Veterinary Bioscience: Metabolism

WEEK 1 – THE LIVER IN HEALTH

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INTENDED LEARNING OUTCOMES

At the end of this lecture, you should be able to:

- understand the microstructure of the liver and relate this to its many functions
- describe the appearance and functions of hepatocytes and Kupffer cell
- define the different classifications of liver lobules based on structural or functional concepts
- list the major constituents of bile
- explain how bile pigments are formed and secreted
- describe the process by which bile is secreted
- explain the structure and function of the bile duct system and the gall bladder
- explain the enterohepatic circulation of biliary constituents.

KEYWORDS

liver, gall bladder, hepatocyte, Kupffer cell, hepatic lobule, portal lobule, liver acinus, gall bladder, bile, bile salts, bile pigments, bilirubin, enterohepatic circulation

LECTURE 2 – STRUCTURE AND FUNCTION OF THE LIVER

FUNCTIONS OF THE LIVER

- Synthesis - sugars, plasma proteins, clotting factors, lipids, urea, ketone bodies
- Secretion - bile salts, bile acids
- Excretion - bile pigments and cholesterol
- Storage - lipids, vitamins, glycogen, iron, copper
- Biotransformations - toxic substances, waste products, drugs, hormones
- Metabolism - lipids, proteins, carbohydrates
- Removal of bacteria and effete red blood cells

MICROSTRUCTURE OF THE LIVER

Capsule and stroma

The liver is entirely covered by a thin **connective tissue capsule**. It gives rise to an extensive framework to support the parenchyma of the liver, as well as the hepatic artery, the portal vein and the bile ducts.

Parenchyma

The hepatic cords are formed by **hepatocytes** (= liver cells). These are **polyhedral shaped** cells, with a centrally placed **spherical nucleus** with prominent nucleoli. Mitochondria and other organelles are abundant; the cytoplasm varies with the functional state of cell, e.g. foamy or vacuolated appearance due to presence of glycogen and lipid inclusions. These cells carry out most of the functions listed above.

Specialised blood capillaries - **sinusoids** extend between cords of liver cells. These are lined by endothelial cells and **Kupffer cells**. The latter are phagocytic cells (macrophages) that are extremely efficient at removing micro-particles and abnormal macromolecules and old red blood cells from the sinusoidal blood. This is one function that the hepatocytes are not able to do.

The liver is defined into 3 lobules based on structural or functional concepts:

Hepatic or classical lobule

- The basic **structural unit** of the liver. In cross-section, it is somewhat hexagonal in shape. The **central vein** (hepatic vein) is present in the centre of the lobule.
- The bile duct, hepatic artery and portal vein - known collectively as the **portal triad** - are at the periphery of the lobule in 3 to 4 of the 6 corners of the hexagon.
- Lymphatic vessels are also present in the portal triad area.
- **Hepatic cords** extend outwards in a radial pattern from the central vein.
    - These are formed by **hepatocytes** (= liver cells).
- Specialised blood capillaries - **sinusoids** extend between the liver cell cords. These are lined by endothelial cells and **Kupffer cells**. The latter are phagocytic cells that are extremely efficient at removing micro-particles and abnormal macromolecules from the sinusoidal blood.
- Sinusoidal blood flows in a centripetal direction - toward the central vein.

Portal lobule

- Defined as a **functional secretory unit** of the liver - the **drainage of bile**
- An important component of bile is bile salts - function to emulsify fats in the small intestine - resulting in micelle formation - to facilitate lipid absorption and activate intestinal lipases
- The portal lobule is triangular in shape – it is **formed by parts of 3 adjacent classical lobules** adjoining a portal canal with the bile duct as its central axis.
- Its boundary is defined by drawing lines between the central veins of 3 adjacent classical lobules.

Liver acinus

- Defined as a **functional unit** of the liver - the **supply of blood** to liver tissue
- Is diamond-shaped, **formed by the contiguous parts of 2 adjacent classical lobules**
- The boundary is defined by drawing lines between 2 adjacent central veins, via their common portal triads.

STRUCTURE AND FUNCTION OF THE BILE DUCTS AND GALL BLADDER

Bile Duct System (biliary system = liver + gall bladder)

Between the hepatocytes are very fine channels - **bile canaliculi**. Bile flows in a centrifugal direction - toward the portal triads. These open into larger ductules that, by successive unions within the connective tissue between the lobules, ultimately form **a few large hepatic ducts**. Before or shortly after leaving the liver at the porta these combine in a single trunk - **the common hepatic duct**.

A tortuous side branch - the **cystic duct** - arises from the common trunk and leads to the pear-shaped gall bladder. The part of the **common trunk** that is **distal to the origin of the cystic duct is** known as **the bile duct or common bile duct**. It eventually runs to the duodenum, entering the dorsal or mesenteric border on the **major duodenal papilla**.

Gall bladder

This **pear-shaped** organ may be regarded as a **diverticulum of the bile duct, enlarged to form a reservoir** for the storage of bile, with its neck continued by the cystic duct. It stores bile during periods of digestive rest. The opening of the bile duct into the duodenum is guarded by the **Sphincter of Oddi**, closed except during meals.

Histologically, the mucosal wall of the gall bladder is lined by simple columnar epithelium, and mucosal crypts (small epithelial diverticulae) are evident. Below the mucosa is a loose connective tissue lamina propria / submucosa, then scant, thin bundles of muscularis externa and a serosal covering.

The bile produced in liver is **stored and concentrated** in the gall bladder (active transport of salts through mucosa followed osmotically by water).

Emptying of the gall bladder occurs in response to food in the duodenum. This causes rhythmic contraction of walls of gall bladder and simultaneous relaxation of the Sphincter of Oddi; peristalsis in the duodenum aids sphincter relaxation.

Mediators of gall bladder emptying:

- **cholecystokinin** (released in response to fat in duodenum) causes contraction of gall bladder and relaxation of sphincter.
- The muscle in the gall bladder wall and duct, including the sphincter at the entrance to the duodenum is supplied by parasympathetic nerves. **Vagal stimulation** is therefore also a stimulus to gall bladder emptying (although weaker than that caused by cholecystokinin).

NB: Horse, rat, elephant, some deer lack a gall bladder. In these species without a gall bladder, they are able to upregulate production of bile in response to demand.

Bile consists of:

- An aqueous alkaline fluid (similar to pancreatic $NaHCO_3$ secretion) = added by **duct cells**
- Plus organic constituents = from **hepatocyte** activity:
    - bile salts
    - cholesterol
    - lecithin
    - bilirubin

Bile primarily functions in the **absorption and digestion of fat**. Bile salts are derivatives of cholesterol, and are synthesized by hepatocytes from cholesterol and then conjugated with one or other of two amino acids, taurine and glycine. This conjugation step makes molecule highly polar - the steroid backbone is lipophilic, and favours interaction with other lipophilic molecules; while the amino acid conjugate is hydrophilic and favours interaction with water.

Conjugated bile salts are thus able to function as **detergents**, and serve to keep fats in solution in an aqueous environment. Fats are then accessible to lipase (see earlier Digestive System lectures).

Bile salts secreted by hepatocytes come from **two sources:** newly formed bile salts synthesized in hepatocytes from cholesterol, and also bile salts that come to the liver in the portal vein, following their reabsorption in the ileum.

Cholesterol

Considerable amounts of cholesterol in bile. Bile salts keep cholesterol in solution, thus allowing cholesterol to be excreted in bile in much higher concentrations than would otherwise be possible.

Bile pigments

Formed mainly from the breakdown of the haem portion of haemoglobin. Effete red blood cells are engulfed and broken down by macrophages of the reticuloendothelial system (in tissues such as the spleen and liver), and the haem moiety is converted to biliverdin and then bilirubin. Bilirubin, bound to albumin in the plasma, is taken up by a specific carrier mechanism into hepatocytes, conjugated with glucuronic acid, then transported into the bile by a specific carrier mechanism. Bilirubin is yellow and contributes to the colour of bile. If circulating bilirubin levels exceed 0.3-0.5 mmol/L, connective tissue becomes stained (**jaundice**)**.**

Enterohepatic circulation

98% of secreted bile salts are reabsorbed. The small loss of bile salts into the colon may help in colonic water absorption, by interacting with lipids in the apical cell membrane of colonic absorptive cells. Bilirubin is converted by bacteria, to urobilinogen (water soluble, reabsorbed and excreted in urine). Also stercobilinogen - stercobilin excreted in faeces.

Other compounds, e.g. vitamins, drugs etc., also secreted in bile and absorbed and returned via portal circulation to liver.

FURTHER READING

Banks, *Applied Veterinary Histology,* 2nd ed. (1986)

Cunningham and Klein, *Textbook of Veterinary Physiology* (2006)

Dellmann and Eurell, *Textbook of Veterinary Histology,* 5th ed. (1998)

Guyton A.C., *Textbook of Medical Physiology,* 8th ed. (1991)

Rhoades and Pflanzer, *Human Physiology,* 3rd ed. (1998)

Sherwood, L., *Human Physiology from Cells to Systems,* 3rd ed. (1997)