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Role of the Gut in Modulating Lipoprotein Metabolism

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Abstract The intestinal production of lipoproteins is one of the key processes by which the body prepares dietary lipid for dissemination to locations throughout the body where they are required. Paramount to this is the relationship between dietary lipid and the enterocytes that line the gut, along with the processes which prepare this lipid for efficient uptake by these cells. These include those which occur in the mouth and stomach along with those which occur within the intestinal lumen itself. Additionally, the interplay between digested lipid, dual avenues for lipid uptake by enterocytes (passive and lipid transporter proteins), a system of intercellular lipid resynthesis and transport, and a complex system of lipoprotein synthesis yield a system open to significant modulation. In this review, we will attempt to outline the processes of lipid digestion, lipoprotein synthesis and the exogenous and endogenous factors which exert their influence.

Keywords Chylomicron · Enterocyte · Free fatty acid · Intestine · Lipase · Lipid · Lipoprotein · Triglyceride · Microbiota · Gut · Metabolism

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Introduction

The average human consumes approximately 35 % of his/her daily energy requirement as lipid [1, 2, 3•], mainly in the form of triglycerides (TG), but also as free fatty acids (FFA), phospholipids (PL) and cholesterol (CL) [4]. Additionally, membrane components of microbial cells and enterocytes further contribute to the intestinal supply of CL and PL on completion of their lifecycle [5, 6]. There is a strong appreciation of the importance of dietary lipid composition, and the manner and efficacy by which the human digestive system processes this lipid in the subsequent co-morbidities of obesity such as type-2 diabetes, dyslipidemia and cardiovascular disease [7–9]. To facilitate the uptake of dietary lipids in the intestine and eventual transfer to the circulatory system, the human digestive system has developed a complex system of digestive and absorptive processes culminating in lipoprotein formation (Table 1). This process involves the interaction of dietary lipids (TG, FFA, CL and PL) with each other, non-lipid dietary components, intestinal secretions (bile acids, digestive enzymes, etc.), as well as the intestinal lining itself [5]. To this end, any physiological condition/state or dietary component which impacts on these interactions can affect not only the efficacy of lipid uptake but also the amount, size and form by which this lipid is presented to the human circulatory system as lipoproteins [10, 11]. This is particularly true of TG, which require significant emulsification and hydrolysis to permit their components to cross into the enterocyte lining of the gut [12, 13].

Table 1 Primary sites of lipid digestion and absorption and some of the critical components involved

Location	Digestive/absorptive activity
Mouth	
Lipid digestion	
Lingual lipase	Acidic lipase, primarily hydrolyses medium and long chain fatty acids at the sn-3 position of TG.
Stomach	
Lipid digestion	
Lingual lipase	Continued digestion by oral lingual lipase.
Gastric lipase	Acidic lipase, primarily hydrolyses fatty acids at the sn-3 position of TG.
Intestinal tract	
Lipid digestion	
Gastric lipase	Continued digestion by gastric lipase. Eventually inhibited as intestinal pH increases due to intestinal secretion of bicarbonate.
Pancreatic lipase	Catalyses the hydrolysis of sn-1 and sn-3 positions of TG. Hydrolysis would eventually be inhibited by the build up of hydrolysis product at the oil water interface.
Bile acids/salts	Act as a surfactant displacing hydrolysis products at the oil water interface preventing inhibition of pancreatic lipase.
Colipase	Amphipathic protein capable of binding to both pancreatic lipase and the surface of the mixed lipid micelle, thus, anchoring the enzyme.
Bile salt stimulated lipase	Produced by the pancreas and present in human breast milk. Catalyses the release of FFA from TG, DG, MG, PL, CL and ceramide.
Alkaline sphingomyelinase	Catalyses the hydrolysis of sphingomyelin to ceramide and phosphocholine in the presence of bile salts.
Neutral ceramidase	Catalyses the conversion of ceramide to sphingosine and FFA.
Lipid absorption	
Passive uptake (FFA)	Dissociation of the mixed lipid micelle at the brush border membrane and subsequent protonation of the FFA released creates a FFA gradient between the interior and exterior of enterocytes facilitating passive uptake of FFA.
Transporter proteins (FFA)	
FABPpm	Mechanism unknown. Inhibition of its activity may reduce FFA uptake by cells.
CD36	Found throughout intestine and in particular caveolae. Deficiency unlikely to cause reduced FFA absorption by intestine. May result in impaired chylomicron formation.
FATP4	May be involved in the metabolic trapping of FFA and improved passive uptake of FFA. Deletion of FATP4 has been associated with fatal outcomes.
Caveolin-1	Found in high concentrations in caveolae. May be involved in FFA uptake by enterocytes via endocytosis
Transporter proteins (CL)	
NPC1L1	Found in high concentrations in the distal intestine
Sodium dependent bile acid transporters	Associated with the recovery of conjugated bile salts from the distal intestine.

Once the digested lipid is absorbed from the intestinal lumen into the enterocytes lining the gut it can be used to reassemble more complex lipids, that are utilized in the formation of lipoproteins which exit the enterocytes via exocytosis [5, 10, 14]. Of the two forms of intestinally derived lipoprotein, it is probably chylomicrons which have the greatest influence on cardiovascular disease risk factors. Indeed, studies have demonstrated that the release of a high volume of intestinally derived chylomicron in the postprandial period can contribute to increased cardiovascular disease risk via 1) elevations of serum TG concentrations (positively correlated with coronary artery disease) and 2) increases in the quantity of chylomicron remnants which accelerate arteriosclerotic plaque formation [15–17].

In this review, we will attempt to describe and assess the role the gut plays in lipoprotein production, along with the influence of other endogenous factors and diet on this process. Also as the principle dietary lipid, much emphasis will be placed on dietary TG within the digestive process and the mechanisms present in the gut which allow these important nutrients to enter the human circulatory system via intestinal lipoprotein formation.

Dietary Lipids and the Human Gastric System

The ingestion of food by humans and subsequent mastication stimulates the production of saliva and digestive enzymes in the mouth. These processes serve to lubricate, mix and emulsify food, but also mark the initiation of the digestive process via the action of digestive enzymes including lingual lipase [18]. This acidic lipase, with its pH optimum of approximately 3.5-6.0, catalyses the hydrolysis of short or medium chain fatty acids (primarily) present at the sn-3 position of dietary TG forming DG and FFA [19–21]. Due to its high stability at acidic pH, lingual lipase can remain active in the stomach hours after consumption of a meal [22]. In adults, the contribution of lingual lipase to overall TG digestion is lower than that of other

digestive lipases [23, 24]. However, in the infant where pancreatic lipase activity is much lower and the diet is high in milk derived TG rich in short and medium chain fatty acids, lingual lipase can contribute substantially to lipid digestion [19, 22].

In addition to continued TG digestion by lingual lipase, the stomach itself produces an acidic lipase from the fundic area of the gastric mucosa. This gastric lipase (pH range of approximately 3.5-6.0) is attributed with catalyzing the release of approximately 15 % of dietary fatty acids primarily via the conversion of TG to DG and FFA [20, 25]. Interestingly, it has been demonstrated that lipase activity within the human stomach is higher in the upper greater curvature of the stomach than in the upper lesser curvature, and lowest in the antral area [24].

Both lingual and gastric lipases exert their activity at the oil water interface of lipid droplets, but their activity here is limited due to the polar nature of the FFA and DG produced from TG, which accumulate at the interface, reducing the ability of the lipase enzyme to access further TG [26, 27]. Although this interfacial accumulation reduces lingual and gastric lipase mediated hydrolysis of TG, it is beneficial for subsequent intestinal digestion of TG by pancreatic lipase, with DG and FFA acting as surfactants, stabilizing lipid droplets in the aqueous intestinal environment [5, 28].

Intestinal Lipid Digestion

From the stomach, the now partially digested food (including lipid) termed chyme passes into the duodenum, or upper intestinal tract. This process is extremely well controlled with the aim of maximizing subsequent intestinal digestion and absorption of nutrients. Indeed, cholecystokinin (CCK) produced by the intestinal mucosa in response to a lipid-rich meal has been shown to delay gastric emptying and inhibit gastric acid and plasma gastrin responses [29, 30]. This may allow the stomach to serve as nutrient reservoir, preventing overburdening of the intestinal digestive processes and the loss of important nutrients. Chyme emerging from the stomach is very acidic (approx pH 2) and as such can sustain gastric lipase activity in the immediate aftermath of its release further contributing to TG digestion [25]. Although gastric lipase initially remains active in the duodenum, intestinal secretions quickly alter environmental conditions away from those which favor its activity.

In early infancy when the intestinal lipase system is underdeveloped, breast fed infants achieve the intestinal digestion of acylglycerides via pancreatic lipase related protein-2 and importantly via the activity of the enzyme bile salt stimulated lipase [31–33]. Bile salt stimulated lipase is activated by the presence of bile salts and is capable of catalyzing the hydrolysis of a range of lipids including TG, DG and MG releasing FFA and glycerol [34–36]. The activity of this enzyme in the neonate is of paramount importance to the intestinal absorption of lipid, but the enzyme does not play as significant a role in TG digestion in adulthood. Indeed, in adults pancreatic lipase produced by pancreatic acinar cells and secreted into the duodenum in response to various stimuli including CCK, acetylcholine, and the hormone secretin represents the major lipolytic enzyme [37–42]. Unlike bile salt stimulated lipase, the hydrolytic activity of pancreatic lipase is confined to the sn-1 and sn-3 positions of acylglycerides resulting in the production of FFA and MG [43–45]. As the principle lipase in human adults the activity and volume of pancreatic lipase, along with the efficacy by which this enzyme accesses lipid droplets, has a major bearing on subsequent intestinal lipid absorption and lipoprotein production. To this effect, the human body has evolved an extensive series of processes designed to maximise the enzymes efficacy, which when negatively impacted on can have wide ranging deleterious effect on lipid metabolism.

Human pancreatic lipase is secreted into the duodenum as a component of pancreatic juice (pH 8) [41]. At the lower pH values which occur after gastric emptying, activity of the enzyme may be significantly decreased, with studies showing inactivation of the enzyme occurring a pH <4 [46]. Thus, the human intestine has developed an efficient mechanism to increase intestinal pH towards neutrality (pH 6.5-7.0), involving the secretion of bicarbonate ions [41, 47, 48]. This system of bicarbonate production is significantly controlled by the hormone secretin produced by S-cells in the duodenal mucosa in response to low duodenal pH (<4.5) or the presence of digestive components within the duodenal lumen [49–52]. With the duodenal pH increased, pancreatic lipase activity increases converting acylglycerides to FFA and MG. However, due to their polarity these lipids begin to accumulate at the oil water interface of lipid droplets, an occurrence which would eventually impede pancreatic lipase activity [53]. To prevent this, the body secretes bile acids from the gallbladder into the duodenum via the biliary duct as bile. These bile acids along with PL act as surfactants, solubilising and displacing lipolysis products at the interface and helping to form mixed lipid micelles, thus increasing lipase access to undigested lipid [41, 53]. The flow of bile from the gall bladder is controlled by the sphincter of Oddi. However, relaxation of the sphincter can be achieved through production by the intestinal mucosa of the hormone CCK in response to the presence of dietary FFA or certain amino acids [54–57]. Furthermore, stimulation of bile release from the gall bladder can be achieved by vagal efferent responses and the hormone motilin [58]. Bile salts originate as bile acids in the liver where they are derived from CL, with the majority being conjugated to glycine or taurine amino acids thereafter to increase solubility in the aqueous environment of the intestinal lumen [59–61]. Following completion of their role in lipid digestion the majority of conjugated bile acids are recovered by apical sodium dependent bile acid transporters in the distal intestine and returned to the liver

with up to 95 % recirculated [59]. This complex process of bile acid circulation has been extensively reviewed elsewhere with scenarios where the production/secretion/absorption/re-circulation of bile is impaired, being shown to result in any of a number of detrimental conditions often characterized by steatorrhea and diarrhoea further highlighting the importance of bile acids in intestinal lipid digestion [59, 60, 62].

Although bile acids are important for lipid digestion by pancreatic lipase, other compounds also play important roles and none more so than colipase. Colipase is produced as procolipase by pancreatic acinar cells. On the loss of a five amino acid peptide from procolipase through proteolytic digestion colipase is formed [63]. In the intestinal environment, colipase is important due to its ability to bind to both pancreatic lipase and to the surface of mixed lipid micelles owing to its amphipathic properties [64, 65]. Through this system of interaction, it is believed that any bile acid mediated inhibition of pancreatic lipase may be reduced and catalytic activity of the enzyme maximized [53, 66]. Investigations have shown that both the environmental ionic strength and pH, along with type of lipid and the presence of non-esterified fatty acids greatly influence interfacial interactions between colipase and mixed lipid micelles [63, 67–69]. Additionally, there is evidence to suggest that the presence of bile acids can enhance pancreatic lipase-colipase interaction [70]. The importance of colipase in mammals was demonstrated by D'Agostino et al., where procolipase deficient mice where shown to have a lower postnatal survival, characterised by lower body weight and higher incidence of steatorrhea, compared with their wild type counterparts [71].

The human intestine is exposed to several other lipid classes in addition to TG, including PL, sphingolipids, and CL. PL can constitute 1-10 % of dietary lipid intake in humans primarily as phosphatidylcholine, which is additionally contributed to by PL from cellular sources (enterocytes and microbes) and biliary secretions [72]. Indeed, it is estimated that bile contributes 10-12 g/d of phosphatidylcholine to the intestine, where it is required for biliary CL solubilisation and along with dietary PL for the stabilisation of mixed lipid micelles [73]. Although, both dietary and biliary PL play an important role in mixed lipid micelle formation they themselves are not immune to intestinal digestion and can be hydrolysed by both bile salt stimulated lipase and pancreatic phospholipase A2 into FFA and lysophosphatidylcholine [8].

Sphingomyelin is the predominant dietary sphingolipid found in the diet, constituting approx 0.3 – 0.4 g/d of lipid intake. In the intestine digestion of sphingomyelin is catalysed by the enzyme alkaline sphingomyelinase in the presence of bile salts, resulting in the production of ceramide and phosphocholine [74, 75]. The activity of this enzyme has been detected throughout the intestine but is maximal in the jejunum [74, 76]. Additional catalytic activity by the intestinal enzyme neutral ceramidase results in the subsequent conversion of ceramide to sphingosine and FFA [77]. Although it is estimated that approximately 0.5 g/d of sphingomyelin enter the bloodstream via lipoproteins, little of this is derived from dietary sphingomyelin, or its digestive products, ceramide or sphingosine [78]. Instead, ceramide and to a greater extent sphingosine have been shown to be absorbed by the intestinal mucosa where the majority is metabolised to palmitic acid for incorporation into chylomicrons, whilst a smaller portion may be reutilized in the intestinal mucosal cells [79]. Additionally, it is believed that in the intestinal lumen, sphingomyelin and its digestive metabolites may play a role in intestinal health and in the inhibition of intestinal CL absorption [78, 80].

Dietary CL constitutes only approximately 300-500 mg/d of total lipid entering the intestine, and is significantly contributed to by biliary CL (800-1200 mg/d) [81]. While biliary CL and the majority of dietary CL is present in an unesterified state and readily absorbed by enterocytes, esterified dietary CL must first undergo hydrolysis by the enzyme bile salt stimulated lipase secreted by the pancreas [82, 83].

Intestinal Lipid Adsorption

Following ingestion of a lipid rich meal, the action of a number of gastrointestinal enzymes results in the production of various lipid fractions. These lipid fractions are stabilized as mixed lipid micelles and carried to the enterocytes which line the intestinal lumen in what is known as the "Brush Border Membrane" the primary site of lipid absorption. The Brush Border Membrane increases the absorptive area of the intestine, but additionally traps water molecules in its immediate vicinity in an area known as the unstirred water layer [84]. This water layer has a pH that is significantly lower than that of the intestinal lumen which on contact with a mixed lipid micelle causes micellar dissociation and protonation of the FFA within [84]. The resulting localized increase in FFA creates a FFA concentration gradient, permitting the passive uptake of FFA by the enterocytes [3•, 5, 85]. In addition to the passive uptake of FFA and MG, certain fatty acid-binding proteins, including peripheral plasma membrane fatty acid binding protein (FABPpm), cluster determinant 36 (CD36), and fatty acid transport protein 4 (FATP4) can additionally contribute to FFA uptake, particularly when the overall concentration of dietary lipid is low [85–87].

FABPpm is found on the plasma membrane of enterocytes, however, little is known regarding the mechanism of FFA uptake by this protein. Evidence for a role in FFA absorption was initially shown during studies using jejunal explants, which demonstrated inhibition of its activity resulted in significant reductions in FFA uptake by cells [88]. However, the results of other studies using normal human intestinal epithelial cells overexpressing FABPpm have drawn

into question its role in lipid transport and further research is necessary [89].

CD36 is a glycosylated trans membrane protein whose role in FFA transport was highlighted by Abumrad et al. [90]. CD36 is found throughout the intestine, but it is particularly prevalent in the caveolae of the proximal intestine, and decreases in prevalence towards the distal intestine [90–92]. The expression of CD36 is increased by high lipid diets and by FFA, and as such is likely to be influenced by lipid digestion [92]. In the proximal intestine CD36 may play an important role in initial FFA uptake but becomes rapidly saturated potentially limiting its overall contribution [3•]. Additionally, in vivo studies have shown that deficiencies in CD36 are unlikely to result in poor FFA absorption, but instead may result in increased FFA absorption in the distal intestine [93, 94]. Interestingly, human deficiencies in CD36 have been associated with the secretion of lipoproteins much smaller than chylomicrons [95]. Researchers have attributed this to impaired chylomicron formation and speculated a role for CD36 in lipid processing in the endoplasmic reticulum (ER) and/or intracellular lipid transport [3•].

FATP4 is found in high concentrations within jejunal enterocytes and may play an important role in intestinal FFA absorption [85, 96]. Indeed, deletion of FATP4 has been associated with fatal outcomes [97, 98]. Although FATP4 plays an important physiological function there is much debate with regard to what this might be. This stems primarily from the cytoplasmic location of the protein within enterocytes, with only a short sequence extending into the extracellular environment on which no FFA binding domain can be identified [85]. FATP4 is however associated with acyl-CoA synthase activity and may be involved in the metabolic trapping of FFA [99, 100]. The fatty acyl-CoA products of this activity undergo rapid conversion to more complex lipid species, maintaining a low cellular FFA concentration and favoring passive diffusion of FFA into the cell [3•, 85].

Caveolin-1 is a small membrane protein associated with lipid rafts found on the brush border membrane and a known FFA binding protein [101, 102]. This protein plays an important function in the activity of caveolae which may be involved in FFA uptake by enterocytes via endocytosis [85, 103]. Indeed, caveolin-1 has been detected in caveolae endocytic vesicles present in the cytosol [104].

Whilst our knowledge of the proteins associated with intestinal FFA absorption is ever increasing, our knowledge of membrane protein associated MG uptake by enterocytes is much less defined, though membrane protein(s) are suspected to play a role [105, 106]. Additionally, it has been postulated that the transport of MG and FFA may be coordinated to maximise later TG reformation [3•, 107].

Niemann-Pick C1 Like 1 (NPC1L1) is a protein found in high concentrations on the membrane of enterocytes in the proximal intestine and has been shown to play a significant role in free CL uptake [108]. Subsequently, this absorbed CL is carried to the ER as NPC1L1-CL where it is esterified via the action of acyl-CoA cholesterol acyl-transferases [109, 110]. In addition to the influence of NPC1L1 and acyl-CoA cholesterol acyl-transferases on CL absorption other dietary lipid fractions have also been shown to have an impact. When rats were fed equal concentrations of sphingomyelin and radiolabelled CL, absorption of CL was substantially reduced, while in vitro studies have shown that the inhibitory effect of sphingomyelin on CL was reduced after hydrolysis [78]. Sphingosine a product of intestinal ceramide hydrolysis has also been shown to down regulate NPC1L1 [111].

Intracellular Lipid Resynthesis

Following absorption into the cytosol, FFA are dispatched to caveolae endocytic vesicles, or along with MG, sequestered by fatty acid binding proteins (FABP) for delivery to the ER. FABP occur in two distinct forms, liver-FABP or intestinal-FABP, and constitute about 4-6 % of the total protein content of the cytosol [86, 112]. The absence of FABP in mouse models has not been associated with reduced FFA absorption, but a reduction in chylomicron production has been observed [113–115].

In the ER, MG and FFA are used to resynthesise TG in a process known as the MG pathway [116]. The first step in this process is catalysed via the combined activity of acyl-coenzyme (acylates the FFA) and MG acyl-transferase (MGAT) enzymes (covalently links acylated FFA to a MG molecule) culminating in the formation of a DG. Two MGAT enzymes have been detected in the human intestine (MGAT2 and MGAT3) [116–118] of which it is believed that MGAT2 plays a prominent role in DG synthesis [119]. MGAT2 knock-out animals have also been shown to exhibit slower intestinal lipid absorption, further emphasizing an important role for this protein [120]. Overall, it is believed that the action of MGAT enzymes contribute 75-80 % of the total DG required for TG resynthesis with the remainder supplied via the glycerol phosphate pathway [86, 121, 122]. DG formed by the action of MGAT or the glycerol phosphate pathway, are converted to TG in the ER by the combined action of acyl-coenzyme A and one of three enzymes with DG acyltransferase activity (DGAT) namely DGAT1, DGAT2 and MGAT3 [86]. Of the three, DGAT1 may mediate the conversion of a significant proportion of DG to TG, nevertheless it has been demonstrated that DGAT1 knockout animals can still adequately absorb lipid, but may exhibit reduced or delayed chylomicron secretion [123–125]. However, studies in mice have indicated that DGAT2 may be essential for TG synthesis and survival [126].

As previously described, intestinally absorbed CL is carried to the ER as NPC1L1-cholesterol complex where it is

esterified via the action of acyl-CoA cholesterol acyltransferase 2 [127]. Similarly, phosphatidylcholine may be produced by re-acylation of intestinally absorbed lysophosphatidylcholine or alternatively synthesised de novo [128]. Reformed phosphatidylcholine plays an important role in lipoprotein formation but is also utilised in the synthesis of sphingomyelin. During this process ceramide is produced in the ER via the action of palmitoyl-CoA-serine and ceramide synthase [78]. Once formed this ceramide is carried to the Golgi vesicles where sphingomyelin synthase catalyses its combination with phosphocholine from phosphatidylcholine to yield sphingomyelin.

Lipoprotein Synthesis

The quantity of dietary lipid exerts a substantial influence on the type of lipoprotein formed by the body with very low density lipoprotein (VLDL) produced during times of low lipid intake and chylomicrons dominating during periods of high lipid intake such as the postprandial period. In the case of chylomicrons, a portion of the reformed TG and esterfied CL are carried to the lumen of the ER by the microsomal TG transfer protein (MTP) and along with PL (primarily phosphatidylcholine) and free CL, are added to apolipoprotein B48 (apoB48) forming a chylomicron [129]. Both MTP and apoB48 are essential for chylomicron formation, and deficiencies can result in reduced plasma CL, plasma TG and lipid absorption, or in the case of MTP deficiency the inability to secrete chylomicrons [5, 86, 116]. As MTP mediated increases in the lipid content of the primordial chylomicron continue, another apolipoprotein termed Apo A-IV is incorporated into its structure. Apo A-IV is a recognized lipid binding protein found in intestinal enterocytes and whose expression is increased by intestinal lipid absorption [86]. It is believed this protein is involved in stabilisation of the primordial chylomicron and in the subsequent TG incorporation, but also may impact on MTP expression [85, 116, 130•, 131].

On completion of lipidation and the incorporation of apo A-IV, the maturing chylomicron or pre-chylomicron is carried from the ER to the Golgi via the pre-chylomicron transport vesicle (PCTV) [86, 132]. Once free of the ER, key proteins found within the PCTV direct this transfer and fusion of the PCTV with the Golgi including coating protein II (COPII), Sar1, vesicle associated membrane protein 7 (VAMP7), Bet1, CD36, sec23, sec24, sec13, etc. [86, 116]. On the Golgi apparatus, the chylomicron undergoes a number of changes including glycosylation of apoB48 and acquisition of the apolipoprotein, apoAI. The now mature chylomicron is carried from the Golgi to the basolateral membrane of the cell, where it exits and subsequently enters the lymphatic system [116].

In addition to the importance of the various components directly involved in lipid digestion/lipid absorption/chylomicron secretion, other endogenous factors also impact on lipoprotein production. This can begin as early as the mouth, where fatty acid receptors such as CD36 and the G-protein-coupled receptors (GPR41 and GPR43) have been implicated with triggering cascade events which impact on the secretion of compounds involved in lipid digestion including CCK, pancreatic proteins and insulin [133, 134]. While the importance of CCK and pancreatic secretions in lipid digestion is clear, studies in animals and humans with insulin resistance have indicated that insulin has an important influence over lipid processing by mammals. This may involve reduced chylomicron secretion potentially via an influence over circulating FFA and on cellular MTP, liver-FABP, MGAT and DGAT [3•, 135•, 136].

The presence of FFA in the intestinal lumen exerts an influence on several indirect modulators of lipid digestion including the incretins, glucagon like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP) and glucagon like peptide-2 (GLP-2). Whilst GIP may exert its influence on lipoprotein production via insulin secretion [137], GLP-1 has been associated with satiety promotion, modulation of insulin secretion, decreased lipid absorption, and delayed gastric emptying. Furthermore, GLP-1 agonist studies have shown stimulation increases intestinally derived lipoprotein concentrations in humans [137, 138]. Production of GLP-1 occurs on stimulation of FFA receptors (GPR40 and GPR120) found on enteroendocrine cells in the intestine [134, 139, 140]. Secretion of GLP-1 occurs simultaneously with GLP-2 at a ratio of 1:1, with the latter being associated with increased chylomicron secretion as a consequence of increased lipid absorption [141, 142]. Additionally, infusion studies in animals have indicated a positive association between GLP-2, CD36 and increased chylomicron secretion [136, 142].

Inositol requiring enzyme 1β (IRE1β) is expressed in the cells of the intestine, which during mouse and cell culture assays has been implicated with potential reductions in MTP [86, 135•]. The hormone leptin produced in the stomach in response to the ingestion of food has also been implicated with reduction of MTP expression via association with receptors found in the enterocytes [86]. Additionally, leptin has been shown to reduce production of apoAIV.

Dietary Components

Much research has been directed at the identification of dietary components that can alter dietary lipid absorption and/or positively influence human plasma lipid profiles to reduce the risk of cardiovascular disease. One of the primary targets has been intestinal CL and TG absorption, where consumption of soluble dietary fibre, catechins, phytosterols/stanols, saponins and PL have all been shown to have a positive impact [72, 108, 143]. Of these compounds, soluble dietary fibres and

phytosterols/stanols have been the most extensively studied. During investigations with various dietary fibre types, researchers have found the CL/TG lowering effect to be similar, indicating a common mechanism of action [72, 144, 145]. The exact mechanism is not well defined, but is believed to be in part related to an ability to bind CL and TG, thus reducing intestinal uptake and increasing excretion [146, 147]. Like soluble fibre, the mechanism by which phytosterols/stanols reduce CL uptake is simple in action and thought to be related to competitive inhibition at the mixed lipid micelle or through modulation of the CL transporter NPC1L1 [148].

Green tea catechins, particularly (-)-epigallocatechin gallate, have also been associated with reducing plasma CL. This has been partially attributed to their impact on the emulsification, digestion, and micellar solubilization of lipids [149, 150]. Additionally, these compounds may modulate hepatic CL production [151, 152].

Increased intestinal PL concentrations have been shown ex vivo and in vivo in both animals and humans to reduce CL absorption, but the exact mechanism remains unclear. Indeed, it has been suggested that this activity may stem from 1) interference with intestinal mixed lipid micelle formation, 2) interference with CL transporters or 3) interference with micellar PL hydrolysis (subsequently interferes with CL absorption) [72, 153].

The activity of saponins to modulate lipid uptake has been associated with their amphipathic structure which imparts them with detergent-like properties [72, 154]. This has been shown to result in increased fecal CL secretion in the case of gymnemic acid derived from *Gymnema sylvestre* [155, 156].

Whilst a number of dietary compounds are known for their ability to influence intestinal lipid absorption and lipoprotein production, dietary lipid and fatty acids themselves possibly exert the greatest influence [157]. It has been shown that stearic acid and n-3 PUFA may exert some effects on circulatory TG profiles [158, 159]. Indeed, consumption of stearic acid in place of other saturated or unsaturated fatty acids can result in reduced postprandial TG in humans/animals and CL in animals [160–162]. Dietary N-3 PUFA have been shown to reduce chylomicron size and increase chylomicron metabolism but may also potentially reduce synthesis and secretion [136]. There is also evidence to suggest that some medium chain fatty acids may enhance CL excretion via the fecal route in animal models [162]. Furthermore, combinations of very long chain PUFA and medium chain fatty acids have proved effective in reducing plasma CL and TG concentrations [163].

Intestinal Microbiota

In addition to being a site of extensive intestinal lipid digestion and absorption, the human gut is home to a diverse microbiota, which having co-evolved with the host, are considered by many as an additional organ. These organisms are capable of modulating dietary lipid composition, digestion and absorption, both through direct interaction or via their metabolites, ultimately altering intestinal lipoprotein formation. Indeed, the potential of the intestinal microbiota to influence chylomicron production has been illustrated using germ free mice, which display 40 % higher plasma chylomicron levels than conventional mice [164]. Conclusive evidence for such an impact in humans has not yet been confirmed, but there are indications that the human microbiota may exert an influence on components associated with lipid metabolism in the gut and that the provision of certain probiotic cultures may also impart a benefit.

It has been experimentally demonstrated that germ free animals or animals in receipt of antibiotics accumulate more CL than control animals, while additionally excreting lower concentrations of CL in their feces [165]. This has been associated with the reduced number of bile salt hydrolase producing cultures, an enzyme capable of deconjugating CL rich bile acids, reducing their solubility and increasing their fecal excretion [166–169]. Interestingly, it has been demonstrated that oral administration of probiotic cultures with bile salt hydrolase activity can lead to lower circulatory CL concentrations [170]. Deconjugated bile salts themselves may also play a role in reducing circulatory CL via their influence on the farnesoid X receptor, which plays a role in CL metabolism by the host (for reviews see [170–172]).

In addition to the deconjugation of bile salts, the intestinal microbiota may also produce compounds which impact on lipid and in particular CL absorption, such as exopolysaccharides or short chain fatty acids. Indeed, exopolysaccharides have previously been reported to exert a hypocholesteremic effect [173–175], while data from our laboratory demonstrate the potential of an exopolysaccharide producing *Lactobacillus* strain (*Lactobacillus mucosae* DPC 6426) to reduce serum CL when administered as a probiotic in an animal model of lipid driven atherosclerosis (Londar et al., in review). Microbially produced short chain fatty acids have also been associated with a plethora of activities in the gut which could impact on lipid uptake and/or lipoprotein formation. These include stimulation of GLP-1 production in vivo [176, 177], along with in vitro evidence from Caco-2 cell studies which indicate that butyric acid exposure could limit lipoprotein release from the small intestine into the circulatory system [178, 179].

Along with the production of compounds which modulate lipid uptake in the gut, the intestinal microbiota may also modify the lipid present in the intestine into compounds which impact on plasma lipoprotein concentrations. Once such group of compounds are the conjugated isomers of linoleic acid known by the acronym CLA, produced from free linoleic acid via the activity of microbial cultures with linoleic acid isomerase activity [180••, 181, 182]. During in vitro and

in vivo studies the provision of CLA isomers has been associated with potential reductions in the concentrations of serum TG, CL and lipoproteins, but their efficacy in humans is still questionable [183–186].

Conclusion

The digestion of dietary lipid and its subsequent absorption and packaging as lipoproteins is a complex process. Paramount to this is efficient TG digestion and formation of the mixed lipid micelle for which other lipid fractions, bile salts/acids, and pancreatic secretions are essential. This process undergoes modulation not only by factors directly involved in the process of lipid digestion and absorption, but also via responses that occur as a result of the ingestion of food (e.g. hormone secretion), as well as the influence of microbes and non-lipid dietary components. The absorption of digested lipid is also crucial to subsequent lipoprotein formation. Although it is plausible to assume passive transport represents the primary source of lipid absorption in the postprandial period, it is evident that lipid transport proteins also play an important role, both when dietary lipid is low but also during the early stages of lipid absorption. Due to its complexity and essential nature, the system of intestinal dietary lipid digestion and absorption has evolved to be highly adaptable and can in most instances cope with inefficiencies or abnormalities in the production or activity of certain components with alternative systems available. Other components are however of a more essential nature and issues with their production can lead to deficiencies in lipoprotein production, often characterised by the cellular accumulation of lipid or excessive lipid excretion in the feces.

Compliance with Ethics Guidelines

Conflict of Interest Alan A. Hennessy, R. Paul Ross, Gerald F. Fitzgerald, Noel Caplice, and Catherine Stanton declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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