Introduction to the Liver

June 8, 2010
Outline

1. Introduction to liver anatomy and physiology (Maher)
2. Regenerative capacity of the liver (Willenbring)
3. Liver injury and repair, including fibrosis (Bissell)
4. Fatty liver in alcoholism and obesity (Maher)
General Features

- Largest *internal* organ in the body
- Approx. 4% of body weight
- Blood flow 1.5 L/min
- Principal functions:
  - uptake, metabolism and excretion of nutrients, endogenous wastes and xenobiotics
  - synthesis and secretion of plasma proteins, clotting factors
  - metabolic homeostasis (glucose, lipids)
  - assistance with digestion of fat (via bile)
Liver embryology

- Buds from ventral endoderm near heart and septum transversum
- Hepatoblasts visible E9.5
- Septum transversum mesenchyme contributes to vasculature
- Albumin expression detectable E8.5
Fetal liver is a hematopoietic organ

Hematopoiesis moves to bone marrow at approx. 7 mos. gestation
Vascular Anatomy

- Dual blood supply: 70% venous, 30% arterial
- Extensive sinusoidal network diverging from portal vein, converging in hepatic vein
- ”First pass” extraction of all materials entering the circulation from the GI tract
Sinusoidal Anatomy
Hepatocytes

- 70-80% of liver mass
- Unusual polarity (apical = canalicular)
- Basolateral membranes have microvilli
- Canaliculi empty into bile ductules → bile ducts
Sinusoidal endothelial cells

- Open fenestrations of approx. 100 nm diameter
- Arranged in groups called sieve plates
- “Incomplete” subendothelial membrane
- Anatomy facilitates access of plasma contents to hepatocyte microvilli
Kupffer cells

- Liver macrophages
- Arise from bone marrow or proliferate locally
- Reside in the sinusoidal lumen
- First line of defense against pathogens or endotoxin from GI tract
Hepatic stellate cells

- Subendothelial location
- Homologous to pericytes - perivascular myofibroblasts
- Normal liver: reservoir for vitamin A
- Diseased liver: produce collagen, ECM
Liver Function
Liver function: biotransformation

- Intermediate step between uptake and excretion
- Goal is to make organic compounds water-soluble

- **Enzyme families:**
  - Cytochromes P450 (CYPs)
  - Glucuronyltransferases
  - Sulfotransferases
  - Glutathione-S-transferases

- **Two “phases:”**
  - Phase I = CYPs (oxidation/reduction)
  - Phase II = conjugation
Multiple transporters for uptake/excretion
Biotransformation of an endogenous compound: bilirubin
Liver function: disposal of nitrogenous waste

- Amino acid catabolism yields ammonia (neurotoxin, suppressant)
- Liver converts ammonia to urea via carbamoyl phosphate synthase
- Ammonia escaping urea synthesis is converted to glutamine
Liver function: bile secretion & digestion of fat

- Liver produces bile acids from cholesterol
- Stored in gall bladder and released with meals
- Bile acids emulsify ingested lipids
- Supplemental to pancreatic lipase
Enterohepatic circulation

- 600 mL bile produced per day
- 500 mg bile acids produced per day (1/3 the pool size)
- Nearly all of bile acids absorbed by intestine
- Approx. 8 rounds recycling per day
Liver function: glucose and lipid metabolism

• **Glucose metabolism**
  – Fed state:
    • glycolysis, glycogen synthesis
  – Fasting state:
    • glycogenolysis, gluconeogenesis

• **Lipid metabolism**
  – Fatty acid synthesis
  – Triglyceride synthesis/secretion
  – Cholesterol and bile acid synthesis
Liver function: synthesis of serum proteins

- **Albumin and alpha-globulins**
  - Maintain oncotic pressure
  - Albumin binds/aids transport of organic molecules
  - 10 g albumin produced daily

- **Clotting factors**
  - Factor I (fibrinogen)
  - Factor II (prothrombin)
  - Factor V
  - Factor VI
  - Factor IX
  - Factor X
Oxygen gradient across the liver lobule
Lobular zonation of hepatic gene expression
Case study: acetaminophen

**Ethanol consumption**

Acetaminophen → Sulfation glucuronidation → P450 → NAPQI → Detoxification → Toxic → Protein

GSSG Prot−S−S → GSH Prot−SH → GSH → NAPQI → Detoxification → Toxic → Protein
Acetaminophen hepatotoxicity: liver failure

- Nausea, malaise
- Impaired blood coagulation
- Altered mental status
- Hypoglycemia
Acetaminophen hepatotoxicity: treatment

N-acetylcysteine