Comp. by: Gkamatchi Stage: Proof Chapter No.: 8 Title Name: El_Pelley
Page Number: 0 Date:18/7/11 Time:21:06:06

B978-0-323-07446-9.00008-8, 00008

c0040 Gluconeogenesis and Glycogen Metabolism 8

CONTENTS

s0010 PATHWAY REACTION STEPS

s0015 Gluconeogenesis—Oxaloacetate to Glucose

p0110 Gluconeogenesis is an anabolic pathway that synthesizes glucose from nonglucose precursors (lactate, amino acids, and glycerol). Since the nonglucose precursors must be mobilized and transported to the liver, this source of glucose does not have the rapid response found with glycogen mobilization (covered later in more detail).

p0115 The gluconeogenic pathway is not a simple reversal of glycolysis (Fig. 8-1). There are three steps in glycolysis that are energetically irreversible: hexokinase, phosphofructokinase (PFK), and pyruvate kinase. The gluconeogenic pathway is thus a mixture of six enzymes that are needed to bypass these three irreversible steps, plus the remainder of the glycolytic steps, which are reversible.

Bypass for Pyruvate Kinase (Phosphoenolpyruvate → Pyruvate) s0020

Pyruvate carboxylase s0025

Carboxylation of pyruvate produces oxaloacetate (OAA). This is an energy-requiring reaction that uses adenosine triphosphate (ATP). p0120

Malate dehydrogenase (mitochondrial) s0030

Reduction of OAA produces malate, which can be transported out of the mitochondrion. This step simultaneously transports carbon skeletons and reducing equivalents to the cytoplasm for gluconeogenesis. p0125

Malate dehydrogenase (cytoplasmic) s0035

Oxidation of malate in the cytoplasm regenerates OAA and nicotinamide adenine dinucleotide (NADH). The latter is needed at reaction step 8 (glyceraldehyde-3-phosphate dehydrogenase; see later discussion). p0130

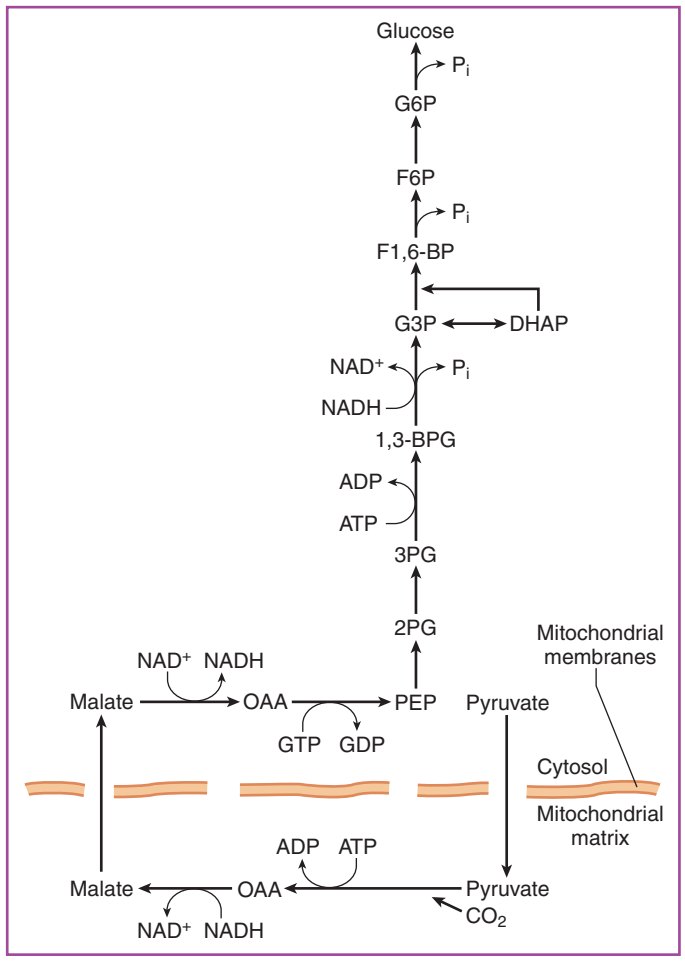
Phosphoenolpyruvate carboxykinase s0040

Decarboxylation of OAA to produce phosphoenolpyruvate (PEP) is accompanied by phosphorylation using guanosine triphosphate (GTP) instead of ATP. p0135

KEY POINTS ABOUT GLUCONEOGENESIS b0010

- Gluconeogenesis is not a simple reversal of glycolysis; three irreversible glycolytic steps must be bypassed. u0110
- The gluconeogenic pathway begins in the mitochondrion and ends in the cytoplasm; it consumes 6 ATP per glucose. u0115
- Gluconeogenesis is regulated at the pyruvate carboxylase step, where acetyl-coenzyme A (CoA) from fatty acid oxidation serves as an allosteric activator; glycolysis is reciprocally regulated to avoid futile cycles. u0120
- The carbon skeletons come from amino acids, lactate, and glycerol, and never from acetyl-CoA. u0125

B978-0-323-07446-9.00008-8, 00008



f0010 **Figure 8-1.** The gluconeogenic pathway.

Bypass for Phosphofructokinase (F1,6-BP → F6P) s0045

Fructose 1,6-bisphosphatase s0050

Dephosphorylation of F1,6-BP produces fructose 6-phosphate (F6P) and inorganic phosphate. p0165

Bypass for Hexokinase (G6P → Glucose) s0055

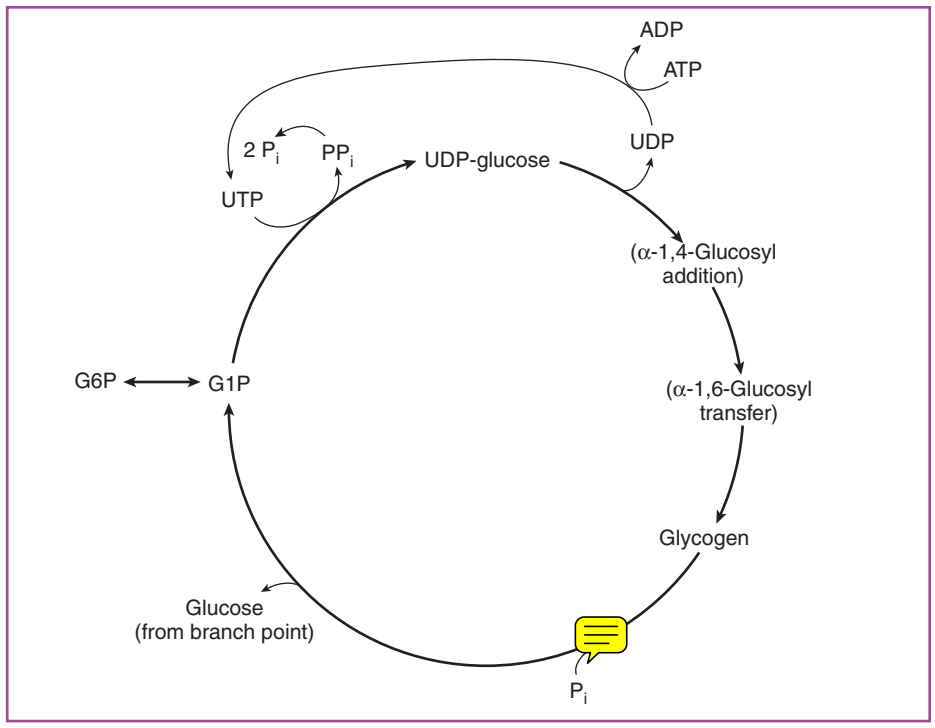
Glucose-6-phosphatase s0060

Dephosphorylation of glucose 6-phosphate (G6P) produces free glucose that can be released into the bloodstream. p0170

Glycogen Metabolism—Glucose 6-Phosphate to and from Glycogen s0065

Glycogen serves the unique purpose of providing a rapid source of glucose. The liver stores glycogen to provide rapid replenishment of blood glucose during fasting. Muscle and other tissues store glycogen as a source of intracellular glucose to be oxidized for energy. As noted above, gluconeogenesis provides a delayed source of glucose. The requirement for mobilization of free fatty acids (FFA) and amino acids delays any significant supply of glucose from gluconeogenesis for several hours. p0175

Glycogen synthesis (glycogenesis) involves the creation of an activated precursor and then the linking of the precursor into a linear growing polymer. Branching is achieved by removing and rejoining short sections from the end of the linear polymers. Glycogenolysis is likewise relatively simple. Only one enzyme is needed to release most of the glucose from glycogen; a second enzyme is needed to remove the branching sugar (Fig. 8-2). p0180



f0015 **Figure 8-2.** Glycogen synthesis and glycogenolysis pathways.

B978-0-323-07446-9.00008-8, 00008

s0070 ### *Three Reactions Create the Glucose Donor Uridine Diphosphate Glucose*

s0075 **Phosphoglucomutase**

p0185 G6P is converted to glucose 1-phosphate (G1P) in a reversible reaction.

s0080 **Uridine diphosphate glucose pyrophosphorylase**

p0190 G1P is esterified with uridine triphosphate (UTP) to produce uridine diphosphate (UDP)-glucose and pyrophosphate.

s0085 **Pyrophosphatase**

p0195 This irreversible reaction produces inorganic phosphate and provides the driving force for glycogen synthesis.

s0090 ### *Two Reactions Use Uridine Diphosphate Glucose to Build Glycogen*

s0095 **Glycogen synthase**

p0200 Glucose units from UDP-glucose are always transferred in an α-1,4 linkage to the C4 terminus of an existing amylose chain. Since the UDP is released from carbon 1, the ring structure of the newly added glucose residue is held closed in the ring form (nonreducing).

s0100 **Branching enzyme**

p0205 As the linear polymer grows, seven terminal residues are removed from an 11-residue amylose chain; it is reattached in an α-1,6 linkage to form a branch point. Branches are always at least four residues from the previous branch point.

s0105 ### *One Reaction Depolymerizes Glycogen to Produce Glucose 1-Phosphate*

s0110 **Glycogen phosphorylase**

p0210 The glycosidic α-1,4 bond is cleaved with inorganic phosphate to produce G1P monomers. Phosphorylase requires pyridoxal 5´-phosphate as a cofactor.

s0115 ### *One Enzyme Catalyzes Two Reactions to Debranch Glycogen*

p0215 Debranching enzyme contains two functional domains, a glucosyltransferase and a glucosidase, that remove the branches in glycogen.

s0120 **Oligo 1,4 → 1,4 glucan transferase (glucosyltransferase)**

p0220 Phosphorylase stops four glycosyl residues from branch points, producing a structure called a limit dextrin. Each branch point has two four-glycosyl residue branches. Glucosyltransferase moves three glycosyl residues from one branch to the end of the other branch.

s0125 **α-1,6–Glucosidase (amylo-1,6–glucosidase)**

p0225 The remaining glycosyl residue is released as free glucose. Thus about 80% of glucose is released from glycogen in the activated form: G1P.

s0130 ### *One Reaction Converts Glucose 1-Phosphate Back to Glucose 6-Phosphate*

s0135 **Phosphoglucomutase**

p0230 G1P is freely interconverted with G6P in a reversible equilibrium.

b0015 **KEY POINTS ABOUT GLYCOGEN METABOLISM**

- u0130 Glycogen synthesis and degradation flow through G1P, which is in equilibrium with G6P.
- u0135 The D form of glycogen synthase can react quickly to sudden changes in blood glucose; it is allosterically activated by G6P.
- u0140 The highly branched structure of glycogen allows for rapid release of glucose, since phosphorylase acts on the end terminal residues.
- u0145 In addition to its role as a precursor for glycogen synthesis, UDP-glucose helps detoxify waste products and drugs.
- u0150 Two high-energy bonds are consumed for each glucose stored in glycogen.
- u0155 Cyclic adenosine monophosphate (cAMP)–directed phosphorylation has reciprocal regulatory effects on glycogen synthase (inhibition) and phosphorylase (activation).

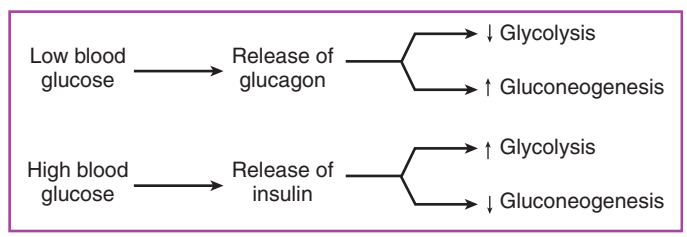
s0140 ## REGULATED REACTIONS

s0145 ### Regulation of Gluconeogenesis

p0270 Since gluconeogenesis and glycolysis have opposite directions, their response to regulatory signals must be opposite or they would work against each other in futile cycles (i.e., energy would be used to synthesize a product, which is then immediately hydrolyzed by a reaction that effectively reverses the biosynthetic reaction. Reciprocal regulation refers to coordinate regulation of opposing pathways by the same metabolic signal (Fig. 8-3).

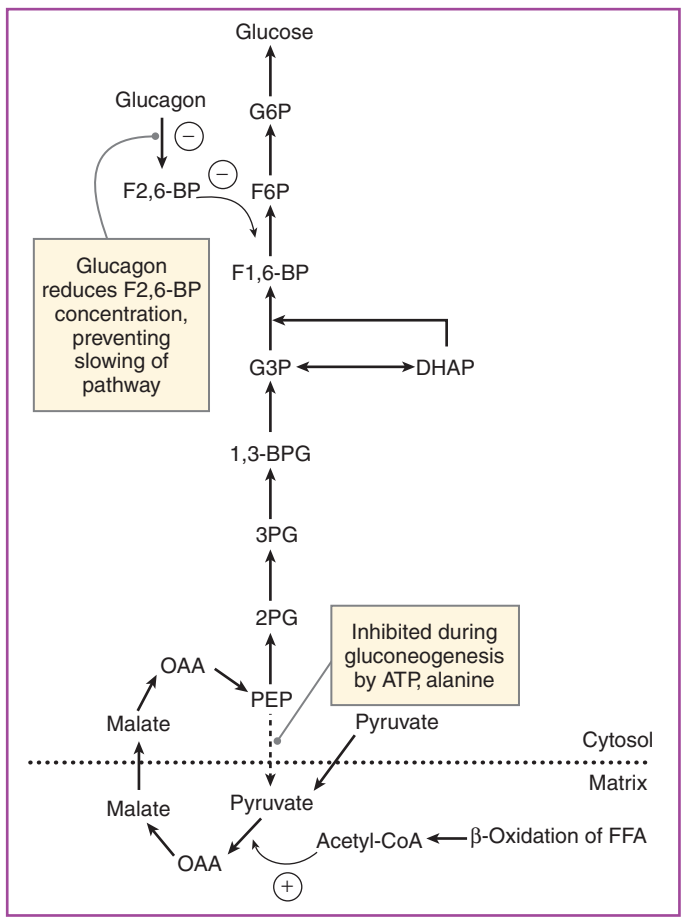
p0275 The gluconeogenesis pathway is primarily regulated at the pyruvate carboxylase reaction. This enzyme controls the entry of pyruvate into gluconeogenesis, and it requires acetyl-CoA as a positive allosteric effector. Thus when fatty acids are mobilized to provide the energy for glucose synthesis, the acetyl-CoA produced during β-oxidation serves as a chemical signal to increase this first step in gluconeogenesis (Fig. 8-4). Overexpression of pyruvate carboxylase in mice produces diabetes.

p0280 Regulation also occurs at the fructose 1,6-bisphosphatase reaction. To prevent futile cycling with the phosphofructokinase (PFK) reaction during the fasting state, glucagon action causes fructose 2,6-bisphosphate (F2,6-BP) concentrations to decrease. This simultaneously removes both the inhibition



f0020 **Figure 8-3.** Reciprocal regulation of glycolysis and gluconeogenesis.

B978-0-323-07446-9.00008-8, 00008



f0025 **Figure 8-4.** Regulation of pyruvate carboxylase and fructose 1,6-bisphosphatase during gluconeogenesis.

of fructose 1,6-bisphosphatase and the stimulation of PFK by F2,6-BP.

p0285 The flow of carbon skeletons for glucose synthesis into the gluconeogenic pathway is favored by an increased supply of amino acids from skeletal muscle to provide increased amounts of OAA. The inhibition of pyruvate dehydrogenase also prevents a flow of pyruvate carbons into the citric acid cycle, which is already supplied with acetyl-CoA from mobilized free fatty acids.

b0020 **PHYSIOLOGY**

s0270 **Insulin/Glucagon Ratio**

p0300 The insulin/glucagon ratio regulates gluconeogenesis and glycogenolysis to maintain blood sugar. High ratios reduce glucose formation, and low ratios increase glucose formation.

s0150 Regulation of Glycogen Metabolism

p0305 Glycogen synthesis is regulated with respect to both number and size of the glycogen particles (molecules) and the rate of polymerization.

p0310 All new glycogen molecules begin with a primer glycoprotein, glycogenin. When glycogen synthase acting at the nonreducing ends becomes separated from the glycogenin primer, synthesis stops. This requirement for glycogenin contact limits the size of the glycogen molecule and prevents indefinite growth. The total number of glycogen particles is determined, therefore, by the number of glycogenin primers.

p0315 The rate of polymerization is determined by phosphorylation of glycogen synthase (Fig. 8-5). The phosphorylated form, the D (dependent) form, is a less active form, but is not inactive—it has basal activity and can be stimulated by G6P. Eventually glycogen synthase is dephosphorylated to the I (independent) form that is fully active, even at low G6P concentration.

p0320 Glycogenolysis is regulated by controlling glycogen phosphorylase activity.

p0325 Phosphorylation of glycogen phosphorylase, under the influence of glucagon, activates it to remove glucosyl residues from the nonreducing ends of the glycogen particle. Dephosphorylation converts the enzyme to an inactive form.

p0330 Glycogen synthesis and glycogenolysis are controlled reciprocally. The cAMP signal causes glucose to be mobilized from glycogen by its reciprocal regulation of glycogen synthase and phosphorylase.

p0335 Either glucagon (liver) or epinephrine (liver and muscle) stimulates an increase in the cellular cAMP levels (see Chapter 5). Au1

p0340 cAMP activates protein kinase A to phosphorylate both the synthase and phosphorylase, but with opposite effects. The synthase is inactivated, whereas the phosphorylase is activated.

p0345 As insulin levels rise and glucagon and epinephrine levels decrease, the intracellular cAMP levels also drop. This leads to the activation of protein phosphatase 1 (PP1) that dephosphorylates both enzymes, activating the synthase and inactivating the phosphorylase (see Fig. 8-5).

s0155 UNIQUE CHARACTERISTICS

s0160 Energy Cost of Gluconeogenesis

p0350 Gluconeogenesis requires a total of six high-energy bonds to synthesize glucose from pyruvate: four from ATP (pyruvate carboxylase and 3-phosphoglycerate-dehydrogenase) and two from GTP (phosphoenolpyruvate carboxykinase [PEPCK]).

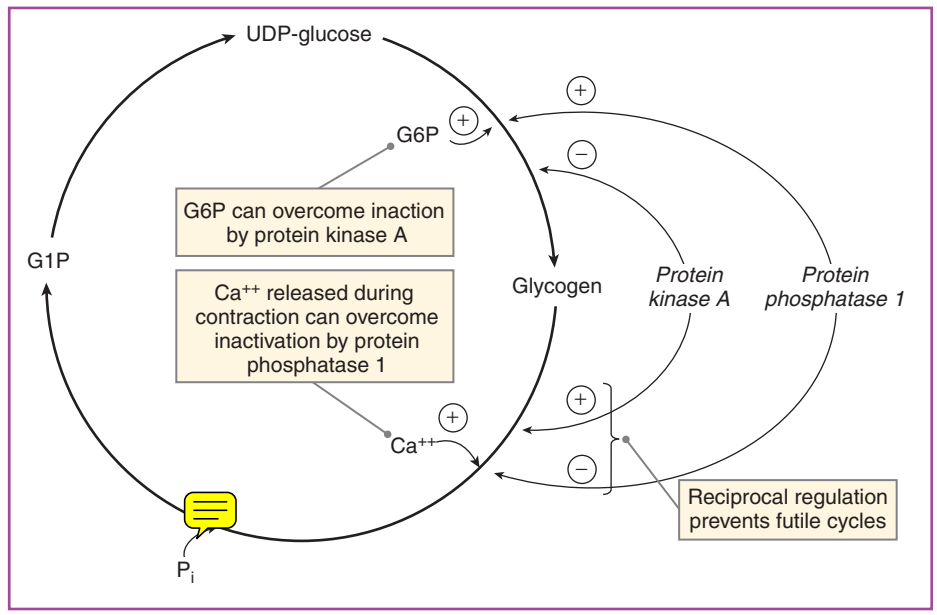
s0165 Carbon Skeletons for Glucose

p0355 Although acetyl-CoA from fatty acid oxidation provides the energy for gluconeogenesis, it does not supply the carbon skeletons for net synthesis of glucose. Acetyl-CoA is metabolized in the citric acid cycle. Both carbons from acetyl-CoA are released as CO_2 during the cycle, leaving no residual carbon for gluconeogenesis. The carbon skeletons come only from molecules that can be converted to oxaloacetate (pyruvate, amino acids) or dihydroxyacetone phosphate (glycerol).

s0170 Location of Glucose-6-Phosphatase

p0360 G6Pase is found only in gluconeogenic tissues that release free glucose into the bloodstream: liver, kidney, and small intestinal epithelium. G6Pase is absent in skeletal muscle, preventing any G6P produced from muscle glycogen mobilization from being released into the bloodstream.

B978-0-323-07446-9.00008-8, 00008



f0030 **Figure 8-5.** Regulation of glycogen metabolism. Inactivated glycogen synthase can be allosterically stimulated by glucose 6-phosphate, and inactivated phosphorylase (dephospho-form) can be stimulated by calcium ions.

s0175 Function of Branched Glycogen Structure

p0365 Branching of the glycogen molecule serves several functions: it increases its solubility compared with a linear molecule, and it also increases the rate of both synthesis and breakdown. The nonreducing ends are the site of action for both processes. Note that branching occurs by a transfer reaction, not by polymerization.

s0180 Energy Cost of Storing Glucose as Glycogen

p0370 Each glucose added to the glycogen molecule expends two high-energy phosphate bonds from UTP.

s0185 Allosteric Control of Glycogen Synthase Covalent Regulation

p0375 The D form of glycogen synthase in both liver and muscle responds quickly to change in glucose availability. It is allosterically activated by G6P (see Fig. 8-5). This allows immediate reactivation when glucose concentrations rise quickly after a meal, even before release of insulin from the pancreas.

p0380 The inactive (dephospho-) form of phosphorylase in muscle can be temporarily activated by Ca^{++} ions that directly stimulate phosphorylase kinase b, the enzyme that activates the phosphorylase enzyme (Fig. 8-6). The release of Ca^{++} from the sarcoplasmic reticulum is triggered by the nerve impulse that contracts the muscle fiber, and the activation of phosphorylase provides glucose via glycogenolysis. (See Fig. 8-5.)

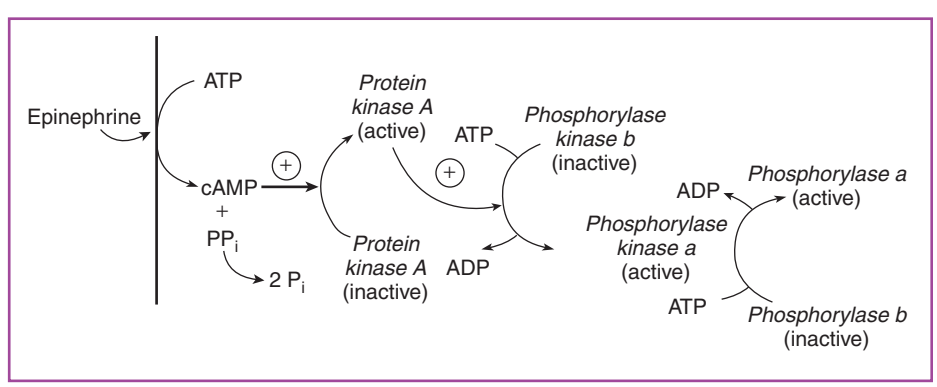
s0190 Glycogen Reducing End Versus Nonreducing Ends

p0385 Because of the polymerization of each new glucose monomer at the carbon 1 position, all sugar residues in the glycogen molecule are in the form of cyclic acetals, making them nonreducing ends. The only end that could be called the reducing end is the glucose residue attached to glycogenin. That is because if it were hydrolyzed from the glycogenin, it would be able to open at carbon 1 and undergo a redox color reaction with Fehling reagent (see Chapter 2). Au2

s0195 INTERFACE WITH OTHER PATHWAYS

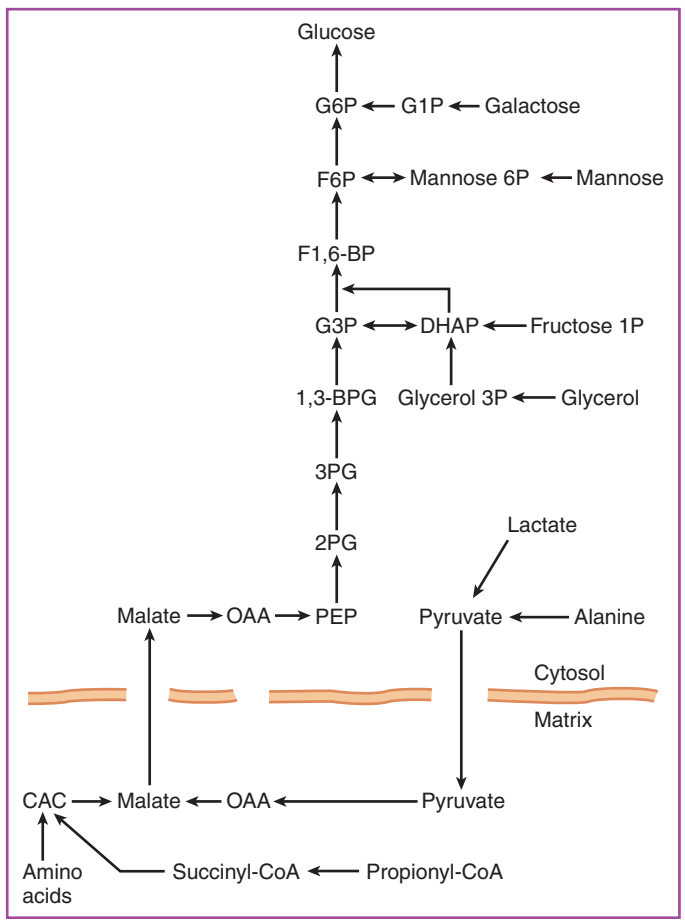
s0200 Gluconeogenesis

p0390 The gluconeogenic pathway has several interfaces with other pathways (Fig. 8-7). For other glucogenic amino acids, see Chapter 12. Au3



f0035 **Figure 8-6.** Cascade activation of glycogen phosphorylase. Each step in the cascade produces an amplification since the product of the reaction is also a catalyst.

B978-0-323-07446-9.00008-8, 00008



f0040 **Figure 8-7.** Interface of gluconeogenesis with other metabolic pathways.

s0205 ### *Lactate*

p0395 The conversion of lactate to pyruvate provides about 30% of the glucose for gluconeogenesis in liver. Lactate is cycled from skeletal muscle and red blood cells to liver for conversion to glucose in a process known as the Cori cycle.

s0210 ### *Alanine*

p0400 Alanine is the primary amino acid that supplies carbon atoms for glucose by transamination to pyruvate. Alanine also serves a major role in transporting amino acid nitrogen from tissues to Au4 the liver for disposal in the urea cycle (see Chapter 12).

s0215 ### *Propionyl-Coenzyme A*

p0405 Propionyl-CoA is a product of odd- and branched-chain fatty acid oxidation and is also produced by the catabolism of several amino acids. Its conversion to succinyl-CoA, a citric acid cycle intermediate, allows production of malate that is transported to the cytosol and converted to OAA.

s0220 ### *Glycerol*

p0410 Free glycerol is released from triglycerides in fasting or starvation conditions due to the mobilization of fatty acids. It is phosphorylated by glycerol kinase, found only in the liver, to form glycerol 3-phosphate. Glycerol-3-phosphate dehydrogenase then converts it to dihydroxyacetone phosphate (DHAP) for gluconeogenesis.

Dihydroxyacetone Phosphate s0225

Fructose 1-phosphate is converted during fructose catabolism p0415 to glyceraldehyde and DHAP.

Mannose 6-Phosphate s0230

F6P is interconverted with mannose 6-phosphate (converted p0420 to guanosine diphosphate [GDP] mannose, a precursor for mannose and fucose residues in glycoproteins).

Galactose s0235

G1P is the end product of galactose metabolism. p0425

Glycogen Metabolism s0240

The pathways of glycogen metabolism interface with glycoly- p0430 sis, gluconeogenesis, and the uronic acid pathway.

Glucose 1-Phosphate s0245

The reversible interconversion between G1P and G6P can p0435 route glucose released during glycogenolysis to gluconeogenesis or glycolysis.

In muscle, G6P cannot be dephosphorylated, since it lacks p0440 the G6P enzyme. Thus, it is routed entirely through the glycolytic pathway to produce energy for muscle contraction.

In the liver, G6P is converted to glucose by G6Pase and re- p0445 leased into the blood.

G1P is also produced during galactose metabolism, provid- p0450 ing a route either for storage in glycogen or for conversion to G6P (see Chapter 9). Au5

Uridine Diphosphate-Glucose s0250

UDP-glucuronic acid is formed from UDP-glucose by oxida- p0455 tion of its glucose moiety. UDP-glucuronate reacts with metabolic waste products and drugs; this results in a water-soluble conjugate called a glucuronide. Glucuronides are formed in liver and excreted in bile (e.g., bilirubin, morphine, and steroid hormones are excreted as glucuronides).

Glucuronic acid is a source of L-ascorbic acid in most mam- p0460 mals, except in primates (including humans) and guinea pigs.

RELATED DISEASES OF GLUCONEOGENESIS AND GLYCOGEN METABOLISM s0255

Idiopathic Neonatal Hypoglycemia s0260

Newborns have a critical need for gluconeogenesis. The sup- p0465 ply of glucose from the placenta is interrupted, but no glucose is immediately available from the diet. Since the brain must have a sustained source of glucose from blood, the genes for the gluconeogenic enzymes are simultaneously activated at birth. Occasionally this activation does not occur, and the newborn must be fed a glucose solution or it will experience hypoglycemia.

B978-0-323-07446-9.00008-8, 00008

s0265 ## Glycogen Storage Diseases

p0470 Genetic deficiencies of the enzymes involved in glycogen metabolism result in abnormalities in the amount and/or structure of glycogen in tissues and in other metabolic abnormalities related to the use of glycogen, such as hypoglycemia or muscle weakness. The most serious of these diseases, Von Gierke disease, results from deficiency of G6Pase that is needed to release glucose into the bloodstream. This prevents glucose from either glycogenolysis or gluconeogenesis from being released by the liver. The hypoglycemia that is produced causes an excess of free fatty acids to be released, leading to ketosis (Table 8-1).

b0025 **PATHOLOGY**

s0275 **Glucose-6-Phosphatase Deficiency**

p0485 G6P deficiency (von Gierke disease) leads to a glycogen storage disease accompanied by lactic acidosis. Patients also have ketoacidosis, hyperlipidemia (tendon xanthomas), prolonged prothrombin time (due to platelet abnormalities), and hyperuricemia (gout).

b0030 **MICROBIOLOGY & IMMUNOLOGY**

s0280 **Amylopectinosis**

p0500 A defective branching enzyme produces abnormal glycogen (amylopectinosis), leading to an autoimmune attack on the liver, which produces cirrhosis.

b0035 **HISTOLOGY**

s0285 **Lysosomal Glycogen Digestion**

p0515 A deficiency of α-1,4–glucosidase (generalized glycogenosis or Pompe disease) prevents lysosomal digestion of glycogen. Although glycogen is synthesized and degraded enzymatically, it is continuously digested in the lysosomes as part of its normal cellular turnover.

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

t0010 **TABLE 8-1. Glycogen Storage Diseases**

ENZYME DEFICIENCY	BIOCHEMICAL FEATURES	CLINICAL FEATURES	GLYCOGEN STRUCTURE
Glucose-6-phosphatase deficiency (von Gierke disease)	Inability to release free glucose into bloodstream; buildup of G6P stimulates significant resynthesis (and accumulation) of glycogen by G6P-dependent form of glycogen synthase; also prevents blood glucose regulation from gluconeogenic pathway.	Hepatomegaly, severe fasting hypoglycemia, ketosis, hyperlipidemia, hyperuricemia, lactic acidosis	Normal
Lysosomal α-1,4-glucosidase deficiency (Pompe disease)	Results in accumulation of lysosomal glycogen deposits; emphasizes importance of lysosomal digestion in normal turnover of glycogen	Hypotonia, cardiomegaly, death by age 2 years	Normal
Debranching enzyme deficiency (Cori disease)	Only terminal glycogen branches used for blood sugar regulation; gluconeogenesis makes up the difference	Mild hypoglycemia, hepatomegaly that diminishes with age	Many short-branched chains (limit dextrins)
Branching enzyme deficiency (Andersen disease)	Very long amylopectin chains cause liver to become cirrhotic.	Cardiac or liver failure, lethal within 2 years	Abnormal, many long chains with few branches
Muscle glycogen phosphorylase deficiency (McArdle syndrome)	Glycolytic pathway deprived of ready supply of G6P from glycogen	Muscle cramps, absent normal anaerobic production of lactate during exercise, abnormal amount of glycogen in muscle	Normal
Liver glycogen phosphorylase deficiency (Her disease)	Causes glycogen storage	Hepatomegaly, mild hypoglycemia	Normal

G6P, glucose 6-phosphate.

Comp. by: Gkamatchi Stage: Proof Chapter No.: 8 Title Name: El_Pelley
Page Number: 0 Date:18/7/11 Time:21:06:10

B978-0-323-07446-9.00008-8, 00008

B978-0-323-07446-9.00008-8, 00008

Query Form

Book:Integrated Biochemistry
Chapter No:00008

AU: Author Query; ED: Editor Query; TS: Query raised by Typesetter;

Query Refs.	Queries	Author's response
Au1	Pls. check cross reference	
Au2	Pls. check cross reference	
Au3	Pls. check cross reference	
Au4	Pls. check cross reference	
Au5	Pls. check cross reference	