Role of Liver in Triglyceride Homeostasis

Larry L. Swift, Ph.D.
Department of Pathology
Vanderbilt University School of Medicine

Metabolic Syndrome

- Abdominal obesity
- Atherogenic dyslipidemia
- Elevated blood pressure
- Insulin resistance
- Prothrombotic state
- Proinflammatory state

Metabolic Syndrome Dyslipidemia

- Elevated plasma triglycerides
- Decreased HDL cholesterol
- Normal levels of LDL cholesterol carried in small dense particles
- Lipoprotein alterations contribute to increased risk for CHD

What are the metabolic alterations underlying these changes in plasma lipoproteins?

Overproduction of VLDL

What are the mechanisms underlying VLDL overproduction?
Lecture Outline

- Lipoproteins, structure, apoproteins, characteristics
- Source of triglyceride for lipoproteins
- Assembly of triglyceride-rich lipoproteins
- Triglyceride-rich lipoprotein catabolism
- Effects of insulin resistance on triglyceride-rich lipoprotein production
- VLDL secretion and fatty liver

Plasma Lipoprotein Classes

<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>Density (g/mL)</th>
<th>Main component</th>
<th>Apoproteins</th>
<th>Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>0.95-1.00</td>
<td>TG</td>
<td>B48 (A, C, E)</td>
<td>75-1200</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.95-1.00</td>
<td>TG</td>
<td>B100 (A, C, E)</td>
<td>26-50</td>
</tr>
<tr>
<td>IDL</td>
<td>1.00-1.06</td>
<td>TG &amp; cholesterol</td>
<td>B100, E</td>
<td>26-35</td>
</tr>
<tr>
<td>LDL</td>
<td>1.063-1.068</td>
<td>Cholesterol</td>
<td>B100</td>
<td>8-25</td>
</tr>
<tr>
<td>HDL</td>
<td>1.063-1.126</td>
<td>Protein</td>
<td>A, A1, A2, C, E, E1</td>
<td>5-12</td>
</tr>
</tbody>
</table>

Lipoprotein Model

Negative Stain of Lipoproteins
Apolipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein Distribution</th>
<th>Tissue Source</th>
<th>Mol Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoA-I</td>
<td>HDL</td>
<td>30K</td>
</tr>
<tr>
<td>apoA-II</td>
<td>HDL</td>
<td>17K</td>
</tr>
<tr>
<td>apoA-IV</td>
<td>HDL</td>
<td>45K</td>
</tr>
<tr>
<td>apoB48</td>
<td>chylomicrons</td>
<td>240K</td>
</tr>
<tr>
<td>apoB100</td>
<td>VLDL, LDL</td>
<td>512K</td>
</tr>
<tr>
<td>apoC-I</td>
<td>HDL</td>
<td>6.9K</td>
</tr>
<tr>
<td>apoC-II</td>
<td>HDL and VLDL</td>
<td>6.9K</td>
</tr>
<tr>
<td>apoC-III</td>
<td>HDL and VLDL</td>
<td>8.8K</td>
</tr>
<tr>
<td>apoE</td>
<td>HDL, LDL, VLDL</td>
<td>34K</td>
</tr>
</tbody>
</table>

Apolipoprotein B

- Structural apoprotein for triglyceride-rich lipoproteins
- Expressed in two forms: apoB100 & apoB48
- B100 is found on VLDL, IDL, and LDL
- B48 is found on chylomicrons
- ApoB synthesis is essential for VLDL and chylomicron assembly

Chylomicrons (CM)

- TG-rich spherical particles 75 to 200 nm in diameter
- Assembled by enterocytes to transport dietary fat to periphery (liver, adipose tissue, cardiac and skeletal muscle)
- ApoB-48 is the sole B apoprotein
- Chylomicron TG is hydrolyzed by lipoprotein lipase (LPL) located in capillary endothelium surrounding fat and muscle producing a “remnant” lipoprotein that is cleared by the liver

Very Low Density Lipoproteins (VLDL)

- TG-rich spherical particles 40-60 nm in diameter
- Synthesized by the liver and transport triglyceride and cholesterol ester to periphery for storage and/or utilization
- Major structural protein is apo B-100
- VLDL TG is hydrolyzed by lipoprotein lipase (LPL) producing intermediate density lipoproteins (IDL) that are cleared by the liver or converted to low density lipoproteins (LDL)
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Sources of Triglyceride for VLDL Assembly

- De novo lipogenesis
- Plasma non-esterified fatty acids (NEFA)
- VLDL and CM remnant fatty acids

Triglyceride

- Glycerol backbone with 3 fatty acids (FA)
- FA can be the same, but generally are not
- Properties of TG are determined by FA
- Highly concentrated source of metabolic energy

Fatty Acids

- Aliphatic carboxylic acids that usually contain an even number of carbon atoms
- Chains may be saturated (no double bonds) or unsaturated (one or more double bonds)
- Position of double bonds described in relation to carboxy-terminus (Δ) or methyl carbon (ω or n)
Common Fatty Acids
- C14:0 - myristic acid
- C16:0 - palmitic acid
- C18:0 - stearic acid
- C18:1 \(\omega 9\) - oleic acid
- C18:2 \(\omega 6\) - linoleic acid*
- C18:3 \(\omega 3\) - \(\alpha\)-linolenic acid*; \(\omega 6\) - \(\gamma\)-linolenic acid
- C20:4 \(\omega 6\) - arachidonic acid
- C20:5 \(\omega 3\) - eicosapentaenoic acid
- C22:5 \(\omega 3\) - docosapentaenoic acid
- C22:6 \(\omega 3\) - docosahexaenoic acid

Essential Fatty Acids (EFA)
- Fatty acids that cannot be synthesized and must be obtained from the diet
- C18:2 \(\omega 6\) - linoleic acid
- C18:3 \(\omega 3\) - \(\alpha\)-linolenic acid
- These fatty acids are starting point for synthesizing longer and more highly unsaturated fatty acids

Fatty Acid Synthesis
- Acetyl CoA is substrate; palmitate is product

Source of Acetyl CoA
- Derived primarily from pyruvate via pyruvate dehydrogenase in mitochondria
- Transported into cytosol as citrate, then regenerated by ATP citrate lyase
- Available for malonyl CoA formation and fatty acid synthesis
Fatty acids

Amino Acids

Glucose

Pyruvate

Cytosol

Acetyl CoA

Fatty Acids

Mitochondria

Pyruvate

e-Succinyl-CoA

Fatty Acid Synthesis

Final product is palmitic acid, C16:0

Fatty Acid Elongation / Desaturation

Mammals and plants

Palmitate (16:0)

Stearate (18:0)

Oleate 18:1 (Δ9 or ω9)

Longer saturated fatty acids

Linoleate 18:2 (Δ6,9,12 or ω6)

γ-linoleate 18:3 (Δ6,9,12 or ω6)

Eicosatrienoate 20:3 (Δ8,11,14 or ω6)

Arachidonate 20:4 (Δ5,8,11,14 or ω6)

α-linoleate 18:3 (Δ9,12,15 or ω3)

Other PUFAs

Plants only

Triglyceride Synthesis

3 Fatty acids + Glycerol → Triglyceride

Fatty Acid Synthesis
Triglyceride Synthesis

- Enzymes for TG synthesis reside primarily in the ER
- Glycerol must be activated (phosphorylated) before incorporation into acylglycerols
- Fatty acids must be converted to acyl CoA derivatives
- In liver, glycerol-3-phosphate is formed via glycerol kinase or reduction of DHAP

Synthesis of Glycerol Phosphate in Liver

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Assembly of Triglyceride-Rich Lipoproteins

- Complex process requiring coordination of lipid and protein synthesis
- Process is constitutive in nature, but can be modulated by variety of factors
- Assembly and secretion of TG-rich lipoproteins are absolutely dependent on the ability of the cell to synthesize apoB and the presence of MTP

Microsomal Triglyceride Transfer Protein (MTP)

- A heterodimeric protein complex consisting of 97 kDa subunit and protein disulfide isomerase (PDI)
- Located in the lumen of the endoplasmic reticulum (ER)
- Facilitates lipid transfer and is essential for assembly of VLDL by the liver
- Inhibition of MTP leads to reduction in plasma triglycerides and cholesterol
Targets for Regulation of VLDL Assembly

Points of Regulation of VLDL Production

- Substrate availability
- Apo B degradation by proteasomal and non-proteasomal (insulin dependent) pathways
- Availability of functional MTP

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VLDL Metabolic Pathway
**Chylomicron Metabolic Pathway**

- Lipoprotein
- FFA
- Glucose
- Insulin
- Intracellular TG
- DAG
- Glycerol-3P
- FA

**Sources of Fatty Acids for Liver and VLDL Triglycerides**

- Adipose Tissue
- NEFA
- FA
- TG
- Liver
- VLDL TG
- NEFA POOL
- DNL
- ApoB
- Glucose

**Hormonal control of adipocyte lipolysis**

- Noradrenaline
- Insulin
- PKA
- AMPK
- ERK 1/2
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Effects of Insulin Resistance on TG-Rich Lipoprotein Production

- Increased fatty acid flux from adipose tissue to the liver
- Increased hepatic uptake of VLDL, IDL, and chylomicron remnants
- Increased de novo lipogenesis
- Decreased degradation of apoB
- Increased activity of MTP

Increased Fatty Acid Flux from Adipose Tissue to the Liver

- Insulin stimulates adipocyte fatty acid uptake and inhibits fatty acid release (HSL) leading to decreased plasma NEFA
- Insulin resistance leads to increased mobilization of fatty acids from adipose tissue and increased plasma NEFA

Substrate Sources for the Assembly of ApoB-Lipoproteins

De Novo Lipogenesis

- Hepatic insulin resistance leads to upregulation of sterol regulatory element-binding protein-1 (SREBP-1c) and activates lipogenic enzymes
- Carbohydrate response element-binding protein (ChREBP) regulates expression of key glucose-responsive genes of lipogenesis
- Synergistic action of SREBP-1c and ChREBP directs conversion of excess glucose to fatty acids and enhances esterification

Decreased Degradation of ApoB

- Insulin regulates degradation of apoB through PI3-kinase pathway
- Insulin resistance leads to decreased apoB degradation and increased secretion

Increased MTP Activity

- Mttp gene has insulin response element in the promoter
- In human liver cells Mttp gene expression is negatively regulated by insulin through the MAPK cascade
- Increased MTP mRNA is associated with enhanced synthesis of VLDL in wild-type animals and in animal models of insulin resistance

Increased MTP Activity

- Forkhead box 01 (Fox01) has been shown to mediate inhibitory action of insulin on target gene expression
- Fox01 stimulates hepatic MTP expression; the effect is counteracted by insulin
- Fox01 gain-of-function is associated with enhanced MTP expression, augmented hepatic VLDL production, and elevated plasma TG levels in Fox01 transgenic mice
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Summary

- Triglyceride-rich lipoproteins
- Source of triglyceride and assembly of these lipoproteins
- Turnover of triglyceride-rich lipoproteins
- How insulin resistance can lead to overproduction of these lipoproteins and how that in turn can lead to hepatic steatosis

Changes in Lipoprotein Metabolism in the Metabolic Syndrome