

Cholesterol Metabolism

November 6, 2003
(Only three more weeks 'til
Thanksgiving)

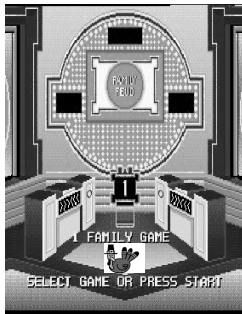




lecture topics

- Overview of cholesterol
- Cholesterol synthesis
 - Regulation
- Cholesterol degradation and elimination
 - Bile acids and bile salts
- Cholesterol/lipid trafficking/delivery
- Steroid hormones

Top four reasons we need cholesterol???????

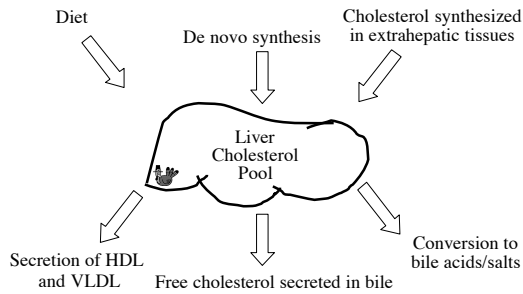


Top four reasons we need cholesterol???????

- 1) Membrane component- controls fluidity
- 2) Precursor of bile acids and bile salts
- 3) Precursor of steroid hormones
- 4) Precursor of vitamin D

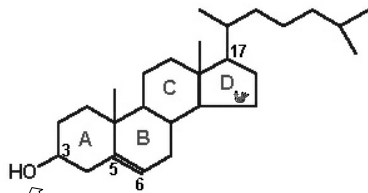


major sources of liver cholesterol



major routes by which cholesterol exits liver

structure of cholesterol



site of attachment of fatty acid in cholesterol ester

lecture topics

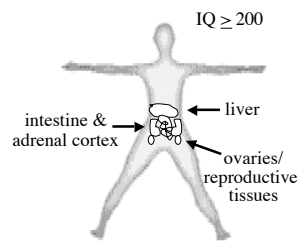
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cholesterol biosynthesis

- ~50% results from de novo synthesis



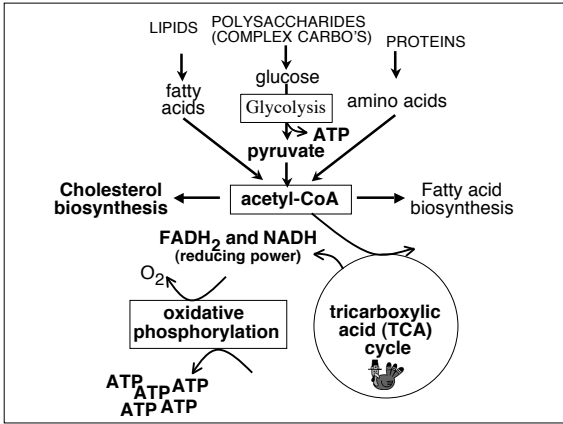
cholesterol biosynthesis

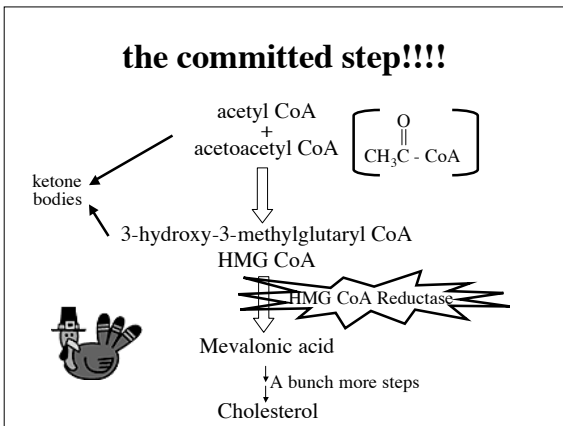


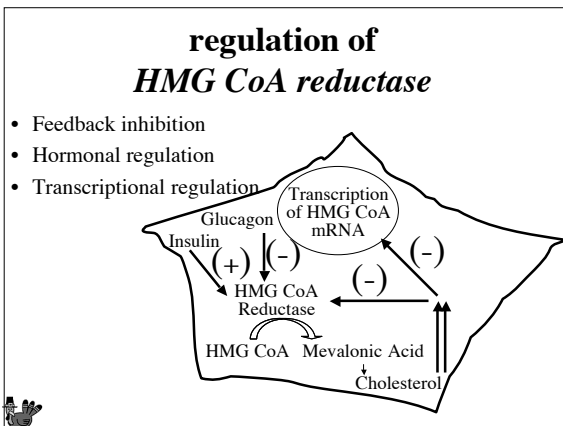
CATEGORY: Precursor for cholesterol biosynthesis

- Also requires NADPH and ATP
- Highly regulated process
- Occurs in the cytoplasm
 - Cytosol
 - Endoplasmic reticulum



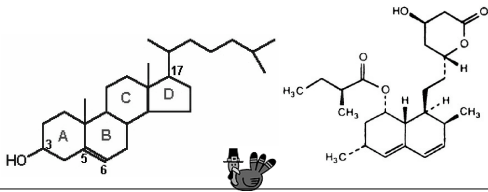






HMG CoA Reductase as a clinical target for statins

- lovastatin (Mevacor®)
- Zocor®
- Lipitor®



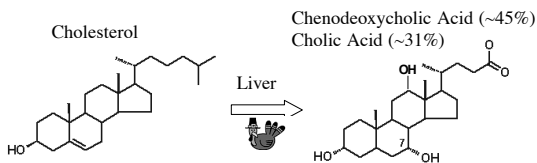
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degradation of cholesterol

- Ring structure not metabolized
- Cholesterol eliminated by two means:
 - Conversion to bile acids (excreted in feces)
 - Secretion into bile (transport to intestine)





clinical correlation

- cholesterol gallstone disease
 - cholelithiasis
- treatment
 - gall bladder removal
 - chenodiol administration (chenodeoxycholic acid)



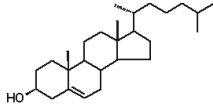
clinical correlation

- Niemann Pick Type C
 - Cholesterol trafficking disorder
 - Molecular basis not understood but cholesterol accumulates in the liver and spleen
 - Mutations in two genes (NPC1 and NPC2) cause the disease
 - Function of the genes is not known BUT we study it in my lab!

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cholesterol trafficking/delivery

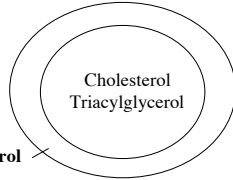


- Plasma lipoproteins carry cholesterol and other lipids (triacylglycerols) throughout the body



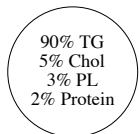
plasma lipoproteins

- Chylomicrons (Intestine)
- Very Low Density Lipoprotein
 - VLDL (Liver)
- Low Density Lipoprotein
 - LDL
- High Density Lipoprotein
 - HDL

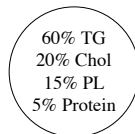


Phospholipid, Cholesterol
Protein

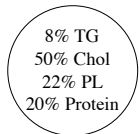
composition of plasma lipoproteins



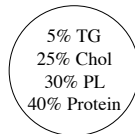
Chylomicrons



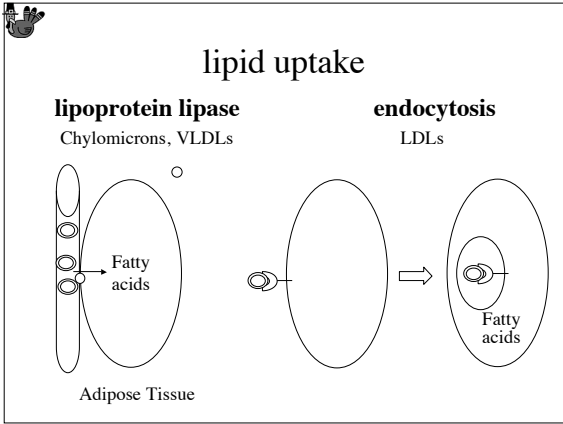
VLDL



LDL





HDL



clinical correlation

- Artherosclerosis (Monday)
- Coronary heart disease
- Hyperlipidemia (lipase deficiency)





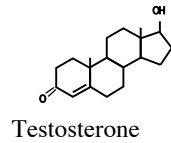
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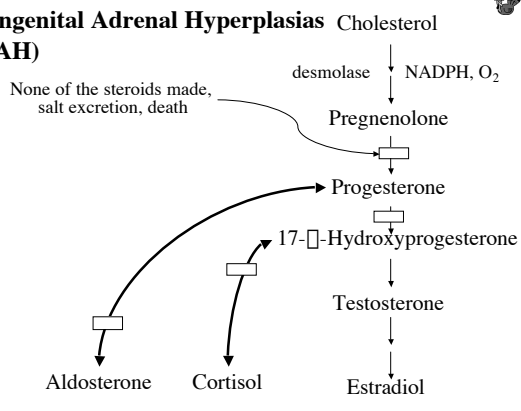


steroid hormones

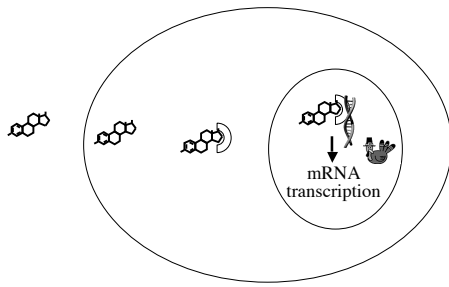
- glucocorticoids (cortisol)
- mineralcorticoids (aldosterone)
- androgens
- estrogens
- progestins



Congenital Adrenal Hyperplasias (CAH)



mechanism of steroid hormone action





take home message



- cholesterol is essential (too much is bad)
- synthesis of cholesterol is carefully regulated
 - HMG CoA Reductase
- cholesterol is not degraded but eliminated through bile
- cholesterol/lipid trafficking requires lipoproteins
- cholesterol is the precursor of steroid hormones
