Gut-liver interaction in triglyceride-rich lipoprotein metabolism

Xiao C, Hsieh J, Adeli K, Lewis GF. Gut-liver interaction in triglyceride-rich lipoprotein metabolism. *Am J Physiol Endocrinol Metab* 301: E429–E446, 2011. First published June 21, 2011; doi:10.1152/ajpendo.00178.2011.—The liver and intestine have complementary and coordinated roles in lipoprotein metabolism. Both organs are involved in maintaining nutrient homeostasis. During development, the endoderm of the yolk sac develops into the primitive gut, which subsequently forms the foregut, midgut, and hindgut. The liver arises from the foregut during the fourth week of embryonic development. The divergence of the intestine and liver from a single yolk sac, responsible for storage and mobilization of lipids, heralds the emergence of organs with more specialized functions. With regard to lipids, the primary function of the intestine is digestion, absorption, assembly, and secretion of dietary fats [triglycerides (TG), cholesterol, and phospholipids], with enormous capacity to respond rapidly and efficiently to large quantities of ingested food. The intestine does not have great capacity for prolonged storage and subsequent mobilization of ingested lipid. The liver, on the other hand, is the master gatekeeper of ingested lipid. This review aims to integrate recent advances in our understanding of these processes and attempts to provide insight into the factors that coordinate lipid homeostasis in these two organs in health and disease.

The liver and the intestine are two important organs involved in maintaining nutrient homeostasis. During development, the endoderm of the yolk sac develops into the primitive gut, which subsequently forms the foregut, midgut, and hindgut. The liver arises from the foregut during the fourth week of embryonic development. The divergence of the intestine and liver from a single yolk sac, responsible for storage and mobilization of lipids, heralds the emergence of organs with more specialized functions. With regard to lipids, the primary function of the intestine is digestion, absorption, assembly, and secretion of dietary fats [triglycerides (TG), cholesterol, and phospholipids], with enormous capacity to respond rapidly and efficiently to large quantities of ingested food. The intestine does not have great capacity for prolonged storage and subsequent mobilization of ingested lipid. The liver, on the other hand, is the master gatekeeper of ingested lipid. This review aims to integrate recent advances in our understanding of these processes and attempts to provide insight into the factors that coordinate lipid homeostasis in these two organs in health and disease.
tions. There is one apoB per TRL particle; thus, measuring apoB secretion is indicative of particle secretion. In humans and some other species such as Syrian Golden hamster, the apoB mRNA is edited to the truncated apoB-48 form in the intestine and negligibly in the liver; thus, in humans, apoB-100 is secreted exclusively by the liver in VLDL, whereas apoB-48 is secreted exclusively by the intestine in chylomicrons. In many other species, such as mouse and rat, apoB-100 is edited in both liver and intestine; therefore, the sources of apoB-100 and apoB-48 are not distinguishable between these two organs. Lipoprotein assembly is initiated by transcription of apoB protein, with the main site of regulation of apoB secretion occurring at the stage of its intracellular degradation rather than transcriptional regulation (72). In both liver and intestine, the apoB protein is cotranslationally translated into the endoplasmic reticulum (ER) lumen, where, facilitated by microsomal triglyceride transfer protein (MTP), lipid droplets are added to the apoB protein to form primordial apoB-containing particles. Further addition of neutral lipid in the ER leads to progressive enlargement of lipoprotein particles. The maturing particles are then transported through the Golgi and secreted from the cell into the hepatic vein and lymphatic system for hepatic and intestinal lipoproteins, respectively. For chylomicron assembly, two different models have been proposed. In the first model, assembly of small, dense (VLDL-like) particles and large TG-rich chylomicrons occurs by continuous addition of lipid to the particle and subsequent particle enlargement (210). In the second model, assembly of chylomicron particles is sequential, occurring by two independent pathways. Primordial lipoproteins are first synthesized, followed by synthesis of TG-rich lipid droplets. Fusion of primordial lipoproteins with lipid droplets leads to “core expansion” of the primordial lipoproteins and synthesis of nascent lipoproteins (90). More detailed accounts of intestinal lipid absorption and chylomicron assembly are reviewed elsewhere (90, 94). The peripheral plasma concentrations of apoB-48 and apoB-100 are determined by both production and clearance. After entering the circulation, TRL particles interact with other lipoprotein fractions and exchange apolipoproteins other than apoB, including acquiring apoC-II, which mediates hydrolysis of TRL-TG by lipoprotein lipase (LPL), and apoC-III, which inhibits LPL. The hydrolysis of TRL particles results in significantly reduced particle size, resulting in formation of IDL, LDL, and chylomicron remnants. Binding of apoE, present on the hydrolysis products of TRL to cell surface receptors (mainly in the liver, but also in the endothelial wall), represents the major pathway of remnant particle catabolism (127). VLDL and chylomicrons share the same saturable removal pathways and therefore compete for LPL and cell surface receptors for their removal from circulation (25). It is important to make the distinction of particle number from particle size. Increased particle size leads to greater lipid loading of an unchanged number of particles. Dietary lipid transport following a meal has generally been believed to be through increased chylomicron particle size, i.e., increased amount of neutral lipid per particle, with a lesser increase in particle number (100). On the other hand, increased TRL particle number leads to increased numbers of chylomicron remnants and LDL and thus increased atherosclerotic risk. Under certain physiological conditions, such as insulin resis-
Chylomicron secretion by the intestine mainly follows meal ingestion, whereas VLDL secretion from the liver occurs during both fasted and postprandial states, with the sources of neutral lipids incorporated into these lipoproteins differing in these two organs. In brief, hepatic TG may be derived from lipoprotein remnant uptake, uptake and reesterification of circulating FFAs (from lipolysis of adipose tissue and from dietary fatty acid spillover), mobilized lipid storage pools in the liver, de novo synthesis of fatty acids, and phospholipidosis (112) (discussed more later). A major source of diacylglycerol (DAG) for de novo TG synthesis in the liver comes from phosphatidate phosphatase activity of multiple lipin isoforms, but microsome-associated lipin-1 is important for secretion of newly synthesized TG as VLDL (23). In contrast, in the intestine, dietary lipids form the major source of TG packaged into chylomicrons. Upon digestion, the major products, fatty acids and monoacylglycerols (MAG), are absorbed into enterocytes and channeled to the ER for synthesis of complex lipids. CD36/fatty acid translocase (FAT) plays a key role in fatty acid uptake and their subsequent secretion as chylomicrons by the enterocytes (55, 56, 145). Scavenger receptor class B, type I (SR-BI) is also present at the apical membrane and has been suggested to mediate cholesterol uptake (103), whereas NPC1L1’s role in cholesterol absorption lies in its internalization and trafficking from the brush border membrane to endosomes (69). Intracellular transportation of fatty acids and MAG is facilitated by intestinal fatty acid-binding proteins (18). Most TG synthesis in the intestine follows the MAG pathway under catalysis of acyl-CoA:monoacylglycerol acyltransferase (MGAT) and further acylation by acyl-CoA:diacylglycerol acyltransferase (DGAT) (182) (discussed later).

Exchangeable apolipoproteins play a role in the intracellular assembly of both VLDL and chylomicrons. In the liver, apoC-III is involved in the “second step” by helping recruit bulk TG to the nascent apoB polypeptide to promote the secretion of larger VLDL (200). The intestine-specific apoA-IV helps expand the lipid core of the nascent apoB-48-containing lipoprotein in the ER (126) in a mechanism that involves increasing MTP activity (226). The massive size of TRL necessitates specialized vesicular machinery to traffic the nascent lipoproteins from the ER to the Golgi for further maturation. In the intestine, the prechylomicron transport vesicle (PCTV) has been characterized to contain COPII proteins and the GTPase Sar1 (187). Budding of the PCTV from the ER is initiated by liver fatty acid-binding protein (L-FABP) (147) and regulated by protein kinase C_\text{\epsilon} phosphorylation (188). CD36 has been detected in ER membranes, where it is also required to bud PCTVs (185); but given that CD36 KO mice are still capable of secreting full-sized chylomicrons (146), this function is likely shared by other proteins in the enterocyte. Nascent VLDL exits from the ER in a specialized ER-derived vesicle, the VLDL transport vesicle, to be transported to the Golgi (186). The fusion of VLDL transport vesicle to hepatic Golgi requires a SNARE complex (184). ADP ribosylation factor, calcium-independent phospholipase A\textsubscript{2}, and phospholipase D\textsubscript{1} are also implicated in VLDL maturation (reviewed in Ref. 199). Recently, sortilin-1 has been identified as an important regulator of VLDL secretion, although currently it is unclear whether it inhibits VLDL secretion (142) or serves as an intracellular sorting receptor in the trans-Golgi network to export VLDL (102). Because sortilin-1 was noted not to bind apoB-48 (102), it is unlikely that it plays a role in chylomicron secretion.

The stability of apoB and its susceptibility to intracellular degradation are some of the key differences between hepatic and intestinal TRL production. apoB-48 degradation does not appear to be a major pathway in the intestine, since in lipid-poor states the enterocyte is still capable of secreting apoB-48 as an HDL (76). Differentiated Caco-2 cells appear to store apoB in an apical compartment until stimulated by a supply of lipids to traffic through the secretory pathway (141). The stimulus requires SR-BI-mediated sensing of luminal postprandial lipid micelles (16). On the other hand, intracellular degradation plays an important role in regulating hepatic apoB, and the handling of such a large, aggregate-prone polypeptide is highly complex and even the subject of much debate (reviewed in Ref. 177). When core lipids are limiting, apoB degradation can occur via the ubiquitin-proteasomal pathway in a mechanism mediated by heat shock protein-70 (66). apoB can be cotranslationally targeted for proteasomal degradation by ubiquitylation by the ER-associated E3 ligase gp78 (122) and through interactions with Bip and the AAA-ATPase p97 in a complex that contains Derlin1, VIMP, and the E3 ligase Hrd1 (65, 176). Conversely, lipid overload induces ER stress and results in proteasomal and nonproteasomal degradation of apoB-100 (151). A nonproteasomal pathway of ER stress-induced apoB-100 degradation is through autophagy (150, 154, 167, 231). Autophagy also comprises the post-ER presecretory proteolysis (PERPP) of apoB aggregates induced by reactive oxygen species (154). Interestingly, one mechanism by which phospholipid transfer protein (PLTP) increases VLDL secretion is to improve hepatic oxidant tone and prevent PERPP degradation of apoB (97). PLTP also appears to play a role in chylomicron secretion in mice, especially with respect to cholesterol secretion (97, 123). For additional information regarding the protein and lipid factors affecting VLDL assembly and secretion, the interested reader is referred to an excellent, recent, comprehensive review of this topic (199).

In summary, there are many similarities but also differences in the process of TRL assembly and secretion in liver and intestine, the latter reflecting the different roles of these two organs in lipid trafficking. The following sections describe some of the key regulatory factors that influence TRL assembly and secretion in liver and intestine. Due to space constraints, we have not attempted to cover all of the known factors that affect TRL metabolism. Instead, we have reviewed some of the key factors that are known to affect gut-liver interactions in TRL metabolism.

**Lipid Availability Plays a Pivotal Role in the Regulation of TRL Production by Liver and Intestine**

TRL production is driven to a large extent by lipid substrate availability. In the absence of sufficient lipid substrates, apoB is degraded and lipoprotein secretion reduced. TG utilized for VLDL synthesis and secretion may be derived from fatty acid acyl chains from at least five sources: 1) circulating plasma free fatty acids (FFA), 2) fatty acids derived from the intracellular lipolysis of TG in TRL remnant particles taken up directly by the liver, 3) cytoplasmic TG lipid droplets, 4) de novo lipo-
degradation (115). Primary culture of hamster enterocytes enhanced intracellular apoB-48 stability and decreased apoB through stabilization of apoB and reduction in its degradation. In Second, FFA may stimulate lipoprotein assembly and secretion lymphatic TGs was increased significantly in the fed state (68). Infusion in rats, incorporation of plasma FFA into intestinal assembly and secretion through increased substrate availability, stimulating TRL production. First, FFAs may stimulate TRL synthesis and secretion see Ref. 199). In vivo in mice, infusion of oleic acid for 6 h, but not an equal amount of Intralipid, increased secretion of apoB (230), suggesting a role of FFA beyond substrate supply. Prolonged elevation of circulating FFA induces hepatic insulin resistance, which may indirectly increase hepatic VLDL production as a consequence of blunted insulin suppression in lipoprotein production (113) (discussed below).

With longer duration and higher doses of oleic acid treatment of cultured McA-RH7777 liver cells, apoB secretion is decreased. The stimulatory effect of oleic acid on apoB secretion is blunted with prolonged infusion of oleic acid in vivo in mice. This effect may be due to increased protein degradation through both proteasomal and nonproteasomal pathways and induction of ER stress (151). Under such a scenario of prolonged supply of FFA with ER stress and decreased apoB secretion, it is expected that inefficient assembly of lipoprotein particles would lead to liver accumulation of lipids and hepatosteatosis. N-3 PUFA infusion into rats inhibits apoB secretion, possibly through induction of PERPP and autophagy (153, 154). We also recently observed that apoB-100 may be a direct inducer of ER stress and ER-associated degradation (ERAD) (198). Increased cellular accumulation of apoB-100 upon FFA stimulation or constant expression of wild-type and N-linked glycosylation mutant apoB-50 in hepatic cells was found to induce ER stress. Activation of ER stress markers by lipid overload occurred simultaneously with the upregulation of apoB. The involvement of ER stress, PERPP, and autophagy in intestinal lipoprotein metabolism and potential strategies targeting these pathways in modulating TRL overproduction require further studies.

In summary, chronic elevation of plasma FFA stimulates both hepatic and intestinal TRL production by a number of postulated mechanisms. Despite the overall stimulatory effect of FFA on TRL secretion, chronic elevation of FFA causes ER stress, which limits the total lipoprotein secretory capacity of liver (not yet demonstrated for intestine).

**Other Regulators of TRL Production in Liver and Intestine**

The following is not a comprehensive list of all hormonal and other regulators of TRL secretion. Some of the key regulators of liver-gut interaction in TRL metabolism are discussed below.

**Insulin.** Although chronic hyperinsulinemic states, which are invariably also characterized by insulin resistance and other metabolic abnormalities, are associated with hypersecretion of TRL particles (discussed below), hepatic apoB-100-containing lipoprotein particle production is acutely suppressed by insulin in vitro (3, 193, 202) and in vivo (5, 119–121, 129, 130, 162) in humans. Incubation of human fetal small intestinal cells with insulin has also been shown to reduce chylomicron secretion (111). In chow-fed hamsters in vivo, intestinal lipoprotein production is also acutely inhibited by insulin (62). We recently demonstrated that acute hyperinsulinemia suppresses intestinal lipoprotein secretion in healthy humans, an effect that is both direct and indirect through suppression of FFAs (162).

The precise mechanisms whereby insulin suppresses intestinal and hepatic lipoprotein production remain unclearly defined and are currently under investigation. Aside from insulin-mediated suppression of circulating FFA in vivo, insulin may directly exert its effects through the insulin signaling cascade via the insulin receptor (20, 79). Insulin-resistant, hyperinsulinemic, obese individuals and patients with T2D, whose insulin signaling pathways are known to be impaired, are resistant to the acute inhibitory effect of insulin on hepatic VLDL production (119, 128), as are primary cultured hepatocytes derived from insulin-resistant rats (194). Recent unpublished evidence from our group supports the notion that insulin suppression of intestinal lipoprotein production is similarly
blunted in patients with T2D. One important pathway whereby insulin suppresses VLDL production is through modulation of MTP. Insulin inhibits the forkhead transcription factor FoxO1 (by phosphorylation and nuclear exclusion), thereby reducing transcriptional activation of the FoxO1 target gene Mttp and apoC-III expression (82, 170). Insulin resistance, through reduced Akt phosphorylation, results in enhanced FoxO1 action in the nucleus, thereby transcriptionally activating MTP and apoC-III and facilitating hepatic VLDL assembly and inhibiting its postsecretory catabolism (170). Insulin signaling can also phosphorylate and inhibit the actions of FoxA2. Active FoxA2, together with peroxisome proliferator-activated receptor-γ coactivator-1β (PGC-1β) upregulates β-oxidation and serves as a transcriptional activator of the Mttp gene, thus driving VLDL secretion (195). Insulin suppression of VLDL production may also occur through MTP-independent pathways. Insulin increases posttranslational apoB degradation (171). Acute insulin injection into apobec-1−/− mice did not affect MTP mRNA levels but instead inhibited gluconeogenesis. Insulin similarly suppressed apoB secretion in rat hepatocytes with and without overexpression of human MTP; therefore, responsiveness of hepatocytes to insulin to suppress apoB secretion is maintained even under conditions of increased hepatic apoB secretion mediated by MTP (190). In addition, degradation of apoB via PERPP may be enhanced by insulin, possibly involving shunting apoB from post-ER compartment to autophagolysosomes for degradation (195). Liver X receptor activation may inhibit the insulin-mediated suppression of VLDL-TG production through enhanced DNL in mice (75).

Glucose and fructose. There is a well-established carbohydrate stimulation of plasma TG (both VLDL and chylomicrons) in the fasted state as well as an effect of carbohydrate feeding on postprandial lipemia, even after a single meal (reviewed in Ref. 156). This carbohydrate-induced hypertriglyceridemia is due to overproduction of both TG (increased particle size) and apoB (increased particle number) along with impaired particle clearance (157). Three days of a high-carbohydrate diet was sufficient to enrich VLDL-TG with fatty acids derived from increased hepatic DNL and stearyl-CoA desaturase activity in humans (38). Overall, DNL is increased during high-carbohydrate feeding, although it contributes only a minor portion of increased TG compared with increased utilization of nonesterified fatty acids in the liver (157). The monosaccharide fructose exhibits highly lipogenic properties (51). Fructose feeding increases intestinal TRL production in hamsters (78). Chronic consumption of dietary fructose specifically increases DNL, promotes dyslipidemia, decreases insulin sensitivity, and increases visceral adiposity in humans (61, 196). Acute fructose feeding also stimulates VLDL-TG in healthy humans, possibly through increased liver re-esterification of fatty acids for subsequent VLDL assembly and enhanced DNL (37, 159). Part of the chronic fructose effect may be due to the induction of hepatic insulin resistance, which leads to VLDL overproduction, accompanied by intrahepatic-cellular lipid accumulation (106). The effect of fructose on postprandial hyperlipidemia can be attributed to a blunted insulin response and coincides with a resumption of FFA levels, which is exacerbated in T2D patients (1). In addition, oral glucose consumed 5 h after oral fat resulted in a postprandial peak in plasma TG, chylomicron-TG, and apoB-48 concentration, indicating oral glucose stimulation of mobilization of intestinally retained lipids (174).

Glucagon. Type 2 diabetes is associated with inappropriately elevated glucagon secretion, a less appreciated feature than the well-described abnormalities of insulin secretion. Although fasting glucagon level in T2D patients is comparable to that in healthy individuals, the capability for glucose to suppress glucagon secretion is diminished, resulting in relative postprandial hyperglucagonemia. Attenuation of glucagon secretion has been proposed as a treatment strategy for diabetes (8, 108). More recently, glucagon signaling has been shown to be important for hepatic lipid metabolism (124). In mice in the fasted state, glucagon, acting through the glucagon receptor, inhibits TG synthesis and secretion, activates AMPK, and subsequently activates PPARα, stimulating fatty acid β-oxidation, thus limiting substrate supply for TG synthesis in the liver (124). Although several studies have indicated involvement of glucagon in lipid metabolism, very limited information is available regarding the role of glucagon per se on lipid and lipoprotein metabolism, since most studies so far have been conducted under chronic conditions, where the direct roles of glucagon cannot be dissected from concomitant changes in glucose and other hormones. In a recent study, we (225) demonstrated that hyperglucagonemia decreased both production and clearance rates of apoB-100 in larger hepatic VLDL without net effects on circulating VLDL concentrations but did not affect the metabolism of intestinally derived lipoprotein particles. This may reflect the relatively less abundant expression of glucagon receptors in the intestine than in the liver (80). It may also suggest a divergent role of glucagon in regulating lipoprotein production in these two organs. Future studies are needed to elucidate the role of glucagon in lipoprotein metabolism in both the liver and the intestine in individuals with metabolic syndrome, more specifically, under the conditions of insulin resistance, hyperinsulinemia, and/or hyperglycemia.

GLP-1. Incretins are intestinally derived hormones that respond to and facilitate the disposal of ingested nutrients. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), the two main incretins, through activation of their distinct and related receptors, execute multiple physiological functions, including enhancing glucose-stimulated insulin secretion by the pancreatic β-cells, inducing β-cell proliferation and inhibiting β-cell apoptosis. GLP-1 also slows gastric emptying, inhibits glucose-dependent glucagon secretion, and promotes satiety (12). The incretins are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Two lines of incretin-based anti diabetic drugs, i.e., the GLP-1 receptor (GLP-1R) agonists and DPP-4 inhibitors, have been developed and are in increasing clinical use (125). The GLP-1R agonists are GLP-1 analogs that are resistant to DPP-4 cleavage, thus providing exogenous incretin activities, whereas DPP-4 inhibitors inhibit the enzymatic activity of DPP-4, thus prolonging the half-life of endogenous incretins in the circulation. Although a number of studies have addressed incretin regulation of carbohydrate metabolism, much less is known about their effects on lipids and lipoprotein metabolism. Both GLP-1 and GIP have been shown to attenuate postprandial lipemia, although by different mechanisms. GIP infusion in dogs attenuated elevation of plasma TG by promoting chylomicron clearance (218). In rats, infusion of recombinant GLP-1 de-
creased lymph flow, TG absorption, and production of apoB and apoA-IV (166). More recently, in fructose-fed hamsters and mice, the DPP-4 inhibitor sitagliptin decreased fasting plasma TG, postprandial TRL-TG, TRL-cholesterol, and TRL-apoB-48. Similarly, the GLP-1R agonist exendin-4 also decreased plasma and TRL-apoB-48 in hamsters and mice and reduced secretion of apoB-48 in hamster enterocytes. On the other hand, GLP-1R antagonism by exendin(9–39) or genetic elimination of GLP-1R in \textit{Glp1r} knockout mice enhanced TRL-apoB-48 secretion in vivo (88). In several clinical trials in T2D patients, 2-wk treatment with exenatide, a GLP-1R agonist, decreased postprandial TG (50, 180) and 4-wk treatment with vildagliptin, a DPP-4 inhibitor, reduced postprandial elevation of apoB-48 and plasma TG (132). In short-term studies, infusion of synthetic GLP-1 prior to a mixed meal acutely and completely prevented the normal postprandial rise in plasma TG in healthy subjects (135). In individuals with impaired glucose tolerance and new-onset T2D, acute GLP-1R activation, with exenatide injection prior to a high-calorie, fat-enriched breakfast meal, reduced postprandial elevation of TG, apoB-48 and apoC-III, remnant lipoprotein-cholesterol, and TG excursion and more persistent FFA elevation (179).

Although the studies described above provide evidence that GLP-1R modulation may affect postprandial lipid metabolism independently of weight loss, the exact mechanism is not clear due to the following limitations. First, GLP-1 profoundly slows gastric emptying and intestinal transit time in humans (134, 135); thus, the hypolipidemic effect of GLP-1R agonist may be at least partly due to decreased gastric emptying. However, delayed GLP-1 administration to obviate the effects of delayed gastric emptying still resulted in attenuated postprandial lipemia in mice (88). Second, the attenuation in TG and lipoprotein increase could be due to reduced production or increased clearance of TRL. Third, stimulation of insulin secretion, which affects intestinal and hepatic lipoprotein metabolism (see above), may have contributed to the observed effects of GLP-1. In addition, although chronic treatment with a novel GLP-1R agonist decreased VLDL secretion in high-fat-fed mice, acute treatment had no such effect (161). Interestingly, chronic administration of the DPP-4-resistant GLP-1 analog liraglutide resulted in significantly decreased hepatic and fasting TG in the UCD-T2DM rat model of adult-onset obesity and insulin resistance. Reductions in food intake and weight gain resulted in less liver lipid accumulation but did not explain the lowering of fasting TG (45). Future studies are needed to further elucidate the role and mechanism of GLP-1R modulation on intestinal and hepatic lipoprotein metabolism under well-controlled experimental settings.

There is emerging evidence that GLP-1 is a regulator of hepatic lipid metabolism. Chronic treatment with a GLP-1R agonist in diet-induced obese mice (82) and \textit{ob/ob} mice (52) reduced liver TG mass to an extent that cannot be completely explained by reduction in weight gain. Hepatocytes express the GLP-1R (52, 77). The signaling pathways activated by GLP-1R agonism ostensibly inhibit lipogenesis given the downregulation of ACC, SCD-1, SREBP-1c, and FAS mRNA, and promote \(\beta\)-oxidation by increasing PPAR\(\alpha\), AOX and CPT-1 mRNA (17, 52). Acute peripheral administration of GLP-1 suppresses VLDL production in mice, but this appears related to its ability to potentiate insulin action (160). However, the role of endogenous GLP-1R signaling on hepatic lipid metabolism is less straightforward. \textit{Glp1r}^{−/−} mice exhibit impaired hepatic insulin signaling (10), yet have decreased liver TG accumulation and nuclear SREBP-1c on a high fat diet, which coincided with relatively improved insulin-stimulated Akt phosphorylation (9). Therefore, GLP-1 appears to modulate hepatic lipid handling both independent of and dependent on insulin action. Further delineation of the contribution of these two pathways is warranted.

**GLP-2.** GLP-2 is an intestinally derived hormone produced by posttranslational proteolytic cleavage of proglucagon from intestinal L cells (12). Aside from intestinotrophic effects, GLP-2 also stimulates glucagon secretion, enhances lipid uptake, and inhibits gastric acid secretion in humans. Changes in postprandial lipid excursion seemed to reflect enhanced intestinal nutrient absorption during GLP-2 administration, whereas gastric emptying was not affected (136). In hamsters, administration of human GLP-2 prior to oral olive oil augmented postprandial lipids by increasing chylomicron secretion. TRL-apoB-48 secretion was increased following acute GLP-2 treatment in vivo and ex vivo in cultured jejunal fragments. The increased apoB-48 secretion was not accompanied by enhanced apoB-48 synthesis or increased \textit{Mttp} mRNA expression. Rather, it can be attributed to increased fatty acid uptake by the posttranslational modification of the FATP CD36, as the augmenting effects of GLP-2 on postprandial lipids were absent in mice lacking CD36 (89). The direct role of GLP-2 on postprandial lipoprotein metabolism in the intestine and liver, independent of its effects on glucagon and gastric acid secretion, remains to be determined.

**MGAT and DGAT.** Recent advances in understanding TG biosynthesis have identified and characterized the enzymes, namely MGAT and DGAT, that catalyze the consecutive steps in TG synthesis pathway (182). MGAT is mainly expressed in the gastrointestinal tract whereas DGAT is expressed in multiple tissues, including the intestine. A number of functions have been described for these enzymes, including fat absorption, fat storage and energy homeostasis, which signify the important clinical applications of pharmacological inhibitors of these enzymes and their isoforms. Increased DGAT activity has been described in both the liver and intestine of hyperlipidemic hamsters (30). In the liver, DGAT1 appears to be instrumental in esterifying exogenous fatty acids (circulating FFA from adipose lipolysis or from “spillover”), as opposed to those derived from DNL (213). In contrast, in the intestine, DGAT1 appears to be dispensable for assimilating dietary fatty acids into TG. However, DGAT1-deficient mice were slower at assembling chylomicrons, resulting in the persistence of large neutral lipid droplets within enterocytes of the proximal intestine in the fed state (26). It is interesting to note that while whole-body DGAT1 knockout mice were resistant to high fat diet-induced hepatosteatosis (189), restoration of DGAT1 expression in the intestine was permissive to fat accumulation in the liver and adipose (107). This study thus underscores the importance of chylomicron secretion to diet-induced obesity. MGAT2 is abundant in the proximal intestine (28) and MGAT3 predominates in the distal small intestine in humans (34). While MGAT2-deficient mice do not have gross lipid malabsorption, the kinetics of dietary fat uptake is delayed, shifting the bulk of absorption distally (228). Interestingly, such observations are reminiscent of L-FABP\(\text{EF}^{−/−}\) mice, which also exhibit delayed fat absorption (148), perhaps hinting at coordinated activities of these two proteins. It thus appears that
the functional importance of TG synthesis enzymes in the intestine is highly dependent on their expression along the longitudinal axis of the organ. Results from current clinical studies of inhibitors of MGAT and DGAT1 should provide information on efficacy and adverse effects (22).

**MTP.** MTP is an ER membrane-associated chaperone responsible for the transfer of lipids (TG, phospholipids, and cholesterol ester) to nascent apoB-containing lipoprotein particles, which prevents the apoB from proteasome- and ER-associated degradation (91, 92). Impaired MTP activity, due to genetic deficiency or pharmacological inhibition, results in misfolded apoB that is subjected to ER-associated degradation (64). Diurnal variations of plasma lipids correlate with the patterns of MTP expression (155). Mutations in the MTP gene lead to nonfunctional MTP and abetalipoproteinemia, with virtual absence of apoB-containing lipoproteins (170, 223). Modulation of MTP activity significantly affects circulating apoB lipoproteins, thus MTP inhibitors were postulated to be beneficial for lipid lowering, especially for those unable to attain LDL-cholesterol targets or with familial hypercholesterolemia (44, 178). However, MTP inhibition is associated with several adverse effects, including impaired intestinal fat absorption, fatty engorgement of enterocytes, steatorrhea and hepatic steatosis due to inefficient TG transfer to lipoprotein particles (44, 169, 178). To circumvent hepatotoxicity, intestinal-specific MTP inhibitors are being developed (81, 137). Recently, inositol-requiring enzyme-1β (IRE1β), an ER stress sensor protein mainly expressed in the intestine, has been found to promote degradation of MTP mRNA and inhibit chylomicron secretion in mice (93). Upregulation of IRE1β may thus provide benefits in attenuating postprandial lipemia. Intestinal MTP may also be regulated by other factors, such as local intestinal signaling receptors for leptin and melatonin (95). Regulation of Mtp by FoxO1 and insulin was discussed above. VLDL apoB-100 production is intricately linked to ER stress (151, 198). Whether intestinal ER stress is similarly linked to chylomicron production remains unknown. The clinical evaluation of MTP inhibitors, intestinal specific MTP inhibitors, or ER stress inhibitors on intestinal and hepatic lipoprotein metabolism awaits further study.

**Cytokines and adipokines.** Several adipokines and cytokines have been shown to affect TRL metabolism (reviewed in Ref. 229). Insulin resistance and T2D are generally regarded as proinflammatory states (183). TNFα infusion in hamsters promotes apoB-48 secretion in both fasted and postprandial states along with increased MTP mRNA and protein levels and impaired insulin signaling (78, 164, 165). Another proinflammatory cytokine, interleukin-6, also has been shown to stimulate hepatocytes secretion of apoB (191). Collectively, these studies suggest a role of inflammation in overproduction of TRL in conditions that are characterized by chronic inflammation. Resistin, an adipokine secreted by adipocytes and macrophages in the adipose tissue, has been associated with features of insulin resistance and elevated apoB (149). Recently, it has been reported that human resistin at physiological levels stimulates apoB/VLDL secretion and lipid accumulation in hepatocytes (43). These effects may be through increased DNJ via the sterol-regulatory element-binding protein (SREBP)1 and SREBP2 pathways, enhanced MTP activity, and impaired insulin signaling. Another adipokine, adiponectin, is favorably associated with insulin sensitivity, plasma TG, lipoprotein particle size, and liver fat in humans (13, 222). The hypolipidemic effect of adiponectin is largely attributed to its promotion of VLDL-TG catabolism, as shown in mice and humans (105, 163).

**PPAR agonists.** PPARγ and PPARα agonists are known to affect TRL metabolism. Several studies in T2D patients have shown slight improvement (203, 212) or unfavorable effects with the PPARγ agonist rosiglitazone on lipid metabolism, e.g., increased fasting and postprandial TG and apoB-48 (32, 74, 96). In fructose-fed and high-fat-fed insulin-resistant hamsters we have demonstrated that rosiglitazone prevents intestinal lipoprotein overproduction (109, 118). However, in healthy individuals, despite improvement in insulin sensitivity, rosiglitazone tended to increase production and decrease clearance of both hepatic and intestinal lipoprotein (58), which suggests a dissociation between insulin sensitization and TRL metabolism with this agent. Another PPARγ agonist (but in this case with some PPARα activities as well), pioglitazone, lowered fasting VLDL-TG and postprandial TG and chylomicron in T2D patients in association with an increase in hepatic lipase activity (6). Lowering of VLDL-TG by pioglitazone was also shown to be due to increased clearance in association with increased LPL mass and decreased apoC-III production in T2D patients, perhaps secondary to its PPARα activity (143).

In general, PPARα agonists, fibrates, act to reduce VLDL-apoB and TG through enhanced clearance (70, 181). For instance, fenofibrate increased clearance of TRL-apoB-100 and apoB-48 in subjects with T2D and marked hypertriglyceridemia (86), individuals with both heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (208), individuals with metabolic syndrome (219, 220), and individuals with combined hyperlipidemia (21). These effects have been associated with increased activities of LPL (70) and plasma lipid transfer protein (220). In obese subjects with nonalcoholic fatty liver disease, fenofibrate increased VLDL-TG clearance and decreased VLDL-apoB production (60). PPARα/γ dual agonists have been shown to have promising effects in animal models (e.g., Ref. 171), although their clinical uses in humans requires further study.

**Role of Cholesterol Homeostasis on TRL Metabolism**

Cholesterol homeostasis also plays a role; thus, modulation of intestinal absorption, de novo synthesis, and esterification of cholesterol may affect TRL metabolism. Several recent comprehensive reviews have addressed cholesterol metabolism (94, 207). Dietary and biliary cholesterol are transported via NPC1L1 (Niemann-Pick C1 Like 1) located on the brush border membrane of the jejunum. The NPC1L1 inhibitor ezetimibe decreases LDL-c in humans (178, 208, 209). In patients with primary hypercholesterolemia, VLDL-apoB-100 clearance was enhanced with ezetimibe treatment while TRL-apoB-48 kinetics was not affected (208). This is consistent with concomitant upregulation of hepatic LDL receptor with inhibition of intestinal cholesterol absorption (49) and competition for removal between apoB-48- and apoB-100-containing particles (25). Since upregulation of cholesterol synthesis also occurs with inhibition of intestinal cholesterol absorption, combination therapy with ezetimibe and HMG-CoA reductase inhibitors (statins) have been shown to dramatically decrease plasma cholesterol. In patients with combined hyperlipidemia,
coadministration of ezetimibe and simvastatin decreased LDL-c and plasma TG, along with reduction in TRL-apoB-48 concentration and production and VLDL-apoB-100 clearance (209). In heterozygous familial hypercholesterolemia and patients with T2D who have marked hypertriglyceridemia, simvastatin decreased plasma concentration of TG-rich remnants and apoB-48, mainly due to decreased production without affecting remnant clearance (47, 86). In normolipidemic patients with coronary artery disease, atorvastatin decreased fasting and postprandial apoB-48, with increased LDL receptor activity (48). Atorvastatin or rosuvastatin decreased apoB-48 in dyslipidemic individuals, which may have been due to increased clearance (31, 152). In addition, cholesterol esterification by acyl-CoA:cholesterol acyltransferase-2 (ACAT2) promotes intestinal cholesterol absorption and hepatic secretion of cholesteryl ester-rich VLDL. Mice lacking ACAT2 or liver-specific deletion of ACAT2 with antisense oligonucleotides have increased plasma TG, and liver ACAT2 deficiency promoted VLDL-TG secretion (7).

In summary, many systemic factors play important regulatory roles in both intestinal and hepatic TRL metabolism, suggesting that there is coordinated regulation of TRL production by these organs, to be discussed below.

Gut-Liver Interaction: Postprandial vs. Postabsorptive Transition Between Two States

TRL metabolism in intestine and liver exhibits well-coordinated, cyclic dynamics between postabsorptive and postprandial states. Intestinal lipid absorption virtually ceases in the postabsorptive state, whereas secretion of lipid-poor apoB-48-containing lipoproteins and hepatic VLDL persists. Hepatic VLDL-TG production, calculated from production rates estimated during fasting (4, 41), is ~20–30 g/day, which is significantly lower than a typical transport rate of lipids from the intestine (in the rage of 100 g/day with nearly complete absorption) (67). In the fasted state, the majority of VLDL-TG is derived from circulating FFA from adipose tissue lipolysis. In healthy subjects, following an overnight fast, adipose tissue lipolysis is higher compared with the fed state, leading to higher VLDL-TG secretion (14). FFA from this source comprises 70–80% of VLDL-TG following an overnight fast and may increase to more than 90% during prolonged fasting (14, 158). With prolonged fasting (>20 h), however, although FFA delivery to the liver is increased, VLDL-TG and apoB secretion decline (42, 197), leading to hepatic lipid accumulation (139).

The shift from postabsorptive to postprandial state is initiated by food ingestion and coordinated by many of the factors discussed above in addition to neural signals (summarized in Fig. 2). Postprandial lipemia is predominantly due to an increase in TG in the apoB-48 TRL particle (82%), with the remaining being attributed to apoB-100 TRL (39). In addition, the TRL-TG increase is greater than the increase in protein; therefore, apoB-48 secretion (i.e., the secretion of chylomicron particles) is stimulated by lipid absorption, but the major increase in capacity for transport of ingested lipid occurs by lipid enrichment and many-fold enlargement of each apoB-48-containing chylomicron particle (40). In part due to an increase in VLDL secretion postprandially, but mainly because of increased competition with chylomicrons for removal, the majority of the postprandial apoB increment in the circulation is contributed by apoB-100 and not apoB-48 (e.g., Ref. 100).

Distinct changes in sources of VLDL-TG synthesis occur during transition from fasted to fed states. Postprandially, adipose tissue lipolysis of stored TG is minimized due to hyperinsulinemia, resulting in a reduction in the contribution of adipose-derived FFA for VLDL-TG synthesis. Chylomicrons secreted into the circulation are hydrolyzed by insulin-stimulated LPL to cholesteryl ester-rich remnant lipoproteins, some of which are taken up by the liver, thereby contributing to hepatocyte TG and fatty acid pools and indirectly stimulating VLDL synthesis. Following a meal, the majority of the chylomicron TG is sequestered by extrahepatic tissues (mainly adipose) following LPL lipolysis in the capillary microcirculation (19, 175). A portion of dietary-derived FFA escapes uptake by extrahepatic tissues, with this dietary fatty acid “spillover” entering the circulation with subsequent delivery to liver for oxidation, storage, and VLDL production (15, 83, 84, 138). Parks and colleagues (14, 15) quantified the sources of VLDL-TG during fasted and fed states in healthy subjects receiving intestinal lipid infusion. In the fed state, the contribution of FFA to VLDL-TG from adipose tissue lipolysis decreases to 44%, while chylomicron remnant TG and dietary spillover account for 15 and 10% of secreted VLDL-TG, respectively. Although the contribution of DNL in the liver is slightly increased, from 4% during fasting to 8% in the fed state, newly formed fatty acids remain a quantitatively minor source of VLDL-TG. In response to meal ingestion, the contribution of circulating FFA to VLDL-TG is relatively comparable to that seen with continuous feeding, but there is a
transient greater contribution from dietary fatty acids (up to 35%) and DNL (up to 25%) to VLDL-TG (205, 206).

Hormonal secretion is also rapidly altered in the fasted-to-fed transition. Immediately following meal ingestion, L and K cells in the distal small intestine are stimulated; possibly through neurohormonal pathways and direct nutrient stimulation, to secrete GLP-1 and GIP, respectively. Postprandial hyperglycemia, coupled with GLP-1, stimulates pancreatic β-cell insulin secretion. Postprandial hyperinsulinemia, and possibly increased GLP-1 secretion (the latter shown in animals but not yet in humans), may acutely suppress lipoprotein assembly and secretion in liver (insulin) and intestine (insulin and GLP-1) (see above). The acute suppressive effect of insulin on hepatic lipoprotein production in the postprandial state can be understood on the basis of the need to reduce competition for LPL lipolysis and other removal mechanisms between secreted VLDL and incoming chylomicrons, whereas the acute suppressive effects of insulin (and potentially GLP-1 in humans; study underway) on intestinal lipoprotein production in the postprandial state is more difficult to understand. In addition, decreased glucagon levels due to glucose-mediated suppression of glucagon secretion may affect hepatic VLDL production as described above. There is evidence in animals that a gut-brain-liver neural pathway is operative; thus, the accumulation of certain lipids, such as long-chain fatty acids, in the upper intestine suppresses liver glucose production through the gut-peptide hormone cholecystokinin (36, 215). Selective increase in brain glucose is capable of inhibiting liver VLDL-TG secretion (104).

Several other factors have also been implicated in regulation of TRL metabolism during the fasted-to-fed transition. Triacylglycerol hydrolase (TGH) is an ER-localized lipase that mobilizes TG stored in hepatic lipid droplets for secretion as VLDL (221). TGH expression is inhibited by glucocorticoids, which fall in the postabsorptive state, thereby increasing hepatic lipoprotein mobilization during the postmeal meal (reviewed in Ref. 53). Interestingly, TGH expression has been noted in the proximal small intestine (54), and adipose triglyceride lipase deficiency results in distal intestinal TGH expression (77a) making it tempting to speculate on their role in the lipolysis/ reesterification cycle in the enterocyte. Cell death-inducing DFF45-like effector B (Cibed) associates with cytoplasmic lipid droplets and DGAT-containing smooth ER and interacts with apoB-100 to promote VLDL lipidation (227). PGC-1α is strongly induced in the liver during fasting and robustly up-regulates Cideb expression to increase TG secretion (33). Notably, PGC-1α has also been shown to up-regulate apoC-III (173) and lipin-1 (63) expression. FoxO1 has also been shown to play an important role in adaptation in the fasted-to-fed transition (192). FoxO1 promotes expression of genes involved in gluconeogenesis (85, 133), and more recently its role in hepatic lipoprotein production is becoming increasingly recognized. Increased portal insulin following meal leads to phosphorylation and nuclear exclusion of FoxO1, thus limiting its nuclear transcriptional activity. When the insulin stimulation is absent, FoxO1 is dephosphorylated, and its translocation into the nucleus renders its transcriptional activity (35). The hypolipidemic effects of PPARα have been shown to be through antagonizing FoxO1 (168). Mtp gene was recently shown to be a target of FoxO1; hence, its expression is regulated by FoxO1 (99). Therefore, postprandial hyperinsulinemia may regulate hepatic VLDL secretion through decreased MTP expression in addition to its inhibition of apoB to fuse with TG and thereby promotion of apoB degradation. Novel FoxO1 inhibitors are being developed to treat T2D (144). Application of such compounds in alleviating TRL overproduction warrants future studies.

In summary, the transition from fasted to fed state is a coordinated process involving numerous signals (nutrient, neural, hormonal, etc.) to intestine and liver, ensuring efficient digestion, absorption, transport, and storage of lipids, with subsequent redistribution and utilization of stored lipids as energy substrates, as the body once again transitions from the postprandial to postabsorptive state.

Lipoprotein Metabolism in Insulin Resistance and T2D

Overproduction of VLDL is a well-documented feature of insulin resistance and T2D (5, 29, 71, 114, 115, 118, 119, 128, 194). Several metabolic changes lead to hepatic overproduction of VLDL in these conditions (for detailed review see Ref. 113). 1) In insulin-resistant states, the normal suppressive effect of insulin on VLDL production is impaired. 2) FFA flux from extrahepatic tissues to the liver is increased. 3) Hepatic DNL is stimulated by hyperinsulinemia. 4) There is preferential esterification vs. oxidation of FFA in the liver. 5) Hepatic TG storage pool availability is thus increased for VLDL production. 6) Hepatic uptake of lipoprotein remnants is increased, especially postprandially, and with intestinal overproduction of chylomicrons in insulin resistance.

Impaired insulin signaling plays a key role in hepatic VLDL overproduction. Glucose and lipid homeostasis are regulated differentially in insulin-resistant liver; thus, insulin fails to suppress gluconeogenesis but continues to stimulate lipogenesis by stimulating the transcription factor SREBP-1c, leading to hyperglycemia and hypertriglycerideremia (24). Fructose-fed, insulin-resistant hamster and cultured hamster hepatocytes overproduce VLDL-apoB accompanied by whole body insulin resistance and attenuated hepatic insulin signaling (201, 202). Fructose feeding was associated with hyperinsulinemia, enhanced MTP expression in the liver, increased intracellular apoB stability, and facilitated assembly of apoB-containing lipoproteins leading to VLDL oversecretion (201). Induction of insulin resistance was accompanied by increased production of hepatic VLDL-apoB and VLDL-TG. Although there was an increase in total apoB secretion, the apoB fraction secreted as VLDL was more prominently enhanced in fructose-fed hamsters, suggesting an increase in both the number of VLDL particles and the proportion secreted as VLDL. Enhanced apoB secretion appeared to be caused by increased intracellular stability of apoB, elevated levels of MTP, and enhanced assembly of VLDL particles, without apparent changes in apoB translocation status. Conversely, amelioration of VLDL production in hamsters is associated with normalization of MTP (29, 118) and hepatic lipase mRNA, protein, and plasma activity (114). As mentioned above, activated FoxO1 due to insulin resistance and reduced Akt phosphorylation results in upregulation of the Mttp gene and MTP protein, which appears to play an important role in enhancing the assembly and secretion of apoB-100-containing TRL. The hepatic insulin receptor is known to be directly involved in regulation of VLDL apoB and lipid secretion (20, 79). Mice with liver-
specific insulin receptor knockout have increased apoB secretion and an atherogenic lipid profile, indicating that insulin resistance in the liver alone is sufficient to induce dyslipidemia (20). On the other hand, mice with low levels of insulin receptor in the liver and absence of insulin receptor in peripheral tissues on the LDL receptor (LDLR)-deficient background show decreased apoB and lipid secretion and improved lipid profile via the IRS-1/p85/Akt/GSK3 signaling arm (79). Knocking down hepatic insulin receptor expression in wild-type or ob/ob mice reduced VLDL secretion together with decreased hepatic LDL receptor. This study may point to the important role of LDLR in insulin-modulated VLDL secretion, given that the LDLR can promote apoB-100 degradation (211). In addition, apoB-100 accumulation has been demonstrated to induce hepatic insulin resistance via induction of ER stress in liver cells (198). All together, these studies highlight the important and complex role of insulin signaling in mediating hepatic VLDL secretion.

Intestinal lipoprotein overproduction is a relatively recently identified feature of insulin resistance. Increased postprandial elevation in circulating chylomicrons and remnants in insulin resistance has been largely attributed to impaired removal. Since intestinal and hepatic TRL may share common, saturable removal mechanisms, clearance of chylomicrons and remnants may be impaired as a result of elevated VLDL. In addition, decreased LPL activity is also implicated in the slow removal of chylomicrons and remnants in insulin resistance due to diminished insulin regulation of LPL. However, recent studies from our laboratory and others’ provide strong evidence that the intestine actively overproduces TRL in the insulin resistant state, contributing to elevated circulating TRL levels (reviewed in Ref. 2). Basal apoB-containing lipoprotein secretion is increased in the insulin-resistant and T2D intestine (76). In animal models of insulin resistance and T2D, intestinal overproduction of lipoproteins has been shown to contribute to postprandial dyslipidemia (78, 214, 232). Conversely, insulin sensitization, such as occurs with administration of the PPARγ agonist resiglitzazone, ameliorates apoB-48-containing lipoprotein secretion in hamsters (109, 115, 118). In humans with various degrees of insulin sensitivity, we have demonstrated an inverse relationship between apoB-containing lipoprotein production and insulin sensitivity (57). In patients with T2D, apoB-48-containing lipoprotein production is increased, together with decreased clearance of these particles (87). More recently, we have also observed that T2D patients have a diminished response to insulin’s suppressive effects on intestinal lipoprotein production (unpublished observation) compared with healthy subjects. These studies indicate that the intestinal production of TRL may be less effectively controlled in insulin resistance and T2D, contributing to elevated circulating TRL in these conditions.

The molecular mechanisms of intestinal overproduction of TRL particles in insulin-resistant states are being actively investigated. Intestinal insulin resistance has been demonstrated in the enterocytes derived from the fructose-fed, insulin-resistant hamster (78). Similar to the liver, the intestine also exhibits impaired insulin responsiveness/signalizing in insulin-resistant states. In primary cultured enterocytes of fructose-fed, insulin-resistant hamsters, apoB-48-containing particle secretion is increased, accompanied by increased intracellular stability of apoB, enhanced DNL, and increased MTP mass and activity (78, 118). This increased apoB-48 secretion is related to decreased IRS-1 and Akt phosphorylation and activation of protein tyrosine phosphatase-1B, ERK, and SREBP-1c (62). PCTVs from fructose-fed hamsters also exhibit an altered proteomic profile, including increased apoB-48, MTP, Sar1, and VAMP7 (224). Psammomys obesus is another rodent model of nutritionally induced insulin resistance that overproduces chylomicrons, and this was associated with increased DNL, apoB-48 biogenesis, MGAT and DGAT activity, and L-FABP levels in the intestine (232). Increased LXRs and decreased PPARβ/δ mRNA was also observed in the intestine of these animals, along with a paradoxically decreased capacity to absorb cholesterol (110). apoB-48 oversecretion has also been observed in the mesenteric lymph of the leptin-deficient, insulin-resistant JCR:LA-cp rat (131).

Collectively, TRL overproduction in insulin resistance and T2D is closely linked to impaired insulin signaling in both the liver and the intestine. Amelioration of hepatic and intestinal insulin resistance may provide clinical benefits in dyslipidemia management. The insulin sensitizer resiglitzazone ameliorates TRL overproduction in fructose-fed hamsters but not in humans, where the effect on insulin sensitization is accompanied by increased TRL-apoB production (58). The effects of other insulin-sensitizing agents remain to be explored.

Future Directions

Our understanding of TRL metabolism by the intestine and its coordination with other organs is far from complete, and many outstanding gaps in our knowledge and questions remain. Some recently identified areas described above need to be further investigated and better defined. Furthermore, many unexplored areas of TRL metabolism as it relates to intestine-liver interactions still remain to be understood. These include 1) more thorough description of insulin signaling and other molecular mechanisms in regulation of intestinal lipoprotein production; 2) the role and mechanism of incretins in TRL production; 3) the involvement of ER stress in regulating both hepatic and intestinal TRL metabolism; 4) efficacy and potential of organ-specific therapeutic agents; and 5) translational studies to investigate several newly proposed mechanisms of intestine in mediating whole body lipid metabolism in humans. For instance, the rat upper intestine may respond to lipids to initiate a gut-brain-liver axis to modulate hepatic metabolism (104, 215). The gut microbiota has also recently been implicated in the etiology of obesity and metabolic syndrome (11, 172, 217). The contributions of these mechanisms to lipid homeostasis in health and disease in humans remain to be investigated. Finally, recent genome-wide association studies have identified several common variants and many rare variants at several genes, such as APOA5, GCKR, LPL, APOB, MLXIPL, TRIB1, and ANGPTL3, that are associated with hypertriglyceridemia and other lipid traits in humans (e.g., Refs. 98 and 101). The mechanistic basis for the association between lipid traits and these newly identified genetic variants is still largely unknown, and functional studies of these genes and their variants in lipoprotein metabolism are needed. A recent study in mice indicates that Trib1 regulates hepatic lipogenesis and VLDL metabolism (27).
Conclusion

There is increasing recognition that the physiological role of the intestine in lipid homeostasis goes beyond dietary lipid digestion and absorption responding primarily to food ingestion. Instead, the intestine is actively involved in the dynamics of whole body lipid homeostasis via hormonal and metabolic factors and neural pathways. The mechanisms of TRL production and overproduction by intestine and liver in compromised metabolic conditions remain incompletely understood despite recent advances in this field. Although the quantitative contribution of intestinal TRL overproduction to diabetic dyslipidemia is not precisely defined, the potential atherogenic properties of apoB-48-containing remnant particles, their role in postprandial hyperlipidemia, and their effects on other lipoproteins such as HDL and LDL composition call for further understanding of intestinal TRL metabolism. The more in-depth understanding of the physiological role of the intestine and its coordinated lipoprotein metabolism with other organs, such as the liver, the more it opens future possibilities of targeting the intestine for treatment and prevention of diabetic dyslipidemia and dyslipidemia of insulin-resistant states such as the metabolic syndrome. Novel therapeutic strategies to target the intestine and liver may offer significant clinical benefits.

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