Chapter 15 Principles of Metabolic Regulation

Multiple Choice Questions

1. The metabolism of glycogen in animals
Page: 562 Difficulty: 1 Ans: C
Glycogen is converted to monosaccharide units by:

A) glucokinase.
B) glucose-6-phosphatase
C) glycogen phosphorylase.
D) glycogen synthase.
E) glycogenase.

2. The metabolism of glycogen in animals
Pages: 568-569 Difficulty: 2 Ans: C
The glycogen-branching enzyme catalyzes:

A) degradation of ($\alpha 1 \rightarrow 4$) linkages in glycogen
B) formation of ($\alpha 1 \rightarrow 4$) linkages in glycogen.
C) formation of ($\alpha 1 \rightarrow 6$) linkages during glycogen synthesis.
D) glycogen degradation in tree branches.
E) removal of unneeded glucose residues at the ends of branches.

3. The metabolism of glycogen in animals
Pages: 569-570 Difficulty: 2 Ans: D
Glycogenin:

A) catalyzes the conversion of starch into glycogen.
B) is the enzyme responsible for forming branches in glycogen.
C) is the gene that encodes glycogen synthase.
D) is the primer on which new glycogen chains are initiated.
E) regulates the synthesis of glycogen.

4. The metabolism of glycogen in animals
Pages: 568, 586 Difficulty: 2 Ans: B
Which of the following is true of glycogen synthase?

A) Activation of the enzyme involves a phosphorylation.
B) It catalyzes addition of glucose residues to the nonreducing end of a glycogen chain by formation of ($\alpha 1 \rightarrow 4$) bonds.
C) It uses glucose-6-phosphate as donor of glucose units
D) The conversion of an active to an inactive form of the enzyme is controlled by the concentration of cAMP.
E) The enzyme has measurable activity only in liver.

5. The metabolism of glycogen in animals
Pages: 568-569 Difficulty: 2 Ans: E
Which one of the following statements abour mammalian glycogen synthase is *not* correct?

A) It is especially predominant in liver and muscle.
B) The donor molecule is a sugar nucleotide.
C) The phosphorylated form of this enzyme is inactive.
D) This enzyme adds glucose units to the nonreducing end of glycogen branches.
E) This enzyme adds the initial glucose unit to a tyrosine residue in glycogenin.

6. The metabolism of glycogen in animals
Page: 562 Difficulty: 2 Ans: B
The enzyme glycogen phosphorylase:

A) catalyzes a cleavage of $\beta(1 \rightarrow 4)$ bonds.
B) catalyzes a hydrolytic cleavage of $(\alpha 1 \rightarrow 4)$ bonds.
C) is a substrate for a kinase.
D) uses glucose 6-phosphate as a substrate.
E) uses glucose as a substrate.

7. Regulation of metabolic pathways
Page: 571 Difficulty: 2 Ans: B
Aside from maintaining the integrity of its hereditary material, the most important general metabolic concern of a cell is:

A) keeping its glucose levels high.
B) maintaining a constant supply and concentration of ATP.
C) preserving its ability to carry out oxidative phosphorylation.
D) protecting its enzymes from rapid degradation.
E) running all its major metabolic pathways at maximum efficiency.

8. Regulation of metabolic pathways
Pages: 572-573 Difficulty: 2 Ans: C
If the mass action ratio, Q, for a reaction under cellular conditions is larger than the equilibrium constant, K_{eq}, then:

A) the reaction will be at equilibrium.
B) the reaction will go backward and be endergonic.
C) the reaction will go backward and be exergonic.
D) the reaction will go forward and be endergonic.
E) the reaction will go forward and be exergonic.

9. Regulation of metabolic pathways
Pages: 574-575 Difficulty: 2 Ans: A
Which one of the following types of mechanisms is *not* known to play a role in the reversible alteration of enzyme activity?

A) Activation by cleavage of an inactive zymogen
B) Allosteric response to a regulatory molecule
C) Alteration of the synthesis or degradation rate of an enzyme
D) Covalent modification of the enzyme
E) Interactions between catalytic and regulatory subunits

10. Coordinated regulation of glycolysis and gluconeogenesis
Pages: 575-576 Difficulty: 2 Ans: D
Gluconeogenesis must use "bypass reactions" to circumvent three reactions in the glycolytic pathway that are highly exergonic and essentially irreversible. Reactions carried out by which three of the enzymes listed must be bypassed in the gluconeogenic pathway?

1) Hexokinase
2) Phosphoglycerate kinase
3) Phosphofructokinase-1
4) Pyruvate kinase
5) Triosephosphate isomerase

A) 1, 2, 3
B) 1, 2, 4
C) 1, 4, 5
D) 1, 3, 4
E) 2, 3, 4

11. Coordinated regulation of glycolysis and gluconeogenesis
Pages: 579-580 Difficulty: 2 Ans: B
Cellular isozymes of pyruvate kinase are allosterically inhibited by:

A) high concentrations of AMP.
B) high concentrations of ATP.
C) high concentrations of citrate.
D) low concentrations of acetyl-CoA.
E) low concentrations of ATP.

12. Coordinated regulation of glycolysis and gluconeogenesis
Pages: 580-583 Difficulty: 2 Ans: C
Which of the following statements about gluconeogenesis in animal cells is true?

A) A rise in the cellular level of fructose-2,6-bisphosphate stimulates the rate of gluconeogenesis.
B) An animal fed a large excess of fat in the diet will convert any fat not needed for energy production into glycogen to be stored for later use.
C) The conversion of fructose 1,6-bisphosphate to fructose 6-phosphate is *not* catalyzed by phosphofructokinase-1, the enzyme involved in glycolysis.
D) The conversion of glucose 6-phosphate to glucose is catalyzed by hexokinase, the same enzyme involved in glycolysis.
E) The conversion of phosphoenol pyruvate to 2-phosphoglycerate occurs in two steps, including a carboxylation.

13. Coordinated regulation of glycolysis and gluconeogenesis
Page: 582 Difficulty: 2 Ans: D

There is reciprocal regulation of glycolytic and gluconeogenic reactions interconverting fructose-6-phosphate and fructose-1,6-bisphosphate. Which one of the following statements about this regulation is *not* correct?

A) Fructose-2,6-bisphosphate activates phosphofructokinase-1.
B) Fructose-2,6-bisphosphate inhibits fructose-1,6-bisphosphatase.
C) The fructose-1,6-bisphosphatase reaction is exergonic.
D) The phosphofructokinase-1 reaction is endergonic.
E) This regulation allows control of the direction of net metabolite flow through the pathway.

14. Coordinated regulation of glycogen synthesis and breakdown
Pages: 583-584 Difficulty: 2 Ans: D
Which of the following statements is true of muscle glycogen phosphorylase?

A) It catalyzes phosphorolysis of the ($\alpha 1 \rightarrow 6$) bonds at the branch points of glycogen.
B) It catalyzes the degradation of glycogen by hydrolysis of glycosidic bonds.
C) It degrades glycogen to form glucose 6-phosphate.
D) It exists in an active *(a)* form and an inactive *(b)* form that is allosterically regulated by AMP.
E) It removes glucose residues from the reducing ends of the glycogen chains.

15. Coordinated regulation of glycogen synthesis and breakdown
Page: 584 Difficulty: 2 Ans: A
Which of the following is true of glycogen synthesis and breakdown?

A) Phosphorylation activates the enzyme responsible for breakdown, and inactivates the synthetic enzyme.
B) Synthesis is catalyzed by the same enzyme that catalyzes breakdown.
C) The glycogen molecule "grows" at its reducing end.
D) The immediate product of glycogen breakdown is free glucose.
E) Under normal circumstances, glycogen synthesis and glycogen breakdown occur simultaneously and at high rates.

16. Coordinated regulation of glycogen synthesis and breakdown
Page: 584 Difficulty: 2 Ans: E
Glycogen phosphorylase *a* can be inhibited at an allosteric site by:

A) AMP.
B) calcium.
C) GDP.
D) glucagon.
E) glucose.

17. Coordinated regulation of glycogen synthesis and breakdown
Page: 586 Difficulty: 2 Ans: B
Which one of the following directly results in the activation of glycogen synthase?

A) Binding of glucose-6-phosphate
B) Dephosphorylation of multiple residues by phosphoprotein phosphorylase-1 (PP1)
C) Phosphorylation of specific residues by casein kinase II (CKII)
D) Phosphorylation of specific residues by glycogen synthase kinase-3 (GSK-3)
E) The presence of insulin

18. Coordinated regulation of glycogen synthesis and breakdown
Pages: 586-588 Difficulty: 2 Ans: E
Which one of the following is *not* a characteristic of phosphoprotein phosphorylase-1 (PP1)?

A) PP1 can be phosphorylated by protein kinase A (PKA).
B) PP1 can dephosphorylate glycogen phosphorylase, glycogen synthase, and phosphorylase kinase.
C) PP1 is allosterically activated by glucose-6-phosphate.
D) PP1 is inhibited by activated glycogen phosphorylase
E) PP1 is phosphorylated by glycogen synthase kinase-3 (GSK3).

19. Analysis of metabolic control
Pages: 592-595 Difficulty: 2 Ans: E
The flux control coefficient for an enzyme in a multistep pathway depends on:

A) the concentration of the enzyme itself.
B) the concentration of other enzymes in the pathway.
C) the levels of regulatory molecules.
D) the amounts of substrate molecules present at each step.
E) all of the above.

20. Analysis of metabolic control
Pages: 593, 595 Difficulty: 2 Ans: E
The elasticity coefficient for an enzyme in a multistep pathway depends on:

A) the concentration of the enzyme itself.
B) the levels of regulatory molecules.
C) the amounts of substrate molecules present at each step.
D) both A and C.
E) both B and C.

Short Answer Questions

21. The metabolism of glycogen in animals
Pages: 562-563 Difficulty: 2
Describe the process of glycogen breakdown in muscle. Include a description of the structure of glycogen, the nature of the breakdown reaction and the breakdown product, and the required enzyme(s).

Ans: Muscle glycogen consists of linear polymers of ($\alpha 1 \rightarrow 4$)-linked D-glucose, with many branches formed by ($\alpha 1 \rightarrow 6$) glycosidic linkages to D-glucose. Glycogen phosphorylase in muscle catalyzes phosphorolytic cleavage of the terminal residue at the nonreducing ends, producing glucose 1-phosphate. When phosphorylase approaches ($\alpha 1 \rightarrow 6$) branch points, a second enzyme (the "debranching enzyme") removes the four glucose residues nearest the branch point and reattaches them in ($\alpha 1 \rightarrow 4$) linkage at a nonreducing end. Now phosphorylase can continue to degrade the molecule.

22. The metabolism of glycogen in animals
Pages: 562, 568, 584, 586 Difficulty: 3
Glycogen synthesis and glycogen breakdown are catalyzed by separate enzymes. Contrast the reactions in terms of substrate, cofactors (if any), and regulation.

Ans: Glycogen synthesis is catalyzed by glycogen synthase and employs UDP-glucose as the activated precursor:

$$\text{UDP-glucose} + \text{glycogen (glucose)}_n \longrightarrow \text{UDP} + \text{glycogen (glucose)}_{n+1}$$

Glycogen synthase is inactivated by phosphorylation, catalyzed by cAMP-dependent protein kinase; it is activated by dephosphorylation, catalyzed by phosphoprotein phosphatase. Glycogen breakdown is catalyzed by glycogen phosphorylase, which employs pyridoxal phosphate (PLP) as a cofactor. The reaction is a phosphorolysis; the glycosidic bond is broken by the attack of P_i:

$$\text{Glycogen (glucose)}_n + P_i \longrightarrow \text{glycogen (glucose)}_{n-1} + \text{glucose 1-phosphate.}$$

Glycogen phosphorylase is activated by phosphorylation, catalyzed by phosphorylase kinase, and it is inactivated by dephosphorylation, catalyzed by phosphorylase *a* phosphatase.

23. The metabolism of glycogen in animals
Pages: 563-564 Difficulty: 2
In mammalian liver, glucose-1-phosphate, the product of glycogen phosphorylase, can enter glycolysis or replenish blood glucose. Describe the reactions by which these two processes are carried out.

Ans: To enter glycolysis, glucose-1-phosphate must undergo isomerization to glucose-6-phosphate by phosphoglucomutase. To replenish glucose in the bloodstream, glucose-1-phosphate must be hydrolyzed to free glucose by glucose-1-phosphatase.

24. The metabolism of glycogen in animals
Pages: 567-569 Difficulty: 3
Diagram the pathway from glucose to glycogen; show the participation of cofactors and name the enzymes involved.

Ans:

(1) Glucose + ATP $\xrightarrow[\text{hexokinase}]{}$ glucose 6-phosphate + ADP

(2) Glucose 6-phosphate $\xrightarrow[\text{phosphoglucomutase}]{}$ glucose 1-phosphate

(3) Glucose 1-phosphate + UTP $\xrightarrow[\text{UDP-glucose pyrophosphorylase}]{}$ UDP-glucose + PP_i

(4) UDP-glucose $\xrightarrow[\text{glycogen synthase}]{}$ glycogen + UDP

25. The metabolism of glycogen in animals
Page: 568 Difficulty: 2
Show the reaction catalyzed by glycogen synthase.

Ans: The reaction is the addition of a glucose moiety from UDP-glucose to the nonreducing end of a glycogen chain; the linkage formed is ($\alpha 1 \rightarrow 4$). (See Fig. 15-8, p. 568.)

26. The metabolism of glycogen in animals
Page: 568 Difficulty: 2
What is the biological advantage of synthesizing glycogen with many branches?

Ans: Highly branched glycogen is more soluble than unbranched glycogen. In addition, both glycogen synthase and glycogen phosphorylase act at the nonreducing ends of glycogen chains. Branched glycogen has far more ends for these enzymes to work on than would the equivalent amount of linear glycogen chains. Having more ends effectively increases the concentration of substrate for the enzymes, thereby increasing the rate of glycogen synthesis and breakdown.

27. The metabolism of glycogen in animals
Page: 568 Difficulty: 3
Show all of the reactions that occur in the pathway from galactose to glycogen in an adult human. You do not need to give structures or name enzymes; just name the intermediates along the path and show any required cofactors.

Ans:

(1) Galactose + ATP $\longrightarrow$ Galactose 1-phosphate + ADP
(2) Galactose 1-phosphate + UDP-glucose $\longrightarrow$ UDP-galactose + glucose 1-phosphate
(3) UDP-galactose $\longrightarrow$ UDP-glucose (catalyzed by UDP-glucose epimerase, which requires NAD^+)
(4) UDP-glucose + glycogen $(glucose)_n \longrightarrow$ UDP + glycogen $(glucose)_{n+1}$
(For galactose metabolism, see Fig. 14-11, p. 537.)

28. The metabolism of glycogen in animals
Pages: 569-570 Difficulty: 2
Explain the role of glycogenin.

Ans: Glycogenin is a protein that acts as the "primer" for the initiation of new glycogen molecules. It catalyzes the transfer of a glucose residue from UDP-glucose to a tyrosine hydroxyl group in glyco-

genin, then forms a complex with glycogen synthase. As more glucose residues are added, this first glucose residue, still attached to glycogenin, becomes the reducing end of the growing glycogen chain.

29. Regulation of metabolic pathways
Pages: 571-572 Difficulty: 2
What are the regulatory implications for the cell with regard to ATP and AMP, given that the former are generally high, and the latter are low?

Ans: Normally, [ATP] is 5-10 mM, while [AMP] is < 0.1 mM, thus AMP is a much more sensitive indicator of a cell's energetic state. Small changes in ATP concentration are amplified into large changes in AMP concentration (see Table 15-1), hence many regulatory processes hinge on changes in the concentration of AMP.

30. Regulation of metabolic pathways
Page: 572 Difficulty: 2
Describe four major principles of metabolic regulation that have selectively evolved throughout evolution.

Ans: 1. Maximize the efficiency of fuel utilization by preventing the simultaneous operation of opposing pathways (i.e., futile cycles). 2. Partition metabolites appropriately between alternative pathways. 3. Draw on the fuel best suited for the immediate needs of the organism. 4. Shut down biosynthetic pathways when their products accumulate.

31. Regulation of metabolic pathways
Pages: 572-573 Difficulty: 2
In the glycolytic path from glucose to phosphoenolpyruvate, two steps are practically irreversible. What are these steps, and how is each bypassed in gluconeogenesis? What advantages does an organism gain from having separate pathways for anabolic and catabolic metabolism? What are the disadvantages?

Ans: The two irreversible steps in glycolysis are conversion of glucose to glucose 6-phosphate, catalyzed by hexokinase, and conversion of fructose 6-phosphate to fructose 1,6-bisphosphate, catalyzed by phosphofructokinase-1 (Table 15-2, p. 573). The first reaction is bypassed during gluconeogenesis by the reaction catalyzed by glucose 6-phosphatase, an enzyme unique to the liver. The second is bypassed by fructose 1,6-bisphosphatase-1 (FBPase-1). By having separate pathways that employ different enzymes, an organism is able to control anabolic and catabolic processes separately, thus avoiding futile cycles. A potential disadvantage is the need to produce separate sets of enzymes for catabolism and anabolism.

32. Coordinated regulation of glycolysis and gluconeogenesis
Pages: 579-581 Difficulty: 2
Why is citrate, in addition to being a metabolic intermediate in aerobic oxidation of fuels, an important control molecule for a variety of enzymes?

Ans: As the key biochemical intermediate in the citric acid cycle resulting from the condensation of oxaloacetate and acetyl-CoA, citrate is at a junction of amino acid, fatty acid, and pyruvate oxidation, serving as an intracellular signal that the cell's current energy needs are being met. In particular, it is an allosteric regulator of PFK-1, increasing the inhibitory effect of ATP, and further reducing the flow of glucose through glycolysis.

33. Coordinated regulation of glycolysis and gluconeogenesis
Pages: 581-582 Difficulty: 3
Under what circumstances does the bifunctional protein phosphofructokinase-2/fructose 2,6-bisphosphatase (PFK-2/FBPase-2) become phosphorylated, and what are the consequences of its phosphorylation to the glycolytic and gluconeogenic pathways?

Ans: Glucagon, signaling low blood sugar, stimulates cAMP synthesis, which activates protein kinase A (PKA) to phosphorylate PFK-2/FBPase-2 (among other proteins). This phosphorylation enhances FBPase-2 activity and inhibits PFK-2 activity of the enzyme, resulting in lower levels of fructose 2,6-bisphosphate (F26BP). In the absence of F26BP as an allosteric effector, the activity of PFK-1 is reduced (inhibiting glycolysis) and the activity of FBPase-1 is enhanced (stimulating gluconeogenesis), thus enabling the liver to replenish blood glucose. See Figs. 15-22 and 15-23.

34. Coordinated regulation of glycolysis and gluconeogenesis
Pages: 582-583 Difficulty: 3
What is a "futile cycle"? Give an example of a potential futile cycle in carbohydrate metabolism, and describe methods used by cells or organisms to avoid the operation of the futile cycle.

Ans: A futile cycle is a pair of reactions or pathways in one of which A is converted into B, and in the other, B into A. For example, conversion of fructose 6-phosphate into fructose 1,6-bisphosphate (catalyzed by phosphofructokinase-1) is effectively reversed by the reaction catalyzed by fructose 1,6-bisphosphatase. The sum of the two reactions is the hydrolysis of ATP and the dissipation of energy as heat, a wasteful process except when the organism needs to generate heat to maintain body temperature.

Fructose 6-phosphate + ATP $\longrightarrow$ fructose 1,6-bisphosphate + ADP
Fructose 1,6-bisphosphate $\longrightarrow$ fructose 6-phosphate + P_i
Sum: ATP $\longrightarrow$ ADP + P_i (+ heat)

Cells use reciprocal regulation of the pathways such that when a reaction in the pathway in one direction is stimulated, the reaction in the reverse pathway is inhibited, and vice versa.

35. Coordinated regulation of glycogen synthesis and breakdown
Page: 590 Difficulty: 2
Order the steps leading to glycogen breakdown resulting from the stimulation of liver cells by glucagon.

1) Activation of protein kinase A (PKA)
2) cAMP levels rise
3) Phosphorylation of phosphorylase *b*
4) Phosphorylation of phosphorylase *b* kinase
5) Stimulation of adenyl cyclase

Ans: The correct temporal order is 5-2-1-4-3.

36. Analysis of metabolic control
Page: 593 Difficulty: 2
Explain the distinction between metabolic "regulation" and metabolic "control" in a multienzyme pathway.

Ans: Regulation refers to rebalancing the levels of metabolites along a pathway in response to a change in flux through the pathway, while control is what determines the total flux through the pathway.