

c0065

Integration of Carbohydrate, Fat, and Amino Acid Metabolism

13

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activate enzymes in one pathway and to inactivate enzymes in a competing pathway. Each hormone that affects carbohydrate and amino acid metabolism has consistent effects on its target tissues through its signaling mechanism. It is important to keep in mind that hormone action is always in concert with the underlying allosteric properties of individual enzymes.

Insulin—A Hormone for Feasting

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The metabolic actions of insulin are most pronounced in liver, muscle, and adipose tissue (Fig. 13-1). The overall effect of insulin is to promote fuel storage. This involves synthesis of glycogen in liver and muscle as well as synthesis of triglycerides primarily in liver and also in adipose tissue. Simultaneous insulin activation of energy-storing enzymes (e.g., glycogen synthase) and inactivation of energy-mobilizing enzymes (e.g., glycogen phosphorylase) is the result of dephosphorylation of these enzymes. Insulin also promotes increased enzyme synthesis (e.g., glucokinase and phosphofructokinase) through effects on gene transcription. Insulin additionally increases glucose uptake by muscle and adipose tissue by promoting translocation of vesicles containing glucose transporter (GLUT4) receptors to the cell surface. Insulin also increases K^+ uptake because its signaling pathways up-regulate the Na^+/K^+ -ATPase membrane transporter.

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Insulin is a hormone that is released in response to ingestion of carbohydrates. It is synthesized by pancreatic β -cells as an inactive precursor—proinsulin. Proteolytic cleavage of proinsulin yields C peptide (C = connecting) and active insulin, composed of disulfide-linked A and B chains. The release of both insulin and C peptide is influenced primarily by the blood glucose concentration, although it is also influenced by some amino acids (e.g., arginine), gastrointestinal peptides (gastric inhibitory peptide and glucagon-like peptide-1), and neural stimulation.

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The insulin receptor is a tetramer whose cytosolic domain has tyrosine kinase activity that is activated when insulin binds to the extracellular domain (see Fig. 5-10). Insulin binding triggers autophosphorylation of the cytosolic domain, followed by phosphorylation of a cytosolic signaling protein,

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HORMONAL INFLUENCES ON METABOLISM

All metabolic pathways are coordinated by hormone signaling. The metabolic activity within various tissues is regulated to store energy when ingested fuel is plentiful and to draw on energy stores to maintain blood glucose during fasting or starvation. The actions of hormones regulate critical points in pathways to avoid competing reactions—a process called reciprocal regulation (Table 13-1). Thus if a hormone triggers a wave of phosphorylation within the cell, the effect will be to



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TABLE 13-1. Allosteric and Hormonal Regulation of Metabolic Pathways

CHARACTERISTIC	UNTREATED TYPE 1 DIABETES	STARVATION
1. Gluconeogenesis	Increased	Decreased
2. Glycogenolysis	Increased	Glycogen absent
3. Blood glucose	Above normal range	Below normal range
4. Muscle protein	Degraded for gluconeogenesis	Conserved
5. Ketone body synthesis	Pathologic ketoacidosis	Ketosis, but not ketoacidosis
6. Brain fuels	Glucose only	Glucose and ketones

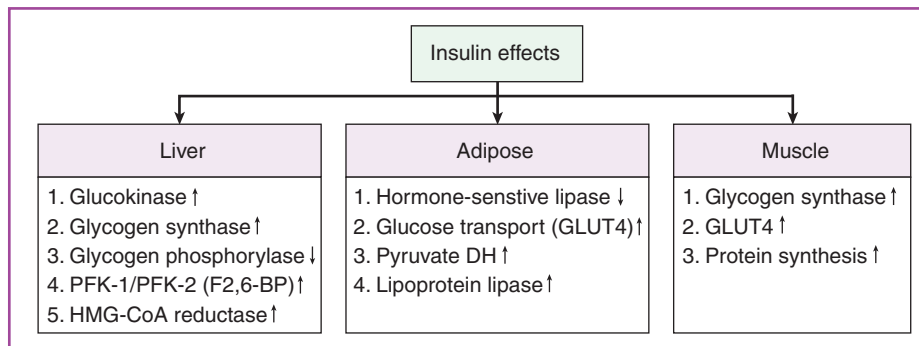


Figure 13-1. Metabolic effects of insulin in liver, adipose, and muscle tissue.

the insulin receptor substrate (IRS-1). This initiates signaling pathways that produce the intracellular responses to insulin. Increased adipose tissue leads to down-regulation of insulin receptor synthesis, whereas weight loss leads to up-regulation of receptor synthesis.

Glucagon—A Hormone for Fasting

s0025

The metabolic actions of glucagon are most pronounced in the liver (Fig. 13-2). The overall effect of glucagon is to promote glycogenolysis and gluconeogenesis in the liver to prevent fasting hypoglycemia. Secretion of glucagon from pancreatic- α -cells is stimulated by below normal concentrations (<70 mg/L) of circulating glucose. Glucagon receptors are coupled to stimulatory G-proteins, which send a wave of phosphorylation through the cell by stimulating adenylate cyclase to increase intracellular cyclic adenosine monophosphate (cAMP). Phosphorylation by protein kinase A simultaneously stimulates some enzymes and inhibits others. For example, phosphorylation stimulates glycogen phosphorylase to mobilize glycogen, whereas it inhibits enzymes such as glycogen synthase that store glycogen; phosphorylation also stimulates hormone-sensitive lipase in adipose tissues.

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PHYSIOLOGY

Biphasic Insulin Secretion

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Insulin is released in two phases. The first, a rapid release phase, represents preformed proinsulin, which is rapidly depleted. The second phase represents new synthesis of insulin, showing that glucose also stimulates messenger ribonucleic acid (mRNA) transcription.

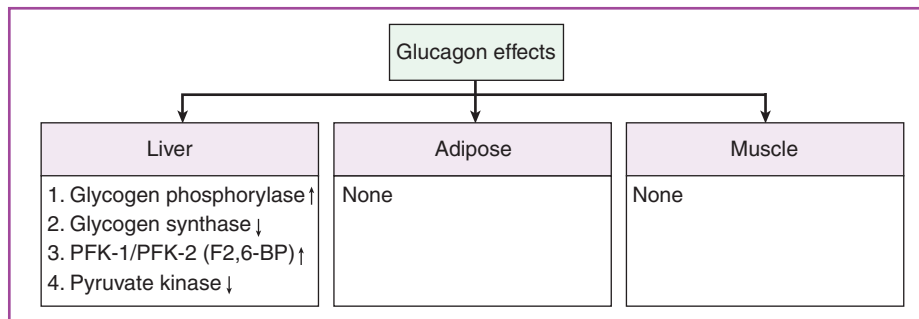


Figure 13-2. Metabolic effects of glucagon in liver, adipose, and muscle tissue.

To provide energy for gluconeogenesis, fats must be mobilized from adipose depots.

s0030 **Epinephrine—A Hormone for Fleeing or Fighting**

p0165 The metabolic actions of epinephrine are most pronounced in muscle and adipose tissue, but it also acts on the liver (Fig. 13-3). Along with norepinephrine, epinephrine acts to mobilize energy for the flight-or-fight response. This includes glycogenolysis in muscle and the liver and fat mobilization in adipose tissue.

p0170 Epinephrine receptors in muscle and adipose tissue are β -adrenergic (i.e., they act through stimulatory G-proteins that, like the glucagon response, create a wave of phosphorylation through the cell by stimulating adenylate cyclase). This leads to the mobilization of glucose from glycogen for energy in muscle and the mobilization of free fatty acids from adipose tissue for use as an energy source both in muscle and the liver.

p0175 Epinephrine receptors in the liver are α_1 -adrenergic (i.e., they act through the G_q -proteins that activate phospholipase C and stimulate a Ca^{++} -dependent protein kinase). This also leads to glycogen phosphorylase activation as seen with glucagon.

b0015 **PHYSIOLOGY**

s0035 **Epinephrine Secretion**

p0180 Secretion of epinephrine from the adrenal medulla is triggered by impulses from preganglionic sympathetic nerves in response to stress, prolonged exercise, hypoglycemia, or trauma.



s0040 **Glucocorticoids—Hormones for Sustained Stress**

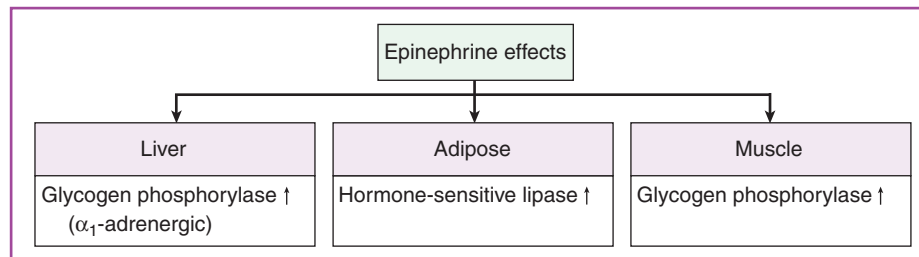
p0185 The glucocorticoids are steroid hormones produced by the adrenal glands to help tissues respond to long-term metabolic stress (Fig. 13-4). They are synthesized in response to adrenocorticotropic hormone (ACTH) that is released from the pituitary; thus they have a response time of days rather than minutes as with epinephrine. Since one action of the glucocorticoids is to down-regulate IRS-1, the general effect of the glucocorticoids is anti-insulin or “counter-regulatory.” Rather than exert their effects through second messenger pathways, glucocorticoids act on nuclear DNA to alter the rates of enzyme synthesis.

b0020 **KEY POINTS ABOUT HORMONAL INFLUENCES ON METABOLISM**

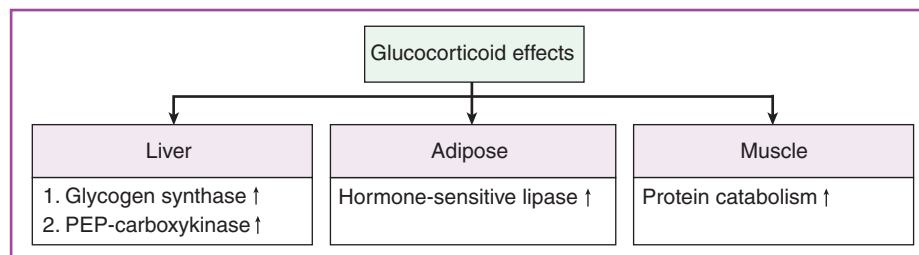
- Insulin and glucagon are the key hormones in the short-term regulation of blood glucose concentration under normal physiologic conditions. u0135
- Insulin acts to reduce blood glucose (hypoglycemic effect); glucagon acts to increase blood glucose (hyperglycemic effect). u0140
- Insulin primarily dephosphorylates enzymes, whereas glucagon primarily phosphorylates them. u0145

s0045 **THE WELL-FED STATE**

p0210 The regulation of metabolism in the well-fed state (Fig. 13-5) is determined primarily by the influx of glucose from the gut. The period extending for up to 4 hours after ingestion of a normal meal is marked by a high insulin/glucagon ratio, which is caused by the absorption of dietary glucose.



f0020 **Figure 13-3.** Metabolic effects of epinephrine in liver, adipose, and muscle tissue.



f0025 **Figure 13-4.** Metabolic effects of glucocorticoids in liver, adipose, and muscle tissue.

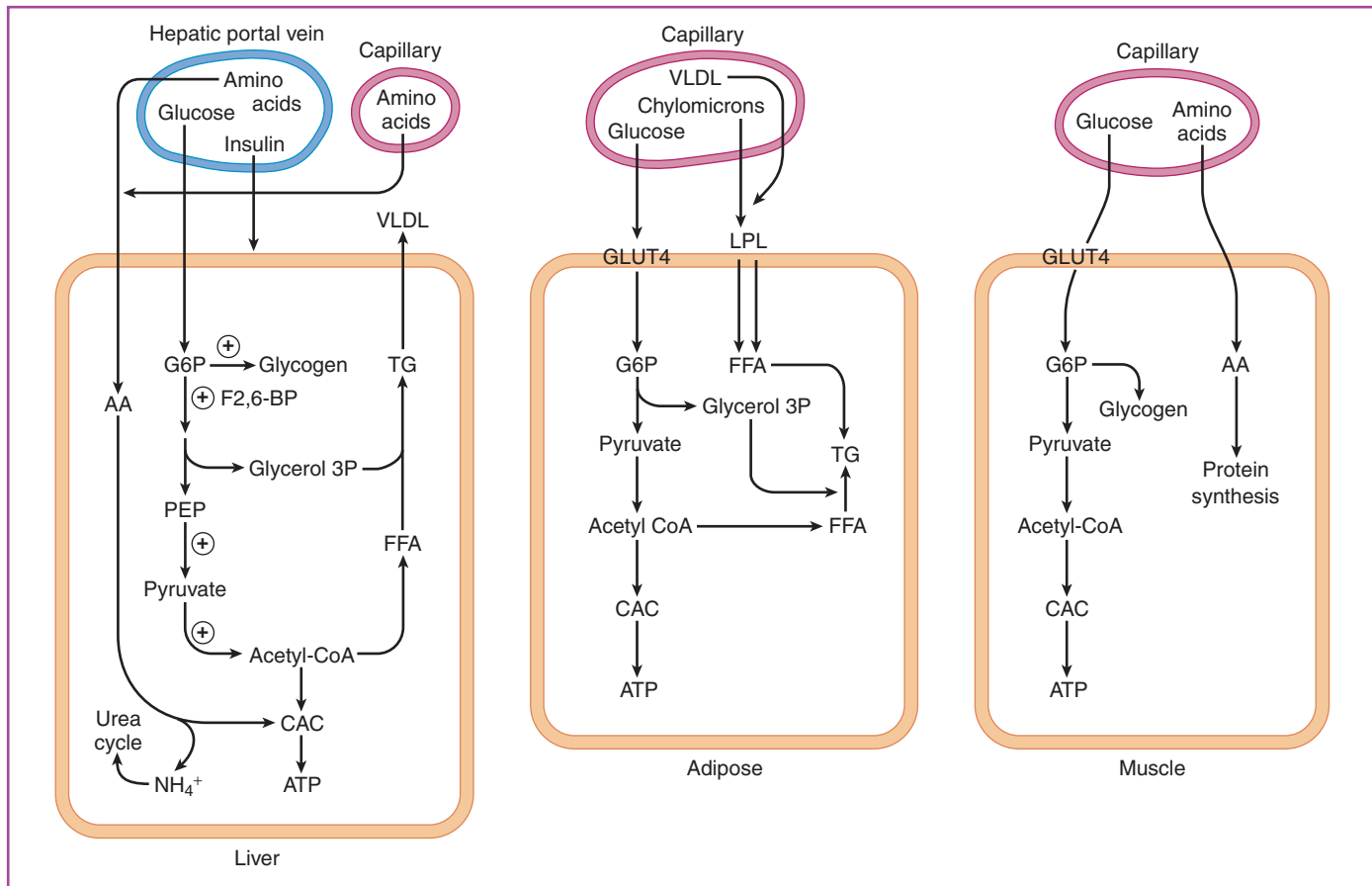


Figure 13-5. Liver, adipose, and muscle metabolism in the well-fed state. Hormones and fuels in the hepatic portal vein are delivered directly to the liver, whereas those in the capillaries are from the general circulation.

With the exception of long-chain fatty acids, all other digestible dietary components, such as amino acids and medium-chain plus short-chain fatty acids, are also transported directly to the liver. Epinephrine and glucocorticoids do not play a significant role in the hormonal response to the fed state.

Liver Metabolism in the Well-Fed State

In the well-fed state, insulin causes the liver to synthesize glycogen, fat, and cholesterol. Glucokinase is adapted to trap the large glucose influx from the hepatic portal vein after a meal. This enzyme is active only at high (10 to 20 mmol/L) glucose concentrations and is not inhibited by its product, glucose 6-phosphate (G6P) (as is hexokinase, found in other tissues). Also, the less active phosphorylated form of glycogen synthase, formed during fasting, is able to respond quickly to store the increased G6P concentrations as glycogen because it is allosterically stimulated by G6P. Eventually insulin effects the conversion of glycogen synthase to the fully active dephospho- form through a generalized increase in phosphatase activity.

The active dephospho- form of pyruvate dehydrogenase, also induced by insulin, provides abundant acetyl-coenzyme

(CoA) for free fatty acid (FFA) synthesis and cholesterol synthesis. The increased G6P also provides the substrate needed by the oxidative branch of the pentose phosphate pathway (PPP) to provide the nicotinamide adenine dinucleotide phosphate (NADPH) required for FFA synthesis. FFAs are esterified as triglyceride and transported to adipose tissue in very-low-density lipoprotein (VLDL) particles. Insulin also stimulates the conversion of acetyl-CoA to cholesterol through the activation of β -hydroxy- β -methylglutaryl (HMG)-CoA reductase. The VLDL particles transport the newly synthesized cholesterol and triglycerides to peripheral tissues.

HISTOLOGY

Adrenal Stress Hormones

Glucocorticoids are steroid hormones produced in the adrenal cortex, whereas epinephrine is produced in the adrenal medulla. Thus both regions of the adrenals participate in the short-term and long-term response to stress.



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ANATOMY



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Hepatic Portal Vein

The hepatic portal vein carries blood directly from the capillary bed in the gut to the capillary bed in the liver without passing through the heart. This arrangement ensures that, with the exception of long-chain fatty acids, the liver sees everything in the diet first. That includes not only nutrients but also xenobiotics (both drugs and toxins) that need detoxification. Even the release of insulin and glucagon is by way of the hepatic portal vein, thus ensuring that the liver sees newly released insulin and glucagon first.

Adipose Tissue Metabolism in the Well-Fed State

Following a meal, the high insulin/glucagon ratios stimulate pathways in adipose tissue, leading to triglyceride synthesis and storage. Increased glucose uptake by insulin-mobilized GLUT4 increases glycolysis for the production of glycerol 3-phosphate, the backbone for esterification of FFAs. Increased activity of pyruvate dehydrogenase provides acetyl-CoA for fatty acid synthesis, which can supplement the synthesis of fatty acids in the liver. Increased insulin levels also inhibit hormone-sensitive lipase, preventing fat mobilization. Up-regulation of lipoprotein lipase by insulin promotes release and uptake of fatty acids from chylomicrons and VLDL (see Lipoproteins section in Chapter 20) for incorporation into triglycerides.

AU3

Muscle Metabolism in the Well-Fed State

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The high insulin/glucagon ratio promotes energy storage in muscle. Increased glucose uptake by insulin-mobilized GLUT4 coupled with activation of glycogen synthase leads to formation of glycogen. Increased amino acid incorporation into muscle protein leads to muscle growth. This muscle mass also serves as a source of carbon skeletons for hepatic gluconeogenesis during fasting. Thus protein synthesis serves, in part, as an energy storage mechanism.

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Brain Metabolism in the Well-Fed State

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The brain cannot use FFAs for energy, and it has no stored glycogen reserves. Aerobic glucose metabolism is its only source of energy (except in periods of extreme starvation, when it can use ketone bodies). This is evident from the overlap in symptoms for hypoxia and hypoglycemia, such as confusion, motor weakness, and visual disturbances.

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THE FASTING STATE

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The regulation of metabolism in the fasting state (Fig. 13-6) is determined primarily by the disappearance of glucose from the blood, signaling an end to fuel absorption from the gut. Fasting begins approximately 3 hours after the last meal (post-prandial) and can extend to 4 to 5 days before entering the starvation state. The declining insulin/glucagon ratio causes metabolism to shift to increasing reliance on glycogenolysis followed by gluconeogenesis to maintain blood glucose.

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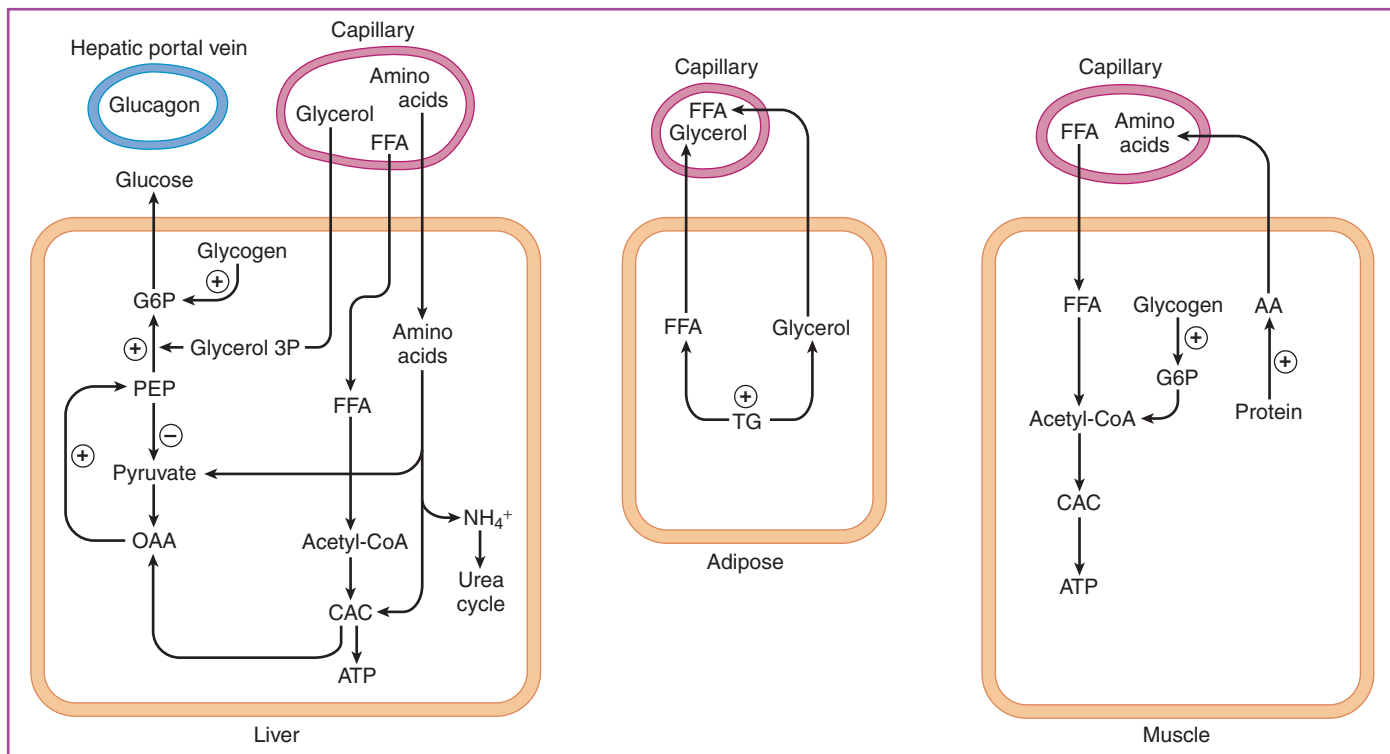


Figure 13-6. Liver, adipose, and muscle metabolism in the fasting state. Hormones and fuels in the hepatic portal vein are delivered directly to the liver, whereas those in the capillaries are from the general circulation.



Because extended fasting is physiologically stressful, epinephrine can play a role in fasting metabolism.

ANATOMY

Lymphatic Dietary Uptake

Long-chain fatty acids are esterified back to triglycerides after absorption from the gut and repackaged into chylomicron particles. They enter the lymphatic circulation and pass through the thoracic duct into the junction of the left subclavian and internal jugular veins. Other fat-soluble components of the diet such as fat-soluble vitamins are also absorbed through this route.



Liver Metabolism in the Fasting State

In the fasting state, glucagon causes the liver to mobilize glucose from glycogen (glycogenolysis) and to synthesize glucose from oxaloacetate and glycerol (gluconeogenesis). Glucagon stimulates an increase in cAMP, leading to an increase in phosphorylation by protein kinase A. The wave of phosphorylation that spreads through the liver cell activates enzymes such as glycogen phosphorylase that are involved in glycogen degradation while simultaneously inhibiting glycogen synthesis. Inhibition of glycogen synthase prevents futile resynthesis of glycogen from glucose 1-phosphate (G1P) via uridine diphosphoglucose (UDP-Glc). Glucose-6-phosphatase (G6Pase), a gluconeogenic enzyme that is present in the liver but not in muscle, then converts G6P to glucose for release into the blood.

Gluconeogenesis, a second source of glucose, is stimulated by glucagon via two mechanisms:

1. Reduction of F_{2,6}-BP formation. Reduced F_{2,6}-BP synthesis simultaneously removes the stimulation of phosphofructokinase-1 while increasing the activity of fructose-1,6-bisphosphatase. This results in an increase in conversion of F_{1,6}-BP to F₆P.

2. Inactivation of pyruvate kinase. Phosphorylation of pyruvate kinase by protein kinase A reduces futile recycling of phosphoenolpyruvate (PEP) back to pyruvate. Instead PEP is converted to F_{1,6}-BP through reverse glycolysis. Pyruvate kinase is further inhibited by alanine and adenosine triphosphate (ATP), both of which are elevated during gluconeogenesis.

The increased liver uptake of amino acids (derived from protein catabolism in muscle) during fasting provides the carbon skeletons for gluconeogenesis (e.g., alanine is transaminated into pyruvate). The increased concentrations of NH₄⁺ resulting from deamination of amino acids are metabolized in the liver by the urea cycle, leading to increased excretion of urea in urine and a negative nitrogen balance.

Oxidation of fatty acids derived from adipose tissue lipolysis provides the energy for gluconeogenesis. Thus fatty acid oxidation elevates ATP concentrations and the concentration of both acetyl-CoA and citrate. ATP, acetyl-CoA, and citrate are important effectors during gluconeogenesis:

● Acetyl-CoA activates pyruvate carboxylase, which converts pyruvate to oxaloacetate (OAA) for use in the gluconeogenic pathway.

● Inhibition of pyruvate dehydrogenase by acetyl-CoA also increases shunting of pyruvate toward oxaloacetate.

● Citrate allosterically inhibits phosphofructokinase 1, preventing a futile cycle with fructose 1,6-bisphosphatase.

● Increased ATP concentrations inhibit glycolysis while providing energy for gluconeogenesis.

The glycerol that is derived from lipolysis in adipose tissue is taken up by the liver and phosphorylated by glycerol kinase, thus contributing additional carbon skeletons for hepatic gluconeogenesis.

Some ketogenesis occurs in the liver, especially with prolonged fasting, with ketone bodies primarily going to muscle as an alternative fuel. At this point, ketosis is mild and not clinically important.

Adipose Tissue Metabolism in the Fasting State

A low insulin/glucagon ratio and release of epinephrine promote formation of the active phosphorylated form of hormone-sensitive lipase, which splits triglycerides into glycerol and FFAs. The FFAs are transported in the circulation bound to serum albumin. Liver and muscle use released FFAs as a major energy source during fasting via β -oxidation in the mitochondria. Glycerol is converted to glycerol 3-phosphate in the liver and is used as a substrate for gluconeogenesis.

Muscle Metabolism in the Fasting State

In the absence of insulin, an inducer of protein synthesis, there is a shift toward net degradation of muscle protein. The increased supply of amino acids provides the carbon skeletons needed for hepatic gluconeogenesis. Most amino acids released from muscle protein are transported directly to the liver, where they are transaminated and converted to glucose. Alanine and glutamine are the major amino acids released from muscle, indicating extensive reshuffling of carbon and nitrogen in muscle tissue. The branched-chain amino acids (isoleucine, leucine, and valine) are converted to their α -keto acids in muscle by transamination of pyruvate, yielding alanine, which is transported to the liver. The transport of alanine to the liver followed by its conversion to glucose that returns to muscle to form more pyruvate is called the alanine cycle (Fig. 13-7). The alanine cycle results in a net transport of nitrogen from branched-chain amino acids to the liver but results in no net production of glucose.

While glycogen degradation can provide glucose as fuel for short periods of exertion, FFAs serve as a major fuel source for muscle during fasting. Because skeletal muscle lacks G6Pase, degradation of muscle glycogen cannot contribute to blood glucose.

Brain Metabolism in the Fasting State

The brain depends on hepatic glycogenolysis and gluconeogenesis to maintain normal blood glucose concentrations because it continues to use glucose as an energy source during periods of fasting.

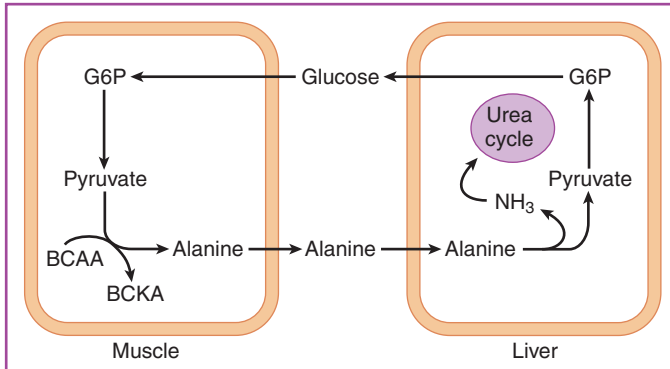


Figure 13-7. The alanine cycle as a nitrogen transport mechanism. Alanine is created in muscle to transport the nitrogen from the branched-chain amino acids. These must be metabolized in muscle because the liver lacks the necessary enzymes. After transamination in muscle, the branched-chain keto acids that are produced enter the citric acid cycle to produce adenosine triphosphate. Alanine is converted to glucose in the liver, leading to its release into the blood and conversion to pyruvate in muscle. Thus no net glucose synthesis occurs.

- Muscle tissue responds to insulin by synthesizing protein and glycogen; it responds to epinephrine by mobilizing its own glycogen for energy.
- The brain uses glucose exclusively for fuel except during starvation, when it burns ketone bodies to use less blood glucose.

THE STARVATION STATE

Starvation metabolism is not just extended fasting metabolism. Fasting metabolism anticipates the next meal and is able to shift quickly back to the well-fed state. Starvation metabolism, on the other hand, cannot anticipate the next meal. Thus, instead of breaking down protein to maintain blood glucose, metabolism shifts to conserve blood glucose and to spare protein from continual degradation (Fig. 13-8).

After 3 to 5 days of fasting, increasing reliance on fatty acids and ketone bodies for fuel enables the body to maintain blood glucose at 60 to 65 mg/dL (normal 70 to 100 mg/dL) and to save muscle protein for prolonged periods without food. Less NH_4^+ is produced, and therefore less urea is excreted in the urine.

KEY POINTS ABOUT THE WELL-FED AND FASTING STATES

- Liver tissue responds to increased insulin by storing glycogen and synthesizing fat; it responds to increased glucagon by synthesizing glucose and burning fat.
- Adipose tissue responds to insulin by increasing uptake of fat and storing it; it responds to epinephrine by mobilizing fat.

Liver Metabolism in the Starvation State

Ketosis resulting from increased hepatic production of ketone bodies is the hallmark of starvation. In the absence of insulin, mobilization of FFAs from adipose tissue continues to increase. Because the only site for regulation of fat oxidation is at the level of adipose tissue, oxidation of fatty acids in the liver continues unabated. Accumulating acetyl-CoA is

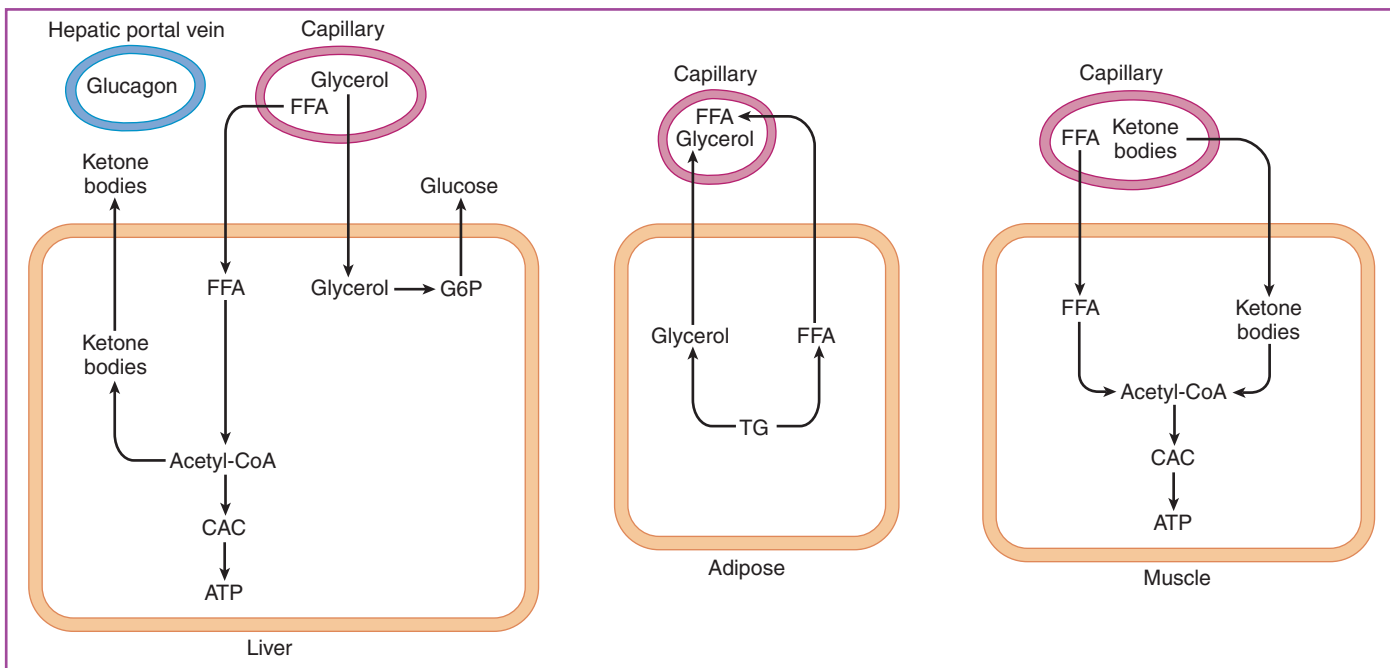


Figure 13-8. Liver, adipose, and muscle metabolism in the starvation state. Hormones and fuels in the hepatic portal vein are delivered directly to the liver, whereas those in the capillaries are from the general circulation.



shunted through ketogenesis to produce the ketone bodies acetoacetate and β -hydroxybutyrate. These substrates, which are water-soluble forms of fat, are metabolized to acetyl-CoA and used for energy production by many tissues (e.g., muscle, brain, kidney) but not by red blood cells or the liver. Acetone, a ketone formed spontaneously by decomposition of acetoacetate, gives a fruity odor to the breath.

p0380 Gluconeogenesis slows down as the supply of amino acid carbon skeletons from muscle protein catabolism decreases. However, glycerol released by lipolysis in adipose tissue supports a low level of gluconeogenesis in liver, which is the only tissue that contains glycerol kinase (glycerol \rightarrow glycerol 3-phosphate $\rightarrow\rightarrow\rightarrow$ glucose).

s0120 **Adipose Tissue Metabolism in the Starvation State**

p0385 The combined effects of the absence of insulin and elevated epinephrine concentrations due to the stress of starvation activate hormone-sensitive lipase, the only site for hormonal regulation of fatty acid oxidation. The mobilized FFAs serve not only as a source of ketone body formation in the liver but also as a fuel for most other tissues, such as muscle and heart (but not red blood cells). Glycerol released from lipase activity is the only significant adipose source of carbons for gluconeogenesis.

s0125 **Muscle Metabolism in the Starvation State**

p0390 Degradation of muscle protein is decreased in starvation, with most of its energy supplied by FFA and ketone bodies. As starvation persists, muscle relies increasingly on FFAs, saving glucose and ketone bodies for use by the brain.

s0130 **Brain Metabolism in the Starvation State**

p0395 Increasing ketone body use by the brain saves blood glucose for use by red blood cells, which rely solely on glucose for energy production. Decreasing glucose use by the brain reduces the need for hepatic gluconeogenesis from muscle and thus indirectly spares muscle protein.

PATHOLOGY

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Protein-Calorie Malnutrition

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Protein-calorie malnutrition is a condition involving inadequate intake of protein and/or carbohydrate. This occurs in some trauma or surgical patients that are in a highly catabolic state or in populations of underdeveloped countries. Kwashiorkor is a form of malnutrition in which the protein deficiency is greater than the carbohydrate deficiency. Although many tissues suffer from degeneration, the key characteristic of these patients is a swollen abdomen from edema (ascites) produced by a reduced serum albumin concentration. Marasmus is a form of malnutrition in which the carbohydrate deficiency is greater than the protein deficiency. Ascites is not seen in this form of starvation, although tissue degeneration such as muscle wasting still occurs. Most of the protein in a marasmus patient is spent on gluconeogenesis.

●●● **THE UNTREATED TYPE 1 DIABETIC STATE**

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Type 1 diabetes, sometimes still referred to as insulin-dependent diabetes mellitus, is caused by β -cell destruction, which removes the body's only source of endogenous insulin. The absence of insulin also typifies the starvation state, leading to some similarities between untreated type 1 diabetes and starvation (Fig. 13-9). Four characteristic metabolic abnormalities caused by the absence of insulin are the following:

1. Hyperglycemia is caused by increased hepatic glucose production and reduced glucose uptake by insulin-sensitive GLUT4 in adipose tissue and muscle. o0020
2. Muscle wasting results from excessive degradation of muscle protein. o0025
3. Ketoacidosis results from excessive mobilization of fatty acids from adipose tissue. o0030
4. Hypertriglyceridemia is caused by reduced lipoprotein lipase activity in adipose tissue and excessive fatty acid esterification in liver. o0035

However, upon closer inspection, the metabolic response in diabetes is different from that in starvation in several ways because starvation is due to a lack of fuel, not of insulin. Thus when fuel is plentiful and insulin is lacking, the normal mechanisms for fasting and starvation respond abnormally. p0430

Liver Metabolism in Type 1 Diabetes

s0145

The liver interprets the low insulin/glucagon ratio as a signal of low blood sugar, leading to stimulation of gluconeogenesis. Thus the hepatic output of glucose is increased despite ample or excessive glucose in the blood. Amino acids mobilized from muscle are used as the carbon skeletons, as described for fasting metabolism. Excessive amounts of acetyl-CoA produced by mobilization of FFAs are shunted away from the already saturated citric acid cycle and into production of ketone bodies. Significantly, the rate of ketone production in diabetes is much greater than in starvation, making this a life-threatening condition. p0435

Adipose Tissue Metabolism in Type 1 Diabetes

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The absence of insulin leads to uncontrolled mobilization of FFAs, which serves as the source of excess ketone body production by the liver. Lipoprotein lipase, which is increased by insulin, is decreased in its absence, leading to an elevation in chylomicrons and VLDL levels. Because glucose uptake in adipose cells is insulin dependent, the defective transport further contributes to an abnormally elevated blood glucose level. p0440

Muscle Metabolism in Type 1 Diabetes

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The lack of insulin prevents glucose uptake by muscle tissue, further contributing to abnormally high blood glucose concentrations. Protein synthesis is decreased and

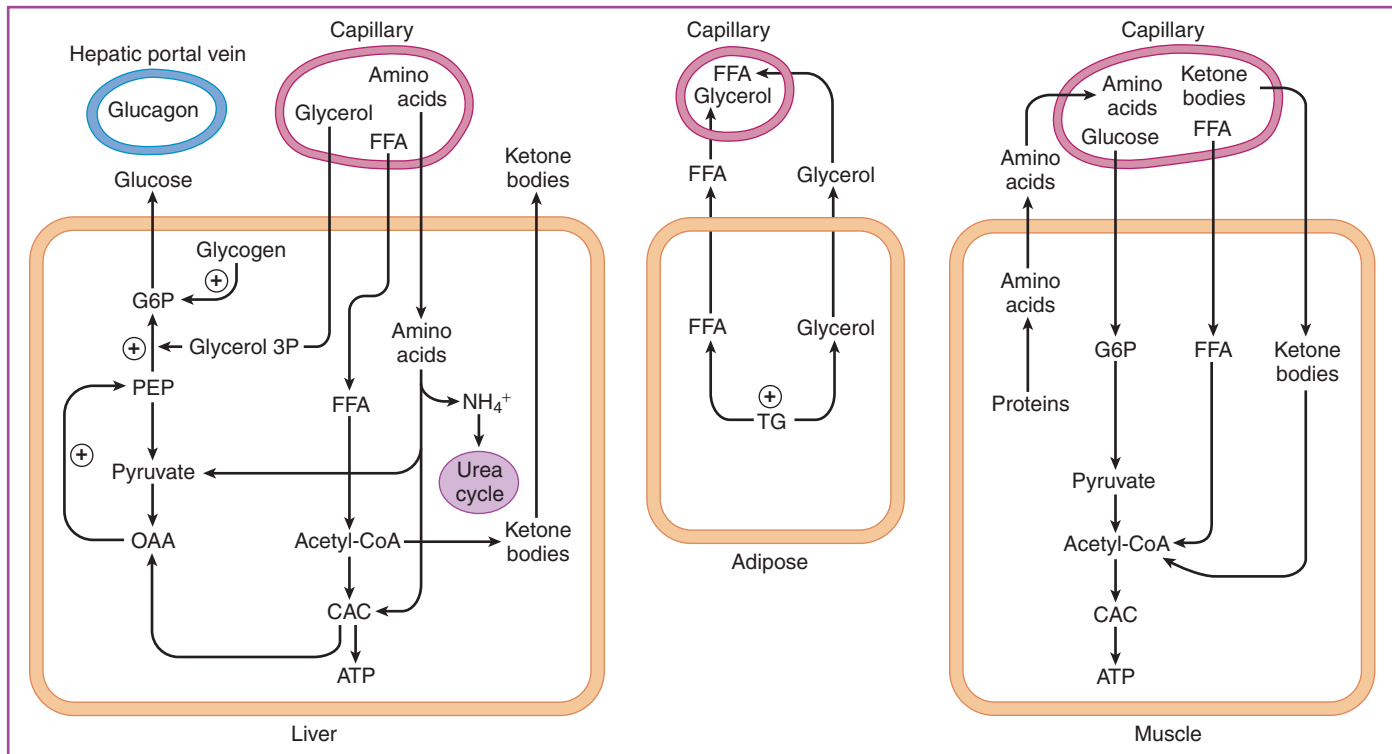


Figure 13-9. Liver, adipose, and muscle metabolism in the untreated type 1 diabetic state. Hormones and fuels in the hepatic portal vein are delivered directly to the liver, whereas those in the capillaries are from the general circulation.

degradation increased in the diabetic state, as would be seen during fasting, to mobilize carbon skeletons for use in gluconeogenesis, even though it is not needed. Muscle amino acids are also consumed in the citric acid cycle to make up for the loss of glucose, which cannot be transported into the cell.

Brain Metabolism in Type 1 Diabetes

In the untreated diabetic, blood glucose remains the sole source of fuel because it is in plentiful supply. Therefore ketones are not used by the brain as they are during starvation.

KEY POINTS ABOUT THE STARVATION STATE AND UNTREATED TYPE 1 DIABETES

- During starvation, fatty acids mobilized from adipose tissue and ketone bodies produced in the liver supply the energy needs of all tissues except red blood cells and the liver.
- Type 1 diabetes is characterized by an absence of insulin and therefore displays characteristics of both fasting and starvation.
- People with diabetes are threatened by short-term damage from ketoacidosis and electrolyte imbalances and by long-term damage from hyperglycemia and hypertriglyceridemia.

Additional self-assessment questions can be accessed at www.StudentConsult.com





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Au5	IDDM is no longer the preferred term for this form of diabetes; the preferred term is "type 1 diabetes." Please note changes throughout chapter.	