Basic science for the clinical gastroenterologist: A review of the recent literature on the small bowel – Part I

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ABR THOMSON. Basic science for the clinical gastroenterologist: A review of the recent literature on the small bowel – Part I. Can J Gastroenterol 1994; 8(3):213-218. For small bowel science, as for all parts of medicine, there has been a recent explosion of information. This is the first of a two-part series in which the scientific basis of clinical gastroenterology practice and its future are considered. Advances in an understanding of the mechanisms of intestinal transport will be considered, followed by a perspective of intestinal adaptation in health and disease. The author also discusses clinically important areas of motility and bloodflow.

Key Words: *Absorption, Minerals, Motility, Secretion, Vitamins*

Sciences fondamentales pour le gastro-entérologue clinique : Survol de la littérature récente sur l'intestin grêle – Partie I

RÉSUMÉ : On a assisté récemment à une explosion de connaissances dans tous les domaines de la médecine et cela s'applique également aux connaissances sur l'intestin grêle. Voici la première d'une série de deux articles qui porteront sur les fondements scientifiques de la pratique clinique en gastro-entérologie et sur son avenir. Les connaissances acquises au sujet des mécanismes du transport intestinal seront abordées, ainsi que l'adaptation de l'intestin aux situations normales et morbides. L'auteur traitera également de thèmes importants sur le plan clinique relativement à la motilité et à la circulation sanguine.

THERE HAS BEEN A RECENT EXPLOsion of information for small bowel science. This is the first of a two-part series in which the scientific basis of clinical gastroenterology practice and its future are considered.

MOTILITY

Electrophysiological studies have shown the existence of a tonic muscular activity in the small bowel, and there are reflex changes in intestinal tone induced by intestinal distension. For example, the proximal jejunum relaxes in response to distension of the distal jejunum. In contrast, the distal jejunum does not respond to distension of the proximal jejunum, despite similarity in perception in human volunteers of proximal or distal distension (1). This dissociation between perception and intestinal tone reflexes suggests that both responses to intestinal distension are mediated by specific, but potentially different, mechanisms (2). Ileal perfusion with partially digested lipid emulsions slow intestinal transport; this phenomenon has been described as the 'ileal brake'. Ileal lipids also affect motility in other parts of the gastrointestinal tract: oleate perfused in the ileum of dogs reduces duodenal spikeburst frequency and delays the gastric emptying of liquids and solids (3).

Prostaglandin (PG) F_2 has a direct excitory effect on the intestinal smooth muscle. This excitory effect is calcium channel-dependent, but is independent of intrinsic nerves. In contrast, PGE_2 has an inhibitory effect both on the spontaneous and PGF_2-induced small intestinal myoelectric and contractile activity (4).

Duodenal phase 2 motor activity of the migrating motor complex (MMC) is suppressed during psychological stress in normal persons, as well as in those with symptoms suggestive of the so-called irritable bowel syndrome (5). Hypnosis induces a state of relaxation,

and this is associated with longer orocecal transit than during the control period (6).

Prolonged motility studies in normal humans have revealed large variations in MMC rhythmicity (7); this variability may restrict the clinical usefulness of MMC measurements. Although the lactulose breath hydrogen test is widely used to measure intestinal transit time, its use is limited by extensive variability between and within subjects, and different phases of fasting gastrointestinal motility may be major determinants of the transit time estimated by this test (8).

The long-acting somatostatin analogue octreotide stimulates intestinal motility in normal subjects, as well as in patients with scleroderma (9). Octreotide is effective in preventing the development of severe vasomotor and gastrointestinal symptoms in patients suffering from the 'dumping syndrome' (10). Small intestinal transit time in hypothyroid patients is prolonged, and is decreased towards normal upon reinstitution of thyroid replacement therapy (11).

Leuprolide acetate, a gonadotropin-releasing hormone analogue, may be useful to treat the debilitating symptoms of 'functional' bowel disease because of its effect on gastrointestinal motility (12). Neuropeptide Y and peptide YY inhibit gut motility, are potent vasoconstrictors, and inhibit gastric emptying and acid secretion, as well as pancreatic exocrine secretion (13).

TUMOURS

Tumours of the small intestine are uncommon. Benign lesions are seen more frequently in the jejunum, while malignant lesions are more common in the ileum (14). Bleeding, perforation, obstruction and a mass effect are common presenting features, particularly in patients with malignant tumours. Only about one-third of patients with a small bowel tumour have a diagnosis correctly made before surgery, and operative mortality and morbidity rates are high. Small bowel enteroscopy may be useful to diagnose small bowel tumours, even when enteroclysis and angiography have been negative (15).

The treatment of gastrointestinal lymphoma includes surgery, chemotherapy, radiotherapy or combinations of the three. Surgical resection prior to the administration of combination chemotherapy does not influence response or survival rates, although the number of patients available for study is small (16).

BRUSH BORDER MEMBRANE: FORM AND DIGESTIVE FUNCTION

The topic of structure-function relationships in intestinal brush border membrane (BBM) has been reviewed (17). Intestinal alkaline phosphatase may be secreted from adult rat enterocytes by way of surfactant-like particles containing saturated phosphatidylcholine, which form multilamellar membrane whorls containing other BBM enzymes and which reduce membrane surface tension. Electron microscopy reveals abundant particles in one-day-old rats, declining in frequency by day 14 (18).

The intestinal villus epithelium is implicated in immune responses to luminal antigens of dietary and bacterial origin. Major histocompatibility complex antigen II and regulation of the class II Ii (invariant) chain gene is associated with the ontogeny of intestinal immunity (19).

Changes in the lipid composition and/or the physical state of the BBM may influence enzyme activities, transport, sodium and hydrogen exchange, and water permeability. The fluidity of the exofacial (outer) hemileaflet of the BBM is greater than the cytofacial (inner) hemileaflet of rat intestine (20), and these differences are explained, in part, by variations in the distribution of phosphatidylcholine and phosphatidylethanolamine, with more of the former in the exofacial and more of the latter in the cytofacial leaflets. Fluidizing the exofacial leaflet decreases leucine aminopeptidase activity, but not that of maltase, sucrase, alkaline phosphatase or gamma-glutamyltranspeptidase; in contrast, fluidizing the cytofacial leaflet increases sodium gradient-dependent D-glucose transport, but not sodium gradient-dependent L-leucine trans-

port. The reason for this apparent dissociation between fluidity and function is unknown.

Immunohistochemical techniques have demonstrated actin, villin, fimbrin, 110 kDa protein and calmodulin in the microvillus core, and myosin, tropomyosin, actin, vinculin, filamin, TW 260/240, gelsolin and caldesmon in the terminal web. Dense networks of keratin tonofilaments are present in the terminal web and may play a role in the morphological and structural alterations accompanying intestinal cell differentiation in vivo (21). The rat intestinal keratin has been studied and cDNA clone has been identified (22). These new techniques cannot be applied to the consideration of clinical conditions in which there may be alterations in intestinal permeability as a result of altered function of tight junctions, microfilaments and microtubules.

The polyamines spermidine spermine, and putrescine and have been implicated in the control of cell proliferation and differentiation, and polyamines promote the synthesis of nucleic acids and proteins. Luminal polyamines may be important stimulants of gastrointestinal mucosal growth (23); "because food contains polyamines and intestinal epithelial cells accumulate these compounds from the luminal side, the gut lumen is likely an important source of polyamines for the cells lining the digestive tract". The rate-limiting step in the biosynthesis of polyamines is the decarboxylation of ornithine by ornithine decarboxylase to form putrescine. In cultured Caco-2 cells, epidermal growth factor stimulates DNA synthesis and diamine oxidase (DAO), the enzyme which catalyzes the oxidation of putrescine and is therefore involved in the regulation of its cellular concentration. Caco-2 proliferation and differentiation were not correlated with the levels of cellular DAO, suggesting that this enzyme does not play a major role in the regulation of intestinal epithelial cell turnover (24).

Heparin releases DAO from binding sites on intestinal microvascular endothelial cells or the basolateral mem-

brane (BLM) of villus epithelial cells, and this postheparin DAO activity is influenced by intestinal maturation and mucosal integrity. For example, postheparin DAO activity is altered in several intestinal disorders including celiac disease, gastroenteritis, intestinal injury after ischemia, radiation, chemotherapy and Crohn's disease. The reduced plasma postheparin DAO activity in patients with Crohn's disease is unrelated to the Crohn's disease activity index (CDAI), the extent of small bowel disease or the presence of colonic involvement (25). The clinical usefulness of the measurements of postheparin DAO activity as a measure of small intestinal function or response to therapy remains to be explored.

Approximately 80% of the mass of intestinal mucins are carbohydrate, and this helps to provide mucin with its viscosity and lubrication properties. Four human mucins have been described and partially characterized, and partial cDNA derived from two different human intestinal mucin genes have been cloned (MUC-2 and MUC-3). MUC-2 cDNA is expressed in the colon, small intestine, colonic tumours, and other tissues, and there are two distinct regions of MUC-2 with a high degree of internal homology (26). Different characteristics are found for the molecular cloning of rat intestinal mucin (27). With the development of these refined techniques, it waits to be determined whether mucins change in disease conditions.

Increasing attention has focused on the mechanisms whereby the level of hydrolase gene expression is controlled during enterocyte differentiation. Sucrase-isomaltase (SI) expression may be differentiation-dependent, but is also influenced by nutritional and/or metabolic factors. SI activities are undetectable before postnatal day 16 in the rat, then appear and rise sharply to adult levels during the following week. SI is essential for the digestion of sucrose and for the terminal digestion of starch, and developmental changes in sucrase enzyme activity are correlated with changes in the quantity of sucrase protein. The complete sequence of rabbit SI mRNA has been published, and a par-

tial cDNA for rabbit SI has been cloned and used to quantitate rat SI mRNA (28).

Expression of SI as enterocytes emerge from intestinal crypts is regulated primarily at the level of mRNA accumulation (29), which has been suggested to be the 'result of activation of sucrase-isomaltase gene transcription'. In situ hybridization methodology demonstrates the absence of SI mRNA in jejunal crypt cells; this suggests that the gene is not transcribed in undifferentiated, proliferating cells located in the intestinal crypt. Other studies have shown that in human duodenal biopsy specimens, SI mRNA levels are maximal in lower and midvillus cells, with decreased levels at the villus lips (30). There may also be differences in the postbasolateral processing of SI protein, such as variations in glycosylation (31). The use of Caco-2 and HT-29 cultured cells have also provided evidence for both transcriptional and post-translational control sites of SI and lactase expression (32). Along the villus to crypt axis of adult rat jejunum, gradients of SI mRNA abundance correspond with SI activity (33). However, along the longitudinal axis of the intestine no variations in SI mRNA levels are observed, thus not accounting for the observed differences in SI activities between jejunum and ileum. There may be differences in the regional regulation of translation which may determine sucrase activity along the longitudinal axis of rat small intestine.

Dipeptidyl peptidase IV (DPP IV) does not undergo metabolic or nutritional modulation. DPP IV enzyme activity is lower in crypt than in villus cells. Indirect immunofluorescence studies using a polyclonal antibody raised against purified DPP IV show a gradient of immunoreactivity from the crypts to the villi. Also, there is approximately seven times less DPP IV mRNA in crypt cells than in villus cells. This suggests that the differentiation-dependent expression of DPP IV in rat jejunum is primarily controlled at the mRNA level (34).

Localization by in situ hybridization of mRNA for liver fatty acid binding protein, aminopeptidase N, and cyto-

chrome P-450 II B1 suggests that a major mechanism for differential expression of these genes along the crypt-villus axis is the relative abundance of mRNA. Transcriptional activation of genes may be an important mechanism for enterocyte differentiation as cells move along the crypt-villus axis.

Lactase activity is associated with a bifunctional protein, lactase-phlorizin hydrolase (LPH). LPH is synthesized as a large single chain precursor that is subsequently converted by intracellular proteolysis to the final BBM form. Pro-LPH is an enzymatically active molecule, and intracellular proteolysis of pro-LPH is not essential for the generation of transport-competent forms of LPH. Lactase is synthesized as a lactase precursor, transported to the BBM and cleaved by luminal proteases; the amino and polypeptide cleaved from lactase precursor is released in the lumen (35).

The regulation of lactase expression has been shown to take place essentially at the post-transcriptional level in the jejunum, since LPH mRNA accumulates at a constant rate throughout development, irrespective of the specific activity of lactase (36). The pattern of expression of lactase mRNA and protein in rat small intestine during fetal and postnatal development has been analyzed using in situ hybridization and immunohistochemistry (37). Expression of lactase mRNA and protein is seen exclusively in villus epithelial cells.

Large amounts of jejunal lactase mRNA and protein are detected during postnatal development as well as in adult rats, despite the 10-fold decline in lactase specific activity which occurs at weaning (38). This suggests that the expression of lactase is mainly regulated at the post-transcriptional level in the jejunum, whereas it is controlled at the pretranslational level in the colon. A post-translational regulatory mechanism would be compatible with the synthesis, processing and generation of an enzymatically inactive form of lactase or of a transport-incompetent molecule that is retained intracellularly and eventually degraded.

The application of molecular bio-

logical techniques to the understanding of normal physiological events in the small intestine is in its infancy. In time, a better understanding will be obtained of the mechanisms controlling the expression of the activity of the digestive and transport proteins in the intestine, and only then will it be possible to understand how the processes 'go wrong' in disease states.

BRUSH BORDER MEMBRANE ABSORPTIVE FUNCTION

Amino acids, peptides and macromolecules: There are several systems for the active transport of amino acids by mammalian small intestine. Entry of amino acids into the enterocyte across the BBM is thought to include sodium-dependent and sodium-independent mechanisms. Their transport across the BLM is also thought to occur via sodium-dependent and as well as sodium-independent systems (39). Alpha-hydroxy analogues are partly or completely converted in vivo into their corresponding amino acids.

Hydrogen gradient-driven transport of the L- and D-stereoisomeric hydroxy analogues of L-leucine has been described in rabbit BBM. Glutamine is a nonessential amino acid that is the principal nutrient used by the small intestine. Jejunal BBM transport of glutamine occurs via a sodium-dependent pathway, and to a lesser extent by way of a sodium-independent process. There is a reduction in the maximal transport rate (Vmax) for glutamine uptake into BBM vesicles obtained from loops of bowel excluded from continuity with the intestinal stream in dogs with a surgically prepared roux-en-Y gastrojejunostomy (40). It is unknown why the energy use of the intestine changes in response to this surgical procedure.

In some mammalian species, the intestine is highly permeable to macromolecules in the postnatal period, allowing the offspring to absorb circulating maternal antibodies from colostrum and from milk. In humans and in guinea-pigs, there is a prenatal transfer of passive immunity via the placenta and the yolk sac. At birth, the small intestine of guinea-pigs is capable of macromolecular uptake and transfer into the circulation. This ability decreases with age, and leads to 'intestinal closure' after one week of age (41). Cholecystokinin raises IgA- and IgG-specific antibody activity in the lumen of the rat intestine, and promotes the translocation of albumin, electrolytes and water into the lumen of the rat intestine (42). The closure of the intestine to macromolecular absorption, which occurs in pigs at about 24 h of age, is not due to a decrease in the endocytotic ability of the enterocytes, nor to a higher degradation rate within these cells (43); the mechanism of closure remains to be established.

Nucleosides are taken up into mammalian cells by facilitative diffusion and by a sodium-dependent transport mechanism. In mouse intestinal epithelial cells, there are two sodium-dependent nucleoside transporters, one of which accepts purine nucleosides and uridine. The other transporter has substrate specificity for pyrimidine nucleosides, adenosine and for analogues of adenosine. The adenosine transporter has been expressed in *Xenopus laevis* oocytes (44). There is a family of sodium/glucose cotransporter-related proteins, and one of these is a sodium/nucleoside cotransporter (45).

VITAMINS AND MINERALS

Iron: Iron present in the intestinal lumen as $Fe(OH)_3$ is poorly soluble; the availability of iron for active mucosal uptake may be increased by adding dietary ligands. Low concentrations of taurocholate increase iron uptake into all regions of rat small intestine (46). Infant iron absorption from human milk is higher than from infant formula based on bovine milk, yet the iron content of human milk is similar to that of iron-unsupplemented infant formula. The high bioavailability of iron from human milk suggests that lactoferrin, a major iron-binding protein in human milk, may be a factor contributing to iron absorption in infants. A lactoferrin receptor has been isolated from human fetal intestinal BBM (47), but its physiological and nutritional significance needs to be established.

Iron absorption responds to the status of the body iron stores, to blood loss and to changes in the dietary level of iron. The topic of the regulation of intestinal iron absorption and mucosal iron kinetics in hereditary hemochromatosis has been reviewed (48). The mRNA for transferrin is absent in human duodenal tissue, suggesting that transferrin does not play a role in the transport of iron across the enterocyte. Transferrin receptor mRNA increases with anemia and decreases in secondary iron overload, and yet it inappropriately increases in patients with genetic primary hemochromatosis. There is an abnormally low level of both H- and L-ferritin transcripts in patients with hemochromatosis, along with the expected increase in transcripts in patients with secondary iron overload. Thus, in patients with genetic hemochromatosis, there may be a primary defect in ferritin transcription in mucosal cells, or a defect in the coordinate regulation of the genes for transferrin receptor and for ferritin.

There is an iron-binding glycoprotein on the BBM, and this may function to transport iron (49,50). Ferritin may be predominantly a storage protein that protects the cell from the oxidative damage of ionic iron. Mobilferrin has been described in the rat as well as in the human duodenum, is distinct from transferrin or ferritin, and may play a role in iron absorption (51). Cytochemical and autoradiographic studies have demonstrated that iron is associated with the BLM during absorption; thus, the iron binding site on the BLM may play an important role in the transfer of iron out of the enterocyte (52).

Calcium and vitamin D: Active absorption of calcium from the transcellular route in the proximal small intestine is dependent on the circulating concentration of $1,25(OH)_2D_3$. There is a calmodulin-stimulated ATP-dependent calcium pump on the BLM which represents the major efflux pathway of calcium in enterocytes. The stimulatory effects of vitamin D on intestinal calcium transport most likely result from its effects on BBM influx and facilitation of cytosolic calcium diffusion by calcium-binding proteins, not from an in-

crease in calcium pumping capacity in the BLM (53).

Vitamin D deficient animals exhibit a decrease in steady-state mRNA for the calcium pump, and there is a biphasic increase in calcium pump mRNA in response to repletion with $1,25(OH)_2D_3$ (54). The uptake of calcium into the BBM is a passive process, and vitamin D stimulates the rate of ATP-dependent calcium uptake in the BLM. At an early stage of the $1,25(OH)_2D_3$-induced intestinal calcium transport process, the vitamin regulates the calcium pumping activity of chick intestinal BLM by phosphorylation and dephosphorylation, and not by a stoichiometric change in the pump (55).

In addition to the animals' vitamin D status, the capacity of the intestine to absorb calcium is influenced by the dietary intake of calcium and phosphorus; there is an inverse relationship between dietary levels and absorption of calcium and phosphorus. Dietary variables that enhance intestinal calcium absorption also increase the amount of the BLM calcium pump (56).

Magnesium is secreted across the short-circuited duodenum (whereas calcium is absorbed), and pericellular movement of magnesium is an important pathway in rat intestine (57). However, much less magnesium than calcium is absorbed from human intestine, and the relationship between the dose of administered magnesium and magnesium uptake is curvilinear (58).

Biotin: The water-soluble vitamin biotin is essential for several normal cellular functions and for growth. The uptake of biotin by the BBM is by a sodium-driven transport system regulated by the level of the vitamin in the diet. Biotin uptake is mediated by a histidyl residue at or near the substrate-binding site (59). Biotin movement across the rat BLM is mediated by an electroneutral sodium-independent transporter, a process which is sensitive to the effects of anion transport inhibitors (60).

Folates: Folates occur in the diet as pteroylpolyglutamates. Intestinal absorption of dietary folates occurs by hydrolysis of pteroylglutamate_n and by transport of pteroylglutamate. Hydrolase activity is much higher in the jejunum than in the ileum (61), and jejunal BBM folate hydrolase is essential and rate-limiting in folate absorption. In pigs, the active form of jejunal BBM folate hydrolase has a molecular weight of 240 kDa, and is probably a homodimer of the 120 kDa protein found after immunoprecipitation with specific antibodies (62).

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