Update in
Anaesthesia

Liver Physiology

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Summary

The liver has a unique anatomical structure essential to its diverse functions. This article gives an overview of the role of the liver in body metabolism, as well as its relevance to anaesthesia and critical care. Bilirubin metabolism and the causes of jaundice are described.

ANATOMY

The liver weighs 1.5 to 2kg and is divided into right and left lobes, the right lobe being larger than the left. The functional unit of the liver is known as a 'hepatic lobule'. These are roughly hexagonal in cross section and contain a central vein from which cords of hepatocytes radiate outwards (Figure 1). In between the lobules lies the portal triad consisting of hepatic artery, portal vein and bile duct. Radial spaces between the hepatocytes are called sinusoids and carry mixed hepatic arterial and portal venous blood towards centre of the lobule where it drains into the central vein. Central veins join to form the hepatic vein that drains into the inferior vena cava.

Hepatocytes are highly active metabolically and the walls of the sinusoids are also lined by macrophages, known as Kupffer cells, that are an active part of the reticuloendothelial system.

Blood Supply

The liver receives about 1.5l.min^{-1} blood supply (about 25% of the total resting cardiac output) and is responsible for over 20% of the body's resting oxygen consumption. It has a dual vascular supply from the portal vein and the hepatic artery. The hepatic artery is a high pressure and high resistance system which deliver 30% of total hepatic blood flow directly from the aorta and contributes to about 50% of total hepatic oxygen supply. The portal vein is a valveless system, bringing deoxygenated blood from the large and small intestines, spleen, stomach, pancreas and gall-bladder. It contributes to 70% of total liver blood flow and 50-60% of total oxygen supply, containing blood with a saturation of about 85%.

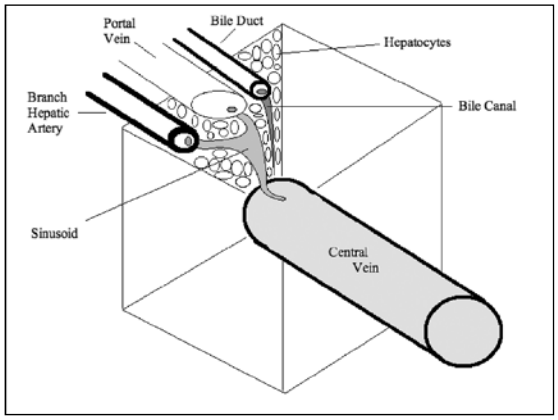

Figure 1. *The hexagonal hepatic lobule showing the portal triad of hepatic artery, portal vein and bile duct at the periphery of the lobule and central vein in the centre of the lobule*

FUNCTIONS OF THE LIVER

The functions of liver may be summarised as:

1. Metabolism of carbohydrates, proteins and fat,
2. Detoxification of drugs and toxins,
3. Storage of glycogen, vitamins (e.g. A,D,E,C), iron and copper,
4. Reservoir of blood,
5. Filtration of bacteria, degradation of endotoxins and lactate metabolism,
6. Excretion of bile and urea,
7. Immunological functions with synthesis of immunoglobulins and phagocytic action by Kupffer cells ,
8. Haemopoeisis in the foetus.

Protein metabolism

The liver has a central role in both protein metabolism and anabolism. It removes amino acids from blood for gluco-neogenesis and protein synthesis. It also releases amino acids into the blood for utilisation by peripheral tissues and plays a major role in breakdown of amino acids, removing nitrogen in the form of urea.

The liver synthesizes many important proteins such as albumin, which is responsible for maintaining colloidal osmotic pressure, globulins such as the lipoproteins and glycoproteins with transport functions. Examples of the latter are ferritin, ceruloplasmin, α_1 antitrypsin, α_2 macroglobulin, complement factors and haptoglobins, which bind and conserve free haemoglobin. It also synthesizes antithrombin-3, α acid glycoprotein and C-reactive protein, which are acute phase proteins, produced under conditions of physiological stress.

Synthesis of almost all clotting factors occurs in the

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liver. Coagulopathies can occur with either failure of hepatic synthesis or failure of bile excretion, leading to a reduction in absorption of vitamin K. Vitamin K is required for the synthesis of factors II (prothrombin), VII, IX and X.

The liver also synthesizes acute phase proteins in response to numerous stimuli.

Protein catabolism

Amino acids degradation is by transamination, deamination and decarboxylation. The products are acetylcoenzyme A, which enters the citric acid cycle. The nitrogenous end-product of amino acid degradation is ammonia. Ammonia is a toxic end product and is eliminated from the body as urea.

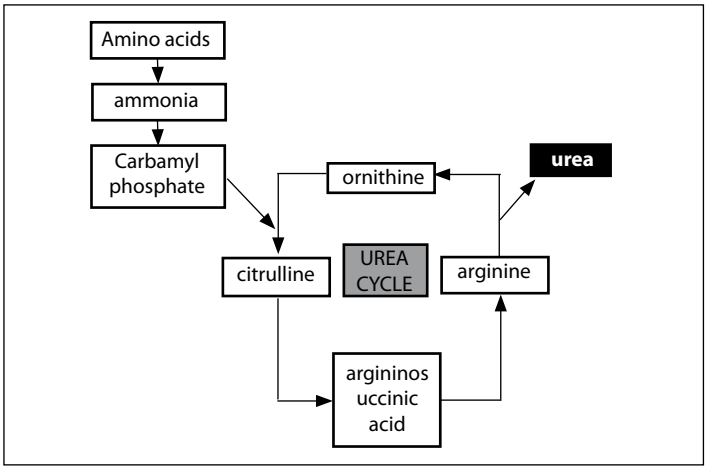

Figure 2. *The urea cycle*

Urea is synthesized from ammonia by the ornithine cycle, an energy-dependent process (Figure 2). Creatinine is also synthesized in the liver from methionine, glycine and arginine. Phospho-creatine formed in the muscle is a back-up energy store for ATP production. Creatinine is formed from phospho-creatine and is excreted in urine.

Carbohydrate metabolism

The liver maintains glucose homeostasis during fasting by gluconeogenesis and formation of ketone bodies. It is also a major site for glycogen storage, glycogenolysis and gluconeogenesis when glycogen stores are depleted.

Lipid metabolism

Fatty acids and lipoproteins are synthesised and the liver is the major site for endogenous cholesterol and prostaglandin production.

Bilirubin metabolism

Haemoglobin is broken down into haem and globin. The globin

Box 1. *Detoxification of steroid hormones and drug metabolism*

Phase	Reaction
Phase 1	oxidation, reduction, hydrolysis, hydration, dealkylation
Phase 2	glucuronidation, sulphation, acetylation, glutathione conjugation

Formation of Bile: Formation of bile and bile salts by enterohepatic circulation

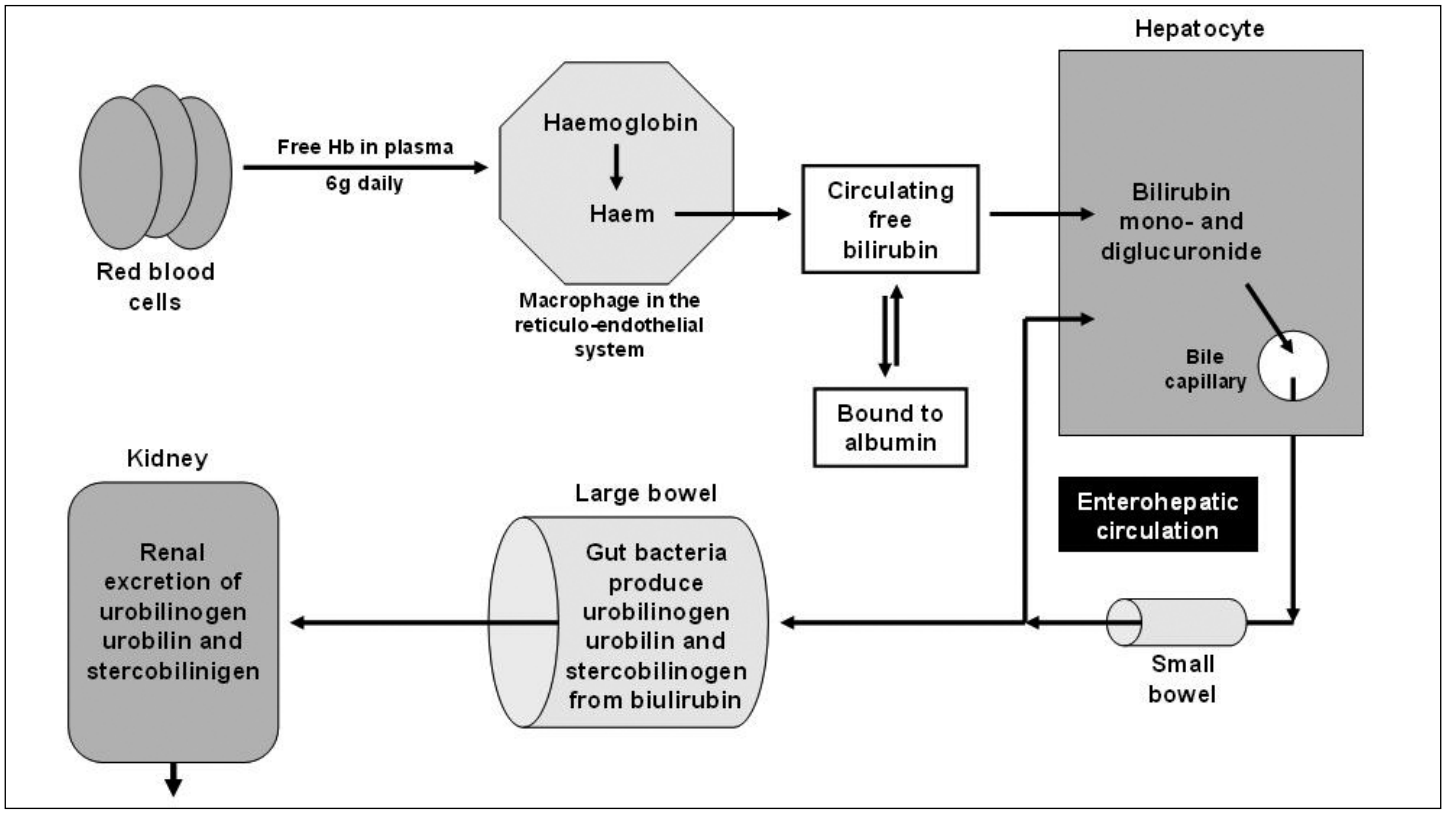

Figure 3. *Bilirubin metabolism*

Table 2. *Liver function tests*

Test	Relevance	
Serum bilirubin	A raised bilirubin is seen clinically as jaundice. Jaundice can be pre-hepatic, hepatocellular and obstructive:	
	Type of jaundice	**Bilirubin elevated**
	Pre-hepatic	Unconjugated
	Hepatocellular	Unconjugated or mixed
	Obstructive	Conjugated
Serum proteins	Impaired synthesis of proteins leading to hypo-proteinaemia and hypo-albuminaemia	
Clotting factors	Impaired synthesis leading to raised prothrombin time and INR	
Alanine transaminase (ALT) and Aspartate transaminase (AST)	Enzymes released into the circulation by damaged hepatocytes	
Alkaline Phosphatase (ALP)	Enzyme localized near bile cannaliculi and is raised in biliary obstruction	
Other tests	Haemoglobin levels, blood film for evidence of haemolysis, plasma urea and creatinine	

part goes into the common amino acid pool. The tetrapyrole ring of haem opens up to release iron and is converted to biliverdin. Biliverdin is then converted to bilirubin by biliverdin reductase enzyme. This bilirubin remains attached to albumin in the blood as unconjugated or free bilirubin. This then undergoes glucuronidation in the liver to form conjugated bilirubin, which can be excreted in bile. A proportion of the conjugated bilirubin is reabsorbed into the circulation and is excreted by the kidneys as urobilinogen, and some is excreted via the gut as stercobilin and stercobilinogen.

Bile production

The liver produces about one litre of bile per day which passes into the gall bladder and gets concentrated to one fifth of its original volume. Bile consists of electrolytes, proteins, bilirubin, bile salts and lipids. Bile acids are produced in the liver from cholesterol. They are acted upon by bacteria in the gut to form secondary bile acids which are then conjugated to form bile salts. Bile salts are important for emulsification of fat and absorption of the fat soluble vitamins A, D, E and K.

EFFECTS OF ANAESTHESIA ON LIVER FUNCTION

Inhalational anaesthetics affect carbohydrate metabolism in several ways. Ether, unlike the newer agents, enhances the breakdown of glycogen in the liver. Halothane has been shown experimentally, to decrease the rate of glycogenesis, inhibit insulin release and inhibit the effect of insulin on the tissues. The catacholamine mediated stress response to surgery and trauma also increases glycogenolysis, so the overall effect of both surgery and inhalational anaesthesia is to elevate blood glucose. Protein synthesis is reduced by halothane but this is of questionable clinical significance.

Halothane and ether both inhibit the cytochrome p450 enzyme system, slowing the oxidative metabolism of drugs; gluconuride conjugations are not affected. As a result many drugs have a prolonged half-life in the presence of halothane – examples are fentanyl, ketamine, lignocaine, pancuronium and propranolol.

Hepatic blood flow is decreased by halothane in parallel with an overall decrease in cardiac output. Intermittent positive pressure ventilation and decreased $PaCO_2$ potentiate this effect whilst hypoventilation and increased $PaCO_2$ results in an increase in hepatic blood flow. These effects are unlikely in isolation to lead to liver hypoxia or damage.

Isoflurane, sevoflurane and desflurane are metabolised by the cytochrome P450 enzyme system and have no deleterious effects on the liver or its metabolism.

Table 3. *Metabolism of volatile agents*

Drug	Liver metabolism (%)
Halothane	25
Isoflurane	0.2
Sevoflurane	3
Desflurane	0.02

Opioids such as morphine, pethidine and fentanyl are known to cause spasm of the Sphincter of Oddi and increase biliary pressure, the effect lasting about two hours in the case of morphine. This should not however preclude their use to provide adequate analgesia in biliary surgery.

Halothane induced hepatic injury

It has been reported that between 1 in 7000 and 1 in 30,000 patients anaesthesised using halothane developed jaundice from severe hepatic damage, after a second halothane anaesthetic. The cause is thought to be multifactorial.

The risk of liver injury due to volatile anaesthetic agents appears to be related to their degree of metabolism with formation of toxic metabolites and an immunological reaction. Coexisting factors, such as reduced hepatic blood flow due to prolonged hypotension and hypoxia, are also partly responsible.