning.

The molecular events that result in the allocation of the intestinal stem cell descendants into specific lineages are poorly understood. The mechanisms that restrict the expres-

sion of genes in each of the four epithelial phenotypes are unknown. Studies performed in transgenic mice and in cell lines suggest that transcription of the SI gene is normally repressed in nonenterocyte cells, possibly via a transcriptional silencer residing outside of the SI gene (17).

Both SI and LPH are modified extensively after their initial translation. Multiple precursor isoforms (pro-SI and pro-LPH), differing in their molecular weights and in the nature and extent of glycosylation, can be isolated by immunoprecipitation and electrophoresis. Although activation of the transcription of the SI and LPH genes initiates the appearance of both enzymes during development, the complex pathways that lead to the final insertion of enzymatically active sucrase and lactase in the BBM offer other possible mechanisms for the regulation of enzyme levels once gene transcription is activated. For example, in vivo methods to assess the rate of synthesis in processing of pro-SI and pro-LPH isoforms have been used in infant pigs to demonstrate that the low rate of BBM SI synthesis reflects a slow rate at which the complex glycosylated precursor is processed to the BBM form (18).

Feeding rats a high sucrose diet results in an increase in SI mRNA and sodium-dependent glucose transporter (SGLT1) mRNA levels in rat intestine, but a high medium chain triacylglyceride diet also produces similar changes. This diet-associated effect may be achieved through modulation of translation and/or post-translational modification of the SI complex (19).

Synthesis of acute phase proteins in enterocytes is influenced by inflammatory cytokines. Interleukin (IL)-6 and interferon-gamma down-regulate SI protein in the Caco-2 intestinal epithelial cell line. Interferon-gamma also decreases, and tumour necrosis factor-alpha (TNF-α) increases, SI synthesis in Caco-2 cells (20); these findings provide evidence for a previously unrecognized mechanism for the disaccharide deficiency occurring in patients with intestinal inflammation.

Clinical learning point: Cytokines produced by intestinal inflammation may reduce the activity of sucrose-isomaltase in distant portions of normal bowel. This action may represent one mechanism to explain the disaccharide deficiency that occurs in some inflammatory bowel disease (IBD) patients.

Sugar transport: The topic of glucose transporters in the intestine has been reviewed (21). Sodium-dependent uptake of glucose across the BBM is achieved by the sodium/glucose extransporter SGLT1. Fructose uptake by the BBM is via the sodium-independent transporter GLUT5. Both apical and basolateral sugar transport can be modified by dietary, hormonal and developmental factors. Although Caco-2 cells have been used to assess sugar uptake, their transport kinetics are such that they cannot be considered as equivalent to either fetal colonic cells or normal enterocytes (22).

Human, rat and rabbit SGLT1 amino acid sequences are 87% homologous and share identical secondary and tertiary structures. However, there are kinetic and substrate specificity differences among the SGLT1 isoforms (23). SGLT1 is detected in the small intestine of the rat but not in the esophagus, stomach, colon or rectum (24). SGLT1 is restricted to the BBM, and the amount of SGLT1 increases from the base of the villus to the tip. In the human intestinal epithelial cell clone HT-29-D4, SGLT1 protein is detected in both undifferentiated and differentiated cells. These findings suggest that sodium/glucose cotransport depends on post-translational events controlling the efficient targeting of the protein in the plasma membrane (25).

Clinical learning point: The intestinal uptake of glucose across the BBM by SGLT1 is controlled by SGLT1 mRNA abundance, as well as by post-translational events.

The appearance of transporter function in the BBM is blocked by an inhibitor of protein kinase C (PKC) activity. The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-stimulated chloride channel found in the apical membrane of several types of epithelial cells. Using cystic fibrosis (CF) knockout mice, it has been shown that cAMP stimulates intestinal glucose/sodium cotransport (26), which suggests that the effectiveness of oral rehydration solutions (ORS) may be amplified by cAMP-mediated up-regulation of glucose/sodium cotransport by SGLT1.

Clinical learning point: Improved efficacy of ORS may be achieved by stimulating cAMP and thereby up-regulating SGLT1, which enhances the untreated uptake of both glucose and sodium, and thereby water.

After only 3 h of feeding on a 60% fructose-enriched diet, the levels of GLUT5 mRNA and protein are elevated, whereas GLUT2 (the BLM transporter for glucose and fructose) protein is rapidly down-regulated (27). SGLT1, GLUT2 and GLUT5 mRNA levels increase before the onset of peak feeding. GLUT5 protein levels also vary in a diurnal fashion, but are out of phase with the observed changes in GLUT5 mRNA levels. In contrast, GLUT2 protein levels remain relatively constant over 24 h. The sodium-independent GLUT2 is the only hexose transporter identified on the BLM of the jejunum of mammals, including humans (28). GLUT5 mRNA levels are higher at the end of the light cycle and at the beginning of the dark cycle, versus during the early light period. GLUT5 protein content in BBM is also increased at the beginning of the dark cycle compared with at the start of the light cycle (29).

Streptozotocin-induced diabetes is associated with an increase in GLUT5 mRNA levels in the mucosa of the proximal jejunum, and GLUT5 mRNA levels increase during the postnatal period. However, weaning onto a high fat diet partially prevents the induction of GLUT5 gene expression. Feeding a fructose-enriched diet increases GLUT5 protein,

but GLUT5 protein levels do not change after feeding animals glucose- or sucrose-enriched diets. Glucose, and to a lesser extent fructose, feeding results in increased BLM GLUT2 protein (30). Feeding glucose increases SGLT1 protein levels. Fructose feeding increases GLUT5 mRNA. Because sucrose does not increase GLUT5 protein levels, there may be alternative transport pathways in the small intestine for monosaccharides when they are generated from sucrose.

AMINO ACIDS, DIPEPTIDES, PROTEINS AND FOOD ALLERGY

Amino acids: Chloride-dependent amino acid transport in the small intestine has been reviewed (31). In the rabbit small intestine, the sodium-dependent carrier of imino acids (2-methyl-amino-isobutyric acid and proline) and the carriers of taurine and beta-alanine are chloride-dependent. The rat imino acid carrier is the principal carrier of taurine and the only carrier of beta-alanine and gamma-amino butyric acid (GABA) (32). A high affinity carrier of beta-amino acids that is both sodium- and chloride-dependent is also present in the small intestine of pigs (33). This difference in chloride dependence emphasizes the variation in carrier specificity between species. In the human small intestine, chloride-dependent transport processes are present for 2-methyl-amino-isobutyric acid, taurine and glycine (34).

GABA is a major inhibitory neurotransmitter in the central nervous system of vertebrates. GABA represents a model system for the study of the intestinal absorption gamma-amino acids. The uptake of GABA in perfusion studies in rat jejunum obeys Michaelis-Menten and first-order kinetics (35). Calcium and zinc reduce the absorption of L-threonine (36). Genetic and nutritional obesity (Zucker *fa/fa*) in rats increases the capacity of intestinal transport of L-alanine (37). In contrast, starvation of rabbits for 72 h results in decreased uptake of glutamine and arginine, with maintenance of transport of leucine and alanine (38). Arginine is a nonessential amino acid for adult mammals including humans. However, after massive resection of rat small intestine, arginine becomes a strictly essential amino acid (39). Arginine is also conditionally an essential amino acid in humans during periods of rapid growth and development, as well as following acute trauma.

Human intestinal Caco-2 cells have been extensively used to study the characteristics of amino acid transport. These cells contain a H^+-coupled, Na^+-independent alpha-methylaminoisobutyric acid carrier (40). Amino acid carriers in the BBM include a sodium-dependent neutral amino acid system, a sodium-dependent L system and a sodium-dependent system A at the BLM. Amino acids can be observed in part by simple diffusion. L-alanine absorption in Caco-2 cells is driven by the proton electrochemical gradient (41). L-lysine is transported in Caco-2 cells by a sodium-dependent and -independent mechanism, and there is sodium-dependent lysine efflux across the BLM of these cells (42). Acidic amino acids and their analogues are transported across Caco-2 monolayers (43), as are L-methionine (44).

Caco-2 cells demonstrate uptake of sodium/glucose, sodium/phosphate and hydrogen ion/dipeptide, with a progressive increase in uptake as the cells differentiate. In contrast, the capacity of Caco-2 to transport arginine appears to be down-regulated by post-translational modifications in confluent cells, compared with differentiated cells (45). Primary afferent fibres in the small intestine sensitive to capsaicin (the pungent component of red pepper) exert a tonic inhibitory effect upon alanine absorption (46).

Little is known regarding the signals involved in the regulation of epithelial membrane amino acid transport. The analogue of epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), up-regulates L-arginine transport in Caco-2 cells; this action is blocked by an inhibitor of PKC (47). Taurine uptake by Caco-2 cells is inhibited by *Escherichia coli* heat-stable enterotoxin, regulated at a post-translational level by protein kinase A (PKA) (48).

Glutamine: Glutamine is the most abundant amino acid in the plasma and cellular free amino acid pool. Glutamine turns over rapidly in the body and is an essential precursor for the synthesis of proteins and purine and pyrimidine nucleotides. Glutamine metabolism in the small intestine produces citrulline, the precursor of renal arginine. Arginine synthesis from glutamine in these cells is of physiological significance because it is necessary to provide arginine for use by the neonate (49).

Glutamine is the preferred substrate for the small intestine, and growth hormone treatment before the induction of trauma increases glutamine uptake in the intestinal tract of piglets (50). L-glutamine is the primary metabolic fuel of the mammalian small bowel. In addition, glutamine is a powerful stimulator of intestinal sodium chloride and water absorption in normal animals and in those with diarrheal disease. Glutamine may stimulate mucosal growth, and the methotrexate damage to the small intestine of rats recovers more rapidly if the animals are given parenteral glutamine. The morbidity and mortality of these rats are also decreased. Glutamine and L-asparagine are precursors of ornithine. These amino acids enhance proliferation through stimulation of ODC, the rate-limiting enzyme in polyamine biosynthesis required for intestinal cell proliferation and repair. Glutamine also stimulates cellular incorporation of [^{3}H]-thymidine incorporation, and a Na^+/H^+ exchange inhibitor blocks the enhancement of ODC by glutamine (51). Whether the administration of glutamine in humans facilitates epithelial recovery in the injured small intestine is unknown. In the postoperative period, factors such as malnourishment, surgical trauma, endotoxin and/or cytokine exposure, as well as a period of bowel rest, are stress factors to the intestine. Glutamine concentrations in tissue are decreased for long periods after major trauma. Glutamine supplementation in animal studies has shown beneficial effects, including decreased mortality after cytotoxic treatments. In malnourished rats, glutamine results in better absorption of small polyethylene glycols and greater thymidine incorporation (52). Arterial, and to lesser extent luminal, fuels provide nutrition for the enterocyte. Enterocytes are responsible for most gut glutamine metabolism, and the

high fluctuations of glucose and glutamine metabolism in the enterocyte may result from the need for de novo synthesis of purines, pyrimidines and ribose sugars for nucleic acid synthesis (53).

Peptides and macromolecules: Dipeptides and tripeptides are actively transported into the intestinal epithelial cells by the H^+/dipeptide cotransport system localized in the BBM. Orally active aminocephalosporin antibiotics are transported by the H^+/dipeptide cotransport system. In Caco-2 cells the uptake of ceftibuten is mediated by the apical H^+/dipeptide cotransport system which is regulated by cell growth, differentiation or both (54).

Peptides are absorbed by a H^+-coupled transport system, and the cDNAs encoding the H^+/peptide cotransporter have been isolated. The exit of dipeptides across the BLM of rat small intestine may be rate-limiting for their transepithelial transport (55). A H^+-coupled peptide transporter is present in the small intestine of humans and accepts dipeptides, tripeptides and amino beta-lactam antibiotics, but not free amino acids (51). Chromosomal assignment studies with somatic cell hybrid analysis and in situ hybridization have located the gene encoding the cloned human H^+/peptide cotransporter to chromosome 13q33→34. The basolateral dipeptide transporter in Caco-2 cells is distinct from the apical H^+/dipeptide cotransporter (56). This transporter is also involved in the movement of antibiotics across the intestine. This H^+/peptide transporter has been localized immunohistochemically to the small intestine, particularly in the villi and on the BBM (57). The uptake of dipeptides precedes hydrolysis in rat small intestine (58), and this transporter may be involved in the absorption of orally active amino beta-lactam antibiotics and other peptide-like drugs.

Intestinal absorption of beta-lactam antibiotics is by the dipeptide carrier system. Amiloride, an inhibitor of the Na^+/H^+ exchanger (NHE), reduces the absorption of amoxicillin in healthy volunteers; this process may also involve an inhibitory effect of amiloride on Na^+/K^+-ATPase in the BLM (59).

Clinical learning point: Bacterial translocation due to intestinal barrier dysfunction may contribute to the development of multiple organ failure.

Intact macromolecule uptake occurs across the gastrointestinal tract. Bacterial translocation due to intestinal barrier dysfunction has been recognized as a possible mechanism for the development of septic complications and multiple organ failure in various disease states. The goal of a drug enhancer is to improve membrane permeability without unwanted side effects. Surfactants have been used increasingly as adjuvants in oral pharmaceutical preparations (60). Young adult rats absorb 2 μm fluorescent polystyrene latex microparticles (61). EGF is also absorbed from the intestine (62). Small amounts of insulin may be absorbed from the intestine, and this action can be enhanced by coadministration of protease inhibitors (63), use of bile salt-fatty acid mixed micelles (64), use of polyacrylmanide nanoparticles (65) and possibly by inhibition of the insulin-degrading enzyme in rat intestinal enterocytes (66). Water-in-oil-in-water multiple emulsions stabilized by gelatin may improve ileal and colonic absorption of insulin (67). The *E coli* heat-stable, heat-labile enterotoxin-treated mice have an increased absorption of gliadin and lactalbumin (68), which may prove to be useful in enhancing intestinal permeability to antigens.

Food allergies: The oral administration of cortisone in doses corresponding to levels normally found in breast milk enhances the process of intestinal closure and decreases the uptake of macromolecules in weanling rats receiving formula feeding. Spermidine and cortisone do not reduce the intestinal uptake of bovine serum albumin or immunoglobulin (Ig) G (69). Forskolin is an activator of adenyl cyclase, stimulating PKA, and carbachol is a cholinergic agonist. The uptake of the protein horseradish peroxidase into rat intestine is decreased by forskolin and increased by carbachol (70), which suggests that cholinergic activation can increase the uptake of intact protein by endocytosis and can increase the transepithelial passage by the induction of an diffusional paracellular pathway. Horseradish peroxidase absorption is higher in children with atopic eczema than in controls (71), raising the possibility that environmental antigens may initiate this disorder.

Clinical learning point: The intestinal uptake of intact proteins may be influenced by activation of cholinergic pathways.

Food allergies are defined as an abnormal immune response to food antigens. They are characterized by type I immediate hypersensitivity reactions whose clinical manifestations are rhinitis, urticaria or eczema, and gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhea. Antigen uptake from the human intestinal lumen results in the production of antibodies, mainly IgE and IgG. Intestinal inflammation resulting in disruption of the mucosal barrier function has been proposed as a cause of an increased incidence of allergic diseases. In guinea pigs with 2,4,6-trinitrobenzene sulphone acid-induced intestinal inflammation, colonic secretion and permeability to ^{51}Cr-EDTA are increased, but are unchanged after antigen challenge (72).

Double-blind, placebo-controlled food challenge is reportedly the only conclusive way to establish the presence of adverse reactions to foods in children and adults. There are conflicting data on the role of IgE-mediated allergy; in adults with stable food-induced gastrointestinal symptoms, objectively verified by double-blind, placebo-controlled food challenge, there is no indication of IgE-mediated allergy to relevant foods (73). Intestinal anaphylaxis in response to milk proteins may be enhanced during experimental malnutrition in guinea pigs (74). Inhibition of inducible nitric oxide synthase results in lower rates of antibodies, leading to a reduced secretory response upon antigen challenge (75). Na-

loxone exacerbates both systemic and intestinal anaphylaxis to ovalbumin in rats. This suggests that components of the systemic hypersensitivity reaction are mediated through central opioid receptors, whereas the changes in gut function characterizing intestinal anaphylaxis are mediated through peripheral opioid receptors (76). Activated CD4+ cells in the lamina propria of the small intestinal mucosa may play an important role in contributing to mucosal damage in patients with food-sensitive enteropathy, possibly via the release of cytokines (77).

Clinical learning point: The diagnosis of food allergies is difficult, but the best approach is the use of the double-blind, placebo controlled food challenge.

Nucleosides, nucleotides and polyamines: The nucleosides include adenosine, cytidine, guanosine, thymidine, uridine and inosine. Nucleosides are important substrates involved in many essential metabolic reactions including lipid, carbohydrate and nucleic acid synthesis. Enterocytes have a limited capacity for the de novo synthesis of nucleotides and must salvage them from nucleosides in the diet and endogenous sources. The uptake of nucleosides from the BBM is by a carrier-mediated, sodium-dependent as well as sodium-independent processes. Nucleotides that dephosphorylate to nucleosides before intestinal absorption are present in milk, and have trophic effects on the development of the gastrointestinal tract. The uptake of uridine by the suckling rat intestine involves a carrier-mediated process that is energy- and temperature-dependent, requires sodium and undergoes a progressive decrease in the value of the maximal transport rate with ageing (78).

In young rats, dietary nucleotides enhance intestinal repair after injury or malnutrition, and in old rats a nucleotide-supplemented diet accelerates the normal physiological intestinal response to refeeding after food deprivation (79). Dietary nucleosides and nucleotides reduce the mortality rate in protein-deficient mice injected with lipopolysaccharide, and reduce bacterial translocation (80). DNA, lactase, sucrase and maltase activities increase in animals with chronic diarrhea treated with a nucleotide-supplemented diet. In a lactose diet-induced diarrhea model in weanling rats, recovery was accelerated by giving a nucleotide-enriched diet (81). The role of dietary nucleotide supplementation in humans remains to be reported.

Clinical learning point: Supplementation of the diet with nucleosides and nucleotides may accelerate the recovery of intestinal function that occurs in certain disease states.

Dietary nucleotides affect the proliferation and maturation of the intestinal mucosa of young rats, and may influence gene expression in the intestinal epithelium. Deprivation of dietary nucleotides in rats leads to a decrease in the content and specific activity of alkaline phosphatase, leucine-aminopeptidase, maltase, sucrase and lactase in the villous tip, but not in the crypt (82). This finding supports the idea that dietary nucleotides affect the maturation status of the small intestinal epithelium. This modulating effect on protein synthesis may be the result of tissue-specific nucleic acid changes (83).

The polyamines spermidine and spermine, as well as their precursor putrescine, are organic polycations involved in a variety of cellular functions: membrane stabilization, translation processes, regulation of RNA and DNA synthesis, regulation of protein kinase activity and transfer-RNA acylation reactions. Polyamines are involved in and are required for cell growth as well as differentiation, and their intracellular concentrations are closely regulated. Spermidine increases and putrescine decreases the value of the maximal transport rate for glucose uptake into BBM vesicles in rabbits, an effect that is unrelated to membrane lipid composition or fluidity (84). The high concentrations of polyamines in the intestinal lumen may originate from food and colonic bacterial microflora. Spermidine and spermine and their precursor, putrescine, may be regulated by enzymatic synthesis and interconversion, as well as by membrane exchange. Putrescine uptake into the intestine involves a single substrate-selected transport system with inhibition in uptake between the different polyamines (85). Putrescine uptake across the BBM and extrusion across the BLM of the rabbit enterocyte are two independent carrier processes (86).

Clinical learning point: Polyamines in the diet or derived from bacteria may modify the function of the intestine.

SALT AND WATER ABSORPTION, DIARRHEA

Sodium and chloride: Sodium absorption may occur via passive diffusion using transcellular or paracellular pathways, or via active transport mechanisms such as sodium/substrate cotransport, Na^+/H^+ exchange or Na^+/K^+-$2Cl^-$ cotransport. The NHE catalyzes the electroneutral transport of extracellular Na^+ for intracellular H^+, with a stoichiometry of one-to-one (exchange of one Na^+ for one H^+). The NHE plays a major role in regulation of intracellular pH and functions in the transcellular absorption of Na^+, cell volume regulation and probably cell proliferation (87). NHE1 is localized on the BLM of rabbit ileal epithelial villus and crypt cells. It appears to be involved in the homeostatic control of cell volume and pH, and perhaps cell division. NHE2 and NHE3 are epithelial isoforms. NHE2 and NHE3 are present in human small intestinal and colonic epithelial cell BBMs (88). The role of NHE2 is unknown. NHE2 mRNA is present in the villus but not in the crypt epithelial cells of the small intestine (89). NHE3 is involved in basal and meal-stimulated ileal water and sodium absorption (90).

In the fasting state there is net absorption of water and electrolytes from the proximal jejunum. In response to a meal, the magnitude of this absorption is increased, stimulated by luminal contents and influenced by meal composition, mucosal anesthesia, hormonal events and mediators of

inflammation. Sodium/glucose cotransport is the primary mediator of meal-stimulated jejunal absorption, whereas Na^+/H^+ exchange has been implicated in meal-stimulated ileal absorption (91,92). Postprandial ileal absorption is independent of neural blockade, implicating circulating hormones, paracrine mediators or neurotransmission within the myenteric plexus of the enteric nervous system, as the primary modulators of meal-stimulated ileal absorption (93).

BBM phosphatidyl inositol 3-kinase is involved in the EGF stimulation of sodium chloride absorption and BBM Na^+/H^+ exchange (94). Carbonic anhydrase catalyzes the hydration of carbon dioxide and dehydration of carbonic acid, and is present in the BBM of the mucosal epithelium in distal small intestine and large intestine of the rat (95). Prostaglandin E_2 -stimulated water and electrolyte secretion depends in part on mucosal carbonic anhydrase activity, as well as on the enteric nervous system (96).

A peptide proposed to be an endogenous ligand for the *E coli* heat-stable enterotoxin receptor – given the name guanylin – has been purified. Guanylin activates an intestinal guanylate cyclase and stimulates electrolyte movement across the gut epithelium. Cells expressing guanylin mRNA have been localized to the epithelial cell layer of the intestine, and guanylin is expressed in mature goblet cells (97).

Calcium ions play a pivotal role in the stimulus-secretion coupling process, and hormone or neurotransmitter stimulation of these cells generates an increase in the intracellular free calcium concentration. This calcium signal then triggers fluid and electrolyte secretion via activation of a number of plasma membrane calcium-dependent ionic conductances in the plasma membrane of the exocrine cells, as well as via exocytotic release of various digestive enzymes (49).

Diarrhea: The utility of stool water analysis in the management of patients with chronic undiagnosed diarrhea has been examined in a retrospective analysis of six years' experience in a specialized laboratory at a major referral centre. Of 202 patients, 30 had factitious diarrhea due to laxative abuse and five due to stool dilution; 31 had microscopic or collagenous colitis and 14 had a malabsorption syndrome due to sprue, chronic pancreatitis or diarrhea after gastrectomy (98). Twenty-two patients were said to have functional diarrhea due to the 'irritable bowel syndrome'. In previous healthy men with induced diarrhea, there were no changes in anorectal physiology, but in women, ingestion of an iso-osmotic laxative increased rectal sensitivity with a reduction in the volume needed to induce internal anal sphincter relaxation, and in the volume needed to induce sustained internal anal sphincter relaxation (99).

Clinical learning point: Stool water analysis may be useful to diagnose obscure causes of chronic diarrhea.

CF is a genetic disease that affects the secretory function of many epithelial cells. This disease is caused by mutations in the CF gene that alter the function of its product, CFTR. CFTR functions as a cAMP-activated Cl^- channel, and most CFTR mutations alter cellular Cl^- transport, which contributes to the pathological production of a thickened secretory product that can lead to progressive organ dysfunction. CFTR is localized to the apical pole of crypt epithelial cells of rat and human proximal small intestine, with lesser amounts present scattered on the villus cells (100). Fluidity of the intestinal contents is maintained by a balance between the rates of liquid absorption and secretion, which are osmotically linked, primarily through the rates of Na^+ absorption and Cl^- secretion, respectively. cAMP-regulated secretion is absent in the gastrointestinal epithelium of human CF patients. In the intestine, CF may manifest as a mechanical small bowel obstruction (meconium ileus and its equivalent states), caused by the accumulation of viscous luminal contents.

CF mice bred by targeted disruption of the CFTR gene do not express CFTR protein and lack cAMP-mediated Cl^- secretion in the gastrointestinal tract. This mouse model of CF has proven useful in the study of CFTR in Cl^- secretion (26). In the human fetus, CFTR is expressed throughout the epithelium as early as 12 weeks of age, and keeps the same distribution until birth (101). The villous enterocytes play a role in human intestinal Cl^- secretion (102). Ammonia selectively inhibits and activates cAMP and cyclic guanosine monophosphate (cGMP) – but not Ca^{2+}-regulated Cl^- secretion – when applied to either the apical or basolateral epithelial surface (103). Ammonium may play an important role as an inhibitory modulator of Cl^- secretion.

The inflict of Cl^- across the BLM of Cl^--secreting epithelia occurs primarily via $Na^+/K^+/2Cl^-$ cotransport. Cl^- entry into the enterocytes must increase in order to balance the rate of apical Cl^- exit. cAMP activates basolateral $Na^+/H^+/2Cl$ transport by a process with components independent of, as well as dependent on, cAMP-elicited Cl^- efflux (104). cAMP-mediated agonists activate apical membrane Cl^- channels via cAMP-dependent PKA. This enhances the Cl^- conductance of the apical membrane and Cl^- movement into the intestinal lumen. The BLM $Na^+/H^+/2Cl$ cotransporters and Na^+/H^+-ATPase act in conjunction with K^+ conductances to maintain the electrochemical gradient required for a sustained Cl^- secretory response. In rat duodenal crypts there are two populations of K^+ channels that have important roles in sustaining the small intestinal Cl^- secretory responses triggered by a variety of cAMP-and Ca^{2+}-mediated agonists (105). K^+ conductances in human intestinal goblet cells are activated by Ca^{2+} and by cAMP (106).

Cl^- secretion may be elicited by agonists that are mediated by cAMP, cGMP or Ca^{2+}. Novel secretagogues, apparently acting independently of cyclic nucleotide or Ca^{2+} signalling pathways, have been identified. These include the neutrophil-derived secretagogue 5′-AMP, which activates basolateral $Na^+/K^+/2Cl^-$ cotransport. Thus, cotransport is regulated in part by an indirect activation of apical Cl^- channels, a pathway of regulation that may require cytoskeletal remodelling (107).

The transmembrane guanylyl cyclase increases cGMP. There are multiple effectors of cGMP action, including cGMP-gated channels, cGMP-regulated phosphodiesterases, cGMP-dependent protein kinases (cGK) and possibly cAMP-dependent protein kinases. cGMP activation of Cl^- secretion is mediated by a novel intestinal BBM isoform of cGK, designated cGK II. cGK II is located in the brush border and is a mediator of heat-stable enterotoxin and cGMP effects on Cl^- transport (108). Noradrenaline increases intestinal absorption when administered intravascularly or intraluminally in vivo, or when applied in vitro to intestinal tissues. Dopamine is found in high concentrations in the mucosal layers of the intestine, and luminal dopamine may serve as a proabsorptive modulator of ileal transport acting via α_1, α_2 and dopaminergic receptors (109). The development of potent proabsorptive dopamine analogues may be useful in the treatment of some diarrhea conditions.

Clinical learning point: Dopamine analogues may promote the intestinal absorption of sodium and water, and may prove useful for the treatment of patients with diarrhea.

Thyrotropin-releasing hormone is a central nervous system transmitter that stimulates net ileal and jejunal water secretion in rats and dogs. This secretion is mediated by vagal pathways (by a vasoactive intestinal polypeptide [VIP]-sensitive mechanism) and in part by a muscarinic mechanism (110). Growth hormone receptors are located along the rat intestine, and growth hormone induces water and ion transport in rat jejunum, ileum and colon (111).

Weanling animals have a greater jejunal sodium absorption than older animals, probably because of higher nonadrenergic tone (112). A challenge with a high salt diet results in a decrease in the intestinal Na^+ absorption in weaning rats but not in adult rats, and endogenous dopamine may play a role in this regulation.

Nitric oxide: Nitric oxide is an endogenous intracellular messenger mediating various biological activities. Endogenously released nitric oxide is synthesized from L-arginine by the enzyme nitric oxide synthase. Nitric oxide is a transmitter in the inhibitory neurons in the enteric nervous system, and may mediate the nonadrenergic, noncholinergic (NANC) relaxation of circular smooth muscle. Nitric oxide produces a net proabsorptive effect on ion transport in mouse ileum, and release of nitric oxide from NANC nerves is involved in the tonic regulation of basal ion transport in this tissue (113). The nitric oxide-dependent proabsorptive tone in the intestine may also involve suppression of prostaglandin formation (114). Castor oil-induced diarrhea in rats involves the nitric oxide pathway (115).

The role of nitric oxide in the digestive system has been reviewed (116). Inhibition of endogenous nitric oxide synthesis causes secretion of water and ions in the rabbit ileum, and this secretion is reversed by administration of the nitric oxide synthase substrate L-arginine (117). Inhibition of nitric oxide synthesis activates mast cells in the mucosa of rat intestine, and consequently increases epithelial permeability (118). Nitric oxide reduces ATP levels, and reversibly increases the permeability of tight junctions (119). Nitric oxide donors may improve mucosal function in intestinal allografts subjected to prolonged hypothermic ischemia (120), an effect that appears to be unrelated to the action of nitric oxide donors on the microvasculature.

Clinical learning point: Nitric oxide has a proabsorptive effect on intestinal ion transport and may mediate the nonadrenergic, noncholinergic relaxation of circular smooth muscle.

5-Hydroxy tryptamine: 5-Hydroxy tryptamine (5-HT) is present in mast cells and in enteric neurons. 5-HT induces ion and fluid secretion in the intestine in a variety of different species by a process that involves simultaneous inhibition of neutral sodium chloride absorption and stimulation of electrogenic Cl^- secretion. 5-HT2, 5-HT3 and 5-HT4 receptors have been identified in the intestine. 5-HT4 receptors may play a small role in the secretory response in the rat ileum and colon (121). Exposure of a previously sensitized intestinal mucosa to a specific allergen leads to mast cell degranulation and to a decrease in water and electrolyte absorption, known as 'intestinal anaphylaxis'. The water secretion that occurs in the early stages of intestinal anaphylaxis is thought to be partly 5-HT-dependent because it can be reversed by 5-HT2 and 5-HT3 receptor antagonists (122). These receptors play a role in cholera toxin-induced secretion, but are not involved in *E coli* heat-stabile or heat-labile toxin-induced secretion (123). The mucin secretion induced by cholera toxin is mediated primarily through the activation of a 5-HT4-like receptor (124).

Antidiarrheal therapy: The topic of antidiarrheal pharmacology and therapeutics has been reviewed (125). A variety of different agents are being explored for their possible use as antidiarrheal therapy. There is an interaction among the immune, enteric-neural and endocrine systems, and mesenchymal cells in the regulation of intestinal water and electrolyte transport. Prostaglandins and reactive oxygen metabolites stimulate Cl^- secretion and inhibit sodium chloride absorption. The cytokine TNF-α induces the secretion of prostaglandins and reactive oxygen metabolites. The effect of TNF-α on Cl^- secretion in the porcine intestine is via a paracrine mechanism involving prostaglandin release from subepithelial cells (126). Neuromodulation of transport may be altered by adrenergic, cholinergic or peptidergic influences. In crypt cells both cAMP and Ca^{2+} stimulate Na^+ exchange on the BLM. Clonidine, an alpha-2 agonist, stimulates sodium chloride absorption and inhibits HCO_3^- secretion by stimulating Na^+/H^+ exchange in villous cells, whereas in crypt cells, clonidine inhibits Na^+/H^+ exchange (127). The combination of a luminally administered mixture of alpha- and beta-adrenergic agonists (noradrenaline) with α_2 receptor blockade (yohimbine) may prove to be useful in some pathological secretory states causing diarrhea. Neither basal

nor meal-stimulated ileal absorption of water and electrolytes is altered by α_1-adrenergic receptor blockade. This finding suggests that nonadrenergic neural pathways or humoral factors are the likely mediators of meal-induced intestinal absorption (114).

Intestinal inflammation often results in excess secretion of electrolytes and water, leading to diarrhea. The neuropeptide substance P is increased in the mucosa and enteric ganglia of rats with experimental gut inflammation. The number of substance P receptors has been shown to be increased in IBD patients. Substance P binds with high affinity to the neurokinin-1 receptor, and in the intestine, substance P-induced intestinal ion secretion is due to binding of the COOH terminus to neurokinin-1 receptors (128). Mast cells and enteric nerves also participate in the regulation of substance P-induced intestinal ion secretion. Neuropeptide Y co-exists with VIP in nerves of the small intestine. Neuropeptide Y has proabsorptive and antisecretory actions on the small intestine, and this effect is mediated by inhibition of cAMP-stimulated secretion (129).

Glucocorticosteroid hormones stimulate the transcription rate of Na^+/K^+-ATPase, and may alter the phospholipid composition of cell membranes. Corticosteroid induction of Na^+/K^+-ATPase mRNA also may play an important role in the maturation of colonicepithelial ion transport capacity in the preweaning animal (130). Steroid hormones bind to cytoplasmic receptors, which are transported into the nucleus where they regulate the transcription of target genes by binding to specific DNA sequences.

The long-acting somatostatin analogue octreotide provides effective hormonal therapy for a variety of endocrine and intestinal disorders. Octreotide inhibits 5-HT-stimulated electrogenic Cl^- secretion in rabbit ileal mucosa, likely mediated by activation of the inhibitory subunit of membrane-bound GTP-binding regulatory proteins (131). Octreotide is approved for the treatment of patients with carcinoid syndrome or VIP-secreting tumour-induced diarrhea. Octreotide in doses as high as 300 μg tid is not effective in the management of AIDS-associated diarrhea (132).

Clinical learning point: Octreotide, a long-acting somatostatin analogue, has a number of important uses in gastroenterology, including the treatment of patients with various causes of secretory diarrhea.

Diets high in polyunsaturated fatty acids may be both prosecretory and proabsorptive in the small intestine of rats (133). The enhanced responsiveness to secretory stimuli noted in animals fed a high polyunsaturated fatty acid diet may have clinical implications for the choice of formula feed used in the nutritional rehabilitation of infants with protracted diarrheal diseases.

Oral rehydration treatment: The widespread use of oral rehydration treatment has provided a dramatic decline in the morbidity and mortality of acute infectious diarrhea throughout the developed and developing world. The World Health Organization (WHO) ORS does not reduce stool volume, but this desired effect may be achieved with rice-based hypotonic solutions (134). Magnesium can be added to ORS when used in patients who have had a major distal small resection and who encounter significant hypomagnesium. Hypotonic ORS reverses Na^+ secretion to absorption, and promotes net water absorption, which is greater with hypotonic solutions than with those with an osmolality of 310 mOsm/kg (135). Using these hypotonic solutions may achieve improved rates of rehydration. Adding carboxymethylcellulose as a viscosity-enhancing agent to the WHO ORS improves the effectiveness of the solution by increasing Na^+ and water absorption (136). Adding HCO_3^- to ORS does not achieve any clinically significant effect on the absorption efficiency (137). Na^+ concentrations of 0, 25 or 50 mEq/L have a similar effect on the absorption of water, Na^+ and glucose as a 6% carbohydrate solution, so adding Na^+ to fluid replacement beverages may not be a factor in fluid absorption (138).

LIPIDS

Digestion and absorption: Fat digestion and absorption is a complex process involving insoluble substrates, neutral and amphipathic lipids, and lipases acting in the stomach and small intestine. Emulsification is the physical chemical process by which a given amount of oil-water interface, depending on the concomitant availability of an energy supply and neutral amphipathic molecules, is created. Most dietary lipids are present in the human duodenum as emulsified droplets 1 to 50 μm in size, and little further emulsification of dietary fat occurs in the duodenum (139). Pancreaticobiliary responses to meals include a cephalic, a gastric and an intestinal phase. Intestinal responses are considered to be the most important for appropriate release of enzymes responsible for the digestion of nutrients. The regulation of pancreaticobiliary secretion at the intestinal level is subject to feedback control in which proteolytic activity plays an important role. Protein digestion is required to stimulate plasma cholecystokinin release, gallbladder emptying and pancreatic enzyme secretion in humans (140). The regulation of cholecystokinin secretion by intraluminal releasing factors has been reviewed (141).

The topic of pancreatic triglyceride lipase and colipase has been reviewed (142). Pancreatic triglyceride lipase is essential for the efficient digestion of dietary triglyceride. This lipase requires colipase to achieve full activity in the intestinal lumen. Luminal phophatidylcholine stimulates the synthesis of intracellular triacylglycerols. A particle enriched for phospholipids and IAP with surfactant-like properties increases after triacylglycerol feeding. These particles surround fat droplets inside the enterocytes. The lamina propria may play a physiological role as a reservoir and/or as a filter in the extracellular processing of these surfactant-like particles (143).

Proteins isolated with this phospholipid/IAP particle are synthesized by the enterocyte in response to fat feeding. When an inhibitor of chylomicron formation and transcel-

lular transport (pluronic L-81) is given with triacylglycerols, secretion of IAP and surfactant-like particles into the lumen is decreased, and total lamina propria is decreased. IAP particle appears to have a role in transepithelial transport of triacylglycerols in the rat enterocyte (144).

Phospholipids are integral to all cell membranes, and a variety of fatty acids are required for phospholipid synthesis. Fatty acid chain desaturation is a necessary step in the production of the polyunsaturated fatty acids present in membrane phospholipids. In Caco-2 cells, supplemented with either linoleic acid or eicosapentaenoic acids, Δ6- and Δ5-desaturase activities are inhibited (145). This raises the possibility that enterocyte membrane fatty acid composition and desaturase enzyme activity are regulated by both dietary fat intake and cell migration.

Older studies that suggested that fat is absorbed largely in the proximal intestine were based on the use of an aqueous phase marker. However, the transit of the fat phase of an emulsion may be different than that of the aqueous phase. In fact, the intestinal length required for fat absorption depends on the load of fat in the meal; in dogs even after usual meals, the absorption of fat is not complete by the mid-intestine (146).

Medium chain triglycerides (MCTs) are neutral lipids containing fatty acid molecules with chain lengths ranging from six to 12 carbon atoms. They are more rapidly and completely hydrolyzed than long chain triglycerides (LCTs), even in the absence of pancreatic lipase. The absorption of MCTs is less dependent on the action of bile salts, because MCTs are more water-soluble than LCTs. Although MCTs are better absorbed than LCTs in the presence of pancreatic insufficiency, pancreatic extracts increase their absorption (147). Thus, if patients with pancreatic insufficiency are given pancreatic supplements, there may be no additional benefit to lipid absorption when giving MCTs compared with using LCTs.

The availability of orally administered hydrophilic drugs to the systemic circulation is generally limited by the barrier properties of the intestinal membrane. The sodium salts of medium chain length fatty acids enhance the absorption of hydrophilic drugs across the intestinal mucosa, and structurally similar medium chain fatty acids (MCFAs) display differences in their mechanism of action (148).

Butyrate is the preferred oxidated fuel of colonocytes. Butyrate, acetate and propionate are short chain fatty acids (SCFA) produced in the colon by microbial fermentation of dietary polysaccharides. SCFAs are trophic to rat colon and jejunum. They require direct mucosal contact, but may react on the jejunum by a systemic mechanism involving the autonomic nervous system. Both the parasympathetic and sympathetic divisions of the autonomic nervous system must be intact for colonic SCFA-mediated jejunal trophism. These effects are mediated in part by gastrin (149). Structured triglycerides (STG) contain one or two MCFAs, and may provide a vehicle for rapid hydrolysis and absorption due to their smaller molecular size and greater water solubility, compared with LCTs. Although STGs retain some characteristics of MCT and LCT, they may represent an alternative lipid source that could overcome the gastrointestinal intolerance related to the use of MCT or LCT in critically ill patients. The position of MCFAs and long chain fatty acids (LCFAs) on the glycerol backbone of a STG affects its intestinal hydrolysis, site of absorption, uptake and lymphatic transport (150). STGs do not affect the absorption of cholesterol.

The absorption of cholesterol by BBM of rabbit small intestine is protein-mediated; there are two proteins that are part of the integral BBM protein. These facilitate cholesterol and phosphatidyl choline absorption (151). The intestinal uptake of alpha-linolenic acid is carrier-mediated in hamsters. The addition of other polyunsaturated LCFAs to the incubation mixture inhibits linoleic acid uptake by more than 80%. This suggests that the intestinal uptake of both linoleic and alpha-linolenic acids is mediated by a membrane carrier common to LCFAs (152).

FABPs: The topic of intracellular binding proteins for fatty acid-mediated signal transduction pathways has been reviewed (153,154). The liver form (L-FABP) and the intestinal form (I-FABP) of the soluble cytoplasmic FABP differentially affect both fatty acid uptake and intracellular esterification (155). I-FABP binds both saturated and unsaturated LCFAs in vitro, and facilitates the cellular uptake and/or transport of LCFAs within enterocytes. There is a polymorphism in the second exon of the $FABP_2$ gene that encodes human I-FABP. Caco-2 cells expressing the threonine substitution of codon 54 in I-FABP transports LCFAs and secretes triglycerides to a greater degree than Caco-2 cells expressing alanine at this position (156).

Clinical learning point: FABPs are being recognized as having an increasingly important role in lipid absorption.

The ileal lipid-binding protein (ILBP), also known as gastrotropin, is a member of the FABP gene family that binds bile acids in the cytosol, and acts as an intracellular bile acid carrier. The human ILBP has been cloned and localized to chromosome 5, and is not linked to any other known FABP family member (157). ILBP does not bind LCFAs. There is a dose-dependent increase in ILBP mRNA in the presence of bile, which suggests that biliary components regulate ILBP gene expression (158).

Intracellular metabolism: The enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase catalyzes the condensation of acetoacetyl-CoA and acetyl-CoA to form HMG-CoA plus free CoA. This is the rate-limiting enzyme in the cholesterol synthetic pathway. The phospholipid lysophosphatidylcholine increases cholesterol synthesis by increasing the expression of HMG-CoA reductase at the level of the expression of both the gene and the protein (159).

The bile salt-dependent cholesteryl ester hydrolase indirectly modulates the absorption of esterified cholesterol present in the intestinal lumen by a mechanism involving the hydrolysis of the cholesterol ester by cholesteryl ester hydrolase. This increases the free cholesterol concentration

gradient between the micelle and plasma membrane pools, thereby enhancing the passive cellular uptake of free cholesterol (160). Cholesterol acyltransferase inhibitors reduce cholesterol absorption by limiting cholesteryl ester incorporation into chylomicrons and their subsequent diffusion out of the enterocyte across the BLM (161). Long chain cholesteryl esters may be taken up by the BBM as such, and need not be hydrolyzed before absorption (162).

Lipoproteins: Field and Mathur (163) have reviewed the topic of intestinal lipoprotein synthesis and secretion. Apolipoprotein (apo) B is an essential structural component of triglyceride-rich lipoproteins secreted by the liver and small intestine. Apo B circulates in two distinct forms, apo B-100 and apo B-48. The mammalian small intestine secretes apo B-48. The cues that modulate the post-transcriptional regulation of human fetal small intestinal apo B gene expression may include both temporal programming as well as events related to the emergence of lipid transport capability (164).

Intestinal epithelial cells express mRNA for or secrete the following: cytokines IL-1, IL-6, IL-8 and TGF-β_1. These cells also contain surface receptors for TGF-β_1, IL-1 and IL-6. In Caco-2 cells, IL-1 beta, IL-6 and TNF-α decrease the basolateral secretion of apo B, whereas IL-6 also inhibits triacylglycerol secretion (165). TGF-β_1 increases the secretion of apo B and triacylglycerol. This suggests that in conditions of small intestinal inflammation, cytokines may contribute to the observed malabsorption of fat and other nutrients by the small intestine. Inhibition of lipid secretion by TNF-α, as well as decreased secretion of phospholipids, triglycerides and cholesteryl ester, has been demonstrated in Caco-2 cells, together with reduced de novo synthesis of apo A-1, apo B-100 and apo B-48 (166).

Clinical learning point: Cytokines arising from bowel inflammation may suppress fat absorption and contribute to the malnutrition that may occur in some IBD patients.

The chylomicron remnant is a lipoprotein particle resulting from the lipolysis of chylomicron triglyceride by the lipoprotein lipase present on the capillary surfaces of muscle, adipose tissue and other organs. Chylomicron remnants are taken up by a receptor-mediated process across the BLM of enterocytes, particularly in the villous tip cells of the proximal intestine (167). These remnants may provide a source of endogenous triglyceride fatty acids for the enterocytes.

Bile acids: Bile acids are water-soluble and products of cholesterol metabolism that participate in fat digestion in the gastrointestinal tract (168). Bile acids are synthesized in the liver and secreted into the intestine. They are subsequently recirculated back into the liver by active absorption in the terminal ileum and by ionic and nonionic diffusion across the small intestine and colonic epithelia. Na^+-dependant bile acid uptake system is associated with a 99 kDa and 93 kDa protein in the ileal BBMs. An 87 kDa protein, independent of the presence of Na^+, which is present in jejunal and ileal BBM vesicles, may facilitate passive carrier-mediated uptake along the length of the intestine. Some studies suggest (169) whereas others refute (170) the presence of carrier-mediated absorption of conjugated bile acids in the jejunum.

The uptake of glycine- or taurine-conjugated bile acids by the guinea pig jejunum occurs by at least two mechanisms: carrier-mediated transport and passive absorption in the protonated (uncharged) form of glycine conjugates (169). An ileal bile acid transporter has been cloned and characterized, and this 48 kDa protein and its mRNA expression increase dramatically at weaning (171). The development of this transporter is influenced by transcriptionally regulated increases in mRNA and protein levels, with changes in apparent molecular weight of the protein after weaning. The ileal Na^+/bile acid cotransport system is, in its functional state, a protein complex comprising several subunits (172). A mutant form of the ileal sodium-dependent bile acid transporter has been identified (173).

BBM hydrolases may turn over more rapidly in the presence of conjugated bile acids, arising from solubilization of the hydrolases caused by the detergent activity of bile salt (174). Contaminated small bowel syndrome is the term given to bacterial overgrowth of the upper small intestine caused by intestinal anatomical or motility abnormalities. Lipid malabsorption is common and may be related to abnormal morphology or to the release of a product from the anaerobic bacterium having a direct effect on fatty acid uptake (175).

Only a small fraction of the bile acid pool escapes the enterohepatic circulation to enter the colon. In patients who have lost normal ileal absorptive function, bile acids are malabsorbed, and diarrhea may result from the effect of certain dihydroxy bile acids stimulating colonic secretion by a process that is inhibited by H_1-histamine receptor antagonists and modified by the cyclooxygenase inhibitor indomethacin (176).

METALS AND VITAMINS

Iron: Iron homeostasis is maintained primarily by controlling its absorption in the proximal intestine. The absorptive process for nonheme iron involves intestinal uptake, intracellular transport and transfer across the BLM of the enterocyte. The rate-limiting uptake step is affected by a variety of dietary as well as physiological and pathological factors. Reduction of nonheme ferric iron (Fe III) within the intestinal lumen or at the cell surface is required for transfer of this essential micronutrient across the intestinal BBM (177).

The rates of mucosal Fe III reduction parallel changes in iron absorption induced by changes in body iron stores or by metabolic inhibitors. In the mouse, the reduction of Fe III to Fe II is a prerequisite for iron uptake by the proximal intestine. In duodenal mucosal biopsy specimens from patients with genetic hemochromatosis (GH), the rates of Fe III reduction and uptake are increased in untreated GH as well as in those with GH treated with venesection (178).

While an excess intake of iron-containing wine may lead to an enhanced deposition of iron in the liver, the iron in wine is not well absorbed, and red wine in particular impairs

the absorption of nonheme iron. The low availability of iron in red wine is due to the binding of iron to polyphenols, and absorption of radioiron is two- to threefold higher from white wine containing a low concentration of polyphenols than from red wines containing a higher concentration (179). When the alcohol concentration of wine is reduced, there is a decrease in nonheme iron absorption from red but not from white wine.

Intracellular levels of free iron must be tightly regulated because iron is able to catalyze the production of free radicals, which result in oxidated tissue damage. Ferritin is the major soluble cytoplasmic iron storage protein that sequesters excess iron in the cell and prevents oxidated cellular damage. Cellular uptake of iron depends on the level of transferrin receptor (TfR) expression. TfR increases with low cellular iron levels and with increased rates of cellular proliferation. In the iron-deficient and normal rat intestine, TfR mRNA is expressed normally only by proliferating crypt epithelial cells, but in iron-loaded rats, the enterocytes express both TfR mRNA and increased ferritin mRNA (180). Mucosal ferritin does not appear to act as a shuttle protein in iron absorption (181). The role of transferrin is unclear, but may be "...to inform the absorptive cells of the iron status of the body as observed in other organs" (181).

Transferrin and its receptor have no direct role to play in iron absorption from the intestinal lumen. In the homozygous Belgrade rat, the absorption of both Fe III and Fe II is reduced, and iron absorption is not up-regulated by low dietary iron levels (182); this is presumably due to a defective iron carrier in the BBM.

In GH the regulation of iron absorption (both the 'uptake' and 'transfer' steps) is defective, and dietary iron absorption is high and inappropriate for the elevated levels of the body iron stores. The 'uptake' and 'transfer' steps in iron absorption are independently regulated and are increased in GH. Immunological and molecular biological methods have been used on duodenal tissue specimens obtained from subjects with GH; a diffuse cytoplasmic pattern is noted in immunostaining for ferritin protein, and there are lower levels of ferritin mRNAs for the ferritin H and L subunits (183). A common sequence of RNA called the 'iron-responsive element' (IRE) has been found in the untranslated sequences of both TfR and ferritin mRNA. Regulation of these proteins is accomplished through the binding of IRE sequences, in both mRNAs of a transacting protein, the iron-responsive element-binding protein (IRE-BP). IRE-BP also has been called the iron regulatory protein or the ferritin repressor protein. While intestinal endogenous IRE-BP activity, total IRE-BP activity and iron concentration do not differ between GH and controls, mean hepatic endogenous IRE-BP is less in GH than in controls (184).

Lactoferrin is an iron-binding protein contained in milk; receptors for lactoferrin have been found on the surface of some cells, including the BBM of the enterocytes (185). The iron-saturated forms of human lactoferrins enhance cell proliferation in Caco-2 cells, while iron-unsaturated forms suppress it (186).

Akin to how calcium binds, Fe^{2+} binds to taurocholate with high affinity premicellar binding and low affinity micellar binding. Premicellar taurocholate produces an enhancement of Fe^{2+} uptake, and intestinal bile salt depletion decreases iron absorption (187). Thus, certain bile salts may be important for iron absorption. It is uncertain whether iron deficiency is a complication of long term cholestasis.

Clinical learning point: Depletion of the intestinal bile salt pool may lead to impaired iron absorption because of the normal stimulating effect of bile acids on vein absorption.

Chronic experimental iron overload in rats leads to morphological changes in the intestine, including a decrease in crypt depth, but there are no changes in intestinal permeability to lactulose, rhamnose or mannitol (188).

Although occult gastrointestinal bleeding may occur in patients with undiagnosed anemia, other possible causes of iron deficiency anemia, such as malabsorption due to celiac disease, should not be forgotten (189).

Calcium: The topic of the intestinal absorption of calcium has been reviewed (190). Intestinal absorption of Ca^{2+} occurs by both a saturable and a nonsaturable paracellular pathway. The transcellular transport of Ca^{2+} is a multistep process, comprising the uptake of luminal Ca^{2+} into the enterocyte, the translocation of Ca^{2+} from the BBM to the BLM, and its active extrusion across the BLM into the circulatory system. Each step in the transcellular movement of Ca^{2+} has a vitamin D-dependent component, as also does the paracellular pathway. The saturable process of Ca^{2+} uptake may be competitively inhibited by strontium and noncompetitively inhibited by magnesium. Polyarginine reduces the saturable component of Ca^{2+} uptake by competitive and noncompetitive means, and increases the rate constant for nonsaturable Ca^{2+} uptake (191).

Intestinal Ca^{2+} absorption is a major determinant of Ca^{2+} homeostasis, and approximately 50% of postmenopausal women with osteoporosis have malabsorption of Ca^{2+}. This may be due in part to a deficiency of, or intestinal resistance to, calcitriol. The biologically active form of vitamin D3 – 1,25-dihydroxyvitamin D3 ($1,25[OH]_2D3$) – binds to a high affinity vitamin D nuclear receptor that modulates gene transcription or translation, as well as by nongenomic mechanisms. $1,25(OH)_2$ D3 rapidly increases the breakdown of phosphoinositides, raises intracellular calcium concentration, activates PKC, and PKC from the cytosolic to the particulate fraction of Caco-2 cells (192). The absorption of Ca^{2+} is not greatly influenced by gastric emptying rate (193).

The capacity of 1,25-dehydroxy vitamin D ($1,25[OH]_2D$), the biologically active metabolite of vitamin D, to stimulate active Ca^{2+} transport declines with age, as also does the absorption of Ca^{2+}. The rat plasma membrane Ca^{2+} pump has been cloned, and the isoform found in the intestine has been identified. The mRNA for this isoform of the Ca^{2+} pump is increased by $1,25[OH]_2D$. The levels of Ca^{2+}

pump mRNA fall with age; this is explained by an age-related decrease in serum 1,25$[OH]_2$D rather than by changes in the capacity of 1,25$[OH]_2$D to increase Ca^{2+} pump mRNA levels (194).

Vitamins: Folate is central to the 1-carbon transfer reactions required for purine and pyrimidine synthesis, aminopropylation reactions, and methylation of both proteins and DNA. Folate deficiency may be important in the development of epithelial tumours. However, serum folate and red cell folate correlate poorly with the concentrations of folate in colon tissue (195). This suggests that reduced serum or red cell folate values will not necessarily identify individuals who might benefit from folate supplements.

The water-soluble vitamin riboflavin is essential for normal cellular functions and growth. A variety of membrane transport processes are regulated by PKA and PKC. The activities of PKA and PKC are regulated by the level of their respective second messengers, which in turn are regulated by the actions of a variety of biologically active substances. In Caco-2 cells, compounds that increase intracellular cAMP levels down-regulate riboflavin intestinal uptake, possibly acting through a PKA-mediated pathway (196).

Vitamin A is an essential fat-soluble nutrient required for normal vision, growth and fetal development, along with the development and function of many epithelial tissues. Enterocytes play a central role in the assimilation and metabolism of dietary retinal and pro-vitamin carotenoids. Dietary retinyl esters obtained from animal sources are hydrolyzed in the intestinal lumen by nonspecific pancreatic hydrolases and a BBM retinal ester hydrolase. After hydrolysis, free retinyl is solubilized in mixed micelles and is absorbed by a saturable, passive, carrier-mediated process. Within the enterocyte, retinyl is esterified with LCFAs, and the retinal esters are secreted mainly in chylomicron particles. Cellular retinol binding protein (CRBP) and cellular retinol binding protein II (CRBP II) play a role in intestinal retinol uptake, retinyl ester synthesis and retinyl ester secretion in Caco-2 cells. The hydrophobic retinoids are bound in the cytoplasm to CRBP and CRBP II. The effects of CRBP on retinyl ester secretion are distinguished from those of CRBP II in Caco-2 cells. Intestinal retinal uptake, retinyl ester synthesis and retinyl ester secretion are correlated with levels of CRBP and CRBP II (197). CRBP II plays an important role in directing the absorbed retinyl to the retinol acyltransferase located in the microsomes, where re-esterification of retinol and chylomicron formation occur. Feeding rats a diet rich in long chain triacylglycerols increases CRBP II protein and mRNA (198).

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