28 Formation and Degradation of Glycogen

Glycogen is the storage form of glucose found in most types of cells. It is composed of glucosyl units linked by α -1,4 glycosidic bonds, with α -1,6 branches occurring roughly every 8 to 10 glucosyl units (Fig. 28.1). The liver and skeletal muscle contain the largest glycogen stores.

The formation of glycogen from glucose is an energy-requiring pathway that begins, like most of glucose metabolism, with the phosphorylation of glucose to **glucose 6-phosphate**. Glycogen synthesis from glucose 6-phosphate involves the formation of uridine diphosphate glucose (**UDP-glucose**) and the transfer of glucosyl units from UDP-glucose to the ends of the glycogen chains by the enzyme **glycogen synthase**. Once the chains reach approximately 11 glucosyl units, a **branching enzyme** moves six to eight units to form an α (1,6) branch.

Glycogenolysis, the pathway for glycogen degradation, is not the reverse of the biosynthetic pathway. The degradative enzyme *glycogen phosphorylase* removes glucosyl units one at a time from the ends of the glycogen chains, converting them to *glucose 1-phosphate* without resynthesizing UDP-glucose or UTP. A *debranching enzyme* removes the glucosyl residues near each branchpoint.

Liver glycogen serves as a source of blood glucose. To generate glucose, the glucose 1-phosphate produced from glycogen degradation is converted to

Glycogen degradation is a phosphorolysis reaction (breaking of a bond using a phosphate ion as a nucleophile). Enzymes that catalyze phosphorolysis reactions are named phosphorylase. Because more than one type of phosphorylase exists, the substrate usually is included in the name of the enzyme, such as glycogen phosphorylase or purine nucleoside phosphorylase.



• Glucose residue linked α -1,6 Ø Nonreducing ends

Fig. 28.1. Glycogen structure. Glycogen is composed of glucosyl units linked by α -1,4-glycosidic bonds and α -1,6-glycosidic bonds. The branches occur more frequently in the center of the molecule, and less frequently in the periphery. The anomeric carbon that is not attached to another glucosyl residue (the reducing end) is attached to the protein glycogenin by a glycosidic bond.

glucose 6-phosphate. *Glucose* 6-phosphatase, an enzyme found only in liver and kidney, converts glucose 6-phosphate to free glucose, which then enters the blood.

Glycogen synthesis and degradation are regulated in liver by **hormonal changes** that signal the need for blood glucose (see Chapter 26). The body maintains fasting blood glucose levels at approximately 80 mg/dL to ensure that the brain and other tissues that are dependent on glucose for the generation of adenosine triphosphate (ATP) have a continuous supply. The lack of dietary glucose, signaled by a decrease of the **insulin/glucagon ratio**, activates liver glycogenolysis and inhibits glycogen synthesis. **Epinephrine**, which signals an increased utilization of blood glucose and other fuels for exercise or emergency situations, also activates liver glycogenolysis. The hormones that regulate liver glycogen metabolism work principally through changes in the **phosphorylation** state of glycogen synthase in the biosynthetic pathway and glycogen phosphorylase in the degradative pathway.

In skeletal muscle, glycogen supplies glucose 6-phosphate for ATP synthesis in the glycolytic pathway. Muscle glycogen phosphorylase is stimulated during exercise by the increase of adenosine monophosphate (AMP), an allosteric activator of the enzyme, and also by phosphorylation. The phosphorylation is stimulated by calcium released during contraction, and by the "fight-or-flight" hormone epinephrine. Glycogen synthesis is activated in resting muscles by the elevation of insulin after carbohydrate ingestion.

The neonate must rapidly adapt to an intermittent fuel supply after birth. Once the umbilical cord is clamped, the supply of glucose from the maternal circulation is interrupted. The combined effect of epinephrine and glucagon on the liver glycogen stores of the neonate rapidly restore glucose levels to normal.



THE WAITING ROOM

A newborn baby girl, **Getta Carbo**, was born after a 38-week gestation. Her mother, a 36-year-old woman, had moderate hypertension during the last trimester of pregnancy related to a recurrent urinary tract infection that resulted in a severe loss of appetite and recurrent vomiting in the month preceding delivery. Fetal bradycardia (slower than normal fetal heart rate) was detected with each uterine contraction of labor, a sign of possible fetal distress.

At birth Getta was cyanotic (a bluish discoloration caused by a lack of adequate oxygenation of tissues) and limp. She responded to several minutes of assisted ventilation. Her Apgar score of 3 was low at 1 minute after birth, but improved to a score of 7 at 5 minutes.

Physical examination in the nursery at 10 minutes showed a thin, malnourished female newborn. Her body temperature was slightly low, her heart rate was rapid, and her respiratory rate of 35 breaths/minute was elevated. Getta's birth weight was only 2,100 g, compared with a normal value of 3,300 g. Her length was 47 cm, and her head circumference was 33 cm (low normal). The laboratory reported that Getta's serum glucose level when she was unresponsive was 14 mg/dL. A glucose value below 40 mg/dL (2.5 mM) is considered to be abnormal in newborn infants.

At 5 hours of age, she was apneic (not breathing) and unresponsive. Ventilatory resuscitation was initiated and a cannula placed in the umbilical vein. Blood for a glucose level was drawn through this cannula, and 5 mL of a 20% glucose solution was injected. Getta slowly responded to this therapy.

The Apgar score is an objective estimate of the overall condition of the newborn, determined at both 1 and 5 minutes after birth. The best score is 10 (normal in all respects).



Jim Bodie, a 19-year-old body builder, was rushed to the hospital emergency room in a coma. One-half hour earlier, his mother had heard a loud crashing sound in the basement where Jim had been lifting weights and completing his daily workout on the treadmill. She found her son on the floor hav-

ing severe jerking movements of all muscles (a grand mal seizure). In the emergency room, the doctors learned that despite the objections of his family and friends, Jim regularly used androgens and other anabolic steroids in an effort to bulk up his muscle mass.

On initial physical examination, he was comatose with occasional involuntary jerking movements of his extremities. Foamy saliva dripped from his mouth. He had bitten his tongue and had lost bowel and bladder control at the height of the seizure.

The laboratory reported a serum glucose level of 18 mg/dL (extremely low). The intravenous infusion of 5% glucose (5 g of glucose per 100 mL of solution), which had been started earlier, was increased to 10%. In addition, 50 g glucose was given over 30 seconds through the intravenous tubing.

Ι. STRUCTURE OF GLYCOGEN

Glycogen, the storage form of glucose, is a branched glucose polysaccharide composed of chains of glucosyl units linked by α -1,4 bonds with α -1,6 branches every 8 to 10 residues (see Fig. 28.1). In a molecule of this highly branched structure, only one glucosyl residue has an anomeric carbon that is not linked to another glucose residue. This anomeric carbon at the beginning of the chain is attached to the protein glycogenin. The other ends of the chains are called nonreducing ends (see Chapter 5). The branched structure permits rapid degradation and rapid synthesis of glycogen because enzymes can work on several chains simultaneously from the multiple nonreducing ends.

Glycogen is present in tissues as polymers of very high molecular weight $(10^7 - 10^8)$ collected together in glycogen particles. The enzymes involved in glycogen synthesis and degradation, and some of the regulatory enzymes, are bound to the surface of the glycogen particles.

FUNCTION OF GLYCOGEN IN SKELETAL MUSCLE П. **AND LIVER**

Glycogen is found in most cell types, where it serves as a reservoir of glucosyl units for ATP generation from glycolysis.

Glycogen is degraded mainly to glucose 1-phosphate, which is converted to glucose 6-phosphate. In skeletal muscle and other cell types, the glucose 6-phosphate enters the glycolytic pathway (Fig. 28.2). Glycogen is an extremely important fuel source for skeletal muscle when ATP demands are high and when glucose 6-phosphate is used rapidly in anaerobic glycolysis. In many other cell types, the small glycogen reservoir serves a similar purpose; it is an emergency fuel source that supplies glucose for the generation of ATP in the absence of oxygen or during restricted blood flow. In general, glycogenolysis and glycolysis are activated together in these cells.

Glycogen serves a very different purpose in liver than in skeletal muscle and other tissues (see Fig. 28.2). Liver glycogen is the first and immediate source of glucose for the maintenance of blood glucose levels. In the liver, the glucose 6-phosphate that is generated from glycogen degradation is hydrolyzed to glucose by glucose 6-phosphatase, an enzyme present only in the liver and kidneys. Glycogen degradation thus provides a readily mobilized source of blood glucose as dietary glucose decreases, or as exercise increases the utilization of blood glucose by muscles.



Jim Bodie's treadmill exercise and most other types of moderate exercise involving whole body movement (running, skiing, dancing, tennis) increase the utilization of blood glucose and other fuels by skeletal muscles. The blood glucose is normally supplied by the stimulation of liver glycogenolysis and gluconeogenesis.



Fig. 28.2. Glycogenolysis in skeletal muscle and liver. Glycogen stores serve different functions in muscle cells and liver. In the muscle and most other cell types, glycogen stores serve as a fuel source for the generation of ATP. In the liver, glycogen stores serve as a source of blood glucose.

Regulation of glycogen synthesis serves to prevent futile cycling and waste of ATP. Futile cycling refers to a situation in which a substrate is converted to a product through one pathway, and the product converted back to the substrate through another pathway. Because the biosynthetic pathway is energy-requiring, futile cycling results in a waste of highenergy phosphate bonds. Thus, glycogen synthesis is activated when glycogen degradation is inhibited, and vice versa.

The pathways of glycogenolysis and gluconeogenesis in the liver both supply blood glucose, and, consequently, these two pathways are activated together by glucagon. Gluconeogenesis, the synthesis of glucose from amino acids and other gluconeogenic precursors (discussed in detail in Chapter 31), also forms glucose 6-phosphate, so that glucose 6-phosphatase serves as a "gateway" to the blood for both pathways (see Fig. 28.2).

III. SYNTHESIS AND DEGRADATION OF GLYCOGEN

Glycogen synthesis, like almost all the pathways of glucose metabolism, begins with the phosphorylation of glucose to glucose 6-phosphate by hexokinase or, in the liver, glucokinase (Fig. 28.3). Glucose 6-phosphate is the precursor of glycolysis, the pentose phosphate pathway, and of pathways for the synthesis of other sugars. In the pathway for glycogen synthesis, glucose 6-phosphate is converted to glucose 1-phosphate by phosphoglucomutase, a reversible reaction.

Glycogen is both formed from and degraded to glucose 1-phosphate, but the biosynthetic and degradative pathways are separate and involve different enzymes (see Fig. 28.3). The biosynthetic pathway is an energy-requiring pathway; highenergy phosphate from UTP is used to activate the glucosyl residues to UDPglucose (Fig. 28.4). In the degradative pathway, the glycosidic bonds between the glucosyl residues in glycogen are simply cleaved by the addition of phosphate to produce glucose 1-phosphate (or water to produce free glucose), and UDP-glucose is not resynthesized. The existence of separate pathways for the formation and degradation of important compounds is a common theme in metabolism. Because



Fig. 28.3. Scheme of glycogen synthesis and degradation. S1. Glucose 6-phosphate is formed from glucose by hexokinase in most cells, and glucokinase in the liver. It is a metabolic branchpoint for the pathways of glycolysis, the pentose phosphate pathway, and glycogen synthesis. S2. UDP-Glucose (UDP-G) is synthesized from glucose 1-phosphate. UDP-Glucose is the branchpoint for glycogen synthesis and other pathways requiring the addition of carbohydrate units. S3. Glycogen synthesis is catalyzed by glycogen synthase and the branching enzyme. D1. Glycogen degradation is catalyzed by glycogen phosphorylase and a debrancher enzyme. D2. Glucose 6-phosphates in the liver generates free glucose from glucose 6-phosphate.



Fig. 28.4. Formation of UDP-glucose. The high-energy phosphate bond of UTP provides the energy for the formation of a high-energy bond in UDP-glucose. Pyrophosphate (PP_i), released by the reaction, is cleaved to 2 P_i .

the synthesis and degradation pathways use different enzymes, one can be activated while the other is inhibited.

A. Glycogen Synthesis

Glycogen synthesis requires the formation of α -1,4-glycosidic bonds to link glucosy1 residues in long chains and the formation of an α -1,6 branch every 8 to 10 residues (Fig. 28.5). Most of glycogen synthesis occurs through the lengthening of the polysaccharide chains of a preexisting glycogen molecule (a glycogen primer) in which the reducing end of the glycogen is attached to the protein glycogenin. To lengthen the glycogen chains, glucosyl residues are added from UDP-glucose to the nonreducing ends of the chain by glycogen synthase. The anomeric carbon of each glucosyl residue is attached in an α -1,4 bond to the hydroxyl on carbon 4 of the terminal glucosyl residue. When the chain reaches 11 residues in length, a 6- to 8-residue piece is cleaved by amylo-4:6-transferase and reattached to a glucosyl unit by an α -1,6 bond. Both chains continue to lengthen until they are long enough to produce two new branches. This process continues, producing highly branched molecules. Glycogen synthase, the enzyme that attaches the glucosyl residues in 1,4-bonds, is the regulated step in the pathway.

The synthesis of new glycogen primer molecules also occurs. Glycogenin, the protein to which glycogen is attached, glycosylates itself (autoglycosylation) by attaching the glucosyl residue of UDP-glucose to the hydroxyl side chain of a serine residue in the protein. The protein then extends the carbohydrate chain (using UDP-glucose as the substrate) until the glucosyl chain is long enough to serve as a substrate for glycogen synthase.

B. Degradation of Glycogen

Glycogen is degraded by two enzymes, glycogen phosphorylase and the debrancher enzyme (Fig. 28.6). The enzyme glycogen phosphorylase starts at the end of a chain and successively cleaves glucosyl residues by adding phosphate to the terminal glycosidic bond, thereby releasing glucose 1-phosphate. However, glycogen phosphorylase cannot act on the glycosidic bonds of the four glucosyl residues closest to a branchpoint because the branching chain sterically hinders a proper fit into the catalytic site of the enzyme. The debrancher enzyme, which catalyzes the removal of the four residues closest to the branchpoint, has two catalytic activities: it acts as a transferase and as an α 1,6-glucosidase. As a transferase, the debrancher first removes a unit containing three glucose residues, and adds it to the end of a longer chain by an α -1,4 bond. The one glucosyl residue remaining at the 1,6-branch is hydrolyzed by the amylo-1,6-glucosidase activity of the debrancher, resulting in the release of free glucose. Thus, one glucose and approximately 7 to 9 glucose 1-phosphate residues are released for every branchpoint.



Fig. 28.5. Glycogen synthesis. See text for details.

Branching of glycogen serves two major roles; increased sites for synthesis and degradation, and enhancing the solubility of the molecule.

A genetic defect of lysosomal glucosidase, called type II glycogen storage disease, leads to the accumulation of glycogen particles in large, membrane-enclosed residual bodies, which disrupt the function of liver and muscle cells. Children with this disease usually die of heart failure at a few months of age.

0

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Glucose residue Glucose residue linked α -1,4 linked α -1,6 CCCCC Glycog 8 P_i glycogen phosphoryla 8 Glucose-1-F $\infty \alpha$ $\overline{\mathbf{m}}$ 4:4 transferase Contraction Clycogen c α−1,6-glucosidase Glucose (

) alvcogen phosphoryla Degradation continues

Fig. 28.6. Glycogen degradation. See details.



A series of inborn errors of olism, the glycogen stora eases, result from deficien the enzymes of glycogenolysis (see 28.1). Muscle glycogen phosphoryla key regulatory enzyme of glycogen de tion, is genetically different from live gen phosphorylase, and thus a perso have a defect in one and not the other. Why

do you think that a genetic deficiency in muscle glycogen phosphorylase (McArdle's disease) is a mere inconvenience, whereas a deficiency of liver glycogen phosphorylase (Hers' disease) can be lethal?

Some degradation of glycogen also occurs within lysosomes when glycogen particles become surrounded by membranes that then fuse with the lysosomal membranes. A lysosomal glucosidase hydrolyzes this glycogen to glucose.

IV. REGULATION OF GLYCOGEN SYNTHESIS AND DEGRADATION

The regulation of glycogen synthesis in different tissues matches the function of glycogen in each tissue. Liver glycogen serves principally for the support of blood glucose during fasting or during extreme need (e.g., exercise), and the degradative and biosynthetic pathways are regulated principally by changes in

| Туре | Enzyme Affected | Primary Organ Involved | Manifestations ^a |
|------|---|----------------------------------|---|
| 0 | Glycogen synthase | Liver | Hypoglycemia, hyperke- tonemia, FTT ^b early death |
| lc | Glucose 6-phosphatase (Von Gierke's disease) | Liver | Enlarged liver and kidney, growth failure, fasting hypoglycemia, acidosis, lipemia, thrombocyte dys function. Hypoglycemia the most severe. |
| II | Lysosomal α- glucosidase | All organs with lysosomes | Infantile form: early-onset progressive muscle hypo tonia, cardiac failure, deat before 2 years; juvenile form: later-onset myopa- thy with variable cardiac involvement, adultform: limb-girdle muscular dys- trophy-like features.Glyco gen deposits accumulate in lysosomes. |
| III | Amylo-1,6-glucosidase (debrancher) | Liver, skeletal muscle, heart | Fasting hypoglycemia; hepatomegaly in infancy in some. myopathic fea- tures. Glycogen deposits have short outer branches. |
| IV | Amylo-4,6-glucosidase (branching enzyme) | Liver | Hepatosplenomegaly; symptoms may arise fro a hepatic reaction to the presence of a foreign body (glycogen with long outer branches). Usually fatal. |
| V | Muscle glycogen phos- phorylase (McArdle's disease) | Skeletal muscle | Exercise-induced muscula pain, cramps, and pro- gressive weakness, sometimes with myoglobinuria |
| VI | Liver glycogen phosphorylase | Liver | Hepatomegaly, mild hypo- glycemia, good prognosis |
| VII | Phosphofructokinase-I | Muscle, red blood cells | As in type V, in addition, enzymopathic hemolysis |
| IXd | Phosphorylase kinase | Liver | As in VI. Hepatomegaly. |
| Х | cAMP-dependant Protein kinase A | Liver | Hepatomegaly. |

Table 28.1. Glycogen Storage Diseases

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^a All of these diseases but type O are characterized by increased glycogen deposits.

^b FTT = failure to thrive

^c Glucose 6-phosphatase is composed of several subunits that also transport glucose, glucose 6-phosphate, phosphate, and pyrophosphate across the endoplasmic reticulum membranes. Therefore, there are several subtypes of this disease, corresponding to defects in the different subunits.

^d There are several subtypes of this disease, corresponding to different mutations and patterns of inheritance.

| State | Regulators | Response of Tissue |
|-----------------------------|---|---|
| Fasting | Liver Blood: Glucagon ↑ Insulin ↓ Tissue: cAMP ↑ | Glycogen degradation \uparrow Glycogen synthesis \downarrow |
| Carbohydrate meal | Blood: Glucagon ↓ Insulin ↑ Glucose ↑ Tissue: cAMP ↓ Glucose ↑ | Glycogen degradation↓ Glycogen synthesis↑ |
| Exercise and stress | Blood: Epinephrine ↑ Tissue: cAMP ↑ Ca ^{2 +} -calmodulin ↑ | Glycogen degradation \uparrow Glycogen synthesis \downarrow |
| Fasting (rest) | Muscle Blood: Insulin↓ | Glycogen synthesis↓ Glucose transport↓ |
| Carbohydrate meal (rest) | Blood: Insulin ↑ | Glycogen synthesis ↑ Glucose transport ↑ |
| Exercise | Blood: Epinephrine ↑ Tissue: AMP ↑ Ca ²⁺ -calmodulin ↑ cAMP ↑ | Glycogen synthesis↓ Glycogen degradation↑ Glycolysis↑ |

Table 28.2. Regulation of Liver and Muscle Glycogen Stores^a

 a f = increased compared with other physiologic states; \downarrow = decreased compared with other physiologic states.

the insulin/glucagon ratio and by blood glucose levels, which reflect the availability of dietary glucose (Table 28.2). Degradation of liver glycogen is also activated by epinephrine, which is released in response to exercise, hypoglycemia, or other stress situations in which there is an immediate demand for blood glucose. In contrast, in skeletal muscles, glycogen is a reservoir of glucosyl units for the generation of ATP from glycolysis and glucose oxidation. As a consequence, muscle glycogenolysis is regulated principally by AMP, which signals a lack of ATP, and by Ca²⁺ released during contraction. Epinephrine, which is released in response to exercise and other stress situations, also activates skeletal muscle glycogenolysis. The glycogen stores of resting muscle decrease very little during fasting.

A. Regulation of Glycogen Metabolism in Liver

Liver glycogen is synthesized after a carbohydrate meal when blood glucose levels are elevated, and degraded as blood glucose levels decrease. When an individual eats a carbohydrate-containing meal, blood glucose levels immediately increase, insulin levels increase, and glucagon levels decrease (see Fig. 26.8). The increase of blood glucose levels and the rise of the insulin/glucagon ratio inhibit glycogen degradation and stimulate glycogen synthesis. The immediate increased transport of glucose into peripheral tissues, and storage of blood glucose as glycogen, helps to bring circulating blood glucose levels back to the normal 80- to 100-mg/dL range of the fasted state. As the length of time after a carbohydrate-containing meal increases, insulin levels decrease, and glucagon levels increase. The fall of the insulin/glucagon ratio results in inhibition of the biosynthetic pathway and



Muscle glycogen is used within the muscle to support exercise. Thus, an individual with McArdle's disease (type V glycogen storage disease) experiences no other symptoms but unusual fatigue and muscle cramps during exercise. These symptoms may be accompanied by myoglobinuria and release of muscle creatine kinase into the blood.

Liver glycogen is the first reservoir for the support of blood glucose levels, and a deficiency in glycogen phosphorylase or any of the other enzymes of liver glycogen degradation can result in fasting hypoglycemia. The hypoglycemia is usually mild because patients can still synthesize glucose from gluconeogenesis (see Table 28.1).

Maternal blood glucose readily crosses the placenta to enter the fetal circulation. During the last 9 or 10 weeks of gestation, glycogen formed from maternal glucose is deposited in the fetal liver under the influence of the insulin-dominated hormonal milieu of that period. At birth, maternal glucose supplies cease, causing a temporary physiologic drop in glucose levels in the newborn's blood, even in normal healthy infants. This drop serves as one of the signals for glucagon release from the newborn's pancreas, which, in turn, stimulates glycogenolysis. As a result, the glucose levels in the newborn return to normal.

Healthy full-term babies have adequate stores of liver glycogen to survive short (12 hours) periods of caloric deprivation provided other aspects of fuel metabolism are normal. Because Getta Carbo's mother was markedly anorexic during the critical period when the fetal liver is normally synthesizing glycogen from glucose supplied in the maternal blood, Getta's liver glycogen stores were below normal. Thus, because fetal glycogen is the major source of fuel for the newborn in the early hours of life, Getta became profoundly hypoglycemic within 5 hours of birth because of her low levels of stored carbohydrate.



Plasma glucose levels in the neonate. The normal range of blood glucose levels in the neonate lies between the two black lines. The stippled blue area represents the range of hypoglycemia in the neonate that should be treated. Treatment of neonates with blood glucose levels that fall within the dashed blue box, the zone of clinical uncertainty, is controversial. The units of plasma glucose are given in millimoles/L. Both milligrams/dL (milligrams/100 mL) and millimoles/L are used clinically for the values of blood glucose: 80 mg/dL glucose is equivalent to 5 mmol/L (5 mM). From Mehta A. Arch Dis Child 1994;70:F54.



A patient was diagnosed as an infant with type III glycogen storage disease, a deficiency of debrancher enzyme (see Table 28.1). The patient had hepatomegaly (an enlarged liver) and experienced bouts of mild hypoglycemia. To diagnose the disease, glycogen was obtained from the patient's liver by biopsy after the patient had fasted overnight and compared with normal glycogen. The glycogen samples were treated with a preparation of commercial glycogen phosphorylase and commerical debrancher enzyme. The amounts of glucose 1-phosphate and glucose produced in the assay were then measured. The ratio of glucose 1-phosphate to glucose for the normal glycogen sample was 9:1, and the ratio for the

patient was 3:1. Can you explain these results?

| Length of Fast (hours) | Glycogen Content (μmol/g liver) | Rate of Glycogenolysis (µmol/kg-min) |
|---------------------------|------------------------------------|---|
| 0 | 300 | _ |
| 2 | 260 | 4.3 |
| 4 | 216 | 4.3 |
| 24 | 42 | 1.7 |
| 64 | 16 | 0.3 |

Table 28.3. Effect of Fasting on Liver Glycogen Content in the Human

activation of the degradative pathway. As a result, liver glycogen is rapidly degraded to glucose, which is released into the blood.

Although glycogenolysis and gluconeogenesis are activated together by the same regulatory mechanisms, glycogenolysis responds more rapidly, with a greater outpouring of glucose. A substantial proportion of liver glycogen is degraded within the first few hours after eating (Table 28.3). The rate of glycogenolysis is fairly constant for the first 22 hours, but in a prolonged fast the rate decreases significantly as the liver glycogen supplies dwindle. Liver glycogen stores are, therefore, a rapidly rebuilt and degraded store of glucose, ever responsive to small and rapid changes of blood glucose levels.

1. NOMENCLATURE CONCERNS WITH ENZYMES METABOLIZING GLYCOGEN

Both glycogen phosphorylase and glycogen synthase will be covalently modified to regulate their activity (Fig. 28.7). When activated by covalent modification, glycogen phosphorylase is referred to as glycogen phosphorylase a (remember a for active); when the covalent modification is removed, and the enzyme is inactive, it is referred to as glycogen phosphorylase b. Glycogen synthase, when not covalently modified is active, and can be designated glycogen synthase a or glycogen synthase I (the I stands for *independent* of modifiers for activity). When glycogen synthase is covalently modified, it is inactive, in the form of glycogen synthase b or glycogen synthase **D** (for *dependent* on a modifier for activity).

REGULATION OF LIVER GLYCOGEN METABOLISM BY INSULIN 2. AND GLUCAGON

Insulin and glucagon regulate liver glycogen metabolism by changing the phosphorylation state of glycogen phosphorylase in the degradative pathway and glycogen synthase in the biosynthetic pathway. An increase of glucagon and decrease of insulin during the fasting state initiates a cAMP-directed phosphorylation cascade, which results in the phosphorylation of glycogen phosphorylase to an active enzyme, and the



Fig. 28.7. The conversion of active and inactive forms of glycogen phosphorylase (A) and glycogen synthase (B). Note how the nomenclature changes depending on the phosphorylation and activity state of the enzyme.

phosphorylation of glycogen synthase to an inactive enzyme (Fig. 28.8). As a consequence, glycogen degradation is stimulated, and glycogen synthesis is inhibited.

3. GLUCAGON ACTIVATES A PHOSPHORYLATION CASCADE THAT CONVERTS GLYCOGEN PHOSPHORYLASE b TO GLYCOGEN PHOSPHORYLASE a

Glucagon regulates glycogen metabolism through its intracellular second messenger cAMP and protein kinase A (see Chapter 26). Glucagon, by binding to its cell membrane receptor, transmits a signal through G proteins that activates adenylate cyclase, causing cAMP levels to increase (see Fig. 28.8). cAMP binds to the regulatory subunits of protein kinase A, which dissociate from the catalytic subunits. The catalytic subunits of protein kinase A are activated by the dissociation and phosphorylate the enzyme phosphorylase kinase, activating it. Phosphorylase kinase is the protein kinase that converts the inactive liver glycogen phosphorylase b conformer to the active glycogen phosphorylase a conformer by transferring a phosphate from ATP to a specific serine residue on the

With a deficiency of debrancher enzyme, but normal levels of glycogen phosphorylase, the glycogen chains of the patient could be degraded in vivo only to within 4 residues of the branchpoint. When the glycogen samples were treated with the commercial preparation containing normal enzymes, one glucose residue was released for each α -1,6 branch. However, in the patient's glycogen sample, with the short outer branches, three glucose 1-phosphates and one glucose residue were obtained for each α-1,6 branch. Normal glycogen has 8-10 glucosyl residues per branch, and thus gives a ratio of approximately 9 moles of glucose 1-phosphate to 1 mole of glucose.



Fig. 28.8. Regulation of glycogen synthesis and degradation in the liver. 1. Glucagon binding to the glucagon receptor or epinephrine binding to a β receptor in the liver activates adenylate cyclase, via G proteins, which synthesizes cAMP from ATP. 2. cAMP binds to protein kinase A (cAMP-dependent protein kinase), thereby activating the catalytic subunits. 3. Protein kinase A activates phosphorylase kinase by phosphorylation. 4. Phosphorylase kinase adds a phosphate to specific serine residues on glycogen phosphorylase b, thereby converting it to the active glycogen phosphorylase a. 5. Protein kinase A also phosphorylates glycogen synthase, thereby decreasing its activity. 6. As a result of the inhibition of glycogen synthase and the activation of glycogen phosphorylase, glycogen is degraded to glucose 1-phosphate. The blue dashed lines denote reactions that are decreased in the livers of fasting individuals.

To remember whether a particular enzyme has been activated or inhibited by cAMP-dependent phosphorylation, consider whether it makes sense for the enzyme to be active or inhibited under fasting conditions (In a **PHast**, **PHosphorylate**).

Most of the enzymes that are regulated by phosphorylation have multiple phosphorylation sites. Glycogen phosphorylase, which has only one serine per subunit, and can be phosphorylated only by phosphorylase kinase, is the exception. For some enzymes, the phosphorylation sites are antagonistic, and phosphorylation initiated by one hormone counteracts the effects of other hormones. For other enzymes, the phosphorylation sites are synergistic, and phosphorylation at one site stimulated by one hormone can act synergistically with phosphorylation at another site.



Most of the enzymes that are regulated by phosphorylation also can be converted to the active confor-

mation by allosteric effectors. Glycogen synthase b, the less active form of glycogen synthase, can be activated by the accumulation of glucose 6-phosphate above physiologic levels. The activation of glycogen synthase by glucose 6-phosphate may be important in individuals with glucose 6-phosphatase deficiency, a disorder known as type I or von Gierke's glycogen storage disease. When glucose 6-phosphate produced from gluconeogenesis accumulates in the liver, it activates glycogen synthesis even though the individual may be hypoglycemic and have low insulin levels. Glucose 1-phosphate is also elevated, resulting in the inhibition of glycogen phosphorylase. As a consequence, large glycogen deposits accumulate, and hepatomegaly occurs.

phosphorylase subunits. As a result of the activation of glycogen phosphorylase, glycogenolysis is stimulated.

4. INHIBITION OF GLYCOGEN SYNTHASE BY GLUCAGON-DIRECTED PHOSPHORYLATION

When glycogen degradation is activated by the cAMP-stimulated phosphorylation cascade, glycogen synthesis is simultaneously inhibited. The enzyme glycogen synthase is also phosphorylated by protein kinase A, but this phosphorylation results in a less active form, glycogen synthase b.

The phosphorylation of glycogen synthase is far more complex than glycogen phosphorylase. Glycogen synthase has multiple phosphorylation sites and is acted on by up to 10 different protein kinases. Phosphorylation by protein kinase A does not, by itself, inactivate glycogen synthase. Instead, phosphorylation by protein kinase A facilitates the subsequent addition of phosphate groups by other kinases, and these inactivate the enzyme. A term that has been applied to changes of activity resulting from multiple phosphorylation is hierarchical or synergistic phosphorylation-the phosphorylation of one site makes another site more reactive and easier to phosphorylate by a different protein kinase

5. REGULATION OF PROTEIN PHOSPHATASES

At the same time that protein kinase A and phosphorylase kinase are adding phosphate groups to enzymes, the protein phosphatases that remove this phosphate are inhibited. Protein phosphatases remove the phosphate groups, bound to serine or other residues of enzymes, by hydrolysis. Hepatic protein phosphatase-1 (hepatic PP-1), one of the major protein phosphatases involved in glycogen metabolism, removes phosphate groups from phosphorylase kinase, glycogen phosphorylase, and glycogen synthase. During fasting, hepatic PP-1 is inactivated by a number of mechanisms. One is dissociation from the glycogen particle, such that the substrates are no longer available to the phosphatase. A second is the binding of inhibitor proteins, such as the protein called inhibitor-1, which, when phosphorylated by a glucagon (or epinephrine)-directed mechanism, binds to and inhibits phosphatase action. Insulin indirectly activates hepatic PP-1 through its own signal transduction cascade initiated at the insulin receptor tyrosine kinase.

6. INSULIN IN LIVER GLYCOGEN METABOLISM

Insulin is antagonistic to glucagon in the degradation and synthesis of glycogen. The glucose level in the blood is the signal controlling the secretion of insulin and glucagon. Glucose stimulates insulin release and suppresses glucagon release; one increases while the other decreases after a high carbohydrate meal. However, insulin levels in the blood change to a greater degree with the fasting-feeding cycle than the glucagon levels, and thus insulin is considered the principal regulator of glycogen synthesis and degradation. The role of insulin in glycogen metabolism is often overlooked because the mechanisms by which insulin reverses all of the effects of glucagon on individual metabolic enzymes is still under investigation. In addition to the activation of hepatic PP-1 through the insulin receptor tyrosine kinase phosphorylation cascade, insulin may activate the phosphodiesterase that converts cAMP to AMP, thereby decreasing cAMP levels and inactivating protein kinase A. Regardless of the mechanisms involved, insulin is able to reverse all of the effects of glucagon and is the most important hormonal regulator of blood glucose levels.

BLOOD GLUCOSE LEVELS AND GLYCOGEN SYNTHESIS 7. AND DEGRADATION

When an individual eats a high-carbohydrate meal, glycogen degradation immediately stops. Although the changes in insulin and glucagon levels are relatively rapid (10–15 minutes), the direct inhibitory effect of rising glucose levels on glycogen degradation is even more rapid. Glucose, as an allosteric effector, inhibits liver glycogen phosphorylase a by stimulating dephosphorylation of this enzyme. As insulin levels rise and glucagon levels fall, cAMP levels decrease and protein kinase A reassociates with its inhibitory subunits and becomes inactive. The protein phosphatases are activated, and phosphorylase a and glycogen synthase b are dephosphorylated. The collective result of these effects is rapid inhibition of glycogen degradation, and rapid activation of glycogen synthesis.

8. EPINEPHRINE AND CALCIUM IN THE REGULATION OF LIVER GLYCOGEN

Epinephrine, the "fight-or-flight" hormone, is released from the adrenal medulla in response to neural signals reflecting an increased demand for glucose. To flee from a dangerous situation, skeletal muscles use increased amounts of blood glucose to generate ATP. As a result, liver glycogenolysis must be stimulated. In the liver, epinephrine stimulates glycogenolysis through two different types of receptors, the α - and β -agonist receptors.

a. EPINEPHRINE ACTING AT THE β-RECEPTORS

Epinephrine, acting at the β -receptors, transmits a signal through G proteins to adenylate cyclase, which increases cAMP and activates protein kinase A. Hence, regulation of glycogen degradation and synthesis in liver by epinephrine and glucagon are similar (see Fig. 28.8).

b. EPINEPHRINE ACTING AT α-RECEPTORS

Epinephrine also binds to α -receptors in the liver. This binding activates glycogenolysis and inhibits glycogen synthesis principally by increasing the Ca²⁺ levels in the liver. The effects of epinephrine at the α -agonist receptor are mediated by the phosphatidylinositol bisphosphate (PIP₂)-Ca²⁺ signal transduction system, one of the principal intracellular second messenger systems employed by many hormones (Fig. 28.9) (see Chapter 11).

In the PIP_2 -Ca²⁺ signal transduction system, the signal is transferred from the epinephrine receptor to membrane-bound phospholipase C by G proteins. Phospholipase C hydrolyzes PIP2 to form diacylglycerol (DAG) and inositol trisphosphate (IP₃). IP₃ stimulates the release of Ca^{2+} from the endoplasmic reticulum. Ca²⁺ and DAG activate protein kinase C. The amount of calcium bound to one of the calcium-binding proteins, calmodulin, is also increased.

Calcium/calmodulin associates as a subunit with a number of enzymes and modifies their activities. It binds to inactive phosphorylase kinase, thereby partially activating this enzyme. (The fully activated enzyme is both bound to the calcium/calmodulin subunit and phosphorylated.) Phosphorylase kinase then phosphorylates glycogen phosphorylase b, thereby activating glycogen degradation. Calcium/calmodulin is also a modifier protein that activates one of the glycogen synthase kinases (calcium/calmodulin synthase kinase). Protein kinase C, calcium/calmodulin synthase kinase, and phosphorylase kinase all phosphorylate glycogen synthase at different serine residues on the enzyme, thereby inhibiting glycogen synthase and thus glycogen synthesis.



An inability of liver and muscle to store glucose as glycogen contributes to the hyperglycemia in patients, such as Di Abietes, with type 1 diabetes mellitus and in patients, such as Ann Sulin, with type 2 diabetes mellitus. The absence of insulin in type 1 diabetes mellitus patients and the high levels of glucagon result in decreased activity of glycogen synthase. Glycogen synthesis in skeletal muscles of type 1 patients is also limited by the lack of insulinstimulated glucose transport. Insulin resistance in type 2 patients has the same effect.

An injection of insulin suppresses glucagon release and alters the insulin/glucagon ratio. The result is rapid uptake of glucose into skeletal muscle and rapid conversion of glucose to glycogen in skeletal muscle and liver.

In the neonate, the release of epinephrine during labor and birth normally contributes to restoring blood glucose levels. Unfortunately, Getta Carbo did not have adequate liver glycogen stores to support a rise in her blood glucose levels.



Fig. 28.9. Regulation of glycogen synthesis and degradation by epinephrine and Ca^{2+} . 1. The effect of epinephrine binding to α -agonist receptors in liver transmits a signal via G proteins to phospholipase C, which hydrolyzes PIP₂ to DAG and IP₃. 2. IP₃ stimulates the release of Ca²⁺ from the endoplasmic reticulum. 3. Ca²⁺ binds to the modifier protein calmodulin, which activates calmodulin-dependent protein kinase and phosphorylase kinase. Both Ca²⁺ and DAG activate protein kinase C. 4. These three kinases phosphorylate glycogen synthase at different sites and decrease its activity. 5. Phosphorylase kinase phosphorylates glycogen phosphorylase b to the active form. It therefore activates glycogenolysis as well as inhibiting glycogen synthesis.

The effect of epinephrine in the liver, therefore, enhances or is synergistic with the effects of glucagon. Epinephrine release during bouts of hypoglycemia or during exercise can stimulate hepatic glycogenolysis and inhibit glycogen synthesis very rapidly.

B. Regulation of Glycogen Synthesis and Degradation in Skeletal Muscle

The regulation of glycogenolysis in skeletal muscle is related to the availability of ATP for muscular contraction. Skeletal muscle glycogen produces glucose

Jim Bodie gradually regained consciousness with continued infusions of highconcentration glucose titrated to keep his serum glucose level between 120 and 160 mg/dL. Although he remained somnolent and moderately confused over the next 12 hours, he was eventually able to tell his physicians that he had self-injected approximately 80 units of regular (short-acting) insulin every 6 hours while eating a highcarbohydrate diet for the last 2 days preceding his seizure. Normal subjects under basal conditions secrete an average of 40 units of insulin daily. He had last injected insulin just before exercising. An article in a body-building magazine that he had recently read cited the anabolic effects of insulin on increasing muscle mass. He had purchased the insulin and necessary syringes from the same underground drug source from whom he regularly bought his anabolic steroids.

Normally, muscle glycogenolysis supplies the glucose required for the kinds of highintensity exercise that require anaerobic glycolysis, such as weight-lifting. Jim's treadmill exercise also uses blood glucose, which is supplied by liver glycogenolysis. The high serum insulin levels, resulting from the injection he gave himself just before his workout, activated both glucose transport into skeletal muscle and glycogen synthesis, while inhibiting glycogen degradation. His exercise, which would continue to use blood glucose, could normally be supported by breakdown of liver glycogen. However, glycogen synthesis in his liver was activated, and glycogen degradation was inhibited by the insulin injection. 1-phosphate and a small amount of free glucose. Glucose 1-phosphate is converted to glucose 6-phosphate, which is committed to the glycolytic pathway; the absence of glucose 6-phosphatase in skeletal muscle prevents conversion of the glucosyl units from glycogen to blood glucose. Skeletal muscle glycogen is therefore degraded only when the demand for ATP generation from glycolysis is high. The highest demands occur during anaerobic glycolysis, which requires more moles of glucose for each ATP produced than oxidation of glucose to CO_2 (see Chapter 22). Anaerobic glycolytic enzymes, and higher levels of glycogen, or fast-twitch glycolytic fibers. It occurs most frequently at the onset of exercise–before vasodilation occurs to bring in blood-borne fuels. The regulation of skeletal muscle glycogen degradation therefore must respond very rapidly to the need for ATP, indicated by the increase in AMP.

The regulation of skeletal muscle glycogen synthesis and degradation differs from that in liver in several important respects: (*a*) glucagon has no effect on muscle, and thus glycogen levels in muscle do not vary with the fasting/feeding state; (*b*) AMP is an allosteric activator of the muscle isozyme of glycogen phosphorylase, but not liver glycogen phosphorylase (Fig. 28.10); (*c*) the effects of Ca^{2+} in muscle result principally from the release of Ca^{2+} from the sarcoplasmic reticulum after neural stimulation, and not from epinephrine-stimulated uptake; (*d*) glucose is not a physiologic inhibitor of glycogen phosphorylase a in muscle; (*e*) glycogen is a stronger feedback inhibitor of muscle glycogen synthase than of liver glycogen synthase, resulting in a smaller amount of stored glycogen per gram weight of muscle tissue. However, the effects of epinephrine-stimulated phosphorylation by protein kinase A on skeletal muscle glycogen degradation and glycogen synthesis are similar to those occurring in liver (see Fig. 28.8).

Muscle glycogen phosphorylase is a genetically distinct isoenzyme of liver glycogen phosphorylase and contains an amino acid sequence that has a purine nucleotide



Fig. 28.10. Activation of muscle glycogen phosphorylase during exercise. Glycogenolysis in skeletal muscle is initiated by muscle contraction, neural impulses, and epinephrine. 1. AMP produced from the degradation of ATP during muscular contraction allosterically activates glycogen phosphorylase b. 2. The neural impulses that initiate contraction release Ca^{2+} from the sarcoplasmic reticulum. The Ca^{2+} binds to calmodulin, which is a modifier protein that activates phosphorylase kinase. 3. Phosphorylase kinase is also activated through phosphorylation by protein kinase A. The formation of cAMP and the resultant activation of protein kinase A are initiated by the binding of epinephrine to plasma membrane receptors.

binding site. When AMP binds to this site, it changes the conformation at the catalytic site to a structure very similar to that in the phosphorylated enzyme (see Fig. 9.9). Thus, hydrolysis of ATP to ADP and the consequent increase of AMP generated by adenylate kinase during muscular contraction can directly stimulate glycogenolysis to provide fuel for the glycolytic pathway. AMP also stimulates glycolysis by activating phosphofructokinase-1, so this one effector activates both glycogenolysis and glycolysis. The activation of the calcium/calmodulin subunit of phosphorylase kinase by the Ca^{2+} released from the sarcoplasmic reticulum during muscle contraction also provides a direct and rapid means of stimulating glycogen degradation.

CLINICAL COMMENTS

Getta Carbo's hypoglycemia illustrates the importance of glycogen stores in the neonate. At birth, the fetus must make two major adjustments in the way fuels are used: it must adapt to using a greater variety of fuels than were available in utero, and it must adjust to intermittent feeding. In utero, the fetus receives a relatively constant supply of glucose from the maternal circulation through the placenta, producing a level of glucose in the fetus that approximates 75% of maternal blood levels. With regard to the hormonal regulation of fuel utilization in utero, fetal tissues function in an environment dominated by insulin, which promotes growth. During the last 10 weeks of gestation, this hormonal milieu leads to glycogen formation and storage. At birth, the infant's diet changes to one containing greater amounts of fat and lactose (galactose and glucose in equal ratio), presented at intervals rather than in a constant fashion. At the same time, the neonate's need for glucose will be relatively larger than that of the adult because the newborn's ratio of brain to liver weight is greater. Thus, the infant has even greater difficulty in maintaining glucose homeostasis than the adult.

At the moment that the umbilical cord is clamped, the normal neonate is faced with a metabolic problem: the high insulin levels of late fetal existence must be quickly reversed to prevent hypoglycemia. This reversal is accomplished through the secretion of the counterregulatory hormones epinephrine and glucagon. Glucagon release is triggered by the normal decline of blood glucose after birth. The neural response that stimulates the release of both glucagon and epinephrine is activated by the anoxia, cord clamping, and tactile stimulation that are part of a normal delivery. These responses have been referred to as the "normal sensor function" of the neonate.

Within 3 to 4 hours of birth, these counterregulatory hormones reestablish normal serum glucose levels in the newborn's blood through their glycogenolytic and gluconeogenic actions. The failure of Getta's normal "sensor function" was partly the result of maternal malnutrition, which resulted in an inadequate deposition of glycogen in Getta's liver before birth. The consequence was a serious degree of postnatal hypoglycemia.

The ability to maintain glucose homeostasis during the first few days of life also depends on the activation of gluconeogenesis and the mobilization of fatty acids. Fatty acid oxidation in the liver not only promotes gluconeogenesis (see Chapter 31) but generates ketone bodies. The neonatal brain has an enhanced capacity to use ketone bodies relative to that of infants (fourfold) and adults (40-fold). This ability is consistent with the relatively high fat content of breast milk.

Jim Bodie attempted to build up his muscle mass with androgens and with insulin. The anabolic (nitrogen-retaining) effects of androgens on skeletal muscle cells enhance muscle mass by increasing amino acid flux into muscle and by stimulating protein synthesis. Exogenous insulin has the potential to increase muscle mass by similar actions and also by increasing the content of muscle glycogen.

The most serious side effect of exogenous insulin administration is the development of severe hypoglycemia, such as occurred in **Jim Bodie**. The immediate adverse effect relates to an inadequate flow of fuel (glucose) to the metabolizing brain. When hypoglycemia is extreme, the patient may suffer a seizure and, if the hypoglycemia worsens, may lapse into a coma and die. If untreated, irreversible brain damage occurs in those who survive.

BIOCHEMICAL COMMENTS

The regulatory effect of insulin is frequently described as one of activating protein phosphatases. The effects of insulin on the regulation of hepatic and skeletal PP-1 are complex and not yet fully understood.

PP-1 is targeted to glycogen particles by four tissue-specific targeting factors: G_M is found in striated muscle; G_L is found in liver; PTG (protein targeting to glycogen) is found in almost all tissues; and R6 is also found in most tissues. The targeting factors bind to PP-1 and glycogen and localize the PP-1 to the glycogen particles, where the enzyme will be physically close to the regulated enzymes of glycogen metabolism, phosphorylase kinase, glycogen phosphorylase, and glycogen synthase. Regulation of the phosphatase will involve complex interactions between the target enzymes, the targeting subunit, the phosphatase, and protein inhibitor I. The interactions are also tissue specific in the case of G_M and G_L .

A simplistic view of hepatic PP-1 regulation is as follows. PP-1 is bound to G_L and the glycogen particle. Glycogen phosphorylase a binds to the complex, and in so doing alters the conformation of PP-1, rendering it inactive. When glucose levels rise in the blood (for example, after eating a meal), the glucose is transported into the liver cells via GLUT 2 transporters, and the intracellular glucose level increases. Glucose can bind to glycogen phosphorylase a, which relieves the inhibition of PP-1, and glycogen phosphorylase a will be converted to glycogen phosphorylase b by active PP-1. Additionally, as the intracellular glucose is converted to glucose 6-phosphate by glucokinase, the increase in glucose-6-P levels activates PP-1 to dephosphorylate glycogen synthase, thereby activating the glycogen synthesizing enzyme. The complicated view of hepatic PP-1 regulation also must take into account the PTG-PP-1 interactions (PTG is also expressed in the liver) and the kinases that are activated by either insulin or glucagon/epinephrine, which lead to alterations in glycogen metabolizing enzyme activities.

In contrast to hepatic regulation, muscle regulation of PP-1 activity via G_M is directly responsive to phosphorylation by kinases. A phosphorylation event that appears to be critical is that of ser-67 in G_M . Phosphorylation of ser-67 by the cAMPdependent protein kinase leads to a dissociation of PP-1 from G_M , and, therefore, the phosphatase is removed from its substrates and cannot reverse the phosphorylation of the target enzymes. If ser-67 is altered to a threonine, the phosphorylation at that site is blocked, and PP-1 does not dissociate from G_M . This indicates the importance of the phosphorylation event in regulating PP-1 action in the muscle.

Future work will be needed before a complete understanding of how insulin reverses glucagon/epinephrine stimulation of glycogenolysis is obtained.

Suggested Readings

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REVIEW QUESTIONS—CHAPTER 28

- 1. The degradation of glycogen normally produces which of the following?
 - (A) More glucose than glucose 1-phosphate
 - (B) More glucose 1-phosphate than glucose
 - (C) Equal amounts of glucose and glucose 1-phosphate
 - (D) Neither glucose or glucose 1-phosphate
 - (E) Only glucose 1-phosphate
- 2. A patient has large deposits of liver glycogen, which, after an overnight fast, had shorter than normal branches. This abnormality could be caused by a defective form of which of the following proteins or activities?
 - (A) Glycogen phosphorylase
 - (B) Glucagon receptor
 - (C) Glycogenin
 - (D) Amylo 1,6 glucosidase
 - (E) Amylo 4,6 transferase
- 3. An adolescent patient with a deficiency of muscle phosphorylase was examined while exercising her forearm by squeezing a rubber ball. Compared with a normal person performing the same exercise, this patient would exhibit which of the following?
 - (A) Exercise for a longer time without fatigue
 - (B) Have increased glucose levels in blood drawn from her forearm
 - (C) Have decreased lactate levels in blood drawn from her forearm
 - (D) Have lower levels of glycogen in biopsy specimens from her forearm muscle
 - (E) Hyperglycemia
- 4. In a glucose tolerance test, an individual in the basal metabolic state ingests a large amount of glucose. If the individual is normal, this ingestion should result in which of the following?
 - (A) An enhanced glycogen synthase activity in the liver
 - (B) An increased ratio of glycogen phosphorylase a to glycogen phosphorylase b in the liver
 - (C) An increased rate of lactate formation by red blood cells
 - (D) An inhibition of protein phosphatase I activity in the liver
 - (E) An increase of cAMP levels in the liver
- 5. Consider a type 1 diabetic who has neglected to take insulin for the past 72 hours and has not eaten much as well. Which of the following best describes the activity level of hepatic enzymes involved in glycogen metabolism under these conditions?

| Glycogen Synthase | Phosphorylase Kinase | Glycogen Phosphorylase |
|-------------------|----------------------|------------------------|
| (A) Active | Active | Active |
| (B) Active | Active | Inactive |
| (C) Active | Inactive | Inactive |
| (D) Inactive | Inactive | Inactive |
| (E) Inactive | Active | Inactive |
| (F) Inactive | Active | Active |