Synthesis of bile acids

-Bile acids are derived from *cholesterol* .

-*Cholesterol* is converted in several steps into a compound called *cholic acid*

 Cholic acid is a bile acid , it looks like cholesterol with steroid ring but there are **some differences** :

 1-Shorter side chain (5 instead of 8 carbons) ends with carboxyl group .

 2-Two more hydroxyl groups .

-Cholic acid is an **amphipathic** molecule ; it contains hydrophilic polar region (carboxyl group and hydroxyl groups ) and hydrophobic non polar region .

-The synthesis of bile acids requires *a rate- limiting step* which is : **Hydroxylation at carbon #7**

After this we could have hydroxylation on carbon #11 to get a cholic acid or another bile acid if we couldn’t have the hydroxylation .

-As any rate-limiting step, *this step is regulated* by:

 **Feedback inhibition** : the end product “cholic acid” inhibits an early step (On the other hand Cholesterol stimulates the synthesis by stimulate *cholesterol 7-alpha- hydroxylase* to add hydroxyl group on carbon #7).

-Bile acids are *relatively weak acids* ,therefore we make stronger acids by :

 **Conjugation** with :1-Glycine(Amino acid with carboxyl group)

 2-Taurine(Amino acid with sulfate group-acidic group-)

 **\*\*You don’t have to memorize the structures , Recognizing that the structure is a bile acid is enough.**

**-**Bile salts **:** have a conjugated amino acids ,stronger acids in the ionized state .

-Bile acids and bile salts can be used interchangeably .

(Conjugated bile acids = bile salts )

**-In liver** cholesterol is converted into *primary bile acid*

 *Primary bile acids :Before reaching the intestine .*

- Primary bile acids are conjugated and secreted **into the intestine** to act as *emulsifiers .*

-Bacterial action on the bile salts acts to remove one hydroxyl group to have *secondary bile acids*/secondary bile salts.

-95% of the bile acids are reabsorbed and the other 5% (~0.5 g/day)are excreted with feces .

-The reabsorbed bile acids go back to liver to get conjugated but in this case they are called *secondary bile acids not primary (because they have reached the intestine and acted upon the bacterial enzymes ).*

Lowering cholesterol level

-Cholesterol is bad for your health , its one of the factors that increase the risk of coronary artery diseases/heart diseases .

-To lower cholesterol level:

 **1-Lowering the intake** :

 Cholesterol is synthesized by most cells(about 1 g/day) and obtained by the diet (0.3 g/day by the diet that contains low cholesterol )

 -If we lower the intake to make it zero ,synthesis will increase so lowering cholesterol intake by itself isn’t sufficient for lowering plasma cholesterol level .

**2-Increasing the ratio of poly unsaturated fatty acids to saturated fatty** acids will decrease cholesterol level .

**3-Increasing dietary fibers(Binding to the bile acid and preventing the re-absorption )and daily ingestion of plant steroid esters (They act to reduce absorption of cholesterol from gut )**

**4-Inhibiting the synthesis** (HMG CoA reductase)

**5-Enterohepatic Circulation of Bile Acids (By decreasing it )**

Inhibition of synthesis

*Simvastatin (from Statins drugs*) can bind to the active site of HMG CoA reductase (Where HMG CoA binds)and cause inhibition of the enzyme .

Atorvastatin in Lipitor acts to inhibit the senthysis.

*cholestyramine /Polyamines* can bind to the bile acid and prevent their re-absorption so the amount that is secreted with the feces will be more than 10% and less than 90% is re-absorbed.

If the amount of bile acid is decreased this will lead to convert more cholesterol to bile acid by *releasing the inhibition of hydroxylase* and by this we lower the cholesterol level in plasma .

Esterification of Cholesterol

Cholesterol could be in “Cholesterol ester phase “🡪By having a fatty acid on carbon #3

**Esterification could happen in the plasma or in the cells “for the purpose of storage-Cholesterol is stored in cells as ester”**,we need to add fatty acid so we use the active form “fatty acyl CoA which is the active donor of fatty acids in the cell”

**In the cell:**

We *transfer* fatty acid from fatty acyl CoA to cholesterol :

 -**Substrates for this reaction are fatty acyl CoA and Cholesterol**

 **-Type of the reaction is transfer of fatty acid**

 **So the the name of the enzyme is :*Acyl CoA Cholesterol acyltrasferase (ACAT)***

**In plasma :**

CoA is needed in the cell ,not found in the plasma so acyl CoA isn’t the donor of the fatty acid in plasma .

We can find cholesterol in plasma in *lipoproteins* that contain phospholipids too, so the donor of the fatty acid in this case is Lecithin with 2 fatty acids on carbon #1and2 “Phosphatedyl cholin “

If one of the fatty acids is removed then we get Lyso-Lecithin “Lyso-Phosohatedyl cholin”

**So in this case the enzyme is : Lecithin: Cholesterol Acyl Transferase (LCAT)**

**This reaction occurs in plasma in lipoproteins**

**Phospholipids of lipoproteins is the donor of the fatty acid**

**-**We have to pay attention for serum cholesterol because by increasing it increases the risk of *death from coronary heart disease (CHD).*

The target always is to have a *level of cholesterol less than normal* .

All cells have the ability to make cholesterol but not all of them really synthesize cholesterol ,since some cells receive cholesterol so they don’t need to synthesize it ,to regulate we always regulate HMG CoA reductase

Regulation of HMG CoA reductase

When cholesterol level increases it inhibits HMG CoA reductase.”an early step to inhibit all the intermediates “

 -**Regulation of gene expression**

Transcriptional factors are required to bind DNA upstream from certain genes , so at 5’ “up stream “

We have a sequence **SRE “STEROL REGULATORY ELEMENT “** binds to transcriptional factors called**( SRE-BP )STEROL REGULATORY ELEMENT BINDING PROTEIN .**

Low cholesterol level means dissociation of binding proteins to transcript HMG CoA reductase .

 **- Covalent Modification**

Addition of a group to the enzyme covalently like phosphate group .

Phosphorylated from of HMG CoA reductase :Inactive

Dephosphorylated form :Active.

Amp dependent protein kinase : high level of AMP activate it to add phosphate group to HMG CoA reductase to make it inactive .

AMP level is high = energy level is low =level of ADP is low

**Note :Its not cyclic AMP protein kinase.**

Phosphatase reverses the mechanism .

 -**Hormonal Regulation**

Clucagon :stimulates the phosphorylated form “low blood glucose level so we should not synthesize”

Insulin :Well-fed state ,Stimulates phosphatase to keep the dephosphorylated form

 **- Proteolytic Regulation**

**High cholesterol level increases HMG CoA reductase proteolysis so decreases HMG CoA reductase.**

**Cholesterol** is vital for cells but can be fatal to the organism  **.**

**-Regulatory elements are attached to the endoplasmic reticulum , leave the ER by proteolysis which is activated by low cholesterol level.**

 Transport of Cholesterol in the Blood

In the form of lipoproteins because its in soluble in water

Chylomicron-TAG=remnant chylomicron

Chylomicron remnant ends up in liver, Dietary cholesterol is transported into the liver by Chylomicrons.

Cholesteriol in liver is transported by the form of VLDL that transforms in plasma to IDL ,LDL,HGL

 VLDL

Its function is transport TAG and cholesterol from the liver .

60% of VLDL is TAG they circulate in the plasma , gradually TAG is removed by hydrolysis so the density will be higher “

LDL receptors are found in a region called coated pit after binding LDL is taken by invagination and endocytosis “Coated vesicle “

LDL receptor is recycled and LDL particles are fused with lysosomes for degradation so we find cholesterol in plasma and we need to esterifiy it .

The rate of synthesis of LDL receptors is decreased by the presence of cholesterol in cytoplasm (down regulation for the receptors )

