Section 17

LECTURE

Physiology and Biochemistry of the Liver

Hepatic Pathophysiology

I. Principal Functions of the Liver

A. ***Detoxification*** and excretion of hydrophobic endo- and xenobiotics

B. ***Metabolic regulation*** of carbohydrate, lipid and protein biosynthesis and degradation

1. Facilitated by unique location of liver with regard to the portal circulation (all absorbed nutrients must pass through the liver)

C. ***Synthesis*** of essential proteins and lipids

1. Proteins: albumin, clotting factors, apolipoproteins, enzymes
2. Lipids: bile acids, cholesterol

II. Overview of Hepatic Structure

A. Embryology (***Fig. 1***)

1. The *hepatic diverticulum* (liver bud) forms as an outgrowth of the endodermal epithelium at the distal end of the foregut during the third week of gestation.
   a. The liver bud penetrates the mesodermal plate between the pericardial cavity and the yolk sac stalk (septum transversum)
   b. The epithelial liver cords interdigitate with the vitelline and umbilical veins to form the hepatic sinusoids
   c. Hematopoietic, Kupffer, and other non-parenchymal connective tissue cells are derived from the mesoderm of the septum transversum
2. Functions of the liver *in utero*
   a. *Hematopoiesis*: The liver serves as the principal site of hematopoiesis during the first 30 to 35 weeks of gestation
   b. *Bile production*: Commences at the 12th week of gestation

B. Traditional Structure (***Fig.2***)

1. *Hepatic Lobule*: 1 cell thick cords of hepatocytes arranged radially around a central hepatic venule
2. *Portal Triads*:
   a. Located at the periphery of the lobule
   b. Consist of a portal venule, hepatic arteriole and an interlobular bile duct
3. *Sinusoids*: endothelial-lined blood channels with large fenestrations that extend between the portal tract and the central vein (***Fig. 3***)
   a. Each hepatocyte is exposed to the blood plasma of at least two sinusoids, representing up to 40% of the cell surface area
   b. Nonparenchymal sinusoidal cells
      1) Endothelial cells
         a) Unique in that they lack a true basement membrane and possess 0.1 mm pores (fenestrae)
      2) Kupffer cells
         a) Phagocytosis and clearance of microorganisms, immune complexes, and other particulate matter
         b) Largest population of fixed macrophages in the body
      3) Ito cells (lipocytes)
         a) Store lipids and fat soluble vitamins
         b) Thought to play important role in collagen production in cirrhosis
      4) Pit cells
         a) Exhibit natural killer activity
   c. Space of Disse: separates sinusoids from the hepatocytes

C. Functional Hepatic Unit - The Liver Acinus (***Fig. 4***)

1. The *hepatic acinus* is the functional unit of the liver
   a. Consists of a cluster of hepatocytes centered on a terminal hepatic arteriole and portal venule

b. Zonation: blood flows from the terminal hepatic arterioles in the portal triads through the sinusoids to the terminal hepatic venules (***Fig. 5***)

1) Zone 1: hepatocytes nearest the portal triad (periportal)

a) exposed to greatest substrate concentrations

b) highest oxygen tension

c) largest surface to volume ratio

2) Zone 2: intermediate zone

3) Zone 3: perivenular (central) hepatocytes

a) lowest substrate concentrations

b) poorest oxygenation

1)) Zone 3 hepatocytes are at increased risk from systemic hypoxia

c. -Functional and metabolic heterogeneity between the acinar zones (***Table1***)

1) Variations in levels of enzymes depending on zonation

a) Periportal hepatocytes (zone 1): ALT, LDH, GGT

b) Perivenous hepatocytes (zone 3): AST, glucokinase, pyruvate kinase

2) Recruitment of hepatocytes occurs at high substrate delivery rates

2. Hepatocyte "streaming" along hepatic cords

D. Structure of the Hepatocyte

1. Hepatocyte is highly polarized with transport directed from the sinusoidal (***basolateral***) domain of the cell to the canalicular (***apical***) domain

2. Sinusoidal (basolateral) membrane (85 - 90% of hepatocyte surface area)

a. Contains active transport systems for the uptake of substrates into the hepatocyte

1) Numerous microvilli increase surface area

2) Na^+/K^+-ATPase provides main driving force

3. Canalicular (apical) membrane (10 - 15% of hepatocyte surface area)

a. Active secretion of bile acids, organic anions into bile

b. Phospholipid flipases responsible for biliary lipid excretion

4. How does the liver cell maintain structural and functional polarity?
   a. In contrast to most epithelial cells, all newly synthesized proteins are transported to the *basolateral* pole
   b. *Apical* membrane proteins are subsequently removed and translocated to the canalicular domain
   c. Cytoskeletal components of the *tight junctions* between adjacent hepatocytes maintain polarity by creating a barrier between the two membrane domains
      1) Also serves as a barrier between plasma and bile (*paracellular route*), which appears to be under hormonal control

II. Carbohydrate Metabolism

A. Role of the liver in glucose homeostasis (***Fig. 6***):

1. In the postprandial (fed) state, the liver converts carbohydrates to (***Fig.6A***):
   a. *Glycogen*: a tree-like polymer of 20,000 to 30,000 glucose molecules
      1) Accumulates to a maximum of 65 g (5 - 8% of hepatic weight)
   b. *Fatty acids*
      1) Glucose in excess of liver glycogen capacity is converted, by the process of *glycolysis*, to fatty acids for storage in extrahepatic fat cells
2. In the postabsorptive (fasted) state, the liver mobilizes glucose for systemic distribution by (***Fig. 6B***):
   a. Glycogen breakdown (*glycogenolysis*)
   b. Glucose production via amino acid and fatty acid degradation (*gluconeogenesis*)

B. Glycogenesis

1. Glucose absorption by the liver (***Fig. 7***)
   a. The liver is perfused directly by splanchnic blood, which contains high concentrations of absorbed glucose
   b. Uptake into the hepatocyte occurs by carrier-mediated facilitated diffusion

c. Phosphorylation to glucose 6-phosphate by glucokinase prevents back-diffusion into the sinusoids

2. Glycogen synthesis (***Fig. 8***)
   a. Glycogen is produced by polymerization of glucose molecules via 1:4 glucoside linkages
   b. Formation of multiple short-chain branch points via 1:6 bonds ensure that nearly 10% of glucose residues are terminal and, hence, directly accessible to degradative enzymes
   c. Most of the glycogen precipitates as insoluble granules, facilitating glucose storage without altering intracellular osmolarity

C. Glycogenolysis
   1. Glycogen breakdown occurs by successive removal of glucose units (***Fig. 9***)

D. Glycolysis (***Fig. 10***)
   1. Glucose is converted to lactate and pyruvate, with the generation of energy in the form of ATP
   2. The glycolytic pathway represents the only mechanism whereby glucose is anaerobically oxidized to produce energy
      a. Under anaerobic conditions, lactate diffuses out of the cell into the systemic circulation
   3. Pyruvate serves as a precursor for acetyl-CoA, which is utilized for:
      a. Energy production via the tricarboxylic acid (TCA) cycle (***Fig. 11***)
      b. Fatty acid synthesis

E. Gluconeogenesis
   1. Glucose is synthesized from pyruvate, lactate, amino acids and tricarboxylic acids
   a. Alanine generally serves as the principal substrate for gluconeogenesis
   2. Occurs via reversal of the glycolytic pathway, except for 3 major unidirectional steps:
      a. pyruvate carboxylase
      b. fructose-1,6-bisphosphatase

c. glucose 6-phosphatase

F. Regulation of glucose metabolism

1. Glucagon (and catecholamines): stimulate glucose release by the liver
   a. Activate glycogenolysis and gluconeogenesis
   b. Inhibit glycogenesis and glycolysis
2. Insulin: released in response to hyperglycemia
   a. Stimulates hepatic glycolysis
   b. Enhances uptake of glucose by adipose and muscle
3. Glucose
   a. Stimulates glycogen synthesis and glycolysis by the liver
   b. Suppresses glycogenolysis and gluconeogenesis

G. Clinical correlates:

1. Prolonged starvation (weeks):
   a. Decreased availability of protein for conversion to glucose results in diminished hepatic gluconeogenesis
   b. Ketones (from fat breakdown) replace glucose as oxidative fuel for heart, kidney, muscle and, eventually, brain
2. Hypoglycemia of liver disease
   a. Acute hepatitis
      1) Anorexia results in decreased caloric intake and glycogen depletion
      2) Gluconeogenesis impaired by hepatocellular dysfunction
      3) Cases of hyperinsulinemic hypoglycemia suggest failure of liver to extract and degrade insulin from the systemic circulation (normal 50% first-pass metabolism)
   b. Alcoholism
      1) Typically observed in the setting of binge drinking
      2) Mechanism
         a) Starvation depletes glycogen stores

b) Ethanol oxidation by the liver generates high NADH concentrations, which diverts oxaloacetate into malate, diminishing the bioavailability for gluconeogenesis

c. Glycogen storage diseases

1) Type Ia (von Gierke): glucose 6-phosphatase deficiency

a) Characterized by severe hepatomegaly (glycogen accumulation) and profound hypoglycemia

2) Type III: amylo-1,6-glucosidase (debrancher) deficiency

3) Type IV: a-1,4 glucan-6-glycosyl transferase deficiency

IV. Protein and Amino Acid Metabolism

A. Role of the liver in protein metabolism

1. The liver is the primary site of protein synthesis and metabolism
   a. Over 90% of plasma proteins are secreted by the liver
      1) Albumin accounts for > 50% of hepatic protein secretion
      2) All coagulation factors except von Willebrand's factor are synthesized by the liver
2. Half of the 20 standard amino acids are synthesized in the liver from the tricarboxylic acid cycle precursors: pyruvate, a-ketoglutarate, and oxaloacetate
   a. The remaining "essential" amino acids are obtained from ingested plants and bacteria
3. Obligatory protein loss in fasting individuals is approximately 20 - 30 g/day

B. Hepatocellular uptake

1. Amino acids: to date, 6 distinct amino acid transporters have been identified on the sinusoidal membrane of the hepatocyte
2. Proteins: uptake of large protein molecules occurs via receptor-mediated endocytosis, with degradation into constituent amino acids occurring in the lysosomal compartment

C. Amino acid catabolism

1. Amino acids are degraded by the liver and, to a lesser extent, by the kidney
   a. In the liver cell, amino acids are utilized primarily for protein synthesis
2. Excess amino acids undergo oxidative degradation and deamination
3. The resultant amino group is eliminated by way of the urea cycle

D. Urea cycle (***Fig. 12***)

1. The liver is the only organ capable of urea synthesis, producing 20 - 30 g/day
2. Complex compartmentalization of the urea cycle enzymes prevents significant accumulation of free ammonia

E. Clinical correlation

1. Findings in hepatic dysfunction
   a. Hypoalbuminemia: decreased synthesis
      1) Contributes to accumulation of ascites and interstitial edema
   b. Coagulopathy:
      1) Decreased coagulation factors
         a) PT is a sensitive indicator of early, severe hepatic failure, with Factor VII exhibiting the shortest half-life (5 - 8 hours)
      2) Thrombocytopenia as a result of hypersplenism
   c. Encephalopathy
      1) Accumulation of ammonia
      2) Portal hypertension results in shunting of blood away from the liver
   d. Renal function
      1) Disproportionately low BUN (diminished urea production)
      2) Disproportionately low creatinine (decreased creatine release from muscle as a result of protein malnutrition)
2. Urea cycle defects
   a. Deficiency in urea cycle enzymes:
      1) Carbamoyl-phosphate synthase
      2) Ornithine transcarbamylase (most common)
      3) Argininosuccinic acid synthase

4) Argininosuccinic acid lyase
5) N-acetylglutamate synthetase

b. Clinical features: lethargy, coma
1) hyperammonemia

c. Management
1) Eliminate protein from the diet
2) Glucose infusion (prevent inhibition of TCA cycle by increased ammonia levels)
3) Sodium benzoate and sodium phenylacetate administered to eliminate ammonia as hippuric acid and phenylacetyl glutamate

3. Alpha$_1$-antitrypsin deficiency

a. - a_1-antitrypsin is the major circulating serine protease inhibitor
1) Anti-elastase activity prevents neutrophil elastase from destroying the lung
2) Elastocytolytic attack in patients deficient in this protein results in pulmonary disease, which is exacerbated by additional pulmonary insults (e.g., smoking, toxins, infections)

b. Variable phenotypes leading to a_1-antitrypsin deficiency
1) Gene frequency 1 in 40
2) Most common mutation is Z deficiency variant (Glu 342 to Lys substitution)

c. Produced in the liver
1) Only 12 - 15% of homozygotes exhibit liver disease (cirrhosis)
2) Accumulation of mutant protein in hepatocytes is important in the pathogenesis of liver disease (***Fig. 13***)
a) Liver injury results from the concordant existence of the expression of the abnormally folded Z a_1-antitrypsin protein and a delay in the ER protein degradation pathway
b) This is the reason why patients who produce Z a_1-antitrypsin but are able to clear the abnormal protein do not develop liver disease

V. Lipid Metabolism

A. Role of the liver in lipid metabolism

1. Essential in the homeostasis of:
   a. Fatty acids
   b. Cholesterol
   c. Phospholipids
   d. Triacylglycerols (triglycerides)
2. Lipoprotein assembly and metabolism
3. Bile production

B. Fatty acid metabolism (***Fig. 14***)

1. Fatty acids are vital for cellular function:
   a. Major source of energy (via TCA cycle)
   b. Precursors for eicosanoids
   c. Esterification of cholesterol
   d. Essential constituent of membrane lipids (phospholipids, triacylglycerols)
2. Fatty acid biosynthesis and storage
   a. Fatty acids are produced by the action of fatty acid synthase, which catalyzes the cyclic addition of 2 carbon fragments from acetyl-CoA to the growing acyl chain
      1) The principal fatty acid product is an unsaturated 16 carbon chain *(palmitate)*
      2) Odd-number fatty acids are formed when the elongation process is initiated with propionyl-CoA (C_3) in place of acetyl-CoA (C_2)
   b. Triacylglycerols (triglycerides) are synthesized predominantly in the liver and adipose tissue and represent the primary intracellular storage form of fatty acids
   1) Formed by the interaction of fatty acyl-CoA with glycerol 3-phosphate
3. Fatty acid uptake and oxidation (***Fig. 15***)

a. Triacylglycerol hydrolysis in adipocytes gives rise to free fatty acids which are transported to the liver bound to serum albumin
b. Hepatocellular uptake is rapid with a 30 to 40% first-pass extraction
    1) Mechanism whereby fatty acids traverse the plasma membrane remains controversial
        a) Experimental support for spontaneous transmembrane movement of long-chain fatty acids
        b) Evidence for the existence of a 43-kDa integral plasma membrane protein which facilitates fatty acid uptake ($FABP_{PM}$)
c. Fatty acid catabolism (***Fig. 16***)
    1) Chemically inert fatty acids are converted to coenzyme A derivatives by cytosolic long-chain acyl-CoA synthetase
    2) b-oxidation of fatty acids, which involves the cleavage and release of 2 carbon units as acetyl-CoA, occurs predominantly in the mitochondria
        a) Short- and medium-chain fatty acids ($< C_{12}$) readily traverse the mitochondrial membranes
        b) Mitochondria are impermeable to long-chain acyl-CoA derivatives
            1) Translocation of long-chain fatty acids is facilitated by the combined action of carnitine acyltransferases I and II located at the inner and outer surfaces of the inner mitochondrial membrane
            2) The fatty acid is esterified to carnitine, and the resultant fatty acyl carnitine is transported across the mitochondrial membrane, where the acyl chain is cleaved and re-esterified to coenzyme A
        c) Acetyl-CoA generated by fatty acid oxidation is further catabolized via the TCA cycle or converted to ketone bodies (***Fig. 17***)

1) Ketone bodies are formed only when acetyl-CoA is produced in excess of the capacity of citrate synthase, the first enzyme in the TCA cycle

3) Fatty acid oxidation also occurs in hepatocyte peroxisomes, but to a lesser extent

a) Role of peroxisomal fatty acid oxidation is unclear, as this system is incapable of generating ATP and, therefore, wastes the energy stored in fatty acids

4. Clinical correlates

a. Acute fatty liver of pregnancy

1) Decreased mitochondrial b-oxidation of fatty acids

a) Deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase activity

b) Exhibit marked hepatic accumulation of fat (microvesicular steatosis) in the form of triacylglycerols

2) Homozygotes manifest early in life with fasting induced hypoketotic hypoglycemic coma and hepatic steatosis, episodic muscle weakness and moderate cardiac dysfunction

a) Reflect the inability of the liver to make ketones during fasting

b) Obligate requirements of cardiac and skeletal muscle for long-chain fatty acids as fuels for normal energy metabolism

3) Other diseases with similar manifestations:

a) Carnitine palmitoyltransferase deficiency

b) Systemic carnitine deficiency (defective carnitine transport)

C. Cholesterol metabolism

1. Functions of cholesterol

a. Essential constituent of biological membranes (decreases fluidity)

1) Cholesterol gradient: increases as move from center to periphery of the cell

2) Important component of myelin sheath

b. Precursor for bile salts and steroid hormones

c. Important role in atherogenesis

2. Sources of cholesterol

a. Exogenous - dietary (***Fig. 18***)

1) Absorbed by small intestinal epithelium following solubilization in bile salt micelles

2) Cholesterol is esterified to long-chain fatty acids and packaged into chylomicrons for transport to the liver

3) Chylomicrons are converted to chylomicron remnants by the action of lipoprotein lipase located on the surface of endothelial cells

4) Chylomicron remnants are rapidly taken up by the liver through the concerted action of hepatic lipase and hepatocyte LDL receptors (see below)

b. Exogenous - reverse cholesterol transport

1) LDL receptor (***Fig. 19***)

a) Cell surface glycoprotein expressed in clathrin-coated pits

b) High affinity for apoprotein B-100 (found in LDL) and apoprotein E (on IDL and HDL subclass)

c) Bound lipoprotein internalized by receptor-mediated endocytosis

1) Endocytic vesicles fuse to form endosomes, and internal pH is reduced by the action of ATP-driven proton pumps

2) LDL dissociates from the receptor in the acid environment and LDL receptor is recycled to the cell surface (1 cycle every 10 min)

3) Endosomes fuse with lysosomes, and cholesteryl esters are hydrolyzed to free cholesterol by acid hydrolase

2) HDL receptor

a) Efflux of cholesterol from peripheral cells to HDL is essential for cholesterol homeostasis, as most cells are not able to catabolize accumulated exogenous cholesterol

b) Recent identification of SR-BI, a plasma membrane "docking" receptor for HDL

1) Facilitates selective hepatocellular uptake of HDL cholesterol and cholesterol esters, without endocytosis of the lipoprotein particle

2) The partially lipid-depleted HDL particle dissociates from the cell surface and continues circulating in the blood

c. Endogenous - biosynthesis

1) Liver produces approximately 20% of total biliary cholesterol

2) The rate-limiting step in cholesterol synthesis is the formation of mevalonate by the microsomal enzyme, *HMG-CoA reductase*

a) Exquisitely sensitive to feedback inhibition by dietary cholesterol

3. Intracellular storage of cholesterol

a. Cholesterol stored intracellularly esterified to long-chain fatty acids (primarily oleic acid)

b. Esterification occurs in the endoplasmic reticulum through the action of acyl-CoA:cholesterol acyltransferase (ACAT)

c. Cholesterol esters condense to form cytoplasmic lipid droplets or are assembled into lipoproteins and secreted into plasma

4. Cholesterol elimination

a. Biliary secretion

1) Cholesterol and phospholipid secretion into bile occur in parallel (ratio 0.3)

b. Lipoprotein assembly

1) The liver synthesizes primarily VLDL and HDL

2) Driving force for lipoprotein assembly is the active synthesis of phospholipid and cholesterol

c. Bile acid synthesis (***Fig. 20***)

1) Primary bile acids: cholic acid, chenodeoxycholic acid

a) Synthesized in the liver

b) Constitute over 70% of circulating bile acids

c) Rate-limiting step in bile acid synthesis is the introduction of an hydroxyl group at the 7 position by cholesterol 7a-hydroxylase

1)) Negative feedback inhibition by chenodeoxycholic and deoxycholic acid

2)) Up-regulation by cholesterol

2) Secondary bile acids: deoxycholic acid, lithocholic acid

a) Generated in the ileum and colon by anaerobic bacterial degradation of the primary bile acids via 7a-dehydroxylation

b) The secondary bile acids accumulate to a significant extent in the enterohepatic circulation as the human liver is unable to 7a-hydroxylate bile acids

c) An additional secondary bile acid, 7-oxolithocholic acid, is produced in the gut as a result of 7a-dehydrogenation

3) Tertiary bile acids: sulfolithocholic acid, ursodeoxycholic acid

a) Formed via metabolism of secondary bile acids by the liver and gut

4) Enterohepatic circulation of bile acids (***Fig. 21***)

a) Cycling of bile acids between the liver and intestine involving:

1)) Conjugation and secretion of bile acids by the liver

2)) Temporary storage in the gallbladder

3)) Release into the small intestine

4)) Absorption in the terminal ileum

5)) Transport in the portal vein and uptake by the liver

b) Total bile acid pool cycles 8 to 10 times daily

5. Cholesterol homeostasis - balance between cholesterol intake, storage, and elimination (***Fig. 22***)

a. Cholesterol input

1) Dietary intake via LDL receptor

2) Reverse cholesterol transport via HDL receptor

3) De novo synthesis (HMG-CoA reductase)

b. Cholesterol storage

1) Cholesterol esterification (ACAT)

2) Breakdown of cholesterol esters (neutral cholesteryl ester hydrolase, nCEH)

c. Cholesterol output

1) Biliary secretion

2) Bile acid synthesis (7a-hydroxylase)

3) Lipoprotein assembly

c. Major control points: HMG-CoA reductase, ACAT, nCEH, 7a-hydroxylase

6. Clinical correlates

a. Wolman's disease/cholesterol ester storage disease

1) Marked accumulation of cholesterol esters and triacylglycerols as a result of a deficiency in lysosomal acid hydrolase activity

2) Liver enlarged with marked steatosis

a) Hepatocyte organelles distorted by accumulation of lipid droplets

b. Primary biliary cirrhosis

1) Inability to secrete bile acids associated with marked hypercholesterolemia, xanthelasma, xanthoma

a) No increased risk of atherosclerosis due to incorporation of cholesterol into lipoprotein X

D. Phospholipid metabolism

1. Biosynthesis

a. Phospholipids are formed predominantly in the E.R. and Golgi apparatus through the addition of various polar head groups to phosphatidic acid

2. Biliary phospholipid secretion

a. Phospholipids comprise 15-25% of total biliary lipid, with diacylphosphatidylcholines accounting for over 95% of biliary phospholipids

b. Delivery of lipids to the bile canaliculus involves vesicular transport
    1) Phospholipids derived primarily from the endoplasmic reticulum
c. Phosphatidylcholine transfer protein (PC-TP) facilitates the intracellular movement of phosphatidylcholine
    1) Bile salts enhance the unidirectional delivery of phosphatidylcholine to the canalicular membrane

3. Clinical correlate
    a. Amiodarone toxicity
        1) Iodinated benzofuran derivative used in the treatment of refractory arrhythmias
        2) Up to 3% of patients develop liver disease
        3) Amiodarone and its metabolites inhibit phospholipase activity
            a) Cationic nature leads to entrapment in lysosomes
            b) Causes accumulation of phospholipids and amiodarone in lysosomes resulting in lamellated lysosomal inclusions

VI. Intracellular Transport/Trafficking

A. Elimination of endo- and xenobiotics from the systemic circulation

1. Role of kidney
    a. The kidney is able to excrete water-soluble hydrophilic organic compounds
        1) Molecular weight must be below ~1,000 to be filtered by the glomerulus
    b. Hydrophobic substances are generally transported in the blood bound to soluble binding proteins
        1) These hydrophobic compounds cannot be excreted in the urine since the proteins to which they are bound are unable to pass the glomerulus

2. Role of liver

a. Hydrophobic, protein bound compounds

1) Hydrophobic compounds are dissociated from plasma proteins and taken up by the hepatocyte

B. Overview of hepatic transport and excretion

1. Major steps involved in hepatic transport and excretion of endo- and xenobiotics:

a. Delivery

1) Compounds taken up from the gastrointestinal tract
2) Carried through the portal system and percolate through the sinusoidal fenestrae to the space of Disse

b. Uptake

1) Across the basolateral (sinusoidal) membrane of the hepatocytes
2) Role of membrane transport systems
   a) Na^+/K^+ ATPase

c. Intracellular binding proteins/storage

1) Specialized cytosolic proteins which bind hydrophobic substrates
2) Role in prevention of reflux

d. Biotransformation/metabolism

1) Biochemical conversion of hydrophobic precursors to more polar hydrophilic derivatives
2) Enzyme complexes predominantly localized in the endoplasmic reticulum (microsomes)

e. Secretion

1) Hydrophilic metabolites are transported across the canalicular membrane into the bile canaliculus
2) Generally believed to be the rate limiting step for most compounds

f. Biliary flow

1) Absorption of some compounds by the biliary epithelium
2) Recent success in the isolation and culture of biliary ductular epithelial cells will facilitate further study

2. Unique features of liver which promote excretion of hydrophobic compounds
   a. Large *fenestrae* in sinusoidal endothelium permit free access of plasma proteins (and their ligands) to the hepatocyte sinusoidal membrane
   b. Carrier proteins (*transporters*) in basolateral cell membrane facilitate uptake of dissociated compounds
   c. *Cytosolic binding proteins* limit reflux back into the plasma
   d. Rapid *biotransformation* into more hydrophilic compounds which decreases reflux and facilitates secretion into bile
   e. Active *secretion* into bile continuously depletes the intracellular pool

C. Mechanisms of intracellular transport (***Fig. 23***)
   1. Cytoplasmic (aqueous) diffusion
      a. Intracellular diffusion of larger particles inhibited by cellular cytomatrix
   2. Protein-mediated diffusion
      a. Fatty acid binding protein (FABP)
      b. Phospholipid transfer proteins (phosphatidylcholine transfer protein, PC-TP)
         1) Role in biliary phospholipid selection/secretion
      c. Sterol carrier protein
   3. Cellular membranes
      a. Binding of hydrophobic compounds controls rate of transfer
      b. Vesicular transport along tubulovesicular pathway
         1) Mediated by microtubules and intracellular motor proteins
   4. Cytoplasmic flow (cytocirculation)

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