

Glycerolipid and Sphingolipid Metabolism

1. Phosphatidic acid is an immediate precursor of CDP-diacylglycerol, which is a precursor of the various glycerophospholipids. CTP combines with phosphatidic acid to yield a pyrophosphate and CDP-Diacylglycerol. Activation by CDP yields a high energy activated intermediate that can be readily converted to phosphatidyl glycerophospholipids.
2. From CDP-diacylglycerol, phosphatidyl serine can be made, as can phosphatidyl ethanolamine and phosphatidyl choline. Synthesis of phosphatidyl choline from phosphatidyl ethanolamine requires methyl groups donated by S-Adenosyl-Methionine (SAM). Loss of the methyl groups by SAM yields S-Adenosyl-Homocysteine (I incorrectly said S-adenosyl-homoserine in the lecture).
3. Phosphatidyl ethanolamine (and phosphatidyl choline - derived from phosphatidyl ethanolamine) can both be made independently of phosphatidic acid biosynthesis. For this pathway, CDP-ethanolamine is the activated intermediate and the phosphoethanolamine of it is added to diacylglycerol to form phosphatidylethanolamine. Phosphatidyl choline can be made by the same methylation scheme in point 4.
4. Sphingolipids are synthesized beginning with palmitoyl-CoA and serine. Addition of a fatty acid to the amine group yields a ceramide. Addition of sugars to a ceramide yields either a cerebroside (single sugar added) or a ganglioside (complex sugar added).
5. Deficiencies in enzymes that degrade sphingolipids (particularly cerebroside and gangliosides) are linked to neural disorders. One such disorder is Tay-Sachs disease.
6. Cholesterol is an important component of membranes, particularly in the brain. Cholesterol can be synthesized totally from acetyl-CoA.
7. Steroids include all compounds synthesized from cholesterol. This includes steroid hormones, vitamin D, bile acids, and other related compounds.
8. Isoprenes (also called isoprenoids) include the steroids and other compounds, such as Vitamin A and E that are also made from isoprene units.
9. Isoprene - 5 carbon units - 1) isopentenyl pyrophosphate and dimethylallyl pyrophosphate. Each is made from acetyl-CoA molecules. Synthesis of isopentenyl pyrophosphate and dimethylallyl pyrophosphate comes from mevalonate, which, in turn, comes from HMG-CoA, so isoprenoid biosynthesis overlaps partly with ketone body synthesis.
10. The most important enzyme in cholesterol biosynthesis is HMG-CoA reductase. It converts HMG-CoA to mevalonate and is the primary regulatory enzyme in cholesterol biosynthesis. Cholesterol is a feedback inhibitor of the enzyme.
11. Reaction of isopentenyl pyrophosphate with dimethylallyl pyrophosphate yields a 10-carbon intermediate, geranyl pyrophosphate

12. Reaction of geranyl pyrophosphate with isopentenyl pyrophosphate yields a 15 carbon intermediate - farnesyl pyrophosphate.

13. Reaction of two farnesyl pyrophosphates yields a 30 carbon intermediate - squalene.

14. Further reaction of squalene yields a cyclic intermediate, lanosterol. Synthesis of cholesterol from lanosterol requires an additional 19 steps. From cholesterol, one can synthesize the bile salts, which are useful in solubilizing fat in the diet. Cholesterol also leads to synthesis of the steroid hormones.

End of material for exam 1

New material for exam 2 starts here - Note this may be different from what it says on the video for the classroom version.

15. Cholesterol in the body is either there as a result of 1) synthesis; 2) diet; or 3) storage/recycling.

16. In the digestive system, bile acids and mechanical agitation of the stomach help emulsify fats.

17. In the intestines, hydrolysis of fatty acids from fats by lipases (pancreatic lipase), yield soapy like substances that help emulsify lipids for transport across the intestinal wall.

18. After movement across the intestine, lipids are packaged in chylomicrons. They move through the lymph system into the capillaries where they get stuck.

19. Action of lipoprotein lipase in the capillaries removes some of the fat from the chylomicrons and they shrink in size and exit the capillaries and move to the liver. They are taken up there and released, when needed as VLDLs. These travel the blood system and get converted to IDLs and ultimately LDLs. Note that cholesterol ONLY gets into cells via receptor-mediated endocytosis of the LDL at the target cells.

20. The liver is involved in sensing the body's need for lipids via LDL receptors. If it senses lipids are needed, VLDLs are packaged by the liver and released these get degraded by lipases and other enzymes to IDLs and LDLs. If the liver LDL receptor cannot detect LDLs in the blood, it continues to release more lipids in lipoprotein complexes, thus elevating the LDL concentration in the blood.