Update in small bowel physiology: Part 1

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ABSTRACT: The recent advances in clinically important diseases of the small intestine have been reviewed; however, the basis for many of these clinical advances rests with important observations on alterations in the physiology of the small intestine, as well as mechanistic observations of alterations in small intestinal function in models of human disease. In this review a summary of the past year's literature is presented which will draw attention to the considerable areas of progress in small bowel physiology which will soon be translated into an improved understanding of the pathophysiology of a variety of intestinal disorders. **Can J Gastroenterol 1990;4(6)243-254**

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Derniers développements dans la physiologie du grêle: Première partie

RESUME: Le présent article procède à la revue des progrès récemment réalisés dans les maladies du grêle qui sont d'intérêt clinique; néanmoins, nombre de ces progrès cliniques sont fondés sur des observations importantes des altérations de la physiologie du grêle, ainsi que sur des observations mécaniques des altérations fonctionnelles du grêle dans des modèles expérimentaux de maladies humaines. Les auteurs proposent un sommaire de la littérature de l'année précédente, soulignant ainsi l'ampleur considérable des progrès réalisés dans la physiologie de l'intestin grêle, lesquels se traduiront bientôt par une meilleure compréhension de la physiopathologie d'une variété d'affections intestinales.

THE RECENT ADVANCES IN CLINICALLY important diseases of the small intestine have been reviewed (1); however, the basis for many of these clinical advances rests with important observations on alterations in the physiology of the small intestine, as well as mechanistic observations of alterations in small intestinal function in models of human disease. In this review, a summary of the past year's literature is presented which draws attention to the considerable progress in small bowel physiology which will soon be translated into an improved understanding of the pathophysiology of a variety of intestinal disorders.

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CARBOHYDRATES

The molecular organization of the intestinal brush border membrane (BBM) has been reviewed (2). Unique isoactins have been identified in the BBM of rat intestinal epithelial cells (3). The plasma membranes of most mammalian cells have an externally exposed layer of carbohydrates. These carbohydrate moieties are associated with glycoproteins and glycolipids, playing an important role in growth regulation, cell adhesion, recognition and antigenicity. There are differences in the glycoprotein and glycolipid compositions of BBM and basolateral membranes (BLM) of rat small intestine (4). Perhaps the best characterized of the stalked membrane proteins is the sucrase-isomaltase complex which projects from the BBM surface into the intestinal lumen. Phospholipase B also has the characteristics of a stalked BBM protein (5).

Glucose: Intestinal uptake of glucose is initiated by sodium-dependent transport across the BBM. Intracellular glucose is released into the blood across the BLM through a facilitated glucose transporter. The biology and biochemistry of the glucose transporter

have been reviewed (6). Wright and co-workers (7) have cloned and sequenced the rabbit BBM sodium/glucose cotransporter. It has no sequence homology to either of the two cloned facilitated-diffusion glucose transporters. The sodium/glucose cotransporter gene has been identified on human chromosome 22 (8). This chromosomal localization of the gene may be helpful in elucidating the molecular basis of the rare autosomal recessive disorder 'glucose/galactose malabsorption', and will improve understanding of glucose transporter processing and its control at the molecular level.

Thorens and colleagues (9) have reported the cloning and functional expression of a facilitated-diffusion liver glucose transporter. This transporter is also present in the intestine, the kidney and the beta cells of the islet of Langerhans. It is different from the well characterized erythrocyte glucose transporter which is also expressed in brain, adipocytes, kidney, muscle and transformed cells. This liver glucose transporter perhaps represents the glucose permease of the BLM, which may be rapidly regulated by a combination of modulation of carriers already in the membrane and subsequent changes in carrier site density (10).

Human intestinal vesicles: D-glucose and L-leucine transport have been characterized in human intestinal BBM vesicles obtained from organ donor intestine. The magnitude of their transport under sodium gradient conditions is higher for proximal than distal intestine (11). Eadie-Hofstee plot analysis suggests that there is a high-affinity transport system along the length of the human small intestine. A second low-affinity high-flux transport system is limited to the jejunum. It has been suggested that two glucose transporters coexist in animal intestine (12). D-glucose transport into rat jejunal BBM vesicles is unaffected by the variation in morphology arising from the technique used to purify the membranes. Membrane preparations yielded similar Hofstee transformations, displaying the curvilinear relationship thought to be consistent with the existence of multiple BBM transporters for D-glucose (13). Both high- and low-affinity transporters for D-glucose are fully expressed in the small intestine when glucose uptake is measured in BBM vesicles of newborn piglets (14). It must be stressed, however, that two glucose transporters in the BBM have not been identified by methods of molecular biology.

Adaptive regulation: The BBM glucose transporter is subject to adaptive regulation. It is possible but as yet unproven, that there is a single BBM sodium/glucose cotransporter which has different kinetic properties dependent, for example, on the dietary content of lipids. Brasitus and co-workers (15) have demonstrated that BBM vesicles obtained from jejunal enterocytes of rats fed fish oil (an omega-3 polyunsaturated fatty acid-containing lipid) have a higher maximal transport rate than vesicles obtained from animals fed butter fat (saturated fatty acids). Rates of sodium-dependent glucose transport are high in the villus tip but lower in enterocytes from the crypts (16). These kinetic differences may be due to variations in the fluidity of the BBM (17).

Activation of the sodium/glucose cotransporter alters absorptive cell tight junction permeability, thereby allowing substantial paracellular glucose absorption (18). Glucose absorption and lactate reabsorption across the BBM are driven by transmembrane sodium gradients generated by the Na^+,K^+-ATPase of the BLM. Vanadium is a powerful inhibitor of membrane-bound Na^+,K^+-ATPase, and in rat intestine has a concentration-dependent effect on glucose absorption and metabolism (19).

Signals involved in the regulation of intestinal glucose transport are currently being defined. Hyperglycemia due to either glucose infusion or streptozotocin-induced diabetes mellitus enhances intestinal glucose absorption. Changes in plasma insulin but not glucose concentrations cause specific and reversible increases in the maximal transport rate of intestinal glucose absorption, with hypoinsulinemia having a more potent signal than hyperinsulinemia (20). It is unknown whether this effect of insulin is at the level of the BBM or the BLM, since events occurring both in the intestinal lumen and at the interface between the lumen and the BBM may influence carbohydrate absorption. For example, dietary carbohydrate load modulates intestinal glucose transport, as does the type of dietary lipid (15).

Fibre: A reduction in glucose uptake is achieved by adding pectin (a soluble dietary fibre) to the intestinal perfusate. This is due to enhanced intestinal unstirred water layer resistance, rather than to a membrane-related phenomenon (21). Pectin also induces hyperplasia of the small intestinal mucosa and increases enzyme activity in the ileal BBM in rats (22).

Glucose transport in the small intestine is reduced in animals infected with *Giardia lamblia* (23). It is enhanced in hyperthyroid chicks (24). Interestingly, in a megacolonic mouse model for Hirschsprung's disease, disease of the colon and associated growth retardation result in adaptive enhancement of small intestinal absorption of glucose (25). The mechanism(s) of this proximal adaptation is unclear. It is unknown whether other colonic diseases also lead to small intestinal adaptation.

Hydrolase inhibitors: Acarbose, a competitive inhibitor of intestinal alpha-glucoside hydrolases obtained from bacteria, is a complex oligosaccharide with a molecular weight of 645 Daltons. It acts as a competitive inhibitor of BBM sucrase-isomaltase. Acarbose also reduces the hydrolytic degradation of starch. Inhibition of glucosidase by acarbose results in starch malabsorption, with resultant increased stool weight, water content and transit time. Breath hydrogen is increased, likely due to stimulation of fermentation in the large intestine (26). After acarbose administration, ileal loads of glucose and total carbohydrates are considerably higher, whereas postprandial plasma concentrations of glucose, insulin and gastric inhibitory polypeptide are lower (27). Insulin response is reduced but enteroglucagon response is enhanced (28). This is likely due to retention of hyperosmotic unabsorbed carbohydrate in the distal intestine and

proximal colon. The absorption of proteins, triglycerides and monosaccharides is unaffected by acarbose (29). In clinical studies acarbose has been found effectively to lower meal-induced hyperglycemic responses in insulin-dependent and noninsulin-dependent diabetics. Its use in the treatment of obesity is unclear.

D-xylose: The D-xylose tolerance test is used in clinical practice to assess small intestinal function. In vivo perfusion studies as well as in vitro uptake experiments using human jejunal BBM vesicles have suggested that at concentrations used clinically D-xylose absorption occurs by passive diffusion, and that this process overrides a minor D-glucose cotransport component (30). Thus, the D-xylose tolerance test likely reflects the state of the jejunal mucosal BBM surface area and passive intestinal permeability rather than active nutrient absorption capacity.

AMINO ACIDS, PROTEINS AND PEPTIDES

Proteins which contain large amounts of proline are not readily hydrolyzed by most digestive proteases. Yet proteins such as collagen, gliadin and casein are important dietary constituents. BBM carboxypeptidase may play an important role in the digestion of proline-containing peptides and proteins (31). The carboxypeptidase in BBM of rat enterocytes is distinct from pancreatic proteases, has maximal activity in the mid-region of the small intestine, and is twice as active in villus as in crypt cells.

Glutamine, a neutral nonessential amino acid, acts as a precursor for other amino acids and for various nucleotides. The small intestine is a major site of glutamine metabolism. Glutamine is delivered to the small intestine from the lumen as well as from the arterial blood supply, and is rapidly hydrolyzed under the action of BBM transpeptidases and intracellular glutaminases. Glutamine uptake into dog BBM vesicles occurs via two transport processes: a sodium-dependent high-affinity system similar to the neutral BBM system and a sodium-independent lower-affinity pathway (32).

Taurine is a beta-amino acid that represents one of the most abundant free amino acids in the body. It can be synthesized in adult humans, but biosynthetic capacity is almost negligible in the human fetus and infant. Thus, intestinal absorption of dietary taurine probably represents the only source of this essential nutrient during early postnatal development. Intestinal absorption may also be important in meeting taurine requirements in adults. Uptake is sodium-dependent, with one chloride and three sodium ions involved for the transport of each taurine molecule (33).

In humans, very little is known about the intestinal absorption of acidic amino acids. In human BBM vesicles, L-glutamic, L-aspartic and D-aspartic acids are transported in an electroneutral manner, using an inward sodium and outward potassium gradient (34).

Peptides consisting of three or possibly four amino acids may be actively transported across the intestinal mucosa (35). Absorption of fragments intermediate in size between oligopeptides and intact proteins has been demonstrated in mature animals. In suckling rats, prolactin is selectively and nonselectively absorbed in the jejunum and ileum. It is directed either to lysosomes for degradation or across enterocytes by means of an undefined transcellular pathway (36).

Dietary influences: The interplay between physiology and ecology in digestion has been reviewed (37). Regulation of intestinal absorption by dietary substrate levels has received much attention in the case of sugar and amino acids. The naturally occurring dipeptide carnosine is absorbed intact from the gut lumen and is not hydrolyzed until it reaches the liver and kidneys. A high protein diet stimulates carnosine uptake into everted intestinal sleeves of mice, even in the presence of peptidase inhibitors that block cell surface hydrolysis of dipeptides. Thus, carnosine uptake is regulated by dietary levels of amino acids, peptides and proteins, all of which seem equally effective in the induction of carnosine transporters (38). However, the regulators of each process involved in protein digestion are not necessarily that process's substrate (39).

Food hypersensitivity: The topic of diseases of food hypersensitivity has been reviewed (40). Food intolerance is a common but controversial clinical problem. The majority of allergic reactions appear to be due to a type I immunoglobulin E (IgE)-dependent hypersensitivity. In an animal model of anaphylaxis, immune-mediated reaction to food protein was associated with diarrhea as well as altered intestinal myoelectric and motor activity (41). The mucosa may appear structurally normal by light microscopy. In 10 infants and children with chronic diarrhea associated with dietary protein intolerance, the most striking and consistent finding on scanning and electron microscopy of enterocytes was the widespread loss of surface glycocalyx from the surface of enterocytes (42).

Immediate (type I) hypersensitivity reactions in the gut are frequently accompanied by disturbed intestinal function including vomiting, abdominal cramps and diarrhea. When rats are infected with *Trichinella spiralis*, there is mast cell proliferation in the muscle layers of the small bowel. Re-exposure to antigen results in mast cell degranulation, 5-hydroxytryptamine release and contraction of smooth muscle (43). The extent and severity of mucosal damage in the proximal duodenum and jejunum has a critical bearing on the development of clinical symptoms in children with cow's milk protein-sensitive enteropathy (44). An association between non-IgE milk enteropathy and previous rotavirus infection has been demonstrated (45). It has been postulated that viral infections induce deregulation of T suppressor cell function leading to increased IgE synthesis. Dietary protein hypersensitivity is probably not the cause of colic in most healthy young infants (46). Cow's milk allergy occurs with gastrointestinal manifestations during early infancy and can be elicited by the ingestion of single cow's milk proteins. Developmental changes altering the interaction between these proteins and elements of the small intestinal mucosal

barrier are of interest to the pediatrician. Newborn BBM binds more cow's milk proteins than adult controls with increased binding of lower relative to higher molecular weight proteins.

Bovine milk proteins are a major source of dietary proteins for humans and are often incriminated in the development of hypersensitivity reactions. The casein in milk is degraded by proteolytic enzymes in the gastrointestinal tract, but the whey protein fraction (beta-lactoglobulin) is resistant to intraluminal digestion and may therefore be responsible for milk protein immunoreactivity and intolerance. Infants may develop food sensitivity when gastrointestinal permeation of intact food antigens leads to systemic absorption and sensitization, with immunologic damage to the gastrointestinal tract developing when the same food is ingested a second time. Beta-lactoglobulin is absorbed by the intestinal mucosa of adult rabbits by a transcellular route as measured by enzyme-linked immunosorbent assay and radiolabelled protein transfer (47).

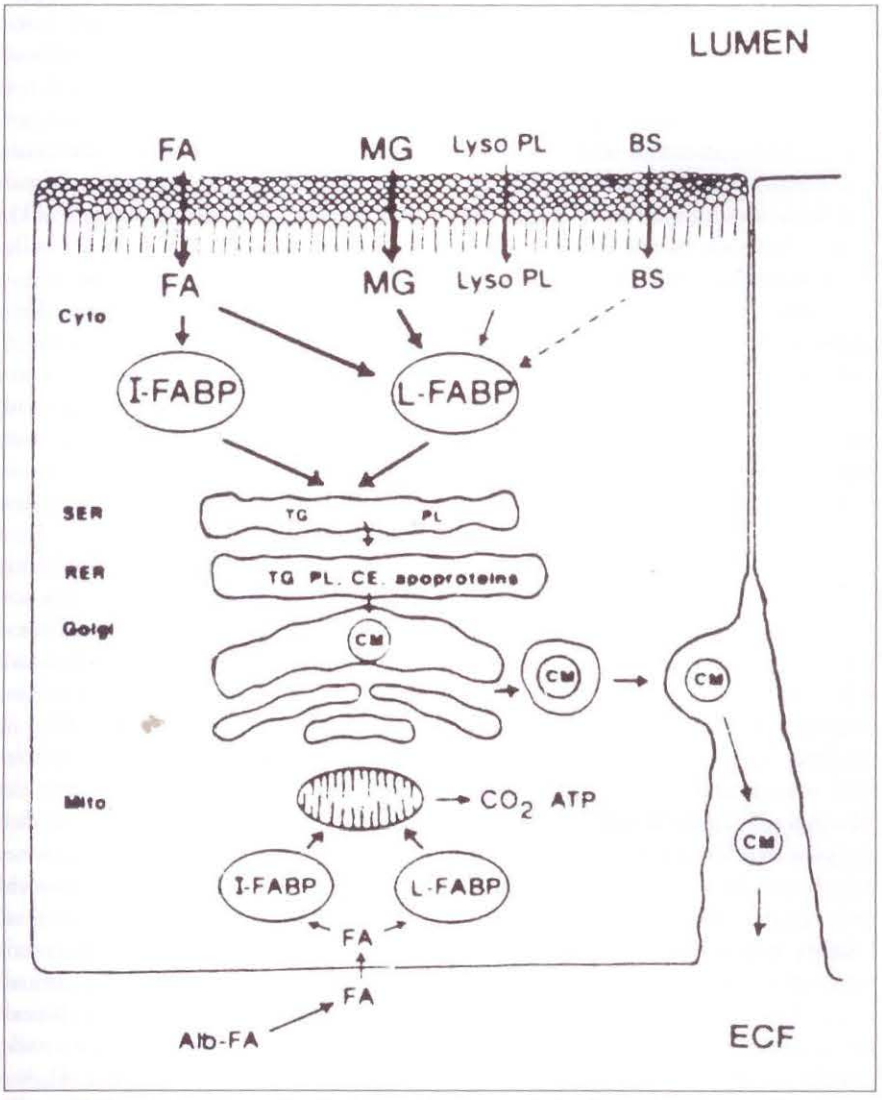

Figure 1) *Hypothetical scheme for the distinct roles of intestinal and liver fatty acid-binding proteins (I-FABP and L-FABP) in lipid uptake and transport in small intestinal enterocytes. Fatty acid (FA) produced by the action of pancreatic lipase on dietary triglyceride in the intestinal lumen translocates across the brush border membrane and binds to cytosolic intestinal fatty acid-binding protein (proposed to be a fatty acid-specific transport protein) and liver fatty acid-binding protein (proposed to be a nonspecific lipid transport protein). Other absorbed lipids such as 2-monoacylglycerols, lysophospholipids, and bile salts (in the distal ileum) putatively bind to liver and intestinal fatty acid-binding protein, and liver fatty acid-binding proteins increase the solubility of these lipids in the cytosol (Cyto) and facilitate their transport to the smooth endoplasmic reticulum (SER) where activation and esterification enzymes are located. The primary fate of these luminally absorbed lipids is chylomicron (CM) formation in the rough endoplasmic reticulum (RER) and Golgi apparatus (Golgi), and exocytosis into the extracellular fluid (ECF). In the basal portion of the cell, fatty acids absorbed from the circulation via albumin-fatty acid complexes in the extracellular fluid are proposed to bind to cytosolic intestinal and liver fatty acid-binding proteins and are targeted primarily to mitochondria (Mito) where they undergo beta-oxidation. Absorption and transport of cholesterol derivatives probably involves a separate transport system and is not shown here. MG 2-monoacylglycerols; Lyso PL Lysophospholipids; BS Bile salts; TG Triacylglycerols; PL Phospholipid; CE Cholesteryl esters; ATP Adenosine triphosphate. (Reprinted with permission from reference 50)*

Patients with hypersensitivity to food (documented by a double-blind, placebo controlled, oral food challenge) have been reported to have a high rate of histamine release from basophils in vitro (48). Mononuclear cells from persons with food allergies spontaneously produce a histamine-releasing factor in vitro. This histamine-releasing factor provokes the release of histamine from basophils of other food-sensitive persons, but not from the basophils of normal individuals. Food-sensitive persons adherent to a restricted diet had reduced rates of generation of this factor. Therefore, in a patient with a diagnosis of food hypersensitivities, the rate of histamine release may be monitored to assess compliance with avoidance diets and to indicate a failure to detect and eliminate all relevant food allergens from the diet. The clinical use of the basophil histamine release test for the diagnosis of food allergies and monitoring of compliance with avoidance diets needs to be explored further.

LIPIDS

Arachidonic acid (20:4) is present in large amounts in phospholipids in the intestinal mucosa. This fatty acid may be transported to mucosal cells by blood (as unesterified fatty acid in lipoproteins), absorbed from the intestinal lumen after the action of pancreatic phospholipase A_2 on biliary phosphatidylcholine, or synthesized by chain elongation and desaturation of linoleic acid (18:2). Following a lipid feed in rats, more 20:4 than 18:2 is

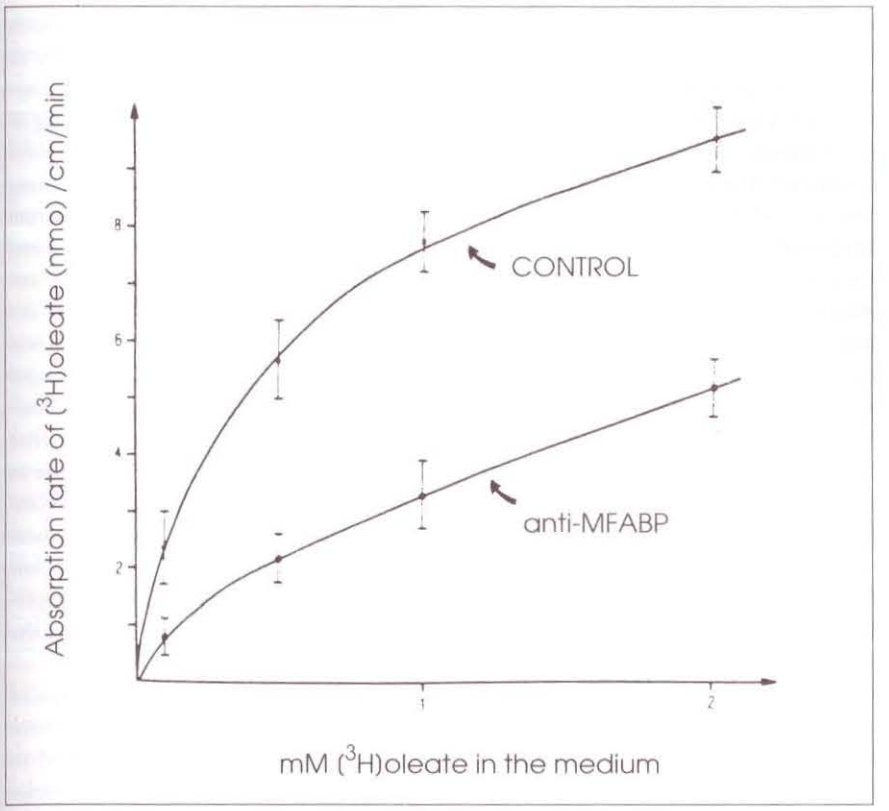

Figure 2) *Effect of the antibody to microvillus membrane fatty acid-binding protein (MFABP) on the absorption rate of [^{3}H] oleate. Jejunal segments were pretreated with the IgG fraction of the antiserum to microvillus MFABP or of the pre-immune serum as controls. Thereafter, the segments were perfused with increasing concentrations (0.1 to 2.0 mM) of [^{3}H] oleate and absorption rates determined. (Reprinted with permission from reference 57)*

retained in intestinal phospholipids, whereas the converse is true for triacylglycerol in the small intestine and plasma (49). The importance of this differential effect remains to be established.

Binding proteins: Intestinal and liver fatty acid-binding proteins are 14 to 15 kDa cytosolic proteins that bind amphiphilic ligands, particularly nonesterified fatty acids. Rat intestinal and liver fatty acid-binding proteins exhibit distinct tissue distribution, and are generally thought to function in the intracellular solubilization and transport of fatty acids. These proteins are distinct with regard to their fatty acid binding stoichiometries, binding mechanisms and sensitivity to pH (50). Yet based on their amino acid sequence homology, intestinal and liver fatty acid-binding proteins must share similar tertiary structures. They represent approximately 2% of the total cytosolic protein. Intestinal fatty acid-binding proteins may function primarily in the cytoplasmic transport of luminally derived fatty acids, whereas liver fatty acid-binding proteins function in the transport of plasma-derived fatty acid (51). Both intestinal and liver fatty acid-binding proteins exhibit intense staining in apical regions of the enterocyte, suggesting that they are involved in cytoplasmic transport of lipids derived from the intestinal lumen (52). It has been proposed that intestinal fatty acid-binding protein exclusively binds and transports fatty acid and is functionally analogous to the fatty acid-specific sites on serum albumin (50). This contrasts with liver fatty acid-binding protein, which binds and transports a variety of ligands such as fatty acid, monoacylglycerols, lysophospholipids, bile salts, and fatty acyl-CoA esters, and is functionally analogous to the nonspecific sites on serum albumin (Figure 1). Each mole of intestinal fatty acid-binding protein could transport up to one mole of fatty acid and each mole of liver fatty acid-binding protein could simultaneously transport two to three moles of fatty acid, monoacylglycerols or lysophospholipids. This multifunctional cytosolic transport system would obviate the need for separate individual transport proteins for monoacylglycerol, lysophospholipid and bile salts. Intestinal and liver fatty acid-binding proteins increase the solubility of these lipids in the cytosol and facilitate their transport to smooth endoplasmic reticulum where activation and esterification enzymes are located. The primary fate of these luminally absorbed lipids is chylomicron formation in the rough endoplasmic reticulum and Golgi apparatus, with subsequent exocytosis into the extracellular fluid. In the basal portion of the cell, fatty acids absorbed from the circulation via albumin-fatty acid complexes in the extracellular fluid are believed to bind to cytosolic intestinal and liver fatty acid-binding proteins and are targeted primarily to mitochondria where they undergo beta-oxidation. Absorption and transport of cholesterol derivatives probably involves a separate transport system.

Retinol-binding proteins: Two cellular retinol-binding proteins are present in the intestine, one in the lamina propria (I) and one in the enterocyte (II). Cellular retinol-binding protein II is essential for export of vitamin A from the intestine within chylomicrons. Cellular retinol-binding protein II increases dynamically during pregnancy and lactation (53), suggesting that this may be an adaptive prerequisite to greater absorption and transfer of vitamin A from the small intestine to the mammary glands in the postpartum period.

Simple or facilitated diffusion: Most previous studies of intestinal absorption of fatty acids in vivo and in vitro have suggested that simple diffusion is the main mechanism of transport. This passive uptake is modified by the resistance of the unstirred water layer and by a number of other luminal factors. Studies using vesicles isolated from BBM of small intestinal segments have confirmed that lipids are taken up by passive diffusion and are either bound to or incorporated into the membrane bilayers, with little accumulation in the

vesicular lumen (54). Recently, Hollander's group (55) demonstrated that transport of up to 100 µM linoleic acid (18:2) is passive in BBM vesicles isolated from rabbit small intestine. The concept of passive diffusion of fatty acids being the only mechanism of uptake is challenged by the identification of high affinity binding sites for long chain fatty acids on jejunal BBM, and by the isolation of a 40 kDa fatty acid binding protein from these membranes (MFABP) (56).

Cellular influx kinetics of radiolabelled oleate were examined in isolated rat jejunal mucosal cells (57). Maximal transport rate (V_{max}) and Michaelis constant (K_m) were identified. Pretreatment of the cells with a monospecific antibody to MFABP inhibited influx of oleate, as well as long chain fatty acids and D-monopalmitin but not L-alanine. In the presence of anti-MFABP in vivo, oleate absorption was reduced (Figure 2). This transport system has a high affinity for fatty acid with a K_m of 93 nM. The predominantly noncompetitive inhibition of oleate uptake suggested that this monospecific polyclonal rabbit antibody may interact with various domains of the MFABP, leading to conformational changes in the protein, which are accompanied by impairment of its carrier function.

Analysis of oleate absorption in vivo demonstrates that fatty acid absorption by jejunal mucosa results from a dual, concentration-dependent uptake mechanism consisting of a passive diffusional transport process and an active carrier-mediated translocation mechanism which predominates at low substrate concentrations. The separate additions of equimolar concentrations of various long chain fatty acids, methyl stearate, D-monopalmitin, L-lysophosphatidylcholine and cholesterol significantly decreased the absorption of oleate. This possibly resulted from enlargement of micelles in the perfusate with resultant decreased diffusion across the unstirred water layer. Alternatively, these compounds might compete with oleate for binding sites of the MFABP, serving as common membrane fatty acid carriers. This suggestion of a common membrane carrier protein mediating the intestinal absorption of the bulk of lipolytic products generated by pancreatic enzymes represents a new concept of the overall fatty acid absorption process. This does not exclude the possibility that absorption is in addition determined by the diffusion of fatty acid-containing mixed micelles across the unstirred water layer. This fatty acid transport may be driven by an active, sodium-dependent, potential-sensitive translocation process, as suggested by the reduction in fatty acid uptake in the absence of sodium or in the presence of ouabain.

Lipid transfer protein: Using a nonspecific lipid transfer protein, Brasitus and colleagues (58) altered the cholesterol/phospholipid molar ratios in rat BBM and demonstrated that cholesterol loading or depletion was accompanied by a decrease or increase, respectively, in membrane fluidity. Increasing the cholesterol/phospholipid molar ratio decreased alkaline phosphatase-specific activity, whereas decreasing this ratio increased enzyme activity. Sucrase, maltase and lactase specific activities were not affected. Benzyl alcohol restored the fluidity of cholesterol-enriched preparations to control levels but did not change the cholesterol/phospholipid molar ratio, and failed to alter alkaline phosphatase activity. This suggests that the cholesterol/phospholipid molar ratio of BBM is more important than membrane fluidity as a regulator of enzyme activity.

Diet lipid manipulation: Can these in vitro findings be achieved in vivo by dietary manipulation? Rat intestinal BBM vesicles from animals fed fish oil had higher percentages of saturated fats and n-3 unsaturated fatty acids and lower percentages of monounsaturated and n-6 unsaturated fatty acids than those prepared from animals fed a butter fat diet (15). BBM from rats fed fish oil had lower fluidity and a higher maximum velocity of sodium-dependent D-glucose transport. In some studies, feeding fish oil has had an antiabsorptive effect (59).

The significance of fish oil to human health has been reviewed (60). Evidence for a beneficial effect of fish oil rich in n-3 polyunsaturated fatty acids (PUFA), compared with n-6 PUFA in vegetable oils, in the prevention of hyperlipidemia has been accumulating in experimental animals and in humans. Fish oil may be of value in preventing an age-dependent increase in serum lipid levels. Delta-6 desaturase converts 18:2n-6 into 18:3n-6. Feeding rats sardine oil reduced delta-6 desaturase activity compared to linseed oil and was hypolipidemic in rats of different ages (61). Moderate dietary changes in healthy humans support the view that dietary lipid modification alters the in vivo production of E-series prostaglandins (62). Modification of prostaglandin E_2 may affect important cardiovascular variables and may represent one of the mechanisms for the benefit of fish oil.

Isocaloric alterations in the type of dietary lipid alters intestinal nutrient transport (63). Adding oleic acid to rabbit small intestinal BBM vesicles reduces vesicle uptake of sodium, glucose and alanine (64), with unsaturated fatty acids showing more inhibition than saturated fatty acids. The inhibition of the Na^+/H^+ exchanger by fatty acid was not due just to the accelerated dissipation of the H^+ gradient, but appeared also to be related to enhanced collapse of the sodium gradient rather than a direct effect on the carrier systems. In enterocytes, Na^+/H^+ exchanger activity is enriched in the BBM and is responsible for the maintenance of an H^+ gradient. Therefore, in an acid microclimate at the mucosal surface, oleic acid reduces maximal transport velocity for sodium uptake, suggesting that the inhibition is noncompetitive in nature.

Several specific functions of cell membranes depend on their unsaturated or saturated fatty acid contents. With the development of dietary essential fatty acid deficiency in pigs, the cholesterol/protein, phospholipid/protein and cholesterol/phospholipid ratios as well as the phospholipid class distributions are unchanged. However, the fatty acid composition of phospholipids is modified, leading to decreased membrane lipid fluidity (65). Cholesterol intake restriction in

neonatal piglets results in higher BBM fluidity and net weight loss compared to cholesterol-fed animals (66). Thus, modification of dietary lipids alters BBM lipid composition as well as transport function.

Partitioning: There is limited information on the partitioning of lipids inside the enterocyte during active lipid absorption. Electron microscopic studies have demonstrated that after fat feeding, triacylglycerol is first identified in the rough endoplasmic reticulum. It then becomes more prominent in the smooth endoplasmic reticulum, flows into the Golgi apparatus, and finally, the lipid vesicles are exocytosed at the BLM (Figure 1). The membranes isolated from the fat-fed intestine were not Golgi but rough endoplasmic reticulum (67). This suggests that the rough endoplasmic reticulum plays a quantitatively more important role during absorption and transport of neutral lipids than was previously believed. Triacylglycerol output into the lymph can be increased by adding phosphatidylcholine to triacylglycerol infusate, but despite obtaining multiple subcellular fractions, the chylomicron precursor pool cannot be clearly identified in the mucosa (68).

Apolipoproteins: Enterocytes are a major site of apolipoprotein synthesis and lipoprotein secretion, and contribute a significant fraction to the total pool of circulating lipoproteins. The rat intestine synthesizes apoB-48, apoA-IV and apoA-I. In the suckling pig there is a proximal to distal gradient in intestinal synthesis rates for both apoB and apoA-I, and acute absorption of dietary lipid does not necessarily increase apoB or apoA-I synthesis in either location (69). However, dietary protein has been shown to influence serum cholesterol concentrations, and lymphatic transport of cholesterol in casein-fed swine is higher than in swine fed soya protein (70). Higher apoB-48 secretion is probably responsible for the greater transport of cholesterol in the chylomicrons of casein-fed swine. Similarly, the transport of lymph very low density lipoprotein (VLDL) cholesterol parallels the amount of accompanying apoB-48. This suggests that dietary proteins influence the intestinal synthesis of apoB-48, which in turn affects cholesterol transport into the lymphatics. The hypocholesterolemic response to soy protein is likely related, at least in part, to intestinal events, and these are probably caused by reduced enterocyte synthesis of apoproteins and lipoproteins.

In humans, apoB-100 is found in the liver, while apoB-48 is found in the intestine. Humans with abetalipoproteinemia do not synthesize either primary species of apoB, and neither VLDL nor chylomicrons are produced. This suggests that secretion of VLDL and chylomicrons is dependent upon the B apoproteins.

The composition, plasma concentration and intravascular metabolism of plasma lipoproteins is influenced by nutritional factors. ApoA-IV is a plasma glycoprotein whose metabolism may be partially sensitive to changes in nutritional status. In humans, the gene for apoA-IV is expressed only in the enterocytes. Thus, the apoA-IV present in the plasma is exclusively of intestinal origin. The synthesis and secretion of apoA-IV is specifically stimulated by the absorption of dietary triglyceride. ApoA-IV is initially incorporated into the surface of nascent chylomicrons, but once the chylomicrons have passed into the bloodstream, apoA-IV rapidly dissociates from the chylomicrons.

The serum apoA-IV level appears to be sensitive to the cessation of enteral feeding, and rapidly falls during prolonged fasting (71). High density lipoprotein (HDL) binding sites are abundant in human small intestinal epithelium and the binding of HDL_3 to human enterocytes is of high affinity, specific, saturable and reversible. HDL_3 enterocyte binding is regulated by cell cholesterol content, accompanied by internalization and degradation of HDL, by cholesterol efflux and by an increase in cholesterol synthesis. These HDL binding sites may supply cholesterol to enterocytes for chylomicron synthesis when the diet is poor in cholesterol and may facilitate the removal of excess cholesterol when the diet is rich in this sterol. While apoA-I may be the determinant of the low density lipoprotein (LDL) receptor in humans, the lipid composition of the lipoprotein may affect its interaction with receptors (72).

The beginning of oral fat consumption at birth may promote intestinal apoprotein synthesis and may account for the abrupt rise in the apoA-I concentration found in suckling rat plasma. Glucocorticoids potentiate prenatal apoA-I synthesis in the rat intestine (73). Increased food intake stimulates small intestinal cholesterol synthesis, but cholesterol synthesis in bypassed intestine is also increased, suggesting that circulating or neurologic factors may play a role in stimulating intestinal cholesterol synthesis (74).

The small intestine contributes up to 10% of total cholesterol synthesis in patients with normocholesterolemia and up to 50% in those with hypercholesterolemia. In the intestine, bile acids appear to be strong regulators of cholesterogenesis. There is a lesser degree of feedback regulation of intestinal cholesterogenesis by exogenous cholesterol. Cholesterol synthesis has been studied in organ culture of small bowel biopsies from children with different forms of malabsorption; for example, intestinal cholesterol synthesis is increased in patients with celiac disease (75). The increased intestinal cholesterol synthesis and esterification which occurs in diabetes mellitus is reversed by insulin therapy, due to a direct effect of insulin on the enterocytes (76). Thus, the regulatory system for cholesterol in enterocytes differs from that in most organs.

Pluronic L-81, a nonionic hydrophobic surfactant, is a potent inhibitor of chylomicron formation by the small intestine. It prevents the expected increase in lymph apoA-IV output which occurs following infusion of a lipid emulsion into the intestine (77). Following fat loading, puromycin treatment and the administration of pluronic L-81, there are large accumulations of nonmembrane-bound lipid droplets in the enterocyte. It is unknown whether triacylglycerol incorporation from the surface of lipid droplets occurs into preformed, endoplasmic reticulum-derived vesicles

with subsequent chylomicron synthesis. De novo synthesis of vesicular membranes from triacylglycerol-derived fatty acids and cytosolic proteins at the surface of the lipid droplets may occur with concomitant chylomicron production. The surfaces of these large accumulated lipid droplets lack a unit membrane, but intense staining of the lipid droplet following tannic acid treatment suggests that there is a high concentration of phosphatidylcholine (78). The large, nonmembrane-bound lipid droplets decrease in size and number over the 2 h period following pluronic L-81 exposure, while the number and size of electron-dense-containing vesicles increase. These vesicles are subsequently concentrated in the Golgi region, suggesting recycling of lipid for chylomicron production and secretion.

Short chain fatty acids: Water-soluble short chain fatty acids pass unesterified into the portal vein. It has long been accepted that long chain fatty acids, whether fed as free fatty acid or as triacylglycerol, are incorporated predominantly into mucosal triacylglycerol before being discharged as chylomicrons into lymphatics. McDonald and co-workers (79) demonstrated that a substantial proportion of essential unsaturated long chain fatty acids are transported from rat intestine into portal venous blood, particularly at low rates of absorption.

Lymph: Gut lymph flow is a major determinant of fluid homeostasis within the intestinal wall. It is recognized that changes in physical forces within the intestinal interstitial spaces, capillaries and lymphatics allow for the movement of absorbed fluid from the mucosal interstitium into the bloodstream. Increased lipid absorption results in markedly increased lymph flow, bloodflow and capillary pressure, and reduced interstitial oncotic pressure (80). These effects on microvascular and lymphatic fluid dynamics are quantitatively different from those produced by glucose absorption, and may be explained by lipid absorption-induced increases in bloodflow and microvascular permeability.

Bile acids: Bile acids are transported across small intestinal mucosa by ionic or nonionic passive diffusion. In addition, they cross the ileal BBM by an active transport process which is sodium-dependent and subject to cyclic AMP-related stimulation at the mucosal cellular level (81). A putative transport protein involved in coupled sodium-bile acid transport across the ileal BBM has been identified as a 99,000 molecular weight polypeptide (82,83). Photoaffinity labelling studies have suggested that at least two polypeptides are present in the BLM of the ileal epithelial cell and are involved in facilitative diffusion of bile acids out of the enterocyte (84).

Bile acids may be injurious to the small intestine. Prostaglandin (16,16-dimethyl prostaglandin E_2) pretreatment reduces and indomethacin treatment increases the morphologic and functional mucosal injury caused by perfusing the small intestine of rats with 5 mmol/L chenodeoxycholic acid (85).

VITAMINS

With ageing, there is a shift from portal to lymphatic transport of vitamin E, with an overall age-associated increase in the total vitamin E absorbed (86,87).

Thiamine absorption occurs by active transport at low concentrations and by passive diffusion at high concentrations. Severe folate deficiency has no effect on thiamine absorption (88).

Biotin is a water-soluble vitamin which is required for normal cellular function, growth and development. It acts as a coenzyme in many metabolic reactions and is considered an essential vitamin. The uptake of biotin by BBM vesicles from rat and human intestine demonstrates a carrier-mediated, sodium-dependent and electroneutral process which is more active in the jejunum than the ileum (89,90). Biotin transport is higher in biotin-deficient rats compared to pair-fed biotin-sufficient control animals. This is due to an enhancement of the maximal transport rate for biotin uptake; supplementation of the diet with pharmacological doses of biotin decreases the maximal transport rate (91).

Dietary cobalamin binds to the glycoprotein intrinsic factor secreted by the stomach. The subsequent calcium-dependent binding of cobalamin-intrinsic factor complex to a specific ileal receptor is necessary for active absorption of this vitamin. Intrinsic factor-mediated uptake of cobalamin has not been demonstrated in ileal crypt or jejunal villus or crypt cells. In ileal villus cells, cyanocobalamin uptake has been described, with uptake of cobalamin-intrinsic factor complex being 30 times greater than that of free cobalamin (92). Thus, cobalamin is rapidly taken up into the ileal mucosa; the fate of intrinsic factor, however, remains debatable. The uptake of iodinated human intrinsic factor by guinea pig ileum was studied in vivo using electron microscopy radioautography (93); intrinsic factor appears to be internalized into enterocytes during cobalamin absorption, and part of the intrinsic factor appears to enter the circulation through transcytosis.

The absorption of vitamin B_{12} in aqueous form may be measured clinically with the Schilling test. While this correlates with the absorption of vitamin B_{12} in food from healthy subjects, there may be normal aqueous but decreased protein-bound vitamin B_{12} absorption associated with achlorhydria, partial gastrectomy or vagotomy, atrophic gastritis and treatment with H_2-receptor antagonists. A dual test of vitamin B_{12} absorption may prove useful in determining the importance of a subnormal serum vitamin B_{12} concentration where the cause of this apparent deficiency is not clinically apparent or where the absorption of vitamin B_{12} in aqueous form appears to be normal (94).

MINERALS

Calcium: The mechanism of intestinal calcium transport and the clinical aspects of disturbed calcium absorption have been reviewed (95). Dietary calcium is absorbed by both cellular and paracellular pathways across small intestinal and colonic epithelium. The cellular pathway is a saturable energy-dependent process stimulated by calcitriol [$1\alpha,25(OH)_2D_3$]. Calcitriol

increases calcium influx across the BBM and calcium extrusion across the BLM. Calcium exit across the BLM is an energy-dependent step mediated by a calmodulin-sensitive Ca^{+},Mg^{+}-dependent ATPase with a high affinity of activation for calcium. In vitro bidirectional calcium fluxes were measured under short-circuited conditions using proximal duodenum from rats fed diets adequate in vitamin D and containing normal or low calcium diets (96); calcitriol increased epithelial flux of calcium from the mucosa to the serosa by mechanisms which do not involve ATP-dependent BLM calcium efflux. The ATP-dependent, calmodulin-stimulated calcium pump is capable of transporting calcium against the concentration gradient at the BLM. The properties of a phosphoprotein at 130 kDa are consistent with those expected for the plasma-membrane calcium pump (97).

The coingestion of a light meal of varied composition and calcium enhances the efficiency of calcium absorption (98). Lactose enhances calcium absorption in subjects with normal lactase activity but decreases it in lactase-deficient patients (99). Glucose and galactose increase calcium absorption, whereas lactitol decreases calcium absorption (100). Thus, dietary factors influence calcium absorption.

Vitamin D_3 is absorbed in the intestine by a nonsaturable passive transepithelial process. After penetrating the BBM, vitamin D_3 is transferred by a carrier protein through the cytosol to the intracellular organelles (101). Vitamin D_3 may be more readily channelled through an esterification process than 1,25-dihydroxyvitamin D_3.

Phosphate: In BBM vesicles isolated from human jejunum, both sodium-gradient-dependent carrier-mediated transport and passive diffusion of phosphate have been identified (102). Uptake is primarily by passive diffusion, with most transepithelial uptake occurring in the proximal small intestine. A 130 kDA polypeptide has been tentatively identified as the intestinal sodium-phosphate cotransporter. This polypeptide band contains both sodium and phosphate substrate sites (103).

Zinc: Zinc is essential for human health; many metalloenzymes involved in the metabolism of carbohydrates, lipids, protein and nucleic acids require zinc for their functions. Poor intake of zinc and absorption defects have been proposed as major causes of zinc deficiency. Acrodermatitis enteropathica is a zinc malabsorption syndrome which is transmitted via an autosomal recessive mode of inheritance, and which, if untreated with zinc, is fatal in early childhood. Zinc absorption involves both carrier- and nonmediated components. In man the jejunum has the highest rate of absorption of zinc which is stimulated by the presence of glucose in the intestinal lumen (104). Zinc transport may involve the action of a low molecular weight zinc-binding ligand which is present in human milk and chelates zinc and carries it across the BBM. This ligand has not been identified in cow's milk. In the rat small intestine it appears to be an arachidonic acid-like substance (105). Zinc uptake across the BBM but not across the BLM is increased following a short period of dietary zinc restriction (106). Zinc malabsorption appears to contribute to zinc deficiency in nonalcoholic cirrhotics and seems to result, in part, from pathological changes in the mucosa (107).

Iron: Enterocytes appear to be responsible for the regulation of iron absorption. There is enhanced uptake and transfer of iron to the body when the dietary content of iron is reduced or when body iron stores are depleted. Absorbed iron stimulates ferritin synthesis in iron-deficient and iron-repleted animals. Iron deficiency is associated with decreased mucosal ferritin levels and increased mucosal transferrin content. The iron content of the duodenal mucosa of iron-deficient animals is less than that of control animals. As iron absorption and retention is greater in iron-deficient animals, this suggests a mucosal mechanism which transfers iron to the blood side of mucosa more efficiently than in control animals. This mechanism might be at the basolateral side of the absorbing enterocytes (108).

Desferrioxamine is an iron-chelating agent that, administered orally, interferes with gut absorption of inorganic iron. Administered parenterally, it binds iron and is excreted as ferrioxamine in bile and urine. Parenterally administered desferrioxamine can enter the small intestinal mucosa, bind intracellular iron and block the absorption of inorganic iron, transferrin iron and hemoglobin iron (109). This suggests that all three iron species enter a common chelatable pool within the small intestinal mucosa, and may share a common pathway of absorption.

Bran inhibits the absorption of nonheme iron in man, due to its phytate content. Short term studies suggest that high bran and phytate intake over prolonged periods might induce changes in the intestinal absorption of iron. From a long term perspective, iron absorption is fortunately similar in vegetarians with a regular high phytate intake as in a control group (110). Egg white and soy bean protein inhibit iron absorption in humans, whereas substitution of beef, lamb, pork, liver, fish or chicken for egg white results in enhanced iron absorption. Casein and whey protein in bovine milk appear to be responsible, at least in part, for the poor bioavailability of iron in some infant formulas (111). Thus, the intestinal absorption of iron is influenced by body stores of iron but also by the content of other nutrients in the intestinal mucosa.

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