Small bowel review: Part I

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ABR Thomson, M Keelan, A Thiesen, MT Clandinin, MJ Ropeleski, G Wild. Small bowel review: Part I. Can J Gastroenterol 2000;14(9):791-816. In the past year, there have been many advances in the area of small bowel physiology and pathology. More than 1500 papers were assessed in preparation for this review. Some were selected and reviewed, with a particular focus on presenting clinically useful information for the practising gastroenterologist. Relevant review articles have been highlighted, and important clinical learning points have been stressed. The topics are varied in scope, and wherever possible show a logical progression from basic physiology to pathophysiology to clinical disorders and management.

Key Words: *Absorption; Adaptation; Celiac disease; Motility; Secretion*

Revue de l'intestin grêle : 1re partie

RÉSUMÉ : De nombreux progrès ont été réalisés au cours de la dernière année en ce qui concerne la physiologie et la pathologie de l'intestin grêle. Plus de 1 500 articles ont été évalués dans le cadre de la présente revue. On a d'abord sélectionné et examiné un certain nombre d'entre eux, notamment ceux qui contenaient de l'information utile sur le plan clinique pour les gastro-entérologues praticiens, puis on a retenu les articles les plus intéressants et fait ressortir les points importants à retenir pour l'apprentissage clinique. Les sujets traités sont très diversifiés et les articles présentent, dans la mesure du possible, un lien logique entre la physiologie, la physiopathologie, les troubles cliniques et le traitement.

GASTROINTESTINAL HORMONES AND PEPTIDES

The topic of the biology of gut cholecystokinin (CCK) and gastrin receptors has been reviewed (1). Hyperinsulinemia increases plasma noradrenaline concentrations as well as muscle sympathetic nerve activity, even in the absence of hypoglycemia. In guinea pig-isolated ileal synaptosomes, insulin stimulates in a concentration-dependent manner the secretion of noradrenaline. This is mediated by signalling that involves insulin receptors through downstream activation of calcium influx (2). The luminal CCK-releasing factor is present throughout the gastrointestinal tract. Immunohistochemical analysis shows diffuse CCK immunoreactivity throughout the gastrointestinal tract and the pancreas (3).

Luminal nutrients and neuroendocrine peptides exert differential effects on somatostatin-28 release from the rat intestine compared with those of somatostatin-14 (4). The somatostatin analogue octreotide is effective in the treatment of the diarrhea and flushing that occur in patients with carcinoid syndrome. Octreotide retards colonic and small bowel transit. This action may be mediated by the associated reduction in circulating levels of peptide Y (PYY), neurotensin, vasoactive intestinal polypeptide (VIP) and substance P (SP); however, octreotide has no effect on plasma motilin concentrations (5). The topics of VIP and secretin receptors, and the G protein-coupled receptors have been reviewed (6).

The inactive proforms of gastrointestinal peptide hormones and neuropeptides (such as VIP, PYY and glucagon-like peptides) are processed in part by specific endoproteases through selective cleavage at the C-terminal side of paired basic amino acid sites. Prohormone convertase (PC)-6A mRNA is expressed throughout the entire gastrointestinal tract, with the highest levels in the small intestine (7). Ileal PC-6A mRNA expression increases with fasting and declines with refeeding, whereas dietary fat increases PC-6A mRNA levels in the ileum.

Neuropeptide Y (NPY) and PYY are structurally related peptides that mediate inhibitory activity in terms of gastro-

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intestinal motility, secretion and blood flow. NPY receptors are present in the rabbit ileum and are subject to interaction by receptor antagonism (8). Several receptor subtypes of these peptides have been identified and cloned. Double immunofluorescence studies demonstrate that subpopulations of Y1 receptor-positive nerve cell bodies are immunopositive for NPY, VIP and nitric oxide synthase (NOS) (9). The Y receptor subtypes for PYY, NPY and pancreatic polypeptide bind to intestinal receptors and exert an antisecretory effect (10). Intestinal fluid secretion occurs in conjunction with some enteric infections and is mediated by prostaglandin (PG) H synthase (11).

After raising the intraluminal pressure, serotonin is released into the cytoplasmic matrix and then diffuses or is transported into the intestinal lumen (12).

INTESTINAL INFECTIONS AND INFLAMMATION

The bacterial, viral and parasitic infections of the intestine have been reviewed (13-15). Also reviewed are the topics of gastrointestinal infections in children (16) and their treatment (17). The Practice Parameters Committee of the American College of Gastroenterology has suggested guidelines for the care of adults with acute infectious diarrhea (18).

***Entamoeba histolytica*:** *E histolytica* is caused by two genetically distinct species, the invasive parasite *E histolytica* (which is the etiological agent of amoebic colitis and liver abscess) and the noninvasive *Entamoeba dispar*. A new approach to the detection of *E histolytica* and *E dispar* is based on antigen detection in the stool (19). In the severe combined immunodeficient mouse-human intestinal xenograft model of disease, infecting the human xenografts with *E histolytica* trophozoites increases the production of interleukin (IL)-1 and IL-8 (20). Humans are the only important host for *E histolytica*, and an effective vaccination program could potentially eradicate amebiasis. In gerbils, protective immunity against *E histolytica* after vaccination is correlated with the development of an antibody response to a region of 25 amino acid residues of the galactose- and *N*-acetylgalactosamine-inhibitable lectin (21). The use of such vaccines would be of great value in countries where the environmental conditions are not ideal.

***Giardia lamblia*:** *G lamblia* is a highly relevant gastrointestinal protozoal disease that usually manifests as a self-limited clinical course. Trophozoites are usually found in the mucosa of the duodenum (83%), ileum (12%), gastric antrum (9%) and jejunum mucosa (2%) (22). In less than 5% of giardia-infected subjects, the histological lesion resembles celiac sprue in the mild intestinal villus shortening, as well as inflammation in the lamina propria.

***Yersinia enterocolitica*:** The enterobacterium *Y enterocolitica* causes a broad range of gastrointestinal syndromes, ranging from acute enteritis and enterocolitis to mesenteric lymphadenitis. *Y enterocolitica* invades M cells located in the follicle-associated epithelium overlying Peyer's patches, and this infection results in the secretion of IL-8 (23). The clinical relevance of this finding is unknown.

***Vibrio cholera*:** Both *V cholera* and enterotoxigenic *Escherichia coli* (ETEC) colonize the small intestine and produce diarrhea by elaborating enterotoxins. The secretory effect of cholera toxin (CT) and of the heat-labile ETEC declines in the aboral direction along the small intestine. In contrast, the effect of the heat-stable ETEC is greatest in the distal small intestine. Mucosal glucose and amino acids stimulate electroneutral and electrogenic sodium ion absorption to the same degree in the normal and cholera-treated small intestine. This is the physiological basis for placing glucose in oral electrolyte replacement solution. There is no segmental difference in stimulated electroneutral sodium chloride absorption, while electrogenic sodium ion absorption is highest in the mid and distal portions of the small intestine (24).

V cholera liberates its classic CT, a zonula occludens toxin. A membrane-damaging toxin, a hemolysin, also known as the *V cholera* cytolysin, is a second type of vibrio exotoxin. *V cholera* cytolysin produces pores in the enterocyte, resulting in ATP depletion and cell death (25). These toxins interact with specific high-affinity receptors on the intestinal brush border membrane (BBM). This activates adenylate cyclase within the enterocytes, thereby increasing the cellular concentration of the second-messenger 3':5'-cAMP. The CT then ribosylates alpha subunits of G protein (Gs), inhibiting GTPase activity, which results in maintenance of Gs in its activated state (simulating adenylate cyclase). This increase in cAMP results in secretory diarrhea.

***E coli*:** In the critically ill patient, translocation of enteric bacteria across the intestinal mucosa is thought to play a critical role in the pathogenesis of multiple organ failure. The interaction between enteric bacteria and their products with enterocytes, the influence of gut-associated lymphoid tissue and the secretion of cytokines by the enterocyte may alter intestinal function. Polarized monolayers of human enterocytes (Caco-2 cells) in culture increase the secretion of IL-6 and tumour necrosis factor (TNF) upon stimulation with *E coli*) (26). The cytokines may 'crosstalk' with mucosal mononuclear cells as well as with neutrophils, and may modulate intestinal epithelial barrier function. Also, the cytokines may increase enterocyte surface expression of molecules such as major histocompatibility complex antigens. Interferon (IFN)- and IFN- are upregulated by rotavirus infection, suggesting that cytokines also play a role in host defence against viral agents (27). While proinflammatory cytokines can be detected in biopsy specimens from the intestinal mucosa of individuals with inflammatory bowel disease (IBD), celiac disease or infectious colitis, their precise pathophysiological role in these diseases remains to be determined.

Clinical learning point: Cytokines modify intestinal function, and some may play a role in host defence against infections.

There is a growing body of evidence that suggests that en-

cally, enterocytes play a major role as a source of proinflammatory cytokines and cytotoxins. A key proinflammatory mediator produced in the intestinal mucosa is the free radical nitric oxide, which is synthesized by inducible NOS (iNOS). Bacterial-induced expression of iNOS in Caco-2 cells induces the synthesis of nitric oxide, which can be blocked by inhibitors of nuclear factor kappa B such as glucocorticosteroid (GC) and of tyrosine kinase activation (28).

ETEC causes significant morbidity and mortality in children as well as in travellers. ETEC produces a heat-labile toxin and/or a heat-stable enterotoxin (either STa or STb). *E coli* 0157:H7 is increasingly recognized as a cause of bacterial diarrhea in the United States, and molecular subtyping methods are used to discriminate the various strains of the organism (29). In some geographic areas and in some age groups, isolation proportions from fecal specimens for *E coli* 0157:H7 surpass those of other common enteric pathogens (30). STa is an important causative agent of diarrheal disease. STa binds to specific receptors in the intestine, activates the guanylate cyclase C receptor, elevates cGMP levels and stimulates chloride secretion via cystic fibrosis (CF) transmembrane conductance regulator (CFTR). Knockout mice lacking guanylate cyclase C receptor are refractory to the secretory action of STa (31). Pharmacological inhibition of guanylate cyclase C and/or blocking of the guanylate cyclase C receptor could be targets for possible therapy in *E coli* infections.

With verotoxin (VT)-producing *E coli*, the diarrhea may be associated with hemorrhagic colitis and with the hemolytic uremic syndrome. Human intestinal epithelial cells (IECs) lack a receptor for VT, but VT-producing *E coli* bacterial strains lower the transmonolayer resistance of cells in culture. Immunoelectron microscopy confirms the transcellular transport of VT (32).

Enteropathogenic *E coli* (EPEC) are an important cause of gastroenteritis in infants under the age of one year. EPEC infections may lead to reductions in both villous height and the ratio of the villous height to crypt length (33). EPEC induce phosphorylation of the 20 kDa myosin light chain and thereby alter intestinal epithelial permeability (34).

Binding of *E coli* to the 32 to 33 kDa BBM proteins plays an important role in bacterial colonization (35). EPEC are not invasive and result in diarrhea as the result of a characteristic 'attaching and effacing' lesion in the BBM. After the initial attachment, signal transduction to the host cells leads to disruption of the BBM cytoskeleton and effacement of the microvilli. This is followed by further adhesion of bacteria to the BBM and accumulation of host cell cytoskeletal elements beneath the attached bacteria. Signal transduction to the host cells requires EPEC-secreted proteins. After initial adhesion, EPEC stimulate chloride secretion via CFTR, for which signal transduction to the host cells is a prerequisite (36). Infection with EPEC activates nuclear factor kappa B, which in turn initiates transcription of the anti-inflammatory cytokine and IL-10 (37). A pathogenic island of 35 kilobases, known as the 'locus of enterocyte effacedadhesin called 'intimin', a type III secretion apparatus, as well as EspA, EspB and a new gene *esp*D (38). The EspD protein is secreted via the type III apparatus.

Enteroaggregative *E coli* are also an important cause of persistent diarrhea, especially in children in the developing world. These *E coli* release IL-8 from Caco-2 cells by way of a new heat-stable, high molecular weight protein (39). Enteroaggregative *E coli* may be a cause of outbreaks of gastrointestinal illness (40).

A proteolytic extract obtained from a chemical in pineapple, known as bromelain, prevents intestinal fluid secretion. This bromelain-inhibited secretion is mediated by secretagogues that act via 3':5'-cAMP, 3':5'-cGMP and calcium-dependent signalling cascades (41). Bromelain needs to be tested in humans to determine its antidiarrheal potency.

Antimicrobial proteins and peptides are components of phagocytes, one of which is known as defensin. Defensins are a group of microbicidal peptides expressed in Paneth cells. Human intestinal defensin may protect against invasion and parasitization by microbes (42,43). The clinical application of this observation is awaited.

Clinical learning point: The toxins produced by *V cholerae* and by ETEC bind to BBM receptors, increase intracellular second messengers and result in secretory diarrhea. The clinical usefulness of bromelain, an extract of pineapple, needs to be tested in persons with secretory diarrhea.

Human immunodeficiency virus: In human immunodeficiency virus (HIV)-infected persons, the incidence of diarrhea varies from 30% to 60% of patients from industrialized countries, to 97% of patients from developing countries. The topic of the therapy of gastrointestinal infections associated with acquired immune deficiency syndrome (AIDS) has been reviewed (44). When controlling for the level of lipid malabsorption, HIV-infected patients have lower energy intake than do HIV-negative patients with chronic malabsorption (45). The diarrhea is often associated with cytomegalovirus or *Mycobacterium avium* infection. HIV replication in the mucosa may lead to villus shortening, but there is no evidence that AIDS is associated with mucosal T-cell activation. In persons with HIV-associated diarrhea and malabsorption, wasting is greater in those with cryptosporidiosis than with microsporidiosis. While patients with HIV-related diarrhea have reduced villous height and increased crypt death compared with healthy controls, there is no difference between HIV-positive controls (46).

The entry of HIV into human intestinal cells involves both the gp120 receptor galactosylceramide and the CXCR4/fusin receptors (47). The intestinal permeability to lactulose/mannitol is greater in HIV-positive patients with or without diarrhea, as well as in those with diarrhea due to cryptosporidiosis, than in controls (48).The clinical presentation of cryptosporidiosis may mimic that of Crohn's disease (49). In addition, cryptosporidiosis may cause an acute

epithelial lymphocyte (IEL) may be important in the generation of immunity to cryptosporidium through a mechanism involving the production of IFN- (50). The depletion of CD4 T cells in the lamina propria is an early event in the course of HIV infection. This may lead to impaired secretory immunity because these cells play a critical role in mucosal B-cell differentiation and antibody production. Interestingly, immunoglobulin (Ig) A and IgM levels are normal in the supernatant of short term cultured biopsy samples from HIV-infected patients, whereas IgG levels are increased (51). HIV core protein p24 may be detected in higher concentrations in intestinal biopsies of HIV-infected patients than in serum. However, proviral loads may be similar in blood and intestinal biopsies, indicating that the intestinal mucosa is a major reservoir for HIV in these patients (52).

Computed tomography scanning of the abdomen may complement colonoscopy and biopsy for diagnostic purposes in patients with HIV-associated intestinal symptoms (53).

Microsporidiosis: Microsporidiosis has been reported in up to 39% of patients with AIDS and diarrhea, and is the most common organism detected among enteric pathogens present in this group of individuals. Two main species, *Enterocytozoon bieneusi*, the most commonly identified species, and *Encephalitozoon intestinalis*, may be responsible for disseminated disease. A recently described polymerase chain reaction (PCR) assay appears to be a rapid and reproducible method for the detection and identification of each intestinal species (54). Transmission and establishment of a persistent infection of *E bieneusi* from a human with AIDS to simian immunodeficiency virus-infected rhesus monkey have been described (55).

Albendazole may successfully eradicate *E intestinalis* from the intestinal tract of HIV-seropositive patients. Albendazole and metronidazole may reduce the volume of diarrhea, although neither clears the spores from the stool. Thus, clinical relapse is common. Thalidomide inhibits TNF- which is elevated in microsporidiosis, and has been shown to reduce stool frequency and improve weight in subjects with E *bieneusi* (56,57).

Clinical learning point: Microsporidiosis is a common cause of diarrhea in patients with AIDS. Treatment is with albendazole, metronidazole or possibly thalidomide.

HIV-infected patients display severe impairment of gastrointestinal function, characterized principally by diarrhea and malabsorption despite the absence of demonstrated opportunistic infections. HIV-1 proteins and nucleic acids have been detected in several cell types of the intestinal mucosa. HIV-1 infection impairs cellular differentiation, decreases transepithelial electrical resistance and inhibits BBM sodium/glucose cotransporter (sodium-dependent glucose transporter) 1, possibly by disrupting microtubules rather than necessarily directly infecting the IECs (58). Intestinal protein leakage may contribute to the hypoalbuminemia

***Salmonella typhi* and shigellosis:** Strains of *S typhi* that are resistant to chloramphenicol, ampicillin and trimethoprim have been responsible for numerous outbreaks in countries in the Indian subcontinent, Southeast Asia and Africa. Ciprofloxacin and azithromycin may be useful in the treatment of shigellosis (60). Unfortunately, resistance to ciprofloxacin has now emerged in multidrug-resistant strains of *S typhi* (61). Strains of *Shigella dysenteriae* type 1, the most virulent serotype of *Shigella* species, are caused by strains that are resistant to ampicillin and to trimethoprim-sulphamethoxazole. The shigella toxin induces fluid secretion by a process that involves protein kinase C (PKC), intracellular (but not extracellular) calcium stores and PGs (62). Growth retardation following diarrheal diseases in children has been documented in several studies, and a randomized clinical trial in Bangladesh demonstrated that feeding children an energy-dense, high-protein diet in addition to antibiotics during the acute phase of shigellosis is associated with greater weight for age and weight for height sustained at home one month after discharge (63).

Clinical learning point: Energy and protein supplementation in addition to antibiotics may be needed in the treatment of acute shigellosis in children.

***Tropheryma whippelii*:** Whipple's disease is a chronic disorder with both intestinal and extraintestinal symptoms. It is caused by a Gram-positive, rod-shaped bacterium named *T whippelii*. Involvement of the central nervous system (CNS) is a serious problem for some patients with Whipple's disease. CNS involvement is not always possible to diagnose using cerebral spinal fluid (CSF) examination for periodic acid-Schiff-positive particles. In some patients with Whipple's disease, a brain biopsy is necessary to diagnose CNS involvement. PCR testing of CSF may be useful to diagnose Whipple's disease of the CNS, both in persons with and persons without neurological symptoms (64).

Clinical learning point: PCR technology may be applied to the CSF of patients with Whipple's disease to diagnose CNS involvement with *T whippelii*, without the need to perform a brain biopsy.

In patients with Whipple's disease, there is altered cell-mediated immunity and delayed-type hypersensitivity, accompanied by persistent immunological alterations in the peripheral blood mononuclear cells. The peripheral blood mononuclear cells in patients with Whipple's disease have reduced monocyte IL-12 production, as well as decreased IFN- secretion (65). The pathophysiological significance of this finding is unknown.

***Clostridium difficile*:** *C difficile* toxin A mediates intestinal inflammatory responses by binding to a specific receptor on intestinal cells. This binding leads to activation of enteric

agent that ablates sensory neurons, inhibits fluid secretion and intestinal inflammation in response to C *difficile* toxin A. The inflammation and hypersecretion produced by toxin A from C *difficile* are abolished when rats are treated with antisecretory factor (AF). AF also markedly reduces the intestinal fluid response induced by this toxin (66). IL-11 is a novel cytokine that may have a protective effect against gastrointestinal injuries, altering the intestinal effects of C *difficile* toxin A activity. This may occur through the inhibition of the release of inflammatory mediators from mucosal mast cells and intestinal macrophages by IL-11 (67).

Guidelines have been published for the diagnosis and management of patients with C *difficile*-associated diarrhea and colitis (68). The C *difficile* toxin increases intestinal calcitonin gene-related peptide (CGRP) in the ileal mucosa and in the dorsal root ganglia. Pretreatment with a CGRP antagonist before installation of toxin A into ileal loops inhibits the toxin-mediated fluid secretion, as well as the altered mannitol permeability and histological damage (69).

Clinical learning point: An antagonist to CGRP inhibits the effect of C *difficile* on the intestine. AF and IL-11 may have a protective effect. The therapeutic potential of these observations needs to be explored.

Rotavirus: Rotaviruses are the major cause of infectious diarrhea in developing countries as well as in North America. These infections are characterized by viral replication within enterocytes, cell lysis and villus blunting. Rotaviruses contain two outer capsid viral proteins – the spike protein VP4 and the major capsid component VP7. Both of these capsid proteins are implicated in the entry of rotavirus into the cell. This rotavirus VP4-mediated cell entry may involve the 2 1 integrin, whereas VP7 appears to interact with x 2 and 4 1 integrins (70). BBM disaccharidase activities are reduced in rotavirus infection, and osmotically induced watery diarrhea and dehydration may ensue.

Protein-energy malnutrition prolongs diarrhea and delays small intestinal recovery in response to rotavirus infections (71). Natural rotavirus infection results in a specific circulating memory $CD4^+$ response that is limited to the gut-homing 4 7 subpopulation of lymphocytes. This may comprise cellular memory for intestinal antigens. The regulated expression of 4 7 may help to target and segregate intestinal versus systemic immune responses (72).

The rotavirus vaccines that have been evaluated to date are live, attenuated virus vaccines that are derived from bovine or simian strains. These vaccines are delivered orally to mimic natural infections. However, these vaccines have been shown to be only partially protective in humans. Importantly, T and/or B cells are necessary for clearing primary rotavirus infections. $CD8^+$ T cells mediate an in vivo antiviral effect, either by direct lysis of the virus-infected host cell or by the release of cytokines that induce an antiviral effect. This antirotaviral effect of $CD8^+$ T cells is not mediated by

Clinical learning point: Vaccination against rotavirus infection is not yet sufficiently developed for widespread use.

Enterocytes are active participants in the intercellular crosstalk with immune effector cells such as mononuclear cells and neutrophils. This interaction is mediated to a large extent by cytokines, and allows localized and specific modulation of epithelial and immune effector responses. In Caco-2 and HT-29 cells, IFN- and IFN- induce rotaviral resistance. This suggests that cytokines play a role in host defence against viral agents, possibly by changing the phenotype of IECs (27).

Astrovirus: Astroviral infections are a leading cause of acute, nonbacterial gastroenteritis in children. Helper T cells residing in the normal duodenal mucosa of adults recognize a common enteral pathogenic virus, and these $CD4^+$ T cells are presumed to be important in mucosal defense against recurrent astroviral infections (74). Protection against frequent reinfections with astrovirus may be maintained by cellular immune responses in the small intestinal mucosa.

***Blastocystis hominis*:** It is controversial whether *B hominis* is a cause of diarrhea because it is a common inhabitant of the human gastrointestinal tract. A case-control study among German tourists returning from tropical countries suggests that *B hominis* may be associated with the development of diarrhea in travellers to tropical destinations, but the diarrhea may also be associated with concurrent infections (75).

Infections and IBD: The cause of IBD remains elusive, and it is now disputed that a previous measles infection may be important in the cause of Crohn's disease (76). The immunosuppression used to treat some patients with IBD may increase their risk of developing a varicella infection. This is uncommon but must be promptly diagnosed and treated with acyclovir, and with the concomitant reduction in immunosuppressive therapy (ie, reduction in steroid dosage and discontinuation of azathioprine) (77).

DRUG ABSORPTION

Curiously, a glass of grapefruit juice (rich in fructose) increases the bioavailability of some drugs such as nifedipine, verapamil, midazolam and cyclosporin A. This may be the result of selective downregulation by constituents of the fruit juice of CYP3A4, a member of the cytochrome P-450 gene superfamily responsible for the metabolism of different drugs (78). There is considerable variability in the oral bioavailability of beta-lactam antibiotics. These are absorbed by the peptide transport system, as well as by a passive process. Some of the variability in the absorption of this class of drugs is due to the involvement of an energy-dependent efflux system that is distinct from the P-glycoprotein (Pgp)-mediated transporter (79). 5-Fluorouracil is widely used in the treatment of solid tumours, but their bioavailability varies widely due to the large and variable hepatic first-pass extraction (80).

Pgp is one of the important factors involved in the mul-

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