Liver Physiology

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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%.

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. Haemopoiesis 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, α₁ antitrypsin, α₂macroglobulin, complement factors and haptoglobins, which bind and conserve free haemoglobin. It also synthesizes antithrombin-3, α₁ 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
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.

![Urea cycle diagram](image)

**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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Reaction</th>
</tr>
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<tbody>
<tr>
<td>Phase 1</td>
<td>oxidation, reduction, hydrolysis, hydration, dealkylation</td>
</tr>
<tr>
<td>Phase 2</td>
<td>glucuronidation, sulphation, acetylation, glutathione conjugation</td>
</tr>
</tbody>
</table>

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

![Bilirubin metabolism diagram](image)

**Figure 3. Bilirubin metabolism**
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 glycojenolysis, 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; glucuronide 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 PaCO₂ potentiate this effect whilst hypoventilation and increased PaCO₂ 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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Liver metabolism (%)</th>
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</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>25</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>0.2</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>3</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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 anaesthetised 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.