

Carbohydrate Metabolism

1. What are the two key regulated enzymes required for glycogen synthesis and glycogen breakdown? Briefly describe the mechanism(s) that control their activity.
2. Individuals with von Gierke's disease, which is a lack of glucose-6-phosphatase in the liver, accumulate large amounts of glycogen in the liver. Why?
3. Why would individuals with von Gierke's disease release a small amount of glucose into the blood after injection with a high dose of glucagon?
4. Gluconeogenesis and glycolysis are opposing pathways. In what way(s) are they similar and in what way(s) are they different?
5. Gluconeogenesis synthesizes glucose from pyruvate, and glycolysis converts glucose into pyruvate. Give a specific example illustrating how allosteric control modulates these two pathways to prevent futile cycling in liver cells.
6. Lectins are proteins that bind carbohydrates. What is the name given to the class of proteins on the outer membrane of egg cells that interact with lectin?
7. Name the glycolytic enzyme that opposes the reaction in gluconeogenesis catalyzed by fructose 1,6-bisphosphatase? Does AMP activate (+) or inhibit (-) this glycolytic enzyme?
8. Why do glucose molecules produced by the glycogen phosphorylase reaction yield more ATP than dietary glucose? How many more ATPs?
9. What is the metabolic logic of differential control of muscle and liver glycogen phosphorylase by glucose and AMP?
10. What is the effect of glucocorticoids on phosphoenolpyruvate carboxykinase in liver cells, and how does this modulate blood glucose levels?
11. What carbohydrate molecule is common to both the glycogen phosphorylase and glycogen synthetase reactions?
12. What effect does protein kinase A (PKA) activation have on glycogen metabolism with respect to glycogen synthase and glycogen phosphorylase activities? Does PKA activation increase or decrease the amount of stored glycogen in the body?
13. How many ATPs are produced per mole of glucose by aerobic metabolism in muscle cells if the glucose is derived from dietary sources versus glucose produced by glycogen phosphorylase? Explain.
14. A continual supply of reduced glutathione is required to protect red blood cells against the toxic effects of pamaquine. Why would individuals with a defect in the enzyme glucose 6-phosphate dehydrogenase be susceptible to pamaquine-induced hemolytic anemia?

15. What explains the observation that people born with a deficiency in the enzyme glucose 6-phosphate dehydrogenase become clinically anemic if they have a diet rich in fava beans?

Answers

1. Glycogen synthase is the major enzyme required for glycogen synthesis. It is inhibited by phosphorylation. Glucagon, a hormone that signals low glucose levels, stimulates phosphorylation of glycogen synthase, and also promotes inactivation (by phosphorylation) of a protein phosphatase inhibitor, thus ensuring that glycogen synthase remains phosphorylated and inactive. Glycogen phosphorylase is the major enzyme required for glycogen breakdown and it is activated by glucagon through a phosphorylation regulatory mechanism.

2. Glucose-6-P accumulates as a result of stimulated glycogen breakdown (glucagon signals low blood sugar), but because it can't leave the liver, Glu-6-P stimulates glycogen synthase. Moreover, Glu-6-P derived from gluconeogenesis (also stimulated by low blood sugar) is converted to glycogen by the same mechanism (stimulation of glycogen synthase).

3. Glucagon stimulates glycogen breakdown, and the product of debranching enzyme is free glucose, which is released into the blood (~10% of available glucose in glycogen is contained in alpha-1,6 branch points).

4. Similarities

- both involve many of the same carbohydrate intermediates.
- they share some of the same enzymatic reactions.
- both are regulated by many of the same effector molecules.

Differences

- gluconeogenesis is primarily a liver pathway, glycolysis is in every cell.
- gluconeogenesis requires ATP, glycolysis generates ATP.
- regulatory effectors have opposite effects on these two pathways.

5. Phosphofructokinase is activated by F-2,6-BP (AMP) and inhibited by citrate, whereas, Fructose 1,6-bisphosphatase is inhibited by F-2,6-BP (AMP) and activated by citrate.

6. Lectins bind to oligosaccharides that are covalently attached to glycoproteins.

7. Phosphofructokinase is the glycolytic enzyme that opposes the gluconeogenic enzyme fructose 1,6-bisphosphatase, these enzymes interconvert fructose 6-P and fructose 1,6-BP. AMP activates phosphofructokinase.

8. The product of the glycogen phosphorylase reaction is glucose-1-phosphate which is isomerized to glucose-6-phosphate and metabolized by the glycolytic pathway. Since this bypasses the requirement for ATP hydrolysis (by hexokinase) in the first step of the pathway, 1 additional ATP is produced by a glycogen derived glucose unit (31 ATPs rather than 30 ATPs).

9. Muscle phosphorylase is activated by AMP which would signal a low energy state in the cell. Glucose inhibits liver phosphorylase by feedback inhibition signaling that glucose is not being exported at a high enough rate to require more glycogen degradation. Muscle phosphorylase is not inhibited by glucose since muscle cells use glucose for energy production. Degradation of glycogen in the liver for the purpose of glucose export is independent of the energy needs of the liver cell.

10. Glucocorticoids induce the expression of the PEPCK gene leading to an increase in the levels of PEPCK protein in the cell. PEPCK is a key gluconeogenic enzyme and therefore increased PEPCK gene expression leads to an increase in glucose production and export from liver cells via the gluconeogenic pathway.

11. Glucose 1-phosphate is one of the products of the phosphorylase reaction and also a substrate in the glycogen synthase reaction.

12. Protein kinase A activation results in the phosphorylation and inactivation of glycogen synthase, and at the same time, the phosphorylation and activation of glycogen phosphorylase through the phosphorylation and activation of phosphorylase kinase. PKA activation results in decreased amounts of stored glycogen because glycogen synthase is inactivated and glycogen phosphorylase is activated.

13. Dietary glucose must be phosphorylated by hexokinase to produce glucose-6-phosphate, a substrate in glycolysis. This reaction requires an investment of 1 ATP. The total yield of ATP from dietary glucose is 30. In contrast, the isomerization reaction converting glucose-1-phosphate to glucose-6-phosphate bypasses the requirement for ATP hydrolysis, and therefore, glucose units produced by the glycogen phosphorylase reaction yield a total of 31 ATP by aerobic metabolism.

14. NADPH is required to sustain a high level of reduced glutathione in red blood cells. Glucose 6-phosphate dehydrogenase is the required enzyme for the first step in the Pentose Phosphate Pathway, and therefore these individuals are unable to produce sufficient levels of NADPH to protect against pamaquine-induced toxicity.

15. Glucose 6-phosphate dehydrogenase is required in the Pentose Phosphate Pathway to generate reducing equivalents in the form of NADPH. Fava beans contain toxic compounds that must be reduced by glutathione in red blood cells. Since NADPH is required to keep glutathione in the reduced state, the red blood cells in these individuals are highly susceptible to favism, a diet-induced form of anemia.