Bilirubin and Jaundice

Pathways of Bilirubin Synthesis and Catabolism

Sources of bilirubin production in the rat

Labeling of RBC hemoglobin and fecal stercobilin

Reaction Catalyzed by Biliverdin Reductase
**BILIRUBIN CONJUGATION IN MICROSONES INVOLVES TWO STEPS, MEDIATED BY ONE BILIRUBIN-UDPGA TRANSFERASE**

**UDPGA**

**UDPGA**

**UDPGA**

**UDPGA**

**UDPGA TRANSFERASE**

Conjugation prevents internal H-bonding by the -COOH groups of Bilirubin.

**UROBILINOGENS ARE FORMED BY DECONJUGATION AND REDUCTION OF BILIRUBINS BY INTESTINAL BACTERIA**

**CONJUGATED BILIRUBIN**

**UNCONJUGATED BILIRUBIN**

**A UROBILINOGEN**

Deconjugation

2 GA

M = Methyl

E = Ethyl

V = Vinyl
**FRACTIONAL DIAZO REACTION OF PLASMA**

\[
\begin{align*}
\text{DIAZO REAGENT} & \quad \text{Fast} \\
\text{SO}_2\text{H} & \quad \text{CONJUGATED BILIRUBIN} \\
\text{N}^+ & \quad \text{DIRECT reaction} \\
\text{SO}_2\text{H} & \quad \text{UNCONJUGATED BILIRUBIN} \\
\text{N}^+ & \quad \text{INDIRECT reaction}
\end{align*}
\]

**TOTAL DIAZO REACTION OF PLASMA**

\[
\begin{align*}
\text{CONJUGATED BILIRUBIN} + & \quad \text{ACCELERATOR (ALCOHOL, CAFFEINE)} \\
\text{UNCONJUGATED BILIRUBIN} & \quad \text{TOTAL reaction} \\
\text{TOTAL – DIRECT = INDIRECT}
\end{align*}
\]
### Phototherapy for neonatal jaundice

![Image of phototherapy for neonatal jaundice]

### Treatment for Neonatal Jaundice

#### Prevention of kernicterus

![Graph showing prevention of kernicterus]

#### Effect of Sn-protoporphyrin (Sn-PP) and Co-protoporphyrin (Co-PP) when administered once at a dose of 50 μmol/kg body wt on hepatic heme oxygenase activity in the rat.

![Graph showing effect on hepatic heme oxygenase activity]

#### Effect of Sn-protoporphyrin (Sn-PP) (100 μmol/kg body wt) administered once at a dose of 50 μmol/kg body wt on hepatic heme oxygenase activity in the rat.

![Graph showing effect of Sn-PP on hepatic heme oxygenase activity]

#### Effect of Sn-PP (2 x 0.25 μmol/kg body wt) on the levels of serum bilirubin in a patient with primary biliary cirrhosis (PBC).

![Graph showing effect of Sn-PP on serum bilirubin levels]

### Structure of the α and β isomers of bilirubin IX.

![Structure of bilirubin IX α and β]

Structure of the α and β isomers of bilirubin IX. In the IXβ isomer (and in the γ and δ isomers, not shown) the propionic acid groups are moved to positions other than those indicated on the central pyrrole rings B and C of bilirubin IXα.
**Unconjugated Hyperbilirubinemia**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Crigler-Najjar Type I</th>
<th>Gilbert Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma bilirubin</td>
<td>50-60 μM</td>
<td>50-85 μM (increased)</td>
</tr>
<tr>
<td>Plasma BSP retention at 45 min</td>
<td>Normal</td>
<td>Usually normal; elevated in a minority of cases</td>
</tr>
<tr>
<td>Hepatic bilirubin-UDPGT activity</td>
<td>Undetectable</td>
<td>30-50% of normal</td>
</tr>
<tr>
<td>Effect of Phenobarbital on plasma bilirubin</td>
<td>No effect</td>
<td>Reduction</td>
</tr>
<tr>
<td>Pigments in bile</td>
<td>Small amounts of unconjugated bilirubin</td>
<td>Increased proportion of monoglucuronide</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Rare</td>
<td>2-7% of population</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Benign</td>
<td>Rare</td>
</tr>
<tr>
<td>Animal Model</td>
<td>Gunn rat</td>
<td>Bolivian Squirrel Monkey</td>
</tr>
<tr>
<td>Mutation</td>
<td>UDPGT null</td>
<td>UDPGT promoter ACTA2TAA</td>
</tr>
</tbody>
</table>

**Chronic conjugated hyperbilirubinemia**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dubin-Johnson Syndrome</th>
<th>Rotor Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of liver</td>
<td>Grossly black</td>
<td>Normal</td>
</tr>
<tr>
<td>Histology of liver</td>
<td>black pigment; predominantly in centrlobular areas; otherwise normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum bilirubin</td>
<td>Elevated, usually between 2 and 5 mg%, occasionally as high as 20 mg%; predominantly direct-reacting</td>
<td>Elevated, usually between 2 and 5 mg%, occasionally as high as 20 mg%; predominantly direct-reacting</td>
</tr>
<tr>
<td>Routine liver function tests</td>
<td>Normal except for bilirubin</td>
<td>Normal except for bilirubin</td>
</tr>
<tr>
<td>45-min plasma BSP retention</td>
<td>Normal or elevated; secondary rise at 90 min</td>
<td>Elevated; no secondary rise at 90 min</td>
</tr>
<tr>
<td>Urinary coproporphyrin</td>
<td>Normal total &gt;80% as coproporphyrin I</td>
<td>Elevated total; elevated proportion of coproporphyrin I but &lt;80%</td>
</tr>
<tr>
<td>Mode of inheritance</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Uncommon (1:1300 in Persian Jews)</td>
<td>Rare</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Benign</td>
<td>Benign</td>
</tr>
<tr>
<td>Mutation</td>
<td>MRP2</td>
<td>MRP2</td>
</tr>
</tbody>
</table>

**Defective Secretion of Conjugated Bilirubin from Liver Cells**

- **Jaundice**
  - Unconjugated bilirubin
  - Conjugated bilirubin
    - Hepatocellular
    - Cholestatic
  - Hemolysis
    - Defect in Conjugation
      - Intrahepatic
      - Extrahepatic

- **Increased Bilirubin Production Beyond the Liver's Capacity to Conjugate It**

- **Defective Secretion of Conjugated Bilirubin from Liver Cells**

  - Blood
  - Cells
  - Canaliculus
  - Unconjugated bilirubin
  - Conjugated bilirubin
    - Endoplasmic reticulum
    - Conjugated bilirubin

- **Rotor Syndrome**
  - Jaundice
  - Unconjugated bilirubin
  - Conjugated bilirubin
    - Hepatocellular
    - Cholestatic
    - Hemolysis
      - Defect in Conjugation
        - Intrahepatic
        - Extrahepatic

- **Gilbert Syndrome**
  - Plasma bilirubin: 50-85 μM (increased)
  - Plasma BSP retention at 45 min: Usually normal; elevated in a minority of cases
  - Hepatic bilirubin-UDPGT activity: Undetectable
  - Effect of Phenobarbital on plasma bilirubin: No effect
  - Pigments in bile: Small amounts of unconjugated bilirubin
  - Prognosis: Benign
  - Animal Model: Gunn rat
  - Mutation: UDPGT null

- **Crigler-Najjar Type I**
  - Plasma bilirubin: 50-60 μM
  - Plasma BSP retention at 45 min: Normal
  - Hepatic bilirubin-UDPGT activity: Undetectable
  - Effect of Phenobarbital on plasma bilirubin: No effect
  - Pigments in bile: Small amounts of unconjugated bilirubin
  - Prognosis: Benign
  - Animal Model: Gunn rat
  - Mutation: UDPGT null, ACTA2TAA
Liver Function Tests

- Bilirubin
- PT (Prothrombin time)
- Glucose
- Cholesterol
- ALT (alanine aminotransferase)
- AST (aspartate aminotransferase)
- Alkaline phosphatase
- GGT (γ-glutamyltranspeptidase)

Imaging

- Ultrasound
- CT scan
- Liver-spleen scan
- Radionuclide biliary scan
- ERCP (endoscopic retrograde cholangiopancreatography)
- Transhepatic cholangiography

Bilirubin Metabolism

- Blood
  - Conjugated & Conjugated
  - Urine – Urobilinogen
  - Stool – Stercobilin

Jaundice

- Unconjugated bilirubin
- Conjugated bilirubin
- Hemolysis
- Defect in Conjugation
- Hepatocellular

Conversion of protoporphyrin IX to bilirubin IXα. Cleavage of the protoporphyrin ring occurs selectively at the α-methylene bridge. The bridge carbon atom is oxidized to carbon monooxide.
**Biliverdin is produced by oxidation of heme and reduction of the resultant biliverdin**

- **Heme Oxygenase**

- **Biliverdin IXα**

- **NADP⁺**

- **CO₂**

- **O₂**

- **NADPH**

**Conjugation of Bilirubin**

- **Dihydrobilirubin**

- **Two UDP-glucuronic acid**

- **Bilirubin diglucuronide**

- **Blood**

- **Liver**

- **Bile**

**Blood**

- Albumin-B

- **GSH-T**

- Glucuronyl transferase

- **UDPG**

- **UDP glucuronic acid**

- **Endoplasmic reticulum**

**Liver**

- BMG

- DMOAT

- MTR

**Bile**

- Canalicularis

- BMG

- DMOAT

- MTR

- Albumin-B

**Phototherapy of Jaundice**

**Premature Newborns**

**Phototherapy**

- **DAYS AFTER BIRTH**

- **CONCENTRATION (mg/dL)**

- **PHOTO RRT**

- **CONTROL**

- **PHOTO RRT**
Gna-Rats

-Absent bilirubin UDP-glucuronosyltransferase
-Inherited as autosomal recessive trait
-Normal liver function
-Prototype of Crigler-Najjar type I
-No bilirubinuria, small amount of bilirubin in bile
-Excrete bilirubin IXβ into bile
-Excrete unconjugated bilirubin into bile after phototherapy
-Defect corrected by hepatoma cells or kidney transplant