BILE

- COMPLEX LIPID-RICH MICELLAR SOLUTION
- ISO-OSMOTIC WITH PLASMA
- VOLUME OF HEPATIC BILE = 500 – 600 CC/DAY
# COMPOSITION

## COMPOSITION OF BILE

<table>
<thead>
<tr>
<th></th>
<th>Liver Bile (mM)</th>
<th>Gallbladder Bile (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salts</td>
<td>35</td>
<td>310</td>
</tr>
<tr>
<td>Bile Pigments</td>
<td>0.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>3.0</td>
<td>25</td>
</tr>
<tr>
<td>Lecithin</td>
<td>1.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Na⁺</td>
<td>165</td>
<td>280</td>
</tr>
<tr>
<td>K⁺</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ca⁺</td>
<td>2.5</td>
<td>12</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>90</td>
<td>15</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>
FUNCTION OF BILE

- Induce bile flow and phospholipid and cholesterol secretion
- Essential for intestinal absorption of dietary cholesterol, fats and vitamins
- Bind calcium and help to prevent Ca gallstones and oxalate kidney stone formation
- Excretion of lipid soluble xenobiotics, drugs and heavy metals
BILE FORMATION AND CIRCULATION
Figure 1. Cholesterol homeostasis. Input and output pathways of cholesterol in the liver are shown. The input pathways consist of de novo biosynthesis of cholesterol from acetate and the uptake of preformed cholesterol by way of several receptor-mediated mechanisms. The output pathways consist of the conversion of cholesterol to bile acids (neutral and acidic pathways) and biliary cholesterol secretion. Primary and secondary bile acids feedback inhibit cholesterol 7α-hydroxylase (CYP7A) and sterol 27-hydroxylase (CYP27), the two enzymes that initiate bile acid biosynthesis from cholesterol, LDL = low density lipoprotein; HDL = high density lipoprotein.
BILE ACID SYNTHESIS

TWO PATHWAYS

1) CLASSICAL / NEUTRAL
   - RESULTS IN THE SYNTHESIS OF APPROXIMATELY 1:1 RATIO OF CHOLIC AND CHENODEOXYCHOLIC ACIDS

2) ALTERNATE / ACIDIC
   - YIELDS PREDOMINANTLY CHENODEOXYCHOLIC ACID
BILE ACID SYNTHESIS

CLASSICAL / NEUTRAL PATHWAY
- PREDOMINANT PATHWAY IN HEALTH
- POSTCHOLECYSTECTOMY PATIENTS WITH BILE FISTULA
- INFUSED WITH RADIOLABELLED PRECURSORS
  * [3H]7αOH CHOLESTEROL
  * [3H]27-OH CHOLESTEROL
[3H]7αOH CHOLESTEROL
70-95% CONVERTED TO BILE ACIDS

[3H]27-OH CHOLESTEROL
<20% CONVERTED TO BIL ACIDS
BILE ACID SYNTHESIS

ALTERNATE / ACIDIC PATHWAY

- MORE IMPORTANT IN CHRONIC LIVER DISEASE

- CIRRHOTICS

  - LOW RATE OF BILE ACID SYNTHESIS

  - ALMOST EXCLUSIVELY CHENODEOXYCHOLIC
BILE ACID SYNTHESIS

FINAL STEP =

- CONJUGATION OF CHOLIC AND CHENODEOXYCHOLIC ACIDS WITH GLYCINE AND TAURINE

- CONJUGATION ENHANCES THE HYDROPHILICITY, THUS DECREASE THE PASSIVE DIFFUSION OF BILE AS IT MOVES THROUGH THE BILIARY TREE AND SMALL INTESTINE
BILE ACID SYNTHESIS

REGULATION

RATE LIMITING ENZYMES

1) CLASSICAL PATHWAY =
   CHOLESTEROL 7α HYDROXYLASE

2) ALTERNATE PATHWAY =
   STEROL 27 HYDROXYLASE
BILE ACID SYNTHESIS
REGULATION
CHOLESTEROL 7Aα HYROXYLASE
1) BILE ACIDS
2) CHOLESTEROL
3) HORMONES
4) INTESTINAL FACTORS
5) CYTOKINES
BILE ACID SYNTHESIS

REGULATION

CHOLESTEROL 7α HYDROXYLASE

- BILE ACIDS
  - Interruption of enterohepatic circulation-increases bile acid synthesis
  - Intraduodenal reperfusion-reduces bile acid synthesis
Bile acids are not equal in their ability to feedback inhibit CYP7αOH activity
- hydrophobic bile acids – repressed
- hydrophilic bile acids – no effect

URSO = HYDROPHILIC
CLINICAL CORRELATION

1) Resection of Terminal Ileum
   Increased bile acid secretion

2) Infants with inborn errors of bile acid biosynthesis
   - Accumulation of toxic intermediates in the hepatocytes causing cholestasis and chronic liver damage
   - Oral bile acids supplements containing hydrophobic bile acids – decreased accumulation of toxic intermediates
2) CHOLESTEROL
- Increased dietary cholesterol
Rats - Increased CYP7αOH Activity
? Humans - Decreased CYP7αOH Activity

3) HORMONES
- Glucocorticoids
- Thyroid hormones
- Insulin
- Glucagon
CLINICAL CORRELATION

-Hamsters-CYP 7A
-Led to lowered LDL
-May find a role in treating hyperlidiemia
BILE ACID TRANSPORT

-Bile acid pool is recirculated 10-20 times a day
-Bile acid pool is 1.5 to 4 gm
-Circulating bile acid pool is 17 to 40 g
-0.2 to 0.5 gm of bile is lost in feces = replaced by de novo synthesis
ENTEROHEPATIC CIRCULATION

1) TWO PUMPS - LIVER
   - INTESTINE

2) TWO RESERVOIRS
   - INTESTINAL LUMEN
   - BLOOD
ENTEROHEPATIC CIRCULATION PUMPS
- LIVER
  1) Synthesizes new bile acids - <2% of bile acid pool
  2) Extracts bile acids from portal blood
  3) Secretes bile acids into the canaliculi
ENTEROHEPATIC CIRCULATION PUMPS
- INTESTINE
  1) Resorbs bile acids from intestinal lumen
  2) Secretes bile acids into the portal blood
TRANSPORT IN THE LIVER HEPATOCYTE

- APICAL
- BASOLATERAL
- SINUSOIDAL
- LATERAL
TRANSPORT IN THE LIVER
HEPATOCYTE

- BASOLATERAL
- SINUSOIDAL

TWO MAJOR MECHANISMS
1) CARRIER MEDIATED
2) SIMPLE DIFFUSION
TRANSPORT IN THE LIVER
- SINUSOIDAL
1) CARRIER MEDIATED
   a- Na Dependent
   b- Facilitative
TRANSPORT IN THE LIVER

- SINUSOIDAL

1) CARRIER MEDIATED

a- Na Dependent

- Utilizes the low intracellular [Na+] created by Na-K ATPase
- Used to transport hydrophilic glycine or taurine conjugated bile acids
TRANSPORT IN THE LIVER
- SINUSOIDAL
1) CARRIER MEDIATED
a- Na Dependent

-Two Na Dependent Bile Acid transporters
1) NTCP
2) Rats-mEH
TRANSPORT IN THE LIVER
- SINUSOIDAL
1) CARRIER MEDIATED
   b- Facilitative

ANTIPORTER = Exchange uptake of bile acid with the efflux of an intracellular compound
- Nonconjugated secondary bile acids are the preferred substrate
- OAT1 = Organic Anion Transporter
TRANSPORT IN THE LIVER

- SINUSOIDAL

1) SIMPLE DIFFUSION

- Noncharged Hydrophobic bile acids
- Unconjugated bile acids are uncharged at physiologic pH
- Primary bile acids can undergo 7 α dehydroxylation by intestinal bacteria generating the secondary hydrophobic bile acids=lithocholic and daceyholic acids
TRANSPORT IN THE LIVER

HEPATOCYTE

- APICAL = CANALICULAR MEMBRANE

- Occurs across a concentration gradient of between 100 to 1000 fold

-Mechanisms

1) Electrogenic
2) ATP Dependent - Major Mechanism
BILE FLOW

1) BILE ACID DEPENDENT

2) BILE ACID INDEPENDENT
BILE FLOW

1) BILE ACID DEPENDENT

- Bile acids are Anions
- Draw Na+ to maintain electroneutrality
- Na draws water along with it
BILE FLOW

2) BILE ACID INDEPENDENT
Active secretion of organic anions esp. glutathione
TRANSPORT IN THE INTESTINE

ENTEROCYTE
- APICAL
- BASOLATERAL
TRANSPORT IN THE INTESTINE

ENTEROCYTE
- APICAL

MECHANISMS
- Diffusion
- Na Dependent
DIFFUSION

- Bile acids remain trapped in the intestinal lumen because of their net negative charge
- Intestinal bacteria
  Deconjugate a.a. - render them uncharged
  Dehydroxylation - render them more hydrophobic
GALL STONES

GALLSTONE DISEASE

- 10% overall population
- 33% women over 40
- 70% adult American Indian Women
BILE

-BILIRUBIN AND CHOLESTEROL
-BOTH RELATIVELY INSOLUBLE
-SOLUBILISATION BY THE DETERGENT ACTION OF BILE SALTS
BILE

-BILE SALTS and PHOSPHOLIPIDS

- Hydrophilic and hydrophobic portions
  - Self associate so that the exposure of their hydrophobic portion to water is minimised
  - Hydrophobic domains allow the transport of Cholesterol and Bilirubin
• BILIARY LIPID AGGREGATES

• SIMPLE BILE SALT MICELLES
• MIXED DISC MICELLES
• MIXED LIPID VESICLES
PHOSPHOLIPIDS

• Phosphatidylcholine broken down by Phospholipase A from bacteria to Lysolecithin and Fatty Acids

• FA forms soaps with Ca++ - involved in the pathogenesis of brown stones
GALLSTONES

THREE TYPES

- Cholesterol > 80% gallstones in the western world

- Black pigment
  - Calcium salts of unconjugated bilirubin

- Brown pigment
  - Occurs only as a result of bacterial infection of the biliary tree in the presence of bacterial infection
GALLSTONES

CHOLESTEROL

-PRIMARILY A METABOLIC DISORDER

-VICIOUS CYCLE

-Cholesterol hypersecretion

-Gall bladder factor

-Hypomotility

-Mucus hypersecretion

-Intestinal factors
Liver:

Cholesterol Hypersecretion

Gallbladder:

Accelerated Cholesterol Crystal Formation

Hypomotility and Increased Mucin Production

Intestine:

Cholesterol Gallstone

Increased Bile Salt Conversion to Deoxycholate
GALL BLADDER HYPOMOTILITY

• Increased residence time of bile in GB leading to greater time for nucleation

• Greater fraction of bile diverted directly to the intestines-increased bacterial degradation
BILIARY SLUDGE

–Viscous gel containing mucin and microscopic precipitates of multilamellar vesicles, cholesterol and calcium bilirubinate
MUCIN

– Glycoprotein
– Major constituent of GB mucus
– Can bind bilirubin, phospholipids and cholesterol, encouraging cholesterol crystal precipitation
– Viscous nature of mucin gel physically impairs clearance of precipitates
INTESTINAL FACTORS

GB Hypomotility

- More bile directly diverted into the intestines
- Greater exposure to intestinal bacteriathat deconjugate primary bile salts to the more hydrophobic sec bile salts
- After absorption and recycling, the hydrophobic bile salts more effectively extracts cholesterol from canalicular membrane
OTHER FACTORS

–PRONUCLEATING FACTORS
• N Aminopeptidase
• Fibronectin
• Immunoglobulins
• Haptoglobin
• Mucin

–ANTINUCLEATING FACTORS
• Apolipoprotein
• Immunoglobulins
• METABOLIC FACTORS
  – ESTROGEN
  – PREGNANCY
  – OBESITY AND WEIGHT LOSS
  – AGE
  – INTESTINAL HYPPOMOTILITY
  – DIET
  – GENETIC/ETHNIC FACTORS
  – SPINAL CORD INJURY
GALLSTONES

BLACK PIGMENT

COMPOSITION

Calcium bilirubinate
Calcium PO4
CaCO3
GALLSTONES

BLACK PIGMENT

PATHOGENESIS

1) Increased Unconjugated bilirubin
2) Decreased in solubilising micelles & vesicles
3) Increased ionised calcium
GALLSTONES
BLACK PIGMENT
PATHOGENESIS

Increased Unconjugated bilirubin

-Deconjugation
-Enzymatic-B Glucoronidase
-Enzymatic-B Glucoronidase
-Bacterial infection
-Tissue
-Nonenzymatic-tissue
GALLSTONES

BLACK PIGMENT

PATHOGENESIS

Increased Unconjugated bilirubin

- Increased production
  - Hemolysis
  - Alcoholism
Figure 6. Pathogenesis of black pigment gallstones. The major initiating event is a relative increase in conjugated bilirubin secretion. Deconjugation, either by tissue β glucuronidases or non-enzymatically, produces unconjugated bilirubin. Although solubilized in part by biliary micelles and vesicles, the extreme insolubility of calcium bilirubinate enhances precipitation. Inorganic (carbonate and phosphate) calcium salts also precipitate. Mucin in conjunction with calcium-binding protein provides a scaffolding for formation of mature black pigment gallstones. (From Donovan JM, Carey MC. Physical-chemical basis of cholesterol “carriers” in bile. Hepatology 12:945–1055, 1990; with permission.)
Figure 7. Pathogenesis of brown pigment gallstones. Bacterial enzymes degrade biliary lipids, usually in the bile ducts, producing insoluble calcium salts of fatty acids and unconjugated bilirubin. Precipitation of these compounds is exacerbated by degradation of biliary solubilizing agents, bile salts, and phosphatidylcholine. Additionally, solubility of cholesterol is impaired, with consequent precipitation. Brown pigment stones contain bacterial cytoskeletal remains as well as mucin and non-mucin glycoprotein. Obstruction caused by the stone serves as a continuing source of bacterial colonization and further obstruction with biliary stasis.