Lipid Absorption and Intestinal Lipoprotein Formation

P. H. R. Green and J. W. Riley


Lipid absorption is a complex process which involves coordinated gastric, intestinal, biliary and pancreatic function. Emulsification of dietary lipid occurs in the stomach and upper intestine where a series of enzymic events also occur. Phospholipids are digested by phospholipases. Colipase anchors lipase to the emulsion surface overcoming the interfering effect of bile salts. The products of lipolysis, monoglycerides and fatty acids, are removed from the emulsion surface by bile salts in the form of mixed micelles which transport lipid digestive products across the unstirred water layer to the epithelial cell.

Within the intestinal epithelial cell a series of synthetic events occur resulting in the formation of chylomicrons and very low density lipoprotein (VLDL). Chylomicrons consists of an oily core of triglyceride surrounded by a membrane of phospholipids, free cholesterol and apoproteins which maintain the solubility of the particle in plasma. Chylomicrons from both experimental animals and man have specific apoproteins associated with them. These proteins include apoA-I, the major protein of plasma high density lipoproteins. During chylomicron metabolism, apoA-I and phospholipid from the chylomicron surface contribute to plasma high density lipoproteins.

Key Words: Lipids --Gastrointestinal tract --Triglycerides-- Low density lipoprotein.

Introduction

The average western diet contains approximately 100 g of fat, which supplies 40% of the daily caloric intake. Dietary lipid is mainly triglyceride which contains long chain saturated and unsaturated fatty acids, however, about 5-10% of ingested triglyceride is composed of medium chain fatty acids. Other ingested lipids, which are less easily absorbed than triglycerides include complex lipids, cholesterol and sterol esters, fat soluble vitamins, natural hydrocarbons and pollutants. The overall process of lipid absorption is extremely efficient with <5% of ingested triglyceride recovered in the faeces.

Dietary fats are water insoluble compounds which must be markedly altered prior to absorption. They are initially emulsified, hydrolyzed and the products of lipid digestion solubilized in the watery environment of the intestinal lumen. These processes involve a complex series of events including co-ordinated gastric, intestinal, biliary and pancreatic function.

Role of the Stomach in Lipid Absorption

The stomach functions as a receptacle, mixing
food and gastric secretions. It is the site of action of lingual lipase which is secreted by lingual glands in response to oral triglyceride and mastication. Lingual lipase requires an acid medium for maximum hydrolysis of triglyceride, forming diglycerides and fatty acids. Gastric lipases have been reported in experimental animals, but are probably not important in digestion as they have little activity on long chain fatty acids. Partial hydrolysis of triglyceride by lingual lipase provides polar groups (fatty acids and diglycerides) which aid in emulsification of the large triglyceride droplets. Gastric emptying is controlled by both the volume and composition of the meal. The major regulating factor, however, is the caloric density of the ingested food. Isoincrement amounts of fat, protein and carbohydrate equally slow gastric emptying.

**Role of the Small Intestine in Lipid Absorption**

Within the small intestine lipid absorption can be divided into luminal, mucosal and secretory or lymphatic phases.

(1) **Luminal Phase:**

Fatty acids, amino acids and hydrochloric acid stimulate the release of the gut hormones cholecystokinin-pancreozymin (CCK-PZ) and secretin; these in turn, stimulate pancreatic secretion, gallbladder contraction and the delivery of bile into the small intestine. Pancreatic secretions are rich in bicarbonate and contain pancreatic triglyceride lipase, cholesterol esterase, phospholipase A, and colipase. Biliary secretions are composed of bile salts, cholesterol and phospholipids (mainly lecithin). The resultant digestive milieu in the upper small intestine is maintained relatively constant with respect to pH, ionic strength, lipid and enzyme concentration by hormonal regulation of gastric emptying and feedback inhibition of intestinal hormone release. Lipid emulsion particles entering the duodenum are further emulsified by biliary phospholipids, bile salts, monoglycerides and fatty acids, thereby markedly increasing the surface area of the lipid emulsion.

Within the upper small intestine enzymes are sequentially activated. Enterokinase is released from the brush border of intestinal epithelial cells by bile salts allowing conversion of trypsinogen to its active form, trypsin. Trypsin in turn converts prophospholipase A to phospholipase A. Phospholipase A hydrolyses emulsion surface phospholipids to lysolecithin and fatty acids. Colipase, a small molecular weight pancreatic protein, acts as a co-factor for pancreatic lipase. Colipase forms a 1:1 complex with lipase and together with bile salts protects lipase against tryptic digestion. Colipase binds triglyceride, and facilitates the binding of pancreatic lipase to the triglyceride surface. Pancreatic lipase reversibly hydrolyses triglyceride, forming fatty acids and monoglyceride (MG), which is not further hydrolysed. In the presence of bile salts, lipase is prevented from binding to the triglyceride surface and lipolysis is inhibited. Colipase overcomes this inhibitory effect. It is likely that surface coats of phospholipid must be removed from the triglyceride surface before colipase and lipase can bind to the emulsion particle. Evidence for this comes from *in vitro* studies in which maximal hydrolysis of triglyceride coated with phospholipid or protein (similar to dietary triglyceride) by lipase occurs only after the addition of phospholipase and colipase. In this situation, bile salts enhance lipolysis by the removal of the products of lipolysis, through the formation of mixed micelles. A micellar phase is formed in the intestinal lumen when the bile salt concentration exceeds ~3 mM/l (i.e. the critical micellar concentration). This concentration of bile salts is usually exceeded during normal digestion. Mixed micelles contain bile salts, fatty acids, monoglycerides, cholesterol and fat soluble vitamins and are considered to be the major route of delivery of the products of fat digestion to the absorptive cell. Recent evidence suggests that other non-micellar phases exist in the intestinal lumen during triglyceride digestion. These include a liquid crystalline phase and a viscous isotropic phase, the importance of which remains to be determined. These non-micellar phases may provide secondary less efficient routes of lipid absorption dependent on the more distal small intestine.

The bile salt solubilized products of fat digestion are transported across the unstirred water layer which covers the surface of the intestinal mucosa and is considered to be the major barrier to absorption. Once this
barrier is overcome, lipids are readily transported across the lipid membrane of the intestinal epithelial cell.

**Bile Salt Metabolism and Role in Fat Absorption**

Bile salts are either trihydroxy or dihydroxy bile acids conjugated with either taurine or glycine. The primary bile salts, cholic and chenodeoxycholic acid, are synthesized in the liver and comprise 80% of biliary bile salts. Within the gut lumen, bile acids are dehydroxylated and deconjugated by bacteria forming secondary bile salts which are partially reabsorbed and comprise 20% of the bile salt pool. The major secondary bile salts are deoxycholic acid and lithocholic acid. Bile salts are efficiently absorbed by an active process in the distal ileum and undergo an enterohepatic circulation.

Approximately 600-800 mg of bile salts are synthesized by the liver daily, equivalent to the amount lost in the stool. The total bile salt pool is only 2–4 g; however, 20-30 g pass through the small intestine each day via the enterohepatic circulation. The function of bile salts are summarized in Table 1.

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<th>TABLE 1 Functions of Bile Salts in Lipid Absorption</th>
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<tr>
<td>Stabilisation of pancreatic lipase against digestion</td>
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<tr>
<td>Stimulation of enterokinase release</td>
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<td>Inhibition of PZ-CCK release</td>
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<td>Co-factor for cholesterol esterase</td>
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<td>Co-factor for phospholipase A</td>
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<td>Miscellarisation of digestive products</td>
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(2) **Mucosal Phase:**

**Uptake of Fatty Acids**

Uptake of lipids (fatty acids and monoglycerides) across the microvillus membrane is probably a passive process. The rate of fatty acid absorption is determined by chain length and saturation. Unsaturated long chain fatty acids are more efficiently absorbed and esterified than saturated fatty acids and utilize a shorter length of the proximal intestine. Animal experiments have demonstrated that medium chain triglycerides (MCT) are absorbed in the absence of bile salts and pancreatic lipase and do not require re-esterification or chylomicron formation for release from the intestinal cell. MCT is therefore an extremely useful nutritional supplement in bile salt and pancreatic lipase deficient states.

Recently a low molecular weight protein, fatty acid binding protein (FABP), has been isolated from rat intestinal epithelial cells. This protein avidly binds fatty acids and acts as an intracellular transport protein. It appears to have greater affinity for unsaturated fatty acids and may account for their more rapid absorption and esterification.

**Chylomicron Formation**

Lipid formation occurs primarily in the villus tips. As the quantity of ingested lipid increases, progressively more of the villus and length of the intestine are used for lipid absorption. Within the epithelial cell, triglyceride, lysophospholipids and cholesterol esters are resynthesized from fatty acids, monoglyceride, cholesterol and lysolecithin.
Resynthesis of triglyceride occurs in the smooth endoplasmic reticulum of the apical portion of the epithelial cell. The triglyceride droplet can be seen within the endoplasmic reticulum by electron microscopy and its passage followed through the endoplasmic reticulum, Golgi apparatus, towards the basolateral cell membrane. Here Golgi vesicles appear to fuse with the cell membrane and discharge the intact lipoprotein into the intercellular space.27 This is an extremely rapid process occurring within minutes of lipid absorption.28 In its passage through the cell, the triglyceride droplet is covered by a membrane of polar phospholipids, free cholesterol and protein. This is shown diagrammatically in Figure 1.

(3) Secretory Phase:
Chylomicrons are secreted by processes which probably involve microtubular function.29 Chylomicrons pass through intercellular spaces to mesenteric lymphatics where they ultimately enter the blood and gain access to the circulation via the thoracic duct.

<table>
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<th>TABLE 2</th>
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<td>Sites of Plasma Lipoprotein Formation</td>
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<tr>
<td>Chylomicrons</td>
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<td>VLDL</td>
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<td>LDL</td>
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**Characteristics of Intestinal Lipoproteins**
Recent research has explored the origin of plasma lipoproteins (Table 2). Analysis of mesenteric lymph from experimental animals provides evidence that the intestine synthesizes chylomicrons and VLDL during lipid absorption. Chylomicrons from the rat and man have similar chemical compositions (Table 3). VLDL are smaller and contain less TG and comparatively greater quantities of phospholipids, cholesterol and proteins (Table 3). The large triglyceride component reflects the major physiological role of these particles in fat absorption and transport. The more polar constituents--phospholipids, free cholesterol and apoproteins form a monolayer over the apolar, insoluble triglyceride core of the chylomycin. Cholesterol esters are also found in the core of the chylomycin.31 The surface membrane of polar lipids and protein maintains the solubility of the hydrophobic core components in the aqueous body fluids. Between meals the intestine absorbs endogenous lipids (mainly of biliary origin) and secretes them as VLDL-sized particles.32, 33 The intestine is also a site of synthesis of high density lipoproteins (HDL). Rat mesenteric lymph contains HDL-sized particles which exist in two discrete forms.34 There are small, spherical HDL. which resemble plasma HDL and are most likely filtered from plasma. In addition, lymph contains phospholipid-rich discoidal particles which resemble nascent hepatic HDL.35 Discoidal HDL are considered to be precursors of spherical plasma HDL, formed through the action of lecithin: cholesterol acyltransferase (LCAT).35 LCAT converts cholesterol to cholesterol ester which is hydrophobic and moves to the centre of the particle resulting in a smaller spherical lipoprotein.

**Chylomycin Apoproteins**
Although only comprising ~1% of the chylomycin mass, the protein component of chylomicrons appears to be important in chylomycin metabolism. Chylomicrons have a consistent pattern of apoproteins which comprises apoB, apoA-I, apoA-IV, apoE and the C peptides (Fig. 2). These are illustrated in polyacrylamide gels which separate the individual proteins according to their molecular weight. Similarities exist between man30 and experimental animals.36
Each of these apoproteins have a discrete chemical composition, molecular weight, and immunological identity. As well as being important in lipoprotein structure, apoproteins have important metabolic functions (Table 3). Both animal experiments, in the form of isotopic labelling studies, and human experiments have indicated that apoB, apoA-I and apoA-IV are present in intestinal epithelial cells and are synthesized during lipid absorption. ApoE and apoC are synthesized by the liver and transferred to the chylomicron surface after exposure to plasma and lymph lipoproteins.

ApoB, a high molecular weight protein which is also found in plasma VLDL and LDL, appears to be essential for chylomicron formation and secretion. This is underscored by the rare disease abetalipoproteinemia in which there is a complete absence of apoB-containing lipoproteins in plasma and an inability to form chylomicrons. Even though absorption of lipid occurs and triglyceride is resynthesized, there is failure of secretion of chylomicrons and VLDL. The basis of abetalipoproteinemia is considered to be a defect in the synthesis of apoB which is absent in intestinal mucosal cells.

ApoA-I, the principal apoprotein of plasma HDL is also found as a major chylomicron apoprotein. A critical function of apoA-I is to activate the enzyme LCAT. This enzyme is important in cholesterol and HDL metabolism. Glomset has proposed that HDL removes cholesterol from tissues through the LCAT reaction which creates a gradient of free cholesterol due to cholesterol ester formation. This attractive proposal would provide a mechanism for the protective effect of HDL against atherosclerosis. The intestine appears to be a major site of apoA-I synthesis in both experimental animals and man. Studies in man have provided evidence that during lipid absorption, the intestine contributes 30–50% of plasma apoA-I indicating the importance of the intestine as a synthetic site of plasma HDL components.

The lower molecular weight C peptides (apoC) are transferred from HDL present in mesenteric lymph and plasma and are recycled back to HDL during chylomicron metabolism. ApoC-II is the major activator of lipoproteins lipase, the endothelially-bound enzyme responsible for hydrolysis of chylomicron triglyceride. Chylomicrons are metabolized in two phases, initially in the periphery through the action of lipoprotein lipase. The product of lipoprotein lipase action is a smaller particle, the chyl-

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**TABLE 3**

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<th>Major Apoproteins and their Functions</th>
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<td>ApoA-I</td>
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<td>ApoE</td>
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micron remnant, which is avidly taken up by the liver. ApoE (ARP) appears to be an important recognition factor for remnant uptake by the liver while apoC inhibits this process. 

**Acknowledgment**

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**References**


