THE LIVER

A series of critical surveys of the international literature

Annual 1/1981

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Introduction

The liver is a fascinating organ. It is involved in a wide variety of metabolic, hormonal, digestive and excretory processes, and plays a central role in homeostasis. Liver diseases are common and the rapid advances in diagnostic techniques have resulted in an upsurge in interest by clinicians. The increased popularity of hepatology is reflected by a growing number of publications from both basic scientists and clinicians. However, because of the multiplicity of liver functions, the literature is spread throughout the publications of many disciplines, which makes it almost impossible for the individual hepatophile to remain in touch with major developments. This problem of making 'available literature' truly available led to production of this book which will review, on an annual basis, a wide variety of liver-related subjects. The literature is obtained by the abstracting services of the Excerpta Medica Database, which receives more than 4000 journals and other publications annually. Liver-related articles are retrieved, selected and then reviewed by the chapter authors.

It is not our intention to provide a simple summary or series of abstracts of all publications, but to evaluate major developments which have taken place during the course of the year. This annual covers the literature during the period from July 1st, 1979, to June 30th, 1980. Where necessary, older literature is also cited to provide the necessary background information. There is also a slight overlap in subject matter in certain chapters, but we have attempted to keep this to a necessary minimum.

We have tried to provide as complete a coverage as possible, and one which will be useful not only to clinicians interested in liver disease, but also to basic scientists who wish to keep up to date with developments outside their own field.

I.M. Arias
M. Frenkel
J.H.P. Wilson

Contents

1. Carbohydrate metabolism in relation to liver physiology and disease

NIELS TYGSTRUP AND JOHAN IVERSEN

The role of the liver in carbohydrate homeostasis is well established (1). By virtue of its anatomical position and capability for glucose uptake and production, and for ketone production, the liver is the prime organ for maintaining constancy of the blood sugar level. This constancy is maintained in spite of large fluctuations in glucose availability after ingestion of carbohydrate or prolonged exercise and starvation, and ensures an adequate supply of glucose to extrahepatic glucose-requiring tissues.

The metabolic processes involved in this regulation are numerous and include regulation by hormones, many of which are degraded by the liver. The liver is also important in the disposal and formation of other hexoses and pentoses. The liver also converts carbohydrate into precursors for lipid, protein and nucleotide synthesis.

The purpose of this review is to discuss the role of the liver in glucose metabolism with emphasis on adaptive processes and disturbances in glucose metabolism accompanying various hepatic disorders. Hormonal changes will be referred to insofar as they influence hepatic glucose metabolism, and the potential influence of the autonomic nervous system on glycogen synthesis and breakdown will be discussed.

Hepatic glucose homeostasis

Probably all of the processes involved are active during all phases of hepatic glucose homeostasis. For practical purposes, the phases are discussed separately and characteristic features of regulation are analysed in situations with a negative or positive net hepatic glucose balance, respectively, i.e. during starvation and after feeding. Furthermore,

short-, medium-, and long-term starvation are considered, as represented by fasting for 12 hours (the postabsorptive state), 3 days and 3–5 weeks. However, the continuity of responses should be kept in mind.

Starvation

Certain tissues such as the central nervous system, peripheral nerves, red blood cells, white blood cells, kidney medulla and retina have an obligatory requirement for glucose, approximating 160 g/day (2), whereas other tissues such as muscle, liver and kidney cortex can use energy derived from oxidation of free fatty acids and ketone bodies. To meet the glucose requirements of glucose-obligatory tissues during starvation, maintenance of a fairly constant blood sugar level is necessary. This is achieved by hepatic release of glucose at rates equal to glucose utilization. The hepatic processes involved are glycogenolysis and gluconeogenesis.

In the initial stages of starvation (e.g. after an overnight fast) approximately 70–75% of hepatic glucose release results from breakdown of glycogen and the remainder results from *de novo* synthesis from lactate, glycerol and amino acids (3, 4). Lactate is derived mainly from obligatory anaerobic tissues (during exercise also from muscle) and accounts for approximately 15% of total glucose production after an overnight fast (3, 5–7). Because lactate is an end-product of anaerobic glycolysis, reconversion of lactate to glucose in the liver (Cori cycle) does not represent net glucose production for the organism. Glycerol is produced from lipolysis in adipose tissue and contributes a constant, although quantitatively less important, fraction (about 2%) of total glucose production (8). The largest contribution to gluconeogenesis is conversion of amino acids derived from protein degradation, primarily in skeletal muscle (9). The most important precursor amino acid is alanine which accounts for 6–12% of total glucose production (10) (Fig. 1).

Since hepatic glycogen represents a limited carbohydrate reserve, being only 70–80 g after an overnight fast (11), further starvation decreases glycogenolysis and increases gluconeogenesis. After 2–3 days of starvation, gluconeogenesis provides approximately 160 g of glucose per day (12), and provides the total requirement of glucose-obligatory tissues.

After prolonged fasting, gluconeogenesis is the only source of glucose production. As starvation continues, the rate of gluconeogenesis is reduced to about 40 g of glucose per day after 3–5 weeks of fasting (13). This decrease correlates positively with adaptation of the largest glucose-consuming organ in the body, the central nervous system,

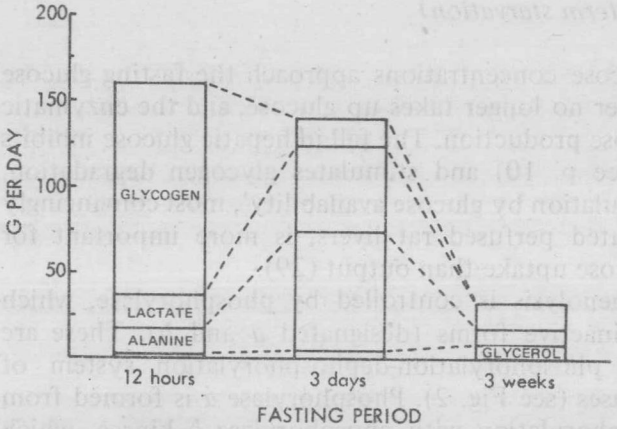

FIG. 1. *Estimated hepatic glucose production from glucogenolysis and gluconeogenesis during fasting.*

for ketone body utilization (14), and with decreased glucose utilization by the bulk of the body, due to free fatty acid and ketone body oxygenation (15, 16).

Apart from the liver, gluconeogenesis also occurs in the kidney. During prolonged fasting, a shift in the relative contribution of the two organs for gluconeogenesis occurs. After 5–6 weeks of fasting, the kidney gradually becomes the dominant tissue, producing about half of the 40 g of glucose per day which is required at this stage of starvation (13, 15). Decreased gluconeogenesis after prolonged fasting results in reduced catabolism of body protein. Death generally occurs after a 30–50% decrease in body protein (16).

The metabolic processes involved in homeostatic control of the blood sugar level during starvation include glycogenolysis, glucose utilization, gluconeogenesis, lipolysis, ketogenesis, protein degradation and amino acid metabolism. These processes are closely interrelated and subject to a high degree of control. The following discussion attempts to analyze metabolic control regarding the liver, how the various metabolic processes are controlled by substrates and hormones, and how they may control each other. Extrahepatic metabolic processes are also involved. Several reviews of the control of the individual processes have appeared elsewhere: glucose uptake by muscle (17, 18), glucose uptake by brain (19), glycogenolysis in liver (20, 21), gluconeogenesis (22, 23), fatty acid mobilization (24), ketogenesis (25, 26) and amino acid metabolism (27, 28).

Glycogenolysis (short-term starvation)

When portal vein glucose concentrations approach the fasting glucose level of 4 mM, the liver no longer takes up glucose, and the enzymatic pattern is set for glucose production. The fall in hepatic glucose inhibits glycogen synthesis (see p. 10) and stimulates glycogen degradation. This so-called 'autoregulation by glucose availability', most convincingly demonstrated in isolated perfused rat livers, is more important for regulating hepatic glucose uptake than output (29).

The rate of glycogenolysis is controlled by phosphorylase, which exists in active and inactive forms (designated *a* and *b*). These are interconverted by a phosphorylation-dephosphorylation system of kinases and phosphatases (see Fig. 2). Phosphorylase *a* is formed from the *b* form by phosphorylation with phosphorylase *b* kinase, which is itself activated by a cyclic-AMP-dependent protein kinase. The activated system inhibits synthesis of glycogen (for details, see p. 10).

During starvation, the main control of glycogen metabolism is exerted by changes in circulating hormone concentrations. An increase in serum glucagon levels during the first 24–48 hours of fasting parallels the high contribution of glycogenolysis to glucose production (30). Glucagon promotes glycogenolysis through an increase in cyclic AMP, which activates protein kinase and, consequently, phosphorylase (31, 32). The concomitant fall in serum insulin concentrations enhances glycogenolysis (33), possibly through deinhibition of glucagon-induced

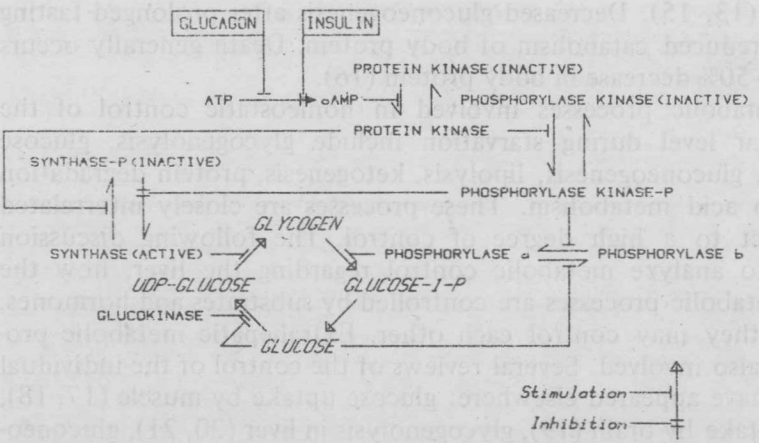

FIG. 2. *Regulatory mechanism of glucogenesis and glycogenolysis.*

cyclic AMP formation (22). Whether insulin exerts a direct antiglycogenolytic effect on the liver through mechanisms other than the adenylcyclase system is not known (34). The concept that the glucagon/insulin ratio in the portal venous blood governs hepatic glycogenolysis has attracted much attention over the past decade and glucagon has been assigned a major role (35). However, the importance of glucagon has been seriously questioned in recent studies by Felig et al. (36), who suggest that insulin is more important than glucagon in determining glycogenolysis. Glucagon may stimulate glycogenolysis acutely, but the deinhibitory effect exerted by insulin deficiency is a more likely long-term regulator of hepatic glucose production.

Catecholamines also activate glycogenolysis. Beta-receptor agonists act through the adenylcyclase system; alpha-receptor agonists activate phosphorylase without affecting cyclic AMP, but may affect calcium transfer (21). In the catecholamine action on hepatic glycogenolysis, norepinephrine is released during increased sympathetic nervous discharge, which also stimulates glycogenolysis (see p. 12).

Several other hormones may stimulate glycogenolysis (3). A simple basis for assessing the importance of these effects is the comparison between the circulating concentration of hormone in various situations and the potency of its tissue effect. A glycogenolytic effect on liver in vivo seems probable for pancreatic glucagon, catecholamines, vasopressin and angiotensin II; each increases in concentration in blood during stress, adaptation or pathological states, and starvation (3). Perhaps the increased serum concentrations of a wide range of hormones with catabolic (e.g. glycogenolytic) effects on tissues in these situations should be looked upon as an integrated response. Any of these hormones may be individually important, but can appear to function as a member of a multihormonal team.

Gluconeogenesis (3 days starvation)

After 2–3 days of starvation, a shift in the relative contribution of glycogenolysis and gluconeogenesis to glucose production occurs. Glycogenolysis decreases due to depleted glycogen stores (8), and gluconeogenesis is augmented to provide about 160 g/24 hr glucose for the brain and anaerobic tissues. Gluconeogenesis later decreases and is correlated with adaptation in various tissues, preferentially the brain for ketone body utilization (14), but still supplies 40 g of glucose for obligatory tissues (13).

Arteriovenous concentration differences across human muscle (during prolonged fasting) and experiments with isolated preparations

of rat muscle indicate that alanine, the gluconeogenic precursor, is released to a greater extent than is any other amino acid (9, 37–39). Alanine is formed preferentially by oxidation and transamination of branched-chain amino acids (40) and is not, as previously postulated by Felig et al. (37, 41), derived from the carbon skeleton of glucose (the glucose-alanine cycle). The latter would mean that no *de novo* glucose synthesis was occurring.

In addition to alanine, a considerable amount of glutamine is released by muscle where it is derived from transamination of α-oxoglutarate obtained from the citric acid cycle (40). After release from muscle, glutamine is removed from the blood and is converted to alanine by the mucosal cells of the small intestine (27, 42). Alanine released from muscle or produced by the intestine is taken up by the liver and converted to glucose via the gluconeogenic pathway.

The factors that control the rate of gluconeogenesis are mainly hormonal and act on extrahepatic tissues to increase the release of precursors and on the liver to metabolize them. Increases in precursor supply in the normal blood of glycerol, lactate and amino acids, as shown by Felig and others (27, 43, 44), appears to be of major importance. The fall in serum insulin levels and the increase in anti-insulin (catabolic) hormones (e.g. glucagon, glucocorticoids) increases protein degradation by muscle and increases splanchnic extraction of alanine (45, 46) and gluconeogenesis. The most important of these changes is probably absence of normal constraints on gluconeogenesis which are exerted by insulin (22, 30, 33, 47, 48), but glucagon also specifically increases the rate of gluconeogenesis (22, 27). These effects have three specific locations in the liver cell: transport of alanine (9, 49), conversion of pyruvate to phosphoenolpyruvate, and conversion of fructose diphosphate to fructose 6-phosphate (50) (see Fig. 3). All can be mediated through an increase in intracellular cyclic AMP concentrations. Glucagon has a more sustained stimulatory effect on gluconeogenesis in the liver than on glycogenolysis (51).

Glucose utilization, free fatty acids and ketones (3–5 weeks starvation)

During prolonged starvation, gluconeogenesis decreases despite unchanged serum levels of hormones, probably due to decreased precursor supply from the periphery (9, 10, 13). Administration of exogenous alanine results in a rapid rise in the blood glucose level (27, 52, 53). Glutamine uptake by the kidney is increased, as is uptake by the intestinal mucosa. Since pyruvate oxidation is severely inhibited due to fatty acid oxidation in the kidney and in other tissues, glutamine

is converted almost quantitatively to glucose. This conversion identifies the kidney as the prime organ for gluconeogenesis under these conditions (2, 13).

Protein degradation and alanine and glutamine release from muscle are assumed to be determined by metabolites which are under hormonal control (33). Free fatty acids are the prime fuel for oxidation during prolonged starvation and are responsible for turning off glucose utilization in muscle and adipose tissue, partly by oxidation to ketone bodies in the liver (54). Increased serum free fatty acids and ketone bodies are responsible for decreased glucose utilization by non-insulin-dependent tissues, e.g. brain (19) and kidney cortex (55). In several tissues, high levels of ketone bodies decrease glucose utilization through decreased membrane transport of glucose, and a decreased activity of phosphofructokinase and pyruvate dehydrogenase (19, 55–58). Over a prolonged period of fasting, the brain gradually adapts to ketone body

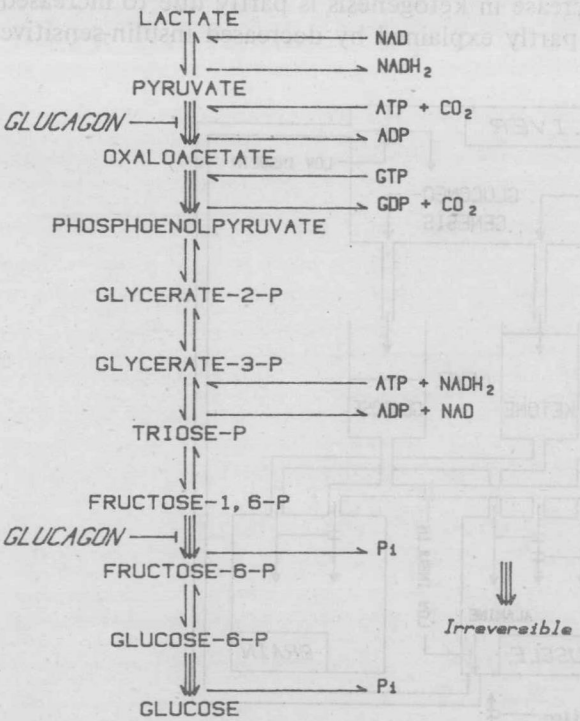

FIG. 3. *Gluconeogenetic pathway. During glycolysis the irreversible steps are bypassed by other enzymes.*