

CHRONIC LIVER DISEASES

DERANGEMENTS OF HEPATIC METABOLISM

The liver plays a central role in the maintenance of metabolic homeostasis. It is therefore not surprising that the development of clinically important liver disease is accompanied by diverse clinical manifestations of disordered metabolism. The liver has considerable reserve capacity, so minimal or even moderate cell injury may not be reflected by measurable changes in its metabolic function. However, some functions of the liver are more sensitive than others (and a variety of defects can be seen, depending on the nature and the extent of the initial insult).

The biochemical functions in which the liver plays a major role include:

- Intermediate metabolism of carbohydrates.
- Regulation of fatty acid, triglyceride, and cholesterol metabolism.
- Amino acid and ammonia metabolism.
- Synthesis and degradation of proteins and glycoproteins.
- Metabolism and degradation of drugs and hormones.
- Metabolism of porphyrins, bilirubin.

Metabolic derangement is most evident in the patient with advanced liver disease, and the manifestations are similar regardless of the initial etiologic insult. Since the many functions of the liver may be affected to varying degrees in individual patients, no single test effectively measures the overall state of liver function.

CARBOHYDRATE METABOLISM.

The liver functions to maintain normal levels of blood sugar by a combination of glycogenesis, glycogenolysis, gluconeogenesis, glycolysis. These pathways are regulated by a number of hormones including insulin, glucagon, growth hormone and catecholamines. The exquisite sensitivity of the hepatocytes to insulin is responsible for the blood sugar buffering effect of the liver after oral carbohydrate load. In the fasting state the liver contributes to glucose homeostasis by glycogenolysis and gluconeogenesis in response to hypoinsulinemia and hyperglucagonemia. Maintenance of the normal blood glucose levels through gluconeogenesis is ultimately related to catabolism of muscle protein, which provides the necessary amino acid precursors, especially alanine. In a complementary fashion in the postprandial state the liver directs branched chain amino acids to peripheral tissues, where they are incorporated into for example muscle protein, or used as an energy source.

Abnormalities of glucose homeostasis are common in cirrhosis. Most frequently hyperglycemia and glucose intolerance are observed. Glucose intolerance is associated with normal or increased level of plasma insulin (except in patients with hemochromatosis), suggesting that insulin resistance rather than insulin deficiency may be responsible. Patients with cirrhosis may also have elevated serum lactate levels.

Hypoglycemia, although more common in acute fulminant hepatitis, may also be seen in patient with end stage liver cirrhosis. Normally, glycogen in the liver accounts for 5 to 7 % of the tissue weight. Because the capacity of the liver to store glycogen is limited (approximately 70 g) and glucose consumption continues in the absence of oral glucose uptake, hepatic glycogen stores are depleted after 1 day of fasting. Hypoglycemia in end-stage cirrhosis may be due to decreased hepatic glycogen stores, diminished glucagon responsiveness, or decreased capacity to synthesize glycogen due to extensive parenchymal destruction.

LIPID METABOLISM. FATTY ACIDS AND TRIGLYCERIDES

Under normal conditions most of the fatty acids taken up by the liver and esterified to triglyceride are derived from the diet. Fatty acids (especially saturated ones) are synthesized from acetyl-CoA in the liver. The fatty acids will then be converted to triglyceride, esterified with cholesterol, incorporated into phospholipids. Most of the triglyceride is produced for export, but in order to be secreted it must be converted to lipoproteins by combining with specific apolipoprotein moieties. This emphasizes the importance of protein synthesis for the secretion of triglycerides from the liver. With the exception of cholestatic disease, clinically significant alterations in lipoprotein and cholesterol metabolism are usually not found in patients with chronic liver disease.

Fatty liver: An increased influx of fatty acids mobilized from adipose tissue due to drugs (e.g. corticosteroids) or secondary to diabetic conditions may lead to a fatty liver. Similarly, increased level of fatty acids in the liver either from enhanced fatty acid synthesis or from decreased oxidation may lead to increased TGC formation.

Increased formation of TGC may also be attributed to elevated concentration of corticosteroids. Since release of TGC involves the formation of VLDL, lipid accumulation may occur because of decreased apoprotein synthesis. This appears to be the case in protein-calorie malnutrition and due to toxins such as carbon tetrachloride, phosphorus, as well as following excessive doses of antibiotics like tetracycline that can inhibit protein synthesis. Finally, alcohol is perhaps the most common agent leading to a fatty liver.

LIPID METABOLISM. CHOLESTEROL

Primarily the liver carries out cholesterol and bile acid synthesis. Cholesterol exists either free or in the form of cholesterol esters. Since there is an exchange of free cholesterol between tissues, changes in plasma cholesterol may reflect changes in total body cholesterol. Severe liver injury often leads to a decrease in total serum cholesterol levels. This may be due to decreased synthesis of cholesterol and cholesterol esters, decreased apoprotein synthesis, or both. In cholestasis either intra- or extrahepatic, total serum cholesterol increases strikingly. Disorders of cholestasis are associated with marked abnormalities of cholesterol metabolism. In biliary cirrhosis there are pronounced elevations in serum free cholesterol and LDL, conversely serum HDL is reduced. The increase of serum free cholesterol and the concomitant decrease in serum esterified cholesterol may relate to decreased hepatic production of LCAT.

AMINO ACID AND AMMONIA METABOLISM

The liver is the major site of amino acid conversion. Amino acids utilized for hepatic protein synthesis are derived from dietary protein, metabolic turnover of endogenous protein (primarily from muscle) and direct synthesis in the liver. Most of the amino acids entering the liver via the portal vein are catabolized to urea. (Except branched chain amino acids). A lesser amount is released into the general circulation as free amino acids. In addition, amino acids are utilized for synthesis of liver intracellular proteins, plasma proteins, and special compounds, such as glutathione, glutamine, taurine, and creatine. Disruption of normal amino acid metabolism may be reflected in altered plasma amino acid concentrations. In general, levels of aromatic amino acids, normally metabolized by the liver are elevated, while those of BCAAs, largely utilized by the skeletal muscle, tend to be normal.

Hepatic catabolism of amino acids involves two major reactions: transamination and oxidative deamination. Transamination is catalyzed by aminotransferases. These enzymes are found with very high activity in the liver, but are also present in other tissues. Glutamate-oxaloacetate

transaminase has been studied most extensively, and increased levels are found in the serum secondary to various types of liver injury. Deamination, which releases the aminogroup of the aminoacids in the form of free ammonia, is catalysed mainly by the following enzymes: glutamate dehydrogenase, glycine-cleavage system, serine-dehydratase and the enzymes of the purine nucleotide cycle. With severe liver damage amino acid utilization is impaired, free amino acids in the bloodstream increase, and an "overflow" type of aminoaciduria may occur.

Urea cycle is intimately related to the metabolic pathways outlined above. The final step of that cycle, the formation of urea by arginase, is irreversible. In advanced liver disease urea synthesis is often depressed, leading to accumulation of NH_3 , usually with a significant reduction of blood urea nitrogen (BUN), an ominous sign of liver failure. This finding may be obscured by superimposed renal impairment, which often develops with severe hepatic failure. The kidney mostly excretes urea, but approximately 25 % is diffused into the intestine where it is converted to NH_3 by bacterial urease. The intestinal production of NH_3 also occurs from bacterial deamination of unabsorbed amino acids and of protein derived from the diet, exfoliated cells, or blood in the gastrointestinal tract.

Gut NH_3 is absorbed and transported to the liver via the portal vein where it is again converted to urea. The kidney also produces varying amounts of ammonia, largely by deamination of glutamine.

The following estimates for the contribution of the various sources of ammonia to urea synthesis in the liver have been made:

- portal vein ammonia, 33%,
- portal vein glutamine (amide), 6-13%,
- mitochondrial glutamate via glutamate dehydrogenase (glutamate derived from, e.g. alanine, glutamine, proline, histidine), 20%
- Other sources, including hepatic artery ammonia and glutamine and many enzymes in liver capable of generating ammonia directly (e.g., from asparagine, aspartate, threonine, glycine, serine) 33-40%

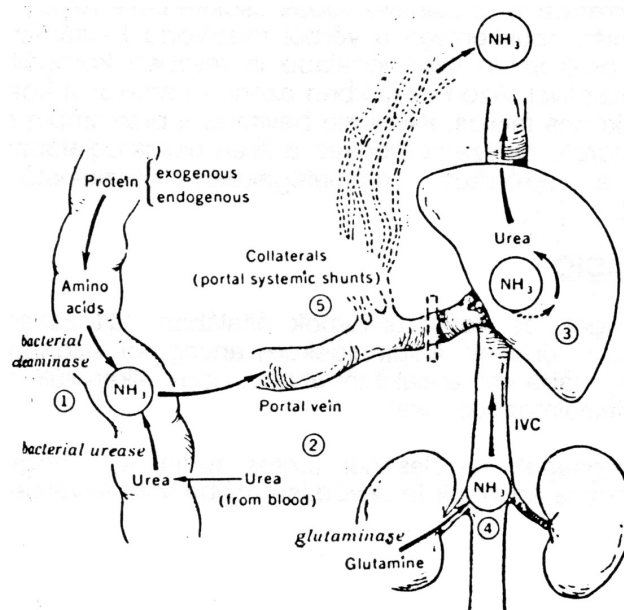


Fig. 1. Major factors (steps 1 to 4) influencing the level of blood ammonia. In cirrhosis with portal hypertension venous collaterals allow ammonia to bypass the liver (5), permitting the entry of ammonia into the systemic circulation (portal systemic shunting)

The contribution of kidney and gut to ammonia synthesis has important implications for the management of hyperammonemic state in advanced liver disease.

While all the chemical mediators of hepatic encephalopathy are unknown, elevated level of blood ammonia correlates with the degree of encephalopathy. In addition, reducing serum ammonia levels lead to clinical improvement. The several mechanisms known to lead to increased blood ammonia level in patients are illustrated in Fig 1.

- Excessive protein in the intestine
- Decline of renal function
- Decreased synthesis of urea
- Central hyperventilation caused by ammonia → alkalosis → decreased renal availability of H^+ s → NH_3 enters the renal vein.
- Portal-systemic shunting of blood.

PROTEIN SYNTHESIS AND DEGRADATION

Although the body muscle mass produces the greatest total amount of protein, the liver has the highest rate of synthesis per gram of tissue. Liver produces numerous export proteins as well. Albumin is produced at a rate of approximately 12 g per day (25 % of total protein synthesis in the liver, 50 % of all exported liver proteins). The proportion of hepatocytes carrying out albumin synthesis varies from 10 to 60 %, depending on the body requirements. Although albumin secreted by hepatocytes lacks significant carbohydrate, it may undergo significant glycosilation in the circulation reflecting ambient glucose concentrations.

Albumin contributes significantly to the plasma osmotic pressure. In addition, it is the principal binding and transport protein for numerous substances, including some hormones, fatty acids, trace metals, bilirubin, and other endogenous or exogenous organic anions. Despite the many important functions of albumin, rare individuals with congenital analbuminaemia appears to have no major physiological derangements other than the excessive accumulation of extravascular fluid. This suggests that other serum proteins may also have the potential for functioning in binding and transport,

The liver also produces a wide variety of secretory glycoproteins. Some of them are very important for the clinicians for example ceruloplasmin, alpha antitrypsin and most other alpha and beta globulins. While the site of albumin catabolism is uncertain, the removal of terminal sialic acid residues after secretion and the resultant exposure of penultimate galactose or N-acetylglucosamine residues appear to result in receptor-mediated uptake of "aged" proteins by hepatocytes and Kupffer cells followed by their subsequent degradation. The receptor is called asialoglycoprotein receptor.

One of the clinically most important derangements in protein metabolism is the development hypoalbuminemia, which results from largely from reduced synthetic activity. To some extents the body attempts to compensate for the decreased albumin synthesis by reducing the rate of degradation. The reduced degradation of albumin is not a general phenomenon in chronic liver disease because other proteins such as fibrinogen are degraded more rapidly than normal.

Other proteins produced by the liver include many of the blood clotting factors: fibrinogen, prothrombin and factors V, VII, IX, and X as well as inhibitors of both coagulation and fibrinolysis. Factors II, VII, IX, and X are vitamin K-responsive and dependent upon normal intestinal fat absorption. Vitamin K activates an enzyme system in the liver endoplasmic reticulum, which catalyzes the gamma-carboxylation of selected glutamyl residues in clotting factor precursors. The liver is involved in the process of haemostasis by virtue of both anabolic and catabolic functions. As expected, severe liver disease leads to reduced synthesis of prothrombin, a vitamin K-dependent clotting factor. The malnutrition or concomitant impairment of fat absorption due to reduction in intestinal bile salt concentration (e.g. cholestasis) may accentuate hypoprothrombinemia by

decreasing the amount of vitamin K that can be absorbed from the intestine. In these cases prothrombin levels may be at least partially corrected by parenteral vitamin K administration. However, when the coagulopathy results from impaired hepatocellular function, exogenous vitamin K is unable to correct or improve prothrombin synthesis. These factors among others (not discussed here) can contribute to the altered haemostasis frequently found in patients with chronic liver disease.

BIOTRANSFORMATION

Water-soluble drugs and endogenous substances usually are excreted unchanged in the urine or bile. However, lipid-soluble compounds tend to accumulate in the body and affect cellular processes, unless they are converted to less active compound or to more soluble metabolites, which are more easily excreted.

Important in the clinical management of patients with chronic liver disease is awareness that there may be varying degrees of impairment in the hepatic uptake, detoxification and excretion of certain drugs. Portal-systemic shunting of blood may decrease the "first pass effect" of drugs absorbed from the gut. In cirrhosis, altered intrahepatic hemodynamics due to a disordered liver architecture may also reduce the rates of hepatic drug clearance. Hypoalbuminemia will permit drugs, usually bound to albumin, to be present in increased concentrations of their unbound form in the circulation and extracellular spaces. Most importantly, a decrease in the amount of function of microsomal enzymes responsible for phase I. and phase II. reactions in biotransformation will result in slower rate of drug (in)activation and elimination. This will lead to decreased dosage requirement and a narrowing of the range between therapeutic and toxic drug levels.

HORMONE METABOLISM

In addition to its role in the metabolism of diverse pharmacologic agents, the liver is also responsible for inactivation or modification of several hormones; therefore, chronic liver disease may be accompanied by signs of apparent hormonal imbalance. Some hormones (e.g. insulin and glucagon) are inactivated in the liver by proteolysis. T₃ and T₄ are metabolized by deiodination. Steroid hormones, such as corticosteroids and aldosterone are first inactivated to their tetrahydro derivative, followed by conjugation mostly with glucuronic acid. Testosterone is metabolized to the isomeric 17-ketosteroids. Estrogens, such as estradiol, may be converted to estriol and estrone and the conjugated with glucuronic acid or sulfate. Abnormalities in estrogen and testosterone metabolism are believed to be involved in the development of spider angiomas, loss of axillary or pubic hair and testicular atrophy frequently seen in patients with chronic liver disease. In addition, increased portal-systemic shunting of testosterone and androstenedione secondary to portal hypertension may lead to the development of gynecomastia in cirrhotic males due to increased peripheral conversion to estradiol and estrone. Estrogens also act directly to impair hepatic secretory activity. Estradiol and related estrogens such as those present in contraceptive pills interfere with bile salt excretion. It has been shown that pregnanediol could stimulate delta-aminolevulinic acid (DALA) synthetase activity leading to increased porphobilinogen excretion.

QUESTIONS:

- Describe those diseases (inherited and acquired ones), which affects the liver metabolism and lead to hypoglycemia! Use your first semester notes! Explain the development of hypoglycemia in these conditions!
- Describe those diseases, which affect the liver function and may cause hyperglycemia!

- Which effects of the insulin, exerted on the liver, cause the decrease of blood sugar concentration!
- Alanine is the major precursor amino acid in the gluconeogenesis. Does this mean that alanine is the most frequently used amino acid in protein synthesis?
- Explain the reasons of hyperglycemia in chronic liver disease! Why can hyperglucagonemia be detected in certain conditions?
- Give an explanation for the elevated serum lactate level!
- What is the mechanism of development of fatty liver in alcoholics?
- List those diseases, which may result accumulation of TGC in liver cells. Explain the pathomechanism.
- Which pathological conditions may result in accumulation of TGC in peripheral cells? Use your first semester tutorial, and lecture notes!
- Does plasma cholesterol level reflect cellular cholesterol content in familiar hypercholesterolemia? Defend your statement.
- Discuss the role of BCAAs in the metabolism.
- How would you treat a patient with hepatic encephalopathy caused by chronic liver disease? Use Fig.1.
- What are the metabolic consequences of portal hypertension?
- What is the effect of chronic liver disease on the biotransformation reactions? Discuss the clinical importance of altered metabolism of xenobiotics.
- What is the connection between hormone metabolism - biotransformation - and liver disease?

ACUTE LIVER FAILURE

CASE DESCRIPTION

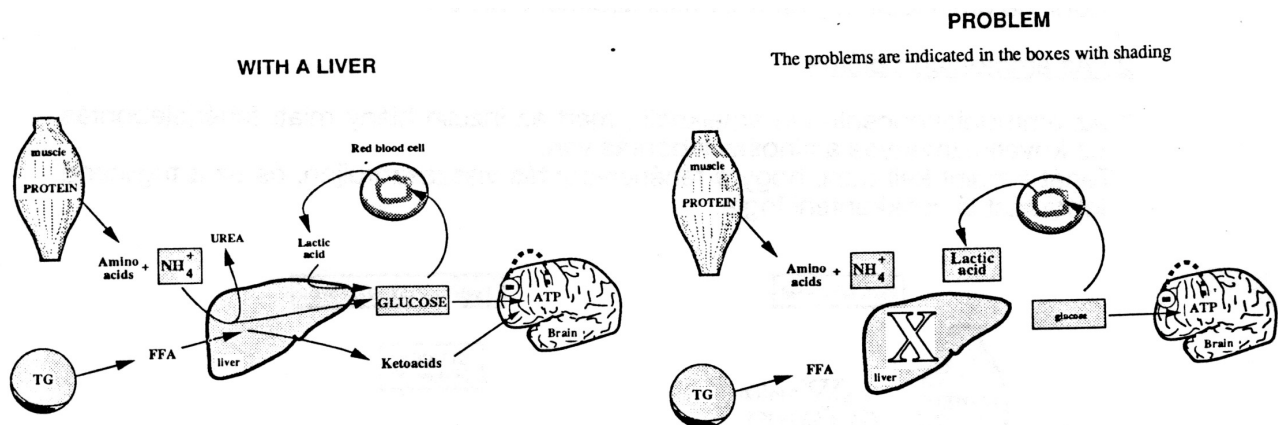
Vic, a surgeon, pierced his finger with a needle while performing an operation on a patient with infectious hepatitis (viral inflammation of the liver, a disease which is readily transmitted by needles). Over the next week, Vic became severely ill with acute and massive destruction of most of his liver cells. When the case was discussed, it was decided that Vic could survive only if the nutrition team could do the jobs of the liver and maintain ATP balance in other organs for the next 7 days. What advice might be given?

Problem to be solved

- Nutritional management has to replace temporarily the handling of energy fuels by the liver in the hope that the liver will recover with time.

Functions of the normal liver in the energy metabolism:

- Produce glucose from glycogen or protein
- Produce ketone bodies from fatty acids during fasting
- Remove lactic acid from circulation
- Detoxify ammonia from the breakdown of amino acids by making urea
- Other functions not included in the list above.



With the sick liver none of the above occur! Instead of having normal parameters we have to deal with:

- Hypoglycemia - energetic insufficiency of the brain

As a consequence of low insulin level:

- High release of fatty acids from the adipose tissue
- High release of amino acids from protein.
- Accumulation of lactic acid
- Accumulation of ammonia due to deficient urea cycle activity

PROBLEM

Mortality from massive failure of the liver with normal conservative management is close to 100%. There is no recommended therapy. Therefore ...we have to think.

POSSIBLE TREATMENT FOR VIC

Considerations;

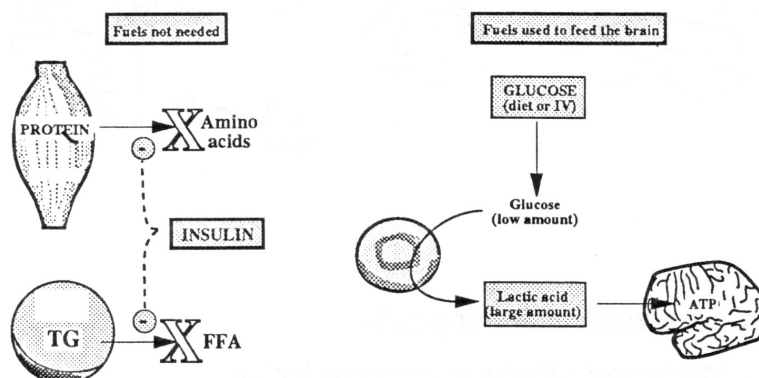
Fuel(s) for the brain:

- There are no ketone bodies and little or no glucose
- Hence the simple routine response is to give glucose, to keep its level at about 5 mmol/l

However, use of glucose involves production of lactic acid (from red cells, muscle and other tissues) and the sick liver cannot reconvert this lactic acid to glucose.

- Hence lactic acid will accumulate in the blood and can become lethal above 20 mmol/l (major factor in mortality with conservative treatment)
- Brain can burn lactic acid if its concentration in the blood is high enough (5-10 mmol/l) and glucose is low (1-2 mmol/l)

Hence possible therapy is to provide glucose iv. to keep blood lactate in the 5-10 mmol/l range; more glucose if lactate falls, less if it rises.



We have to deal with ammonia. This will accumulate from breakdown of amino acids released from proteins due to low insulin levels.

- Hence insulin should be given to limit breakdown of proteins. This will also limit breakdown of triglycerides

Thus a possible treatment for Vic might be to give glucose at a rate determined by the concentration of lactic acid and give insulin at levels to maintain low levels of amino acids in the blood.

The release of ammonium might be reduced further by infusing the ketoacid analogues of essential amino acids and by infusing insulin to stimulate the synthesis of proteins from amino acids.