

Lipoproteins III/Cholesterol--7 Nov. 2002

1) What are the two ways cholesterol can be transported from the peripheral tissues to the liver?

There are two pathways of reverse cholesterol transport.

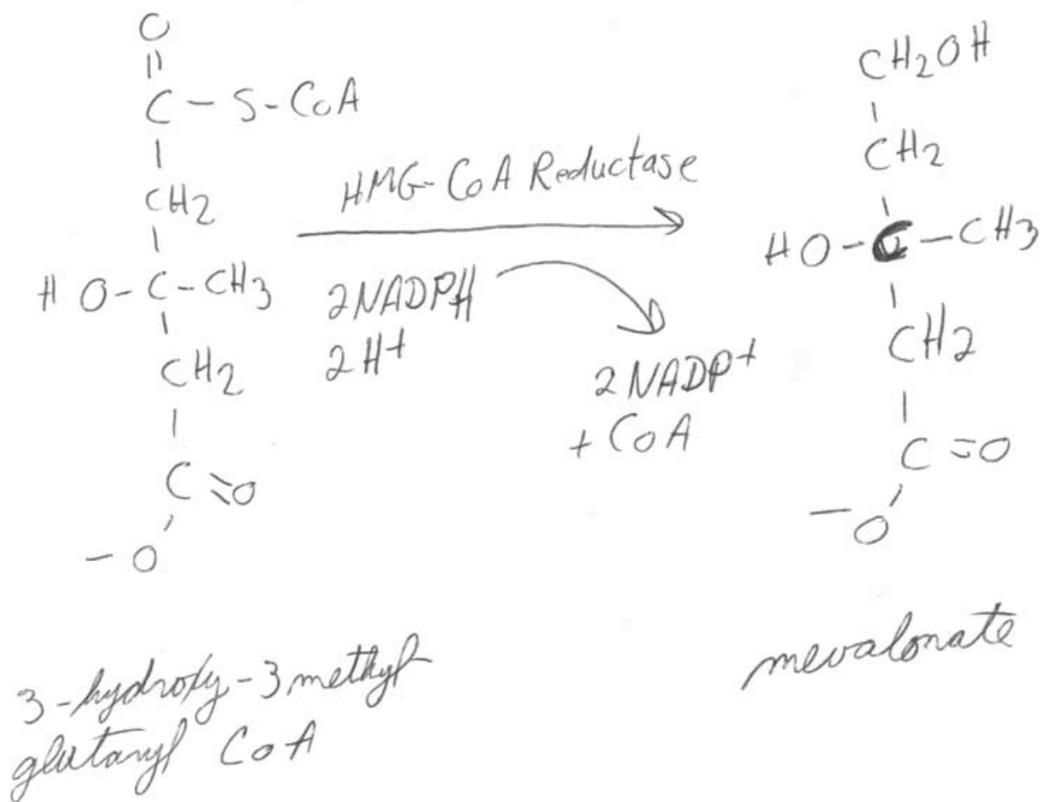
The indirect pathway is for nascent HDL to acquire cholesterol esters from the peripheral tissues in the LCAT reaction to build a cholesterol ester core. CETP then exchanges the chol esters of spherical HDL for TG and PC of VLDL and IDL. IDL is converted into LDL during these exchanges. LDL can be taken up by hepatic LDL receptors to deliver the chol esters to the liver. This results in reverse cholesterol transport. Reverse means from the peripheral tissues back to the liver.

The other pathway is more direct. The spherical HDLs that contain a chol ester/TG core interact with the SR-BI (scavenger receptor, class B, type I) on hepatic cells and the cholesterol esters are unloaded and taken up by the liver. This is the direct pathway of reverse cholesterol transport since the cholesterol that flows into HDL from the peripheral tissues is directly delivered to the liver by HDL. (NOTE: The TGs of spherical HDL are hydrolyzed by HL and are also taken up by the liver.)

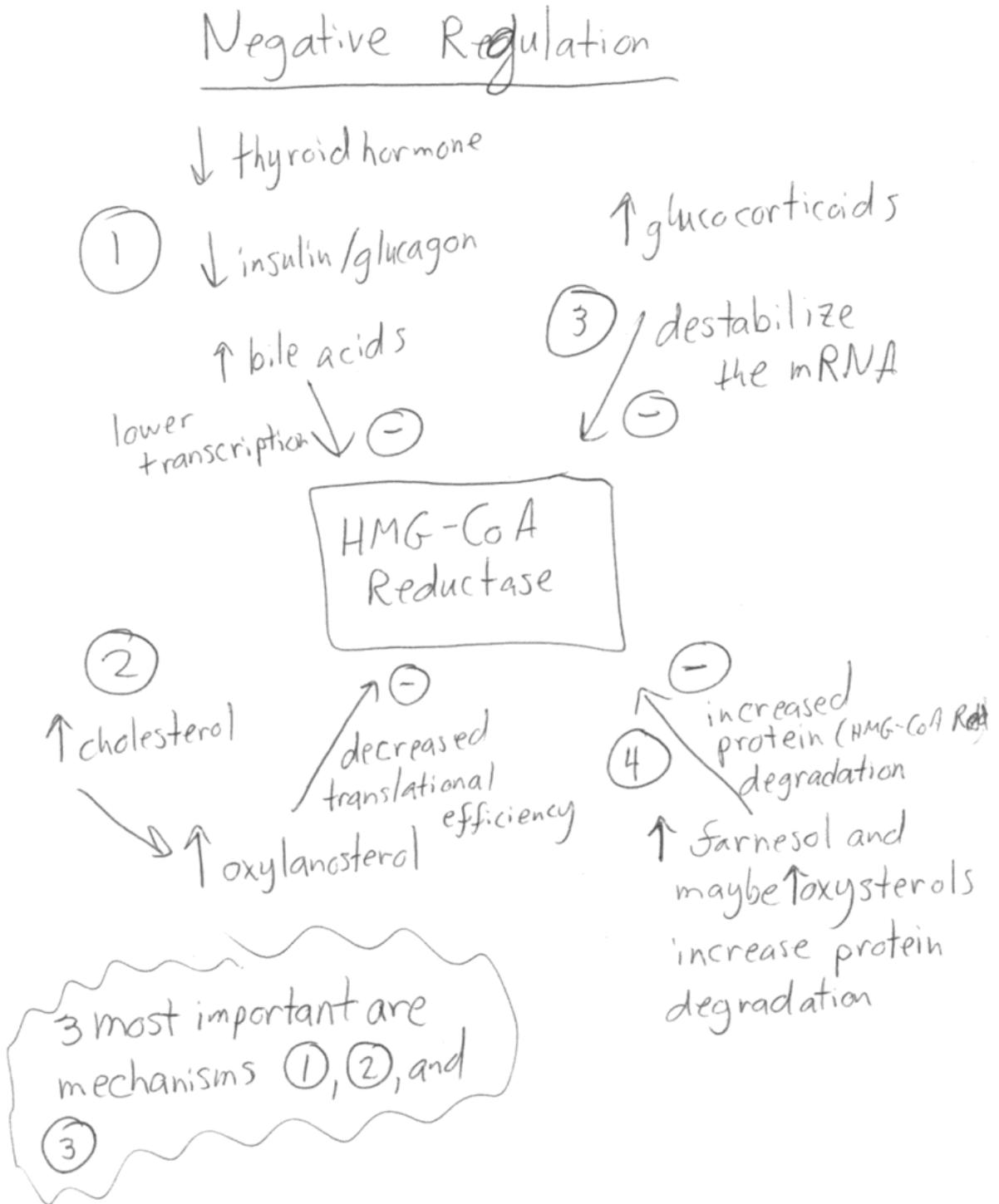
Why is it important to transport cholesterol to the liver?

Because the only way to remove molecules that contain the steroid nucleus (the fused 4 ring structure found in cholesterol, bile acids, and steroid hormones) from the body is by excretion in the feces. Of the amount lost in the feces, about half is lost as cholesterol secreted in the bile and about half is lost as bile acids (especially lithocholic acid) that were not reabsorbed.

2) Draw the reaction catalyzed by HMG-CoA reductase.



Draw a diagram illustrating how HMG-CoA reductase is regulated.



Positive Regulation

↑ Thyroid hormone

↑ Insulin/glucagon

↓ Bile acids

⊕ transcription

HMG-Co
Red.

⊕ increased mRNA
stability

Thyroid hormone

Estrogen

Note that even though increasing levels of thyroid hormone and estrogen increase the amount of HMG-CoA reductase activity in a cell, they don't cause high blood cholesterol. This is because they increase the amount of LDL receptors expressed on the liver increasing clearance of LDL-C.

What class of drugs inhibits HMG-CoA reductase and how do they work?

The drug class is called the statins. They resemble mevalonate and they are competitive inhibitors of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway. They work by both lowering cholesterol synthesis and by causing increased hepatic LDL receptor synthesis. This results in less LDL circulating in the plasma due to increased hepatic LDL uptake.