Cholesterol (1)_231109_085506

Friday, 10 November 2023 8:40 AM

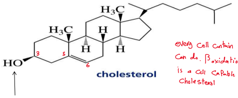
Cholesterol (1)_23110...

Normal Cortisol level : 150-200 mg/dl

All Eukaryotes synthesize cholesterol because it's a cell membrane component

Prokaryotes can't because they can't Produce acetylCoA.

Cholesterol


H₃C
H₃C
H
H
H
HO
3
5
6
cholesterol

every cell contain mitochonedria and can do. β oxidation and CAC is a cell capable of Producing Cholesterol

F.A. for esterification

27 carbon atoms : 8 C atoms in the side chain
17 C atoms in the 4 rings,
2 C atoms in side groups

Cholesterol

- It is the principal sterol synthesized from simpler substances by animals, but small quantities are synthesized in other eukaryotes, such as plants and fungi but almost completely absent among prokaryotes, which include bacteria.

- Although cholesterol is an important and necessary molecule for animals, a high level of serum cholesterol is an indicator for diseases such as heart diseases and arteriosclerosis.

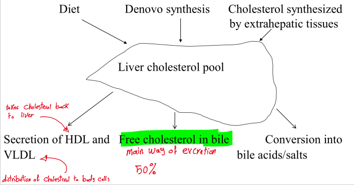
- Cholesterol is recycled, excreted by the liver via the bile into the digestive tract, then, about 50% of the excreted cholesterol is reabsorbed through enterohepatic circulation to liver again.

Bacterial flora in large intestine is very important because before glucose reabsorbtion by the flora converts cholesterol to nuetral steroids wich can't be reabsorbed.

Ergosterol

- Phytosterols (plant sterols) can compete cholesterol reabsorption in intestinal tract back into the intestinal lumen for elimination.

Sources of Cholesterol


Diet

Denovo synthesis

Cholesterol synthesized by extrahepatic tissues

Liver cholesterol pool

takes cholesterol back to liver

Secretion of HDL and VLDL

distribution of cholesterol to body cells

Free cholesterol in bile

main way of excretion

50%

Conversion into bile acids/salts

- MI is more common in males before menopausal age. Estrogen increases expression of LDL receptor gene

F LDL receptors = M LDL Receptors X 10

Functions

1- Cholesterol is required to build and maintain membranes; it regulates membrane fluidity (reducing the permeability of the plasma membrane to protons (H+ and Na+).

2- Within the cell membrane, cholesterol also functions in intracellular transport, cell signaling, formation of lipid rafts in the plasma membrane and nerve conduction providing insulation for more efficient impulses conduction.

3- Some researches indicate that cholesterol may act as an antioxidant.

4- Cholesterol is essential for the structure and function of caveola and clathrin -coated pits for endocytosis which can be investigated by using methyl β-cyclodextrin (MβCD) to remove cholesterol from the plasma membrane.

5- Within cells, cholesterol is the precursor molecule in several biochemical pathways:

A-In the liver, cholesterol is converted to bile acids and bile salts to solubilize fats in the digestive tract and aid in the intestinal absorption of fat molecules as well as the fat-soluble vitamins (A,D,E and K).

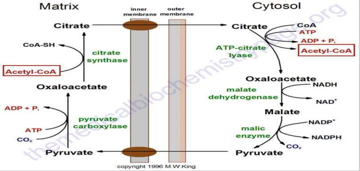
B- Cholesterol is an important precursor molecule for the synthesis of vitamin D3.

C- All the steroid hormones are synthesized from cholesterol. Glucocorticoids – mineralocorticoids – sex hormones

Cortisol ↗ Aldosteron ↗ Estrogen ↗ testosterone ↗

Cholesterol synthesis

- Similar to ketogenic pathway
- Occurs in cytosol and it is highly regulated
- The whole process is very energy-dependent in terms of ATP and NADPH.
- 80 % in liver, ~10% intestine, ~5% skin


Matrix
inner membrane
outer membrane
Cytosol
Citrate
CoA-SH
citrate synthase
Acetyl-CoA
Oxaloacetate
ADP + Pi
ATP
CO2
pyruvate carboxylase
Pyruvate
Citrate
CoA
ATP
ADP + Pi
ATP-citrate lyase
Acetyl-CoA
Oxaloacetate
NADH
malate dehydrogenase
NAD+
Malate
NADP+
malic enzyme
NADPH
CO2
Pyruvate
themedicalbiochemistrypage.org

copyright 1996 M.W.King

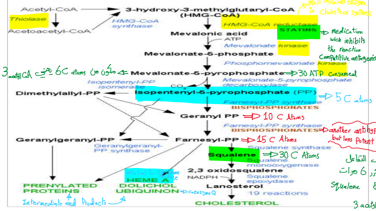
acetyl CoA wants to migrate from mitochondria to cytosol to produce cholesterols but acetyl CoA has no transporter so it joins oxaloacetate to form citrate

Citrate has non-specific transporter called TCA transporter.

ATP-citrate lyase enzyme in the cytosol degrades citrate back to acetyl CoA and oxaloacetate

This is called citrate shuttle.

- The rate limiting step occurs at HMG-CoA) reductase.
- Intermediates in the pathway are used for the synthesis of prenylated proteins, dolichol, coenzyme Q and the side chain of heme *a*.


Acetyl-CoA
Thiolase
Acetoacetyl-CoA
HMG-CoA synthase
3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
HMG-CoA reductase
STATINS
Mevalonic acid
ATP
Mevalonate kinase
Mevalonate-5-phosphate
Phosphomevalonate kinase
Mevalonate-5-pyrophosphate
Mevalonate-5-pyrophosphate decarboxylase
CO2
Isopentenyl-PP isomerase
Dimethylallyl-PP
Isopentenyl-5-pyrophosphate (PP)
Farnesyl-PP synthase
BISPHOSPHONATES
Geranyl PP
Farnesyl-PP synthase
BISPHOSPHONATES
Geranylgeranyl-PP
Farnesyl-PP
Geranylgeranyl-PP synthase
Squalene
Squalene synthase
Squalene monooxygenase
2,3 oxidosqualene
Squalene epoxydase
NADPH
Lanosterol
19 reactions
CHOLESTEROL
PRENYLATED PROTEINS
HEME A
important for Cytochrome oxidase
DOLICHOL
UBIQUINON
coenzyme Q
Intermediate and Products
Most important enzyme in Cholesterol synthesis
medication wich inhibits the reaction Competitive antagonism
3 acetylCoA يعني 6C atoms مكون من
30 ATP consumed
5 C atoms
10 C Atoms
15 C Atoms
another antihypercholestremic but less potent than statin
30 C Atoms

يعني التفاعل حيتكرر 6 مرات لإنتاج Squalene

وكل تفاعل يتطلب 3 acetylCoA

إذاً Cholesterol needs 18 CoA

6x3

=180 ATP

First 2 reaction of Ketogenesis and Cholesterol synthesis are the same but locations are different

the enzymes in Ketogenesis and Cholesterol synthesis are considered as isozymes

« β Keto thiolase + HMG-CoA Synthase

Heme A : Cytochrome Oxidase

Dolechol : GlycoProtiens

UBiquinone : Coenzyme Q

Regulating Cholesterol Synthesis

- Normal cholesterol level in the body (150 - 200 mg/dl) is maintained primarily by controlling the level of *de novo* synthesis which is regulated in part by the dietary intake of cholesterol.

- The cellular supply of cholesterol is maintained at a steady level by three distinct mechanisms:

1- Regulation of HMGR activity and levels

2- Regulation of excess intracellular free cholesterol through the activity of acyl-CoA cholesterol acyltransferase, ACAT ⇒ we basically added FA to cholesterol's hydroxyl group to limit cholesterol's mobility

3- Regulation of plasma cholesterol levels via LDL receptor-mediated uptake and HDL-mediated reverse transport.

Regulation of HMGR activity:

مهم

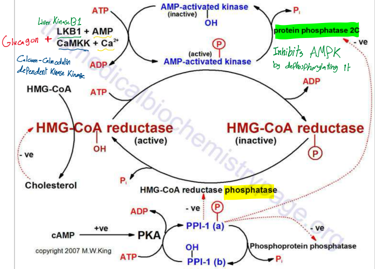
It is carried out by four mechanisms:

1- Feed-back inhibition
2- Rate of enzyme degradation
3- Control of gene expression (long term)
4- Phosphorylation –dephosphorylation (short term)

المحرك الأساسي تركيز الـ Cholesterol
داخل الـ Cell

وعندهم Sterol-sensing domain

- The first three control mechanisms are exerted by cholesterol itself where it acts as a feed-back inhibitor of pre-existing HMGR as well as inducing rapid degradation of the enzyme as a result of cholesterol-induced polyubiquitination of HMGR and its degradation in the proteosome.
- In addition, when cholesterol is in excess the amount of mRNA for HMGR is reduced due to the decrease in expression of gene.


ATP
AMP-activated kinase
(inactive)
OH
Pi
protein phosphatase 2C
- ve
Liver Kinase B1
LKB1 + AMP
Glucagon +
CaMKK + Ca2+
Calcium-Calmodulin dependent Kinase Kinase
(active)
P
AMP-activated kinase
Inhibits AMPK by dephosphorylating it
ADP
HMG-CoA
ATP
ADP
HMG-CoA reductase
(active)
OH
- ve
HMG-CoA reductase
(inactive)
P
Cholesterol
Pi
HMG-CoA reductase phosphatase
- ve
P
ADP
+ve
cAMP
PKA
PPI-1 (a)
- ve
OH
Phosphoprotein phosphatase
PPI-1 (b)
ATP
Pi
themedicalbiochemistrypage.org

copyright 2007 M.W.King

*Watch Out:

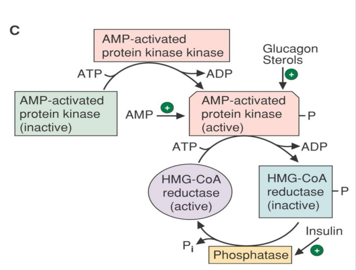
AMP – Kinase : Activated by Phosphorylation

HMG-CoA Reductase : Inactive by Phosphorylation

HMG-CoA Reductase Phosphatase : not affected by Phosphorylation
it could be inhibited by Phosphorylation of PPI1

PPI1 if Phosphorylated inhibits 3 enzymes :-

1- HMG-CoA Reductase Phosphatase
2- Protien Phosphatase 2C «inhibits AMPK»
3- PhosphoProtien Phosphatase


C
AMP-activated protein kinase kinase
ATP
ADP
Glucagon
Sterols
+
AMP-activated protein kinase (inactive)
AMP
+
AMP-activated protein kinase (active)
P
ATP
ADP
HMG-CoA reductase (active)
HMG-CoA reductase (inactive)
P
Insulin
Pi
Phosphatase
+

- The intracellular level of cAMP is regulated by hormonal stimuli, so, regulation of cholesterol biosynthesis is hormonally controlled.
- Insulin leads to a decrease in cAMP, which in turn activates cholesterol synthesis.
- Alternatively, glucagon and epinephrine, which increase the level of cAMP, inhibit cholesterol synthesis.

[illegible]

- Long-term control of HMGR activity is exerted primarily through control over the synthesis and degradation of the enzyme.

- When levels of cholesterol are high, the level of expression of the HMGR gene is reduced, while, reduced levels of cholesterol activate expression of the gene.
- Insulin also brings about long-term regulation of cholesterol metabolism by increasing the level of HMGR synthesis.

سلايد مهم

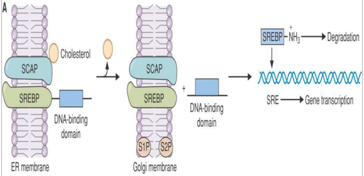
The main regulatory mechanism

- It is the sensing of intracellular cholesterol in the endoplasmic reticulum by the protein SREBP (sterol regulatory element-binding protein 1 and 2, mainly the type 2).
- In the presence of cholesterol, SREBP-2 is bound to two other proteins: SCAP (SREBP-cleavage-activating protein) and Insig-1.

Insulin induced G1 Protien

- When cholesterol levels fall, Insig-1 dissociates from the SREBP-2- SCAP complex, allowing the complex to migrate to golgi apparatus, where SREBP-2 is cleaved by S1P and S2P (site-1 and -2 proteases), two enzymes that are activated by SCAP when cholesterol levels are ↓.
- The cleaved SREBP then migrates to the nucleus and acts as a transcription factor to bind to the SRE (sterol regulatory element) to activate transcription of genes for HMG-CoA Reductase and LDL receptor and other enzymes in cholesterol synthetic pathway.

-The former scavenges circulating LDL from the bloodstream, whereas HMG-CoA reductase leads to an increase of endogenous production of cholesterol.
- SREBP pathway regulates expression of many genes that control lipid formation and metabolism and body fuel allocation.


A
Cholesterol
SCAP
SREBP
DNA-binding domain
ER membrane
SCAP
SREBP
S1P
S2P
Golgi membrane
+
DNA-binding domain
SREBP-NH_3^+ → Degradation
SRE → Gene transcription

Proteolytic Regulation of HMG-CoA Reductase

- The stability of HMGR is regulated as the rate of flux through the mevalonate synthesis pathway changes.
- When the flux is high the rate of HMGR degradation is also high.
- When the flux is low, degradation of HMGR decreases.
- HMGR is localized to the ER and like SREBP contains a sterol-sensing domain, SSD.

* its called Polyubiquitination because multiple ubiquitine gets attached.

- The degradation of HMGR occurs within the proteosome (a multi-protein complex dedicated for protein degradation).
- The primary signal directing proteins to the proteosome is ubiquitination followed by degradation of HMGR.
- Ubiquitin is a 7.6 kDa protein that is covalently attached to proteins targeted for degradation by ubiquitin ligases.

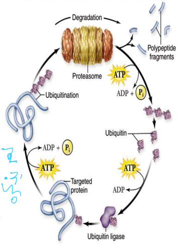
this group of Protiens attach to the enzyme so the lysosomal enzymes recognize it ((Oposonization like))

- These enzymes attach multiple copies of ubiquitin allowing for recognition by the proteosome.
- The primary sterol regulating HMGR degradation is cholesterol itself.

The main causes of hypercholesterolemia include:

1- High fats and carbohydrates diet 2- lack of exercise
3- Obstructive jaundice
4- obesity
5- Hypothyroidism 6- smoking
7- Familial hypercholesterolemia
8- excessive coffee drinking

حفظ


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Degradation
Polypeptide fragments
Proteasome
ATP
ADP + P_i
Ubiquitination
Ubiquitin
ADP + P_i
ATP
ATP
ADP
Targeted protein
Ubiquitin ligase

- Total cholesterol (total-C) is defined as the sum of HDL-C, LDL-C, and VLDL-C.
- Usually, only the total-C, HDL-C, and triacylglycerols are measured.
- VLDL is usually estimated as one-fifth of the triglycerides and the LDL is estimated using the **Friedewald formula**:

LDL-C= [total-C] − [(HDL-C)+(estimated VLDL-C)].

- Direct LDL measures are used when triacylglycerols level is about 400 mg/dl with more error when triacylglycerols level is higher than 400 mg/dl.

Hypocholesterolemia

- It is an abnormally low levels of cholesterol
- Some studies suggest a link with depression, cancer and cerebral hemorrhage and hypocholesterolemia.
- Classified into: primary and secondary hypocholesterolemia

A- Primary hypocholesterolemia: its main causes are:

1- Tangier disease, a rare autosomal recessively inherited disorder characterized by the absence or severe deficiency of HDL in plasma.

2- Familial hypobetalipoprotienemia, an autosomal dominant disorder of apo-B metabolism, is associated with marked hypocholesterolemia (<50 mg/dl in homozygotes) with Low LDL, cholesterol, TG but normal HDL.

3- Abetalipoproteinemia, a rare autosomal recessive disorder caused by a deficiency of MTP (microsomal triglyceride transfer protein) which resulted in a absence of the apo-B-containing lipoproteins in the plasma.

B- Secondary hypocholesterolemia: its main causes are:

1- Severe chronic hepatic insufficiency diseases

2- Hyperthyroidism 3- Fever 4- Trauma

5- Digestive malnutrition (congenital and acquired)

6- Malignancy (as acute myelogenous leukemia)

7- Inflammatory disease (RA, SLE) 8- Depression illness