

Lipid Metabolism

1. What has a higher stored energy potential per gram, glycogen or triglycerides? Explain.
2. How can excess acetyl CoA trapped in the mitochondria, be utilized as a substrate for fatty acid biosynthesis in the cytosol?
3. When the energy charge in liver cells is low, and oxaloacetate levels are limiting, what is the fate of excess mitochondrial acetyl CoA? Name a physiological condition that causes this.
4. Brain cells prefer glucose as a carbon source. Is metabolism of stored triglycerides in fat a good source of intermediates for gluconeogenesis in animals? Explain.
5. Orlistat is a new anti-obesity drug that has been released onto the market. It binds to and inhibits pancreatic lipase activity in the intestine. Why would this function as an anti-obesity drug? What do you think the treatment regimen consists of and what might be some of the side effects?
6. Olestra is a fat substitute composed of a sucrose molecule with several fatty acids attached. Why is this considered a zero calorie fat molecule? Why does Olestra prevent the absorption of fat soluble vitamins?
7. What is Tay Sachs disease and why is it so rare today as compared to 50 years ago?
8. Describe the two primary mechanisms by which intracellular cholesterol levels in the liver are regulated?
9. Why do people with an enzyme deficiency in carnitine acyltransferase have severe hypoglycemia and not show an increase in plasma ketone bodies during starvation?
10. Name two hormones derived from cholesterol and briefly describe their metabolic functions in humans.
11. In addition to limiting dietary intake of cholesterol, describe two different treatments that have been used to lower serum cholesterol levels. Include a brief explanation of how they each work.
12. Name the mode of regulation used by citrate to control acetyl CoA carboxylase activity. Does this activate or inhibit enzyme activity and why does this make sense (metabolic logic)?
13. What is the probability that a baby born to a mother and father that are both carriers of Tay Sachs disease (heterozygous genotype) will be a carrier? Will this baby be afflicted with the disease as a young adult? Explain.
14. What is the clinical manifestation (phenotype) of human 21-hydroxylase deficiency in females? What is the biochemical basis for kidney dysfunction in these individuals?
15. Explain why in humans triglycerides can be utilized to produce glucose via the gluconeogenic pathway, but fatty acids cannot.

16. Write the net reaction of palmitate synthesis. What two metabolic processes generate the large amount of reducing equivalents required for palmitate synthesis?
17. Which organ is the most responsible for de novo cholesterol biosynthesis and what is the key regulated enzyme in this pathway?
18. Glucagon signaling inhibits acetyl CoA carboxylase activity through phosphorylation, whereas, insulin signaling stimulates acetyl CoA carboxylase activity by dephosphorylation. Explain the metabolic logic of this regulation in terms of the functions of acetyl CoA carboxylase, glucagon and insulin.
19. What is the biochemical basis for improved anti-inflammatory action and reduced stomach bleeding in individuals who use Celebrex compared to aspirin?
20. What explains the developmental progression from feminization to masculinization at puberty in males with a 5-alpha-reductase deficiency?

Answers

1. Triglycerides have the higher stored energy potential per gram because fats are essentially unhydrated as compared to glycogen which is very hydrated.
2. Acetyl CoA units are shuttled out of the mitochondria via citrate (which reacts with CoA in the cytosol to produce acetyl CoA and malate). The carbon units are returned to the mitochondria via pyruvate (following decarboxylation of malate).
3. Excess acetyl CoA is converted to ketone bodies when OAA levels are limiting but energy requirements are high. Ketone bodies are produced as a result of starvation (or diabetes).
4. No, because animals cannot convert acetyl CoA to pyruvate. The only major source of stored energy for glucose production is amino acids or OAA. Note that the glycerol component of triglycerides does contribute in a minor way to carbohydrate production, but the vast majority of stored energy in fatty acids cannot be utilized as a source of glucose.
5. Blocking pancreatic lipase in the intestine prevents absorption of dietary fats because triglycerides cannot cross the intestinal lining (they must first be converted to fatty acids). This would function as an anti-obesity drug because obese people tend to eat too much fat and they would lose weight by burning calories from stored fat. Orlistat would need to be eaten prior to eating a meal (or with the meal) as its mode of action is within the small intestine. Side effects would include anything associated with fat in the intestine (intestinal cramping, fecal urgency, etc.).
6. Because pancreatic lipase does not recognize it as a substrate and it passes through the body without giving up its fatty acid components for energy storage. Fat-soluble vitamins associate with the hydrophobic fatty acids and are excreted. Olestra-containing foods are fortified with extra vitamins to replace what is theoretically lost.
7. Tay Sachs disease is a neurological disorder caused by a defect in (or lack of) a required enzyme (beta-N-acetylhexosaminidase) for sphingolipid (ganglioside) metabolism. The disease phenotype is caused by a build-up of the ganglioside GM2 substrate which is not degraded. Tay Sachs disease is rare today because of prenatal diagnosis which is able to detect fetuses with the disease prior to birth. Genetic pre-screening is used to identify prospective parents as Tay Sachs carriers with counseling to assess risks.
8. High intracellular levels of cholesterol inhibit a) the enzyme HMG CoA reductase which shuts down de novo cholesterol synthesis, and b) synthesis of the LDL receptor which reduces receptor-mediated endocytosis and thereby decrease cholesterol uptake from the serum.
9. Without carnitine acyltransferase, there is no fatty acid oxidation and no acetyl CoA is produced for ketone body formation. Hypoglycemia (low blood sugar) results from lack of ATP from fatty acid oxidation (acetyl CoA → citrate cycle → Ox Phos) which is needed to drive gluconeogenesis during starvation.

10. Any two of the following:

- progesterone; prepares uterus for implantation of ovum
- androgens; male secondary sex characteristics
- estrogens; female secondary sex characteristics
- glucocorticoids; gluconeogenesis, fat mobilization
- mineralocorticoids; salt balance, kidney functions

11. Bile salt resins are ingested which bind to bile salts in the intestine and result in the removal of bile salts from the body. This treatment lowers cholesterol levels because the available cholesterol is converted to bile salts to replace what was lost. Lovastatin is an HMG CoA Reductase enzyme inhibitor which blocks the first commitment step in de novo cholesterol biosynthesis.

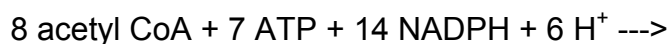
12. Citrate activates acetyl CoA carboxylase by the mechanism of allosteric control. This makes sense because under conditions in which cytosolic citrate levels are high it signals that the mitochondrial matrix is not utilizing excess citrate (or acetyl CoA) and therefore it is time to store energy as fat.

13. The baby has a 50% chance of being a carrier. The baby will grow up to be biologically normal because 50% of the enzyme (beta-N-acetylhexosaminidase) is sufficient to prevent toxic build-up of the sphingolipid (GM2 ganglioside).

14. Deficiency in 21-hydroxylase results in masculinization of females due to overproduction of androgens. Kidney dysfunction is due to the block in aldosterone (mineralocorticoid) production by the 21-hydroxylase deficiency. Aldosterone is required for the control of salt balance and normal kidney functions.

15. Each mole of triglyceride contains one mole of glycerol which can be converted to dihydroxyacetone phosphate, a substrate in gluconeogenesis. Humans do not contain the necessary enzymes to convert fatty acids to gluconeogenic intermediates.

16. The net reaction of palmitate synthesis is:



The 14 NADPH is generated by the citrate shuttle and Pentose Phosphate Pathway.

17. The majority of cholesterol biosynthesis takes place in the liver and the key regulated enzyme is HMG CoA Reductase.

18. Acetyl CoA carboxylase is the key regulated enzyme in fatty acid synthesis. Glucagon is the "hunger hormone" and signals low blood glucose levels. Turning off fatty acid synthesis makes sense because glucose units should be exported to the blood not metabolized by glycolysis to produce more acetyl CoA. Insulin signals high glucose levels in the blood and therefore it makes sense to stimulate fatty acid synthesis by activating the enzyme acetyl CoA carboxylase.

19. COX-1 is an enzyme that protects the stomach lining from damage. COX-2 is a enzyme involved in inflammation and is responsible for clinical symptoms. Celebrex is COX-2 specific inhibitor that has a high affinity for the active site of COX-2, but is too large to bind to COX-1. Aspirin is a relatively small molecule that binds to the active sites of both COX-1 and COX-2. Aspirin is a less effective anti-inflammatory agent because of its low affinity for COX-2 and it also has the associated side effect of stomach bleeding due to inhibition of COX-1.

20. The enzyme 5-alpha-reductase is required to convert testosterone to dihydrotestosterone (DHT) which is a more potent androgenic hormone. A deficiency in this enzyme causes testicular feminization in young boys because they lack sufficient levels of DHT to promote complete development of male reproductive organs. However at puberty, sufficient amounts of testosterone are produced by the underdeveloped testes to result in an androgen surge thus promote masculinization.