Canine and Feline Gastroenterology - Chapter 61

Key points:

- Hepatocytes produce procoagulant, anticoagulant and fibrinolytic proteins, and removes both normal and abnormal clotting factors from circulation
    - Therefore in any hepatic disease a wide variety of coagulation disorders are possible
    - Abnormalities are most commonly seen in chronic liver disease
- Bile provides
    - Source of bile acids for fat digestion and absorption
    - Excretory route for metabolites and toxins
    - Additional HCO3- for buffering H+ in duodenum

Table 61-1 Cells of the Liver and Their Functions

Cell Type	Other Names	Functions
Hepatocytes	Liver cells	Intermediary metabolism
Cholangiocytes	Biliary epithelial cells	Line the bile ducts, secretion
Kupffer cells	Browicz-Kupffer cells, stellate macrophages	Phagocytosis of pathogens and particles
Stellate cells	Ito cells, vitamin A–storing cells, lipocytes	Storage of vitamin A; production of myofibroblasts in injury
Natural killer (NK) cells	Pit cells, large granular lymphocytes, γδ T cells	Immune surveillance–infection, cancer
Vascular endothelial cells	Endothelial cells	Line blood vessels
Lymphatic endothelial cells	Endothelial cells	Line lymphatic vessels
Smooth muscle cells	Myocytes	Regulation of microcirculation
Portal tract fibroblast	Fibroblasts	Integrity of portal triads, supporting function
Stem cells	Progenitor cells, oval cells	Bi-potential progenitor cell for hepatocytes and biliary epithelial cells

Hepatocytes:

- 60-80% of cell mass
- Contribute to nutrient metabolism, coagulation factor synthesis, and immune surveillance
- Generate ‘primary bile’ and transport to canaliculi; secretion is poorly controlled, mostly occurs due to osmotic gradient
- Lifespan of 5-6 months
- Organised into plates separated by sinusoids with a fenestrated endothelial cell lining
    - Endothelial cells separated from hepatocytes by space of Disse which drains lymph

Cholangiocytes:

- 3-10% of liver cell mass
- Secrete water, bicarb and cations to modify the canalicular bile as it passes through the bile ducts; secretion is well regulated
- Antigen presenting cells

Kupffer Cells

- = stellate macrophages -> phagocytose pathogens and particulate matter
- 2-5% of cellular mass, located in sinusoids
- Express complement receptor immunoglobulins
- In disease states produce inflammatory mediators, activate toll-like receptors and TNF-a
- Also involved in metabolism of haemoglobin

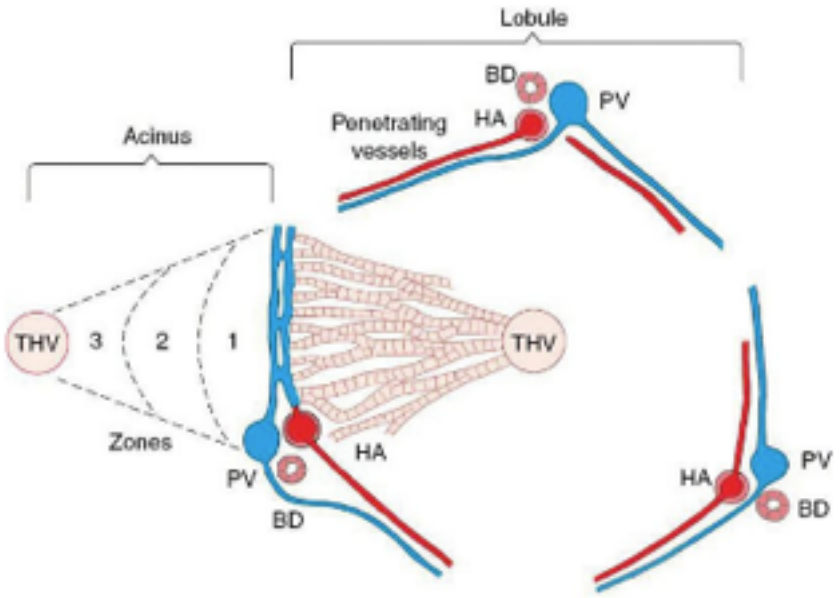

Figure 61-1 The anatomic unit of the liver is the hepatic lobule. The functional unit of the liver is the hepatic acinus. BD, bile duct; HA, hepatic artery; PV, portal vein; THV, terminal hepatic venule. (From Crawford JM: The gastrointestinal tract. In: Cotran RS, Kumar V, Robbins SL, editors: *Robbin's Pathologic Basis of Disease*, Philadelphia, 1994, Saunders.)

- Zone 1 received greatest oxygen supply but also highest concentrations of toxins from portal system

<u>Liver function</u>

Metabolism:

- *Carbohydrates*
  - early in fasting glucose is generated from glycogen in liver and under regulation of hepatic glycogen phosphorylase and phosphorylase kinase
  - After prolonged fasting glucose is generated from gluconeogenesis from substrates like amino-acids, lactate and glycerol
  - Both gluconeogenesis and glycogenolysis produce glucose-6-phosphate which needs to be dephosphorlated by glucose-6-phosphatase-alpha
    - there are altered quantities of this in glycogen storage diseases - fasting will result in severe hypoglycaemia due to lack of all endogenous glucose production

- *Proteins*
  - The liver deaminates amino acids converting them to carbohydrates and lipids
  - Also creates amino acids by maintain and transamination

- Synthesises many proteins including albumin, fibrinogen, many globulins, clotting factors, enzymes

- *Lipids*
  - Exogenous transport
    - For metabolism of dietary lipids (triglyceride, cholesterol, phospholipids and fat soluble vitamins
    - Hepatocytes endocytose chylomicrons in circulation
  - Endogenous transport
    - For metabolism of endogenously produced lipids
    - Liver produces triglycerides and cholesterol, and forms into very-low-density lipoprotein
    - VLDL are transported to capillary beds where triglycerides are hydrolysed
  - Reverse transport
    - Transport of cholesterol from the periphery in HDL
- *Nucleic acid synthesis*
- *Porphyrin excretion*
- *Metals*
  - Stores iron as ferritin
  - Incorporates copper into proteins
    - Cholestasis results in copper retention
- *Vitamins*
  - Bile absorbs fat soluble vitamins (ADEK); cannot be absorbed without normal bile secretion
  - Phosphorylation of water soluble vitamins occurs in the liver to produce important coenzymes
  - Liver stores vitamins
    - 95% of vitamin A is stored in liver (stellate cells and hepatocytes); 1-2year supply
    - Large amounts of all water soluble vitamins except vitamin C are stored

Bile Secretion

Provides:

- Source of bile acids for fat digestion and absorption
- Excretory route for metabolites and xenobiotics
- Additional HCO3- for buffering H+ in duodenum

- In the absence of neural/hormonal stimulation (eg. when fasting) the gallbladder is relaxed and the sphincter of Oddi is contracted so bile is stored
  - Whilst stored there is reabsorption of water and electrolytes so bile becomes more concentrated
- During feeding ACh stimulation and cholecystokinin activate gallbladder contraction and sphincter relaxation

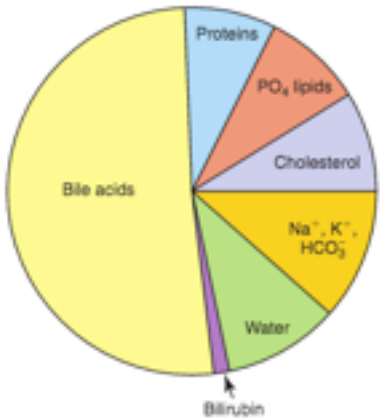

Figure 01-2 The chemical components of bile: bile acids, proteins, phospholipids, cholesterol, water, Na^+, K^+, HCO_3^-, and bilirubin.

- *Bile acids*
  - Sythnesized from cholesterol -> chenodeoxycholic acid and cholic acid
  - Become conjugated and dissociate to salts
  - When in intestinal lumen some of these become dehydroxylated by bacteria -> deoxycholic acid, lithocholic acid
  - Bile salts act as detergent to emulsify fat droplets, and assist absorption by forming micelles
  - Most secrete bile salts are absorbed in ileum and reenter portal flow

Coagulation Factors

- Liver produces procoagulant, anticoagulant and fibrinolytic proteins, and removes both normal and abnormal clotting factors from circulation
- Synthesises I, II, V, VII, ?VIII?, IX, X, XI and XII
- Activates vitamin K dependent factors and protein C
- Hepatic failure may result in a variety of factor deficiencies and may even result in DIC
- Coagulation abnormalities most commonly seen in dogs with chronic hepatitis/cirrhosis

Detoxification

- Cytochrome P450 catalyses the oxidation of a variety of chemicals - both foreign and endobioitc (steroids, vitamins, prostaglandins, fatty acids_
- Diet and ageing induce significant changes in expression of genes involved in production of P450 enzymes
- Occurs in 2 phases
    - 1 = *modification reactions*, drugs are hydrolysed or oxidised
    - 2. = *conjugation reactions*, usually (but not always) occurs after phase 1 reactions
- 75-80% of hepatic blood flow comes from GI tract/spleen via portal vein, bringing drugs, toxins, antigens, nutrients and bacteria
    - Some of the hepatic metabolism detoxifies these compounds, but other compounds will have their toxicity activated
- <u>Ammonia</u>
    - produced by amino acid metabolism
    - converted to urea via the urea cycle to help with excretion
    - In liver failure there is failure of this cycle, so build up of nitrogenous wastes -> hepatic encephalopathy
    - Colon is the most important source of ammonia; it is produced by bacteria then enters portal circulation
- <u>Endogenous hormones</u>
    - Also metabolised by the liver
    - Liver disease has ben reported to result in changes in concentration of free and total cortisol -> clinical and biochem characteristics of PDH including polyuria

Immune surveillance

- Liver must be able to tolerate the large number of antigens derived from the GI tract and to effectively eliminate pathologic microorganisms
- Hepatocytes do not directly interact with leukocytes
    - Sinusoidal endothelial cells and Kupffer cells interact with the leukocytes
    - endothelial cells are primarily responsible for clearance of antigens from the blood
    - These cells can act as antigen presenting cells for T cells

Regeneration

- Carried out by all mature liver cell types
- Two main steps in gene expression for regeneration
    - (1) Priming - transition from quiescent hepatocyte to the cell cycle; must be primed before they can respond to growth factors
        - TND, IL6, IL22 and ROS all very important

    - (2) Progression beyond G1 of cell cycle
        - Hepatocyte growth factor, transforming growth factor-alpha
        - Once cell cycle genes are expressed replication becomes autonomous, independent of growth factors
- Hepatocyte proliferation progresses from the periportal areas outwards, with those surrounding central being the last to undergo replication
- Biliary epithelial cell replication occurs after that of hepatocytes
- Liver function can be restored after loss of 65-70% of liver via hepatectomy, and takes place over 7-14days

QUESTIONS:

1. Describe the pathophysiologic basis of hepatic encephalopathy with particular regard to ammonium concentrations.

2. True or false: Natural killer cells contribute to immune surveillance in the liver by phagocytosis of pathogens and particulate matter.

ANSWERS:

1. Loss of functional liver mass -> inability to clear ammonia via urea cycle. Ammonia is produced primarily by GI flora, enters portal circulation -> increased release of glutamate -> neuronal excitation in brain

2. True or false: Natural killer cells contribute to immune surveillance in the liver by phagocytosis of pathogens and particulate matter.

FALSE. Kupffer cells phagocytose, NK induce apoptosis.