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Cholesterol

Wednesday, January 16, 2008
10:30 AM

1. Know the general pathway for cholesterol biosynthesis.
 - a. All carbons are derived from acetate
 - b. Cytosolic
 - c. Mechanism
 - i. Thiolase:Acetyl-CoA Acetyltransferase: $2 \text{ Acetyl-CoA} \rightarrow \text{Acetoacetyl-CoA} + \text{CoASH}$
 - ii. HMG-CoA Synthase: $\text{Acetoacetyl-CoA} + \text{Acetyl-CoA} \rightarrow \text{HMG-CoA} + \text{CoASH}$
 - iii. HMG-CoA Reductase: $\text{HMG-CoA} + 2 \text{ NADPH} \rightarrow \text{Mevalonate} + 2 \text{ NADP}^+ + \text{CoA}$
 - iv. Mevalonate \rightarrow Squalene
 - v. Squalene \rightarrow Lanosterol
 - vi. Lanosterol \rightarrow Cholesterol
2. Know the major site of regulation. \rightarrow HMG-CoA Reductase
3. Know how HMG-CoA Reductase is regulated.
 - a. Long term feedback control of amount of enzyme
 - i. Decrease in cholesterol concentration \rightarrow release of ER membrane protein
 - ii. Sterol Regulatory Element-Binding Protein and SREBP Cleavage Activating Protein bound together on ER membrane
 - iii. Sterol levels decline and complex migrate to Golgi
 - iv. Two cleavages result in SREBP migrating to nucleus
 - v. Transcription of HMG-CoA reductase and LDL receptor gene
 - vi. Due to this system, dietary cholesterol control alone does not necessarily work because you just produce more cholesterol
 - b. Covalent Modification
 - i. Activated by dephosphorylation by PPP
 - 1) Insulin activates PPP
 - 2) Glucagon \rightarrow PKA \rightarrow AMP Kinase \rightarrow phosphorylates/inactivates HMG CoA Reductase
 - ii. Statins are competitive inhibitors of HMG CoA Reductase