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M1 - GI Sequence

Liver

John Williams, M.D., Ph.D.

Winter, 2009
FUNCTIONS OF LIVER

• Storage, metabolism and release of nutrients and some vitamins.

• Detoxification and elimination of toxins, drugs and metabolites.

• Synthesis of biologically important protein such as albumin, clotting factors, apolipoproteins.

• Synthesis and secretion of bile important for lipid digestion and absorption.

• Role in immune function and clearance of intestinally absorbed bacteria.
Cellular Components of the Liver

- Hepatocytes
- Stellate or Ito Cells
- Kupfer Cells (macrophages)
- Sinusoidal Endothelial Cells
- Bile Ductular Epithelial Cells (Cholangiocytes)
Image of a liver lobule was removed.
Anatomical Relationships in Liver

- space of Disse
- blood sinusoid
- paracellular pathway
- bile canaliculus
- tight junctions
- hepatocyte
- blood sinusoid

Source Undetermined
Components of Bile

Water ~ 1 liter/day
Bile Acids - major organic constituents
Phospholipids
Cholesterol
Bile pigments - bilirubin
Metabolites of Hormones, Drugs
Inorganic ions - $\text{HCO}_3^-$ from duct cells
Transport of Biliary Components by Hepatocytes

John Williams modified from Fig. 6-6 Granger, D, et al. Clinical Gastrointestinal Physiology. W.B. Saunders, Philadelphia, PA; 1985: 125.
MOLECULAR COMPONENTS OF BILE SECRETION

1. Uptake of bile salts by Na\(^{+}\) coupled co-transporter (NTCP)

2. Basolateral membrane also contains several organic anion transport proteins (OATP)

3. Bile salts excreted into bile by the Bile Salt Export Protein (BSEP) an ATP binding cassette protein which belongs to multidrug resistance (MDR) gene family

4. Other apical proteins are MRP2 which transport a number of drugs, ABC 5/8 involved in cholesterol transport and MDR3 a phospholipid transporter (flipase)

5. Gene expression of many of above transporters is regulated by bile salts through the Bile Acid Receptor/ Farnesoid X Receptor (FXR)
**Function of Bile Ducts**

1. Bile ducts are lined by cholangiocytes, columnar epithelial cells specialized to modify bile.

2. Ductules are freely permeable to water so bile rapidly becomes isotonic.

3. Ductules scavenge solutes such as glucose and amino acids that entered leaky canaliculus.

4. Cholangiocytes secrete $\text{HCO}_3^-$ in response to secretin (bile slightly alkaline)

5. Ductules secrete IgA molecules into bile
Chemistry of Bile Acids

Cholesterol

Bile acid
(Cholic acid)
BILE SALT SYNTHESIS

• Bile acids synthesized in the liver from cholesterol

• In the “classical pathway” the first and most important regulated step is 7α hydroxylation by 7α hydroxylase (CYP7A1)

• Next 12α hydroxylation is followed by several steps leading to cholic acid

• The “alternative pathway” starts with initial formation of oxysterols and leads to chenodeoxycholic acid
Primary Bile Acids

Cholic acid (3 OH groups)

Chenodeoxycholic acid (2 OH groups)

7-dehydroxylation by gut bacteria

Secondary Bile Acids

Deoxycholic acid (2 OH groups)

Lithocholic acid (1 OH group)
Bile Acid Conjugation

Conjugation lowers the pKa so bile acids exist in the more soluble dissociated form.
Amphipathic Nature of Bile Acids

Glycocholic acid

Polar groups
Amphipathic Molecules

Exist in micelles when concentration is greater than the CMC (Critical Micellar Concentration)
Mixed Micelle

- Cholesterol
- Lecithin
- Bile Salt

Source Undetermined
The gallbladder concentrates bile and stores much of the body's bile salt pool during fasting.

Epithelia absorb $\text{Na}^+$, $\text{Cl}^-$, and $\text{H}_2\text{O}$.

Isotonicity is maintained as a result of micelles having minimal osmotic activity.

Postprandially, the gallbladder contracts in response to CCK (cholecystokinin).
Role of CCK in Bile Secretion

Duodenum

- FATTY ACID
- CCK SECRETION

PLASMA CCK

Gallbladder
- CONTRACTION

- BILE FLOW INTO COMMON BILE DUCT

Sphincter of Oddi
- RELAXATION

- BILE FLOW INTO DUODENUM
ENTEROHEPATIC CIRCULATION OF BILE SALTS

- **Bile Salt** flows into the **Portal Vein**.
- **Liver** and **Hepatocyte** convert **Cholesterol** to **Bile Salt**.
- **Bile Salt** enters the **Gallbladder** and is **Concentrated**.
- **Salt & Water** are **contracted** to **gallbladder**.
- **CCK** stimulates the **Ileum**.
- **Fat** is digested in the **Jejunum**.
- **Bile Duct** relaxes the sphincter of Oddi.
- **Bile Salts** are absorbed in the **Ileum**.
- **Na+** ions are transported.

John Williams
Metabolism of Bile Pigment (Bilirubin)

1. Senescent red blood cell destruction
2. Hemoglobin → Biliverdin
3. Biliverdin → Bilirubin (BR)
4. BR + UDP Glucuronic Acid → BR Glucuronide
5. BR Glucuronide enters systemic circulation as BR-Albumin Complex
6. In the small intestine, BR is metabolized to urobilinogen and stercobilin
7. Urobilinogen is absorbed and converted to stercobilin in the colon
8. Stercobilin is excreted in the stool
9. Bilirubin glucuronide is excreted in the bile and later in the stool
10. Bilirubin in the blood is transported to the liver as BR-Albumin Complex
11. In the liver, BR-Albumin Complex is metabolized to stercobilin and bilirubin glucuronide
12. Bilirubin glucuronide is excreted in the bile and later in the stool
13. Bilirubin is also excreted in the urine
The Liver Synthesizes a Variety of Plasma Proteins

<table>
<thead>
<tr>
<th>Major Plasma Proteins</th>
<th>Albumin, α fetoprotein, α₂-Microglobulin</th>
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<tbody>
<tr>
<td>Hemostasis Proteins</td>
<td>Fibrinogen, clotting factors and inhibitors</td>
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<tr>
<td></td>
<td>Plasmin (fibrinolysis)</td>
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<td>Complement C3</td>
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<tr>
<td>Binding Proteins</td>
<td>Ceruloplasmin (copper)</td>
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<td></td>
<td>Steroid binding proteins</td>
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<td></td>
<td>Thyroid hormone binding globulin (TBG)</td>
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<td></td>
<td>Transferrin</td>
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<tr>
<td>Prohormones</td>
<td>Angiotensinogen</td>
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<tr>
<td>Apolipoproteins</td>
<td>Apo A-I, -II, and IV</td>
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<td></td>
<td>Apo B-100</td>
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<tr>
<td></td>
<td>Apo D, Apo E</td>
</tr>
</tbody>
</table>
THE LIVER METABOLIZES AND EXCRETES FOREIGN MOLECULES (Drugs, Xenobiotics)

1. Most often involves oxidation (hydroxylation) and/or conjugation

2. Most hydroxylation is by family of enzymes termed cytochromes P450
   a. Now usually referred to as CYPs. Three main gene families CYP1, CYP2, and CYP3
   b. Genetic and nongenetic factors influence P450 activity

3. Conjugation is by UDP glucuronyltransferases (glucuronic acid), glutathione S-Transferase (glutathione) and sulfotransferases (sulfate)

4. Metabolites which are more water soluble are secreted into bile or plasma where can be excreted by kidney.
Slide 7 – Source Undetermined
Slide 8 – Source Undetermined
Slide 10 – John Williams modified from Fig. 6-6 Granger, D, et al. Clinical Gastrointestinal Physiology. W.B. Saunders, Philadelphia, PA; 1985: 125.
Slide 13 – John Williams
Slide 15 – John Williams
Slide 16 – John Williams
Slide 17 – John Williams
Slide 18 – Source Undetermined
Slide 19 – Source Undetermined
Slide 21 – John Williams
Slide 22 – John Williams
Slide 23 - John Williams