Chapter 19 Questions
Fatty Acid Metabolism

1) Study exercises; 2, 3, 5, 6 and 7

- 2 – Lipoprotein package hydrophobic and ampipathic lipids into water-soluble particles for transport in the blood stream. Chylomycrons transport dietary lipids from the intestine through the lymphatic system to the bloodstream. They deliver triacylglycerols to skeletal muscle and adipose tissue, and cholesterol to the liver. The liver makes VLDV particles, which also contain TAGS and cholesterol. The TAGs are degraded by lipoprotein lipase in the capillaries and peripheral tissues so they can be absorbed by the cells. As VLDL gives up its TAGs and becomes smaller and denser, VLDL becomes and IDL and then an LDL before being taken up by the liver. HDL particles transport cholesterol from the tissues to the liver. They are assembled in the plasma and contain mostly cholesterol esters and are transferred to VLDL.
- 3 – Fatty acids are first activated by linkeing them to CoA via a high energy thioester bond (know what that means). The formation of this bond consumes the free energy of one phosphoanhydride bond of ATP. After transport into the mitochondrion, the acyl-CoA is degraded, two carbons at a time, in a process called beta oxidation. A double bond is fromed by a dehydration reaction ant the electrons are transferred to the mito's ETS. Then water is added across the double bond to from a 3-hydroxylacyl-CoA. NAD+ dependent dehydrogenation gives a beta-ketoacyl-CoA and NADH. Finally the double bond is cleaved by attack of a second CoA, eliminating acetyl-CoA and producing an acyl-CoA two carbons shorter than the original substrate. These last four reactions are repeated untill the entire acyl chain has been degraded to acetyl units.
- 5 Ketone bodies are synthesized from ACoA in liver mitochondria. Three A-CoAs are used to produceacetoacetate and an A-CoA. Acetoacetate an be reduced by NADH to procude beta-hydroxybutyrate, or it may be non-enzymatically decarboxylated to acetaone and CO2. Acetoacetate and beta-hydroxybutyrate travel from the liver to tissues to be used as alternative fuels to glucose. ß-hydroxybutyrate is oxidized to NAD+ to produce acetoacetate. Acetoacetate is then linked to CoA donated by succinyl CoA. A free CoA group then attacks the acetoacetyl-CoA to produce 2 acetyl-CoA for further use in the mito of the receiving tissue.
- 6 – A fatty acid in the form of acyl-CoA is transported out of the mitochondrion by a shuttle system. The acyl portion of acyl-CoA is transferred to carnitine and the acyl-carnitine is transported across the inner mito membrane by a carrier protein. In the matrix, the acyl group is transferred back to CoA from the mitochondrial pool of CoA to produce the original acyl-CoA, and carnitine returns to the cytosol. Acetyl-CoA produced in the matrix is shuttled back to the cytosol via an ATP-citrate lyase shuttle. Citrate and not acetyl-CoA or oxaloacetate is transported across the membrane.
- 7 – Fatty acid oxidation and synthesis are both four step cyclic pathways that proceed in increments of C2 units, and many of their intermediates are chemically similar. The differences are a) oxidation occurs in the mito and synthesis occurs in the cytosol; b) the acyl groups is linked to CoA for oxidation and ACP for synthesis; c) FAD and NAD+ are electron acceptors in oxidation, whereas NADPH is the electron donar in synthesis; and d) synthesis but not oxidation involves a C3 unit, malonyl Co-A which is critical for the regulation of fatty acid synthesis

2) Name the irreversible enzyme in fatty acid synthesis. What is the thermodynamics which drive this reaction? Acetyl-CoA carboxylase. The thermodynamics are similar to the other one carbon additon enzymes. The loss

of the ATP irreversibly drives this reaction. Another point to remember is the rebulation of carboxylase 1) citrate allosterically activates by polymerization 2) palmitate allosterically inhibits by forcing the enzyme into the dimer state 3) AMP protein kinase activates by phosphorylation 4) protein phosphatase 2A reactivates the enzyme by removing the phosphate from AMP PK

3) Write each of the lipoproteins and indicate their main biochemical function. (hint where do they come from what do they carry where do they go)
Look at the answer above and know chylomycrons, VLDL, LDL and HDL.

4) Which is the good cholesterol? Is this statement misleading? Is it realy all cholesterol?
In the simple scheme of things, HDL is the good cholesterol. That is an improper statement though. HDL is more than cholesterol it is a lipoprotein transport vesicle that is responsible for carrying cholesterol back to the liver from the extrahepatic tissue so that the cholesterol can be degrades as bile salts and lost through stool. Another fact is that cholesterol is not directly involved with plaque formation. Rather when minor injuries occurs, the platelets form foam cells which in turn take up the cholesterol and harden the arteries. A high cholesterol level, specifically LDLs lead to an increased availability, for these cells to proceed to block the blood flow.

5) T/F Dietary triacylglycrides (TAGs) are transported through the intestinal wall into the lymphatic system unchanged False, They are broken down to free fatty acids and re-assembled on the other side of the intestinal wall.

6) Which of the following statements about the triacylglycerols stored in adipose tissue are correct?
a) They are hydrolyzed to form fatty acids and dihydroxyacetone
b) They are hydrolyzed by a lipase that is activated by covalent modification ***
c) They release fatty acids that can be oxidized to CO_2 and H_2O ***
d) They can yield a precursor of glucose
e) They are mobilized by epinephrine or glucagon ***

7) How is pyrophosphate involved in the activation of fatty acids for ß oxidation?
Skip this one

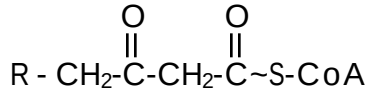
8) In fat cells the initial liberation of fatty acid from triacylglycerol is due to
a) phospholipase A
b) triacylglycerolipase
c) hormone sensitive lipase ***
d) fatty acid-hydrolyase
e) I don't know I have only stored fatty acids never released them

9) The de novo biosynthesis of fatty acids takes place mainly in the
a) Cytosol ***
b) mitochondria
c) extra cellular matrix
d) within the inner mitochondrial matrix
e) endoplasmic reticulum

10) Biotin is involved in which of the following:

a) Malonyl CoA production ***
b) AcetylCoA activation to Acyl-carnitine
c) Transport across the inner mitochondrial membrane
d) The first reduction step in ß oxidation

11) Draw the next step in ß oxidation assuming the following molecule is an intermediate.



the next step would produce beta Hydroxybutyryl- ACP The above shown CoA is wrong, it should have been an ACP.

12) What would the effect of a carnatine transferase deficiency in a person who is in a starvation state? In the starvation sate the fatty acids need to be transported into the mitochondria for beta oxidation. This can not happen with this deficiency. Therefore there would be a sever hypoglycemic condition for this patient due to the lack of FA oxidation. Furthermore there would be little ketone bodies because only amino acids could form acetyl CoA. Remember the main source of A-CoA is from fatty acids.

13) Why were researchers surprised to find that the production of fatty acids is dependent on bicarbonate, yet radioactive bicarbonate is not incorporated into the new fatty acid? Bicarbonate indicates a one carbon is added. This is a common trait when adding carbons onto comounds. However fatty acid does not grow by one carbons at a time, rather by two. In addition the carbon from bicarbonate is only used to activate the acetyl CoA into malonyl CoA. After the two carbons are condensed onto the growing carbon chain the carbon from bicarbonate is lost.

14) Why does the concentration of ketone bodies increase in uncontrolled diabetics and folks on a high protein low carbohydrate diet?

15) Explain the involvement of carnitine in the ß oxidation of fatty acids. – transfer of fatty acids into the mitochondria. It is important to remember that the carnitine transfer by a thermodynamically neutral process.

16) Which of the following statements about acetoacetate and 3-hydroxybutarate are correct?
a) They are normal fuels for heart muscle and brain tissue
b) They are predominately synthesized in the liver ****
c) They both can give rise to acetone
d) They can be regarded as a water soluble transportation form of citrate in the blood

17) Which of the following statements answers the sentence correctly? The major product of the fatty acid synthase complex in mammals is_____
a) oleate
b) stearate
d) linoleate
e) palmitate ****

c) stearoyl CoA f) palmitoyl CoA

18) Calculate the ATP and NADPH requirements for the synthesis of lauric acid (C12:0) from acetyl CoA and from pyruvate. Don't forget to account for the activation and that there is an n-1 number of rounds.