Nutrient absorption and intestinal adaptation with ageing

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Malabsorption of carbohydrates, lipids, amino acids, minerals and vitamins has been described in the elderly. The ability of the intestine to adapt may be impaired in the elderly and this may lead to further malnutrition. Dietary manipulation may prove to be useful to enhance the needed intestinal absorption with ageing. There is an age-associated increase in the prevalence of dyslipidaemia as well as diabetes. These conditions may benefit from nutritional intervention targeted at reducing the absorption of some nutrients. With the continued characterization of the proteins involved in sterol and fatty acid absorption, therapeutic interventions to modify absorption may become available in the future.

Key words: ageing; adaptation; absorption; morphology; nutrition; enteroplasty.

INTRODUCTION

Modern society has benefited from many advances that have reduced morbidity, extended life expectancy and improved the quality of older persons’ lives. Medical treatments, reduction and elimination of infectious diseases through vaccination programmes, improved living conditions and improved nutrition have all contributed to the extension of life in developed nations.¹ In 1999, Statistics Canada reported that 12% of the nations’ thirty million people were older than 64 years. This percentage is expected to grow to almost 15% by the year 2011.² Similar patterns are expected to be seen in other developed countries.

A diet high in fats is associated with an increased risk of cardiovascular disease, a leading cause of death.² Canadians obtain about 38% of their total energy from dietary fats, but this amount should be reduced to less than 30%.³ Dietary cholesterol and saturated fatty acids are considered to be the main culprits in the process of the pathogenesis of vascular disease, as well as several cancers such as breast and bowel

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cancer. This chapter will first discuss current aspects of nutrient absorption and intestinal adaptation. Then it will consider whether ageing changes the ability of the small intestine to absorb nutrients.

PHYSIOLOGY OF INTESTINAL NUTRIENT ABSORPTION

Dietary nutrients or drugs are absorbed from the intestinal lumen by the transcellular and paracellular routes. Enterocytes are joined by tight junctions (TJ), which restrict the free movement of molecules from the intestinal lumen to the blood stream via the paracellular route. The TJs also maintain the polarity of the enterocytes with an apical brush border membrane (BBM) and a basolateral membrane (BLM).

In hamsters, the presence of D-glucose within the enterocyte causes a contraction of the cell, a dilation of the TJ and increased paracellular glucose transport. Studies with human jejunal tissues did not demonstrate increased TJ permeability induced by Na⁺-dependent glucose transport. In dogs, the paracellular route of glucose absorption represents 4–7% of total glucose absorption at physiological concentrations. Thus, the contribution of paracellular transport is likely to be small.

The transcellular route of absorption involves passage through the enterocyte BBM and BLM. Transmembrane proteins facilitate the transport of many molecules across the cell membrane. Absorption via a transport protein is a saturable process and is dependent on the number of transporters available. Therefore, a change in the value of the maximal transport rate (V_max) may be due to an alteration in the number of transporters. A change in the value of the Michaelis–Menten affinity constant (K_m) represents an alteration in the affinity of a transporter for its substrate.

Carbohydrates

Dietary D-glucose is transported from the intestinal lumen by an active transport mechanism in the BBM, the sodium–glucose transporter (SGLT1). Glucose transport across the BBM is driven by an Na⁺ gradient maintained by the Na⁺/K⁺ pump in the BLM. The SGLT1 transporter is an 84 kDa protein and both D-glucose and D-galactose are substrates for it. The stoichiometry for SGLT1 transport is 1 glucose molecule, 2 Na⁺ ions and 210 molecules of H₂O. While there are several possible phosphorylation sites located on the cytoplasmic side of SGLT1, there is no evidence that these sites are actually phosphorylated. The functional SGLT1 cotransporter exists as a homotetramer. The density of SGLT1 is highest in the jejunum, intermediate in the ileum and lowest in the duodenum. The abundance of SGLT1 is either constant along the villus, or increases from the crypt–villus junction to the villous tip. Immunohistochemical studies using a polyclonal antibody against SGLT1 have demonstrated a uniform distribution of SGLT1 immunoreactivity in the BBM of adult rabbit jejunal enterocytes. This is also true for SGLT1 mRNA levels. However, the activity of the transporter increases toward the tip of the villus. It may be that SGLT1 becomes functionally activated only in the upper portion of the villus. This may be due to the formation of a homotetramer of SGLT1 proteins, the presence of regulatory and or catalytic subunits, or the action of protein kinases such as protein kinase C, which may regulate glucose transport by reducing the turnover rate of the transporter.

Transport of sugar by SGLT1 depends on the maintenance of the Na⁺ gradient by the Na⁺/K⁺ ATPase. The Na⁺/K⁺ ATPase α1 and β1 subunits are located in the BLM of the enterocytes. The activity of the Na⁺/K⁺ ATPase increases toward the tip of the
villus, as does the mRNA expression of the α1 and β1 subunits. Phosphatidylinositol 3-kinase may play an important role in the activation of the Na⁺/K⁺ ATPase and the transport of D-glucose.

GLUT2 (sodium-independent glucose and fructose transporter in BLM) and GLUT5 (sodium-independent fructose transporter in BBM) are members of a large family of GLUT facilitative hexose transporters. GLUT5, a 50 kDa protein, is responsible for D-fructose transport across the BBM of the enterocyte. The $K_m$ of GLUT5 for fructose is approximately 15 mM. GLUT2 transports D-fructose, D-galactose and D-glucose across the BLM. GLUT2 may also be located in the BBM. GLUT2 has the highest $K_m$ of all the transporters for glucose, measured between 15–40 mM. This high $K_m$ value may reflect the role of GLUT5 in cells where the intracellular glucose concentration exceeds that of the plasma concentration. GLUT5 and GLUT2 are expressed along the length of the small intestine, with the highest level of expression being in the proximal small intestine. Expression is absent in the crypts, increasing from the crypt–villous junction to the villous tip.

Lipids

Uptake

The majority of dietary fat is in the form of triacylglycerol (TG), which is hydrolysed by lingual, gastric and pancreatic lipases to form monoacylglycerol and free fatty acids. Digestion of phosphatidylcholine occurs in the small intestine by the action of pancreatic phospholipase A2. Dietary cholesterol in the form of free sterols is absorbed in the small intestine. The majority of cholesterol esters are hydrolysed by the action of cholesterol esterase in the lumen and are absorbed as free cholesterol and fatty acid. Cholesterol esters may also be subject to protein-mediated uptake. The absorption of fatty acids occurs primarily in the proximal intestine and in the upper portion of the villi. The absorption of lipids will be considered in three stages: (i) diffusion across the unstirred water layer (UWL), (ii) transport across the BBM and (iii) intracellular binding and trafficking.

Lipids diffuse across the intestinal UWL before contacting the BBM. The effect of the UWL is to reduce the concentration of the lipid presented to the enterocyte. Therefore, it is important to correct for the effect of the UWL on absorption in order to assess the true permeability properties of the BBM. The fatty acid partition coefficient increases with chain length by a factor corresponding to a decrease in the incremental change in free energy moving from an aqueous to a lipid phase.

Phospholipids are found in bile micelles together with cholesterol and bile salts. Bile acid micelles greatly enhance the uptake of fatty acids and cholesterol from the small intestine. Three models of passive lipid uptake have been proposed.

1. The entire mixed micelle is absorbed by the BBM. However, no experimental evidence supports this model.
2. The micelle collides with the BBM allowing the uptake of lipids to occur. Evidence for this model is suggested by the linear relationship between cholesterol uptake and bile acid concentration.
3. The lipids dissociate from the micelle into the aqueous compartment of the UWL before being taken up by the BBM. Support for this model is suggested by the finding that fatty acid uptake decreases with an increase in the number of bile acid micelles, where fatty acid concentration is kept constant.
The dissociation of lipids from bile acid micelles is under the influence of the acidic microclimate adjacent to the BBM. Under acidic conditions, the critical micellar concentration increases and fatty acids become protonated; protonation increases their rate of permeation across the BBM. An increase in membrane fluidity also increases the rate of permeation. Other factors influencing the rate of lipid uptake may be the luminal lipid composition, fatty acid binding proteins and membrane potential. For instance, polyunsaturated fatty acids (oleic [18:1], linoleic [18:2], linolenic [18:3], arachidonic [20:4]) and phosphatidyl choline (PC) may inhibit cholesterol absorption.

Several proteins have been described from the brush border membrane (BBM) that may contribute to fatty acid and cholesterol transport (Table 1). A 43 kDa protein, known as the plasma membrane fatty acid binding protein (FABP_{pm}) has been identified in the BBM and BLM of intestinal cells. This protein binds long-chain fatty acids (LCFA), monoglycerides and cholesterol. Incubation of jejunal BBM vesicles with anti-FABP_{pm} antibody results in a reduction in oleic acid uptake.

The scavenger receptor of class B type 1 (SR-BI) is a 57 kDa integral membrane protein and is located in the BBM. High-density lipoproteins, the physiological ligand for this receptor in the liver, inhibit the uptake of free esterified cholesterol into the BBM. SR-BI may act as a docking receptor for donor particles, such as bile acid micelles, followed by the transfer of lipids to the BBM.

Caveolin-1 is a 22 kDa integral membrane protein located in detergent-resistant microdomains of the BBM. With the influx of micellar cholesterol, plasma membrane cholesterol moves to these microdomains and is transported to the endoplasmic reticulum (ER). Caveolin-1 also exhibits a binding affinity for LCFA. The role of caveolin-1 in the intestine has not been established, but it may be involved in intracellular targeting.

Fatty acid translocase (FAT) is an 88 kDa transmembrane glycoprotein located in the BBM of enterocytes. Rat FAT is 85% homologous to the human scavenger receptor CD36, which is found in platelets, lactating mammary epithelium, monocytes and adipocytes. FAT null mice are viable, but have a reduced uptake of triglycerides into adipocytes. FAT messenger ribonucleic acid (mRNA) is expressed primarily in the BBM and in the upper two-thirds of the villi. Dietary fat up-regulates the expression of intestinal FAT mRNA.

The fatty acid transport protein (FATP) is a 63 kDa membrane protein that is expressed in adipose tissue, heart and skeletal muscle. FATP increases the uptake of oleate in fibroblast cell lines. There is a large family of FATPs, but only FATP4 is present in appreciable levels in the intestine. FATP4 mRNA is expressed in the enterocytes of the jejunum, ileum and at lower levels in the duodenum. Expression is absent from both the crypts of the small intestine and from the colon. Fatty acids containing 10–26 carbon atoms are thought to be substrates for FATP4.

The passive absorption of sterols occurs as a result of collision between mixed bile salt micelles and the BBM, but BBM vesicle transport is significantly reduced following membrane digestion with proteases, suggesting the existence of a transport protein. This ‘cholesterol transport protein’ is an integral membrane protein with at least one hydrophobic domain. Long-chain triacylglycerols may be transported across the BBM by a protein, perhaps by the same protein as cholesterol. The multidrug resistance protein (MDR; known as MDR1 in humans), may be involved in the uptake of cholesterol in intestinal epithelial cells. A sterol glycoside derivative specifically binds to the BBM of enterocytes and blocks the absorption of cholesterol. A 145 kDa integral membrane protein in the BBM of rabbit enterocytes has also been identified and may contribute to intestinal cholesterol absorption.
<table>
<thead>
<tr>
<th>Protein</th>
<th>Molecular weight (kDa)</th>
<th>Localization</th>
<th>Substrate</th>
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<tbody>
<tr>
<td><strong>A. Brush border membrane proteins</strong></td>
<td></td>
<td></td>
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<tr>
<td>Caveolin-1</td>
<td>22</td>
<td>Small intestine</td>
<td>Cholesterol and LCFA</td>
</tr>
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<td>Scavenger receptor class B type I (SR-BI)</td>
<td>57</td>
<td>Liver, peripheral tissue</td>
<td>High-density lipoproteins, phospholipids, triacylglycerol, cholesterol and cholesterol esters</td>
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<tr>
<td>Plasma membrane-fatty acid binding protein (FABP$_{pm}$)</td>
<td>40</td>
<td>Adipose tissue, heart, liver, intestine</td>
<td>LCFA</td>
</tr>
<tr>
<td>Fatty acid transporter (FAT)/CD36</td>
<td>88</td>
<td>Adipose tissue, heart, skeletal muscle, spleen, intestine</td>
<td>LCFA, triglycerides</td>
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<tr>
<td>Fatty acid transport protein-4 (FATP4)</td>
<td>63</td>
<td>Small intestine</td>
<td>LCFA (oleate)</td>
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<tr>
<td>Cholesterol transport protein</td>
<td>145</td>
<td>Small intestine</td>
<td>Cholesterol</td>
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<tr>
<td><strong>B. Intra-cellular proteins</strong></td>
<td></td>
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<tr>
<td>Fatty acid binding protein (FABP)</td>
<td>14–15</td>
<td>Adipose tissue, muscle, heart, brain, kidney</td>
<td>LCFA</td>
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<tr>
<td>Liver-FABP</td>
<td>14–15</td>
<td>Liver and small intestine</td>
<td>LCFA, haem, bile acids, acylcoenzyme A</td>
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<tr>
<td>Intestinal-FABP</td>
<td>14–15</td>
<td>Small intestine</td>
<td>LCFA</td>
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<tr>
<td>Ileal lipid binding protein (ILBP)</td>
<td>14</td>
<td>Ileum (predominant in distal ileum)</td>
<td>Bile acids</td>
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<tr>
<td>Prechylomicron transport vesicle (PCTV)</td>
<td></td>
<td>Small intestine</td>
<td>Triacylglycerol</td>
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LCFA, long chain fatty acids.
A family of cytosolic fatty acid binding proteins has been identified and includes three that are located in the small intestine: the intestinal FABP (I-FABP), the liver-FABP (L-FABP) and the ileal lipid binding protein (ILBP). L-FABP is a 14.1 kDa protein located in the duodenum and jejunum, with maximal expression in the proximal jejunum. I-FABP is a 15.1 kDa protein that is expressed throughout the small intestine, with maximal expression in the distal jejunum. I-FABP expression begins at the crypt–villous junction and extends to the villous tip, but L-FABP is absent in the villous tips.55 The mRNAs for I-FABP and L-FABP are expressed throughout the small intestine and along the length of the villi.45

The tertiary structure of the FABP consists of 10 anti-parallel β strands containing a ligand-binding cavity.55 Both I-FABP and L-FABP bind long chain fatty acids with high affinity. Rats treated with clofibrate (a hypolipidaemic drug) have increased expression of L-FABP protein and mRNA, with no change in the expression of the I-FABP counterparts.56 The fatty acid transfer from I-FABP occurs by direct collisional interaction with the phospholipid bilayer and L-FABP has a role in the uptake or subcellular targeting of fatty acids.57 In contrast, L-FABP may transfer fatty acids in an aqueous diffusion-mediated process and may act as a cytosolic buffer for fatty acids.57

The mRNA expression of I-FABP and L-FABP is increased in rats fed a diet rich in polyunsaturated fats.45 In I-FABP knockout mice, fatty acid uptake is maintained, demonstrating that the I-FABP protein is not required for intestinal lipid uptake.58 Peroxisome-proliferator activator receptors (PPARs) may play an obligatory role on the expression of L-FABP and I-FABP genes.59 The livers of mice fed bezafibrate, a PPAR hypolipidaemic drug, showed a fourfold increase in L-FABP protein and mRNA levels.60 In addition, bezafibrate increases the mRNA expression of FAT, suggesting a complementary role for the FAT and FABP proteins in lipid absorption.60

The ileal lipid binding protein (ILBP) is a 14 kDa cytoplasmic protein that binds bile acids.61 ILBP is structurally related to the FABP family and is located predominantly in the distal ileum. The binding of bile acid to ILBP may increase its affinity for bile acids.62

Mansbach and Dowell63 have suggested that the rate-limiting step in lipid absorption is the trafficking of triacylglycerol from the ER to the Golgi. Specifically, the rate-limiting step may be the formation of a prechylomicron transport vesicle (PCTV) that transports the developing chylomicron from the ER to the Golgi.

The microsomal triglyceride transfer protein (MTP) is an ER-localized co-factor required for the assembly of apolipoprotein B (apo B). MTP is a heterodimer consisting of a 58 kDa subunit of protein disulphide isomerase (a multi-functional ER protein) and a unique 97 kDa subunit.64 MTP is essential for the transfer of TG and cholesterol esters into the hydrophobic core of apo B.65 A defect in the MTP in humans results in abetalipoproteinaemia.66 In human foetal jejunal and colonic tissue, MTP protein is expressed along the crypt–villous axis by the 13th gestational week.67

It is unclear what the relative contribution of these lipid-binding proteins is to the total lipid absorbed by the enterocyte, or whether changes in the abundance of these proteins plays a role in the adaptation of lipid uptake such as that which occurs with ageing.

**Amino acids**

Amino acid transport has been reviewed68 and intestinal amino acid transporters are summarized below. The neutral brush border (NBB) or B system is a Na⁺-dependent system of broad specificity responsible for the transport of zwitterionic amino acids
and di- and tripeptides. IMINO is located in the BBM and transports proline and N-methylated glycine (Na\(^{+}\)-dependent). The rBAT/bo\(^{+}\) system transports cationic amino acids and cystine (Na\(^{+}\)-independent) and zwitterionic amino acids (Na\(^{+}\)-dependent). A defect in this system is responsible for the condition of cisticuria. CAT-1 is a widely expressed cationic (Na\(^{+}\)-independent) and zwitterionic (Na\(^{+}\)-dependent) amino acid transporter. EAAT-3 is highly expressed in the small intestine and transports anionic amino acids (Na\(^{+}\)/K\(^{+}\)-dependent). PepT-I transports di- and tripeptides and is driven by an inwardly directed H\(^{+}\) gradient.\(^6\)

**INTESTINAL ADAPTATION**

Intestinal adaptation is defined as the ability of the intestine to functionally or morphologically change in response to changes in environmental stimuli. Generally, the adaptive changes are beneficial, such as increased nutrient absorption following small intestinal resection, chronic alcohol ingestion and sub-lethal abdominal radiation.\(^8\) In contrast, the enhanced absorptive adaptation observed in diabetes contributes to hyperglycaemia and to the obesity that is associated with this disease. Dietary nutrients also influence intestinal adaptation. For example, increased dietary carbohydrates cause an increase in the maximal transport rate (V\(_{\text{max}}\)) for intestinal glucose uptake capacity.\(^7\) Animals fed on diets that have been enriched with saturated fatty acids (SFAs) have greater glucose uptake, compared to those animals fed polyunsaturated fatty acid (PUFA) diets.\(^7\) Depending on the nutrients available, the intestine adapts to variations in dietary load and composition.\(^7\)

Morphological changes are often associated with intestinal adaptation. Following bowel resection, hyperplasia of the remaining gut is associated with increased nutrient, water and electrolyte absorption.\(^7\) However, hyperplasia does not necessarily correlate with altered absorption:\(^7\) in the rat jejunum, the uptake of glucose is enhanced by dietary fats but is not associated with increased mucosal surface area. Following small bowel resection the mass of the remnant intestine increased to 50–70% of its pre-resection level, but glucose uptake was restored to only 33%.\(^7\) These findings suggest then, that morphological changes do not necessarily accompany alterations in absorption and vice versa.

The dietary induction of intestinal BBM glucose transport takes place in the developing enterocytes.\(^7\) Mice were switched from a high carbohydrate diet to no carbohydrate diet, or vice versa. Glucose-protectable phlorizin binding was used as a measure of glucose transport site density. An increase or decrease in phlorizin site density first appeared in the crypts and then, over the course of 3 days, extended to the villous tips.\(^7\) This suggests that dietary alterations result in a reprogramming of the developing enterocytes in the crypts and that changes in uptake are observed as these cells migrate toward the villous tips. Cell dynamics such as cell turn-over rate, crypt cell production rates and enterocyte migration rates may be key determinants in the process of intestinal adaptation. Ageing results in a higher proliferative rate of crypt cells, possibly reducing the number of transporting enterocytes and thereby reducing nutrient absorption.\(^7\)

Intestinal adaptation that is associated with alterations in glucose uptake is usually due to changes in the value of V\(_{\text{max}}\). The change in V\(_{\text{max}}\) may result from: (i) an alteration in the absorptive surface area, (ii) a change in the lipid membrane fluidity that alters the exposure of binding sites, (iii) variation of transporter gene transcription and a parallel change in protein abundance, (iv) a post-transcriptional or post-translational event
leading to a change in the number of functional transporters per enterocyte, (v) an alteration in the pattern of distribution of transporters along the villus, with more transporters near the villous tip but without necessarily an alteration in the total number of transporters, (vi) insertion of pre-existing transport proteins from intracellular vesicles into the plasma membrane, or removal of the proteins by endocytic retrieval and (vii) covalent modification of the transporter by reversible phosphorylation.\textsuperscript{8,76} Intestinal adaptation in the chronically diabetic rat involves changes at the transcription level as well as a post-transcriptional event leading to increased Na\textsuperscript{+}-coupled sugar absorption.\textsuperscript{77} After inducing acute hyperglycaemia in rats, there is a rapid up-regulation of glucose transport across the BLM of the enterocyte and, in rats, both vascular and luminal glucose infusion causes an increase in glucose transport capacity across the BLM.\textsuperscript{79} However, no significant increase in BLM cytochalasin B binding or in GLUT2 protein abundance was observed, suggesting that there may be a post-translational event that increases the number of GLUT2 proteins available for transport.

The lipid composition of cell membranes alters the passive permeability properties and the transporter activity across the membrane.\textsuperscript{80} Changes in BBM fluidity influence the passive uptake of lipids and carrier-mediated D-glucose uptake.\textsuperscript{81} Low BBM fluidity reflects a low phospholipid-to-cholesterol ratio. Fluidity is greater in the proximal than distal small bowel and decreases as enterocytes migrate from the crypt to the villus.\textsuperscript{82} In the BBM of starved rats, there is an increased ratio of phospholipids and an increased double-bond index.\textsuperscript{83} Also, during starvation there is a decreased ratio of cholesterol, cholesterol esters and free fatty acids. This suggests that membrane fluidity is increased during starvation and may facilitate increased glucose transport across the BBM in spite of decreased levels of glucose transporter protein during the starved state. Diets that are enriched in SFAs increase the saturation of BBM phospholipids, while PUFA enriched diets increase the percentage of unsaturated BBM phospholipids.\textsuperscript{71} However, alteration of dietary cholesterol intake does not change membrane cholesterol content, suggesting that cholesterol content of the BBM is controlled.

AGE-ASSOCIATED CHANGES

Of concern in Canada is the fact that 59% of elderly patients admitted to a tertiary care facility were found to be malnourished or at high risk for malnutrition.\textsuperscript{84} Many factors contribute to this high rate of malnourishment such as poor dentition, medication use and psychosocial issues. Ageing may also result in a decline in nutrient absorption and this reduction also contributes to poor nutritional status.

Carbohydrates

An age-associated decline in D-glucose absorption has been found in mice.\textsuperscript{85} D-Xylose absorption has been shown to decrease in ageing humans. However, D-xylose excretion is dependent on renal function and, when renal function is taken into consideration, there is only a modest reduction in xylose absorption associated with ageing.\textsuperscript{86} When fed a meal containing 100 g carbohydrate, one-third of subjects over 65 years had excess breath hydrogen, suggesting malabsorption.\textsuperscript{87} However, this is a large amount of carbohydrates for one meal and this reduced absorptive capacity may have minimal nutritional impact for persons consuming normal amounts of carbohydrate. In addition, breath hydrogen tests can be falsely positive in the presence of bacterial overgrowth of the small intestine. It should also be noted that bacterial overgrowth
may occur more frequently among the elderly and that anaerobic bacteria can produce proteases that interfere with disaccharidases in the BBM, thereby resulting in reduced carbohydrate absorption.\textsuperscript{98}

**Lipids**

Using in vivo perfusion studies in rats, Hollander and Dadufalza\textsuperscript{89} found an increase in fatty acid and cholesterol uptake associated with ageing. However, in vitro uptake studies done on rabbit jejunal discs reported a decline in the uptake of fatty acids and cholesterol with age.\textsuperscript{90} Radiolabelled fat breath tests have confirmed that lipid absorption is reduced in mature compared to suckling rats.\textsuperscript{91} The digestibility of fatty acids is reduced in old compared to younger cats.\textsuperscript{92} A decrease in intestinal BBM phospholipid composition and membrane fluidity have been reported in ageing and this may contribute to the reduced lipid absorption in the aged.\textsuperscript{81} In ageing there may be reduced gastric lipase and bile acid secretion, decreasing lipid solubilization and thus decreasing lipid absorption.\textsuperscript{93} In contrast, ageing is associated with a decrease in the thickness and resistance of the UWL,\textsuperscript{90} which would tend to increase the net absorption of nutrients, possibly to partially counteract the decreased permeability.

Lipid absorption in humans also decreases with age.\textsuperscript{94} However, in a study of only the healthy aged, there was no correlation between age and 72 h faecal fat excretion.\textsuperscript{95} Previous studies had suggested that reduced serum chylomicron levels following a fatty meal indicated a reduced absorptive capacity among the aged,\textsuperscript{94} but the absorption of fat may take longer in the elderly and this method may not reflect total uptake.\textsuperscript{95} There is also a reduction in post-prandial serum bile acid levels in humans, suggesting that bile acids are absorbed less effectively in the elderly.\textsuperscript{96} It may also be that when the absorption of the fats is delayed post-prandial satiety may be prolonged, thus reducing overall intake in the elderly.\textsuperscript{97}

**Amino acids, vitamins and minerals**

The absorption of tyrosine, arginine and aspartic acid declines in senescent rodents.\textsuperscript{98} In in vivo perfusion studies with rats, vitamin A absorption increases in a linear fashion with age.\textsuperscript{99} Reduced calcium absorption is reported in ageing and may result from attenuated vitamin D metabolite levels.\textsuperscript{100} The pH microclimate of the rat jejunum is less acidic with ageing and this change may play a role in the alterations associated with intestinal absorption of nutrients, in particular amino acids, lipids and calcium.\textsuperscript{101}

**Morphology**

Changes in the morphology of the small intestine may also contribute to age-associated alterations in nutrient absorption. In studies of Fischer 344 rats no age-related change was found in the density of the villi in the small intestine or in the size of the enterocytes, but there was an increase in the width of the villi throughout the intestine, an increase in duodenal and jejunal crypt depth, as well as increased ileal villous height, ileal mass and ileal DNA content.\textsuperscript{102} The number of villi per unit area of intestine decreases in aged rats, suggesting that the overall surface area of the intestine may change without an alteration in villous height or width.\textsuperscript{103} The height, width, depth and number of villi are incorporated into a measurement of surface area and may not be appropriate for predicting changes in mucosal surface area based on alterations in the height of the villi.\textsuperscript{104} In fact here would appear to be an age-related decline in mucosal
surface area in rabbit jejunum. There is no significant difference between young and old enterocytes height and jejunal surface area-to-volume ratios in human subjects. There is a 35% increase in villous height in the ileum of aged rats as well as increased ileal aminopeptidase activity in rats re-fed a high protein diet following 48 h of starvation. This suggests that the ileum may compensate for an age-associated loss of surface area of the jejunum. Furthermore, the ileum of aged rats may be exposed to a greater luminal load due to decreased uptake in the proximal small intestine, thereby causing hyperplasia of the ileum. Supporting this suggestion, ileal–jejunal transposed rats showed an increase in the mucosal mass of the transposed ileum in young, mature and old animals. Morphological changes associated with ageing fail to fully explain altered absorptive capacity in laboratory animals. For example, increased saturated fatty acid uptake was observed in the jejunum of aged rabbits but surface area had decreased. These findings suggest that other factors may be responsible for the altered lipid uptake. For example, differentiation of the enterocytes as they migrate from crypt to villous tip is delayed in ageing animals. There is a greater crypt cell proliferative rate, as well as a broadened zone of proliferation within the crypts of old rats. The immunohistochemical expression of the proliferation cell nuclear antigen is markedly increased in the duodenal villi and crypts of humans over 65 years, compared with younger persons. This suggests that the abnormal proliferation pattern may explain the coexistence of ‘normal morphology’ with impaired absorptive function in the elderly.

Adaptive response

The adaptive response of the aged gut is impaired in ageing. Therefore, in times of stress such as injury or illness, malnutrition may result more readily. For example, dietary restriction initiated in aged rats resulted in a dramatic weight loss, with no weight stabilization after 12 weeks of reintroduction of a normal diet. In addition, the intestine of the animals was atrophied and ileal hydrolase activity was decreased. Following a period of underfeeding, elderly men continued to underfeed themselves for a period of 9–10 days while their younger counterparts increased their energy intake. This suggests that following a period of illness, when nutrient intake is reduced, the elderly may continue to underfeed themselves despite their recovery from the illness.

Practice points

- there is a reduction in the intestinal absorption of carbohydrates, lipids and amino acids associated with ageing that may contribute to the increased incidence of malnutrition in the elderly population
- there is no clear association between morphological and absorptive changes in ageing, but changes in proliferative rate and cell maturity may contribute to reduced nutrient absorption
- elderly patients admitted to hospital are at high risk for becoming malnourished. Elderly patients may have a decreased functional reserve of the intestine and may become malnourished rapidly during periods of stress
- due to a reduction in the adaptive potential of the aged patient, an extended period of intensive nutritional monitoring may be required following illness or injury
Research agenda

- further characterize the role of dietary nutrients in effectively altering absorption in disease processes and in ageing
- determine the role of lipid binding proteins in lipid uptake and how these proteins are affected by the ageing process
- identify the signals of intestinal adaptation and develop strategies to enhance the impaired adaptive response of the aged

This fact, combined with a reduction in nutrient absorptive capacity of the small intestine as well a reduced adaptive response, will put the patient at high risk for becoming malnourished.

REFERENCES


51. Tessner TG & Stenson WF. Over expression of MDR1 in an intestinal cell line results in increased cholesterol uptake from micelles. *Biochimica et Biophysica Acta* 2000; **167**: 565–571.


57. Hsu KT & Storch J. Fatty acid transfer from liver and intestinal fatty acid-binding proteins to membranes occurs by different mechanisms. *Journal of Biological Chemistry* 1996; **271**: 13317–13322.


65. Leiper JM, Bayliss JD, Pease RJ et al. Microsomal triglyceride transfer protein, the apolipoproteinbprotein gene product, mediates the secretion of apolipoprotein B-containing lipoproteins from heterologous cells. *Journal of Biological Chemistry* 1994; **269**: 21951–21954.


