Liver

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Functions of the liver

- The liver has essential synthetic and excretory functions and can be thought of as a large ‘metabolic factory’.
- It also detoxifies and, like the kidneys, excretes the end products of metabolism. The main blood supply to the liver is via the portal vein.

General metabolic functions

- When the glucose concentration is high in the portal vein, it is converted to glycogen and the carbon skeletons of fatty acids, which are transported to adipose tissue as very low-density lipoprotein (VLDL).
- During fasting, the systemic plasma glucose concentration is maintained by the breakdown of glycogen (glycogenolysis) or by the synthesis of glucose from substrates such as glycerol, lactate and amino acids (gluconeogenesis).
- Fatty acids reaching the liver from fat stores may be metabolized in the tricarboxylic acid cycle, converted to ketones or incorporated into triglycerides .

Synthetic functions

- Hepatocytes synthesize:
- * plasma proteins, excluding immunoglobulins and complement,
- * most coagulation factors, including fibrinogen and factors II (prothrombin), V, VII, IX, X, XI, XII and XIII - of these, prothrombin (II) and factors VII, IX and X cannot be synthesized without vitamin K,
- * primary bile acids,
- *the lipoproteins, such as VLDL and high-density lipoprotein (HDL) .

- The liver has a very large functional reserve. Deficiencies in synthetic function can be detected only if liver disease is extensive. Before a fall in plasma albumin concentration is attributed to advanced liver disease, extrahepatic causes must be excluded, such as the loss of protein through the kidney, gut or skin, or across capillary membranes into the interstitial space, as in even mild inflammation or infection .
- Prothrombin levels, assessed by measuring the prothrombin time, may be reduced because of impaired hepatic synthesis, whether due to failure to absorb vitamin K or to hepatocellular damage.
- If hepatocellular function is adequate, parenteral administration of vitamin K may reverse the abnormality.

Excretion and detoxification

- The excretion of bilirubin is considered in more detail below. Other substances that are inactivated and excreted by the liver include the following:
- *Cholesterol - excreted in the bile either unchanged or after conversion to bile acids.
- *Amino acids - which are deaminated in the liver. Amino groups, and the ammonia produced by intestinal bacterial action and absorbed into the portal vein, are converted to urea.
- * Steroid hormones - which are metabolized and inactivated by conjugation with glucuronate and sulphate and excreted in the urine in these water- soluble forms.
- *Many drugs - which are metabolized and inactivated by enzymes of the endoplasmic reticulum system; some are excreted in the bile.
- *Toxins the reticuloendothelial Kupffer cells in the hepatic sinusoids are well placed to extract toxic substances that have been absorbed from the gastrointestinal tract.

- Efficient excretion of the end products of metabolism and of bilirubin depends on:
- *normally functioning liver cells,
- *normal blood flow through the liver,
- *patent biliary ducts.
- **Formation and excretion of bilirubin** .
- At the end of their lifespan, red blood cells are broken down by the reticuloendothelial system, mainly in the spleen.
- The released haemoglobin is split into globin, which enters the general protein pool, and haem, which is converted to bilirubin after the removal of iron, which is reused About 80 per cent of bilirubin is derived from haem within the reticuloendothelial system. Other sources include the breakdown of immature red cells in the bone marrow and of compounds chemically related to haemoglobin, such as myoglobin and the cytochromes.

- Less than 300 umol of bilirubin is produced daily from the breakdown of erythrocytes, while the normal liver is able to conjugate up to about 1 mmol/day, and therefore hyperbilirubinaemia is an insensitive index of parenchymal hepatic disease.
- Bilirubin is normally transported to the liver bound to albumin. In this form it is called unconjugated bilirubin, which is lipid soluble and therefore, if not protein bound, can cross cell membranes, including those forming the blood-brain barrier. In this form it is potentially toxic; however, at physiological concentrations it is all protein bound.

Bilirubin metabolism and jaundice

- Jaundice usually becomes clinically apparent when the plasma bilirubin concentration reaches about 50 umol/L (hyperbilirubinaemia), about twice the upper reference limit.
- It occurs when bilirubin production exceeds the hepatic capacity to excrete it. This may be because:
- * An increased rate of bilirubin production exceeds normal excretory capacity of the liver (prehepatic jaundice).
- *The normal load of bilirubin cannot be conjugated and/or excreted by damaged liver cells (hepatic jaundice).
- * The biliary flow is obstructed, so that conjugated bilirubin cannot be excreted into the intestine and is regurgitated into the systemic circulation (post¬hepatic jaundice).

Retention of bilirubin in plasma: jaundice

- Unconjugated hyperbilirubinemia occurs if there is:
- * a marked increase in the bilirubin load as a result of haemolysis, or of the breakdown of large amounts of blood after haemorrhage into the gastrointestinal tract or, for example, under the skin due to extensive bruising; in cases of haemolysis, plasma bilirubin rarely exceeds 75 umol/L,
- * impaired binding of bilirubin to ligandin or impaired conjugation with glucuronate in the liver.
- In some pathological conditions, plasma unconjugated bilirubin levels may increase so much that they exceed the protein-binding capacity. The lipid-soluble, unbound bilirubin damages brain cells (kernicterus).

- This is most likely to occur in newborn, particularly premature, infants in whom the hepatic conjugating mechanisms are immature. In addition, the proportion of unbound, unconjugated bilirubin, and therefore the risk of cerebral damage, increases if:
- * plasma albumin concentration is low,
- *unconjugated bilirubin is displaced from binding sites, for example by high levels of free fatty acids or drugs such as salicylates or sulphonamides.
- Unconjugated bilirubin is normally all protein bound and is not water soluble and therefore cannot be excreted in the urine.

- Patients with unconjugated hyperbilirubinaemia do not have bilirubinuria (‘acholuric jaundice’) such as Gilbert’s syndrome.
- Conjugated bilirubinaemia is one of the earliest signs of impaired hepatic excretion. In most cases of jaundice in adults, both conjugated and unconjugated fractions of bilirubin are increased in plasma but conjugated bilirubin predominates.
- Conjugated bilirubin is water soluble and is less strongly protein bound than the unconjugated form, and therefore can be excreted in the urine. Bilirubinuria is always pathological. Dark urine may be an early sign of some forms of hepatobiliary disease.
- Conjugated bilirubin enters the gut lumen in bile; it is broken down by bacteria in the distal ileum and the colon into a group of products known as sterco bilinogen (fecal urobilinogen). Some is absorbed into the portal circulation, most of which is re-excreted in bile (enterohepatic circulation). A small amount enters the systemic circulation and is excreted in the urine as urobilinogen, which can be oxidized to a coloured pigment, urobilin.

Urobilinogen

- Urobilinogen, unlike bilirubin, is often detectable in the urine of normal people by testing with commercial strip tests, particularly if the urine, and therefore the ubilinogen, is concentrated. Urinary urobilinogen concentration is increased in the following situations.
- * When haemolysis is very severe: large amounts of bilirubin enter the intestinal lumen and are converted to stercobilinogen. An increased amount of urobilinogen is formed and absorbed. If the hepatic capacity to re-secrete it is exceeded, it is passed in the urine.
- *When liver damage impairs re-excretion of normal amounts of urobilinogen into the bile. The colourless, unabsorbed stercobilinogen is oxidized to stercobilin, a pigment that contributes to the brown colour of faeces. Pale stools may, therefore, suggest biliary obstruction associated with an absence of urinary urobilinogen.

Diseases of the liver

- **Cholestasis**
- Cholestasis may be either:
- * intrahepatic, in which bile secretion from the hepatocytes into the canaliculi is impaired, due to:
- - viral hepatitis,
- - drugs such as chlorpromazine or toxins such as alcohol,
- - inflammation of the biliary tract (cholangitis),
- - autoimmune disease (primary biliary cirrhosis),
- - cystic fibrosis,
- * extrahepatic, due to obstruction to the flow of bile through the biliary tract by:
- - biliary stones,
- - inflammation of the biliary tract,
- - pressure on the tract from outside by malignant tissue, usually of the head of the pancreas,
- - biliary atresia (rare).

It is essential to distinguish between intrahepatic and extrahepatic causes of cholestasis, as surgery may be indicated
for the latter but is usually contraindicated for intrahepatic lesions. The biochemical findings may be similar:
* Bilirubin concentrations in plasma may be normal if only part of the biliary system is
involved by intrahepatic lesions such as cholangitis, early primary biliary cirrhosis or
primary or secondary tumours. The unaffected areas can secrete bilirubin.
* Alkaline phosphatase activity is a sensitive test for cholestasis. Increased synthesis of ALP in the affected ducts increases the activity of this enzyme in plasma. If this is the only abnormal finding, it must be shown to be of hepatic origin before it is assumed to indicate liver disease.

- Patients with prolonged and more widespread cholestasis may present with severe jaundice and pruritus due to the deposition of retained bile salts in the skin; the plasma bilirubin concentration may be more than 800 umol/L.
- More rarely, there is bleeding due to malabsorption of vitamin K, with consequent prothrombin deficiency. Cholesterol retention may cause hypercholesterolaemia. Dark urine and pale stools suggest biliary retention of conjugated bilirubin.
- The jaundice caused by extrahepatic obstruction due to malignant tissue is typically painless and progressive, but there may be a history of vague persistent back pain and weight loss. By contrast, intraluminal obstruction by a gallstone may cause severe pain, which, like the jaundice, is often intermittent.
- Gallstones may not always cause such symptoms.
- If a large stone lodges in the lower end of the common bile duct, the picture may be indistinguishable from that of malignant obstruction. Although most of the findings are directly attributable to cholestasis, biliary back pressure may damage hepatocytes, and plasma aminotransferase activities may increase.