World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i26.3353

World J Gastroenterol 2012 July 14; 18(26): 3353-3374
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

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Recent advances in small bowel diseases: Part Ⅱ

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Received: January 6, 2011 Revised: April 5, 2012
Accepted: April 13, 2012
Published online: July 14, 2012

Abstract

As is the case in all areas of gastroenterology and hepatology, in 2009 and 2010 there were many advances in our knowledge and understanding of small intestinal diseases. Over 1000 publications were reviewed, and the important advances in basic science as well as clinical applications were considered. In Part Ⅱ we review six topics: absorption, short bowel syndrome, smooth muscle function and intestinal motility, tumors, diagnostic imaging, and cystic fibrosis.

Key words: Absorption; Cystic fibrosis; Diagnostic imaging; Intestinal motility; Short bowel syndrome; Smooth muscle function; Tumors

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Thomson ABR, Chopra A, Clandinin MT, Freeman H. Recent advances in small bowel diseases: Part Ⅱ. *World J Gastroenterol* 2012; 18(26): 3353-3374 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i26/3353.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i26.3353

ABSORPTION

Triglycerides

For triglycerides (TG), it has been traditionally considered that lipid uptake is by way of passive permeation through the lipophilic portion of the intestinal brush border membrane (BBM). However, enterocyte-binding or transport proteins have been identified as also being important in this process[1]. Gata4 is a zinc-containing transcription factor, expressed in the epithelium of the upper small intestine, and functions to assist in fat and cholesterol absorption[2]. Lipid micelles at the BBM modulate a large number of genes, and this transcriptome responding to dietary lipids has an impact on cell architecture, signaling and metabolism genes[3]. Most lipids are in the enterocyte, and may be bound to the liver and the intestinal fatty acid (FA) binding proteins (L-FABP and I-FABP). L-/I-FABP function to translocate long chain FAs and monoacylglycerol from the BBM to the endoplasmic reticulum (ER). These long FAs are then used in the resynthesis of diacylglycerol and then triacylglycerol.

The absorption of dietary TG in the small intestine is accompanied by a rise of intestinal alkaline phosphatase (IAP) in the serum, and by the secretion of IAP-containing surfactant-like particles (SLPs) from the enterocytes. IAP is a membrane-bound protein that hydrolyses monophosphate esters at high pH optimum, and limits fat absorption by enterocytes by way of its action as a SLP[4]. Translocation of IAP across the enterocyte BBM occurs within 5 min of lipid intake by way

of induction of endocytosis *via* clathrin-coated pits[5]. After fat has been taken up into the enterocyte, IAP is incorporated into membranes surrounding intracellular lipid droplets, and is also incorporated into basolaterally secreted SLPs. IAP is not associated with chylomicron formation, but rather with chylomicron secretion. Serum IAP levels are correlated with levels of apolipoprotein B-48 (apoB48), a protein exclusive to intestinal chylomicrons in humans[6].

After ingestion of a meal rich in TG, the small intestine continues to form very low density lipoprotein (VLDL), but the predominant TG-rich lipoprotein particles secreted in this postprandial condition are the larger chylomicron particles[7]. In the liver, TG is synthesized and packaged with apoB100 to form VLDL particles, whereas chylomicrons produced by the human gut contain apoB48. ApoB48 provides efficient chylomicron formation and lipid absorption. Apolipoprotein A-IV synthesis in the small intestine is regulated by lipid absorption, and plays a role in the regulation of chylomicron assembly and secretion.

Hepatocyte nuclear factor-4α (HNF-4α) is a nuclear receptor that regulates gene expression during enterocyte differentiation. HNF-4α is also involved with the transcription of genes involved in lipid metabolism, such as *Apo-IV*[8]. In newborn swine intestine, dietary lipid causes ligand-independent transactivation of HNF-4α to induce Apo-A IV and microsomal triglyceride transfer protein (MTP).

The uptake of FAs across the BBM may be partially passive and partially facilitated, mediated by the multiligand scavenger protein CD36. CD36 also participates in the orosensory detection of lipids and the production of the sensation of satiety. Thus, CD36 may play a role in lipid preferences and feeding behaviour[9]. Monoglyceride and free FAs in the cytoplasm reform TG by the successive actions of monoacylglycerol acyltransferase and diacylglycerol acyltransferase at the membrane of the smooth ER. After transfer in the ER lumen, TG droplets associate with primordial lipoprotein comprising apoB48 and phospholipids through the actions of MTP, to form TG-rich lipoproteins (TRL). The lipid droplets fuse with apoB48 plus a resident ER chaperone, MTP. MTP-dependent fusion of lipid droplets with apoB48 in the ER is the crucial restriction point in the formation of chylomicrons. The lipoprotein particle enlarges as more TG is added to the droplet. The maturing lipoprotein particles (prechylomicrons) undergo vectorial vesicular transport through the Golgi membranes. Chylomicrons cross the basolateral membrane (BLM) and into the lacteals.

Glucagon-like peptide-2 (GLP-2) increases lipid absorption, but how does this occur, when enterocytes have no GLP-2 receptors? Perhaps the GLP-2 acts on the enteroendocrine L cells, releasing insulin-like growth factor (IGF-1). GLP-2 increases the glycosylation of CD36 and increases the number of chylomicrons.

After 1 wk of feeding with a high fat diet (HFD) in mice, there is repression of genes involved in FA synthesis, and an increased expression of genes involved n lipoprotein assembly (*apoB*, *MTP*, *apoA-IV*). This process may be coordinated by an increase in the transcription factor SREBP-IC[10]. The number of secreted chylomicrons falls, but there are larger chylomicrons containing increased associated TG, as well as increased amounts and activity of MTP. These changes result in postprandial hypertriglyceridemia, but normal fasting levels of TGs. This postprandial hypertriglyceridemia in the absence of changes in fasting levels may explain some of the risk factors for the development atherosclerosis and cardiovascular diseases.

Cholesterol

Dietary and biliary cholesterols are solubilized by bile acid micelles in the upper intestinal lumen. These are large negatively-charged unilamellar vesicles, smaller mixed micelles or monomeric bile acids. Bile acids promote cholesterol absorption and reduce cholesterol synthesis[11].

It is now recognized that intestinal absorption of cholesterol is a complex process, involving both BBM permeation and cotransporters[12,13]. Uptake of cholesterol from the intestinal lumen across the enterocyte BBM is also mediated by at least five proteins: Niemann-Pick C1-like 1 (NPC1L1), the scavenger receptor B-1 (SR-B1), CD36, the ATP-binding cassette protein 5 (ABCG5) and ATP-binding cassette protein 8 (ABCG8) ATP-binding cassette transporters[14,15]. NPC1L1 protein is predominantly expressed in the liver and in the proximal intestine[16]. Modulation of NPC1L1 expression is by cholesterol, as well as by the involvement of several nuclear receptors, such as liver X receptor (LXR), peroxisome proliferator-activated receptor (PPAR)-α, and by sterol regulatory element (SRE) binding proteins (SREBPs). SREBPs are transcription factors which regulate cholesterol synthesis and metabolism[17]. SSEBP-2 activates the NPC1L1 promoter, which has two sterol regulatory elements.

The ATP-binding cassette transporter ABCG1 promotes cholesterol efflux across the BLM and out of the enterocyte. In contrast, ABCG5/G8 facilitates cholesterol efflux back across the enterocyte BBM and into the intestinal lumen[18]. The ATP-binding cassette transporters are target genes of the nuclear receptor LXR. Mice on a high-fat cholesterol free diet have reduced or downregulated NPC1L1, ABCA1, ABCG5, and ABC8, reduced fractional cholesterol absorption, and a posttranslational increase in 3-hydroxy-3methylgluteral-coenzyme A reductase activity. Downregulation of cholesterol transporters is independent of LXR A[19].

NPC1L1 also occurs in intracellular compartments, and is involved as well in the absorption of dietary saturated FAs such as steric and palmitic acids[20]. The drug ezetimibe binds NPC1L1, reduces intestinal absorption of cholesterol as well as saturated FAs, and reduces weight gain in animals fed a diabetogenic diet. In this way, the drug may protect against diet-induced hyperglycemia and insulin resistance[20]. NPC1L1 and the FA translocase (FAT/CD36), as well as scavenger receptor class B type 1 (SR/B1)

transporter protein, have been shown to be influenced by 5 mmol/L glucose in the intestinal lumen; enhancing protein expression of NPC1L1 and CD36, decreasing SR/B1 protein, but having no effect on the protein expression of ABCA1 and ABCG8[21]. Higher intraluminal glucose concentration increases 3-hydroxy-3methylglutaryl-coenzyme A reductase activity, increasing the transcription factors LXR-α and LXR-β, PPAR-β and PPAR-γ, as well as SREDP2. Thus, reducing the luminal concentration of glucose will also reduce uptake of cholesterol.

Aging enhances cholesterol absorption by suppressing expression of the sterol efflux transporters ABCG5/G8. In contrast, estrogen enhances cholesterol absorption due to upregulated expression of NPC1l1, ABCG5 and ABCG8[22]. Cholesterol absorption is also enhanced in diabetes; medium levels of glucose concentration in Caco-2 cells in culture increase cholesterol uptake as well as the expression of NPC1L1 and CD36 proteins[21].

Liver FA binding protein (L-FABP) increases FA uptake, intracellular transport, esterification, and oxidation in transfected transformed cells, and gene-ablated mice with no L-FABP show reductions in these steps of FA metabolism[23]. L-FABP may also play a role in hepatic cholesterol metabolism[24].

Phytosterols are cholesterol-like compounds found in plants, which reduce cholesterol absorption and plasma concentrations of low density lipoprotein cholesterol. Natural phytosterol glycosides purified from lecithin are bioactive in humans[25].

Two Na^+-coupled (SMIT1 and SMIT2) and one H^+-coupled (HMIT) secondary active intestinal transporters for myo-inositol have been identified[26].

One hypothesis suggests that cholesterol is absorbed by an energy independent passive diffusion process regulated *via* a concentration gradient[14]. The second hypothesis proposes that cholesterol is absorbed through an energy-dependent, protein-mediated process[27].

NPC1L1: NPC1L1 is the main cholesterol transporter in the jejunal BBM[16]. NPC1L1 shares 42% amino acid homology with Niemann-Pick type C1 protein (NPC1), a protein involved in the intracellular transport of cholesterol[28]. Post-translationally, NPC1L1 moves from internal membranes to the mucosal membrane during cellular cholesterol depletion, facilitating absorption[29]. Other studies suggest that NPC1L1 is located at the BBM of enterocytes[30]. NPC1L1 mRNA expression appears to be positively correlated with plasma apoB48 and chylomicron cholesterol content[31].

Scavenger receptor B1: Scavenger receptor B1 (SRB1) is highly expressed in the BBM of the proximal small intestine[32]. Intestinal SRB1 overexpression in transgenic mice has been associated with increased cholesterol absorption[33]. Moreover, antibodies against SRB1 demonstrate abolishment of high affinity binding of cholesterol to BBM vesicles that would normally be observed in *NPC111-/-* mice[32]. SRB1 may play a role in the initial step of cholesterol absorption by facilitating high affinity cholesterol binding to the mucosal BBM, but alternative cholesterol transporters may compensate for the absence of SRB1 in mediating cholesterol absorption in KO models[32].

FAT/CD36: FAT/CD36 (translocase), a human analogue of SRB1, is expressed along the BBM of the duodenum and jejunum. CD36 deficiency correlates with abnormal lipid processing in enterocytes[14].

ABCG5/8: ABCG5 and ABCG8 are located at the enterocyte BBM[14]. Their expression is greatest in the duodenum and jejunum, where they work in tandem to efflux cholesterol (mainly plant sterols) from the enterocyte back into the lumen for excretion[34]. A negative correlation exists between ABCG5/8 and chylomicron cholesterol content[31]. Mutations of *ABCG5* and *ABCG8* in humans enhance intestinal cholesterol absorption, and predisposes these individuals to atherosclerosis[35].

ATP-binding cassette protein 1: ATP-binding cassette protein 1 (ABCA1) not only mediates cholesterol efflux from the basolateral surface of enterocytes to high-density lipoprotein[36], but it also contributes to the efflux of cholesterol out of the enterocyte and back into the intestinal lumen[37].

Bile acids

Bile acids are synthesized from cholesterol in the liver, secreted into the bile ducts, stored in the gallbladder, and intermittently released into the duodenum in response to a meal, where bile acids solubilize lipids in the intestinal lumen by formation of micelles[38]. Bile acids dissociate from the lipids which they stabilize prior to the uptake of the lipids across the BBM of the proximal intestine. The bile acids are absorbed passively along the length of the small intestine. In the ileum, enterocyte BBM sodium-dependent bile acid transporters (ASBTs) also mediate bile acid uptake and bile acids are returned to the portal circulation. This is known as the "enterohepatic" circulation of bile acids. ASBT is, in effect, a salvage mechanism for luminal bile acids, providing for maintenance of cholesterol homeostasis, as well as for efficient lipid absorption.

The apical ASBT in the lipid rafts of the ileal BBM functions in concert with hepatic bile acid efflux transporters to regulate hepatic bile acid synthesis from cholesterol. One of the green tea catechins decreases the maximal transport rate (Vmax) of ASBT, without altering its content in the BBM. This reduction in Vmax is achieved by moving the transporter out of the lipid rafts[39]. This suggests a role for lipid rafts in the modulation of the function of this transporter, reducing the size of the bile acid pool, stimulating the hepatic synthesis of bile acids from cholesterol, and thereby reducing the serum concentration of cholesterol.

Initially, ASBT in the enterocyte cytosol undergoes vesicular trafficking to microdomains in the BBM. These

ASBT lipid rafts are enriched with sphingolipids and cholesterol. Alterations in cholesterol content of the BBM lead to rapid modulation of the activity of ASBT[40]. Obstructive cholestasis leads to downregulation of ASBT mRNA expression. Thus, luminal bile acid levels may be involved in regulation of ASBT gene regulation[41]. In patients with ileal inflammation, such as Crohn's disease, reduced bile acid transport may be due to diminished ASBT protein expression, as the result of ASBT inhibition by inflammatory cytokines *via* direct interactions of c-fos with the ASBT promoter[42].

Once bile acids are in the ileal enterocytes, they bind to ileal bile acid-binding protein (I-BABP). Organic solute transporters (Ost)α and β are located in the BLM of the ileocytes. Ostα/Ostβ expression is induced by bile acids through ligand-dependent transactivation of both *Ost* genes by the nuclear bile acid receptor/farnesoid X receptor (FXR)[43]. "By coordinated control of Ostα/Ostβ expression, bile acids adjust the rate of efflux from enterocytes in response to changes in intracellular bile acid levels". Ostα is a seven transmembrane domain protein, and Ostβ is a single transmembrane domain polypeptide. Ostα-Ostβ is the major BLM transporter of bile acids and conjugated steroids in the intestine, as well as in the kidney and liver[44]. Ostα and Ostβ promoters harbor both FXR and liver receptor homolog-1 (LRH-1) elements. FXR and LRH-1 mediate positive- and negative-feedback regulation, respectively[45].

When the BBM uptake of bile acids is impaired, excess bile acids spill into the large intestine, where bile acids stimulate cAMP and cause a secretory diarrhea. The locally-acting steroid budesonide is beneficial for the symptoms of collagenous colitis, which in turn is associated with bile acid malabsorption. This clinical benefit may be due in part to stimulation of bile acid absorption, with decreased bile acids entering the colon, less stimulation of cAMP, and less secretory diarrhea[46].

Glucose-dependent insulinotropic polypeptide (GIP) is a potent insulin secretagogue. GIP is an incretin, a gut factor released after intestinal transport of hexoses, long-chain FAs and TG, and GIP stimulates insulin secretion at physiological concentrations. GIP is secreted by enteroendocrine K cells in the proximal small intestine. Intestinal lymph contains high concentrations of GIP that respond to both enteral carbohydrate and to fat absorption. The combination of glucose and lipid has a potentiating effect on stimulation of GIP secretion in lymph fistula rats[47].

Approximately 25% of individuals with irritable bowel syndrome (IBS) have a previous history of enteric infection, such as with *Campylobacter* or *Salmonella*. Persistent chronic diarrhea is more frequently associated with infectious IBS, and bile acid malabsorption may be observed in as many as a third of patients with diarrhea-predominant IBS. In a mouse model of IBS, it was shown that ileal uptake of bile acids was reduced. Surprisingly, this was associated not with a decrease but rather with an unexpected increase in expression of the BBM Na^+-dependent bile acid transporter (ASBT)[48].

Bile acids act as detergents to solubilize lipids, but also act as signaling hormones: bile acids activate the G-protein-coupled receptor TGR5, resulting in changes in energy expenditure and glucose homeostasis, as well as having an anti-inflammatory role. Novel patent and selective bile acid derivatives are being developed as TGR5 agonists for possible therapeutic enhancers[49].

Bile acids are synthesized from cholesterol. In the neutral pathway, the rate-limiting enzyme β hydroxylase (Cyp7a7) converts cholesterol to 7-hydroxycholesterol. In the attenuated acidic pathway in mitochondria, sterol 25-hydroxylase or 27-hydroxylase hydroxylates the cholesterol, and a 7β hydroxyl group is added from catalysis by oxysterol 7β hydroxylase (Cyp7b1). The ring structure is then modified, and the side chain is oxidized and shortened, and further hydroxylation occurs to form the primary bile acids, cholic and chenodeoxycholic (chenic) acid. Bile acids regulate their own synthesis by way of negative feedback on the transcription of the rate-limiting enzyme, Cyp7a1. When bile acid concentrations are high, there is activation of the nuclear FXR, which leads to increased transcription of short heterodimeric partner (SHP). Cyp7a1 is activated by the SHP-dependent as well as by the SHP-independent pathway.

The small size of the bile acid pool in neonates is increased as the result of elevated mRNA levels of FXR and SHP, and later by an increase in mRNA and protein levels of Cyp7a1[50]. The increase in Cyp7a1 levels and therefore the increased synthesis of bile acids occurs independently of FXR and SHP, and is not influenced by the administration of sterols[50].

Gangliosides

Gangliosides are sialic acid-containing glycosphingolipids which are found in lipid rafts in outer plasma membranes, such as the BBM of the small intestine. The oligosaccharide portion of the ganglioside faces the cell surface, whereas the lymphatic ceramide portion is anchored into the inner (cytosolic side) layer of the BBM. In the rat intestine, 34% of the glycosphingolipids are gangliosides. The amount of ganglioside in the membranes varies along the intestine, being higher distally than proximally. Gangliosides differ depending upon whether ingested in micelles or unilamellar vesicles. GM3 is localized on the BBM whereas GD3 is mainly localized on the BLM. GD3 uptake into Caco-2 cells is greater across BLM than BBM, and gangliosides taken up by the BLM are largely metabolized by these enterocyte-like cells[51]. In contrast, GD3 uptake across the BBM is time- and concentration-dependent, reaches a plateau, and the GD3 is metabolized, stored, or transported out of the cell across the BLM. GD3 is found in milk and colostrum, and feeding GD3 increases its content in the intestinal lipid rafts, and in the blood membrane: the main ganglioside in the BBM is GM3, whereas GD3 is the main ganglioside in the BLM. This raises the possibility of the oral use of gangliosides to modify or to enhance some of their functions,

such as regulating cell signaling, protein functions, as well as the recognition of microbes and macromolecules.

Sugars

SGLT1, the Na^+-glucose cotransporter in the enterocyte BBM, is a secondary active transport process which requires a favorable intracellular Na^+ gradient. This gradient is provided by Na^+-K^+-ATPase on the BLM of enterocytes. Constitutive nitric oxide (cNO) has opposite effects on the two primary Na^+-absorptive pathways in the mammalian small intestine: reducing cNO inhibits SGLT1 and stimulates the Na^+/H^+ hydrogen exchanger NHE3[52]. cNO also regulates mucosal blood flow, mucous secretion, and intestinal motility. The glucocorticoid-inducible kinase-1 (SGK1) stimulates SGLT1 as well as NHE_3. The effects of glucocorticoid on SGLT1 are fully dependant on SGK1, whereas for NHE_3 the effects of glucocorticoids also involve some additional processes[53].

During chronic intestinal inflammation, there is a transcription-mediated decrease in the number of glucose transporters. This is possibly due to altered binding of Sp1 and Hnf1, transcription binding sites for the SGLT1 promoter regions[54].

When glucose is taken by mouth, there is a fast rise in expression of SGLT1. Intestinal sugar uptake is increased in diabetes and in obesity. Roux-en-Y gastric bypass (RYGB) is a successful form of bariatric surgery. RYGB reduces glucose absorption in the Roux limb, as well as in the remaining intestine[55].

Fructose is prevalent in the diet either as a free hexose, as the disaccharide sucrose, and in the polymerized form, fructans. About 50% of adults are unable to absorb a 25 g load of fructose. Fructans are neither hydrolyzed nor absorbed in the small intestine. This osmotic load may alter intestinal motility and change the microbiota by producing a mucosal biofilm. Restricting dietary intake free of fructose and/or fructan has symptomatic benefits in some persons with diarrhea and bloating[56].

The revised SLC Transporter Gene Tables are available online at http://www.bioparadigms.org/slc/intro.htm.

Carbohydrate malabsorption, as assessed by hydrogen breath testing, is common in persons with Crohn's disease (CD) and celiac disease (CeD)[57]. The absolute increase in the rate of fructose malabsorption is about 20% higher in Crohn's disease, and lactose malabsorption is 30% higher.

The BBM hydrolysis of carbohydrates takes place by the BBM-bound glycoproteins sucrase-isomaltase (SI), maltase-glucoamylase, and lactase-phlorizin hydrolase (LPH). The pro-S1 passes from the ER to the Golgi apparatus. With glycosylation it becomes targeted to the BBM, where it is cleaved by trypsin to form sucrase and isomaltase. Compound heterozygous mutation defects in the protein folding, the direct interaction between sucrase and isomaltase, and an intermolecular chaperone included in the intracellular transport of SI, all have a role in the development of congenital sucrase-isomaltase deficiency[58]. Congenital lactase deficiency results from mutations in the coding region of LPH, with misfolding of LPH which prevents the mutant protein from exiting the ER[59].

Amino acids and proteins

The numerous BBM transporters for amino acids are differentiated functionally by their substrate specificity and driving forces. Neutral amino acids are transported by the system B0+ (Na^+-dependent transporter for neutral and cationic amino acids), as well as by the ASC system (Na^+-dependent transporter for mid-size neutral amino acids).

Glutamine comprises approximately 20% of the total amino acid content in the human blood stream, and as such is an important amino acid. Glutamine is the preferred substrate for enterocytes, and is also important for mucosal integrity and the intestinal permeability barrier. The Na^+-glutamine cotransporter in the BBM of the enterocyte is B0AT1 (SLC6A19)[60]. Glutamine is converted to citrulline in the enterocytes. A citrulline generation test has been developed to assess enterocyte function, and the value of the slope from baseline to peak plasma citrulline concentrations is reduced in persons with celiac disease[61].

Under the influence of cholecystokinin (CCK), bile and pancreatic enzymes are secreted into the duodenal lumen where the pancreatic proteolytic enzymes (trypsin, chymotrypsin, elastase, carboxypeptidase A and carboxypeptidase D) digest proteins and polypeptides into peptides, which are usually 2-6 residues in length. Conjugated bile acids accelerate protein hydrolysis by pancreatic proteases[62].

During chronic intestinal inflammation, there is a decrease in the activity of several transporters such as the short-chain FA-bicarbonate exchanger, H^+-dipeptide cotransporter, Na^+-amino acid transporter, Na^+-glucose cotransporter 1 (SGLT-1), and Na^+-bile acid transporter. There may be a decreased number of SGLT -1 transporters in villus cells (lowering the value of the maximal transport rate, Vmax), and decreased affinity of the cotransporter for Na^+-neutral amino acid transport (increasing the value of the affinity constant, Km).

For amino acids, the reduction in transport during chronic inflammation arises from a decrease in the affinity of the transport systems, and may be mediated through an increase in leukotriene D4 (an eicosanoid pathway product), which is released in chronic inflammation[63].

The proton-amino acid transporter 1 (PEPT1) transports small neutral amino acids as well as small peptides, through mediation of an inwardly directed H^+ gradient across the enterocyte BBM. PEPT1 also transports drugs such as β-lactam and angiotensin-converting enzyme inhibitors. PEPT1 is under diurnal variation, relating to food intake. It is also influenced by transcription factors, such as Sp1, Cdx2, and PPAR-α. Leptin treatment increases enterocyte uptake of di- and tripeptides *via* the PepT1 transporter, through transcription activation of

the MAPK pathway as well as translational activation *via* ribosomal protein S6[64].

The albumin D site-binding protein (DBP) expression is regulated in a circadian manner by oscillators called "circadian clocks". These circadian clocks reside in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. This clock system consists of single-cell circadian oscillators that are composed of several clock genes. The expression of DBP is in phase with that of PEPT1. DBP binds to the DBP binding site in the distal promoter region of the *PEPT1* gene, and thereby induces transcriptional activity[65].

The *SLC6A19* gene encodes the main sodium-independent BBM transporter for neutral amino acids, B0AT1. The expression of B0AT1 requires angiotensin-converting enzyme 2 (ACE2)[66]. It is unknown whether the use of inhibitors of ACE2 in humans alters the protein homeostasis of the body by way of inhibiting the intestinal uptake of neutral amino acids in the small intestine (as well as in the proximal tubule of the kidney).

Small peptides are absorbed predominantly in the proximal small intestine, and free amino acids in the distal intestine. The uptake of sugars is increased by a high carbohydrate diet by upregulation of the Na^+-dependent BBM glucose transporter SGLT, and the amino acid alanine also controls its own absorption, through capsaicin-sensitive primary afferent neuronal fibers as well as by the peptide calcitonin gene-related peptide, CGRP[67].

Glutamines become conditionally essential during metabolic stress. Glutamine prevents apoptosis and also plays a role in regulating glucose metabolism. For example, during fasting as well as in diabetes, the intestine by way of its glucose-6 phosphatase (G6Pase) contributes about a quarter of endogenous glucose production through gluconeogenesis.

After a RYGB, used to treat severe obesity, the glucose sensing vagal afferents in the portal vein influence glucose homeostasis. After RYGB, the absorption of glutamine by B0AT is increased in both the biliopancreatic (3.8-fold increase) and the Roux limbs (1.4-fold increase), but not in the common channel. The levels of glutaminase are also increased, but the levels of GEPase (intestinal gluconeogenesis) and PEPCK-C (cytosolic phosphoenolpyruvate carboxykinase, a measure of glutamine metabolism) were not seen to be affected[68].

Biotin

Biotin is a coenzyme for the "carboxylases" which catalyze essential steps in FA biosynthesis, gluconeogenesis, and catabolism of several amino acids and FAs. Biotin is essential for cellular functions including growth and development. The human intestine utilizes the sodium-dependent multivitamin transporter (hSMVT) for biotin uptake across the enterocyte BBM[69]. The uptake process is adaptively regulated during biotin deficiency, by induction of protein and mRNA levels of hSMVT, mediated by transcriptional regulatory mechanisms.

Two other functionally unrelated nutrients, the water-soluble vitamin pantothenic acid and the metabolically important antioxidant lipoate, share the biotin transport system (hSMVT).

Iron

Dietary non-heme ferric (Fe^{3+}) iron in the intestinal lumen is reduced to the ferrous (Fe^{2+}) form by cytochrome b reductase1 (Cybrd1) in the BBM of the mature villus enterocytes of the proximal small intestine. Iron is transported across the BBM by the divalent-metal ion transporter 1 (DMT1). DMT1 is also known as solute carrier family 11, member 2, (SLC11A2). Fe^{2+} is transported through the cytoplasm of the enterocyte, and is then transferred across the BLM of the enterocyte and into the body by the BLM exporter ferroportin (solute carrier family 40, 1, Slc40a1). There is coordinated expression of ferroportin in enterocytes as well as in tissue macrophages[70].

Ferroxidase (hephaestin) in the BLM promotes the conversion of Fe^{2+} to Fe^{3+}. Once the Fe^{3+} is in the vascular system, it binds to transferrin (Tf). There are two mechanisms by which mRNA levels of iron homeostasis-related genes are regulated; firstly, by post-transcriptional mechanisms mediated by the iron response element/iron regulatory protein system, and secondly, by mechanisms related to transcriptional regulation. In peripheral tissues, the Tf-Tf receptor (TfR) system delivers iron in the Tf-Fe loaded TfR by way of endocytosis. Unlike TfR1, TfR2 mRNA does not contain an Fe-responsive element, and TfR2 mRNA expression is not regulated by intracellular Fe levels. Instead, hepatic TfR2 protein is regulated post-translationally by diferric (Fe^{2+}) transferrin. In this way, TfR2 is a sensor of body iron status, and regulates duodenal Fe^{2+} absorption and liver Fe^{3+} uptake[71]. Hephaestin expression also occurs in gastric antrum, enteric nervous system and pancreatic β-cells[72].

Fe^{2+} uptake across the enterocyte BBM responds to body iron stores, whereas transport across the BLM is regulated by the enterocyte iron status. When the enterocyte intracellular ferritin level is increased, iron will be transferred across the BLM and into the portal blood. In addition to a potential cytoplasmic route for iron across the enterocyte, there is evidence of vesicular transport or transcytosis of apotransferrin (apoTf). Approximately half of iron transfer across the enterocyte BLM is by way of apoTf and non-apoTf-dependent vesicular pathways[73].

Factors that affect hepcidin have recently been reviewed and include body iron stores, rate of erythropoiesis, hypoxia and inflammation[74]. The amount of iron absorbed is regulated by the hepatic synthesis of hepcidin. The most common inheritable form of iron overload is an autosomal recessive disorder caused by mutation in the *HFE* gene, HFE-associated hereditary hemochromatosis (HH). *HFE* codes for a major histocompatibility complex class I (MHC-I)-like molecule. HFE also needs to be associated with a β 2 microglobulin for its appropriate expression of the cell surface.

HFE modulates the expression of hepcidin in the liver. HFE may influence iron status by acting on hepatocytes and/or Kupffer cells, as well as on duodenocytes[75]. Hepcidin inhibits cellular efflux of iron by binding to and inducing degradation of ferroportin[76]. Hepcidin causes ferroportin on the BLM to be internalized and degraded[77]. In macrophages, hepcidin inhibits iron export by inducing ferroportin degradation, whereas in enterocytes hepcidin inhibits DMT1 transcription and thereby reduces BBM iron uptake[76,78]. Other critical regulators of systemic iron homeostasis are intestinal hypoxia-inducible transcription factors (HIFs)[79]. HIFs (HIF-1 and HIF-2) are critical mediators of cellular adaptation to hypoxia. HIF-2α, but not HIF-1α, promotes iron absorption in mice[80].

The normal decline in intestinal iron absorption which occurs from neonatal to adult animals is due to loss of the iron transporters (particularly ferroportin) from the distal small intestine and colon[81]. Curiously, in iron deficiency there is altered intestinal lipid metabolism resulting in production of biologically active lipid molecules (12-HETE, 13-HODE and 13-HOTE), arising as a result of changes in arachidonate12-lipooxygenase (Alox15)[82]. It is unknown if this has any clinical significance.

The cytochrome b reductase in the BBM of the duodenal enterocytes (Dcyt6) reduces dietary iron from Fe^{3+} to Fe^{2+}. Fe^{2+} is transported across the BBM by divalent metal transporter (DMT). The Fe^{2+} is transported into vesicles containing either ferroportin (FPN1) or hephaestin (Heph). These Fe^{2+}-containing FPN1 and Heph-containing vesicles cross the enterocyte cytoplasm to the BLM. The Heph oxidizes the Fe^{2+} to Fe^{3+}. Fe^{3+} binds to transferrin and is released into the circulation[83]. Hepicidin is secreted from the liver in response to the body iron stores: increased body iron stores result in increased hepcidin, decreased FPN1 mRNA expression and increased FPN1 internalization and degradation. The end result of this repositioning of the FPN1 from the BLM is to reduce iron efflux from across the BLM of the duodenocyte, and thereby decrease iron absorption.

Heph, therefore, is a protein in the BLM of the duodenum which has ferroxidase activity to oxidize dietary Fe^{2+} to Fe^{3+}. Heph is also found by immunocytochemistry to extend from the gastric antrum along the length of the entire GI tract, and to be present in both the submucosa and the myenteric plexi of the entire nervous system[72].

In HH, the variable phenotypic expression of the homozygous *HFE* C282Y genotype has been attributed to possible disease-modifying genes which affect the iron transporters. In HH "expressors" and "nonexpressors", there is a significant difference in the expression of *DMT1* and *DMT1 (IRE)*, such that *HFE* C282Y homozygotes without phenotypic expression do not have significantly decreased duodenal gene expression of non-transport genes compared with HH subjects with iron overload[84]. Also, regardless of phenotype, "…there is coordinated regulation between duodenal expression of *FPN1* [ferroportin] and *DMT1* [divalent metal transporter 1], *FPN1* and *DCYTB* [ferriductase duodenal cytochrome b] and *FPN1* and *HEPH* [ferroxidase hephaestin] and also *DCYTB* and *HEPH*…".

Calcium

Canonical transient receptor potential (TRPC)1 acts as a calcium channel, with the total calcium effect being mediated by calcium influx through calcium-permeable channels in the plasma membrane, as well as calcium release from intracellular stores such as the ER and cytoplasmic reticulum[85].

Much of our understanding of calcium (Ca^{2+}) absorption has come from studies in animals. Ca^{2+} enters the enterocyte across the BBM using $TRPV_6$ (aka CAT, or $ECAC_2$), a Ca^{2+} channel. Intracellular Ca^{2+} is bound to calbindin-D9K, maintaining a low intracellular concentration of free Ca^{2+}. PMCAI (a Ca^{2+} ATPase) pumps Ca^{2+} across the BLM. The major storage form of vitamin D is 25-hydroxy vitamin D (25OHD). In humans, 25OHD is metabolized by the gene product of CYP27B1 [25-hydroxy vitamin D 1α-hydroxylase (1αOHase)] to the biologically active 1α, 25-dihydroxycholecalciferol [$1,25(OH)_2O_3$]. 1αOHase forms 25OHD, which increases the transcription of $TRPV_6$, PMCA, and CYP_{24}, thereby enhancing Ca^{2+} absorption[86].

The active hormonal form of vitamin D is 1.25 dihydroxyvitamin D3 [1,25(OH)2D]. 1,25(OH)2D activates the vitamin D receptor (VDR) which heterodimerizes with the retinoid X receptor to interact on response units such as the apical membrane Ca^{2+} channel, TRPV6 (the transient receptor potential cation channel, subfamily V, member 6), and the Ca^{2+} binding protein calcium binding protein D9k (calbindin D9k). VDR and 1,25(OH)2D, acting on TRDV6 and calbindin D9k, maintain high rates of Ca^{2+} absorption[87].

Copper

Copper is a mineral essential for normal growth and development. The level of copper in the body is regulated, because excessive amounts may be toxic. The copper transporter (Ctr1) is copper-specific; its transport function is energy-independent and saturable. Copper efflux from enterocytes across the BLM is mediated by ATP7A. The ability of suckling rat pups to tolerate varying amounts of dietary copper may be due to changes in copper transporters, Ctr1 and ATP7A, facilitated by transcriptional and post translational mechanisms[88].

The Steap proteins on the BBM reduce copper to the cuprous form, which is then transported by Ctr1 across the BBM. In the enterocyte, copper is bound to chaperone Atox1, and reaches ATP7A for export across the BLM[89]. When copper intake is high, Ctr1 is endocytosed into the enterocyte, where there is induction of the copper-binding protein metallothionein, and ATP7A moves to a more basal lateral location. Maturation of small intestinal copper transport occurs by way of increased abundance and local alteration of Ctr1, ATP7A

and ATP7B.

Zinc

The intestinal absorption of zinc is regulated to meet zinc requirements in the body. ZIP4 is a major intestinal zinc transporter; absorptive upregulation of ZIP4 enhances the uptake of zinc from the intestinal lumen, replenishing any deficiency. When the zinc content of the diet is low, there is induction of the transcription factor Kruppel-like factor 4 (KLF4)[90], which leads to increased intestinal zinc uptake, thereby preventing disease manifestations of zinc deficiency such as acrodermatitis enteropathica.

SHORT BOWEL SYNDROME AND TRANSPLANTATION

"Intestinal failure" refers to a condition in which inadequate digestion and/or absorption of nutrients leads to malnutrition and/or dehydration. The most common condition resulting in intestinal failure is the short bowel syndrome (SBS). The SBS occurs following massive resection of the small intestine[91]. SBS may be defined anatomically as less than 30% of the normal intestinal length (less than 200 cm in adults). In the United States, the estimated annual prevalence of SBS in patients who have non-malignant intestinal disease, and who require home parenteral nutrition, is at least 4 per 10^5. The point prevalence is reported to be between 0.6 and 12.7 per 10^5. The commonest cause of SBS is surgical resection of small intestine for Crohn's disease. Other common causes include mesenteric infarction, congenital abnormalities, and multiple strictures due to adhesions or abdominal irradiation.

Early in the adaptive response after an intestinal resection, there is an increase in proliferation of intestinal epithelium, with increased depth of crypts, increased villous height, and increased microvillous surface area. The process of adaptation involves the presence of luminal nutrients, gastrointestinal secretions, the mesenchyme, as well as neuronal and hormonal factors. Expansion of the number of intestinal stem cells (ISC) occurs following intestinal resection. This increases the number of intestinal crypts, through the process of intestinal dilation[92]. These ISCs are located deep in the crypts of Lieberkuhn. Isolation of ISCs has been simplified by the use of side population sorting of viable fractions of cell progenitor characteristics[93].

Wnt proteins are regulators of cell proliferation, differentiation and adhesion. Mutation in mice of the adenomatous polyposis coli (*APC*) gene, together with augmented Wnt signaling in the intestine, results in an enhanced adaptive response to extensive small bowel resection[94]. The increased mucosal surface area occurring following resection is due to sustained increases in crypt depth and villus height. This arises from resetting of proliferative responses, with increases in expression of mRNAs associated with proliferation (c-MYC) and differentiation of goblet cells and Paneth cells[95]. This raises the possibility that early expansion of intestinal secretory lineages within the epithelium may serve to amplify the signal(s) for initiating and sustaining intestinal adaptation. Further proof of concept studies are needed.

The Hedgehog (Hh) signaling pathway plays an important role in epithelial-mesenchymal interactions in gut morphogenesis and in epithelial cell proliferation. Hh proteins are produced in epithelial cells, and interact with underlying mesenchymal/stromal cell receptors. Blocking Hh signaling in the fetus or neonate leads to increased crypt cell proliferation, crypt-villus axis structural abnormalities, and alterations in enterocyte morphology. In Hh antibody-treated mice following intestinal resection, enterocyte migration from the crypt to the villus tip is increased, and apoptosis is also increased[96].

The epidermal growth factor receptor (EGFR) is important in the pathogenesis of intestinal adaptation. This EGFR-mediated induction of enterocyte proliferation requires induced expression of the cyclin-dependent kinase inhibitor p21 to transcribe waf1/cip1, as well as mitogen-activated protein kinase (MAPK)[97]. The cyclin-dependent kinase inhibitor (CDK1) p21waf1/cip1 may be necessary for induction of enterocyte proliferation following initiation of intestinal adaptation[98]. To maintain the new homeostasis achieved with adaptation, the high cell production rate must be matched by an equivalent rate of cell loss. EGFR signaling regulates specific Dcl-2 (Dax and Dcl-w) in the intestinal crypts, and this regulation of Dcl-2 influences apoptosis following extensive small bowel resection[99].

The vascular endothelial growth factor (VEGF) enhances angiogenesis (the growth of new blood vessels from pre-existing blood channels). Angiogenesis is a requirement for successful healing or adaptation. As expected, VEGF is important in the intestinal adaptive response[100].

The bcl-2 family of intracellular proteins has apoptotic properties. An increase in the ratio between pro- and anti-apoptotic members of these pathways occurs after massive small bowel resection, with upregulation of inducers of apoptosis including Fas and TNF-α by way of the death receptor pathway. Angiotensin converting enzyme (ACE) also promotes apoptosis in association with a reduced bax-bcl-2 protein ratio[101]. Thus, ACE may play an important role in epithelial cell adaptive responses.

GLP-2 is released from the ileum and colon in response to nutrients in the intestinal lumen. GLP-2 enhances morphologic and proliferative indices of intestinal adaptation, and this adaptation is inhibited by GLP-2 immunoneutralization[102]. GLP-2 administration enhances intestinal crypt cell proliferation and villus height, and increases expression of glucose transporters. Basal and postprandial GLP-2 levels are correlated with the magnitude of intestinal resection in experimental SBS[103].

A number of hormones and peptides act on the intestinal tract[104]. For example, glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin secretion, pancreatic B-cell proliferation, and reduces lipid absorp-

tion, food intake and the rate of gastric emptying[105]. GLP-2 may reduce Ach release from the enteric nervous system, and thereby reduce neuronally evoked intestinal crypt epithelial Cl^- secretion[106]. GLP-2 enhances the absorption of sugars and lipids[107] and has a therapeutic potential in patients with the SBS[108].

SBS patients with an end jejunostomy and no colon have limited meal-stimulated GLP-2 secretion. This is due to the removal of GLP-2 secreting L cells which are located primarily in the terminal ileum and colon. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant GLP-2 analog, has been administered to enhance the adaptive process in patients with SBS, and to aid intestinal absorption[109]. Thus, there is a therapeutic role for GLP-2 analogs in SBS.

Long-term parenteral nutritional (PN) support may be necessary in persons with SBS. Because of the potential complications of PN, such as infection or cholestatic liver disease, efforts have been undertaken to understand and to improve the intestinal adaptive process, and to thereby enhance nutrient absorption and to possibly reduce the need for PN[110]. The success of surgical procedures designed to optimize intestinal absorptive function, such as bowel tapering or lengthening, has only been modest.

Small intestinal transplantation is an accepted treatment for severe intestinal failure. Over the past 50 years, more than a thousand children have received small bowel transplantation (SBT), alone or with liver and other organs. The one- and five-year graft survival routinely exceeds 90% and 80%, respectively[111]. However, transplantation is usually used only in those persons who have SBS with complications from home PN. With good control of acute rejection and infections, patient and graft survival after small intestinal transplantation is approximately 77% and 65%, respectively. Patient and graft survivals of 60% and 59% are seen in those with combined liver and small bowel transplantation. Unfortunately, almost half of these transplanted patients require enteral nutrition again within two years after transplantation[112]. Thus, small bowel transplantation has its risks and limitations for the SBS patient.

NOD2 is an intercellular microbial sensor present in macrophages, dendritic cells and Paneth cells. *NOD2* polymorphisms may be associated with impaired expression of certain Paneth cell-derived antimicrobial peptides. The likelihood of allograft failure is about one hundredfold higher in small bowel transplantation recipients with mutant *NOD2* alleles, as compared with recipients with wild-type *NOD2* loci[113].

While intestinal stem cell transplantation may play a role in refractory patients with Crohn's disease (CD) or celiac disease, the role of stem cells in treatment of other intestinal disorders remains at an early stage of consideration[114,115].

Patients with short bowel syndrome from other non-CD causes were recently reported to develop CD in the residual intestine. The authors suggested that this shortened intestine may be a predisposing factor because of alterations in the motility of the intestine as well as alterations in the intestinal flora[116]. In persons with a short bowel syndrome, continuous tube feeding alone or with oral feeding enhances nutrient absorption, as compared with oral intake alone[117]. "SBS results from surgical resection, congenital defect, a disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conveniently accepted, normal diet"[118].

SMOOTH MUSCLE FUNCTION AND INTESTINAL MOTILITY

Segmentation in the intestine consists of rhythmic contractions of the inner circular muscle and occurs after meals. These rhythmic contractions are regulated by slow waves, with the enteric nervous system (ENS) having a permissive role. These stationary contractions are independent of slow-wave activity, while simultaneously activating surrounding inhibitory motor neurons[119].

The ENS "…coordinates the peristaltic and secretory activity of the gut and is also involved in the regulation of blood flow and modulation of the immune system"[120]. ENS and enteric glial cells (EGCs) are in the submucosal plexus and the myenteric plexus. The ENS is composed of two ganglionated plexuses, the submucosal and the myenteric plexus, as well as the mucosal plexus. This extends within the lamina muscularis mucosae and the lamina propria mucosae beneath the epithelial lining of the intestine. Activation of human submucosal neurons decreases cellular permeability, and also decreases intestinal epithelial cell proliferation. Neurons respond to changes in intracellular calcium levels or to the expression of activation markers such as c-FOS. TTF-β1 mRNA is expressed and TGF-β1 is secreted by EGCs and they have anti-proliferative effects on intestinal epithelial cells[121]. EGCs promote neuronal survival by regulating substrate supply, and thereby help to maintain neuronal homeostasis. EGCs also synthesize cytokines, and in inflammatory conditions may modulate glia proliferation. Glial disruption alters neurochemical coding of the enteric neurons, and leads to dysmotility[122].

A method has been described for isolation and culture of primary enteric neurons. These cell lines have neuronal characteristics similar to those of primary enteric neurons[123]. It is possible to isolate and expand enteric progenitor cells from human adult tissue[120], thereby providing a potential future role for cell-based therapies for disorders of the ENS.

Patients with IBS may have abnormal colonic transit, as well as increased or decreased rectal sensation. The β3-adrenoceptor (β3-AR) is a member of the family of G-protein-coupled receptors. β3-ARs are co-localized with choline acetyltransferase in human neurons in the cholinergic myenteric and submucosal plexus. Selective β3-AR agonists inhibit cholinergic contractions, and enhance the release of somatostatin without altering carbachol-induced contractions. β3-ARs inhibit cholinergic

contractions and inhibit spontaneous contraction of the human colon, as well as relaxing pre-contracted colonic longitudinal and circular muscle. Somatostatin may act as an endogenous analgesic substance, and a β-adrenergic agonist may modify visceral sensitivity. Solabegron is a β3-AR agonist which has been studied in healthy human volunteers, where it is well tolerated[124]. This raises the possibility that β3-ARs may be useful for the pain suffered by persons with IBS.

The IGF system influences cell development, growth, and apoptosis. IGF-binding proteins (IGFBP-1 to -6) transport IGFs in the blood. IGFBP-3 to -5 are present in human smooth muscle, and modify the interaction of IGF-I with its receptor, IGF-IR. IGFBP-5 has a role in regulating smooth muscle growth independent of IGF-1, by activating the G protein Gi3[125].

Acetylcholine (Ach) is released from cholinergic neurons in the myenteric plexus, and activates M2 and M3 receptors on the smooth muscles of the gastrointestinal tract. This results in smooth muscle contraction. The M2 and M3 receptors are expressed in the ratio of approximately 75%/25%, respectively, and are coupled to TRPC4 and TRPC6 (transient receptor potential channels), which depolarize the intestinal smooth muscle cells[126]. Cholinergic nerves contain substance P, and there are also nitrergic nerves and nerves which release ATP as well as other mediators in the deep muscular plexus.

Substance P (SP)-mediated sustained contraction of the small intestine is negatively regulated at a pre-synaptic level by the M2 receptor, whereas the atropine-sensitive phasic contraction is positively regulated at the M2 receptor[127]. Cytokines exert differential effects on the muscarinic receptors of intestinal longitudinal smooth muscle[128]. Corticotropin-releasing-factor (CRF) acts through both central and peripheral mechanisms. CRF induces Ca^{2+} transients in myenteric neurons *via* a CRF-1 receptor-dependent mechanism[129]. Calcium influx through voltage-operated Ca^{2+} channels, and in particular the R-type channels, causes the calcium transients necessary for muscle contraction.

Nonselective cationic channels in the smooth muscle cells generate muscarinic receptor-induced nonselective cation currents (MICAT), with increased Ca^{2+} influx by way of voltage-dependent Ca^{2+} channels. The Ca^{2+} leads to smooth muscle contraction, and peristalsis.

The gastrointestinal tract contains most of the serotonin (5-hydroxytryptamine, 5-HT) in the body, where it acts as a neurotransmitter, neuromodulator, and a paracrine factor. 5-HT is produced and released by enterochromaffin cells and by enteric nerves of the intestine. In addition to 5-HT having an effect on motility, it also regulates cell survival and proliferation. The 5-HT2D receptors are expressed on the interstitial cells of Cajal (ICC). Exogenous 5-HT regulates the number of ICC through the 5-HT2B receptor, in part by increasing ICC proliferation[130].

The sensory intrinsic primary afferent neurons (IPANs) from an ENS network modify enteric reflexes, which in turn alter gastrointestinal functions. The sensory terminals of IPANs are close to the enterochromaffin cells, which contain serotonin (5-HT). Extrinsic afferents (vagus and spinal afferents) have similar innervation territories, and both respond to chemical and to mechanical stimulation. In response to mechanical stimuli, extrinsic afferent neurons do not crosstalk with the IPANs. 5-HT activates the extrinsic afferents by a Ca^{2+}-dependent pathway which is different from the N-type Ca^{2+} channels in IPANs[131].

The topic of the role of the ICC in gastrointestinal motility has been reviewed[132]. It has become controversial with regard to the way nerves transmit their signals to regulate activity of intestinal smooth muscle[133]: the c-kit receptor may be of importance[134]. ICC help in maintaining the gradient of resting membrane potential, rather than by pacing the slow waves or assisting in their propagation[135]. It is by volume transmission rather than wire transmission *via* the ICC that there is communication between the enteric neuronal varicosities and muscle cells. While the ICC may be impaired in numerous motility disorders, "…a cause-and-effect relationship between ICC impairment and motility dysfunction is not established". In the small intestine, ICC in the deep muscular plexus mediate neurotransmission, whereas ICC surrounding the myenteric plexus generate slow waves. The slow waves are transferred to the adjacent smooth muscles, and can be recorded as straight "…spontaneous, rhythmic, electrical oscillations of the resting membrane potential"[136].

The ICC occur in the myenteric plexus, within either the circular (CM) or longitudinal (LM) muscles, contributing to pacing these muscle slow waves. ICC also line the septa (ICC-SEP) separating circular muscle bundles, and ICC-SEP form an important conduction pathway for spreading excitation deep into muscle bundles in the human jejunum[137]. The $Na^+/K^+/2Cl^-$ cotransporter (NKCC1) is involved in generation of slow waves in the jejunal musculature. ICC at the deep muscular plexus (ICC-DMP) are closely associated with the enteric nerve endings. Varicosities of nitrergic and other nerves are found on ICC-DMP or on CD34-positive, c-kit-negative fibroblast-like cells. The gap junction coupling is necessary for pacing or nerve transmission to the circuit or muscle of the mouse intestine[138].

The ICC act as pacemakers, producing slow waves of depolarization along the intestinal muscle. A transient outward K^+ current may moderate the uptake of the pacemaker potential, resulting in motility arising from the waves of depolarization[139].

Bone morphogenetic protein 2 (BMP-2) is a regulatory molecule which induces the phosphorylation of the Smad1 signaling cascade, and thereby increases the differentiation of the neurons of the ENS[140].

Endogenous adenosine (eADO) is a metabolite of ATP that acts on A1, A2A and A2B receptors on enteric neurons to suppress coordinated responses triggered by immune-histamine H_2 receptor activation[141].

Extracellular adenosine levels control adenosine re-

ceptor signaling. Enzymes that produce CD73 or degrade adenosine deaminase (adenosine), and thereby alter activity of transport systems in the plasma membrane, influence these extracellular adenosine levels, thereby affecting adenosine receptor signaling, which in turn alters intestinal motility[142]. β-Adrenoceptors are G-protein-coupled receptors which, when activated by an agonist, stimulate adenylyl cyclase to produce the second messenger, cAMP. cAMP activates cAMP-dependent protein kinase (PKA). There is compartmentalization of the process by which these proteins form an interaction.

Caveolae are non-clathrin-coded plasma membrane invaginations which are present in a variety of cells, including monocytes. These caveoli are present in microdomains, also known as lipid rafts, an area of the plasma membrane which is rich in cholesterol and sphingolipid. The caveolae are coated on their cytoplasmic side by caveolins, a family of integral membrane proteins including adenylyl cyclase, which are involved in signal transduction. In knockout mice depleted of caveolin-1, there is reduced PKA activity and thereby reduced function of the β-adrenoceptors[143].

Adenosine is generally accepted to be the ligand for the P1 receptor, and ATP is the ligand for P2 receptors. Adenosine A2A receptors on neuronal cells are excitatory in nature, but A1 receptors in the submucosal plexus have inhibitory actions[144]. In the murine enteric nervous system, adenosine "… suppresses synaptic transmission, efferent function of extrinsic capsaicin-sensitive sensory nerves, mucosal reflexes, neuroeffector transmission, and morphine withdrawal diarrhea". Purinergic signaling pathways are important in sensory signaling in enterochromaffin cells and secretomotor reflexes in the intestinal tract; purinergic modulation of synaptic transmission also occurs in human intestine[145].

Intestinal motor activity and secretion are linked, and are changed cyclically in a rhythm called the migrating motor complex (MMC). Submucous neurons are both directly and indirectly mechanosensitive, and myenteric neurons can be activated by stretch. There are both rapid and slow components to the potential difference (PD) response to intestinal stretching or distension. The rapid component operates *via* nicotinic transmission and NK1 receptors; the slow component operates by way of VIPergic transmission and involves both NK1 and NK3 receptors[146].

Intestinal inflammation causes hyperplasia of smooth muscle, and this thickening of the smooth muscle layer results in dysmotility. IL-1β is a proinflammatory cytokine which results in production of PGE2 and NO from macrophages within the ileal smooth muscle tissue, and IL-1β acts as an anti-proliferative mediator[147]. Nematode infection in the small intestine induces a smooth muscle hypercontractility that depends on IL-4 and IL-3 (Th-2 cytokines) activation of the signal transducer and activator of transcription (STAT) 6. 5-HT_{2A} is one of the molecules downstream from STAT6 activation that mediates changes in smooth muscle function[148].

Integrins are a family of transmembrane proteins, and the expression of integrins and their preferred ligands is tissue specific. In the small intestine, occupancy of a specific integrin receptor acts in concert with IGF-I-stimulated receptor tyrosine kinase activity on muscle cell growth[149]. Both insulin and IGF-I prevent apoptosis through the activation of phosphatidylinositosol 3-kinase (PIK3-kinase). Through the subsequent activation of the downstream protein serine/3 kinase, Akt IGF-I stimulates proliferation and inhibits apoptosis in intestinal smooth muscle[150].

Mechanisms underlying the sustained tonic contraction of the intestinal smooth muscle include prolonged myosin-like chain phosphorylation, phosphorylation of cytoskeleton filaments and associated proteins, alterations in Ca^{2+} influx, and increased sensitivity of contractile elements to Ca^{2+}[151]. Muscarinic agonists acting through M3 receptors contract gastrointestinal smooth muscle by a protein kinase C (PKC)-dependent mechanism in the guinea pig ileum; this is thought to be through a novel PKC, PKC-δ[151].

Electrical stimulation may be synchronized with the intrinsic intestinal smooth muscle slow waves [synchronized intestinal electrical stimulation (SIES)]. SIES induces small intestinal contractions during phase I of the MMC in the fed state, and improves postprandial small intestinal hypomotility[152]. SIES remains to be of proven clinical use.

There are olfactory receptors in human mucosal enterochromaffin cells. Odorants present in the luminal environment of the gut may stimulate serotonin release by way of olfactory receptors present in these EC cells[153].

The "ileal break" describes the process by which high concentrations of lipids in the terminal ileum will slow gastric emptying and intestinal transit. High intra-ileal carbohydrate and lipid loads induce phase Ⅲ motility, probably through release of neurohormonal mediators, glucagon-like peptide (GLP-1) and peptideYY (PYY). Physiological postprandial ileal lipid concentrations inhibit human digestive pancreatic protease and bile acid output, but do not influence intestinal motor activity[154].

Acute radiation exposure of the abdomen is associated with accelerated small intestinal transit through involvement of cholinergic receptors. This raises the possibility that M3 receptors "…may provide specific therapeutic targets in acute radiation enteritis"[155]. The mucosal damage in the small intestine produced by abdominal radiation may occur independently of intestinal dysmotility, and may result in diarrhea and nutrient malabsorption. Interestingly, the high molecular weight polyethylene glycol-based copolymer PEG 15-20 prevents radiation-induced intestinal injury in rats, prevents apoptosis and lethal sepsis due to *Pseudomonas aeruginosa* in mice, and protects cultured intestinal epithelial cells from apoptosis and microbial adherence, possibly by binding characteristic lipid raft coalescence during the development of intestinal radiation damage[156].

The mechanisms of drug-associated changes in intes-

tinal motility have been reviewed[157]. Chronic intestinal dysmotility or chronic intestinal pseudo-obstruction may be primary, or secondary to disorders such as diabetes mellitus or scleroderma. These disorders may affect isolated components of the GI tract, or the entire GI tract. There may be absence of the phase Ⅲ component of the MMC, postprandial low amplitude contractions, bursts of sustained uncoordinated phasic contractions, and clusters of contractions. All of these mechanisms contribute to the pathophysiology and the high morbidity of these dysmotility syndromes[158].

Cannabis (CB) and cannabinoid receptors inhibit intestinal motility. The CB1 receptor is present in the central and peripheral nervous system, including the enteric nervous system, as well as in non-neural tissues such as liver and adipose tissue. CB2 receptor expression is present in cells of the immune system as well as in the brain. Lipopolysaccharide (LPS) enhances intestinal transit, and this effect is reversed by cannabinoid CB2 receptor agonists[159].

Lubiprostone is a bicyclic FA compound, a prostone derived from a metabolite of prostaglandin E1. Prostones have highly selective activity on ClC-2 chloride channels, enhancing intestinal fluid secretion, but also accelerating small intestinal and colonic transit[160]. These compounds may be used clinically for the treatment of constipation.

Bowel inflammation may lead to abnormalities in intestinal motor and secretory pattern, through changes in enterochromaffin cell activity, as well as through changes in the excitability of primary afferent neurons of the enteric nervous system. Inflammation at one site of the intestine also alters the cellular components of enteric reflux circuits in non-inflamed regions[161]. Intestinal inflammation is a key event in the pathogenesis of post-operative ileus, and in rats the degree of intestinal paralysis is directly proportional to the degree of intestinal handling and inflammation which occurs at the time of surgery. Intestinal handling triggers mast cell activation and prolongs post-operative ileus[162]. The therapeutic role of this observation in preventing or treating post-operative ileus remains to be proven.

There are three endogenously-produced biologically-active gases, carbon monoxide, hydrogen sulfide and nitric oxide. Methane is also produced by enteric bacteria in one- to two-thirds of humans, and may slow intestinal transit by augmenting small bowel contractile activity[163]. Excess methane production has been recognized in a proportion of persons with constipation-predominant IBS.

Substance P and neurokinin A are the main endogenous tachykinins in the enteric neurons. Stimulation of the NK3R receptor in the GI tract activates protein kinase C, then protein kinase D, leading to noncholinergic slow excitatory postsynaptic potentials in the myenteric intrinsic primary afferent neurons of the guinea pig ileum[164].

The ICC generate pacemaker potentials which drive the electric slow waves that contribute to neuromuscular signaling leading to motor neurotransmission in the GI tract. ICC express receptor tyrosine kinase c-kit. *Kit* gain-of-function mutations lead to hyperplasia of ICC, with maintenance of both pacemaker function and normal enteric neural responses[165]. This is in contrast to the association between fewer ICC and the development of disturbances in GI motility. Ano1 is part of a family of 10 gene products, and labels ICC around ganglia in the deep muscular plexus[166]. Because Ano1 does not label mast cells, it may prove to be a better marker than c-kit for ICC and for mesenchymal tumors.

C-kit immunohistochemistry is used to diagnose gastrointestinal stromal tumors (GIST), since about 94% of mesenchymal tumors are positive for c-kit receptors. Between 80% and 90% of GIST tumors have gain-of-function mutations in *Kit*.

Stimulation of the myenteric plexus of the ENS by food in the intestinal lumen or by stretching of the intestine activates mucosal pathways to produce three different types of slow excitatory post-synaptic potentials (EPSPs) which are mediated by tachykinin or purine nucleotide neurons[167]. The predominant cell type in the ENS, the glial cells, provide functional purinergic neuron-glia communication in the ENS[168].

Myofibroblasts are an intermediate cell type between smooth muscle cells and fibroblasts. In persons with Crohn's disease, there is disruption of the subepithelial myofibroblasts of the epithelial sheath, adding to the suggestion that myofibroblasts may be involved in the pathogenesis of inflammatory bowel disease[169]. This role of myofibroblasts is likely because they serve as a component of the innate immune system, and respond to luminal bacterial adjuvants such as LPS[170].

Manipulation of the intestine rapidly causes activation of the p38 nitrogen-activated protein kinase (MAPK), a stress-activated protein kinase. There is liberation of NO and prostaglandins from the macrophages in the muscularis external to the intestine, and the extravasation of immunocompetent white blood cells[171]. In turn, this leads to postoperative ileus, which can be prevented by giving mice a single preoperative dose of semapimod, which inhibits p38-MAPK and NO production in macrophages. This is an exciting development for its possible future application to humans undergoing abdominal surgery.

An increase in the intracellular concentration of Ca^{2+} in the smooth muscle of the intestine results from the release of Ca^{2+} from intracellular stores, as well as from the entry of Ca^{2+} into the cell through L-type Ca^{2+} channels. With stretching of the wall of the intestine there develops tension in the plasmalemmal membrane. This tension is transmitted to the mechanosensitive L-type Ca^{2+} channels, thereby leading to increased intracellular Ca^{2+} and the possibility for smooth muscle contraction[172].

The peristaltic reflex is mediated by IPANs (intestine sensory efferent neurons), interneurons, as well as excitatory and inhibitory motor neurons. The antipropulsive effect of cannabinoids on the small and large intestine result from the inhibition of the calcitonin gene-related

peptide (CGRP)-containing neurons that begin the peristaltic reflex, as well as the inhibition of both the excitatory cholinergic/tachykininergic and inhibitory VIPergic motor neurons responsible for ascending contraction and descending relaxation, respectively[173].

The balance between myosin light chain kinase (MLCK) and myosin light chain phosphatase (MLCP) controls the overall phosphorylation of the 20-kDa regulatory light chains of myosin Ⅲ. Ca^{2+}-independent contraction of longitudinal ileal smooth muscle is potentiated by a zipper-interacting protein kinase pseudosubstrate peptide[174]. This raises the possibility of developing synthetic peptides from the autoinhibitory region of the smooth muscle myosin light chain kinase to treat hypomotility disorders of the GI tract.

TUMORS

Small bowel cancers represent a heterogenous group of rare tumors, and the prognosis depends upon the cell type. The standardized incidence rate for primary malignant small bowel cancer is $1.2/10^5$ men and $0.8/10^5$ women[175]. The four main histological types are adenocarcinoma (40%), carcinoid (31%), lymphoma (20%) and sarcoma (9%). The five-year survival rate is about 37%, and varies between 57% for neuroendocrine tumors and 18% for sarcomas.

The gastrointestinal tract is the most common extranodal site for non-Hodgkin's lymphoma (NHL). GI NHL may be primary or secondary, the latter usually representing involvement from diffuse nodal disease. GI NHL used to be increased in the HIV-positive population, but with HAART therapy, GI NHL has virtually disappeared[176]. One intestinal nuclear receptor map has been developed, which "…indicates that the localization pattern of a receptor in normal intestine (signature) predicts the modulation of its expression in tumors"[177].

DIAGNOSTIC IMAGING

Imaging techniques for the small intestine include the classic small bowel series, enteroclysis, CT enterography, MR enterography, and more recently capsule endoscopy (CE), push enteroscopy (PE), and double balloon enteroscopy (DBE)[178]. The topic of recent developments in CE has been reviewed[179-182]. Optimal bowel preparation for CE is a PEG solution plus simethicone[183]. Using duodenal histology as the gold standard, the performance characteristics of CE for the diagnosis of celiac disease are: sensitivity 88% (95% CI: 76%-99%), specificity 91% (95% CI: 81%-100%), positive predictive value 97% (95% CI: 90%-100%), negative predictive value 71% (95% CI: 56%-87%), as well as positive and negative likelihood ratios of 9.6 and 0.14, respectively[184]. Of 43 celiac patients, 42% had mucosal changes extending beyond the duodenum, and in 7% the alterations involved the entire small intestine. Interobserver agreement for the diagnosis of celiac disease by CE ranges between 79% and 94%; and κ values range between 0.6 and 0.9. Murray *et al*[185] reported a sensitivity of CE for the detection of small intestinal mucosal atrophy, as compared with upper endoscopy, to be 92% *vs* 55% ($P = 0.0005$), with a specificity of 100%. Other authors have agreed with this high sensitivity of CE (over 90%), but reported a much lower specificity of approximately 64%[186].

The topic of small bowel enteroscopy has been reviewed[187]. CE is contraindicated under a number of circumstances[188]: (1) Swallowing disorder; (2) Known or suspected intestinal obstruction, strictures, or fistulae; (3) Pregnancy; (4) Children less than 10 years old; and (5) Persons with implanted electromedical devices.

In 120 persons on long-term NSAIDs or COX-2 selective agents, CE demonstrated that the 62% with abnormal CE had denuded areas (39%), mucosal breaks (29%), or reddened folds (13%)[189]. CE demonstrated small intestinal polyps in 60% of subjects with familial adenomatous polyposis (FAP) and in 75% of subjects with Peutz-Jeghers Syndrome[190].

A meta-analysis of nine studies compared CE *vs* other diagnostic methods for Crohn's disease. The diagnostic yield for CE *vs* barium radiography was 63% and 23%, respectively. The yield for CE *vs* ileoscopy was 61% and 46%, respectively, and the yield of CE compared to computed tomography (CT) enterography/CT enteroclysis was 69% and 30%, respectively. A meta-analysis of the yield of CE *vs* other modality examinations of the small intestine in patients with non-stricturing Crohn's disease showed that CE was superior to small bowel barium radiography, ileoscopy, CT enterography, CT enteroclysis and PE, as well as small bowel magnetic resonance imaging (MRI)[191]. In patients with previous surgical resection for Crohn's disease, CE is inferior to ileocolonoscopy, but does detect about two-thirds of lesions outside the reach of the colonoscope[192]. These authors suggest that CE "…cannot systematically replace ileocolonoscopy in the regular management of patients after surgery" (for Crohn's disease). The CE findings have an impact on patient management: physicians change post-CE diagnostic strategy in 61% of patients[193]. Clearly, CE has proven its diagnostic potential.

There is an incremental diagnostic yield (yield of CE minus yield of comparative modality) of 38% comparing CE to PE, and 22% compared to small bowel MRI. As compared with PE, CE provides superior identification of obscure bleeding sites in the small intestine (50% *vs* 24%). While CE missed 8% of lesions, these sites were accessible to standard endoscopy; in contrast, PE missed lesions in 26% of patients[194].

DBE may be used from the oral or anal route, or from both. The overall detection rate of small bowel diseases using CE is superior to that with DBE (72% *vs* 41%, respectively), and is also superior for the detection of small bowel diseases in patients with obscure gastrointestinal bleeding (88% *vs* 60%, respectively)[195]. In another study, for detection of causes of obscure gastrointestinal bleeding, 80% of small bowel abnormalities were detected by

CE *vs* 60% with DBE[196]. PE may be inferior to push-and-pull enteroscopy to find lesions in patients with suspected small bowel bleeding[197]. DBE performance has also been evaluated in patients with refractory CD who had circumferential, discreet, or confluent ulcerations[196].

When patients with acute intestinal symptoms after allogeneic stem cell transplantation underwent esophagogastroduodenoscopy (EGD) with duodenal biopsies, as well as CE within 24 h of the onset of their symptoms, acute intestinal graft-*vs*-host disease (GVHD) was diagnosed by EGD with biopsies in 7 out of 13 patients, 3 of whom would have been missed by EGD alone but were detected by CE. In all 7 patients with histologically confirmed acute intestinal GVHD, CE revealed the typical lesions of GVHD[198]. The authors concluded that CE showed comparable sensitivity with EGD plus biopsies, and CE also demonstrated a high negative predictive value for diagnosing acute intestinal GVHD.

After the formation of an ileal pouch anal anastomosis (IPAA) in patients having a colectomy for ulcerative colitis, development of pouchitis is common. It is unknown how frequently lesions occur elsewhere in the small intestine. At small bowel follow-through of persons with pouchitis, 13% showed a focal ectasia of the middle ileum and a stenosis of the pouch, whereas CE performed in patients with chronic pouchitis after IPAA showed diffuse lesions from the duodenum to the ileum in all evaluable patients[199]. These lesions included apthous ulcers, erosions, redness, atrophy, cobblestoning, and deep ulcers or fissures.

A retrospective analysis of the charts of 562 patients who underwent CE at the Mount Sinai Medical Centre (NYC) for a variety of indications showed small bowel tumors in 9%[200]. In a report of the largest series of patients with small bowel tumors detected by CE, half were identified in the jejunum and approximately a quarter were in the ileum or in the mid to distal small bowel[201]. The most common malignant small bowel tumors were adenocarcinoma, carcinoids, melanomas, lymphomas and sarcomas. The most common benign tumors were GIST, hemangiomas, hamartomas, adenomas, and granulation tissue polyps. In a three-center report of Australian experiences with CE, the usefulness of CE was also confirmed, and the authors suggested that "in many patients, detection of a tumor alters management and improves outcomes"[202].

CE found a median of four small bowel polyps greater than 1 cm in size in persons with Peutz-Jeghers syndrome, while barium follow-through detected a median of only one polyp[203]. In persons with known familial adenomatous polyposis (FAP), regular examination of the small intestine for small intestinal tumors is part of the recommended management. CE detected ileal or jejunal polyps in 30% of patients, and all polyps were less than 5 mm in size. Upper gastrointestinal endoscopy detected duodenal polyps in 11 of 23 patients, and only four of these patients were identified as having duodenal polyps on CE. Thus, CE underestimated the number of polyps and did not visualize the ampulla of Vater. This suggests that CE is useful for detection of jejunal and ileal polyps in patients with FAP, but standard forward- and side-viewing endoscopic procedures are advised for detection of duodenal polyps[204].

While duodenal biopsy represents the gold standard for the diagnosis of celiac disease, CE has shown that over a third of celiac patients have mucosal changes extending beyond the duodenum, and in approximately 7% the entire small bowel is involved[184]. As compared with duodenal biopsy for detecting celiac disease, the sensitivity of CE was 88%, specificity 91%, positive predictive value 97%, and negative predictive value 71%.

Although CE provides excellent visualization of the small intestinal epithelium, if a small bowel lesion is identified, it cannot be biopsied. DBE is clinically useful to identify and biopsy such lesions[205-210].

Because of the varying values of the sensitivity and specificity of the various diagnostic methods available to diagnose small bowel disease (such as capsule endoscopy, CT- or MRI- enteroscopy, ileocolonoscopy, small bowel follow-through), it is suggested that except for CE, "…a combination of two of the other available imaging methods is the best diagnostic option for small-bowel Crohn's disease…"[211,212]. While CE gives a diagnostic yield in about two-thirds of patients with obscure gastrointestinal bleeding, DBE (when used within 1 mo after the last episode of overt bleeding) reveals positive findings in 84% and provides a means to control bleeding in 64%[213].

CYSTIC FIBROSIS

Meconium ileus occurs in approximately 20% of newborns with cystic fibrosis (CF). The distal intestinal obstruction syndrome (DIOS) occurs in about 25% of CF adults. Mucus accumulation in the CF intestine is partly due to the dehydrated, acidic environment, as well as to the altered glycosylation of mucins. Mucin glycoprotein levels are increased, due to reduced mucus clearance rather than an enhanced synthesis. This is suggested by the lack of increase in the levels of expression of the major intestinal mucin genes (*Muc2*, *Muc3*). Interestingly, Muc1 is not a major component of the accumulated mucus of CF mice[214]. Mucin binds bacteria, both by nonspecific trapping as well as by binding to specific glycans, which help to carry bacteria aborally for efficient clearance from the small intestine.

In human CF, there are mutations in the *CFTR* gene that result in little or no cystic fibrosis transmembrane conductance regulator (CFTR) activity. Some 30%-50% of CF patients have small intestinal bacterial overgrowth (SIBO), thought to be due to slow small intestinal transit[215]. This SIBO may be due to impaired migrating motor complexes, which lead to less removal of mucus and bacteria from the small intestine. Laxatives and N-acetylcysteine (NAC) reduce bacterial overgrowth in the CF intestine of mice, and this eradication is associated with normalized intestinal transit and a reduction in the innate

immune response[215].

Exogeneous pancreatic replacement enzyme therapy improves, but does not normalize, steatorrhea in CF patients. In CF mice, the crypt-villus axis height is decreased, there are fewer apoptotic cells in the intestinal crypts; there is also goblet cell hyperplasia and inflammatory cell infiltration[216]. In humans with CF, there is more than just defective lipolytic enzyme activity leading to the malabsorption of lipids. Indeed, there is evidence for abnormal enterocyte intracellular lipid processing in intestinal biopsies from CF subjects, such as decreased lipid esterification and lipid secretion, decreased output of triglyceride-rich lipoproteins, as well as diminished synthesis of apoB48 and apoA-1[217].

Factors that may contribute to the incomplete normalization of fat malabsorption in CF patients who are compliant with their intake of adequate amounts of pancreatic replacement enzymes include the use of outdated or inactivated enzymes, incorrect timing of the intake of the supplements with regards to meals, excessive duodenal acid inactivation of the enzymes, or reduced duodenal and pancreatic bicarbonate secretion leading to high intraduodenal acid concentrations, impaired formation of mixed micelles, altered composition of the BBM [decreased linoleic acid (18:2n-6) and docosahexaenoic acid (26:6n-3), as well as increased arachidonic acid (20:4n-6) and elevated (20:3n-9) to (20:4n-6) ES] with changes in its permeability and absorptive function, impaired esterification of lipids in the enterocytes, reduced apolipoprotein synthesis, chylomicron formation or secretion across the BLM. CFTR knockdown in Caco-2 cells stimulates both the synthesis and transport of fat but not cholesterol[218].

Approaches are needed to prevent the CF-associated increased viscosity of the intestinal luminal contents, and hopefully reduce the frequency of meconium ileus in CF newborns, or DIOS in CF adults. The activation of proteinase-activated receptors on the BLM of enterocytes by EGFR activation, MAP kinase signaling, Ca^{2+}, PKA (and possibly PKC), causes chloride secretion. PKC enhances the activation of PKA, or increases BLM NKCCI, thereby enhancing the phosphorylation of CFTR, and thus Cl^- and water secretion. Basolateral PAR2-induced Cl^- secretion induces the activation of PKCBI and PKCS *via* a phospholipase C mechanism, which results in the stimulation of cRaf and ERK 1/2 signaling[219]. Reduction of NHE3-mediated Na^+ and water absorption helps to increase the fluidity of the intestinal contents that would otherwise be very thick and dehydrated if NHE3 activity remained normal in the presence of reduced CFTR activity[220]. Lubiprostone activates CIC-2 chloride channels, causing Cl^- and water secretion[221].

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