CHAPTER 28

# Transport & Metabolic Functions of the Liver

## Second Part

**OBJECTIVES**

*After studying this chapter, you should be able to:*

- Describe the major functions of the liver with respect to metabolism, detoxification, and excretion of hydrophobic substances.
- Understand the functional anatomy of the liver and the relative arrangements of hepatocytes, cholangiocytes, endothelial cells, and Kupffer cells.
- Define the characteristics of the hepatic circulation and its role in subserving the liver's functions.
- Identify the plasma proteins that are synthesized by the liver.
- Describe the formation of bile, its constituents, and its role in the excretion of cholesterol and bilirubin.
- Outline the mechanisms by which the liver contributes to whole body ammonia homeostasis and the consequences of the failure of these mechanisms, particularly for brain function.
- Identify the mechanisms that permit normal functioning of the gallbladder and the basis of gallstone disease.

| | |
|---|---|
| Chapter 28<br>transport and metabolic function of the liver | • function of liver<br>• biliary system |

1. **Carbohydrates**: Conversion of **galactose** and **fructose** to **glucose**; **Glycogenesis**, **glycogenolysis**, **gluconeogenesis** (**glucose buffer function**)
2. **Fats**: **Fatty acid oxidation**; **Triglyceride**; **Cholesterol** and **bile salts** synthesis;
3. **Proteins**: **Conversion** of amino acids to **fat**; **Synthesis** of **plasma proteins**
4. **Detoxification:** **Extraction** of **waste** material from portal and hepatic blood and **biochemical reactions**
5. **Immune** defense: removal of bacteria by Kupffer cells

**TABLE 28–1 Principal functions of the liver.**

| |
|---|
| **Formation and secretion of bile** |
| **Nutrient and vitamin metabolism** |
| Glucose and other sugars |
| Amino acids |
| Lipids |
| Fatty acids |
| Cholesterol |
| Lipoproteins |
| Fat-soluble vitamins |
| Water-soluble vitamins |
| **Inactivation of various substances** |
| Toxins |
| Steroids |
| Other hormones |
| **Synthesis of plasma proteins** |
| Acute-phase proteins |
| Albumin |
| Clotting factors |
| Steroid-binding and other hormone-binding proteins |
| **Immunity** |
| Kupffer cells |

# FUNCTIONS OF THE LIVER

## METABOLISM & DETOXIFICATION

First, the liver plays key roles in carbohydrate metabolism, including glycogen storage, conversion of galactose and fructose to glucose, and gluconeogenesis, as well as many of the reactions . The substrates for these reactions derive from the products of carbohydrate digestion and absorption that are transported from the intestine to the liver in the portal blood. The liver also plays a major role in maintaining the stability of blood glucose levels in the postprandial period, removing excess glucose from the blood and returning it as needed—the so-called **glucose buffer function** of the liver. In liver failure, hypoglycemia is commonly seen. Similarly, the liver contributes to fat metabolism. It supports a high rate of fatty acid oxidation for energy supply to the liver itself and other organs. Amino acids and two carbon fragments derived from carbohydrates are also converted in the liver to fats for storage. The liver also synthesizes most of the lipoproteins required by the body and preserves cholesterol homeostasis by synthesizing this molecule and also converting excess cholesterol to bile acids.

**Biochemical reactions**:

- **Oxidation**, **reduction** and **conjugation**

**Redox reactions**:

- Oxidation and reductions **performed** by cytochrome P450 (**CYP450**) enzymes in hepatocytes
- CYP450 converts xenobiotics and other toxins to **inactive**, **less lipophilic** metabolites and **reducing their half-lives**

**Metabolic phases**

1. **Phase I** : **oxidation**, **hydroxylation** and **reduction** are mediated by CYP450
2. **Phase II**: **conjugations** (esterification) mediated by **esterases** and **transferases**

**Excretion of metabolites**

- Metabolites are ultimately **secreted** into the **bile** and then **into the GIT**
- The metabolism involves **drugs** and **natural hormones** (steroids, amine and proteins)
- **Liver diseases** results in **over activity of hormonal system**

The liver also detoxifies the blood of substances originating from the gut or elsewhere in the body .
Part of this function is physical in nature—bacteria and other particulates are trapped in and broken down by the strategically located Kupffer cells. The remaining reactions are biochemical, and mediated in their first stages by the large number of cytochrome P450 enzymes expressed in hepatocytes. These convert xenobiotics and other toxins to inactive, less lipophilic metabolites. Detoxification reactions are divided into phase I (oxidation, hydroxylation, and other reactions mediated by cytochrome P450s) and phase II (esterification). Ultimately, metabolites are secreted into the bile for elimination via the gastrointestinal tract. In this regard, in addition to disposing of drugs, the liver is responsible for metabolism of essentially all steroid hormones. Liver disease can therefore result in the apparent overactivity of the relevant hormone systems.

# SYNTHESIS OF PLASMA PROTEINS

**Synthesis of plasma proteins**

Acute-phase proteins (in response to stressful stimuli)
Albumin (high amount; transport function; oncotic pressure of plamsa
Clotting factors
Steroid-binding and other hormone-binding proteins

Following blood loss, liver replace plasma proteins in days to weeks
Immunoglobulis are not synthesized by liver (synthesized by plasma cells "B lymphocytes")

**Bile**

- **Composition**: **Bile acids, phosphatidylcholine , cholesterol, bile pigments and others**
  - ✓ **Bile acids**, the **phosphatidylcholine** and **cholesterol** in a **ratio** of **10:3:1** form micelles.
  - ✓ **Deviations** from this ratio may cause cholesterol to precipitate, **leading to one type of gallstones**
- **pH**: alkaline electrolyte solution similar to pancreatic juice
- **Secretion rate:** 500ml/ day
- **Enterohepatic circulation**: some of bile components are reabsorbed in the intestine and then excreted again by the liver
- **Function**: aid the fat digestion and absorption; excretion of lipid-soluble waste products
- **Bile pigments**: bilirubin and biliverdin are excreted as glucuronides into the bile and responsible for the golden yellow color of bile
- **Tonicity**: initially formed bile is hypertonic then water, glucose, calcium, glutathione, amino acids and urea passively enter the bile by osmosis

# BILE

Bile is made up of the bile acids, bile pigments, and other substances dissolved in an alkaline electrolyte solution that resembles pancreatic juice (Table 28–2). About 500 mL is secreted per day. Some of the components of the bile are reabsorbed in the intestine and then excreted again by the liver (**enterohepatic circulation**). In addition to its role in digestion and absorption of fats (Chapter 26), bile (and subsequently the feces) is the major excretory route for lipid-soluble waste products.

The glucuronides of the **bile pigments**, bilirubin and biliverdin, are responsible for the golden yellow color of bile.

# THE BILIARY SYSTEM

## BILE FORMATION

Bile contains substances that are actively secreted into it across the canalicular membrane, such as bile acids, phosphatidylcholine, conjugated bilirubin, cholesterol, and xenobiotics. Each of these enters the bile by means of a specific canalicular transporter. It is the active secretion of bile acids, however, that is believed to be the primary driving force for the initial formation of canalicular bile. Because they are osmotically active, the canalicular bile is transiently hypertonic. However, the tight junctions that join adjacent hepatocytes are relatively permeable and thus a number of additional substances passively enter the bile from the plasma by diffusion. These substances include water, glucose, calcium, glutathione, amino acids, and urea.

**Bilirubin**

- **Formation**: formed in the tissues by **break down of Hb**
- **Transport**: most of bilirubin **bound to albumin tightly** and dissociate in the liver; the **free bilirubin enters hepatocytes** via **OATP** (organic anion transporting polypeptide)
- **Conjugation**: each **bilirubin** molecule is **conjugated** to **two glucuronic acids** via glucuronyl transferase (U**DP-glucuronosyl-transferase**; located in the **smooth endoplasmic reticulum**) to form **bilirubin diglucuronides**
- **Solubility**: glucuronides are **more water soluble** than free bilirubin
- **Excretion**: glucuronides are transported against conc. gradient by active transporter known as multidrug resistance protein-2 (**MRP-2**) **into bile canaliculi** and then into **intestine**. Small amounts of the conjugates escape into the **blood** and **bound less tightly to albumin** than the free bilirubin and **excreted in urine**
- **Blood level**: Total plasma bilirubin "0.1-1.2mg/dL"= **free** "indirect" **bilirubin + conjugated "**direct**" bilirubin**
- **Enterohepatic circulation**:
  - ✓ **Colonic bacteria breakdown conjugated bilirubin** to free one and to a color derivative known as **urobilinogen**.
  - ✓ Intestinal **mucosa** is **impermeable** to **conjugated bilirubin BUT permeable to free bilirubin** and to **urobilinogen**
  - ✓ Some of the free bilirubin and urobilinogen are **reabsorbed** in the portal circulation
  - ✓ Some of **circulating** free bilirubin and urobilinogen are excreted in **urine**

# BILIRUBIN METABOLISM & EXCRETION

Most of the bilirubin in the body is formed in the tissues by the break down of hemoglobin .

The bilirubin is bound to albumin in the circulation. Most of it is tightly bound, but some of it can dissociate in the liver, and free bilirubin enters liver cells via a member of the organic anion transporting polypeptide (OATP) family, and then becomes bound to cytoplasmic proteins (Figure 28–5).

It is next conjugated to glucuronic acid in a reaction catalyzed by the enzyme **glucuronyl transferase** (UDP-glucuronosyl-transferase). This enzyme is located primarily in the smooth endoplasmic reticulum. Each bilirubin molecule reacts with two uridine diphosphoglucuronic acid (UDPGA) molecules to form bilirubin diglucuronide. This glucuronide, which is more water-soluble than the free bilirubin, is then transported against a concentration gradient most likely by an active transporter known as multidrug resistance protein-2 (MRP-2) into the bile canaliculi. A small amount of the bilirubin glucuronide escapes into the blood, where it is bound less tightly to albumin than is free bilirubin, and is excreted in the urine. Thus, the total plasma bilirubin normally includes free bilirubin plus a small amount of conjugated bilirubin. Most of the bilirubin glucuronide passes via the bile ducts to the intestine.

**Jaundice "icterus"**

- **Definition**: High plasma bilirubin (Accumulation of free or conjugated bilirubin in blood. The skin, sclera and mucous membranes turn yellow
- **Cutoff value:** total bilirubin >2mg/dL (hyperbilirubinemia)
- **Causes**:

1. **Excess production**: hemolytic anemia
2. **Hepatic disturbances** by liver diereses
   - Disturbed hepatic uptake; intracellular protein binding; conjugation; or secretion into the canaliculi
3. **Intra- or extrahepatic biliary obstruction** by stones or tumor

- **Disturbed** secretion into the **canaliculi** and **biliary obstructions** raise plasma **conjugated bilirubin**; **WHILE** others increase **free bilirubin**

# JAUNDICE

When free or conjugated bilirubin accumulates in the blood, the skin, scleras, and mucous membranes turn yellow. This yellowness is known as **jaundice** (icterus) and is usually detectable when the total plasma bilirubin is greater than 2 mg/dL (34 μmol/L). Hyperbilirubinemia may be due to (1) excess production of bilirubin (hemolytic anemia, etc; see Chapter 31), (2) decreased uptake of bilirubin into hepatic cells, (3) disturbed intracellular protein binding or conjugation, (4) disturbed secretion of conjugated bilirubin into the bile canaliculi, or (5) intrahepatic or extrahepatic bile duct obstruction. When it is due to one of the first three processes, the free bilirubin rises. When it is due to disturbed secretion of conjugated bilirubin or bile duct obstruction, bilirubin glucuronide regurgitates into the blood, and it is predominantly the conjugated bilirubin in the plasma that is elevated.

- **Bile flow:** between meals the sphincter of Oddi is closed and the bile flows into the gallbladder
- **Bile concentration**: In the gallbladder, the bile is concentrated by absorption of water
  - ✓ Hepatic bile: 97% water
  - ✓ Gallbladder bile: 89% water
  - ✓ When water decrease, the micelles become larger and the bile remain isotonic
- **Bile obstruction**:
  - ✓ When the **bile duct** and **cystic duct** are **clamped**, the **intrabiliary pressure** raises to ~ **320mm of bile** in **30min** and **bile secretion stops**
  - ✓ When the **bile duct** is **clamped** and the **cystic duct is left open**, **water is reabsorbed in the gall bladder**, and the **intrabiliary pressure raises** only to ~ **100mm of bile** in **several hours**

**TABLE 28–3 Comparison of human hepatic duct bile and gallbladder bile.**

| | Hepatic Duct Bile | Gallbladder Bile |
|---|---|---|
| Percentage of solids | 2–4 | 10–12 |
| Bile acids (mmol/L) | 10–20 | 50–200 |
| pH | 7.8–8.6 | 7.0–7.4 |

# FUNCTIONS OF THE GALLBLADDER

In normal individuals, bile flows into the gallbladder when the sphincter of Oddi is closed (ie, the period in between meals). In the gallbladder, the bile is concentrated by absorption of water. The degree of this concentration is shown by the increase in the concentration of solids (Table 28–3); hepatic bile is 97% water, whereas the average water content of gallbladder bile is 89%. However, because the bile acids are a micellar solution, the micelles simply become larger, and since osmolarity is a colligative property, bile remains isotonic. However, bile becomes less alkaline as sodium ions are exchanged for protons (although the overall concentration of sodium ions rises with a concomitant loss of chloride and bicarbonate as the bile is concentrated).

When the bile duct and cystic duct are clamped, the intrabiliary pressure rises to about 320 mm of bile in 30 min, and bile secretion stops. However, when the bile duct is clamped and the cystic duct is left open, water is reabsorbed in the gallbladder, and the intrabiliary pressure rises only to about 100 mm of bile in several hours.

**Bile ejection**

- **Role of CCK:**
  - ✓ Triggered by fatty acids and amino acids in the duodenum
  - ✓ Function: Contraction of gallbladder and relax the sphincter of Oddi allow bile flow into intestine

**Bile formation**

- **Vagus nerve "Ach" stimulation** : increases bile production
- **Secretin**: increase water and bicarbonate contents of the bile
- **Choleretic agents:** are substances that increase bile formations such as : **Secretin**, **Ach** and **bile acids**

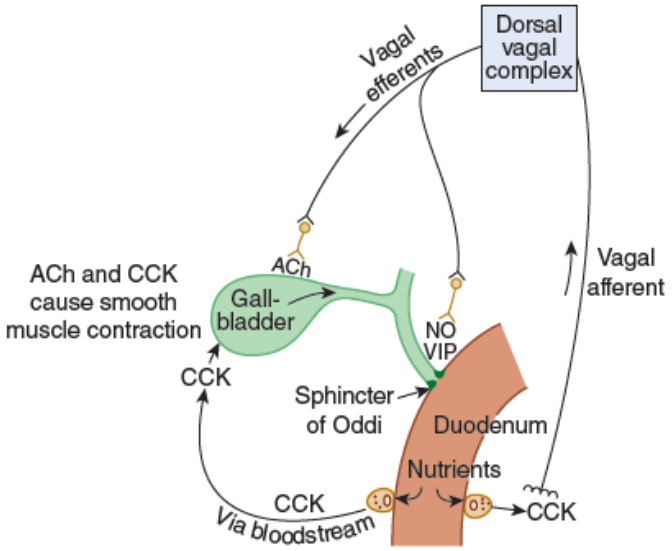


**FIGURE 28–8 Neurohumoral control of gallbladder contraction and biliary secretion.** Endocrine release of cholecystokinin (CCK) in response to nutrients causes gallbladder contraction. CCK, also activates vagal afferents to trigger a vagovagal reflex that reinforces gallbladder contraction (via acetylcholine [ACh]) and relaxation of the sphincter of Oddi to permit bile outflow (via NO and vasoactive intestinal polypeptide [VIP]).

# REGULATION OF BILIARY SECRETION

When food enters the mouth, the resistance of the sphincter of Oddi decreases under both neural and hormonal influences (Figure 28–8). Fatty acids and amino acids in the duodenum release CCK, which causes gallbladder contraction.

The production of bile is increased by stimulation of the vagus nerves and by the hormone secretin, which increases the water and $HCO_3^-$ content of bile. Substances that increase the secretion of bile are known as **choleretics.** Bile acids themselves are among the most important physiologic choleretics.