

## REVIEW

# Small bowel review: Part II

ABR Thomson MD PhD FRSPC<sup>1</sup>, J Hasan MD<sup>2</sup>, M Keelan PhD<sup>1</sup>, G Wild MD PhD FRCPC<sup>2</sup>

ABR Thomson, J Hasan, M Keelan, G Wild. Small bowel review: Part II. *Can J Gastroenterol* 1999;13(1):37-54. In the past year there have been many advances in the area of small bowel physiology and pathology. In preparation for this review, over 500 papers were assessed; some have been selected and reviewed, with a particular focus on presenting clinically useful information for the practising gastroenterologist.

**Key Words:** *Absorption, Adaptation, Inflammatory bowel disease, nutrition*

## À propos de l'intestin grêle : Partie II

**RÉSUMÉ :** Au cours de l'année écoulée, de nombreux progrès ont été accomplis dans le domaine de la physiologie et de la pathologie de l'intestin grêle. En préparation pour ce tour d'horizon, plus de 500 articles ont été évalués, certains ont été sélectionnés et passés en revue. Nous nous sommes particulièrement attardés aux renseignements cliniques utiles à présenter au gastro-entérologue en pratique active.

### SHORT BOWEL SYNDROME, AND ENTERAL AND PARENTERAL NUTRITION

The topic of intestinal adaptation to nutritional stress has been reviewed (1). After distal small bowel resection, the proximal remnant develops a motor pattern similar to that of the intact distal ileal remnant, with prolongation of small intestinal transit time. While structural adaptation of both circular and longitudinal muscle occurs, the changes in smooth muscle function after intestinal resection are relatively minor and transient (2). The surgical approach of intestinal lengthening as a management strategy of the short bowel syndrome actually impairs the nutritional status of the experimental animal, with associated motor disruption and an attenuated increase in the expected postresection enteroglucagon levels (3). After bypass of the ileocolonic junction, there is an increased growth of anaerobic intestinal bacteria and luminal short

chain fatty acids, but this growth does not influence the structural adaptation of the small intestine (4).

For patients with intestinal failure, total parenteral nutrition (TPN) given at home (HPN) may be lifesaving. HPN improves the quality of life, particularly of younger persons or those not dependent on narcotic drugs (5). However, TPN is associated with a loss of mucosal structure and increased intestinal permeability (6). Uptake of microparticles is increased within the Peyer's patch dome in TPN-treated animals (7). TPN-associated cholestasis in infants may be improved by the daily intravenous injection of cholecystokinin (8,9).

Enteral nutrition is the preferable route of nutritional supplementation in patients with an intact intestinal tract. The risk of exogenous microbial contamination of enteral feeds may be reduced by the use of sterile, prepackaged enteral feeds. However, there may be endogenous contamination of the enteral feeds with bacteria from retrograde

<sup>1</sup>Nutrition and Metabolism Research Group, Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta; <sup>2</sup>Division of Gastroenterology and Department of Anatomy and Cell Biology, McGill University, Montreal, Quebec

Correspondence: Dr ABR Thomson, Department of Medicine, Division of Gastroenterology, University of Alberta, Edmonton, Alberta T6G 2C2. Telephone 403-492-6490, fax 403-492-7964, e-mail [alan.thomson@ualberta.ca](mailto:alan.thomson@ualberta.ca)

spread of the patient's own intestinal microflora (10). Oral glutamine decreases bacterial translocation and improves the survival of mice with experimental gut-origin sepsis (11). In contrast, the induction of abscesses by the subcutaneous injection of turpentine in rats followed by their supplementation with enteral glutamine does not appear to be advantageous (12). In patients with upper gastrointestinal cancer, supplementation of the enteral diet with arginine, RNA and omega-3 fatty acids leads to a reduction in the concentration of tumour necrosis factor-alpha (TNF- $\alpha$ ) and interleukin (IL)-6 (13). Adding arginine to TPN solutions decreases bacterial translocation and increases IL-2 production in rats during prolonged administration of TPN (14).

A diet providing 20 g/day of lactose with no more than 4 g/day as milk is well tolerated in most patients with short bowel syndrome, suggesting that a strict lactose-free diet may not be necessary (15). Clearly this diet needs to be adjusted on a person-to-person basis.

### DIABETES MELLITUS

The absorption of fructose is increased in animals with experimental diabetes mellitus (DM) due to enhancement in the levels of the fructose transporter in the brush border membrane (BBM) (GLUT5), as well as to increased amounts of the fructose and glucose transporter in the basolateral membrane (GLUT2). Curiously, GLUT2 is also over-expressed in the BBM of DM patients (16). In the small intestine of diabetic patients, changes in the glucose transporter are accompanied by increases in the number of the enterocytes, but there are no changes in the morphology of the cells (17). Insulin reduces the up-regulated transport of glucose within 12 h in the ileum and within two days in the jejunum. The alterations in ileal uptake of glucose are correlated with changes in the microvillus height (18).

While the uptake of many nutrients is enhanced in DM patients, the uptake and translocation of microparticles are actually reduced. This reduction is possibly the result of gastric retention and altered intestinal permeability (19). Gastroparesis is frequent in diabetic patients, and alterations in small intestinal motility are also common. Slow intestinal transit may be responsible for bacterial overgrowth, whereas rapid transit leads to diarrhea due to 'intestinal hurry'. In patients with type I DM and sympathetic denervation, there is an abnormally rapid transit of a liquid meal through the distal small intestine (20).

### ETHANOL

The effect of alcohol on the gastrointestinal tract has been reviewed (21). Exposure of the intestinal mucosa to physiologically relevant concentrations of ethanol (ie, concentrations found in the human upper small intestine during moderate alcohol intake) results in morphological alterations and increased permeability due to the release of histamine from intestinal mast cells. Mast cell histamine release is mediated by leukocytes and by reactive oxygen

metabolites (especially those generated by xanthine oxidase). The released mast cell histamine promotes leukocyte infiltration and mediates the ethanol-associated effects (22). Pretreatment of animals with alcohol reduces the effects of a subsequent ethanol exposure on permeability and mast cell histamine release, suggesting that adaptive cytoprotection is possible (23).

Clinical learning point: Mast cell histamine release may play a role in the damaging effect of ethanol on the small intestine. Previous exposure to low concentrations of ethanol may be beneficial, leading to adaptive cytoprotection.

The inhibitory effect of acute ethanol toxicity on small intestinal protein synthesis is enhanced by thyroid hormone and reduced by adrenal hormones (24).

### EARLY DEVELOPMENT AND AGEING

The topics of neonatal gut development and postnatal adaptation have been reviewed (25), as have the topics of digestion in the newborn (26), neonatal intestinal metabolism (27) and gastrointestinal motility in the neonate (28). When infants are born before term, their small intestinal functions are incompletely developed and they are unable to tolerate enteral feedings. Postnatal intestinal development is influenced by genetic and dietary factors. For example, colostrum in pigs contains a trypsin-labile component that can increase BBM lactase and alkaline phosphatase activities in the newborn intestine (29).

The process of ageing is associated with functional and structural changes in the small intestine. Gastrointestinal disorders of the elderly are clinically important (30), and the effects of ageing on intestinal lipid absorption have been reviewed (31). The proliferative potential of the intestinal tract may be exaggerated with age. Neurotensin (NT) stimulates growth of the small intestine, reverses the small bowel mucosal atrophy associated with feeding rats an elemental diet and augments intestinal regeneration after small bowel resection. The proliferative potential of the small bowel mucosa in response to the administration of NT is maintained with age. However, the specific activities of sucrase and maltase do not change with NT treatment in old or in young animals, suggesting that the effect of NT is predominantly on the mucosal structure and not specifically on disaccharidase activity (32).

In humans, a substantial reduction in the number of myenteric neurons has been noted with ageing, but small intestinal transit time does not change. The cholinergic responses in the rat small intestine are well maintained with age, while the nitrergic contribution to nonadrenergic noncholinergic (NANC) relaxation decreases with age (33).

### ABDOMINAL IRRADIATION

Radiation therapy is important for the management of patients with certain intra-abdominal neoplastic disorders

such as rectal cancer and Hodgkin's disease. The response of the microvasculature to radiation is the dose-limiting factor for this form of therapy. Within hours of exposure to radiation, there is neutrophil recruitment and increased intracellular generation of reactive oxygen species. Oxygen radicals may be derived from xanthine oxidase and from phagocytic leukocytes, as well as from water radiolysis. Activated leukocytes represent the major source of oxidants generated in the mesenteric microvasculature after abdominal irradiation (34).

The prodromal period of the acute radiation syndrome is characterized by anorexia, nausea, vomiting and diarrhea. There are associated functional alterations in intestinal motility and transport. Increased tone and contractions of the intestine and delayed gastric emptying contribute to the gastrointestinal-related radiation symptoms. Radiation increases the sensitivity of intestinal smooth muscle to cholinergic stimulation. Pretreatment of guinea pigs with a 5-hydroxytryptamine (HT)<sub>3</sub> receptor antagonist prevents the effect of radiation on motility and reduces pellet expulsion to below normal (35). Ionizing radiation attenuates intestinal enzyme activities and vasoactive intestinal peptide (VIP) receptor affinity, but increases VIP receptor numbers (36). Recombinant human IL-11 given to mice abolishes the cytotoxic effect of 5-fluorouracil and prolongs the survival time of the animals by protecting clonogenic cells in the intestinal crypts (37). The clinical role of IL-11 in preventing radiation damage to the bowel remains to be established.

#### CELL PROLIFERATION AND MUCOSAL GROWTH

Despite rapid proliferation of the intestinal epithelium, there is precise spatial differentiation in the crypt-to-villus tip ('vertical') axis as well as in the duodenal-to-colonic ('horizontal') axis. In fetal isograft intestine, expression of apolipoprotein (Apo) A-IV and liver fatty acid-binding protein (FABP) genes is recapitulated during villus morphogenesis, but spatial patterns of gene expression are altered. This suggests that a 'basal' differentiation program is encoded in fetal endoderm and mesenchyme, and that extracellular substances contained in the intestinal lumen or extrinsic to the intestine play an important modulatory role in generating spatial differentiation during ontogeny (38).

Receptors for growth hormone (GH) have been found in the gastrointestinal tract. Many of the growth-promoting effects of GH are mediated by insulin-like growth factor (IGF-1), which has receptors in the intestinal epithelium. GH or GH-dependent factors act as intestinal growth factors whose function it is to promote the homeostatic or steady-state regulation of mucosal epithelial growth (39). IGF-1 is a single-chain peptide with a variety of biological activities, including stimulation of cell proliferation. In young piglets, IGF-1 is absorbed independently of gut closure (40). Cortisone, triiodothyronine and IGF-1 play a causative role in the tim-

ing of the changes of BBM enzymes that coincide with weaning. The concentration of IGF-1 in maternal milk is reflected in the concentration of the peptide in gastric contents (41). IGF-1 increases intestinal weight, protein and DNA content in neonatal pigs (42). IGF-1 synergistically enhances epidermal growth factor (EGF)-stimulated proliferation of intestinal epithelial cells. EGF may serve as a competence factor, priming the cells for the subsequent action of IGF-1 (43). IGF-1 enhances mucosal growth following massive small bowel resection and selectively stimulates growth of the proximal intestine in suckling rats (44). Intestinal adaptation after extensive small bowel resection in rats is augmented by the provision of diet supplemented with the amino acid glutamine or by the administration of IGF-1, which increases ileal DNA content, weight and protein, as well as IGF-1 mRNA expression (45).

Clinical learning point: The administration of intestinal growth factors such as glutamine, arginine, GH, IGF or EGF may accelerate intestinal adaptation in patients with short bowel syndrome.

EGF promotes intestinal growth, ion transport and nutrient absorption, and plays a protective role against ileal mucosal injury induced by Triton X-100 (Union Carbide Corporation, Connecticut) (46). Transforming growth factor (TGF)- $\alpha$  stimulates proliferation, while TGF- $\beta$  is a potent inhibitor of proliferation in intestinal epithelial cells. Acute intestinal epithelial cell injury *in vivo* is associated with compensatory changes in the expression of TGF- $\alpha$  and TGF- $\beta$  (47). TGF- $\alpha$  and IGF-1 are members of the EGF family. TGF- $\alpha$  stimulates proliferation of rat intestinal tissue during the developmental period (48). TGF- $\alpha$  immunoreactive protein is present in the small intestinal crypt epithelium in suckling pigs (49). TGF- $\alpha$  and TGF- $\beta$  play a role in the repair of the intestine after phytohemagglutinin-induced acute epithelial injury (47). In addition, TGF- $\alpha$ , TGF- $\beta$  and EGF are important in the repair of mouse jejunum after radiation treatment (50).

The presence of the receptor for EGF on the basolateral surface of the enterocyte suggests that EGF may play a role in stimulating the repair of the intestine, rather than in maintaining normal gut growth (51). EGF and TGF- $\alpha$  bind to a common receptor in the gastrointestinal tract, and both EGF and TGF- $\alpha$  increase the intestinal crypt cell production rate. EGF increases plasma peptide YY, enteroglucagon and gastrin levels, whereas the equivalent dose of TGF- $\alpha$  causes a rise in only plasma gastrin concentrations (52). TGF- $\alpha$  is less mitogenic and has fewer hormonal effects than EGF.

Various cytokines also play an important part in the modulation of epithelial cell proliferation and differentiation. The intestinal epithelial cell population produces IL-6, IL-8, TGF- $\alpha$ , TGF- $\beta$ , IGF-1 and IGF-2. The cells respond to IL-1, IL-2, interferon- $\gamma$  (IFN- $\gamma$ ), TNF- $\alpha$ , TGF- $\alpha$  and its homologues EGF, TGF- $\beta$  and human

growth factor. In addition, members of the fibroblast growth factor (FGF) family play a role in the regulation of the intestinal epithelium. IL-2 increases the expression of the EGF receptor in Caco-2 cells (53). This demonstrates an integration between cytokines and growth factor ligand-receptor systems in intestinal epithelial cells (IEC), which had not been previously recognized. In IEC-6, IL-6 is secreted across the apical and basal surfaces in response to TNF- $\alpha$  (54). IL-4 has no effect on IL-6 secretion but stimulates epithelial cell proliferation (55). Stimulation of epithelial cell restitution is enhanced by IL-2 and is mediated through a TGF- $\beta$ -dependent pathway (56).

TNF- $\alpha$  exerts its effects through two glycoprotein receptors on the cell membrane. In physiological concentrations, TNF- $\alpha$  stimulates proliferation, yet in pathological concentrations it inhibits proliferation. These effects are mediated differentially by the two TNF- $\alpha$  receptors, with the TNF- $\alpha$  R1 receptor inhibiting proliferation and the TNF- $\alpha$  R2 receptor promoting proliferation (57).

The trefoil peptides are small, highly stable molecules secreted by the mammalian gastrointestinal tract that play a role in tissue repair. The name trefoil (three leaf) derives from the three intrachain loops predicted to arise from the distinctive pairing of six cysteine residues. Three human trefoil peptides have been localized to mucus-secreting epithelia in the gut (58). Human intestinal trefoil factor (hITF) is a secretory polypeptide found mainly in the human gastrointestinal tract. hITF is a member of the newly characterized trefoil factor or P-domain peptide family representing putative growth factors. Localization of hITF in the hypothalamoneurohypophysial system suggests a possible link between intestinal proliferation and the central nervous system.

Bombesin stimulates proliferation in the normal intestine as well as in animals with atrophic or injured mucosa (59).

Clinical learning point: Intestinal proliferation may be influenced by chemicals in the central nervous system, such as hITF.

Nutrient delivery to the apical as well as to the basal surface of the IEC membrane may promote intestinal epithelial differentiation, proliferation and mucosal healing (60). Thyroid hormone is an important regulator of gut mucosal growth, differentiation and intestinal barrier function. Thyroid hormone induces intestinal alkaline phosphatase expression at the level of gene transcription (61). Small IECs express receptors for thyrotropin-releasing hormone (TRH) and are a primary source of intestine-derived thyroid-stimulating hormone (TSH). The gene for the TSH receptor is expressed in intestinal T cells but not in epithelial cells. This raises the possibility that TSH may be a key immunoregulatory mediator in the intestine (62).

Tissue-specific post-translational processing of proglucagon in the intestine liberates a number of proglucagon-

derived peptides, including glicentin, oxyntomodulin, glucagon-like peptide 1 (GLP-1) and GLP-2. GLP-2 stimulates crypt cell proliferation and growth of the bowel (63). Intestinal proglucagon is a polyprotein precursor that undergoes post-translational processing to yield several glucagon-related peptides, such as glicentin and oxyntomodulin (collectively termed the enteroglucagons). The gut peptide oxyntomodulin is one of the four major peptides (glicentin, GLP-1 and GLP-2) derived post-translationally from a single proglucagon precursor. Oxyntomodulin is cosecreted by L cells in the distal small intestine and colon, and stimulates total intestinal glucose uptake in rats (64). In the jejunum, proglucagon mRNA levels fall with fasting and increase with refeeding. Plasma enteroglucagon and GLP-1 levels correlate with jejunal proglucagon mRNA (65). Enteroglucagon gene expression does not play a role in the intestinal adaptation that occurs in the small intestine of lambs infected with *Trichostrongylus colubriformis* (66).

The glucose-dependent insulin-releasing polypeptide (GIP) may function as a GLP-1 secretagogue (67).

Basement membrane matrix proteins promote intestinal epithelial differentiation and inhibit proliferation (68). Basement membranes are composed predominately of laminin, type IV collagen, nidogen/entactin and heparin sulphate proteoglycans. Extracellular matrix proteins (especially fibronectin and type IV collagen) enhance epithelial restitution (69). Laminins and their integrin receptors influence wound-induced epithelial cell migration (70). Laminin promotes the electrophysiological restoration and epithelial restitution of the intestine, and may play an important part in the orchestration of epithelial integrity and barrier function (71). The beta<sub>2</sub>-integrin family of adhesion molecules and their ligands (the intercellular adhesion molecule) are present on the endothelium of human intestine (72). Lactoferrin inhibits cell migration and may play a role in wound healing (73).

Each intestinal crypt is likely served by only one stem cell (74). Levels of regulators of the G1/S transition, cyclin D1 and cyclin-dependent kinase 2, fall as epithelial cells complete their terminal differentiation (75).

## DIAGNOSTIC TECHNIQUES

The presence of a small bowel obstruction may be suspected clinically. Plain abdominal radiographic findings that support the diagnosis include multiple air-fluid levels and minimal colonic gas. In almost 90% of patients, a correct diagnosis of adhesive obstruction may be made by enteroclysis. However, false-negative enteroclysis examinations may occur, particularly when obstruction occurs intermittently. Radiopaque markers may be used in patients suspected of having partial obstructions; these markers coalesce in the region of the obstruction (76).

Infectious gastroenteritis can be divided into the categories of traveller's diarrhea, antibiotic-associated diarrhea and domestically acquired diarrhea. Laboratory tests are

often used in the investigation of patients with acute diarrhea presenting to an emergency department, but these tests seldom contribute to the evaluation of patients with domestically acquired gastroenteritis (77).

During the immediate postoperative period, it may be difficult to distinguish between small bowel obstruction on the basis of paralytic ileus and mechanical obstruction. Computed tomography scanning is both sensitive and specific in making this distinction compared with the much lower sensitivity (19%) of combined clinical and plain film findings (78).

The reliability of the lactulose breath hydrogen test for diagnosing small intestinal bacterial overgrowth is controversial. Both the low sensitivity (16.7%) and specificity (70%) raise the possibility that other diagnostic methods are necessary. Combining the breath hydrogen test with scintigraphy increases the sensitivity of diagnosing bacterial overgrowth to 100% and specificity to 38.9% (79).

**Clinical learning point:** The lactulose breath hydrogen test has an unsatisfactorily low sensitivity and specificity for the diagnosis of bacterial overgrowth in the small bowel.

For detection of inflammatory disease of the small bowel, ultrasonography has a sensitivity of 95% and a specificity of 93%. Ultrasonography may be a reliable method for the investigation of patients suspected of having inflammatory small bowel disease (80).

After careful investigation of the patient with obscure gastrointestinal bleeding, using upper and lower endoscopy, investigation of possible small bowel diseases may be appropriate. Push enteroscopy may demonstrate angiodysplastic lesions in the small intestine in about half of such patients. These lesions may be treated by endoscopic cautery, thereby reducing future rebleeding (81,82).

Magnetic resonance endoscopy (MRE) provides promising results, particularly in the staging of gastrointestinal tumours. In vitro imaging with the MRE shows three- to five-wall layers of the porcine gastrointestinal tract depending on the segment scanned (83).

The two bioactive forms of somatostatin (somatotropin-release inhibiting factors 14 and 28) are processed by differential splicing from a preprosomatostatin precursor. Somatostatin is synthesized in endocrine cells of the stomach and of the pancreatic islets, and is a paracrine and/or autocrine modulator. Somatostatin synthesized in enteric nerves acts as a neurotransmitter. Somatostatin depresses the secretion of a number of gastrointestinal hormones, inhibits gastric and intestinal motility, gastric acid secretion, mesenteric blood flow, and intestinal absorption of glucose and amino acids. Five distinct somatostatin receptors have been cloned, all coupled to G proteins. mRNAs of all five somatostatin receptors are widely expressed in the rat gastrointestinal tract (84). The radiolabelled somatostatin analogue indium-111-pentetreotide is a sensitive imaging agent for the detection

of gastroenteropancreatic neuroendocrine tumours, including carcinoid tumours (85).

**Clinical learning point:** The radiolabelled somatostatin analogue indium-111-pentetreotide is a sensitive imaging agent for the detection of gastroenteropancreatic neuroendocrine tumours.

The long acting somatostatin analogue lanreotide is an effective and convenient treatment in patients with carcinoid syndrome (86).

## CARBOHYDRATES

The topic of the digestion and absorption of fruit juice carbohydrates has been reviewed (87). The enzyme sucrase-isomaltase (SI) is an integral BBM glycoprotein comprising two subunits that are highly homologous and are thought to be derived from the same ancestral gene. SI is synthesized in the rough endoplasmic reticulum (ER) and is then transported through the Golgi apparatus.

BBM SI is an anchored hydrolase synthesized as a single polypeptide and is split into two subunits by a pancreatic protease. Precocious induction of SI activity is primarily regulated at the level of mRNA, and is independent of increases in cellular proliferation or in circulating glucocorticoids (88). Changes in SI activity are paralleled by alterations in SI mRNA abundance and SI gene transcription, with regulation of SI at the transcriptional level. This form of regulation is similar to that of lactase phlorizin hydrolase (LPH).

In a patient with congenital SI deficiency, the SI is synthesized but is not transported to the BBM, accumulating as a mannose-rich precursor in the ER. This abnormal accumulation is due to a point mutation that leads to substitution of a glutamine residue by a proline (89).

Several regulatory elements upstream of the coding sequences of the LPH and SI genes have been identified. An intestinal nuclear factor may be important in transcriptional regulation. SIF1 is upstream to the transcription start site of the SI gene, and this may regulate SI expression during postnatal development (90). L-arabinose inhibits intestinal alpha-glucosidase activity as well as that of SI in an uncompetitive manner (91).

Toxin A produced by *Clostridium difficile* produces mild cytotoxic activity, and inactivates the intracellular GTP-binding proteins Rho A and B. Toxin A binds specifically to carbohydrate domains on rabbit ileal SI (92). The cytochrome P-450 gene superfamily is involved in the metabolism of xenobiotics. Glucose-dependent regulation of SI and hexose transporters occurs in Caco-2 cells. Activation of cytochrome P-4501A1 is involved in the variations of glucose utilization, and in the associated modifications of expression of SI and hexose transporters (93).

Lactase enzyme deficiency is the most common genetic enzyme disorder of humans. The adult form of lactase deficiency occurs independent of morphological or other BBM

enzyme abnormalities. However, it is associated with a variety of defects at the level of lactase gene transcription, translation and post-translational maturation to the enzymatically active form. In humans, both transcriptional and post-transcriptional factors cause the decline of intestinal lactase activity seen after weaning (94). Changes in LPH biosynthesis and slow processing of the protein have been reported, and heterogeneity has been shown in the level of mRNA. Hypolactasia of malnourished infants results from transcriptional suppression of lactase expression or from suppression of mRNA stability (95).

Carbohydrate intake increases LPH mRNA levels in the rat jejunum, and long chain triacylglycerol accelerates inactivation and/or degradation of LPH (96). A marked increase in the number of LPH mRNA molecules per absorptive enterocyte is found throughout the intestine of ethanol-exposed neonatal rats (97). Progesterone therapy has been associated in animals with increased intestinal LPH activity, but gestational hormones (at least at the doses tested) do not influence the intestinal cell number or disaccharidase activity in Caco-2 cells (98). This suggests that the improved lactose handling observed during pregnancy is probably related to another mechanism, such as prolonged small intestinal transit.

Lactose malabsorption causes gastrointestinal symptoms in subjects receiving chemotherapy. Dietary supplementation with yogurt (a lactose-containing food) is well tolerated in children receiving chemotherapy (99). Bone mineral density and calcium intake are lower in women with lactose malabsorption and symptoms of lactose intolerance (100). The differential urinary excretion test of ingested disaccharides provides a reliable, quantitative and noninvasive technique for assessing profiles of intestinal disaccharidase activity (101).

Interestingly, diarrhea, bloating and cramps are no more common in lactase-deficient than in lactase-persistent Afro-Caribbeans, Indians or Caucasians living in the United Kingdom (102). In the United States, there is no significant difference in the prevalence of abdominal pain, altered bowel habits, bloating/distention, or passage of mucus per rectum between individuals with the irritable bowel syndrome (IBS) and those with IBS who also have lactose maldigestion (103). This challenges the concept of the contribution or causation of lactose maldigestion to the symptoms of IBS.

**Clinical learning point:** The mechanism of the symptoms of lactase deficiency in the causation of and/or contribution to gastrointestinal symptoms in patients with IBS may need to be reconsidered.

The sodium/glucose cotransporter (SGLT1) is present in both differentiated and undifferentiated HT-29-D4 cells in culture. Post-translational events control the efficient targeting of SGLT1 to the BBM. Targeting of SGLT1 to the BBM in H2-29-D4 cells in culture is influenced by intracellular pathways regulated by the activity

of protein kinase C (PKC) (104). Kinetic and substrate specificities of SGLT1 differ among rats, humans and rabbits (105). Human, rat and rabbit SGLT1 amino acid sequences are 87% identical. A single amino change in membrane proteins may have profound functional effects, as occurs in children with glucose-galactose malabsorption: the cysteine 355 to serine and leucine 147 to arginine mutations in SGLT1 eliminate the BBM cotransport of sodium and glucose by blocking the transfer of SGLT1 protein from the ER to the BBM (106).

**Clinical learning point:** The absorption of glucose and galactose in children with glucose-galactose malabsorption has been traced to a single amino acid substitution in the BBM sugar transporter protein SGLT1.

Insulin in the portal blood increases intestinal glucose absorption by a signal that is transmitted in a retrograde direction against the blood stream in the portal vein to the small intestine via hepatoenteral muscarinic nerves (107). In acutely diabetic rats, there is increased expression of SGLT1 protein but not mRNA in the BBM, and the increased SGLT1 protein is restored to normal by subcutaneous treatment with insulin (108). This suggests that rat intestinal SGLT1 activity is under translational or post-translational control by insulin.

The response to luminal and vascular hexoses occurs rapidly, and may operate within the time course of a meal. Luminal glucose promotes glucose transport by the BBM within 30 mins, but an intact mucosa is necessary for this up-regulation (109). The presence of hexoses in the intestinal lumen may be signalled by GIP and by GLP-2, but not by GLP-1 (110).

EGF acutely up-regulates small intestinal glucose transport, possibly by a mechanism that involves recruitment of additional BBM transporters. Tyrosine kinase activity is involved in mediating EGF-induced alterations in transport function and in maintaining basal BBM function (111). Dextran feeding stimulates SGLT1-mediated glucose uptake (112). Dextran absorption is low from the intestine but may be mediated by a specific receptor-mediated mechanism (113). Cholecystokinin (CCK) decreases intestinal absorption of hexoses in the small intestine, acting via CCK-A-type receptors (114). Peppermint oil in the intestinal lumen inhibits enterocyte glucose uptake via a direct action at the BBM, possibly by reducing the availability of calcium (115).

Cystic fibrosis (CF) is characterized by defects in epithelial chloride ion secretion attributable to abnormalities in the CF transmembrane conductance regulator (CFTR), which normally acts as a chloride ion channel. The rate of sodium and sodium-linked nutrient absorption is increased in CF, and chloride ion conductance resembling the CFTR is colocalized with sodium/glucose cotransport in rat and human small intestine (116). This supports the possibility that abnormalities in glucose absorption observed in CF patients may be due to a second

dary effect of the defective chloride ion channel function. It is unknown how SGLT1 activity is influenced by the chloride ion channel.

The polyamines spermidine and spermine, and their precursor putrescine are polycationic compounds that play a role in cell proliferation and differentiation. Their intracellular levels are dependent on the activity of ornithine decarboxylase (ODC), one of the initial rate-limiting enzymes in polyamine synthesis, and on an equilibrium between uptake, excretion and catabolism. The maximum velocity for putrescine uptake is higher in fasted animals (117). Dietary polyamines exert a direct and specific maturational effect on the rat small intestine (118). Polyamines are transported into the enterocyte by means of a diffusion mechanism related to their binding to the acidic lipids of the biomembrane, such as phosphatidylserine.

The polyamine spermine increases the maximal transport rate ( $V_{max}$ ) for glucose uptake in rabbit BBM vesicles. In contrast,  $V_{max}$  decreases with the other polyamines, spermidine and putrescine. These alterations in  $V_{max}$  are unrelated to changes in BBM lipid composition or fluidity (119). ODC, the rate-limiting enzyme in polyamine synthesis, catalyzes the decarboxylation of ornithine to form putrescine. Subsequent spermidine and spermine production from putrescine occurs via S-adenosylmethionine decarboxylase activity. Polyamines have a protective action on mitochondria function. In the small intestine, the highest level of ODC activity is seen in villus cells, and ODC levels in these cells increase in response to feeding. As enterocytes migrate from the crypt up the villus, mitochondrial function increases to handle the increased metabolic demands placed on the cell by nutrient absorption (18).

The developmental regulation in early life of the sodium-independent fructose transporter in the BBM (GLUT5) has a circadian rhythm, and depends on the fat and carbohydrate content in the diet at weaning, and its expression is enhanced in patients with streptozotocin-induced diabetes (120). GLUT5 protein levels vary in a diurnal manner but are out of phase with the observed changes in GLUT5 mRNA levels. Isolated fructose malabsorption is an autosomal recessive disorder resulting in pain and diarrhea after the ingestion of fructose. Isolated fructose malabsorption does not result from the expression of mutant GLUT5 protein (121).

Levels of the fructose and glucose transporter in the basolateral membrane (GLUT2) remain relatively constant during the day (122). Feeding a fructose-enriched diet elevates the levels of GLUT5 protein and mRNA, and down-regulates GLUT2 protein, indicating that the level of hexose transporter expression can be modulated by diet.

#### PEPTIDES, AMINO ACIDS AND FOOD ALLERGIES

Intracellular accumulation of lysine across both the BBM and the basolateral membranes of the enterocyte consists of a sodium-independent, membrane potential-sensitive

uptake. Both a saturable and a nonsaturable component are present (123). The sodium-dependent component of alanine influx is inhibited by capsaicin, acting on afferent fibres that contain and release peptides, and neural transmitters such as somatostatin, VIP, substance P and CGRP (124). GH stimulates the intestinal uptake of amino acids but not glucose as a result of an up-regulation of the carrier  $V_{max}$  (125).

The transport system for the amino acids L-glutamate and L-aspartate is sodium-dependent. The relationship between the L-glutamate transport rate and the luminal sodium concentration is sigmoidal in shape, and the stoichiometry of the transport is two sodium to one glutamate to one carrier molecule. The mechanism is sequentially ordered, with the L-glutamate binding occurring after both of the sodium cations bind to the carrier (126).

Glutamine is one of the two major metabolic fuels of enterocytes. Pretreatment of piglets with glutamine increases intestinal glutamine uptake, as does GH, and a combination of GH plus glutamine is additive (127). The active absorption of L-threonine across the rabbit jejunum is decreased by zinc by an unknown mechanism. The rat intestinal sodium/dicarboxylate cotransporter has been cloned (128). The transport of arginine via system  $\gamma+$  may be down-regulated by post-translational modifications in confluent Caco-2 cells (129). Ethanol selectively inhibits sodium-dependent methionine transport and reduces the levels of sodium/potassium-ATPase (130).

The oligopeptide transporter belongs to a superfamily of protein-dependent transporters (131). The human hydrogen/peptide cotransporter exhibits a high degree of homology (81% identity and 92% similarity) to the rabbit transporter (132). The gene encoding the cloned human cotransporter is located on chromosome 13 q33 to q34.

The clinical development of orally active peptide drugs has been restricted by their unfavourable physical chemical characteristics, which limit their membrane permeation, and by their lack of stability against enzymatic degradation (133). The intestinal peptide carrier is a potential transport system for small peptide-derived drugs (134). One way to solve this permeability problem is to formulate the compound with membrane permeation-enhancing excipients (135). Coupling of antigen-containing particles to the pentameric binding subunit of cholera toxin (CTB) is a means for increasing antigen uptake by the CTB receptor, ganglioside G (M1). Ganglioside G is a glycolipid present in the BBM of intestinal epithelial cells. The barrier function of the intestinal epithelial cell glycocalyx may be important in limiting microbial adherence to membrane glycolipids, and in CTB-mediated targeting of vaccines to M cells and the mucosal immune system (136).

The peptide transport system mediates electrogenic uptake into intestinal epithelial cells of the neutral form of beta-lactam antibiotics (137). Luminal degradation of insulin by pancreatic enzymes and by microbial enzymes in the ileum and colon, respectively, can be minimized by

nonabsorbable carbopol. Absorption of insulin in the intestine is usually by receptor-mediated endocytosis. When insulin is acylated with dimethylmaleic anhydride and is conjugated to transferrin via a disulphide linkage, the uptake of insulin-transferrin in Caco-2 cells is mediated by the transferrin receptor but not by the insulin receptor. Brefeldin A, an agent that causes an increase in transferrin receptor transcytosis, further enhances the transport of the transferrin-conjugated insulin (138). This raises the possibility of the use of insulin-transferrin conjugate in combination with brefeldin A to increase the oral absorption of insulin in vivo. However, the insulin-degrading enzyme in the cytosol of the intestinal mucosa may limit the transfer to the portal circulation of any insulin that has been taken up across the BBM (139). Slowing intestinal transit increases protein absorption in a load-dependent fashion (140).

Nucleotides are important molecules for protein synthesis. Nucleotides restore the structure and function of the intestine recovering from starvation, ischemia or injury. Deprivation of dietary nucleotides decreases the concentration of soluble nucleotides in the small intestine and modulates protein synthesis as a result of tissue-specific nucleic acid changes (141).

Cow's milk allergy is common in children. In adults, cow's milk protein allergy can be suspected on the basis of a patient's symptoms and skin tests, as well as elimination/rechallenge with the suspected food allergen. The diagnosis can be confirmed by a double-blind, placebo controlled food challenge. Immunohistochemistry of the small intestine in these patients shows a marked increase of immunoglobulin (Ig)E-positive mast cells (142).

In patients with chronic urticaria following a duodenal histamine challenge, edema is noted in the basolateral intercellular spaces, with no change in the epithelium or in the tight junctions (143).

## VITAMINS AND MINERALS

**Calcium and vitamin D:** Interindividual variation in calcium absorption is due in part to variations in the concentration of serum 25-hydroxy vitamin D, in the mouth-to-cecal transit time and in fasting urinary calcium to creatinine ratios (144). Calcium uptake is by both a saturable and a nonsaturable process. The saturable route is energy-dependent, and the calcium/magnesium-ATPase activity is responsible for extrusion of calcium from the enterocyte, which may be the rate-limiting step (145).

The classical calciotropic hormones are parathyroid hormone (PTH), 1,25-dihydroxyvitamin D<sub>3</sub> and calcitonin. Human calcitonin is a polypeptide hormone that lowers blood calcium levels by increasing urinary calcium excretion and by inhibiting bone resorption. Calcitonin may be administered parenterally by the nasal route or by the intracolonic route of administration (146). Estrogen receptor-like proteins and genes are present in the intestinal mucosal cells of rats (147). Nuclear estrogen receptor-mediated calcium transport may stimulate en-

terocyte calcium influx via the cyclic AMP/protein kinase A pathway (148). Calcitriol, the hormonal form of vitamin D, has specific receptors in human fetal jejunum. Depending on the stage of gestation, calcitriol either enhances or decreases the levels of mRNA coding for its receptor (149). However, calcitriol always up-regulates mRNA coding for the vitamin D-dependent calcium-binding protein 9 kDa. 24,25-(hydroxy)2D<sub>3</sub> increases intestinal calbindin (calcium-binding protein) (150).

Infants with cholestatic cirrhosis due to extrahepatic biliary atresia develop severe bone demineralization and rickets, with the transport capacity of calcium being reduced in association with vitamin D deficiency (151). Inorganic phosphate is absorbed by a sodium-dependent process (152). Milk proteins and casein phosphopeptides improve calcium and zinc absorption from aqueous phytate-containing solutions and from oat diet (153).

**Iron:** The topic of the regulation of nonheme iron absorption has been reviewed (154). Dietary iron is mostly ferric (III), whereas ferrous (II) iron is the form in which most iron is absorbed. The electron donors and/or reducing enzyme for iron (III) reduction are derived from dietary sources, such as ascorbate, as well as from BBM ferric reductase (155). In Caco-2 cells, BBM iron uptake, ferritin synthesis and transepithelial iron transport are regulated within a narrow margin of intracellular iron concentrations (156). The intracellular level of iron is regulated at the transcriptional level of ferritin and by the transferrin receptor. Low levels of intracellular iron activate the iron regulatory protein, a 90 kDa cytoplasmic protein that stabilizes the transferrin receptor mRNA and diminishes translation of the ferritin mRNA.

The basolateral endocytosis of transferrin forms part of the system by which intestinal epithelial cells 'sense' the plasma iron concentrations (157). It is likely that all of the steps of iron absorption (including BBM uptake, intracellular transport and basolateral transfer) are influenced by the systemic iron status. Iron homeostasis is achieved by the regulation of intestinal iron absorption, and the intracellular iron content of the enterocyte is a major factor in this controlling process. Transferrin receptor is absent from the BBM of the duodenal epithelium, and transferrin mRNA is absent from duodenal tissue. Iron absorption can be altered independently of effects of transcripts of genes for iron-related proteins, and it is not essential for iron absorption to be coordinated with the regulation of mucosal iron metabolism (158).

H- and L-ferritin subunits form a protein shell that can store iron atoms. The level of H-ferritin mRNA is higher than the L-ferritin level, and expression of the H-ferritin mRNA is higher in the apex of the villus than in the crypt, and in the proximal versus the distal small intestine. In contrast, the expression of the L-ferritin mRNA does not change along these axes (159).

**Folate and vitamin B12:** Folic acid is an essential nutrient required for the synthesis of purine and pyrimidine precursors of nucleic acids, and used for the metabolism of certain



amino acids and the initiation of protein synthesis in the mitochondria. The sole source of folate for humans and mammals is intestinal absorption of dietary folate. In the diet, folates are mostly in polyglutamate forms, which are hydrolyzed in the intestine by folate conjugate into folate monoglutamates before their carrier-mediated absorption in the proximal intestine. The intestinal folate carrier has been cloned from mouse and from human intestine (160). It is unknown whether the abundance of the carrier or its mRNA is modified by dietary folate levels.

The plasma transport of cobalamin (vitamin B12) occurs bound to a plasma transporter, transcobalamin II, as well as by receptor-mediated endocytosis via the transcobalamin II receptor. Transcobalamin II-cobalamin is processed by a nonlysosomal pathway in which both transcobalamin II and cobalamin are transcytosed. When presented to the basolateral side of the enterocyte, transcobalamin II-cobalamin is processed by the lysosomal pathway in which transcobalamin II is degraded and cobalamin is used (161).

### PERMEABILITY

The intestine has important functions for the digestion and absorption of nutrients, and acts as a barrier against antigens, microorganisms and toxins. The permeability of substances across the intestinal epithelium is reduced by the mucus gel layer (162), presumably acting to increase the effective resistance of the intestinal unstirred water layer. Increases in the flow rate in the intestinal lumen within the normal physiological range decrease the estimated pore size of normal healthy jejunal mucosa (163). This occurs possibly by exposing enterocytes in the intervillus space, where cells may have a lower permeability than those lining the villus tips.

Intestinal permeability is commonly studied as a urinary excretion of probe molecules after an oral load. Different sized polyethylene glycols (PEG) are often used for studies of intestinal permeability. Using different sized PEG suggests that there is a dual pore system for absorption of hydrophilic molecules in the human jejunum (164).

During intestinal inflammation or injury, both the lumen to blood and blood to lumen passage of selected probes increase. Acute exposure of the small intestine to acid increases the passage of probes from the lumen to blood as well as from the blood to lumen (165). Intestinal permeability is increased in patients with Crohn's disease (166) or multiple sclerosis (167). The importance of this permeability change to the pathogenesis of these diseases is unknown.

PEG is a poorly absorbed marker, even when glucose-sodium cotransport occurs. Therefore, PEG represents a useful marker for intestinal perfusion studies (168). The apparent permeabilities of mixtures of PEG are inversely proportional to their molecular weight squared. The major difference between permeability in the proximal and distal intestine is the number (rather than the size distribution)

of the aqueous filled channels, possibly due to a difference in effective surface area for absorption (169).

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase small intestinal permeability. The inhibitory effect of chiral NSAIDs on the synthesis of prostaglandins enhances their efficacy. Toxicity is due to the S enantiomer, but a stereochemically pure enantiomer does not necessarily offer a safer alternative than its racemic form (170). The variability in the demonstration of the effect of NSAIDs on intestinal permeability may be reduced for all permeability markers by using a standardized liquid meal (171).

NSAIDs produce small intestinal damage in approximately 70% of patients chronically treated with these drugs. The damage includes villus smooth muscle contraction, microvascular injury, changes in permeability, intravascular thrombi and mucosal ulceration. NSAIDs inhibit cyclo-oxygenase activity, and a subsequent mucosal prostaglandin deficiency may develop; changes in blood flow do not represent 'trigger factors' for these changes (172).

The intestinal epithelial permeability through the paracellular pathway is mediated by the tight junctions. The tight junctions are regulated at the cellular level by the cytoskeleton and are physiologically modulated by nutrients. Cytokines such as IFN- $\gamma$  or TNF- $\alpha$  increase the paracellular permeability, likely as a result of their action on the tight junctions. Malnutrition is associated with increased intestinal paracellular permeability, and pharmacological doses of zinc prevent these permeability changes (173).

Biliary obstruction, in conjunction with surgical trauma and endotoxin, increases bacterial translocation across the intestine (174). Bacterial enterotoxins open the tight junctions and increase intestinal permeability (175). Endotoxin also delays gastric emptying, but transit time through the small intestine is not affected (176). Portal hypertension and common bile duct ligation increase bacterial translocation as a result of mucosal lipid peroxidation and increase polymorphonuclear neutrophil-derived myeloperoxidase activity (177). These changes can be improved by the administration of allopurinol.

The increased intestinal permeability seen in patients with CF is probably the consequence of exocrine pancreatic insufficiency (178). Ingestion of acetylsalicylic acid during running also increases intestinal permeability (179). Graft-versus-host disease (GVHD) occurring after bone marrow transplantation or in small bowel transplant recipients is associated with an increase in urinary lactulose-to-rhamnose clearance ratios, reflecting an increase in bowel permeability (180). Ileal pouch-anal anastomosis may result in the development of pouchitis, with increased intestinal permeability (181). IgA nephropathy is associated with increased intestinal permeability, and renal function deterioration is greatest in patients with increased intestinal permeability (182).

Autism is a developmental disorder with onset in infancy or childhood, with serious social, communicative

and imaginative development. Intestinal permeability to lactulose is increased in approximately half of autistic patients (183). The mechanism of this defect is unknown.

**Clinical learning point:** Intestinal permeability is altered in a number of nonintestinal diseases such as autism, after bone marrow failure or with IgA nephropathy. The clinical significance of these permeability changes is unknown.

The use of glutamine-supplemented TPN solutions or enteral diets may prevent bacterial translocation (184). For example, mice fed glutamine-enriched diets have a lower degree of bacterial translocation and greater survival (11). Endotoxin-induced permeability changes can be prevented or delayed by supplying luminal glutamine at the time of endotoxin-induced insult (185).

TPN and elemental diets produce intestinal atrophy and increase bacterial translocation. Enteral nutrition decreases bacterial translocation compared with parenteral nutrition, and fibre decreases translocation when administered to rats receiving TPN or enteral diets (186). However, there is no direct evidence that enteral nutrition prevents or modifies bacterial translocation in humans (187).

Branched-chain amino acid-enriched parenteral nutrition solutions reduce intestinal atrophy but not the enhanced permeability associated with parenteral nutrition (188). Short chain fatty acids reduce intestinal permeability in Caco-2 cells in culture (189). In many digestive diseases, the intestinal barrier is weakened by the release of pro-inflammatory cytokines such as TNF- $\alpha$ . These cytokines disrupt the intestinal barrier through the tight junctions (190). Substance P stimulates extravasation in the gastrointestinal tract by interacting with natural killer<sub>1</sub> receptors. Capsaicin and bradykinin induce plasma extravasation by stimulating tachykinin release from sensory nerves (191).

Intestinal ischemia increases intestinal permeability; induction of ischemia in the rat hindlimb also enhances intestinal permeability (192). This distance effect may be important in the understanding of the development of multiorgan dysfunction in patients who sustain lower extremity ischemia-reperfusion injury.

**Clinical learning point:** Ischemia in a part of the body remote from the intestine may lead to mucosal intestinal permeability by an unknown mechanism.

## MOTILITY

**Methods:** The basic electrical rhythm of the gastrointestinal tract creates minute magnetic fields that can be measured in humans by using a superconducting Quantum Interference Device gradiometer (193). Implanted bipolar electrode methodology has been used in rats to measure myoelectrical activity of the bowel (194). Computerized

technology enables the evaluation of myoelectric patterns and intensity (195).

The lactulose breath hydrogen test has been used to assess orocecal transit time (OCTT). However, lactulose accelerates OCTT compared with gastroenterocolonic scintigraphy (196) and, thus, may give false negative results of a delay in intestinal transit. Continuous ambulatory manometric recordings of the human small bowel provide a useful tool for the investigation of motility abnormalities in patients. Computer-based analysis, compared with conventional manual analysis, correctly identifies the number of individual contractions with a 98% CI (197).

**Clinical learning point:** Continuous ambulatory manometric readings of the human small bowel provide a useful tool for the investigation of motility abnormalities. This method may be superior to the lactulose breath hydrogen test to detect abnormalities in intestinal transit.

Regional laser Doppler flowmetry methodology has shown a relationship between fasting motility and blood flow in the human gut (198). Intestinal contractions produce Doppler signals of different amplitudes and duration, thereby allowing differentiation between peristaltic and nonperistaltic movements (199). Gut relaxation is also an important component of gastrointestinal motor activity, and both contractile and relaxant activity can be assessed *in vivo* (200).

**Hormonal effects:** In lactating rats, food intake increases, and there is hypertrophy of the gastrointestinal mucosa. The lactation-associated increases in gastric emptying and intestinal length are correlated with lactation and plasma prolactin levels, but not with plasma progesterone or estradiol concentrations (201). Luteinizing hormone and human chorionic gonadotropin fragment lengthen the phase III of the migrating myoelectric complex (MMC) (202). NT enhances the voltage-dependent inward calcium current in ileal smooth muscle cells, and exerts both excitatory and inhibitory actions via its receptors (203).

VIP is present in enteric neurons and has been proposed as a NANC inhibitory transmitter in the myenteric plexus. VIP is also a stimulatory transmitter of secretory processes in the submucosal plexus and in the mucosa. VIP is tonically released *in vivo*. This release is under cholinergic control, and is suppressed by enkaphalinergic and alpha-adrenergic mechanisms. Inhibition of the tonic release of VIP contributes to the excitatory effect of hormones and transmitters such as opioids and motilin. Nitric oxide is an important inhibitory NANC mediator that is colocalized in neurons with VIP. VIP can be released from enriched synaptosomes by calcium-dependent mechanisms by nitric oxide agonists or nitric oxide-dependent mechanisms (204). This VIP release may be induced by a pre-synaptic stimulatory mechanism of nitric oxide; this effect enhances the action of nitric oxide.

Motilin stimulates gastrointestinal motility and is a physiological mediator for the initiation of the MMC. Motilin is an important mediator of motility in humans, but the pig gastrointestinal smooth muscle lacks functional motilin receptors (205). In rabbits, motilin binds to a basolateral but not to a BBM receptor with one class of binding sites (206). Thus, the choice of the experimental model is important.

5-HT is present in interneurons within the myenteric plexus and is also present in mucosal enterochromaffin cells. 5-HT is a mediator of chloride ion secretion, and the 5-HT-induced change in short circuit current is mediated by a 5-HT<sub>4</sub> receptor via a non-neural pathway (207). 5-HT released from these cells activates sensory neurons that mediate both motor and secretory reflexes.

5-HT release by mucosal stimulation initiates a peristaltic reflex by activating 5-HT<sub>4</sub>/5-HT<sub>1P</sub> receptors on sensory CGRP-containing neurons in human intestine (208). The 5-HT<sub>4</sub> receptor belongs to the seven transmembrane domain G protein-coupled receptor superfamily. Activation of the 5-HT<sub>4</sub> receptor results in the stimulation of adenylyl cyclase and in an elevation of cyclic AMP (3':5a'-cyclic monophosphate). 5-HT<sub>4</sub> receptor stimulation increases peristaltic reflex sensitivity, and the relaxant response to 5-HT in the terminal ileum is mediated directly on the smooth muscle (209). There is specific binding of 5-HT to the 5-HT<sub>4</sub> receptors in longitudinal muscle and myenteric plexus of the guinea pig, with a larger number of binding sites in the proximal than in the distal intestine (210). In rat jejunum, 5-HT produces a biphasic concentration-effect curve, which is mediated by a putative 5-HT<sub>7</sub> (first phase) and 5-HT<sub>3</sub> (second phase) receptor mechanism (211).

Clinical learning point: 5-HT<sub>4</sub> receptor stimulation increases peristaltic reflex sensitivity, and antagonists to 5-HT<sub>4</sub> may play a role in some abnormalities of intestinal motility.

ACh is a major neurotransmitter in the enteric nervous system. Choline acetyltransferase, an enzyme involved in the biosyntheses of ACh, is a marker of cholinergic neurons, and the majority of neurons in the human small and large intestines are cholinergic (212). The muscarinic receptors in the gut are localized at presynaptic, postsynaptic, prejunctional and postjunctional sites. The receptors on smooth muscle cells mediate contractions by G protein-coupled mechanisms, whereas those at presynaptic and prejunctional sites may modulate the release of ACh by negative feedback. Five muscarinic receptor genes have been cloned in humans. Inflammation suppresses the phasic contractile response to muscarinic receptor activation in circular smooth muscle cells acting through M<sub>3</sub> receptors (213). Stimulation of alpha<sub>2</sub>-adrenoceptors inhibits intestinal motility. Stimulation of beta-adrenoceptors reduces the number of activity fronts of MMCs and induces a postprandial-like motility pattern (214). Both nutritive

and non-nutritive factors alter interdigestive motor patterns. Extrinsic innervation of the jejunum and ileum, and enteric neural continuity within the duodenum do not regulate single pressure waves or clustered contractions (215).

IL-1 $\beta$  is a pro-inflammatory protein that modulates the release of neuromediators located in the rat myenteric plexus, such as ACh, noradrenaline and substance P. IL-1 $\beta$  inhibits ACh-induced intestinal contraction. This inhibitory effect involves protein synthesis but is independent of nitric oxide synthesis (216).

The interstitial cells of Cajal (ICC) are excitable, spontaneously active and generate slow wave-like membrane depolarization. The basic contractile activity of the intestine is initiated by ICC through spontaneous pulse generation. Thus, ICC play an important role in the development of the pacemaking system and in the functional development of the contractile properties of the intestinal smooth muscle (217). ICC or pacemaker cells facilitate active propagation of electrical events and mediate neurotransmission (218).

Localized distention of the wall of the intestine evokes a contraction proximal to the point of stimulation (the ascending excitatory reflex) and a relaxation distally (the descending inhibitory reflex). The ascending excitatory reflex may be part of the mechanism underlying the initiation of peristalsis (219).

Nitric oxide and nitric oxide synthase: Nitric oxide is the product of a five-electron reduction of L-arginine, which is catalyzed by the enzyme nitric oxide synthase (NOS). Neuronal NOS (NOS1) functions as a NANC neurotransmitter and is found in the myenteric plexus of the gut. The relaxing effects of nitric oxide involve activation of soluble guanylate cyclase and the production of cGMP. In isolated rat small intestine, cGMP is not involved in the nitric oxide-induced contraction but is related instead to extracellular calcium influx through the L-type calcium channels (220). Endothelial NOS plays a role in the regulation of gastrointestinal blood flow. The third NOS isoform is inducible (iNOS or NOS2). iNOS mRNA is present in the ileum but not in the jejunum or colon of normal mice, and iNOS protein is detected in the ileum but, again, not in the jejunum (221).

Inhibition of NOS in the brain generates a stimulus that selectively inhibits gastric and duodenal phase III motor activities (222). An inhibition of NOS is involved in the induction of the fasting motor pattern, whereas an increase of nitric oxide mediates the occurrence of the fed pattern (223). Inhibition of endogenous nitric oxide synthesis by N<sup>v</sup>-nitro-L-arginine methyl ester (a NOS inhibitor) causes a secretory response in the intestine that can be reversed by the administration of L-arginine, a substrate for NOS (224). Nitric oxide reduces ATP levels and reversibly increases the permeability of tight junctions in Caco-2 cells (225).

NANC but not cholinergic contractions are inhibited by endogenous nitric oxide, and prejunctional and post-

junctional modulation of NANC contractions are mechanisms for the inhibition of gastrointestinal motility by endogenous nitric oxide (226). Nitric oxide is involved in neurally mediated relaxations induced by GABA in rat isolated duodenum (227). There may be an inhibitory pre-junctional enkephalinergic mechanism modulating the nitrergically mediated relaxant events in the longitudinal muscle layer (228). Endogenous nitric oxide also is important in the modulation of spontaneous tone and motility in the rat duodenum. Induction of NOS results in a reduction in spontaneous motility, and inhibition of constitutive nitric oxide biosynthesis unmasks a contractile response (229). Increased nitric oxide formation via the expression of endotoxin-inducible iNOS may be responsible for the pathophysiology of septic shock. iNOS mRNA is present throughout the digestive tract (230). NOS activity is induced by lipopolysaccharide due to an increase in NOS2 mRNA and protein abundance (231). Primary afferent neurons and interneurons as well as motor neurons are present in the enteric nervous system. Primary afferent neurons responsible for mucosal pressure- or glucose-induced enteric and enteropancreatic reflexes are submucosal, whereas myenteric afferent neurons become activated only when the wall of the bowel is distended (232).

Agonists such as histamine evoke a contraction of guinea pig intestinal smooth muscle, both by releasing calcium from the intracellular stores and by stimulating calcium influx from the extracellular space. Refilling of intracellular calcium stores depleted by histamine in guinea pig intestine occurs through the L-type calcium channels (233). There are two types of calcium entry pathways to refill calcium stores, one sensitive and the other insensitive to calcium channel blockers (234). GTPase RhoA or related proteins are involved in carbachol- and high potassium-induced contractions in intact intestinal smooth muscle; these proteins may play a role in agonist-induced increase in calcium sensitivity of force production in intestinal smooth muscle (235). Calcium influx, not acting through either the L- or N-type calcium channels, helps initiate ileal slow waves (236). IL- $\beta$  suppresses neurotransmitter release from rat myenteric plexus via the induction of leukemia inhibitory factor as a downstream intermediate (237).

Clinical considerations: Transection and reanastomosis of the intestinal wall change the temporal and spacial organization of contractions distal to the transection site, with fewer distally propagating contractions and slower intestinal transit (238). After intestinal resection, digestive motility is shortened, and the frequency of MMC cycling increases (239).

Acute hyperglycemia decreases duodenal and jejunal motor activity, and retards small intestinal transit (240). The rate of gastric emptying is a determinant of postprandial blood glucose concentrations, which may contribute at least in part to the gastrointestinal symptoms that may occur in patients with diabetes. Hyperinsulinemia increases sympathetic activity, abolishes antral phase III and makes

duodenal phase III shorter (241). The duration of the postprandial period without duodenal MMC is prolonged in the acute postresection phase, but the magnitude of these compensatory changes decreases over time (242).

The *c-kit*<sup>+</sup> receptor is expressed by ICCs and is a receptor tyrosine kinase. Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a syndrome characterized by a failure of intestinal movement, which may be related to a deficiency of *c-kit*<sup>+</sup> cells in the ICCs (243). Small intestinal manometry is useful in diagnosing CIIP in infancy and may also be useful for predicting clinical outcome (244). In patients with dysfunctional dyspepsia, small intestinal motor abnormalities may occur, especially during fasting (245). The whole gut transit time is shorter in patients with anxiety, as is the orocecal transit time (246). This finding is consistent with the clinical impression that anxiety may be associated with increased bowel frequency. Antidepressants are sometimes used in patients with IBS, and the tricyclic imipramine slows jejunal phase III propagation velocity. This suggests that tricyclic antidepressants may be useful in symptom relief by way of mechanisms unrelated to mood improvement (247). Ambulatory manometry is a useful tool to demonstrate these changes, and alterations in small intestinal motility are also prevalent in patients with diarrhea-prominent IBS (248).

Ondansetron, a highly selective 5-HT<sub>3</sub> antagonist, has been shown to be useful in the treatment of symptoms in patients suffering from IBS or from functional dyspepsia (249). Activation of the sympathetic nervous system selectively increases visceral but not somatic sensitivity, and enhances both vagally and sympathetically driven reflexes in the gut (250). Gut hypersensitivity may be present in some patients with IBS, with selective hypersensitivity of intestinal mechanosensitive pathways associated with a nonspecific, probably central dysfunction of visceral somatic referral (251).

Ileus is common during sepsis; a single, sublethal dose of *Escherichia coli* lipopolysaccharide endotoxin temporarily disrupts fasting, and postprandial canine gastrointestinal motility and transit (252). Motility and secretory IgA are linked by motility-activated chloride secretion from the intestinal crypts (253).

The secretory and motor functions of upper gastrointestinal organs are inter-related, both under fasting and fed conditions. For example, pancreatic enzyme secretion parallels changes of small intestinal motility. Neither the duration of digestive secretory nor motor activity correlate with prandial duodenal nutrient concentrations, but the durations of pancreatic secretory and motor responses are associated with changes in ileal nutrient delivery postprandially, correlating with the determination of digestive pancreatic and motor responses (254). Intestinal transit is inhibited more by oleate in the distal than in the proximal half of the gut (255).

## DRUG ABSORPTION AND METABOLISM

The literature dealing with drug absorption sites in the

gastrointestinal tract has been reviewed (256). The principal goal of oral controlled release delivery systems is to provide the drug within a time-frame that will increase its efficacy and minimize adverse effects. Some drugs are absorbed in specific areas of the intestine due to their low permeability or solubility, their chemical instability and the binding of the drug to the intestinal contents, as well to the degradation of the drug by normal colonic microorganisms. Thus, the delivery site may need to be controlled to influence absorption of the medication. Several possible approaches can be used to increase the oral absorption of drugs, and the use of carrier-mediated transport for bile acids is one such mechanism (257).

Gene products of the P-450 gene superfamily are represented in the small intestinal epithelial cells of numerous species, including humans, as well as in cultured Caco-2 cells (258). When procarcinogens are metabolized by cytochrome P-450, they may undergo bioactivation to putative carcinogens. This represents the metabolic machinery for orally ingested xenobiotics, and the cytochrome P-450 system is the site for xenobiotic first-pass metabolism in the small intestine. Some of the P-450s are inducible. The main cytochrome P-450 in rat small intestine is CYP1A1, which can be induced in both villus and crypt cells (259).

A second major determinant of oral drug bioavailability is the multidrug efflux pump, P glycoprotein. P glycoprotein is present in high levels in the villus enterocytes of the small intestine and may be induced. There is a broad overlap in substrate and in inhibitor specificity for cytochrome P-450 and P glycoprotein, suggesting that they act as a concerted barrier to drug absorption (260).

From a drug discovery perspective, cell culture models can be used to expedite the identification of compounds with desired pharmacokinetic properties (261-263). Estimates of passively absorbed solutes correlate highly between rats and humans, but carrier-mediated absorption may deviate between these two species (264). Thus, actively transported drug uptake is underestimated in cell cultures compared with in vivo data, although a good correlation with fractional absorption is seen for passively transported drugs (265).

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