A central feature of metabolic syndrome is hepatic hypersecretion of very low-density lipoprotein (VLDL), which results in hypertriglyceridemia (HTG), a consistent finding associated with obesity and type 2 diabetes mellitus. Under physiological conditions, insulin signaling regulates VLDL production by targeting apolipoprotein (apo) B for degradation and limiting apoB synthesis.1 Pancreatic release of insulin into the portal vein after eating reduces VLDL output during the postprandial period allowing for transient triglyceride (TG) storage for future secretion. This is consistent with insulin acting as an anabolic hormone stimulating energy storage in both liver and fat. Because of reduced hepatic secretion of VLDL, there is less competition for lipolysis with intestinal lipoproteins resulting in their preferential clearance. Loss of this acute pathway may be the earliest consequence of overnutrition and it is not surprising that the role of insulin in VLDL and lipid metabolism will prove equally complex. (Arterioscler Thromb Vasc Biol. 2012;32:XX-XX.)

Key Words: apolipoproteins ■ cytokines ■ insulin resistance ■ lipoproteins ■ obesity

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VLDL Assembly and Hepatic VLDL Overproduction

VLDL assembly is initiated by the synthesis of B100 (Figure 1), a 550 kDa protein or its shorter form, B48, the protein product of edited apoB mRNA. Editing is a process that introduces a stop codon in the apoB transcript, B48, the protein product of edited apoB mRNA. Editing is a process that introduces a stop codon in the apoB transcript, and for head box 01 (FoxO1) activity.2,4 Sustained nuclear localization of FoxO1 increases expression of microsomal triglyceride transfer protein (MTP)4 and apolipoprotein C-III (apoC-III)5 resulting in substantial increases in VLDL production above and beyond loss of acute VLDL regulation.3 This review summarizes current understanding of insulin action and insulin resistance related to the complex relationships of apoB and TG in formation of VLDL.
translocation into the secretory pathway with each lipoprotein particle being seeded by a single molecule of apoB making apoB content a measure of particle number. Extrusion of the first 1000 residues (βα1 domain) and association with phospholipid within the endoplasmic reticulum (ER) lumen are necessary for the initiation of particle assembly and may not require the activity of MTP. The length of the domain of B100, necessary for MTP–dependent particle assembly, is still under debate. Multiple interactions of apoB with MTP and lipid transfer form partially lipidated particles through size–dependent linear lipidation and result in formation of low-density lipoprotein (LDL)-VLDL2 particles that act as precursors to VLDL1. Conversion of VLDL2 to VLDL1 occurs separately, possibly in a distinct compartment, through bulk addition of lipids by fusion with lipoprotein size TG-rich droplets creating a distinct population of larger VLDL1 particles. Formation of intraluminal lipid droplets requires MTP, and droplets can be stabilized by apoC-III.

In insulin resistant states, loss of insulin suppression of apoB secretion occurs before global hepatic insulin resistance, consistent with the findings of Sørensen et al where insulin suppression of hepatic glucose production is preserved in obese men who have lost insulin-mediated suppression of VLDL-TG secretion. Dysregulation of VLDL production, particularly increased secretion of large VLDL1, is a key pathological mechanism underlying the dyslipidemia commonly observed in insulin resistant states characterized by HTG, reduced high-density lipoprotein, and presence of small, dense LDL. In addition to considerable evidence from animal models, hepatic VLDL overproduction occurs in insulin resistant humans and in patients with type 2 diabetes mellitus.

**Insulin Modulation of Hepatic VLDL Via Induction of ApoB Degradation**

Insulin suppresses hepatic VLDL production through activation of phosphoinositide 3-kinase (PI 3-kinase) (Figure 1). The pathway likely evolved to conserve calories during the fed-to-fasting transition mediated by insulin signaling. In response to feeding, there is rapid release of insulin from the pancreas into the portal vein, followed by insulin binding to hepatic insulin receptors (IR), activation of the intrinsic IR tyrosine kinase, and propagation of signaling via tyrosine phosphorylation of IR substrates (IRS). Tyrosine-phosphorylated IRS complex with and activated PI 3-kinases. Class IA PI 3-kinase consists of a p85 regulatory subunit plus a p110 catalytic subunit whose activation involves disinhibition of the catalytic subunit whose activation involves disinhibition of the catalytic subunit through interaction with tyrosine phosphorylation of IRS substrates (IRS). Tyrosine-phosphorylated IRS complex with and activated PI 3-kinases. Class IA PI 3-kinase consists of a p85 regulatory subunit plus a p110 catalytic subunit whose activation involves disinhibition of the catalytic subunit through interaction with tyrosine-phosphorylated IRS. Activated PI 3-kinase is mobilized and localized to membranes via SH2 domains of p85 allowing interaction with substrate phosphatidylinositol (4,5) bisphosphate (PIP2) and formation of phosphatidylinositol (3,4,5) triphosphate (PIP3). PIP3 is a highly negatively charged phospholipid, which may interfere either directly or through downstream effectors with the coalescence of VLDL precursors with TG droplets, thereby reducing the formation of mainly VLDL1. The acute effect of insulin does not involve inhibition of MTP activity, activation of AKT, and is LDL receptor-independent.
precursors unable to accept lipid droplets are targeted for degradation from a post-ER compartment with final degradation taking place in lysosomes by a process consistent with autophagy.  

ApoB can be degraded in response to a number of stimuli through autophagy leading to decreased VLDL secretion. Studies by Pan et al. have demonstrated autophagic degradation of apoB through post-ER presecretory proteolysis where B100 aggregation is limited by oxidation by polyunsaturated fatty acids (FA). Zhong et al. have shown autophagic degradation of mutant apoB (A31P), which causes apoB misfolding. Induction of ER stress after glucosamine treatment of McArdle RH-7777 cells can also result in increased apoB degradation via autophagy, which can be dramatically induced by transient expression of PRK–like ER kinase. The above studies indicate that autophagic mechanisms can be involved in apoB degradation and that pathways regulating autophagy can affect VLDL assembly and secretion. As insulin is known to suppress starvation-induced autophagy, the stimulation of apoB degradation by insulin through an autophagic mechanism is unexpected, although not without precedent for aggregated proteins such as mutant Huntington protein.

Nascent B100 can be degraded by mechanisms other than autophagy. In the absence of lipid substrates, the availability of B100 is limited by cotranslational degradation via the ubiquitin–proteasome pathway through ER-associated degradation. During translation the N-terminus of B100 translocates into the ER lumen stabilized by interaction with GRP78 (BiP), a chaperone protein. This interaction, if sustained, aids in targeting B100 to proteasomal degradation. Recently, a cystolic ATPase, p97 (valosin-containing protein) has been shown to interact with the C-terminus of B100 in HepG2 cells. In the absence of lipids, p97 associates with longer lengths of B100 (>B72), but not shorter, while GRP78 associates with B100 forms containing the amphipathic C sheet (=20%) important to the initiation of lipid binding. The ATPase activity of p97 is required for delivery of ubiquitinated apoB to the proteasome for degradation. The ER-membrane–anchored ubiquitin (E3) ligase gp78 has been identified as regulating B100 ER-associated degradation. HepG2 cells have reduced lipoprotein assembly based on a defect in lipolysis with failure of adequate mobilization of cytosolic TG droplets to microsomes. Defective TG mobilization may be related to hyperactivity of the MEK-extracellular signal–regulated kinase signaling pathway, as inhibition of extracellular signal–regulated kinase 1/2 results in stimulation of B100 secretion. Proteasomal degradation of B100 blocked by provision of oleate protects apoB from ER-associated degradation and stimulates B100 secretion. Underlipidated apoB degradation mediated by ER-associated degradation could play a role in modulating B100 availability for VLDL assembly.

FA effects are parabolic on apoB secretion and with moderate FA exposure B100 secretion is increased, whereas with greater lipid loading B100 secretion decreases. Various FA have differing effects in McArdle RH-7777 cells on apoB secretion with different time courses, concentration dependence, and mechanisms. Palmitate and oleate decrease B100 secretion through induction of ER stress through a PRK–like ER kinase pathway, which is unrelated to induction of autophagy. In contrast, docosahexaenoic acid inhibits B100 without induction of ER stress and targets B100 for autophagic degradation. Severely dysfunctional hepatocytes, as occurs with streptozotocin–induced diabetes mellitus or with end-stage diabetes mellitus in aged Zucker diabetic fatty rats, have reduced apoB output likely because of the inability to synthesize and properly fold apoB into a form that can accept lipids.

**Insulin Modulation of ApoB mRNA Translation and B100 Synthesis**

Insulin reduces the synthesis of B100, which in combination with its effect on B100 turnover, significantly limits the B100 availability for VLDL assembly. Translational control of apoB mRNA was first suggested in 1990 when it was shown that insulin, while stimulating global protein synthesis, inhibited label incorporated into apoB. Possible translational control of apoB has been implicated in a number of models, including HepG2 cells, mouse hepatocytes, and in liver in streptozotocin–induced diabetes mellitus. Recent studies indicate that insulin decreases apoB translation by inhibiting the interaction of a 110-kDa protein factor with the 5′-untranslated region of the apoB transcript. This factor is regulated by protein kinase C signaling and contributes to the basal rate of apoB translation.

In HepG2 cells, insulin treatment increases localization of apoB mRNA with processing body markers, while decreasing association with active polyribosomes, silencing apoB mRNA translation through message sequestration. The relationship of translational silencing of B100 to insulin–stimulated B100 degradation is not known, although both appear to be regulated by wortmannin–sensitive PI 3-kinases.

**Insulin Regulation Via PIP3 Signaling and Modulation by Membrane Phosphatases**

PTP-1B is a nontransmembrane protein tyrosine phosphatase that dephosphorylates both the IR and IRS attenuating the ability of insulin to activate PI 3-kinase and generate PIP3. PTP-1B is localized to the cytoplasmic face of the ER membrane through its C-terminus. PTP-1B is tightly regulated through a number of mechanisms, including oxidation, phosphorylation, sumoylation, and proteolysis. The induction of hepatic PTP-1B correlates positively with increased VLDL apoB and TG secretion, which occurs in insulin resistant fructose-fed hamsters. The increase in secretion is associated with stabilization of cellular B100 in the context of increased DNL induced by fructose. Liver-specific deletion of PTP-1B improves hepatic insulin signaling, enhances insulin suppression of hepatic gluconeogenesis, and lowers circulating levels of TG and cholesterol.

Evidence that generation of PIP3 is necessary for insulin-mediated suppression of VLDL is provided by recent studies of phosphatase and tensin homolog PTEN, a lipid phosphatase that catalyzes removal of the 3′ phosphate of phosphoinositides. Data suggest that loss of PTEN and associated increases in cellular PIP3 result in suppressed VLDL secretion. In HepG2 cells expressing dominant negative PTEN, there is a 50% lowering of cellular and secreted B100. Overexpression of PTEN renders cells unresponsive to insulin suggesting that rapid elimination of PIP3 by PTEN negates suppression.
Congruent results were shown in McArdle RH-7777 cells where expression of PTEN enhances secretion of VLDL, whereas expression of dominant negative PTEN suppresses secretion of VLDL supporting the role of PI(3)K in modulating VLDL secretion. Although liver-specific disruption of PTEN improves glucose tolerance and reduces plasma FA in vivo, PTEN deletion also results in increased DNL, hepatomegaly, hepatic steatosis, and increased glycogen synthesis because of hyperphosphorylation of AKT. In 1 model, plasma VLDL apoB levels and apoB secretion by hepatocytes were reduced. In contrast, using a different hepatic PTEN knockout mouse model, there was increased secretion of both TG and apoB, and insulin did not suppress VLDL production being regulated mainly by hepatic TG content. Studies of PTEN clearly indicate the importance of PI(3)K; however, findings do not preclude the possibility that other phosphatidylinositides derived from PI(3)K may be involved in insulin–regulated apoB secretion.

Inhibition of PI 3-Kinases Increases VLDL Production
Hepatic VLDL apoB secretion in vivo can be modulated by wortmannin, which inhibits cellular PI 3-kinases inducing chemical insulin resistance. Under basal, chow-fed conditions, wortmannin infusion alone more than doubles hepatic VLDL B100 production in mice suggesting that PI 3-kinase–dependent processes are regulating secretion under fasting conditions. The enhanced secretion of VLDL B100 observed with wortmannin in control mice equaled that observed in fructose-fed mice suggesting that the insulin resistance created chemically equaled that observed with fructose-induced insulin resistance. These studies suggest that there is a maximum capacity for VLDL B100 production, and any requirement for TG export exceeding this capacity would likely result in hepatic TG accumulation.

Physiological loss of hepatic insulin regulation of apoB may be the initial step in the development of hypersecretion of VLDL. The first potential site involved in disruption of PI 3-kinase–generated PI(3)K would be at the level of the IR. Hepatocyte-specific deletion of IR in mice results in a substantial increase in apoB secretion even though TG secretion is markedly suppressed. Secreted apoB-containing lipoproteins are enriched in cholesteryl esters rather than in TG most likely because of the reduced IR-dependent stimulation of DNL. A second potential site involved in resistance is reduced IR tyrosine phosphorylation of IRS. Decreased insulin action at this level can occur through a number of signaling pathways mediated by cytokines that lead to serine phosphorylation of IRS or to blockage of signal propagation by suppressors of cytokines signaling (SOCS) proteins. A third potential site for resistance is alteration in p85 cellular content and proportional changes in other PI 3-kinase regulatory subunits as observed in ob/ob mice. The p85 regulatory subunit may be more favorable than the shorter forms for localization of PI 3-kinase and for interaction with intracellular mediators and PTEN. Overall, these data indicate that reduced IR activation of PI 3-kinase is associated with increased secretion of VLDL apoB-containing lipoproteins.

Hepatic Inflammation and Inflammatory Cytokines and VLDL Hypersecretion
Obesity and insulin resistant states are associated with low-grade inflammation resulting from chronic activation of the innate immune system. This may involve not only the adipose tissue but also the liver and may be critical to the pathogenesis of hepatic insulin resistance and development of steatosis. Kupffer cells are specialized macrophages in the liver lining the walls of the sinusoids that form part of the reticuloendothelial system. Activation of Kupffer cells by endotoxin leads to toll-like receptor signal transduction, which in turn stimulates production of inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6 triggering inflammation. Depletion of Kupffer cells in vivo in mice prevents insulin resistance and complications induced by a high-fat or high-sugar diet.

Figure 2. Links between inflammation and interruption of insulin-mediated suppression of very low-density lipoprotein (VLDL). Insulin binds to its receptor, which leads to activation of the intrinsic tyrosine kinase of the insulin receptors (IR)-β subunit and autophosphorylation of the IR and IR substrates (IRS) 1 and 2. Extensively, tyrosine-phosphorylated IRS interact with SH2 domains of p85, the major regulatory subunit of phosphoinositide 3-kinase (PI(3)K), leading to activation of p110, the catalytic subunit, and blocks signaling downstream of PI(3)K. IKK is capable of serine phosphorylation of IRS1, which reduces its activation downregulating insulin signaling. Increased expression of PTP-1B blocks insulin signaling through dephosphorylation of phosphotyrosine residues of IRS and IR and by decreasing membrane–associated insulin signaling complexes terminating the activity of PI 3-kinase. Membrane PIP3 is also regulated by the activity of phosphatase and tensin homolog (PTEN), which reduces PIP3 concentration and blocks signaling downstream of PI 3-kinase. IKK is capable of serine phosphorylation of IRS1, which reduces its activation downregulating insulin signaling. Thus, increased VLDL B100 secretion can occur by a number of mechanisms that decrease membrane levels of PIP3. Chronic inflammatory processes that occur in obesity result in increased circulating levels of cytokines, including IL-6, leptin, IL-1β and resistin and lead to enhanced expression of suppressor of cytokine signaling (SOCS)3 and blocked insulin action.
diet.72 Coculturing hepatocytes with Kupffer cells leads to significant increases in FA esterification and TG accumulation, an effect that is blocked by TNF-α neutralizing antibodies.72 TNF-α mediates its effects via its cognate receptors (TNF-R) (Figure 2). Systemic administration of TNF-α targets the liver73 and in hamsters stimulates assembly and secretion of B100–containing VLDL1 particles.74 Kupffer cell activation is a causal factor in hepatic insulin resistance that is induced very early in a diet-induced model.75 Kupffer cell activation can initiate the hepatic inflammatory nuclear factor (NF-κB) cascade leading to increased serine/threonine phosphorylation of IRS1 and attenuation of hepatic insulin signaling,76,77 and TNFα increases NF-κB activation.78 NF-κB is a dimeric transcription factor controlling the expression of genes involved in inflammatory processes. NF-κB is controlled largely through sequestration in the cytoplasm by inhibitors of NF-κB (IκB). TNF-α transiently activates IκB kinase (IKK) that phosphorylates IκB and targets the inhibitor for ubiquitination and proteosomal degradation. This process releases NF-κB which undergoes nuclear localization and induces a subset of TNF-α-regulated genes, including IκB providing a negative feedback loop of regulation. Fructose feeding of hamsters reduces levels of IκB suggesting that fructose enhances the NF-κB cascade through activation of IKK.79 Overexpression of IKK stabilizes cellular B100 and inhibition decreases cellular B100 and reduces the overproduction of VLDL B100 induced by fructose. Inhibition of IKK by BMS345541 decreases B100 translation, and overexpression by adenoviral transfer of IKK increases B100 translation. As insulin is known to suppress B100 translation, and IKK is able to inhibit insulin signaling through serine phosphorylation of IRS-1, results suggest that reduced insulin signaling could contribute to NF-κB effects. Iκκβ is only one of a number of serine kinases capable of serine phosphorylation of IRS and blunting insulin signaling.80,84 which include Jun-N-terminal kinase and mammalian target of rapamycin complex 1, which increases with obesity, leads to cytoplasmic localization of Lipin1. Lipin 1 functions as a phosphohydrolase, which converts phosphatidic acid to diacylglyceride and favors formation of TG for assembly into VLDL.97 Thus, activation of DNL through an effect on Lipin 1 corresponds with increased delivery of phosphatidic acid–derived TG destined for VLDL assembly. As more apoB is available by loss of insulin suppression, conditions are favorable for increased secretion of VLDL1.

Hepatic insulin resistance is buffered by SOCS proteins that play important roles in controlling proinflammatory signaling mediated through cytokines, including IL-1β, IL-6, resistin, leptin, and TNF-α, which are produced in the fat tissue where enlarging adipocytes recruit inflammatory cells.87 Hepatic SOCS3 is induced through activation of signal transducers and activators of transcription and NF-κB and downregulates Janus kinases and insulin signaling pathways.88 SOCS3 inhibits insulin signaling by binding to the IR preventing its association with, and tyrosine phosphorylation of, IRS.89,90 In addition, SOCS3 blunts insulin signaling by ubiquitin-mediated degradation of IRS.91 Persistently elevated cytokine levels that occur in obesity induce SOCS3 protein and inhibit insulin signaling, which could contribute to loss of insulin suppression of B100. The availability of apoB can be augmented by cytokine signaling through increasing apob gene transcription. ApoB mRNA is increased by IL-6 in hepatocytes until induction of SOCS3.92 IL-6 transcriptionally controls target genes through Janus kinases/signal transducers and activators of transcription signaling, a pathway shared by leptin. Resistin has also been shown to enhance VLDL production by increasing apoB mRNA abundance and stimulating expression of MTP and DNL while reducing insulin signaling pathways.93 If apob mRNA were increased by inflammatory cytokines there would be additional apoB for VLDL assembly and secretion, which would contribute to VLDL hypersecretion.

**Complex Factors Triggering VLDL Hypersecretion**

Sterol regulatory element binding protein (SREBP) 1–regulated DNL can augment VLDL TG secretion and complement increased availability of apoB attributable to the loss of insulin-mediated suppression. Activation of SREBP1 involves the release of SREBP cleavage–activating protein bound to insulin-induced gene (Insig) in the ER. Released SREBP cleavage–activating protein escorts SREBP to the Golgi via COPII vesicles where it is processed by 2 protease activities allowing the matured cytoplasmic transcription factor to move to the nucleus where it transactivates genes involved in DNL (eg, FA synthase). In the absence of SREBP cleavage–activating protein, the pathway for release from Insig is interrupted, SREBP is retained in the ER, and hepatic steatosis and hypertriglyceridemia associated with insulin resistance are prevented.94 The major regulatory factors for increasing SREBP1 activity are insulin, AKT2 reduction in Insig2a and transcription factors ChREBP, LXR, and SREBP itself. Recently, a major role for target of rapamycin complex 1 in DNL has been demonstrated.95,96 Target of rapamycin complex 1 is critical in energy metabolism, protein synthesis, regulation of cell growth, proliferation, and autophagy. Target of rapamycin complex 1 mediates the phosphorylation of Lipin 1, which prevents Lipin 1 from localization in the nucleus where it normally inhibits SREBP activity through interaction with lamin 1.95 Activation of target of rapamycin complex 1, which increases with obesity, leads to cytoplasmic localization of Lipin1. Lipin 1 functions as a phosphohydrolase, which converts phosphatidic acid to diacylglyceride and favors formation of TG for assembly into VLDL.97 Thus, activation of DNL through an effect on Lipin 1 corresponds with increased delivery of phosphatidic acid–derived TG destined for VLDL assembly. As more apoB is available by loss of insulin suppression, conditions are favorable for increased secretion of VLDL1.

Hepatic insulin resistance pathways progress to involve FoxO1, a transcription factor active in both VLDL and carbohydrate metabolism. Transcriptional activity of FoxO1 depends on AKT, which negatively regulates FoxO1 by insulin-activated PI 3-kinase.98 Membrane-generated PIP3 localizes AKT to membranes via its pleckstrin homology domain where phosphoinositide-dependent kinases phosphorylate and activate AKT. AKT phosphorylation of FoxO1 causes nuclear exclusion of FoxO1 and subsequent FoxO1 degradation. Nuclear FoxO1 regulates expression of phosphoenolpyruvate carboxykinase, a key protein involved in gluconeogenesis, and FoxO1 also regulates expression of MTP and apoC-III, key proteins in the assembly of VLDL.3 Thus, sustained nuclear FoxO1 that occurs in hepatic insulin resistance states increases VLDL assembly by increasing microsomal TG content and MTP-dependent TG transfer to apoB, as well as by increased expression of apoC-III.9
ApoC-III is a small surface protein that is found on TG-rich lipoproteins, which inhibits lipoprotein lipase and hepatic lipase and also interferes with the interaction of B100 and apoE with hepatic receptors.

ApoC-III regulation involves a number of transcription factors, including hepatocyte nuclear factor 4-α, ROR-α, and retinoid X receptor; however, FoxO1 appears to predominate in conditions of overnutrition. When apoC-III is overexpressed in mice, HTG develops, whereas knockdown of apoC-III prevents these changes. In humans, apoC-III production rates correlate with hepatic VLDL TG production, and recent genome-wide association studies indicate that fasting and postprandial TG levels correlate with apoC-III expression. More recent studies indicate that the lipid-binding domain of apoC-III plays a key role in VLDL assembly through stabilization of intraluminal lipid droplets important to the fusion step in VLDL1 formation. Taskinen et al. studied obese humans and found 2 types of hepatic insulin resistance related to VLDL hypersecretion. Obese men, with increased visceral and subcutaneous fat, hepatic steatosis, and increased circulating apoC-III, had HTG associated with VLDL hypersecretion plus decreased VLDL1 fractional catabolic rate. Obese men, with no significant increase in apoC-III, had VLDL hypersecretion with no change in VLDL fractional catabolic rates and were normotriglyceridemic even with increased visceral fat. Although both groups had equivalent increases in visceral fat, the normotriglyceridemic obese group had intermediate levels of subcutaneous and liver fat. If apoC-III is a marker for FoxO1 pathway activation, results suggest that increased VLDL hypersecretion and loss of insulin-mediated suppression of VLDL occurs before FoxO1 induced changes in apoC-III and development of HTG.

Sortilin Is An Emerging Factor Implicated in Control of VLDL B100 Metabolism

Sortilin 1 (Sort1) is an intracellular sorting receptor for B100 recently discovered through genome-wide association studies. Sort1 interacts with B100 in the Golgi and is a determinant in its subcellular distribution. Sort1 is a multiligand type 1 receptor that binds a number of unrelated ligands, including lipoprotein lipase. Sort1 mediates both endocytotic activity and trafficking among intracellular vesicles shuttling between the trans-Golgi network and late endosome. An inverse relationship exists between Sort1 and VLDL secretion: increased expression reduces secretion and knockdown increases secretion of VLDL B100. Sort1 may also be involved in the uptake and degradation of VLDL-derived LDL, as Sort1 enhances LDL endocytosis. Recently it has been shown that induction of mammalian target of rapamycin complex 1 and ER stress in obese mice represses hepatic Sort1 concentration and correlates with increased VLDL secretion, suggesting that Sort1 regulation may contribute to the dyslipidemia of obesity. Knowledge of the role of Sort1 in lipoprotein metabolism is rapidly expanding; however, a role for Sort1 in insulin–mediated apoB degradation remains to be defined.

Conclusions

Acute regulation of hepatic VLDL production through decreased availability of apoB is mediated by cyclical insulin release and portal clearance of insulin that transiently allows TG to be stored for future release as VLDL. As hepatic TG accumulates with overnutrition, there is loss of acute reduction in VLDL secretion leading to continuous VLDL production, which may or may not result in HTG depending on the VLDL catabolic rate after secretion. The signal for increased export of hepatic TG most likely involves interruption of insulin-stimulated activation of PI 3-kinase, which can occur through induction of PTP-1B. PTEN blunting of the PI3K signal generated by localized PI 3-kinase could also be a part of the mechanism for VLDL hypersecretion in insulin resistance. Insulin-mediated degradation of apoB may involve factors, such as Sort1, and degradation most likely involves movement of an autophagy related complex from a post-ER compartment to the lysosome. Resistance to insulin increases availability of apoB for TG export and may also involve induction of hepatic DNL. With continued overnutrition, additional signals may be generated by progressive hepatic insulin resistance and include sustained nuclear localization of FoxO1 resulting in transcriptional induction of genes important to VLDL export, including MTP and apoC-III in addition to those, such as phosphoenolpyruvate carboxykinase, important in gluconeogenesis. Hepatic TG export of B100-containing VLDL1 particles and inappropriate hepatic glucose production are both stimulated by FoxO1 and form the basis for more classic hepatic insulin resistance syndromes, which may progress to type 2 diabetes mellitus. Increased hepatic inflammation results from further TG accumulation and diversion of FA to prooxidative pathways. Eventually, sustained oxidative stress and inflammation interfere with VLDL formation and secretion and progressive, irreversible hepatic damage occurs as steatosis becomes steatohepatitis and eventually cirrhosis. It is important to understand the earliest stages involved in the critical and complex role insulin plays in regulating hepatic VLDL metabolism in order to develop effective therapeutic strategies to treat HTG.

Disclosures

None.

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