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DISTURBANCES OF METABOLIC HOMEOSTASIS IN LIVER DISEASE

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SUMMARY

The liver occupies a major role in metabolic homeostasis with important functions in carbohydrate, fat and protein metabolism. Abnormalities in glucose homeostasis are common in all forms of liver disease although fasting hypoglycaemia is surprisingly rare. Blood concentrations of the gluconeogenic precursors, lactate and pyruvate, are raised in liver disease, particularly hepatic cirrhosis, although glucogenic amino acid levels tend not to be raised except in hepatic coma. The lipid fuels, non-esterified fatty acids and glycerol, are present in elevated concentration in plasma although ketone body levels tend not to be raised. Plasma triglycerides show variable changes.

The metabolic hormones, insulin, glucagon, cortisol and growth hormone both act on and are degraded by, the liver, while catecholamines and thyroid hormones also have major effects on normal hepatic metabolism. In liver disease, particularly cirrhosis, insulin degradation is impaired, with consequent hyperinsulinaemia. There is also insulin resistance due presumably to impaired action of insulin on the liver. Growth hormone levels tend to show paradoxical elevation, while cortisol half-life is prolonged although levels are only variably raised. Plasma glucagon levels are raised only in association with severe liver damage although glucagon action on liver is more often impaired.

The changes in metabolic functions of the liver in liver disease may be explained by the combination of parenchymal damage and disordered hormonal action, although changes are less than expected owing to the large reserve capacity of the liver.

INTRODUCTION

The liver occupies a central position in metabolic homeostasis with major regulatory roles in the metabolism of carbohydrates, fats and proteins. The majority of ingested foods pass direct from the gastrointestinal tract to the liver via the hepatic portal system, and are processed there before being passed on in appropriate form to the rest of the body. In the fasted state the liver maintains normoglycaemia by converting incoming precursors to glucose and mobilising glycogen. At the same time the liver provides alternative substrates for consumption by extrahepatic tissues. All these processes are modulated by hormones, several of which exert their major metabolic effects on the liver. The liver conversely acts as a regulatory centre for hormones by playing a major part in hormone catabolism. Some of these manifold metabolic and hormonal functions of the liver are summarised in Table 1.

In the rest of this review the normal regulatory function of the liver in fuel homeostasis will be briefly presented, followed by an outline of the abnormalities in these mechanisms which may be found in liver disease. Finally disorders of the actions and catabolism of the metabolic hormones will be reviewed. The major emphasis will

be on intermediary metabolism and its regulation. The reader is referred to reviews by Day et al (1979), Tavill (1979) and Johnston and Alberti (1979) for broader accounts of lipid metabolism, protein metabolism and the endocrine system in liver disease.

Table 1

Metabolic and Hormonal Functions of the Liver (adapted from Alberti and Johnston, 1979)

Metabolic Functions	
Carbohydrate Metabolism	Glycogenolysis and glycogenesis
	Gluconeogenesis
	Postprandial glucose assimilation
	Lactate clearance
	Hexose metabolism
Lipid Metabolism	Fatty acid synthesis (for glucose)
	Fatty acid oxidation
	Ketogenesis
	Glycerol clearance
	Triglyceride production
	Lipoprotein synthesis
	Cholesterol synthesis and clearance
Protein Metabolism	Plasma albumin and protein synthesis
	Amino acid clearance
	Ureagenesis
Hormonal Functions*	
Hormone action	Insulin, glugacon, growth hormone, glucocorticoids, catecholamines, thyroxine, triiodothyronine
Hormone production	Somatomedins
Hormone degradation	Insulin, glucagon, growth hormone, glucocorticoids, thyroxine, triiodothryonine

* Only hormones with major metabolic roles are considered.

THE ROLE OF THE LIVER IN METABOLIC HOMEOSTASIS IN NORMAL MAN

The Fasted State (see Cahill 1976)

In fasted man there is an obligatory requirement for both glucose and enough ATP to maintain basal metabolism. Certain tissues in short term starvation have an obligatory need for glucose. These include the central nervous system, peripheral nerves, red blood cells, white blood cells and fibroblasts. This amounts to 160 g/day. Thereafter glucose requirements fall as human tissue adapts to ketone body utilisation. Other tissues such as muscle and liver can use fuels other than glucose, including fatty acids, ketone bodies, lactate and branch chain amino acid ketoacids, for energy production.

The liver is central in these processes. Only liver and kidney can produce glucose, and in post-absorptive man 90% of this production comes from the liver. After an overnight fast approximately 75% of glucose is derived from hepatic glycogen, the rest coming from gluconeogenesis (Felig 1976). Thereafter the contribution of glycogenolysis drops sharply as the liver contains only 70 to 80 g of glycogen. By six weeks of

fasting hepatic glucose production has dropped to 20 g per day with a similar amount coming from kidney.

The main gluconeogenic precursors are lactate, pyruvate, glucogenic aminoacids (primarily alanine, glutamine, glutamate and glycine) and glycerol. Lactate and pyruvate provide approximately half of the precursor requirement. Some of this lactate, about half, is derived from glucose (the Cori cycle), and therefore does not represent a true de novo glucose precursor. However some of this lactate is derived from glycogen in extrahepatic tissues and provides a means whereby extrahepatic glycogen can contribute to blood glucose formation, albeit indirectly (Sugden et al 1976). Aminoacids provide the majority of the de novo glucose precursors. It was originally proposed (Felig 1973) that alanine, which is released in large amounts from extrahepatic tissues, is the major gluconeogenic precursor. It is now probable, however, that 80% or more of the carbon skeleton of alanine is derived from pyruvate produced by glucose breakdown in the tissues. This puts alanine in the same position as lactate as a non de-novo gluconeogenic precursor, although it is obviously still important as an amino group carrier. The most likely candidate aminoacids for a major de novo role are glutamine, glycine and branched chain aminoacids. Glutamine is quantitatively the most important aminoacid released from muscle. Much is taken up by kidney and gut. However, the glutamine taken up by gut is subsequently converted to and released as alanine and then goes to the liver for conversion to glucose. Glycine is non-metabolizable by muscle and again is converted to glucose in the liver. By contrast, branched chain aminoacids are deaminated and can be oxidised in muscle. It seems probable, however, that a significant proportion of the branched chain aminoacid ketoacids are transported to the liver in the circulation and there act as precursors for both glucose and ketone bodies.

There are two main objects to protein metabolism in the liver in starvation. First plasma protein synthesis, particularly albumin, must be maintained and second, as shown above, aminoacids are required as glucose precursors. These aims are served by increased mobilisation of aminoacids from extrahepatic sources during starvation, although requirements for glucose synthesis fall dramatically as starvation continues. Simultaneous with maintenance of normoglycaemia through gluconeogenesis and glycogenolysis, the liver plays an important role in the provision of alternative substrates during starvation. With the onset of starvation the rate of lipolysis in adipose tissue gradually increases in comparison with triglyceride synthesis. The result is an increase in both glycerol and fatty acid release. Glycerol acts as a minor gluconeogenic precursor. Fatty acids have two functions. First they serve as an important fuel for many tissues, thus resting muscle uses predominantly fatty acid rather than glucose as a primary fuel source even in the fed state. Second, fatty acids are taken up in a concentration dependent manner by the liver. In the fasted state the liver is set towards ketogenesis and with the arrival of the fatty acid precursor there is a progressive increase in ketone body formation. Ketone bodies are also important fuels for many tissues, and in long-term starvation are particularly important as an energy source in brain.

All these processes are under hormonal regulation. This is exercised by a balance between insulin, the prime anabolic hormone, and the catabolic hormones, glucagon, cortisol and catecholamines, with growth hormone occupying an intermediate role. As glucose levels fall, so insulin levels decrease. At the same time there is a relative increase in the concentrations of the catabolic hormones. Importantly, however, insulin secretion does not stop altogether. This allows some restraint to be applied to processes such as lipolysis, gluconeogenesis and proteolysis in contrast to insulin-deficient diabetes where control of these processes is completely lost. The relative excess of glucagon switches the fatty acid metabolism in the liver towards oxidation and ketogenesis whilst all the catabolic hormones combine to increase gluconeogenesis. Interestingly thyroxine conversion to tri-iodothyronine is decreased in starvation which will tend to diminish overall energy requirements and this forms a useful energy sparing mechanism.

The Fed State

The liver plays a vital role in preventing violent oscillations in circulating nutrients after feeding. It is important in the storage and conservation of ingested fuels, and in the conversion of food into appropriate storage forms. This is particularly true of carbohydrate.

Perhaps the best example is the handing of a glucose load. If 100 g of glucose were delivered in its entirety into the extracellular fluid, plasma glucose levels would rise by 37 mmol/l, whereas the measured rise is rarely more than 10% of this. There has, however, been considerable argument on the quantitative distribution of such a load between liver and peripheral tissues. Using catheter techniques, Felig and his colleagues have estimated that only 40% of such a load appears in the hepatic vein (Felig, 1976). Simultaneously basal hepatic glucose production is switched off so that a net 80 to 85% of the load is sequestered by the liver. Others, using turnover techniques, have shown that only up to 8% of glucose is taken up by the liver on first pass (Radziuk et al, 1977), but it can be calculated that during the subsequent 2 to 3 hours up to 50 g will be taken up by the liver, close to the figures of Felig.

The uptake of glucose by the liver is heavily dependent on insulin. Ingestion of carbohydrate results in the release of GIP and other, as yet unidentified, *incretin* like substances (Creutzfeldt, 1979). These enhance glucose-induced release of insulin, which in turn promotes hepatic glucose metabolism. Glycogenesis is promoted. At the same time glycolysis is stimulated, pyruvate dehydrogenase activated and hence acetyl CoA synthesis increased. This acts as a precursor for fatty acid synthesis, an insulin stimulated sequence. The liver is switched from the ketogenic to the lipogenic mode, due to the increase in the insulin: glucagon ratio (Unger 1971), and triglycerides are formed and released into the circulation as VLDL. It should be noted that in man the liver is the only site for de novo fatty acid synthesis. These fatty acids will, however, be stored as triglycerides in extrahepatic adipose tissue. At the same time as insulin is promoting these anabolic processes, it will be anticatabolic, inhibiting gluconeogenesis and glycogenolysis.

The liver is also important in the metabolism of other hexoses such as fructose and galactose which are metabolized almost exclusively by the liver. Fructose, 50% of ingested sucrose, is converted 70% to lactate and 30% to glucose.

Ingested protein is also dependent on hepatic metabolism. All amino acids entering the portal vein are taken up in part by the liver, with the exception of the branched chain amino acids. The liver uses some of these taken up amino acids for protein synthesis and will use the rest as oxidative fuels or, in the fed state, as fatty acid precursors, the amino moiety being converted to urea. Amino acid uptake by the liver is enhanced by glucagon, the secretion of which is stimulated by a protein rich meal. Insulin secretion is also promoted by amino acids. This will tend to drive amino acids into extrahepatic tissues and simultaneously promote protein synthesis.

In contrast to carbohydrate and protein metabolism the liver is less important in disposing of ingested fat. Absorbed long chain fatty acids will be reincorporated into triglyceride and bypass the liver as chylomicrons, which will be cleared by peripheral adipose tissue. Only the remnant lipoproteins will eventually be cleared by the liver together with the released glycerol. Absorbed short chain fatty acids will, however, enter the portal vein and be taken by the liver and serve as a further source of acetyl CoA. The hepatic action of the catabolic hormones will tend to be swamped by insulin in the fed state, although it is worth noting that cortisol in the fed state promotes glycogen synthesis while growth hormone will enhance protein synthesis.

METABOLIC STUDIES IN PATIENTS WITH LIVER DISEASE

Ethanol obviously has many and diverse effects on metabolism and these will not be dealt with here. The reader is referred to Salaspuro and Lieber (1979) for details and for further references.

The Fasted State

Carbohydrate metabolism

In view of the importance of the liver in glucose homeostasis, it is noteworthy that fasting hypoglycaemia is the exception rather than the rule in liver disease (Zimmerman et al 1953; Samols and Holdsworth, 1968). It occurs more often in acute fulminating liver disease than in chronic liver disease. Thus it has been reported in acute viral hepatitis, *fulminant* hepatitis, cholangitis and following ingestion of hepatotoxins, as well as primary hepatic carcinoma, and in occasional cases of severe cirrhosis (see Alberti and Johnston, 1979, for references). Owen et al (1976) indeed were unable to induce hypoglycaemia in patients with mild cirrhosis, even after 3 days of fasting. Alcohol will itself cause hypoglycaemia but this is for distinct biochemical reasons unrelated to hepatic disease.

There are several possible reasons for the lack of hypoglycaemia: First, the liver has a large reserve capacity and can probably preserve fasting glucose production after destruction of as much as 80% of parenchyma. Second, the kidney has a marked capacity for gluconeogenesis and could theoretically produce up to half of fasting glucose requirements as it does in starvation. Third, there may be increased utilisation of alternative substrates such as fatty acids.

Glycogen is obviously important in provision of glucose in the fasting state, and defective glycogen storage is probably common to many forms of liver disease. A decreased glycaemic response to glucagon has been reported in patients with acute viral hepatitis (Felig et al, 1970) and cirrhosis (Yeung and Wang, 1974; de Moura and Cruz, 1968), although these are not universal findings. These results could be explained by defective glucagon binding or action as well as by decreased glycogen storage. More positive confirmation comes, however, from the catheter studies of Owen et al (1976) who showed that after an overnight fast only one third of glucose came from glycogen, compared with 70 to 80% in normal subjects.

Gluconeogenesis, from lactate, pyruvate, amino acids and glycerol, provides the other source of glucose in the fasting state. Many workers have measured gluconeogenesis precursor levels in the fasting state, and a selection of their findings is presented in Table 2. In contrast to glucose, levels of these precursors are often elevated. Lactate levels tend to be moderately elevated in cirrhosis, viral hepatitis and drug-induced hepatic necrosis with grosser elevation in hepatic failure. Pyruvate and glycerol follow a similar pattern. Alanine levels are more variable, due to the different metabolic pathways available to this precursor. Thus peripheral hyperinsulinaemia (see below) will tend to drive alanine into extrahepatic tissues. That these findings are due to impaired hepatic uptake of precursors has been corroborated by clearance studies. Many workers have shown impaired lactate clearance and Connor et al (1978) have shown that this is associated with no change in endogenous production. Similarly we have shown impaired glycerol clearance (Alberti et al, 1978), a more specific test than lactate loading in that glycerol is metabolized to a significant extent only by the liver.

Gluconeogenesis has been studied in more detail using radioactive glucose. Perez et al (1978) were unable to show any change in glucose production, utilization or metabolic clearance rate in cirrhotic subjects in the basal state, although when hypoglycaemia was induced there were markedly lowered glucose production and utilization

rates. This failure to switch on glucose production with hypoglycaemia has also been noted by Adlung et al (1977). In preliminary studies of our own in patients with alcoholic cirrhosis, it appears that some patients show both diminished glucose turnover and decreased Cori cycle activity.

Lipid metabolism

Lipid substrates have also received attention. For a review of abnormalities of lipoproteins the reader is referred to Day et al (1979). Total fasting serum triglyceride concentrations in different liver diseases are shown in Table 2. Elevated levels have been found in cirrhosis, but this may well be due to a direct effect of ethanol. In unpublished studies we have found levels to be as high, if not higher, in patients with alcoholic hepatitis compared with alcoholic cirrhosis. Levels are also elevated in acute viral hepatitis and chronic active hepatitis, but interestingly are decreased during induced hepatic necrosis and in hepatic coma. This latter is presumably due to failure of both synthetic and secretory mechanisms.

Table 2

Fasting Blood Metabolite Levels in Patients with Liver Disease

Metabolite mmol/l	Hepatic Coma	Cirrhosis	Acute Viral Hepatitis	Chronic Active Hepatitis	Paracetamol Intoxication
Glucose	5.83 ±0.50[1]	5.2 ±0.1[2]	3.31 ±0.16[3]	4.22 ±0.17[4]	2.60 ±0.20[5]
	(5.44 ±0.39)	(5.1 ±0.1)	(4.26 ±0.06)	(3.67 ±0.17)	(3.80 ±0.10)
Lactate	3.01	0.88 ±0.06[2]	0.96 ±0.13[7]	0.76 ±0.11[4]	1.47 ±0.24[5]
	(1.03 −15.4)[6]*				
	(1.18 ±0.05)	(0.66 ±0.05)	(0.72 ±0.04)	(0.74 ±0.05)	(0.72 ±0.04)
Pyruvate	0.203	0.086±0.005[2]	0.078±0.009[7]	0.064±0.009[4]	0.137±0.026[5]
	(0.106±0.004)	(0.070±0.005)	(0.072±0.005)	(0.070±0.006)	(0.072±0.005)
Alanine	0.48 ±0.10[8]	0.28 ±0.02[2]	0.32 ±0.03[3]	0.26 ±0.02[9]	—
	(0.38 ±0.02)	(0.29 ±0.03)	(0.34 ±0.02)	(0.31 ±0.02)	—
Glycerol	—	0.11 ±0.01[2]	0.087±0.014[7]	0.112±0.013[4]	—
	—	(0.06 ±0.01)	(0.074±0.005)	(0.077±0.006)	—
Non-esterified fatty acids (plasma)	0.86	0.75 ±0.01[10]	0.75 ±0.13[7]	1.30 ±0.80[4]	—
	(0.61 −2.16)[6]	(0.61 ±0.02)	(0.76 ±0.08)	(0.80 ±0.13)	—
Total ketone bodies	0.065	0.15 ±0.03[2]	0.156±0.038[7]	0.208±0.026[4]	0.272±0.037
	(0.012–0.295)[6]	(0.09 ±0.02)	(0.057±0.005)	(0.040±0.002)	(0.057±0.005)
	(0.047±0.003)				
Triglycerides (serum)	0.68				
	(0.36 ±1.99)[6]	1.29 ±0.20[11]	2.23 ±0.03[7]	1.30 ±0.16[4]	0.76 ±0.09
	(0.86 ±0.08)	(0.33 −1.56)	(1.03 ±0.11)	(0.90 ±0.14)[4]	(1.09 ±0.11)

Results are given as mean ± SEM. *Mean and range. Control values are shown on parentheses below patient values. **refers to the sum of 3-hydroxybutyrate and acetoacetate.

[1] Sestoft and Rehfold (1970)
[2] Johnston et al (1980)
[3] Felig et al (1970)
[4] Alberti et al (1972)
[5] Record et al (1975a)
[6] Record et al (1975b)
[7] Record et al (1973)
[8] Rosen et al (1977)
[9] Johnston, Alberti and Wright. Unpublished observations.
[10] Gunnlaugsson and Berkowitz (1977)
[11] Schurberg et al (1977)

It has long been known that non-esterified fatty acid levels are raised in a wide variety of liver diseases (Mortiaux and Dawson, 1961). This increase is relatively small

in cirrhosis, where it may be related more to increased lipolysis (glycerol levels are also elevated) than to impaired hepatic metabolism. In chronic active hepatitis levels are more elevated and we have related this to decreased insulin secretion in this condition (Alberti et al, 1972). Ketogenesis is of considerable interest in hepatic disease in that this is a process specific to the liver, and hypoketonaemia might be predicted in liver disease. As Table 2 shows, this is not the case after an overnight fast. The values shown may be artificially elevated as such patients are often in poor nutritional state, but levels do look appropriate for the fatty acid supply. Even with a 3 day fast, Owen et al (1977) were unable to show diminished ketone body levels in patients with mild cirrhosis. We did find, however, in rats with biliary obstruction, that there was a diminished ketogenic response to fasting (Record and Alberti, 1973). The answer presumably is that the liver has a large ketogenic reserve, and any deficiency will be noticed only with a major stimulus.

Amino acid metabolism

Amino acid metabolism has also been widely studied with particular respect to hepatic encephalopathy (Fischer, 1979). In severe liver disease hepatic clearance of amino acids is decreased with some impairment of ureagenesis. Levels of branched chain amino acids, however, do not change much, whilst the levels of the important metabolic amino acids: alanine, glutamine, glutamate and glycine are unremarkable except in terminal hepatic coma (Record et al, 1976). Owen et al (1977) reported diminished hepatic extraction of alanine in starved cirrhotic patients, but this was probably a supply problem rather than due to hepatic disease per se.

The Fed State

Glucose tolerance

Most emphasis has been placed on the response of patients with liver disease to oral or intravenous glucose loads. Oral glucose intolerance has been recognized for many years and has been reported in all forms of liver disease (see Johnston and Alberti, 1976 for references). The incidence of glucose intolerance is higher with oral than with intravenous loads, due perhaps to portasystemic shunting or to defective gut hormone secretion.

There are many possible reasons for the impaired handling of glucose. If 60% to 80% of a glucose load is normally assimilated by the liver, then impaired hepatic glucose clearence would be expected with parenchymal loss or damage. Impaired insulin secretion or action are also candidates, as is hyperglucagonaemia (see below). Poor nutritional state and potassium deficiency have also been suggested as contributory factors in cirrhosis. A major factor is undoubtedly the inability to synthesize and store glycogen normally — this could be due to parenchymal damage or to defective insulin action.

Extrahepatic mechanisms could also contribute. Thus some workers (Hed et al, 1977) showed diminished glucose uptake by forearm in alcoholic subjects, although we could not confirm this in subjects with cryptogenic cirrhosis (Leatherdale et al, 1980). Another possible cause is the elevation in plasma fatty acid levels, that is often found, which could inhibit peripheral glucose oxidation. However, as Descos et al (1974), have pointed out, there is little correlation between the degree of glucose intolerance and the concentration of fatty acids. On balance, the most likely causes of the glucose intolerance are: a) parenchymal damage, b) impaired insulin action on both the liver and in the periphery. This latter point will be discussed further below.

Changes in intermediary metabolites have also been measured after glucose loading. The lactate response to glucose is increased in alcoholic cirrhosis and decreased in chronic active hepatitis (Johnston & Alberti, 1976), while high pyruvate levels are found after glucose in patients with hepatic failure (Amatuzio et al, 1952). In that no abnormality in forearm lactate output could be demonstrated in cirrhosis (Leatherdale et al, 1980), these changes must represent either increased hepatic glycolysis and/or diminished hepatic pyruvate and lactate uptake.

Other carbohydrates

As pointed out already, many other carbohydrates are metabolized by the liver. Galactose intolerance in liver disease has long been known (Shay et al, 1931) and recently Royle et al (1978) have suggested using an intravenous galactose load as a test of hepatic glucose output. Abnormal handling of fructose also occurs, and we have reported two cases of lactic acidosis which resulted from intravenous fructose administration in hepatic failure (Woods & Alberti, 1972). Similarly xylitol metabolism is impaired in cirrhotic subjects (Oka et al, 1976).

Normal feeding

Much less information is available on circulating fuels in patients with liver disease during normal feeding. We have ourselves examined diurnal metabolite profile in patients with alcoholic cirrhosis and alcoholic hepatitis (Stewart et al, 1980). Few major abnormalities were found beyond an exaggeration of the normal metabolic profiles in alcoholic hepatitis, apart from grossly elevated triglyceride levels. In the cirrhotics, however, glucose rose to 11 mmol/l after breakfast and remained elevated throughout the day without normal diurnal changes. Blood lactate and pyruvate levels were increased already in the fasting state, rose after breakfast and remained grossly elevated thereafter. In contrast, alanine levels, as well as fatty acids and ketone bodies, were unremarkable. These results are of practical importance in that it may be necessary to modify the carbohydrate content of the diet of cirrhotics to avoid symptomatic hyperglycaemia (the *hepatogenous diabetes* of Naunyn). Similarly, with grossly elevated lactate levels, little extra provocation would be required to induce lactic acidosis.

ANABOLIC AND CATABOLIC HORMONES IN LIVER DISEASE

As indicated above, the liver is central to both the action and the degradation of many hormones (Johnston and Alberti, 1979). Here we shall discuss only those hormones with important metabolic functions: insulin, glucagon, growth hormone, cortisol and catecholamines.

Insulin

Peripheral insulin levels have been measured in many different liver diseases (Table 3). In chronic active hepatitis fasting levels are normal and secretion in response to glucose is diminished. This, however, is the exception rather than the rule and in most hepatic disorders, notably cirrhosis, liver failure and acute hepatitis, there is fasting hyperinsulinaemia, and an exaggerated response to stimuli, such as glucose, amino acids and tolbutamide (Creutzfeldt et al, 1970; Greco et al, 1974; Kopetz and Wehrmann, 1970; Megyesi et al, 1967; Sestoft and Rehfeld, 1970; Record et al, 1973).

There has been considerable argument as to the cause of the hyperinsulinaemia. In normal man the pancreatic effluent goes direct to the liver and approximately half of

the insulin therein is degraded by the liver so that peripheral insulin levels are always lower than portal levels. Recent work suggests that in cirrhosis, at least, insulin secretion is normal or even decreased and that the raised peripheral insulin levels are due to the failure of the liver to take up and degrade insulin (Johnston et al, 1977). It has been agreed that portasystemic shunting is important in this respect (Sells et al, 1972), but we have found that in patients with chronic portal venous thrombosis but no liver damage insulin levels are normal (Johnston et al, 1978). This suggests strongly that parenchymal destruction or damage is a prerequisite for peripheral hyperinsulinaemia.

The interesting question now arises as to why there is glucose intolerance and hyperglycaemia in the presence of hyperinsulinaemia. The implication is that there must be insulin resistance. This could be due either to hepatic damage or to failure of extrahepatic insulin action. Almost certainly both are contributory. If insulin is not bound by the liver then equally it must be less effective. Direct proof of this is required. We have, however, recently established that the peripheral hyperinsulinaemia of cirrhosis is accompanied by a decrease in the number of insulin receptors on circulating monocytes. This is an example of *down-regulation*, similar to that found in other hyperinsulinaemic states, such as obesity. Presumptively there will be diminished numbers of insulin receptors on tissues such as muscle and adipose tissue, which would help explain the insulin resistance of cirrhosis.

Glucagon

The insulin resistance and glucose intolerance of liver disease could also be explained by increased concentrations of anti-insulin hormones. Hyperglucagonaemia has been reported in cirrhosis (Marco et al 1973) with much higher levels in patients with portasystemic shunting. The importance of portasystemic shunting has been stressed by Sherwin et al (1974). These authors have suggested more recently that decreased hepatic breakdown is less important than hypersecretion (Sherwin et al 1978), a conclusion also supported by the work of McDonald et al (1979). It is obviously important to know that the apparent increase in glucagon is due to secretion of normal glucagon. McDonald et al (1979) have indeed shown that most of the circulating glucagon present in cirrhotics is of the usual 3500 dalton variety.

The metabolic relevance of this hyperglucagonaemia is less established. It is possible that the liver in patients with hepatic disease is less sensitive to glucagon than is normal liver in terms of glycogenolysis, although this may rather reflect depleted glycogen stores. Recently Greco et al (1980) have suggested that in cirrhotic subjects glucagon is critical in maintaining normoglycaemia in the fasting state. This apart, there is little to suggest that glucagon has important metabolic effects in liver disease.

Growth hormone

As with glucagon, many authors have reported high circulating levels of immunoreactive growth hormone in patients with hepatic disease (Greco et al, 1974; Conn and Daughaday, 1970) (Table 3). It will be noted, however, that this is restricted mainly to patients with cirrhosis. In our own studies, for example, we found elevated values at many times of day in alcoholic cirrhotics but normal values in patients with alcoholic hepatitis (Stewart et al, 1980). Particularly characteristic of the cirrhotic is an inappropriate rise in growth hormone after oral or intravenous glucose loading (Alberti, 1974). One suggestion for the elevated levels is decreased hepatic clearance. Owens et al (1973) showed decreased metabolic clearance of HGH in 10 of 17 cirrhotics although this has not been confirmed by others (Taylor et al, 1972; Pimstone et al 1975).

Again the physiological significance of these elevated values is questionable. Part of the action of growth hormone is through the somatomedins, which are produced as a result of growth hormone action on the liver (McConaghey, 1972). Recent studies have shown somatomedin levels to be low in cirrhosis (Takano et al, 1977; Wu et al, 1974), presumably as a direct result of liver damage. Thus, only the direct actions of growth hormone will be enhanced in cirrhosis whilst those mediated by the somatomedins will be decreased. To date there is little evidence that these direct actions of hGH are of metabolic significance in liver disease.

Table 3

Fasting Plasma (or Serum) Hormone Concentrations in Patients with Liver Disease

Hormone	Cirrhosis	Acute Viral Hepatitis	Chronic Active Hepatitis	Paracetamol Intoxication
Insulin	17 ± 2.4[1]	10.3 ± 2.1	8.1 ± 0.9[3]	4.8±17
mU/l	(8.9 ± 2.1)	(6.4 ± 0.5)	(6.4 ± 0.7)	(6.4± 0.5)
Glucagon	266 ± 23[4]	—	—	—
ng/l	(70 −130)	—	—	—
	45 ± 14[5]	—	—	—
	(35 − 13)	—	—	—
Growth hormone	6.9 ± 0.9	8.6 ± 2.1[2]	3.8 ± 1.0[3]	10.7± 7.0
μg/l	(2.8 ± 0.7)	(6.4 ± 0.5)	(6.7 ± 2.1)	(3.6± 1.2)
Cortisol	437 ± 42[5]	—	342 ± 50[9]	—
nmol/l	(501 ± 58)	—	(248 ± 81)	—
Thyroxine	97 ± 5[6]	147 ±19[7]	102 ± 6[8]	—
nmol/l	(108 ± 3)	(111 ± 4)	(46 −150)	—
Triiodo-	0.51± 0.005[6]	2.29± 0.32[7]	1.85± 0.10[8]	—
thyronine	(1.94± 0.05)	(1.94± 0.06)	(1.5 − 3)	—

Results presented as mean ± SEM with control values (as mean ± SEM or range) presented in parentheses below.

[1] Johnston et al (1977)
[2] Record et al (1973)
[3] Alberti et al (1972)
[4] Greco et al (1980)
[5] Johnston et al (1980)
[6] Chopra et al (1974)
[7] Nomura et al. (1975)
[8] Sheridan et al (1978)
[9] Kley et al (1975)

Cortisol

In contrast with the other metabolic hormones, cortisol levels are not raised in cirrhosis or other forms of chronic liver disease, although the normal diurnal rhythm may be lost (Tucci et al, 1966) (Table 3). Cortisol, being dependent on hepatic metabolism, is cleared more slowly in cirrhotic subjects (Englert et al, 1957), which presumably results in decreased ACTH secretion leaving circulating levels normal. Two groups have, however, failed to show decreased cortisol secretion rates in cirrhotic subjects (see McCann & Fulton, 1975). In that cortisol levels are normal, few cortisol-induced abnormalities in intermediary metabolism occur in liver disease.

Other metabolic hormones

Little is known of the possible changes in catecholamine metabolism in liver disease. In contrast, thyroid hormones have been studied in detail and several workers have shown decreased levels of triiodothyronine with increased TSH levels in cirrhosis

although not in other forms of liver disease (Table 3). The details of these changes are beyond the scope of this chapter, as the metabolic sequelae of these changes are not known.

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