36 Integration of Carbohydrate and Lipid Metabolism

The purpose of this chapter is to summarize and integrate the major pathways for the utilization of carbohydrates and fats as fuels. We will concentrate on reviewing the regulatory mechanisms that determine the flux of metabolites in the fed and fasting states, integrating the pathways that were described separately under carbohydrate and lipid metabolism. The next section of the book covers the mechanisms by which the pathways of nitrogen metabolism are coordinated with fat and carbohydrate metabolism.

For the species to survive, it is necessary for us to store excess food when we eat and to use these stores when we are fasting. Regulatory mechanisms direct compounds through the pathways of metabolism involved in the storage and utilization of fuels. These mechanisms are controlled by **hormones**, by the **concentration of available fuels**, and by the **energy needs** of the body.

Changes in hormone levels, in the concentration of fuels, and in energy requirements affect the activity of key enzymes in the major pathways of metabolism. Intracellular enzymes are generally regulated by activation and inhibition, by phosphorylation and dephosphorylation (or other covalent modifications), by induction and repression of synthesis, and by degradation. Activation and inhibition of enzymes cause immediate changes in metabolism. Phosphorylation and dephosphorylation of enzymes affect metabolism slightly less rapidly. Induction and repression of enzyme synthesis are much slower processes, usually affecting metabolic flux over a period of hours. Degradation of enzymes decreases the amount available to catalyze reactions.

The pathways of metabolism have **multiple control points** and **multiple regulators** at each control point. The function of these complex mechanisms is to produce a graded response to a stimulus and to provide sensitivity to multiple stimuli so that an exact balance is maintained between flux through a given step (or series of steps) and the need or use for the product. Pyruvate dehydrogenase is an example of an enzyme that has multiple regulatory mechanisms. Regardless of insulin levels, the enzyme cannot become fully activated in the presence of products and absence of substrates.

The major hormones that regulate the pathways of fuel metabolism are **insulin** and **glucagon**. In liver, all effects of glucagon are reversed by insulin, and some of the pathways that insulin activates are inhibited by glucagon. Thus, the pathways of carbohydrate and lipid metabolism are generally regulated by changes in the **insulin/glucagon ratio**.

Although **glycogen** is a critical storage form of fuel because blood glucose levels must be carefully maintained, adipose **triacylglycerols** are quantitatively the major fuel store in the human. After a meal, both dietary glucose and fat are stored in adipose tissue as triacylglycerol. This fuel is released during fasting, when it provides the main source of energy for the tissues of the body. The length of time we can survive without food depends mainly on the size of our bodies' fat stores.



ТНЕ WAITING ROOM



Within 2 months of her surgery to remove a benign insulin-secreting β cell tumor of the pancreas, Bea Selmass was again jogging lightly. She had lost the 8 lb that she had gained in the 6 weeks before her surgery. Because her hypoglycemic episodes were no longer occurring, she had no need to eat frequent carbohydrate snacks to prevent the adrenergic and neuroglycopenic symptoms that

she had experienced when her tumor was secreting excessive amounts of insulin.



A few months after her last hospitalization, Di Abietes was once again brought to the hospital emergency room in diabetic ketoacidosis (DKA). Blood samples for glucose and electrolytes were drawn repeatedly during

the first 24 hours. The hospital laboratory reported that the serum in each of these specimens appeared opalescent rather than having its normal clear or transparent appearance. This opalescence results from light scattering caused by the presence of elevated levels of triacylglycerol-rich lipoproteins in the blood



When **Ann Sulin** initially presented with type 2 diabetes mellitus at age 39, she was approximately 30 lb above her ideal weight. Her high serum glucose levels were accompanied by abnormalities in her 14-hour fasting lipid profile. Her serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and triacylglycerol levels were elevated, and her serum high-density lipoprotein (HDL) cholesterol level was below the normal range.

I. **REGULATION OF CARBOHYDRATE AND LIPID** METABOLISM IN THE FED STATE

A. Mechanisms That Affect Glycogen and Triacylglycerol Synthesis in Liver

After a meal, the liver synthesizes glycogen and triacylglycerol. The level of glycogen stored in the liver can increase from approximately 80 g after an overnight fast to a limit of approximately 200–300 g. Although the liver synthesizes triacylglycerol, it does not store this fuel but rather packages it in very-low-density lipoprotein (VLDL) and secretes it into the blood. The fatty acids of the VLDL triacylglycerols secreted from the liver are stored as adipose triacylglycerols. Adipose tissue has an almost infinite capacity to store fat, limited mainly by the ability of the heart to pump blood through the capillaries of the expanding adipose mass. Although we store fat throughout our bodies, it tends to accumulate in places where it does not interfere too much with our mobility: in the abdomen, hips, thighs, and buttocks.

Both the synthesis of liver glycogen and the conversion by the liver of dietary glucose to triacylglycerol (lipogenesis) are regulated by mechanisms involving key enzymes in these pathways.

1 **GLUCOKINASE**

After a meal, glucose can be converted to glycogen or to triacylglycerol in the liver. For both processes, glucose is first converted to glucose 6-phosphate by glucokinase, a liver enzyme that has a high K_m for glucose (Fig. 36.1). Because of the enzyme's low affinity for glucose, this enzyme is most active in the fed state, when the concentration of glucose is particularly high because the hepatic portal vein



Fig. 36.1. Regulation of glucokinase, PFK-1, and pyruvate kinase in the liver.



Fig. 36.2. Regulation of glycogen synthase. This enzyme is phosphorylated by a series of kinases, which are initiated by the cAMP-dependent protein kinase, under fasting conditions. It is dephosphorylated and active after a meal, and glycogen is stored. Circled P = phosphate; a circled + sign = activated by; a circled - sign = inhibited by.



Fig. 36.3. Regulation of pyruvate dehydrogenase (PDH). A kinase associated with the PDH complex phosphorylates and inactivates the enzyme.

carries digestive products directly from the intestine to the liver. Synthesis of glucokinase is also induced by insulin (which is elevated after a meal) and repressed by glucagon (which is elevated during fasting). In keeping with the liver's function in maintaining blood glucose levels, this system is set up such that the liver can only metabolize glucose when sugar levels are high, and not when sugar levels are low.

2. GLYCOGEN SYNTHASE

In the conversion of glucose 6-phosphate to glycogen, the key regulatory enzyme is glycogen synthase. This enzyme is activated by the dephosphorylation that occurs when insulin is elevated and glucagon is decreased (Fig. 36.2) and by the increased level of glucose.

3. PHOSPHOFRUCTOKINASE-1 AND PYRUVATE KINASE

For lipogenesis, glucose 6-phosphate is converted through glycolysis to pyruvate. Key enzymes that regulate this pathway in the liver are phosphofructokinase-1 (PFK-1) and pyruvate kinase. PFK-1 is allosterically activated in the fed state by fructose 2,6-bisphosphate and adenosine monophosphate (AMP) (see Fig. 36.1). Phosphofructokinase-2, the enzyme that produces the activator fructose 2,6-bisphosphate, is dephosphorylated and active after a meal (see Chapter 22). Pyruvate kinase is also activated by dephosphorylation, which is stimulated by the increase of the insulin/glucagon ratio in the fed state (see Fig. 36.1).

4. PYRUVATE DEHYDROGENASE AND PYRUVATE CARBOXYLASE

The conversion of pyruvate to fatty acids requires a source of acetyl CoA in the cytosol. Pyruvate can only be converted to acetyl CoA in mitochondria, so it enters mitochondria and forms acetyl CoA through the pyruvate dehydrogenase (PDH) reaction. This enzyme is dephosphorylated and most active when its supply of substrates and adenosine diphosphate (ADP) is high, its products are used, and insulin is present (Fig. 36.3).

Pyruvate is also converted to oxaloacetate. The enzyme that catalyzes this reaction, pyruvate carboxylase, is activated by acetyl CoA. Because acetyl CoA cannot directly cross the mitochondrial membrane to form fatty acids in the cytosol, it condenses with oxaloacetate, producing citrate. The citrate that is not required for tricarboxylic acid (TCA) cycle activity crosses the membrane and enters the cytosol.

As fatty acids are produced under conditions of high energy, the high NADH/NAD⁺ ratio in the mitochondria inhibits isocitrate dehydrogenase, which leads to citrate accumulation within the mitochondrial matrix. As the citrate accumulates, it is transported out into the cytosol to donate carbons for fatty acid synthesis.

5. CITRATE LYASE, MALIC ENZYME, AND GLUCOSE 6-PHOSPHATE DEHYDROGENASE

In the cytosol, citrate is cleaved by citrate lyase, an inducible enzyme, to form oxaloacetate and acetyl CoA (Fig. 36.4). The acetyl CoA is used for fatty acid biosynthesis and for cholesterol synthesis, pathways that are activated by insulin. Oxaloacetate is recycled to pyruvate via cytosolic malate dehydrogenase and malic enzyme, which is inducible. Malic enzyme generates NADPH for the reactions of the fatty acid synthase complex. NADPH is also produced by the two enzymes of the pentose phosphate pathway (see Chapter 29), glucose 6-phosphate dehydrogenase is also induced by insulin.



Fig. 36.4. Regulation of citrate lyase, malic enzyme, glucose 6-phosphate dehydrogenase, and fatty acid synthase. Citrate lyase, which provides acetyl CoA for fatty acid biosynthesis, the enzymes that provide NADPH (malic enzyme, glucose 6-phosphate dehydrogenase), as well as fatty acid synthase, are inducible (circled \uparrow).

6. ACETYL CoA CARBOXYLASE

Acetyl CoA is converted to malonyl CoA, which provides the 2-carbon units for elongation of the growing fatty acyl chain on the fatty acid synthase complex. Acetyl CoA carboxylase, the enzyme that catalyzes the conversion of acetyl CoA to malonyl CoA, is controlled by three of the major mechanisms that regulate enzyme activity (Fig. 36.5). It is activated by citrate, which causes the enzyme to



Fig. 36.5. Regulation of acetyl CoA carboxylase (AcC). AcC is regulated by activation and inhibition, by phosphorylation (mediated by the AMP-activated protein kinase) and dephosphorylation (via an insulin-stimulated phosphatase), and by induction and repression. It is active in the fed state.







Why does Ann Sulin have a hypertriglyceridemia?



Di Abietes has insulin-dependent diabetes mellitus (type 1), a disease associated with a severe deficiency or absence of insulin production by the β cells of the pancreas. One of the effects of insulin is to stimulate production of LPL.

Because of low insulin levels, Di Abietes tends to have low levels of this enzyme. Hydrolysis of the triacylglycerols in chylomicrons and in VLDL is decreased, and hypertriglyceridemia results.

polymerize, and inhibited by long-chain fatty acyl CoA. A phosphatase stimulated by insulin activates the enzyme by dephosphorylation. The third means by which this enzyme is regulated is induction: the quantity of the enzyme increases in the fed state.

Malonyl CoA, the product of the acetyl CoA carboxylase reaction, provides the carbons for the synthesis of palmitate on the fatty acid synthase complex. Malonyl CoA also inhibits carnitine:palmitoyltransferase I (CPTI, also known as carnitine:acyltransferase I), the enzyme that prepares long-chain fatty acyl CoA for transport into mitochondria (Fig. 36.6). In the fed state, when acetyl CoA carboxylase is active and malonyl CoA levels are elevated, newly synthesized fatty acids are converted to triacylglycerols for storage, rather than being transported into mitochondria for oxidation and ketone body formation.

7. FATTY ACID SYNTHASE COMPLEX

In a well-fed individual, the quantity of the fatty acid synthase complex is increased (see Fig. 36.4). The genes that produce this enzyme complex are induced by increases in the insulin/glucagon ratio. The amount of the complex increases slowly after a few days of a high-carbohydrate diet.

Glucose 6-phosphate dehydrogenase, which generates NADPH in the pentose phosphate pathway, and malic enzyme, which produces NADPH, are also induced by the increase of insulin.

The palmitate produced by the synthase complex is converted to palmityl CoA and elongated and desaturated to form other fatty acyl CoA molecules, which are converted to triacylglycerols. These triacylglycerols are packaged and secreted into the blood as VLDL.

B. Mechanisms That Affect the Fate of Chylomicrons and VLDL

The lipoprotein triacylglycerols in chylomicrons and VLDL are hydrolyzed to fatty acids and glycerol by lipoprotein lipase (LPL), an enzyme attached to endothelial cells of capillaries in muscle and adipose tissue. The enzyme found in muscle, particularly heart muscle, has a low K_m for these blood lipoproteins. Therefore, it acts even when these lipoproteins are present at very low concentrations in the blood. The fatty acids enter muscle cells and are oxidized for energy. The enzyme found in adipose tissue has a higher $K_{\rm m}$ and is most active after a meal when blood lipoprotein levels are elevated.

C. Mechanisms That Affect Triacylglycerol Storage in Adipose Tissue

Insulin stimulates adipose cells to synthesize and secrete LPL, which hydrolyzes the chylomicron and VLDL triacylglycerols. The C_{II} apoprotein, donated to chylomicrons and VLDL by HDL, activates LPL (Fig. 36.7).

Fatty acids released from chylomicrons and VLDL by LPL are stored as triacylglycerols in adipose cells. The glycerol released by LPL is not used by adipose cells because they lack glycerol kinase. Glycerol can be used by liver cells, however, because these cells do contain glycerol kinase. In the fed state, liver cells convert glycerol to the glycerol moiety of the triacylglycerols of VLDL, which is secreted from the liver to distribute the newly synthesized triglycerides to the tissues.

Insulin causes the number of glucose transporters in adipose cell membranes to increase. Glucose enters these cells, and is oxidized, producing energy and providing the glycerol 3-phosphate moiety for triacylglycerol synthesis (via the dihydroxyacetone phosphate intermediate of glycolysis).



Fig. 36.7. Regulation of the storage of triacylglycerols (TG) in adipose tissue. Insulin stimulates the secretion of LPL from adipose cells and the transport of glucose into these cells. ApoC_{II} activates LPL. FA = fatty acids.

II. REGULATION OF CARBOHYDRATE AND LIPID METABOLISM DURING FASTING

A. Mechanisms in Liver That Serve to Maintain Blood Glucose Levels

During fasting, the insulin/glucagon ratio decreases. Liver glycogen is degraded to produce blood glucose because enzymes of glycogen degradation are activated by cAMPdirected phosphorylation (Fig. 36.8). Glucagon stimulates adenylate cyclase to produce cAMP, which activates protein kinase A. Protein kinase A phosphorylates phosphorylase kinase, which then phosphorylates and activates glycogen phosphorylase. Protein kinase A also phosphorylates but, in this case, **in**activates glycogen synthase.

Gluconeogenesis is stimulated because the synthesis of phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase, and glucose 6-phosphatase is induced and because there is an increased availability of precursors. Fructose 1,6-bisphosphatase is also activated because the levels of its inhibitor, fructose 2,6-bisphosphate, are low (Fig. 36.9). During fasting, the activity of the corresponding enzymes of glycolysis is decreased.

B. Mechanisms That Affect Lipolysis in Adipose Tissue

During fasting, as blood insulin levels fall and glucagon levels rise, the level of cAMP rises in adipose cells. Consequently, protein kinase A is activated and causes phosphorylation of hormone-sensitive lipase (HSL). The phosphorylated form of this enzyme is active and cleaves fatty acids from triacylglycerols (Fig. 36.10). Other hormones (e.g., epinephrine, adrenocorticotropic hormone [ACTH], growth hormone) also activate this enzyme (see Chapter 43). Glyceroneogenesis and resynthesis of triglyceride by the adipocyte regulates the rate of release of fatty acids during fasting.

C. Mechanisms That Affect Ketone Body Production by the Liver

As fatty acids are released from adipose tissue during fasting, they travel in the blood complexed with albumin. These fatty acids are oxidized by various tissues, particularly muscle. In the liver, fatty acids are transported into mitochondria Ann Sulin has type 2 diabetes mellitus. She produces insulin, but her adipose tissue is resistant to its actions. Therefore, her adipose tissue does not produce as much LPL as a normal person, which is one of the reasons why VLDL and chylomicrons remain elevated in her blood.

Twenty to thirty percent of patients with an insulinoma gain weight as part of their syndrome. **Bea Selmass** gained 8 lb in the 6 weeks before her surgery. Although she was primed by her high insulin levels both to store and to use fuel more efficiently, she would not have gained weight if she had not consumed more calories than she required for her daily energy expenditure during her illness (see Chapter 1). Bea consumed extra carbohydrate calories, mostly as hard candies and table sugar, to avoid the symptoms of hypoglycemia.

Induction of enzyme synthesis requires activation of transcription factors. One of the factors that is activated is CREB, which stands for cAMP response element binding protein. CREB is phosphorylated and activated by the cAMPdependent protein kinase, which itself is activated on glucagon or epinephrine stimulation. A second set of transcription factors activated are the C/EPBs (CCAAT/ enhancer binding proteins), although the regulation of their activity is still under investigation.

Di Abietes suffers from hyperglycemia because her insulin levels tend to be low and her glucagon levels tend to be high. Her muscle and adipose cells do not take glucose up at a normal rate, and she produces glucose by glycogenolysis and gluconeogenesis. As a result, her blood glucose levels are elevated.

Ann Sulin is in a similar metabolic state. However, in this case, she produces insulin, but her tissues are resistant to its actions.



Would **Ann Sulin's** serum triacylglycerol level be elevated?





Fig. 36.8. Regulation of the enzymes of glycogen degradation in the liver. 1. Glucagon (or epinephrine) binds to its cell membrane receptor, initially activating a G protein, which activates adenylate cyclase. 2. As cAMP levels rise, inhibitory subunits are removed from protein kinase A, which now phosphorylates phosphorylase kinase (step 3). 4. The cAMPdependent protein kinase also phosphorylates glycogen synthase, inactiving the enzyme. 5. Phosphorylated phosphorylase kinase phosphorylates glycogen phosphorylase. 6. Phosphorylated glycogen phosphorylase catalyzes the phosphorolysis of glycogen, producing glucose 1-phosphate. These events occur during fasting and produce glucose to maintain a relatively constant level of blood glucose.

because acetyl CoA carboxylase is inactive, malonyl CoA levels are low, and CPTI (carnitine:acyltransferase I) is active (see Fig. 36.6). Acetyl CoA, produced by β oxidation, is converted to ketone bodies. Ketone bodies are used as an energy source by many tissues (Table 36.1) to spare the use of glucose and the necessity of degrading muscle protein to provide the precursors for gluconeogenesis. The high levels of acetyl CoA in the liver (derived from fat oxidation) inhibit pyruvate dehydrogenase (which prevents pyruvate from being converted to acetyl CoA) and activate pyruvate carboxylase, which produces oxaloacetate for gluconeogenesis. The oxaloacetate does not condense with acetyl CoA to form citrate for two reasons. The first is that under these conditions (a high rate of fat oxidation in the liver mitochondria), energy levels in the mitochondrial matrix are high; that is, there are high levels of NADH and ATP present. The high NADH level inhibits isocitrate dehydrogenase. As a result, citrate accumulates and inhibits citrate synthase from producing more citrate. The second reason that citrate synthesis is depressed is that the



Insulin normally inhibits lipolysis by decreasing the lipolytic activity of HSL in the adipocyte. Individuals such as Di Abietes, who have a deficiency of insulin, have an increase in lipolysis and a subsequent increase in the concentration of free fatty acids in the blood. The liver, in turn, uses some of these fatty acids to synthesize triacylglycerols, which then are used in the hepatic production of VLDL. VLDL is not stored in the liver but is secreted into the blood, raising its serum concentration. Di also has low levels of LPL because of decreased insulin levels. Her hypertriglyceridemia is the result, therefore, of both overproduction of VLDL by the liver and decreased breakdown of VLDL triacylglyc-

The serum begins to appear cloudy when the triacylglycerol level reaches 200 mg/dL. As the triacylglycerol level increases still further, the degree of serum opalescence increases proportionately.

erol for storage in adipose cells.



Fig. 36.9. Regulation of gluconeogenesis and glycolysis during fasting. The gluconeogenic enzymes phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase, and glucose 6-phosphatase are induced. Fructose 1,6-bisphosphatase is also active because, during fasting, the level of its inhibitor, fructose 2,6-bisphosphate, is low. The corresponding enzymes of glycolysis are not very active during fasting. The rate of glucokinase is low because it has a high K_m for glucose and the glucose concentration is low. Phosphofructokinase-1 is not very active because the concentration of its activator fructose 2,6-bisphosphate is low. Pyruvate kinase is inactivated by cAMP-mediated phosphorylation.

Tissue	Glucose	Fatty Acids	Ketone Bodies
Nervous system	++	_	++
Skeletal muscle	_	++	++
Heart muscle	_	++	++
Liver	_	++	—
Intestinal epithelial cells	_	_	++
Kidney	_	+	+

Table 36.1. Fuel Utilization by Various Tissues during Starvation (Fasting)



Fig. 36.10. Regulation of hormone-sensitive lipase (HSL) in adipose tissue. During fasting, the glucagon/insulin ratio rises, causing cAMP levels to be elevated. Protein kinase A is activated and phosphorylates HSL, activating this enzyme. HSL-P initiates the mobilization of adipose triacylglycerol by removing a fatty acid (FA). Other lipases then act, producing fatty acids and glycerol. Insulin stimulates the phosphatase that inactivates HSL in the fed state.

high NADH/NAD⁺ ratio also diverts oxaloacetate into malate, such that the malate can exit the mitochondria (via the malate/aspartate shuttle) for use in gluconeogenesis.

D. Regulation of the Use of Glucose and Fatty Acids by Muscle

During exercise, the fuel that is used initially by muscle cells is muscle glycogen. As exercise continues and the blood supply to the tissue increases, glucose is taken up from the blood and oxidized. Liver glycogenolysis and gluconeogenesis replenish the blood glucose supply. However, as insulin levels drop, the concentration of GLUT4 transporters in the membrane is reduced, thereby reducing glucose entry from the circulation into the muscle.

Thus, as fatty acids become available because of increased lipolysis of adipose triacylglycerols, the exercising muscle begins to oxidize fatty acids. β -Oxidation produces NADH and acetyl CoA, which slow the flow of carbon from glucose through the reaction catalyzed by pyruvate dehydrogenase (see Fig. 36.3). Thus, the oxidation of fatty acids provides a major portion of the increased demand for ATP generation and spares blood glucose.

III. THE IMPORTANCE OF AMP AND FRUCTOSE 2,6-BISPHOSPHATE

The switch between catabolic and anabolic pathways is often regulated by the levels of AMP and fructose 2,6-bisphosphate in cells, particularly the liver. It is logical for AMP to be a critical regulator. As a cell uses ATP in energy-requiring pathways, the levels of AMP accumulate more rapidly than that of ADP because of the adenylate kinase reaction (2 ADP \rightarrow ATP and AMP). The rise in AMP levels then signals that more energy is required (usually through allosteric binding sites on enzymes and the activation of the AMP-activated protein kinase), and the cell will switch to the activation of catabolic pathways. As AMP levels drop, and ATP levels rise, the anabolic pathways are now activated to store the excess energy.

Muscle GLUT4 transporters also can be induced by AMP levels (see Chapter 47), through the actions of the AMP-activated protein kinase. Thus, if energy levels are very low, and AMP levels increase, glucose can still be transported from the circulation into the muscle to provide energy. This most often occurs during exercise.

The levels of fructose 2,6-bisphosphate are also critical in regulating glycolysis versus gluconeogenesis in the liver. Under conditions of high blood glucose, and insulin release, fructose 2,6 bisphosphate levels will be high because PFK-2 will be in its activated state. The fructose 2,6 bisphosphate activates PFK-1, and inhibits fructose 2,6 bisphosphatase, thereby allowing glycolysis to proceed. When blood glucose levels are low, and glucagon is released, PFK-2 is phosphorylated by the cAMP-dependent protein kinase and is inhibited, thereby lowering fructose 2,6-bisphosphate levels and inhibiting glycolysis, while favoring gluconeogenesis.

CLINICAL COMMENTS

Bea Selmass's younger sister was very concerned that Bea's pancreatic tumor might be genetically determined or potentially malignant, so she accompanied Bea to her second postoperative visit to the endocrinologist. The doctor explained that insulinomas may be familial in up to 20% of cases and that in 10% of patients with insulinomas, additional secretory neoplasms may occur in the anterior pituitary or the parathyroid glands (a genetically determined syn-

drome known as multiple endocrine neoplasia, type I or, simply, MEN I). Bea's tumor showed no evidence of malignancy, and the histologic slides, although not always definitive, showed a benign-appearing process. The doctor was careful to explain, however, that close observation for recurrent hypoglycemia and for the signs and symptoms suggestive of other facets of MEN I would be necessary for the remainder of Bea's and her immediate family's life.

Diabetes mellitus is a well-accepted risk factor for the development of coronary artery disease; the risk is three to four times higher in the diabetic than in the nondiabetic population. Although chronically elevated serum levels of chylomicrons and VLDL may contribute to this atherogenic predisposition, the premature vascular disease seen in **Di Abietes** and other patients with type 1 diabetes mellitus, as well as Ann Sulin and other patients with type 2 diabetes mellitus, is also related to other abnormalities in lipid metabolism. Among these are the increase in glycation (nonenzymatic attachment of glucose molecules to proteins) of LDL apoproteins as well as glycation of the proteins of the LDL receptor, which occurs when serum glucose levels are chronically elevated. These glycations interfere with the normal interaction or "fit" of the circulating LDL particles with their specific receptors on cell membranes. As a consequence, the rate of uptake of circulating LDL by the normal target cells is diminished. The LDL particles, therefore, remain in the circulation and eventually bind nonspecifically to "scavenger" receptors located on macrophages adjacent to the endothelial surfaces of blood vessels, one of the early steps in the process of atherogenesis.

BIOCHEMICAL COMMENTS

All of the material in this chapter was presented previously. However, because this information is so critical for understanding biochemistry in a way that will allow it to be used in interpreting clinical situations, it was summarized in this chapter. In addition, the information previously presented under carbohydrate metabolism was integrated with lipid metabolism. We have, for the most part, left out the role of allosteric modifiers and other regulatory mechanisms that finely coordinate these processes to an exquisite level. Because such details may be important for specific clinical situations, we hope this summary will serve as a framework to which the details can be fitted as students advance in their clinical studies.

Because Di Abietes produces very little insulin, she is prone to developing ketoacidosis. When insulin levels are low, HSL of adipose tissue is very active, resulting in increased lipolysis. The fatty acids that are released travel to the liver, where they are converted to the triacylglycerols of VLDL. They also undergo β-oxidation and conversion to ketone bodies. If Di does not take exogenous insulin or if her insulin levels decrease abruptly for some physiologic reason, she may develop a ketoacidosis (DKA). In fact, she has had repeated bouts of DKA.

For reasons that are not as well understood, individuals with type 2 diabetes mellitus, such as Ann Sulin, do not tend to develop ketoacidosis. One possible explanation is that the insulin resistance is tissuespecific; the insulin sensitivity of adipocytes may be greater than that of muscle and liver. Such a tissue-specific sensitivity would lead to less fatty acids being released from adipocytes in type 2 diabetes than in type 1 diabetes, although in both cases the release of fatty acids would be greater than that of an individual without the disease.



Fig. 36.11. Regulation of carbohydrate and lipid metabolism in the liver. Solid blue arrows indicate the flow of metabolites in the fed state. Solid black arrows indicate the flow during fasting. G = glucose; GK = glucokinase; F = fructose; PFK = phosphofructokinase-1; PEP = phosphoenolpyruvate; PK = pyruvate kinase; OAA = oxaloacetate; $\alpha KG = \alpha$ -ketoglutarate; GS = glycogen synthase; Phos = glycogen phosphorylase; PhK = phosphorylase kinase; AcC = acetyl CoA carboxylase; FA = fatty acid or fatty acyl group; TG = triacylglycerol; circled P = phosphate group.

Figure 36.11 is a comprehensive figure, and Tables 36.2 and 36.3 provide a list of the major regulatory enzymes of carbohydrate and lipid metabolism in the liver, an order to the events that occur, and the mechanisms by which they are controlled. This figure and tables should help students to integrate this mass of material.

Now that many of the details of the pathways have been presented, it would be worthwhile to re-read the first three chapters of this book. A student who understands biochemistry within the context of fuel metabolism is in a very good position to solve clinical problems that involve metabolic derangements.

Table 36.2. Flowchart of Changes in Liver Metabolism

When blood sugar increases: Insulin is released, which leads to the *dephosphorylation* of:

- PFK-2 (now active)
- Pyruvate kinase (now active)
- Glycogen synthase (now active)
- Phosphorylase kinase (now inactive)
- Glycogen phosphorylase (now inactive)
- Pyruvate dehydrogenase (now active)
- Acetyl CoA Carboxylase (now active)

Which leads to active

- Glycolysis
- Fatty acid synthesis
- Glycogen synthesis

When blood sugar decreases: Glucagon is released, which leads to the *phosphorylation* of:

- PFK-2 (now inactive)
- Pyruvate kinase (now inactive)
- Glycogen synthase (now
- inactive)Phosphorylase kinase (now active)
- Glycogen phosphorylase (now active)
- Pyruvate dehydrogenase (now inactive)
- Acetyl CoA Carboxylase (now inactive)
- Which leads to active
- Glycogenolysis
- Fatty acid oxidation
- Gluconeogenesis

Table 36.3. Regulation of Liver Enzymes Involved in Glycogen, Blood Glucose, and Triacylglycerol Synthesis and Degradation

LIVER ENZYMES REGULATED BY ACTIVATION/INHIBITION					
Enzyme	Activated By	State in Which Active			
Phosphofructokinase-1 Pyruvate carboxylase Acetyl CoA carboxylase Carnitine: palmitoyltransferase I	Fructose-2,6-bisP, AMP Acetyl CoA Citrate Loss of inhibitor (malonyl CoA)	Fed Fed and fasting Fed Fasting			

LIVER ENZYMES REGULATED BY PHOSPHORYLATION/DEPHOSPHORYLATION				
Enzyme	Active Form	State in	Which Active	
Glycogen synthase Phosphorylase kinas Glycogen phosphory Phosphofructokinase 6-bisphosphatase (a a kinase, increasing fructose- 2,6-bisP le	lase Phosphorylated 2/F-2, Dephosphorylat acts as	Fasting Fasting		
Phosphofructokinase 6-bisphosphatase (a a phosphatase, dec fructose- 2,6-bisP le	acts as reasing	Fasting		
Pyruvate kinase Pyruvate dehydrogei Acetyl CoA carboxyla		ed Fed		

LIVER ENZYMES REGULATED BY INDUCTION/REPRESSION				
Enzyme	State in Which Induced	Process Affected		
Glucokinase Citrate lyase Acetyl CoA carboxylase Fatty acid synthase Malic enzyme Glucose-6-P dehydrogenase	Fed Fed Fed Fed Fed Fed	$\begin{array}{l} \text{Glucose} \rightarrow \text{TG} \\ \text{Glucose} \rightarrow \text{TG} \\ \text{Glucose} \rightarrow \text{TG} \\ \text{Glucose} \rightarrow \text{TG} \\ \text{Production of NADPH} \\ \text{Production of NADPH} \end{array}$		
Glucose 6-phosphatase Fructose 1, 6-bisphosphatase Phosphoenolpyruvate carboxykinase	Fasted Fasted Fasted	Production of blood glucose Production of blood glucose Production of blood glucose		

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REVIEW QUESTIONS—CHAPTER 36

- 1. A 20-year-old woman with diabetes mellitus was admitted to the hospital in a semiconscious state with fever, nausea, and vomiting. Her breath smelled of acetone. A urine sample was strongly positive for ketone bodies. Which of the following statements is correct concerning this woman?
 - (A) A blood glucose test would probably show that her blood glucose level was well below 80 mg/dL.
 - (B) An insulin injection would decrease her ketone body production.
 - (C) She should be given a glucose infusion to regain consciousness.
 - (D) Glucagon should be administered to stimulate glycogenolysis and gluconeogenesis in the liver.
 - (E) The acetone was produced by decarboxylation of the ketone body β -hydroxybutyrate.
- 2. A woman was told by her physician to go on a low-fat diet. She decided to continue to consume the same number of calories by increasing her carbohydrate intake while decreasing her fat intake. Which of the following blood lipoprotein levels would be decreased as a consequence of her diet?
 - (A) VLDL
 - (B) IDL
 - (C) HDL
 - (D) Chylomicrons
 - (E) HDL
- 3. Assume that an individual has been eating excess calories daily such that they will gain weight. Under which of the following conditions would the person gain weight most rapidly?
 - (A) If all the excess calories were due to carbohydrate
 - (B) If all the excess calories were due to triacylgycerol
 - (C) If all the excess calories were split 50%-50% between carbohydrate and triacylgycerol
 - (D) If all the excess calories were split 25%-75% between carbohydrate and triacylgycerol
 - (E) It makes no difference what form the excess calories are in
- 4. A chronic alcoholic has been admitted to the hospital because of a severe hypoglycemic episode brought about by excessive alcohol consumption for the past 5 days. A blood lipid analysis indicates much higher than expected VLDL levels. The elevated VLDL is attributable to which of the following underlying causes?
 - (A) Alcohol-induced inhibition of lipoprotein lipase
 - (B) Elevated NADH levels in the liver
 - (C) Alcohol-induced transcription of the apoB-100 gene
 - (D) NADH activation of phosphoenolpyruvate carboxykinase
 - (E) Acetaldehyde induction of enzymes on the endoplasmic reticulum

- 5. Certain patients with abetalipoproteinemia frequently have difficulties in maintaining blood volume; their blood has trouble clotting. This symptom is attributable to which of the following?
 - (A) Inability to produce chylomicrons
 - (B) Inability to produce VLDL
 - (C) Inability to synthesize clotting factors
 - (D) Inability to synthesize fatty acids
 - (E) Inability to absorb short-chain fatty acids