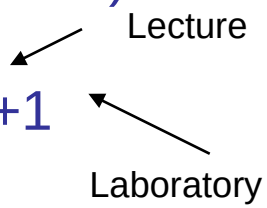
CDL Advances Chemical Studies (ACS)

Metabolic Biochemistry 7 CFU = 6+1



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Fatty acid *synthesis*

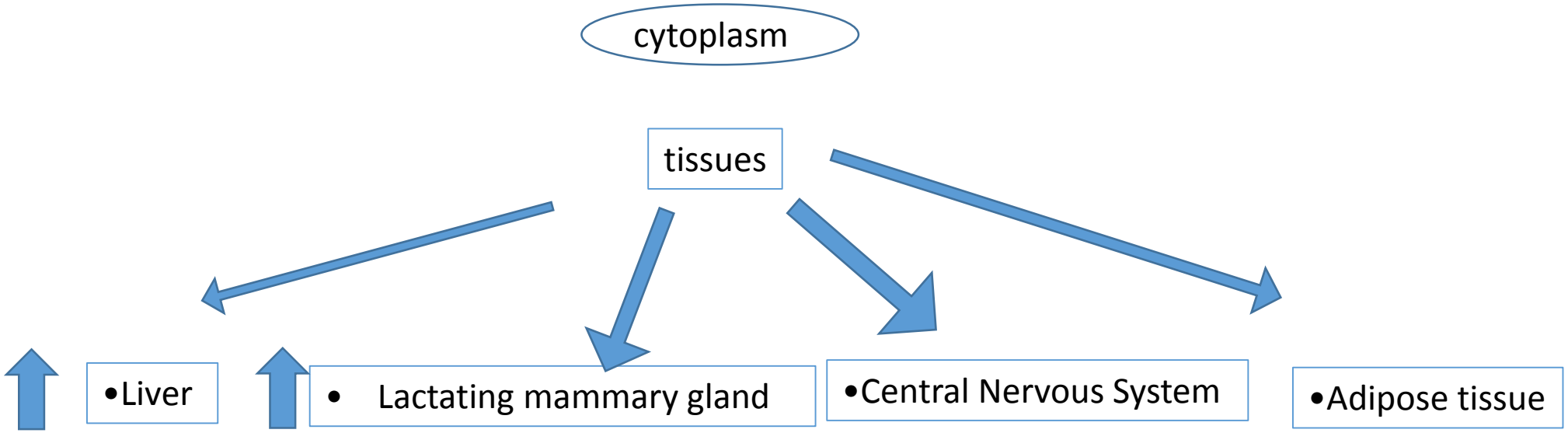
Fatty acid biosynthesis and breakdown occur by different pathways

Catalysed by different sets of enzymes

Take place in different compartments of the cell.

Fatty acid *synthesis*

(Lipogenesis)



Fatty acids come mainly from the diet,
however in the presence of excess carbohydrates and proteins
these can be converted into fatty acids

Fatty Acid Synthesis and β-Oxidation

1

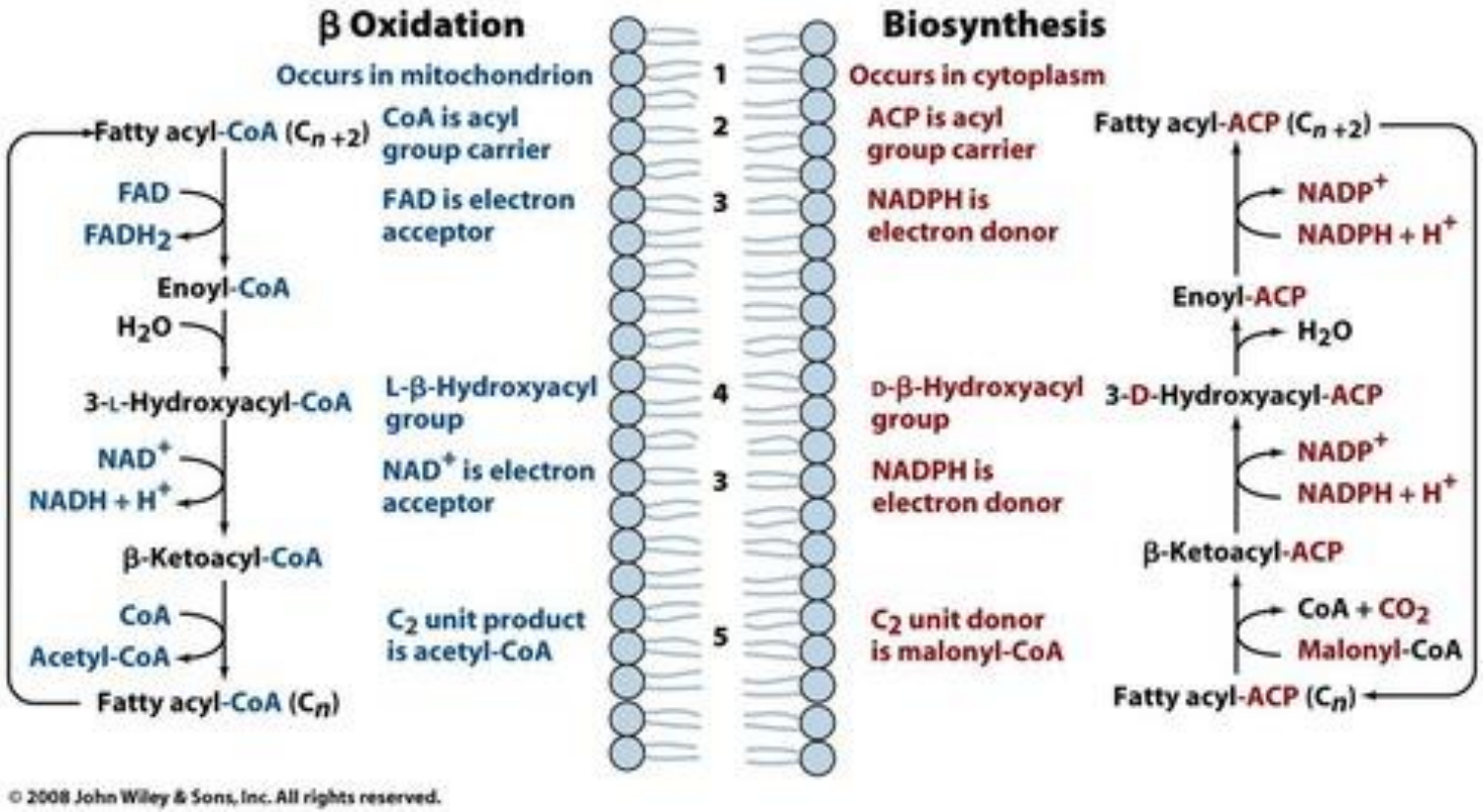
Fatty acid synthesis occurs cytoplasm.
Fatty acid oxidation occurs in mitochondria.

2

Lipogenesis involves ***oxidation*** of NADPH.
Fatty acid oxidation involves ***reduction*** of FAD & NAD+.

3

Lipogenesis occurs by a multi-enzyme complex (*fatty acid synthase*).
Fatty acid degradation uses different enzymes.

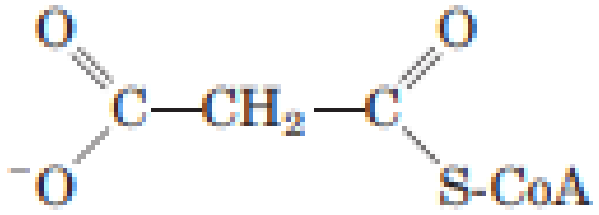


4

Lipogenesis intermediates are carried by ACP (acyl carrier protein)
CoA is the carrier for intermediates formed in fatty acid oxidation

Biosynthesis of Fatty Acids

Biosynthesis requires the participation of a three-carbon intermediate

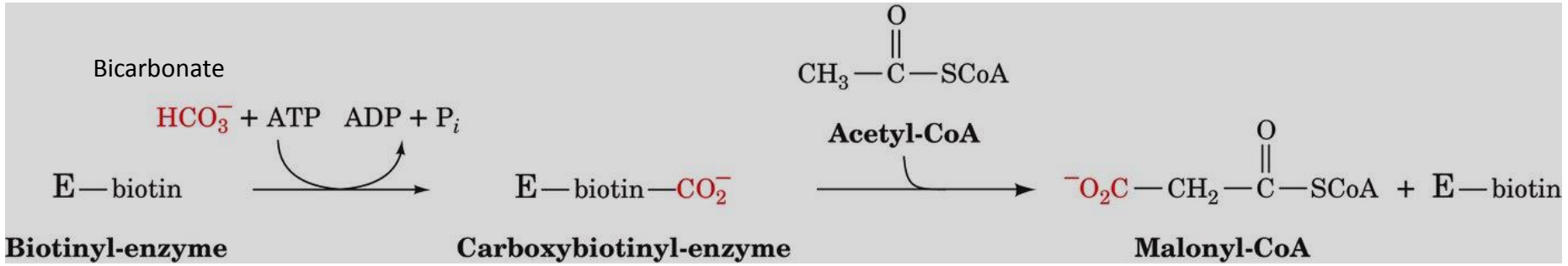


Malonyl-CoA

Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate

Derives from the oxidative decarboxylation of pyruvate (pyruvate dehydrogenase), and from β-Oxidation of fatty acids

Formation of malonyl-CoA from Aceyl-CoA is an irreversible process, catalyzed by acetyl-CoA carboxylase (ACC)

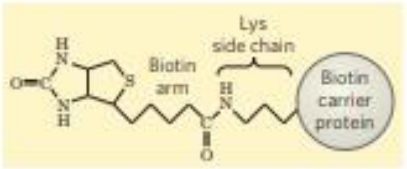


Two-stage mechanism involving BIOTIN:
-activation of CO_2
- subsequent decarboxylation of the enzyme

Acetyl-CoA carboxylase (ACC) .

Single multifunctional polypeptide.

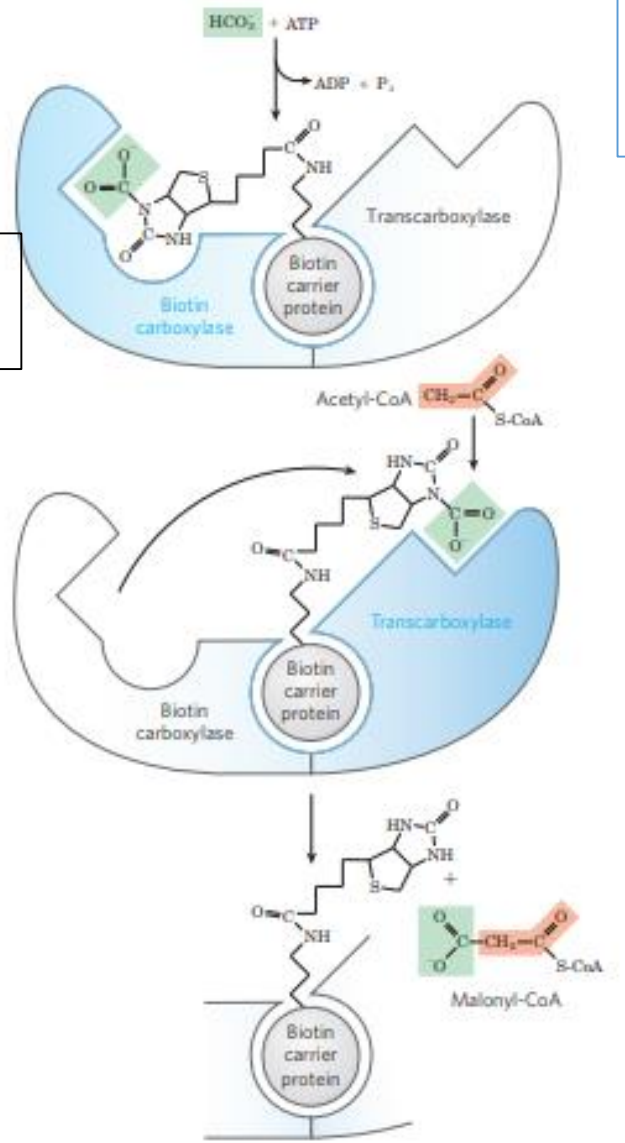
Acetyl-CoA carboxylase has three functional regions:



(1)
Biotin carrier protein

The enzyme contains a biotin prosthetic group covalently bound in amide linkage to the -amino group of a Lys residue

(2)
biotin carboxylase,



(3)
transcarboxylase,

transfers activated CO2 from biotin to acetyl-CoA, producing malonyl-CoA.

A carboxyl group, derived from bicarbonate (HCO_3),
A carboxyl group is transferred to biotin in an ATP-dependent reaction.

The biotinyl group serves as a temporary carrier of CO_2, transferring it to acetyl-CoA in the second step to yield malonyl-CoA.

The long, flexible biotin arm carries the activated CO_2 from the biotin carboxylase region to the transcarboxylase active site

Acetyl-CoA carboxylase (ACC) Reaction.

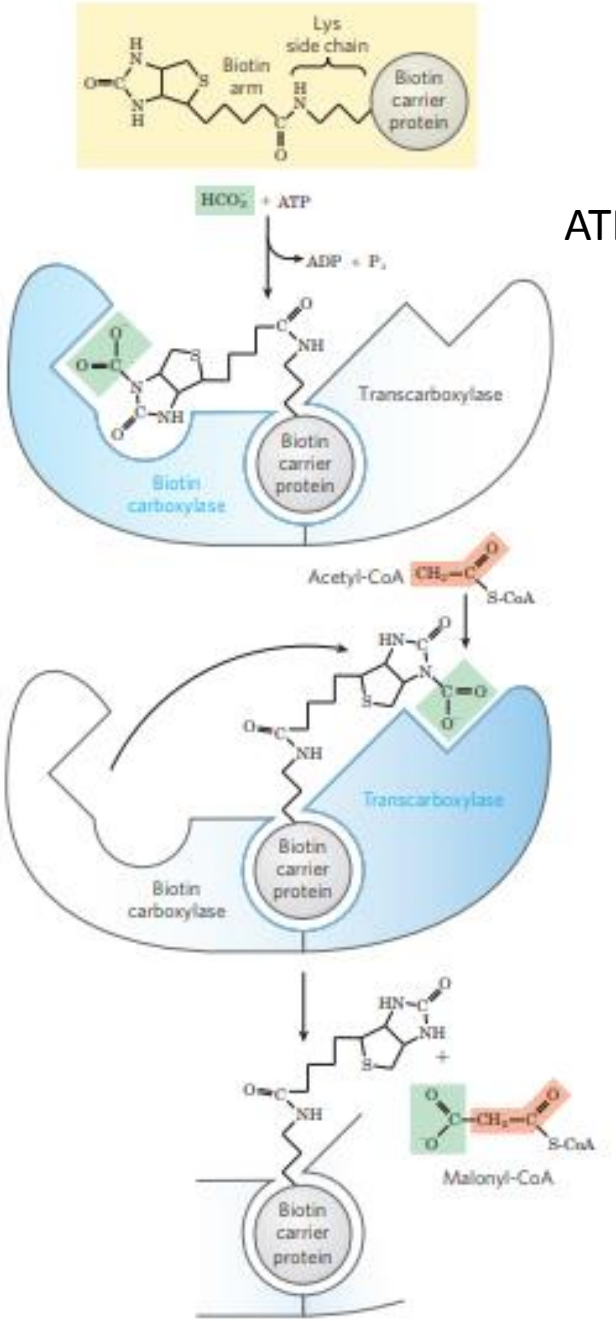
Formation of malonyl-CoA from Aceyl-CoA is an irreversible reaction

Biotin prosthetic group is covalently bound to Lys residue in one of domains of the enzyme molecule.

A carboxyl group, derived from HCO_3^- is transferred to biotin

The biotinyl group is a carrier of CO_2

transfers CO_2 it to acetyl-CoA in the second step to yield malonyl-CoA



ATP-dependent reaction.

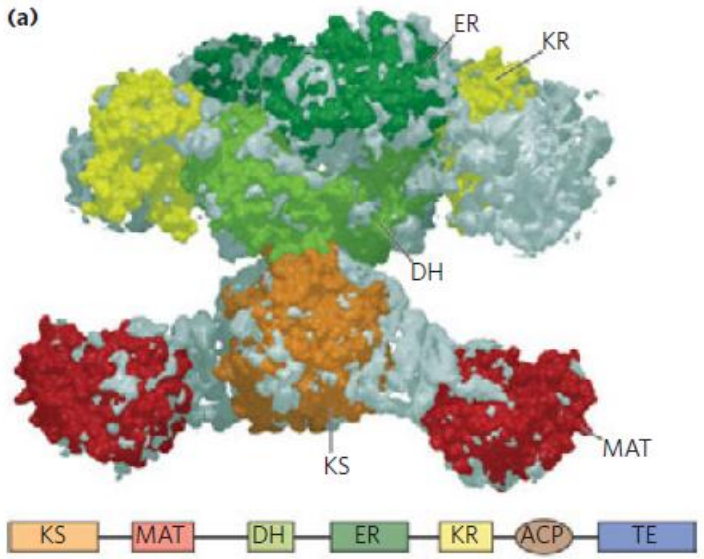
Fatty Acid Synthase (FAS)

Two major variants

→ Fatty acid synthase I (FAS I), { Vertebrates, Fungi,

→ Fatty acid synthase II (FAS II), { Plants, Bacteria.

FAS I — a single multifunctional polypeptide chain (M_r 240,000).



The mammalian polypeptide functions as a homodimer (M_r 480,000).

Seven active sites for different reactions lie in separate domains

The different enzymatic activites are:

1. Ketoacyl-ACP Synthase (KS)

2. Malonyl/Acetyl-CoA–ACP Transferase (MAT)

3. Hydroxyacyl-ACP Dehydratase (DH)

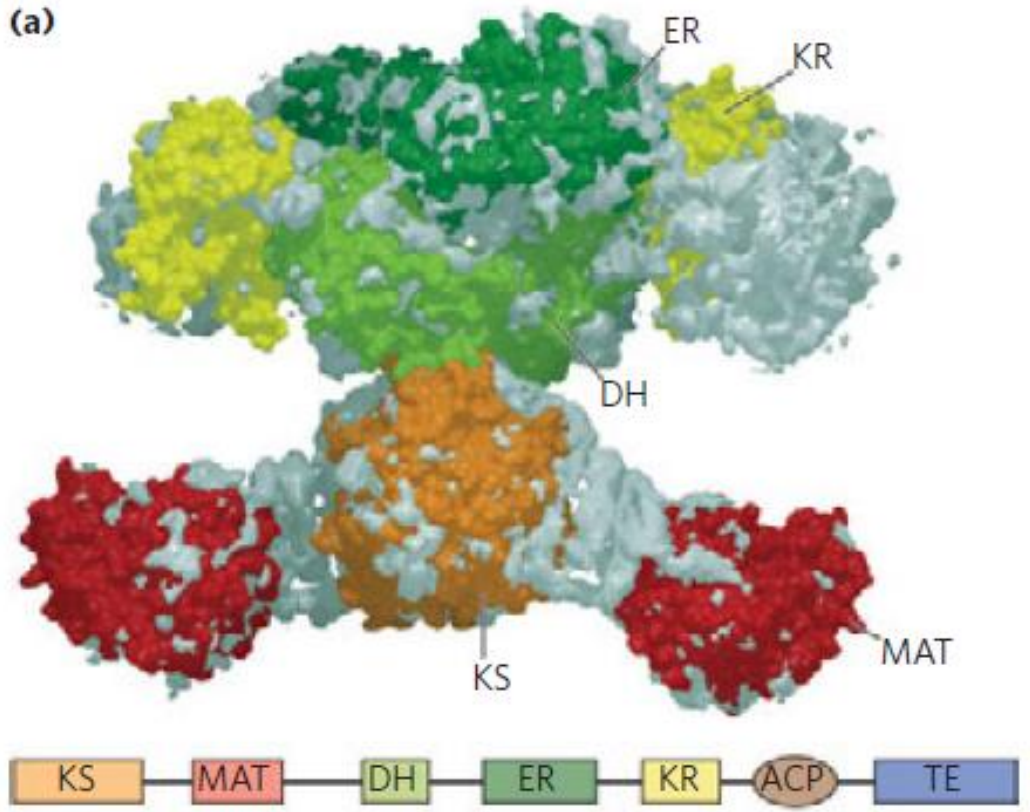
4. Enoyl-ACP Reductase (ER)

5. Ketoacyl-ACP Reductase (KR)

6. ACP is the acyl carrier protein.

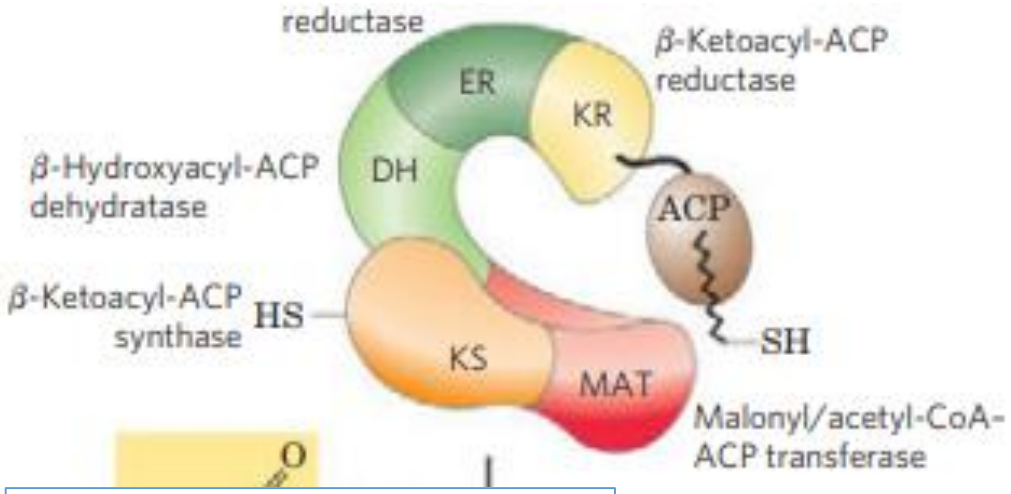
7. Thioesterase (TE)

releases the palmitate product from ACP when the synthesis is completed.



BIosynthesis of Fatty acids is catalized by Fatty Acid Synthase (FAS)

CYTOSOL



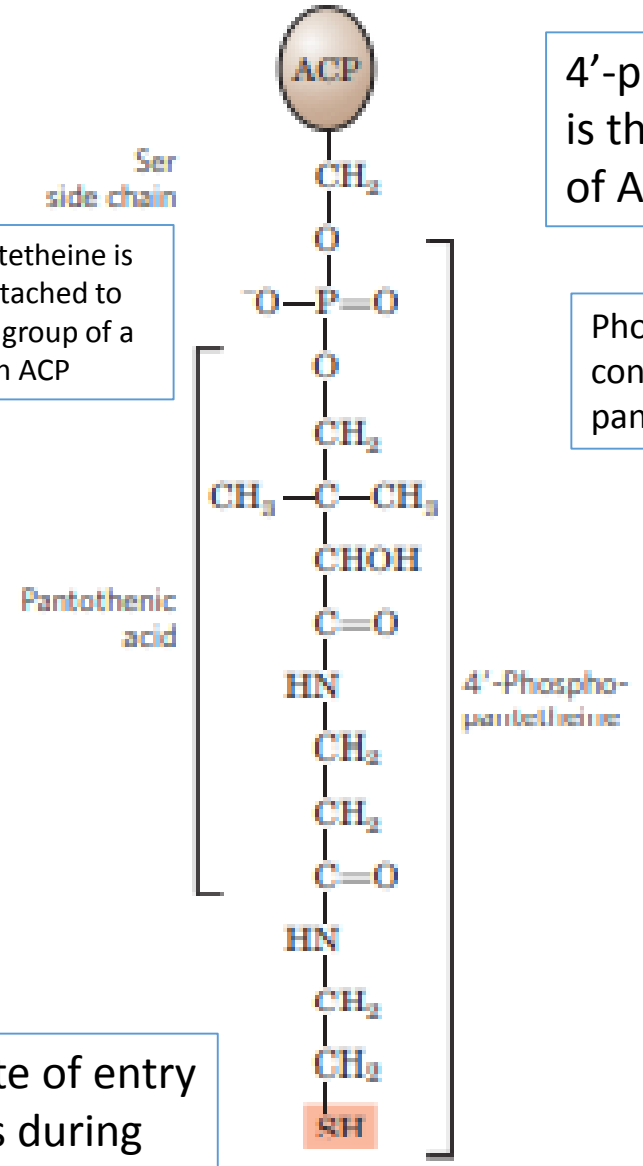
(MULTIENZYMATIC System
7 domain in mammals)

Acyl carrier protein (ACP).

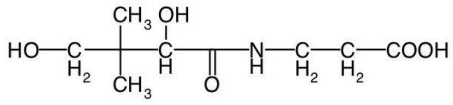
4'-phosphopantetheine is the prosthetic group of ACP

Phosphopantetheine is covalently attached to the hydroxyl group of a Ser residue in ACP

Phosphopantetheine contains the B5 vitamin pantothenic acid



SH group is the site of entry of malonyl groups during fatty acid synthesis.



Pantothenic acid (B5 vitamin)

Fatty Acid Synthase Receives the Acetyl and Malonyl Groups

In the formation of the chain there are 4 repeating stages:

1. **Condensation**
2. Reduction
3. Dehydration
4. Reduction

Seven active sites

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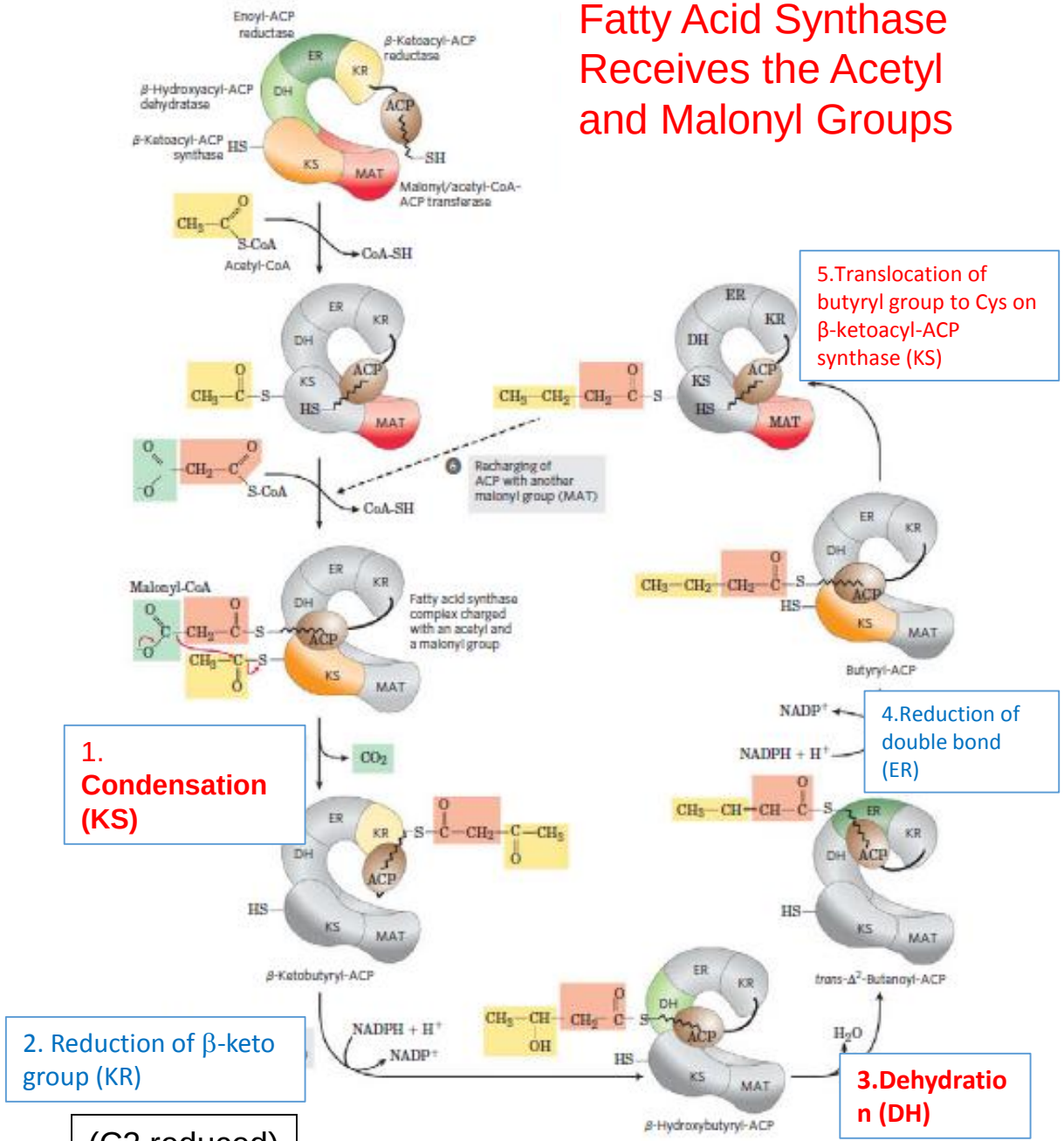


5.Translocation of butyryl group to Cys on β-ketoacyl-ACP synthase (KS)

6.Recharging of ACP with another malonyl group (MAT)

Fatty acid synthase complex charged with an acetyl and a malonyl group

1. **Condensation (KS)**

4.Reduction of double bond (ER)

reduces double bond

2. Reduction of β-keto group (KR)

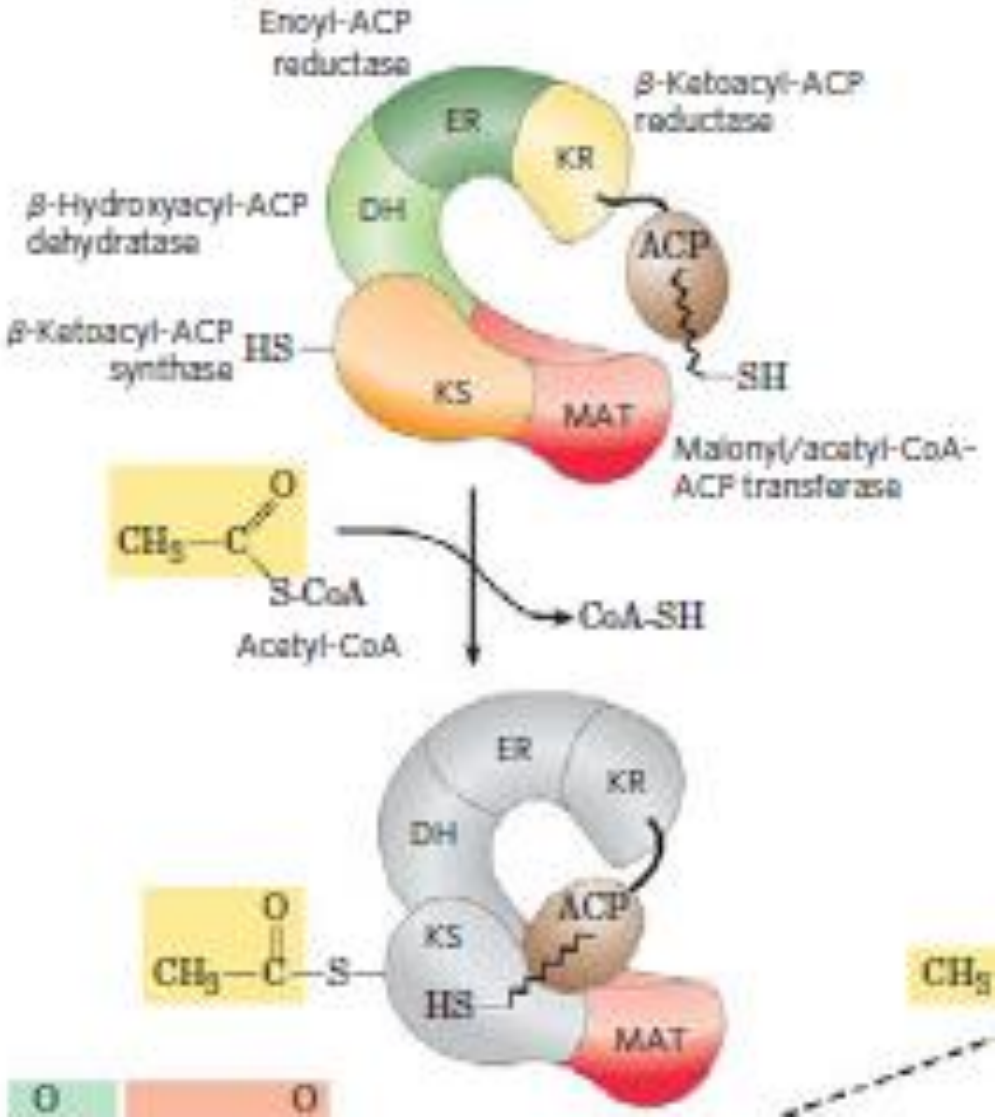
(C2 reduced)

3.Dehydration (DH)

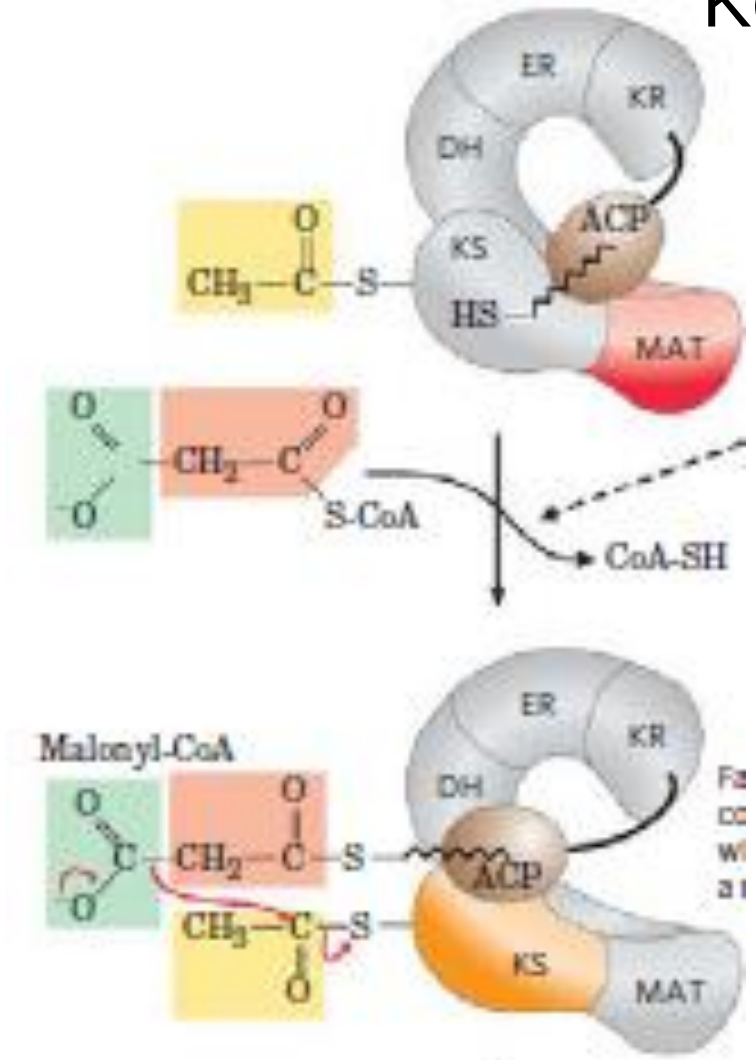
remove H2O from C2-C3

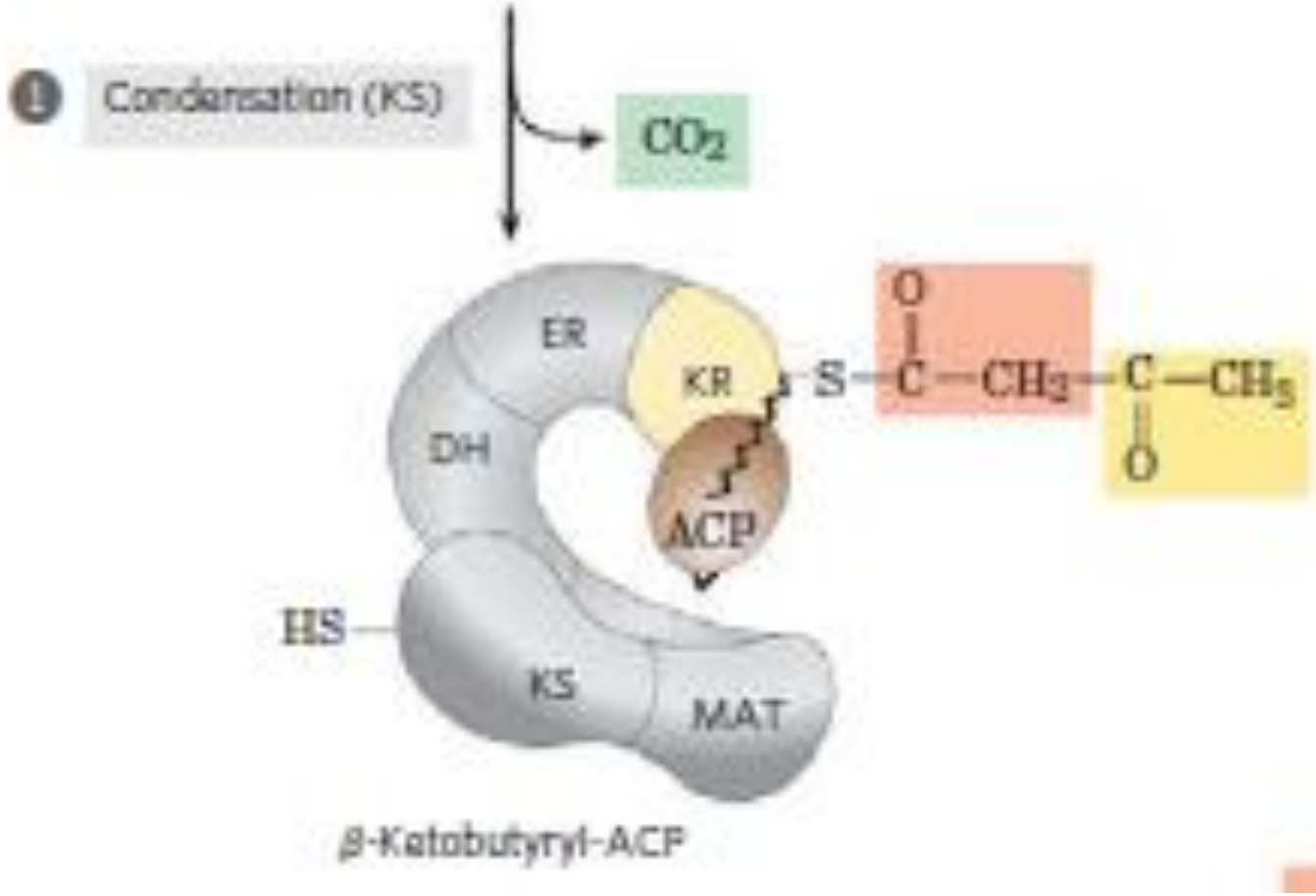
-2 Reductions + 1 dehydration

2 NADPH molecules are used


Enoyl-ACP reductase
β-Ketoacyl-ACP reductase
ER
KR
β-Hydroxyacyl-ACP dehydratase
DH
ACP
β-Ketoacyl-ACP synthase
HS
KS
MAT
SH
Malonyl/acetyl-CoA-ACP transferase
CH3—C(=O)—S-CoA
Acetyl-CoA
CoA-SH
ER
KR
DH
ACP
KS
CH3—C(=O)—S
HS
MAT
CH3
O
O

Ketoacyl-ACP Synthase (KS)



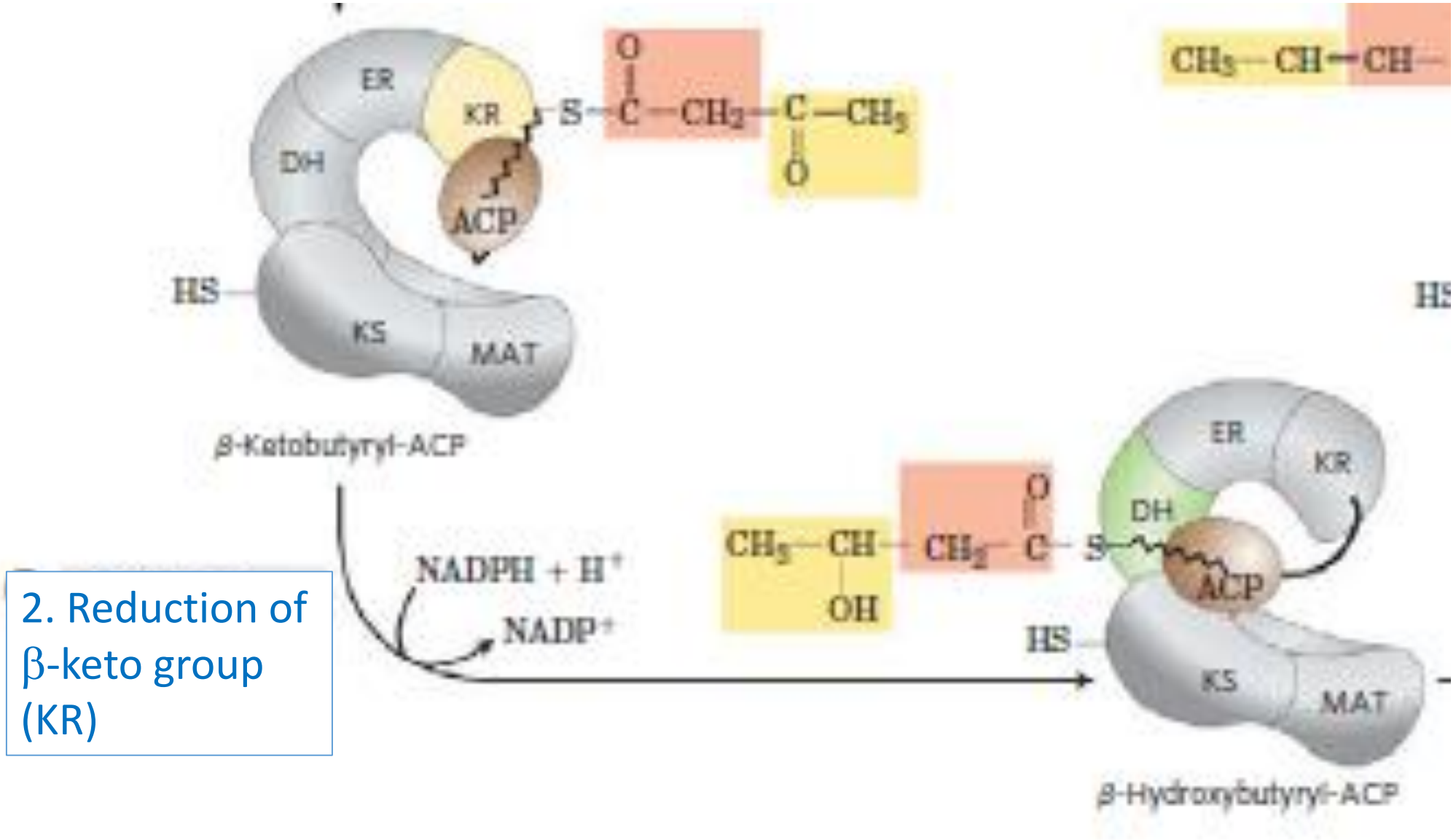


Condensation

Activated acyl group and two carbons derived from malonyl-CoA,

CO_2 from the malonyl group, extends the acyl chain by two carbons.

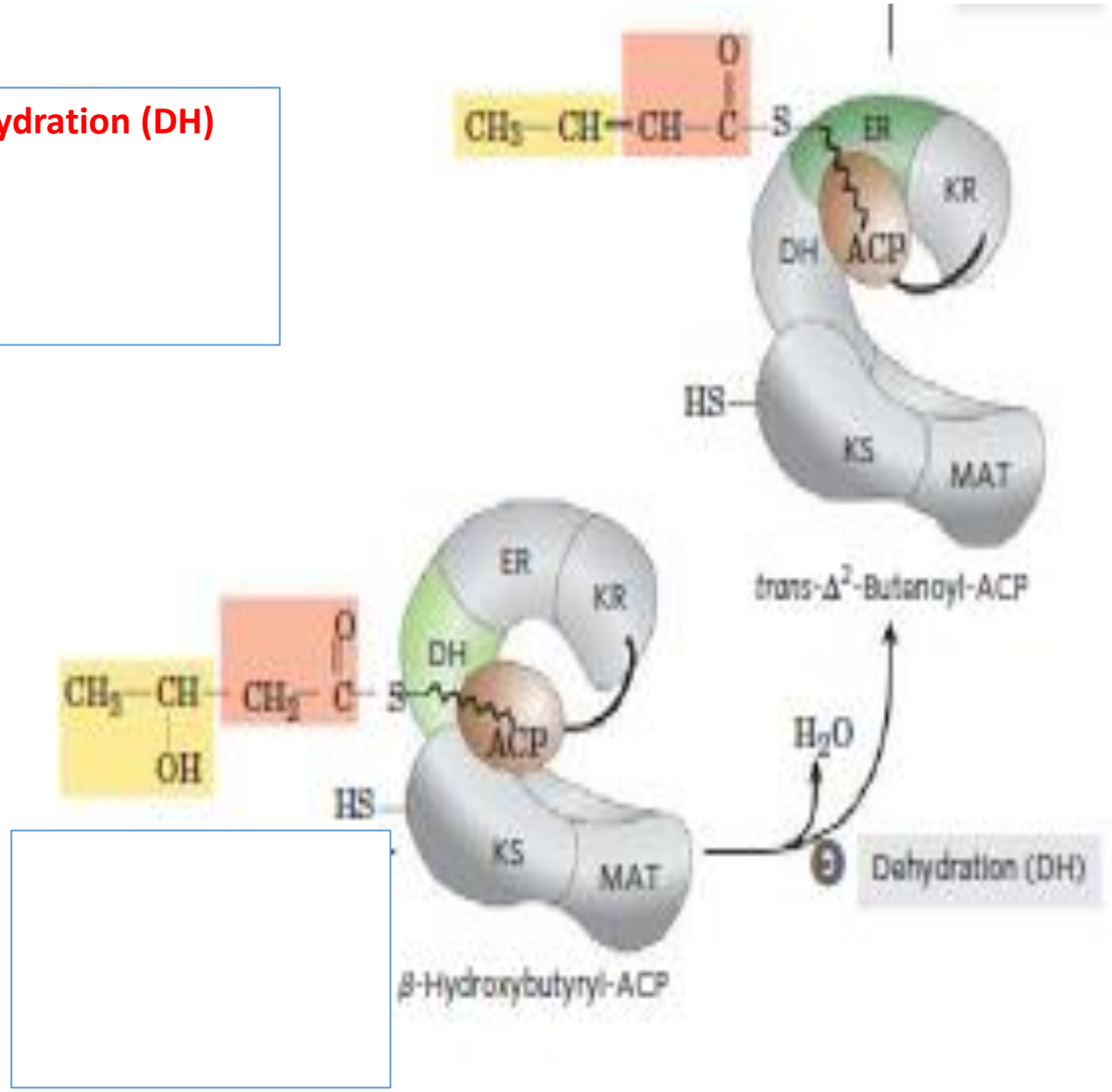
. Ketoacyl-ACP Reductase (KR)



2. Reduction of β-keto group (KR)

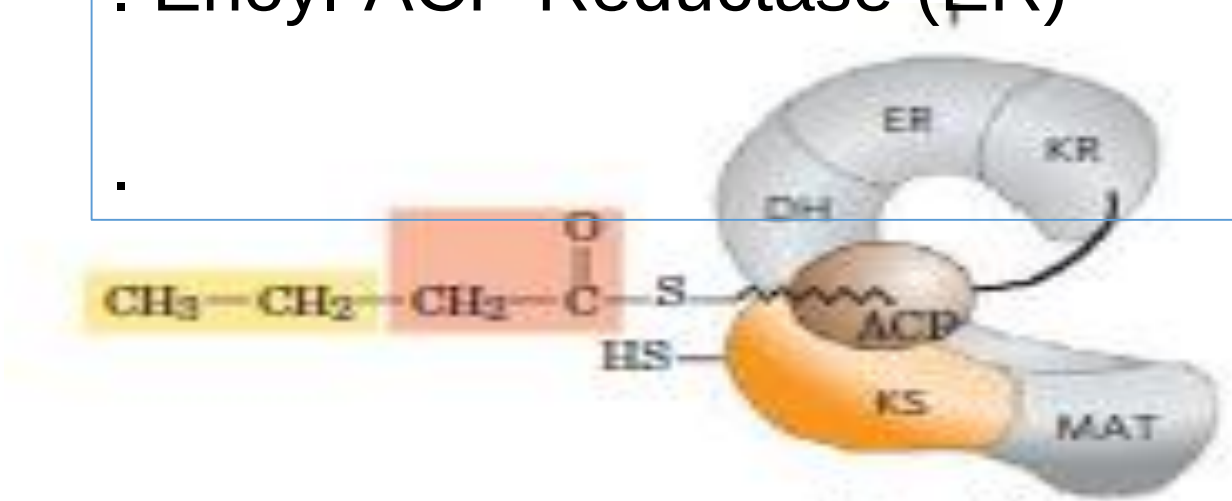
. Hydroxyacyl-ACP Dehydratase (DH)

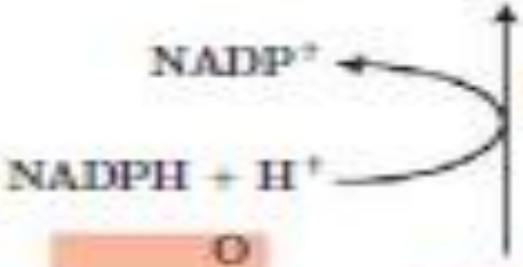
3.Dehydration (DH)



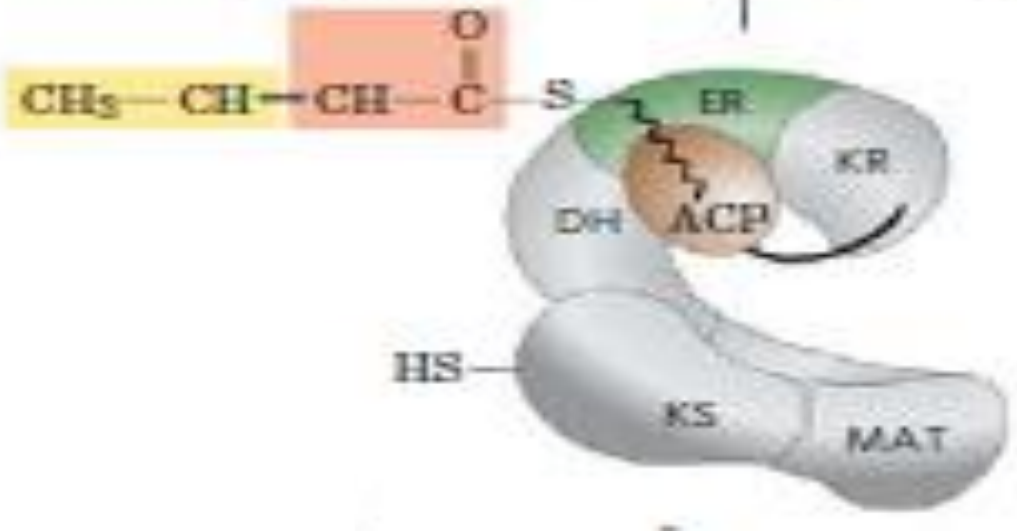
. Enoyl-ACP Reductase (ER)

.





4.Reduction of double bond (ER)



In the formation of the chain there are 4 repeating stages:

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Seven active sites

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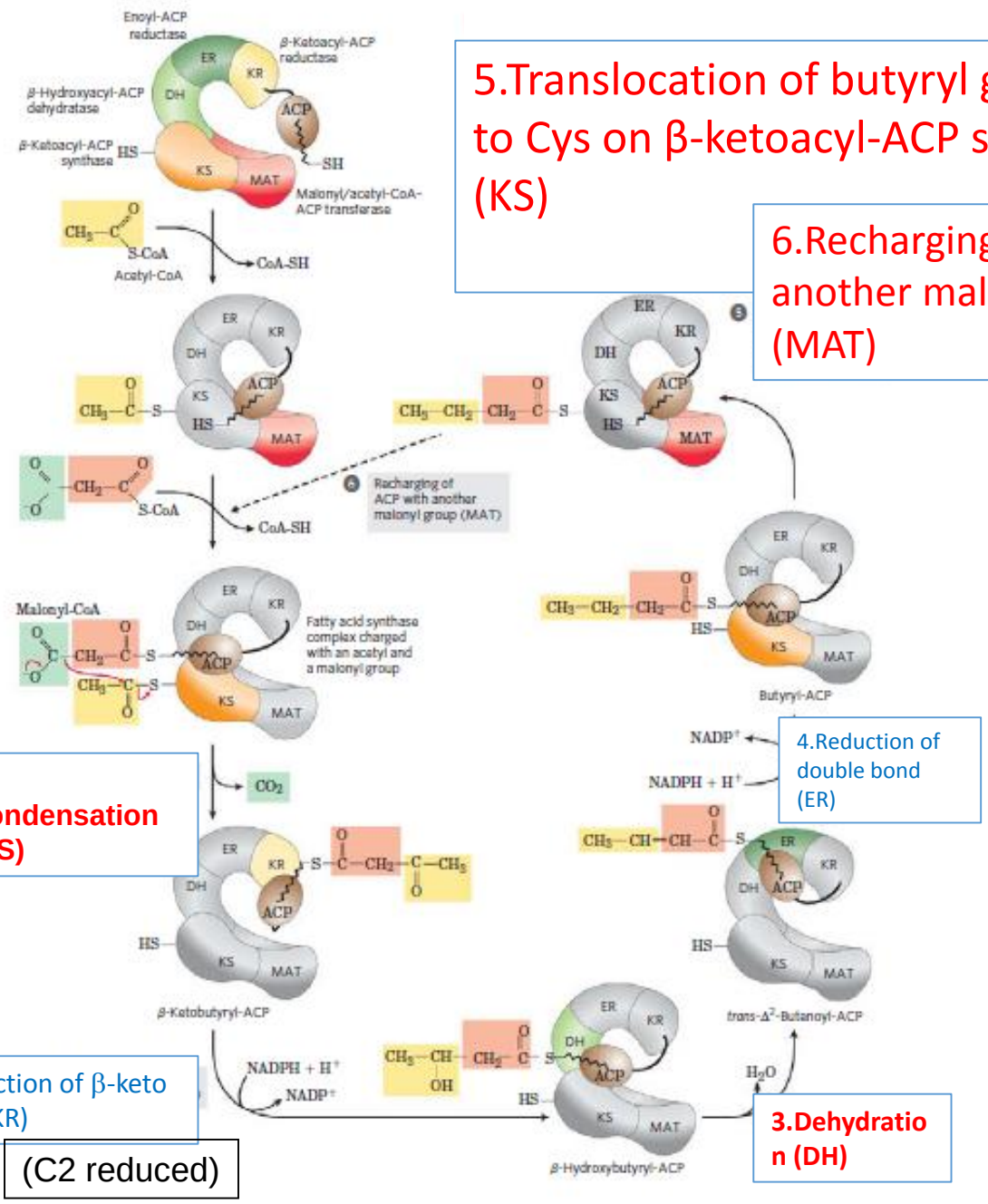
-2 Reductions + 1 dehydration

2 NADPH molecules are used



Long-Chain Saturated Fatty Acids Are Synthesized from Palmitate

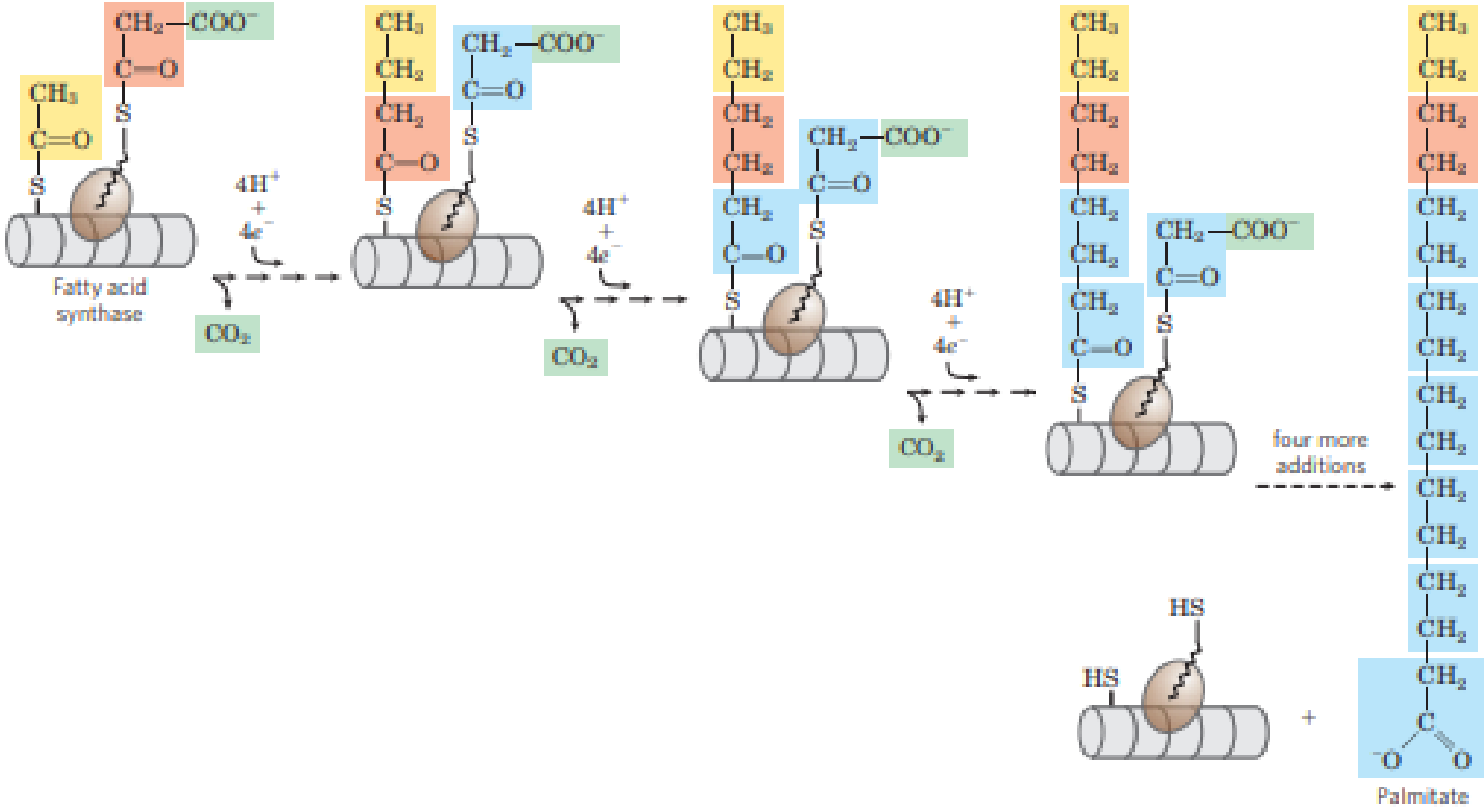
Palmitate synthesis.

The fatty acyl chain grows by two-carbon units donated by activated malonate, with loss of CO2 at each step.

The initial acetyl group is shaded yellow, C-1 and C-2 of malonate are shaded light red, and the carbon released as CO2 is shaded green.

After each two-carbon addition, reductions convert the growing chain to a saturated fatty acid of four, then six, then eight carbons, and so on.

The final product is palmitate (16:0).



Palmitate forms stearate (18:0) or even longer saturated fatty acids by further additions of acetyl groups, through the action of fatty acid elongation systems present in the smooth endoplasmic reticulum and in mitochondria.

Acetyl-CoA used for fatty acid synthesis is produced within the mitochondria

AcetylCoA used in fatty acid synthesis

- pyruvate oxidation (mitochondria)
- catabolism of the carbon skeleton of amino acids.

The inner mitochondrial membrane is not permeable to acetyl-CoA.

A shuttle system is required for transport.

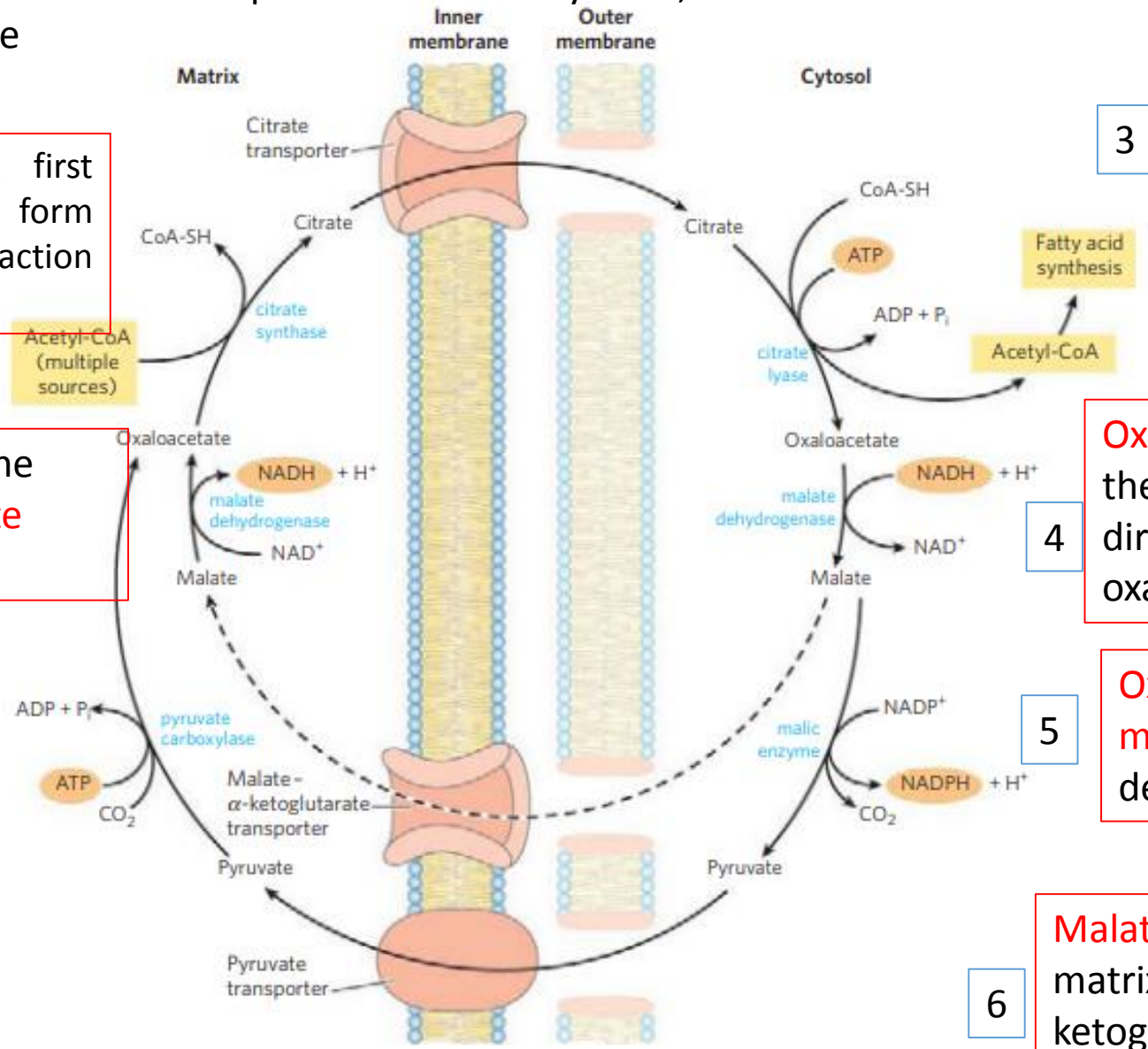
The mitochondrial inner membrane is impermeable to acetyl-CoA, so an indirect shuttle transfers acetyl group equivalents across the inner membrane

1

Intramitochondrial acetyl-CoA first reacts with oxaloacetate to form citrate, in the citric acid cycle reaction catalyzed by citrate synthase

2

Citrate then passes through the inner membrane on the citrate transporter.



3

Citrate cleavage by citrate lyase regenerates acetyl-CoA and oxaloacetate in an ATP-dependent reaction

4

Oxaloacetate cannot return to the mitochondrial matrix directly, as there is no oxaloacetate transporter.

5

Oxaloacetate is reduced to malate by cytosolic malate dehydrogenase

Fatty acid *synthesis*

(cytosol)

6

Malate return to the mitochondrial matrix on the malate–-ketoglutarate transporter

7

In the matrix, malate is reoxidized to oxaloacetate to complete the shuttle

Regulation of fatty acid synthesis

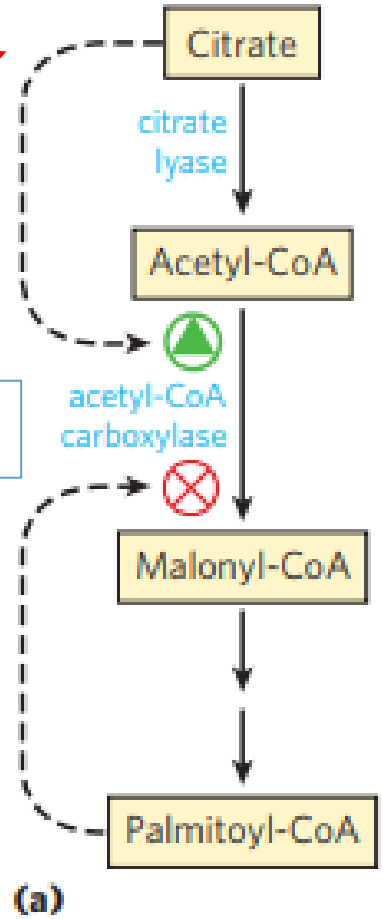
Allosteric regulation and hormone-dependent covalent modification influence the flow of precursors into malonyl-CoA.

Allosteric regulation

Great availability of nutrients
Increased citrate

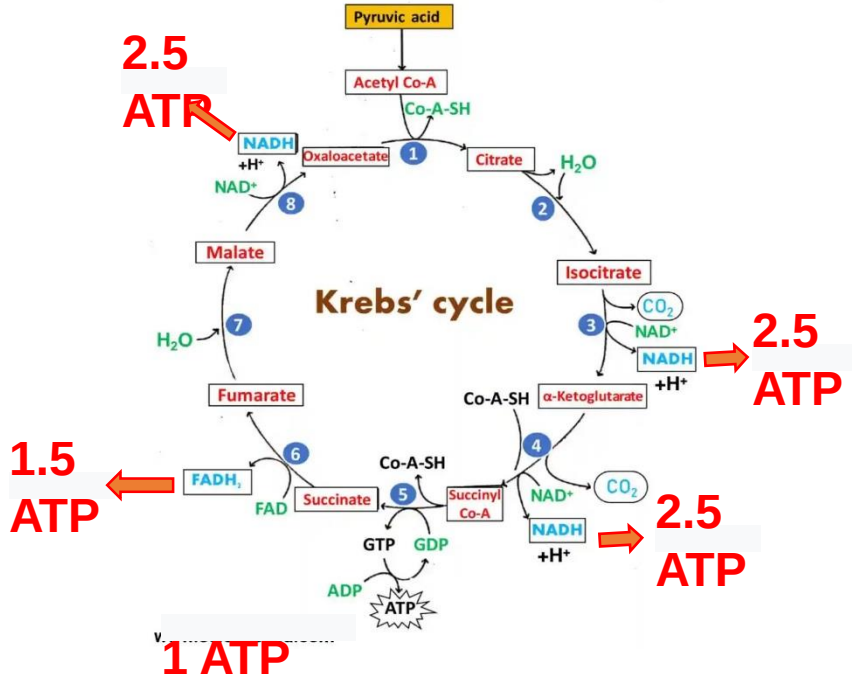
stimulates fatty acid synthesis

(ACC)



Low availability of nutrients (Palmitoyl-CoA)

therefore blocks the way of conservation



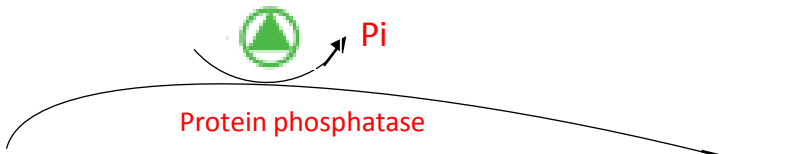
Fatty acids come mainly from the diet, however in the presence of excess carbohydrates and proteins these can be converted into fatty acids

Regulation of fatty acid synthesis

Hormone regulation

Insulin

stimulates fatty acid synthesis



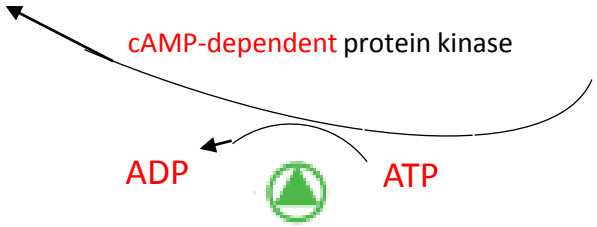
Acetyl-CoA carboxylase (ACC)

P

inactive

Acetyl-CoA carboxylase (ACC)

active



Glucagon and epinephrine inhibit fatty acid synthesis

Coordinated regulation of fatty acid synthesis and breakdown

When the diet provides a ready source of carbohydrate as fuel, oxidation of fatty acids is unnecessary and is therefore downregulated.

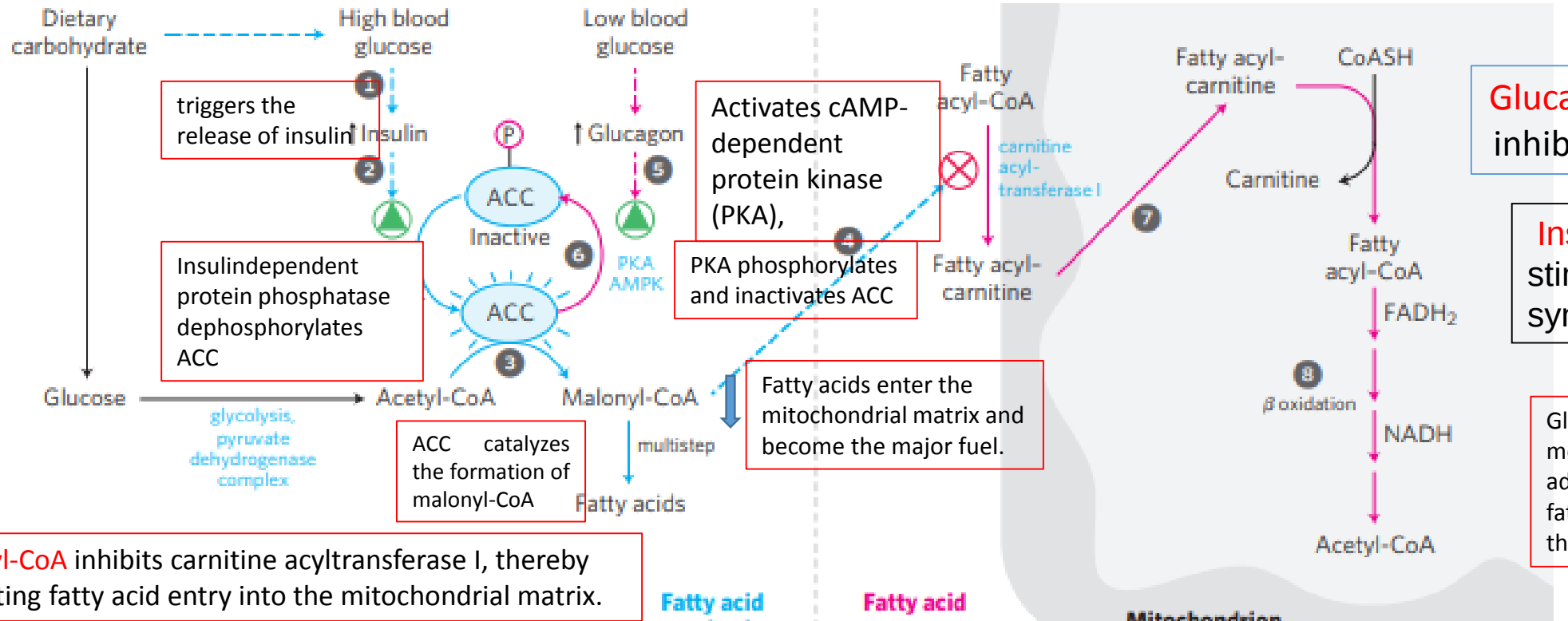
Two enzymes are key to the coordination of fatty acid metabolism:

- acetyl-CoA carboxylase (ACC), the first enzyme in the synthesis of fatty acids
- -carnitine acyltransferase I, which limits the transport of fatty acids into the mitochondrial matrix for oxidation

Ingestion of a high-carbohydrate meal

raises the blood glucose level

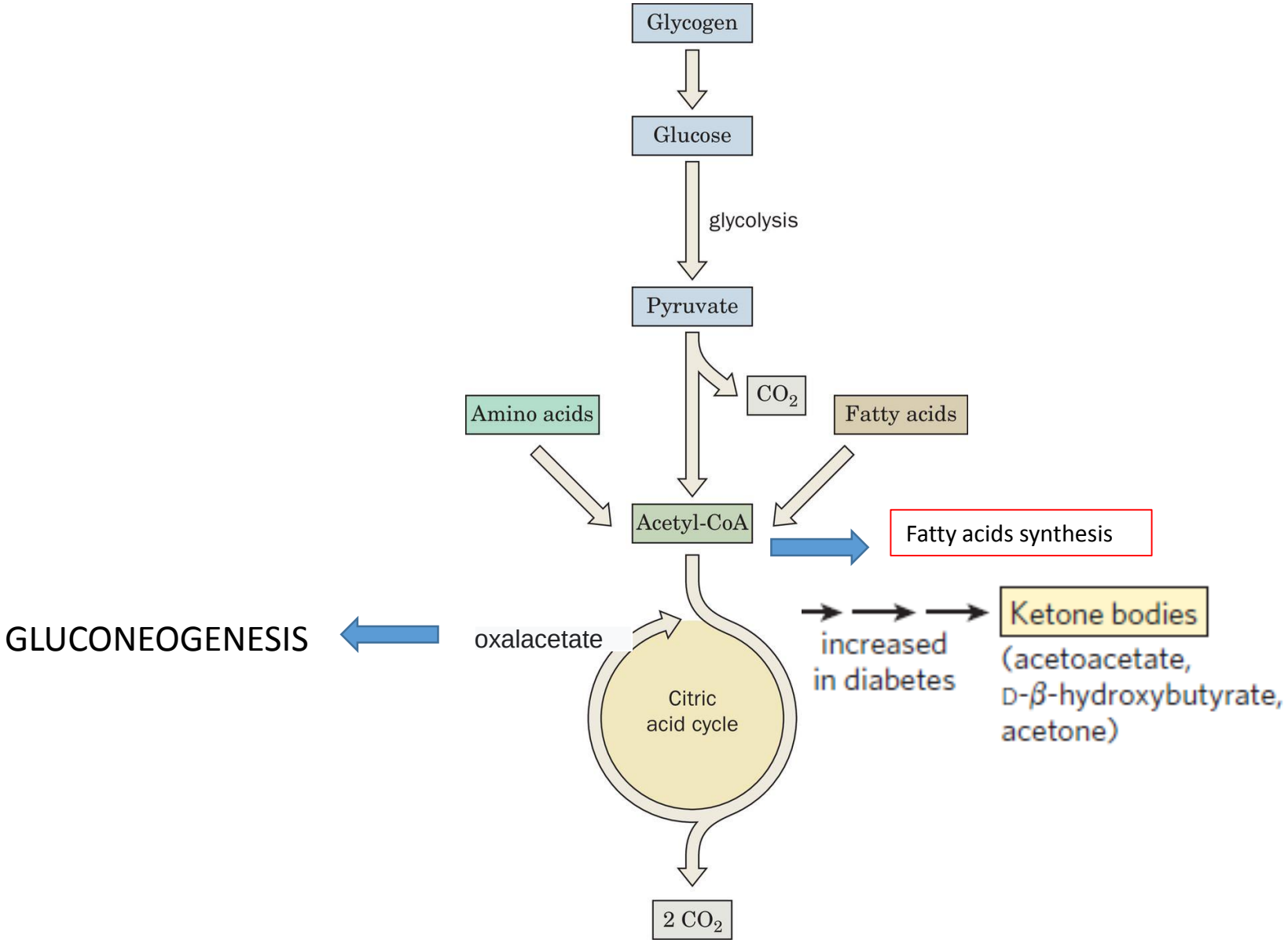
When blood glucose levels drop between meals

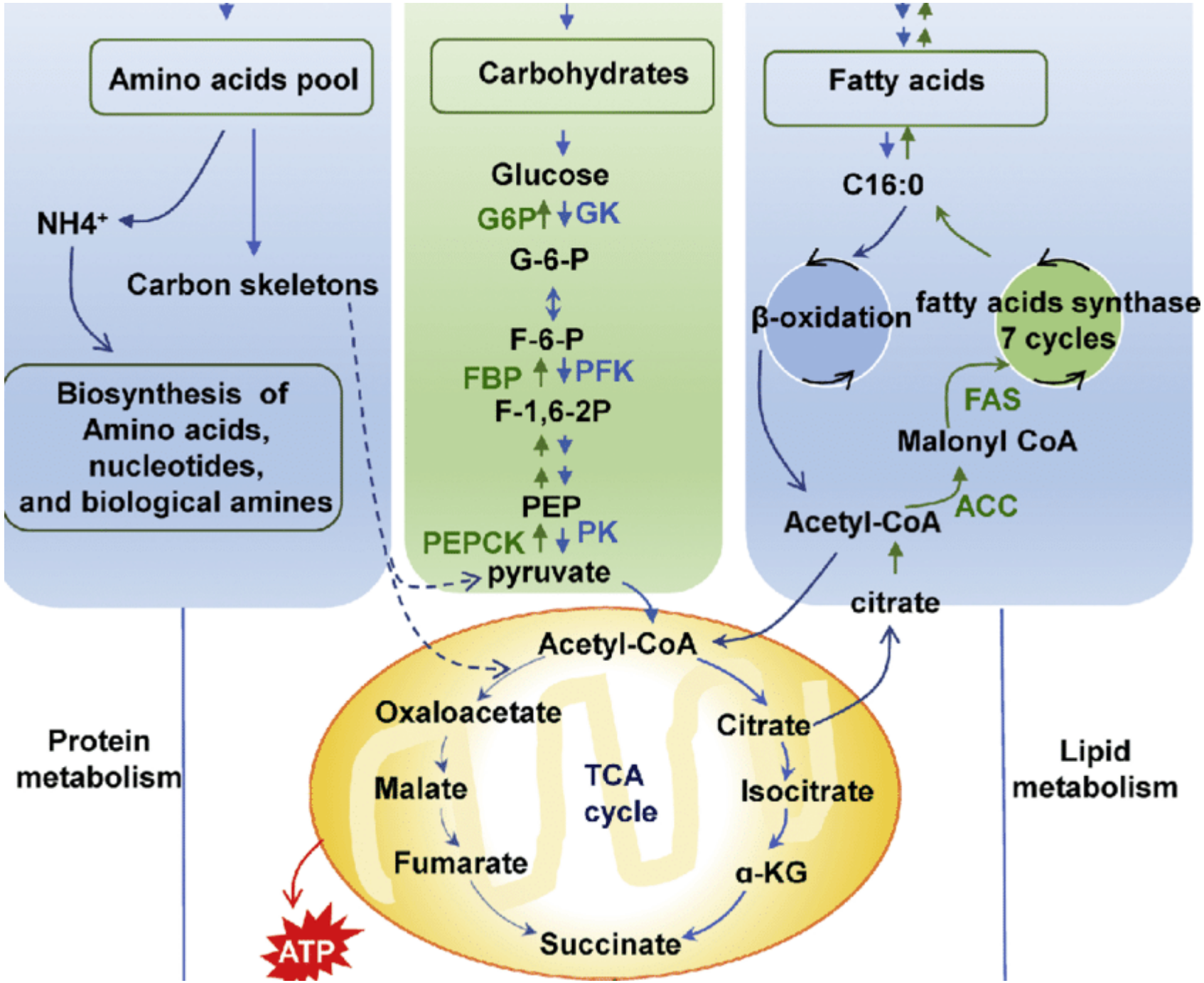


Glucagon and epinephrine inhibit fatty acid synthesis

Insulin stimulates fatty acid synthesis

Malonyl-CoA inhibits carnitine acyltransferase I, thereby preventing fatty acid entry into the mitochondrial matrix.


Glycogen
Glucose
glycolysis
Pyruvate
CO_2
Amino acids
Fatty acids
Acetyl-CoA
Fatty acids synthesis
GLUCONEOGENESIS
oxalacetate
Citric acid cycle
increased in diabetes
Ketone bodies
(acetoacetate, D-β-hydroxybutyrate, acetone)
2 CO_2


Amino acids pool
NH4+
Carbon skeletons
Biosynthesis of Amino acids, nucleotides, and biological amines
Carbohydrates
Glucose
G6P
GK
G-6-P
F-6-P
FBP
PFK
F-1,6-2P
PEP
PEPCK
PK
pyruvate
Fatty acids
C16:0
β-oxidation
fatty acids synthase 7 cycles
FAS
Malonyl CoA
ACC
Acetyl-CoA
citrate
Acetyl-CoA
Oxaloacetate
Citrate
Malate
TCA cycle
Isocitrate
Fumarate
α-KG
Succinate
ATP
Protein metabolism
Lipid metabolism

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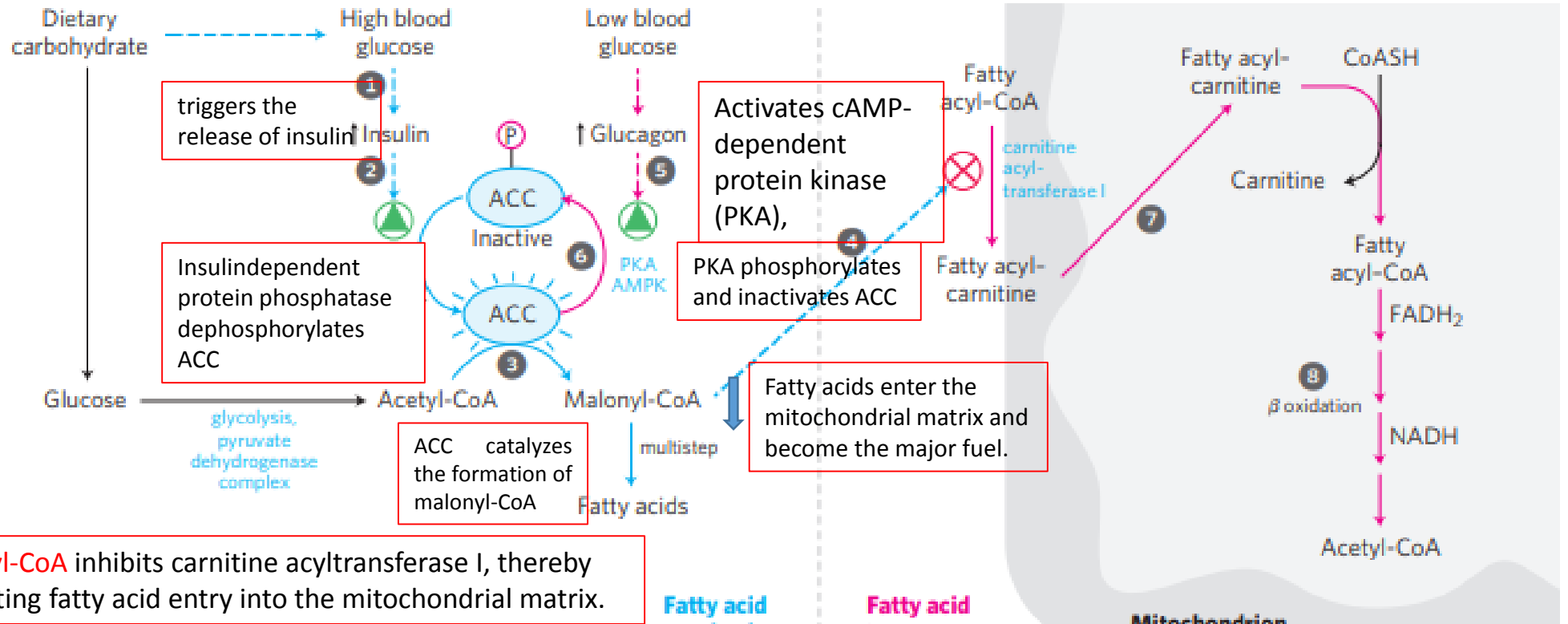


Glucagon also triggers the mobilization of fatty acids in adipose tissue, a supply of fatty acids begins arriving in the blood.

Malonyl-CoA inhibits carnitine acyltransferase I, thereby preventing fatty acid entry into the mitochondrial matrix.

Fatty acid

Fatty acid

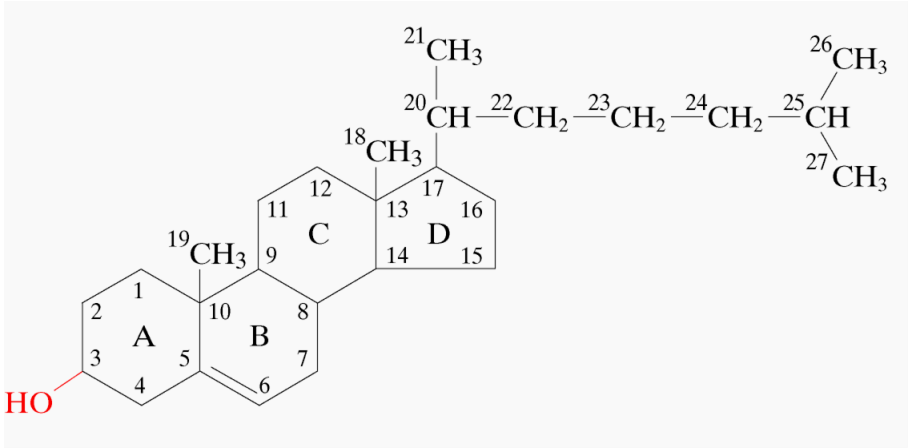
Cholesterol

Strong correlation
high levels of cholesterol in the blood and the incidence of human cardiovascular diseases.

Component of cellular membranes

Precursor of steroid hormones

Precursor of bile acids.

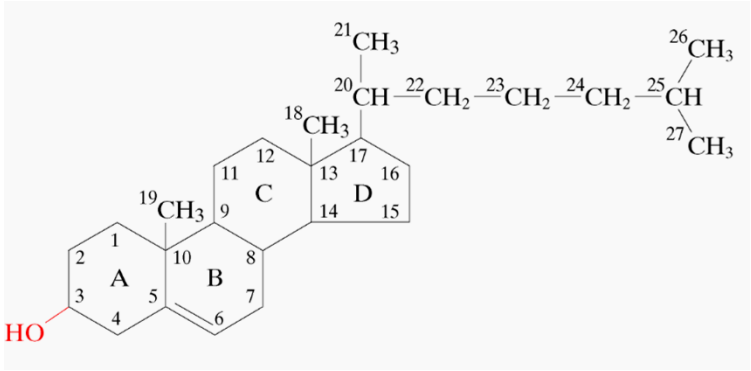


Cholesterol is an essential molecule

is not required in the diet

all cells can synthesize it from simple precursors.

Cholesterol

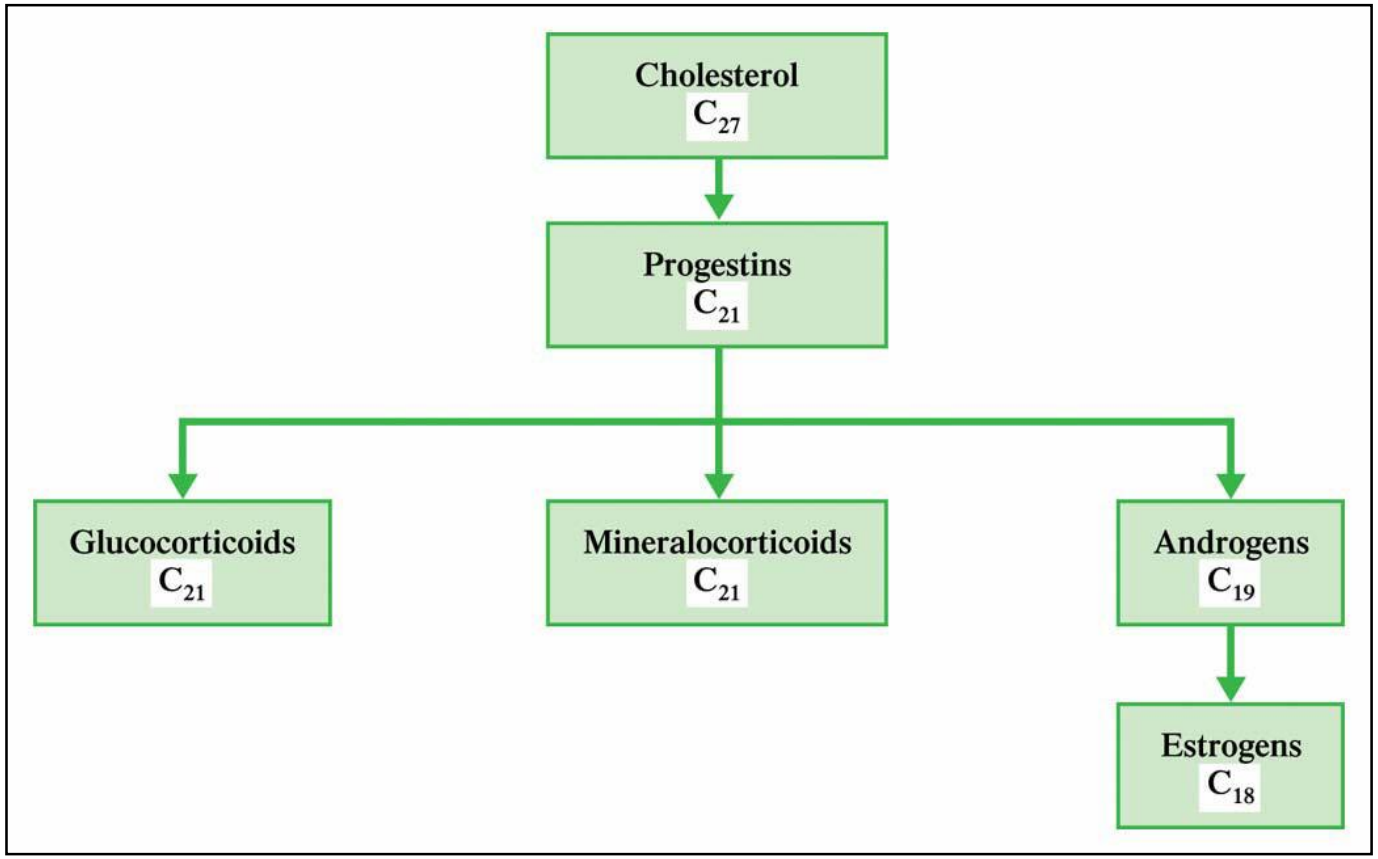


27-carbon atoms

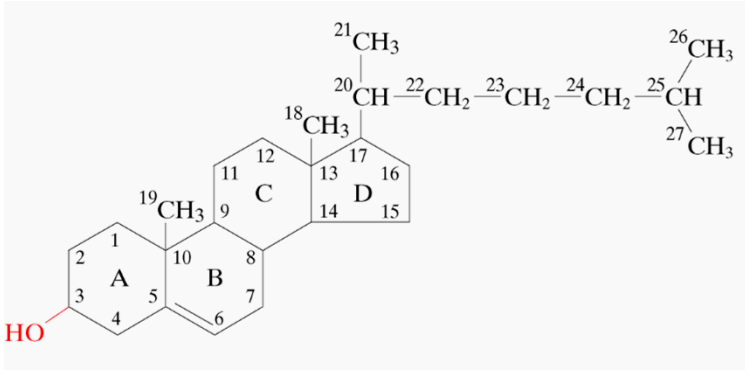
Precursor of:

Adrenal hormones:
- Glucocorticoids
- Mineralocorticoids

Sex hormones:
- Estrogens (female)
- Progestins (pregnancy)
- Androgens (male)



Cholesterol synthesis

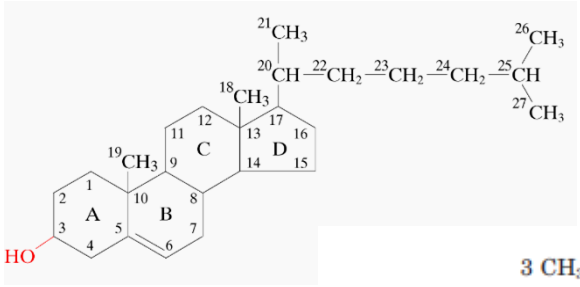


- Cholesterol has 27 carbons
- Synthesis takes 15 Acetyl CoA molecules
- 27 separate enzymatic steps
- Occurs in the **liver**, makes 1.5 to 2.0 g / day
- Average diet takes in 0.3 g cholesterol / day

Cholesterol synthesis

Cytosol

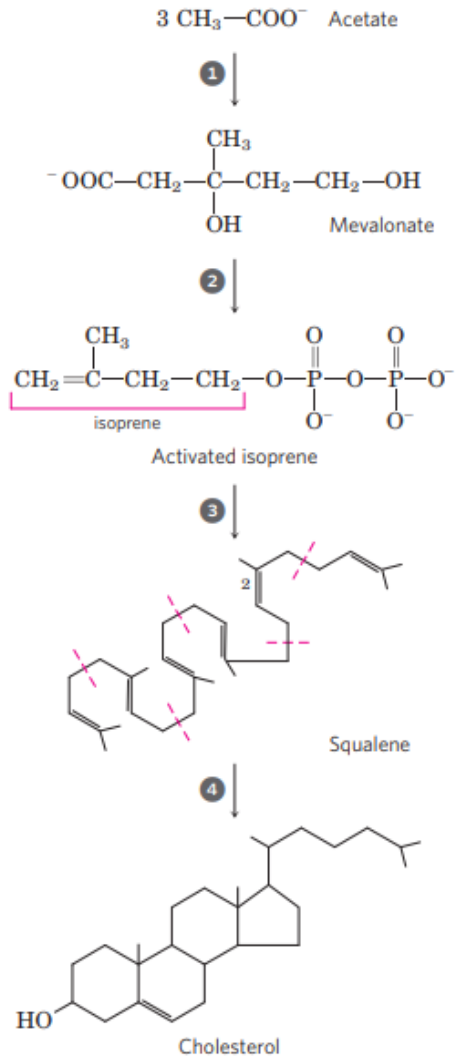
Occur in the liver.



27-carbon atoms

Not required in the mammalian diet

Cells can synthesize it from simple precursors → acetate.



Cholesterol Is Made from Acetyl-CoA in Four Stages

1. condensation of three acetate units to form a six-carbon intermediate, mevalonate;

2. conversion of mevalonate to activated isoprene units;

3. polymerization of six 5-carbon isoprene units to form the 30-carbon linear squalene;

4. cyclization of squalene to form the four rings of the steroid nucleus, with a further series of changes (oxidations, removal or migration of methyl groups) to produce cholesterol

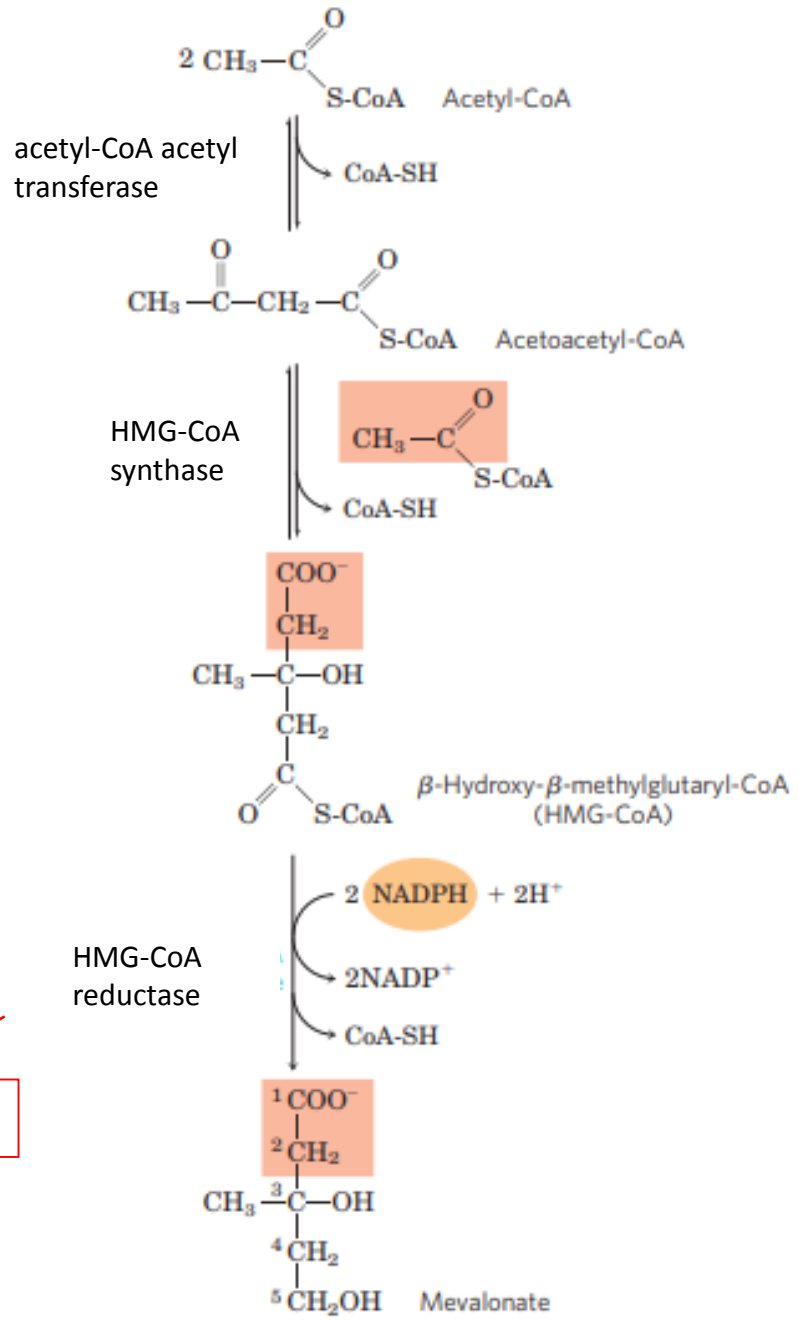
1 **Formation of mevalonate from acetyl-CoA.**

- Condensation of three acetate units to form a six-carbon intermediate, mevalonate.

- Two molecules of acetylCoA condense to form acetoacetyl-CoA

- Condenses with a third molecule of acetyl-CoA to yield the six-carbon compound: β-hydroxy-βmethylglutaryl-CoA (HMG-CoA).

  - Reduction of HMG-CoA to mevalonate, (2 molecules of NADPH)



Integral membrane protein of the smooth ER

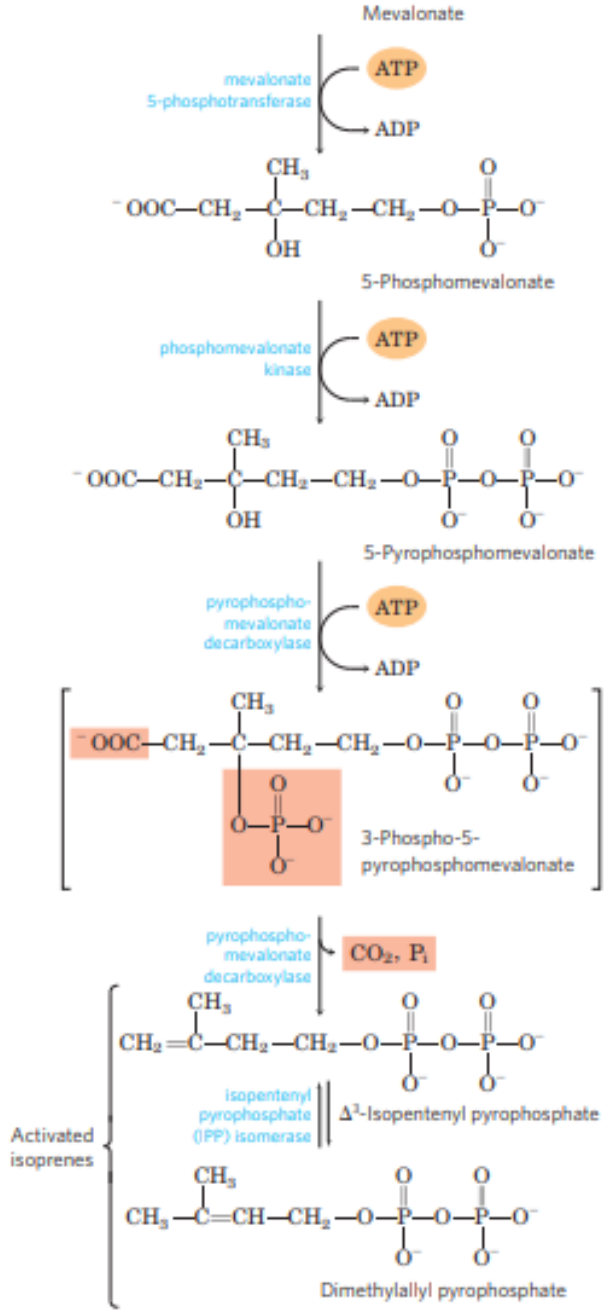
Point of regulation

The cytosolic HMG-CoA synthase is different from the mitochondrial isozyme that catalyzes HMG-CoA synthesis in ketone body formation.

2

Conversion of Mevalonate to Two Activated Isoprenes

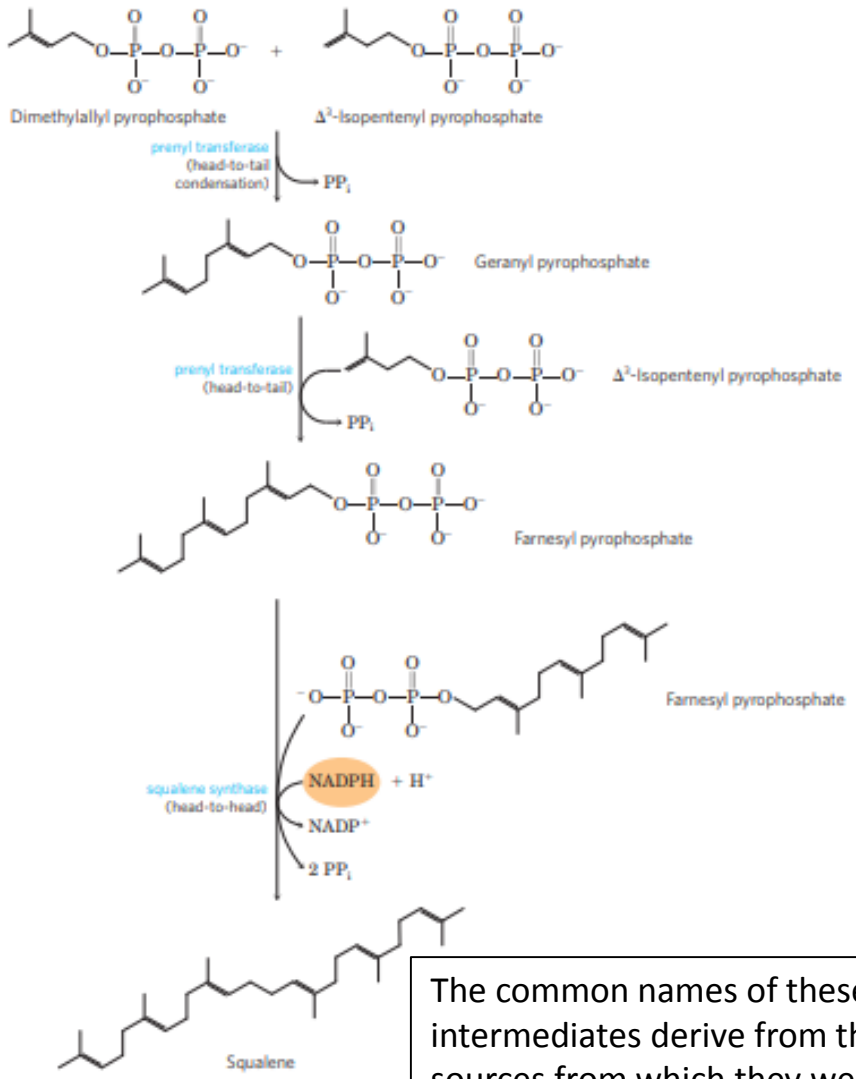
- Transfer of three phosphate groups from three ATP molecules to mevalonate
- The phosphate attached to the C-3 is released
- A double bond in the five-carbon product, $\Delta 3$ -isopentenyl pyrophosphate (the first of the two activated isoprenes)
- Isomerization of $\Delta 3$–isopentenyl pyrophosphate yields the second activated isoprene, dimethylallyl pyrophosphate



3

Condensation of Six Activated Isoprene Units to Form Squalene

- Isopentenyl pyrophosphate and dimethylallyl pyrophosphate undergo a condensation and form geranyl pyrophosphate (10-carbon chain)
- Geranyl pyrophosphate undergoes another condensation with isopentenyl pyrophosphate, and forms farnesyl pyrophosphatethe (15-carbon chain)
- Two molecules of farnesyl pyrophosphate by the elimination of both pyrophosphate groups form squalene.



30 carbon atoms

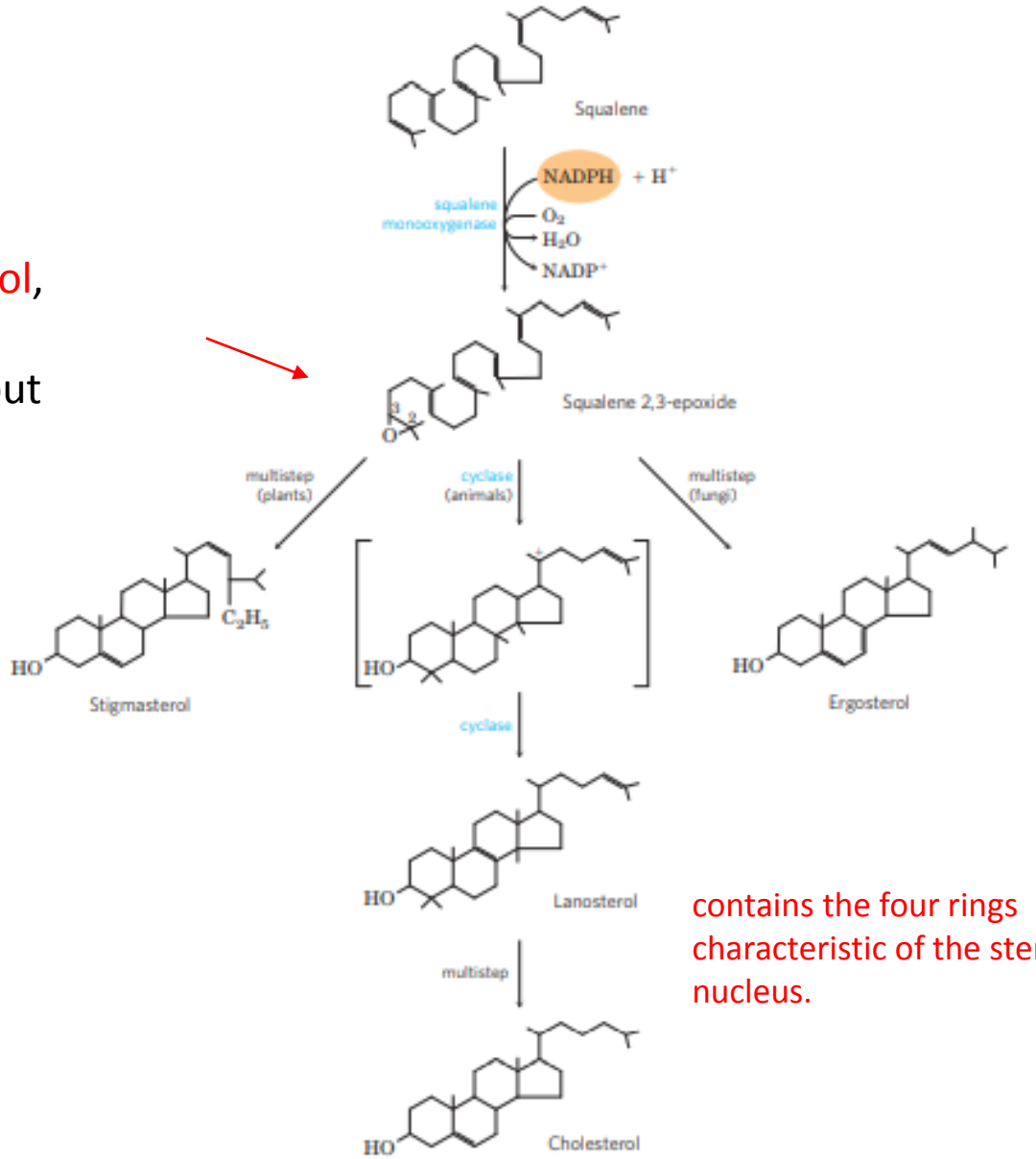
Geraniol, a component of rose oil, has the aroma of geraniums, Farnesol is an aromatic compound found in the flowers of the Farnese acacia tree.
Squalene, first isolated from the liver of sharks (genus Squalus),

The common names of these intermediates derive from the sources from which they were first isolated.

4

Conversion of Nucleus Squalene to the Four-Ring Steroid

- Squalene monooxygenase adds one oxygen atom from O2 to the end of the squalene chain, forming an epoxide.
  - Cyclization of epoxide undergoes to the formation of lanosterol,
  - Lanosterol is finally converted to cholesterol in a series of about 20 reactions



contains the four rings characteristic of the steroid nucleus.

Cholesterol Synthesis and Transport Are Regulated at Several Levels

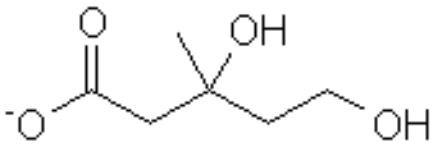
Cholesterol synthesis is a complex and energy-expensive process.

Excess cholesterol cannot be catabolized for use as fuel, and must therefore be excreted.

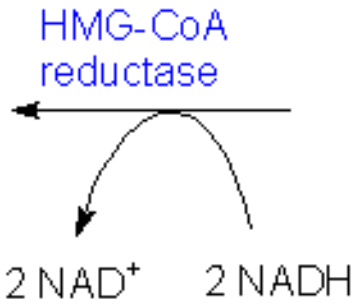
In mammals, cholesterol production is regulated

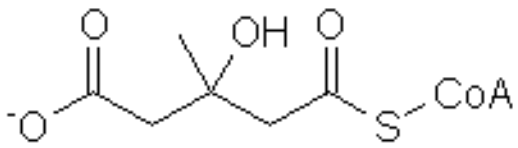
- Intracellular cholesterol concentration
- Supply of ATP
- Glucagon and insulin.

Major site of regulation is the reaction catalyzed by HMG-CoA reductase



Mevalonate





β-hydroxy-βmethylglutaryl-CoA (HMG-CoA).

β-hydroxy-β-methylglutaryl-CoA reductase (HMG-CoA reductase).

dephosphorylates (actives) HMG-CoA reductase ⇄ P–HMG-CoA reductase phosphorylates (inactives); Reversible covalent modification

AMP-Kinase phosphorylates HMG-CoA reductase when high AMP concentration

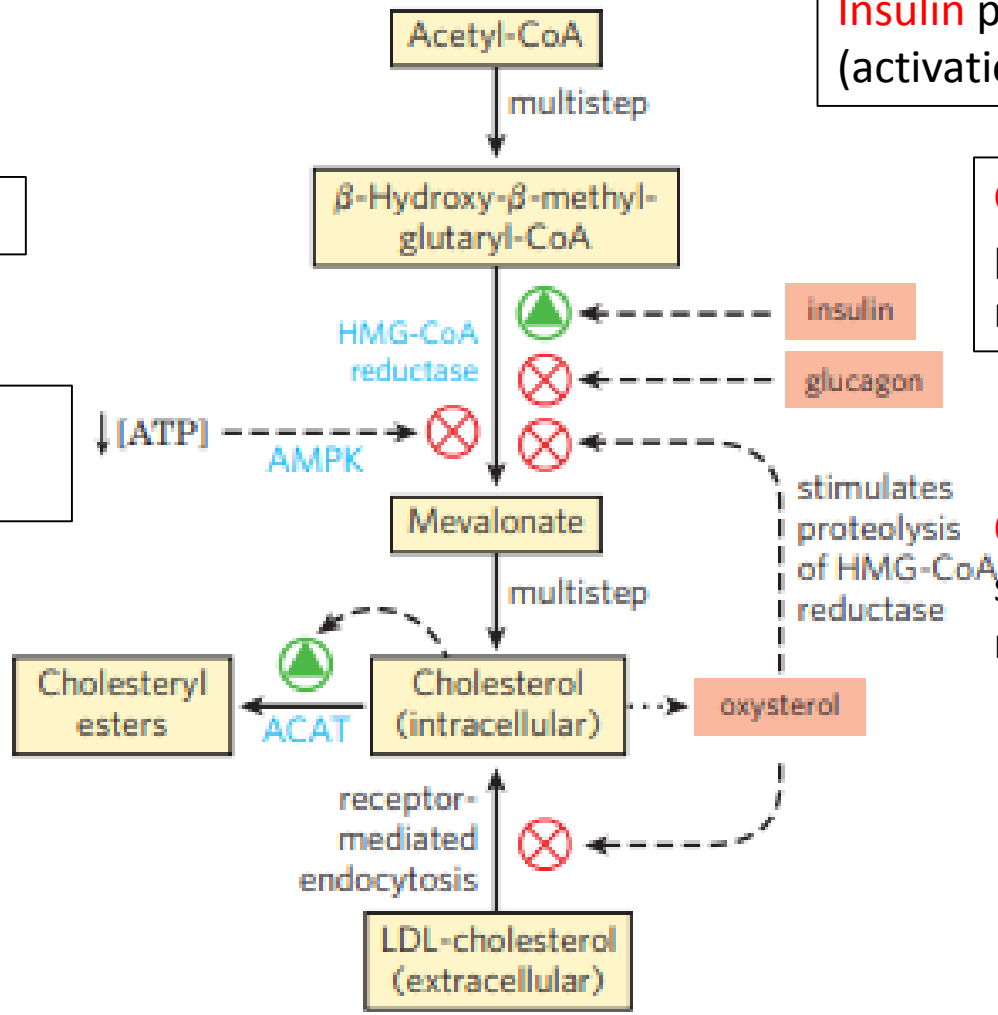
Low [ATP] respect to [AMP],

↓

AMP-dependent protein kinase

↓

phosphorylates HMG-CoA reductase (inactivation);



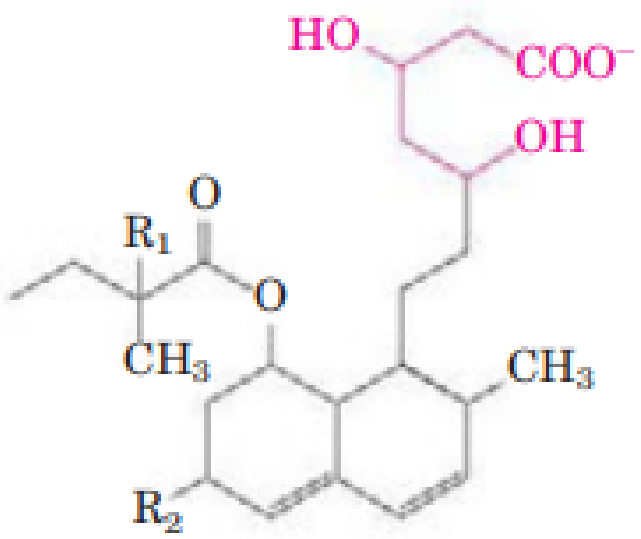
Insulin promotes dephosphorylation (activation) of HMG-CoA reductase.

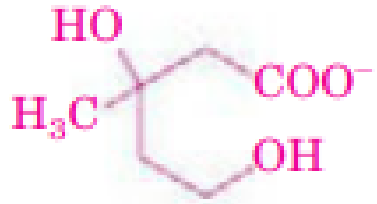
Glucagon promotes phosphorylation of HMG-CoA reductase (inactivation);

Oxysterol metabolites of cholesterol stimulate proteolysis of HMG-CoA reductase

Statins: cholesterol lowering drugs

The statins are similar to mevalonate and are competitive inhibitors of HMG-CoA reductase.





Mevalonate

$R_1 = H$	$R_2 = H$	Compactin
$R_1 = CH_3$	$R_2 = CH_3$	Simvastatin (Zocor)
$R_1 = H$	$R_2 = OH$	Pravastatin (Pravachol)
$R_1 = H$	$R_2 = CH_3$	Lovastatin (Mevacor)

Cholesterol Fates

Small fraction are incorporated into the membranes of hepatocytes,

most of it is exported in one of three forms: bile acids, cholesteryl esters

Other tissues

Cholesterol is converted

Steroid hormones
(adrenal cortex and gonads)

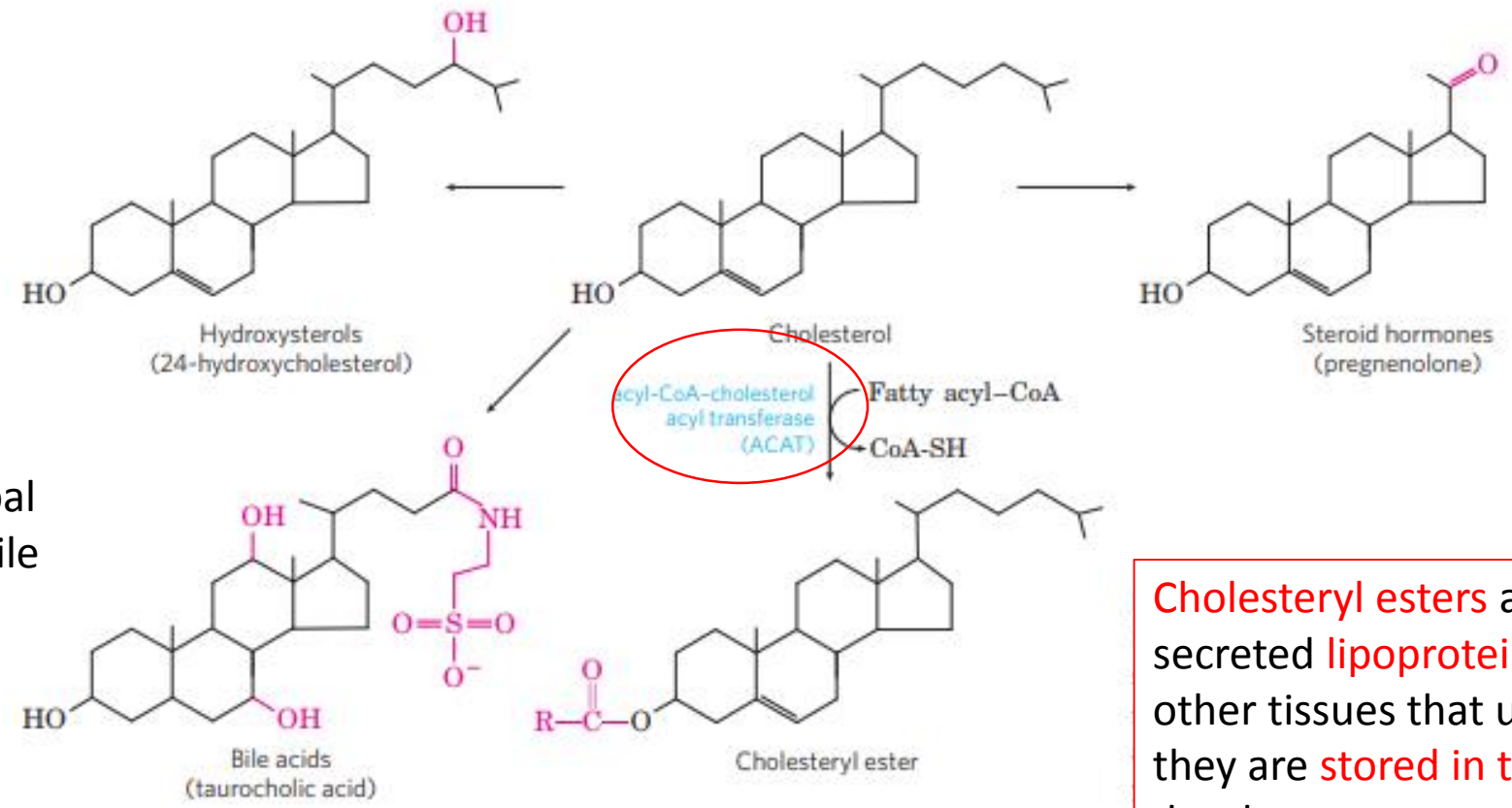
vitamin D hormone
(liver and kidney)

Small quantities of oxysterols such as 25-hydroxycholesterol are formed in the liver, and act as regulators of cholesterol synthesis

Cholesteryl esters

Cholesteryl esters are formed in the liver through the action of acyl-CoA–cholesterol acyl transferase (ACAT).

This enzyme catalyzes the transfer of a fatty acid from coenzyme A to the hydroxyl group of cholesterol



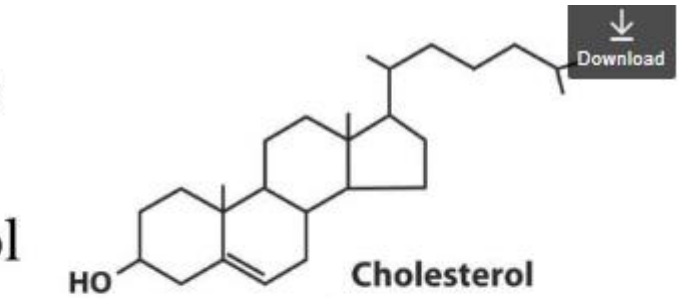
Bile acids, principal components of bile

Bile, a fluid stored in the gallbladder and excreted into the small intestine to aid in the digestion of fat-containing meals

Bile salts by emulsifying triglycerides perform the function of exposing them to enzymes

Cholesteryl esters are transported in secreted lipoprotein particles to other tissues that use cholesterol, or they are stored in the liver in lipid droplet

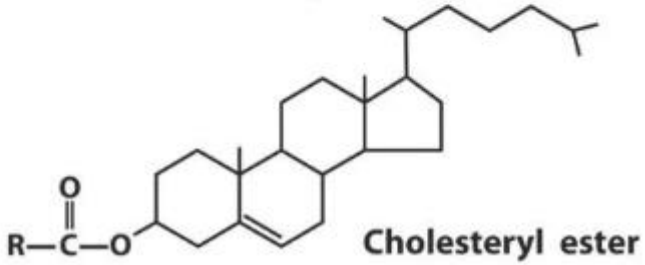
Synthesis of Cholesterol Esters



acyl-CoA–cholesterol acyl transferase (ACAT)

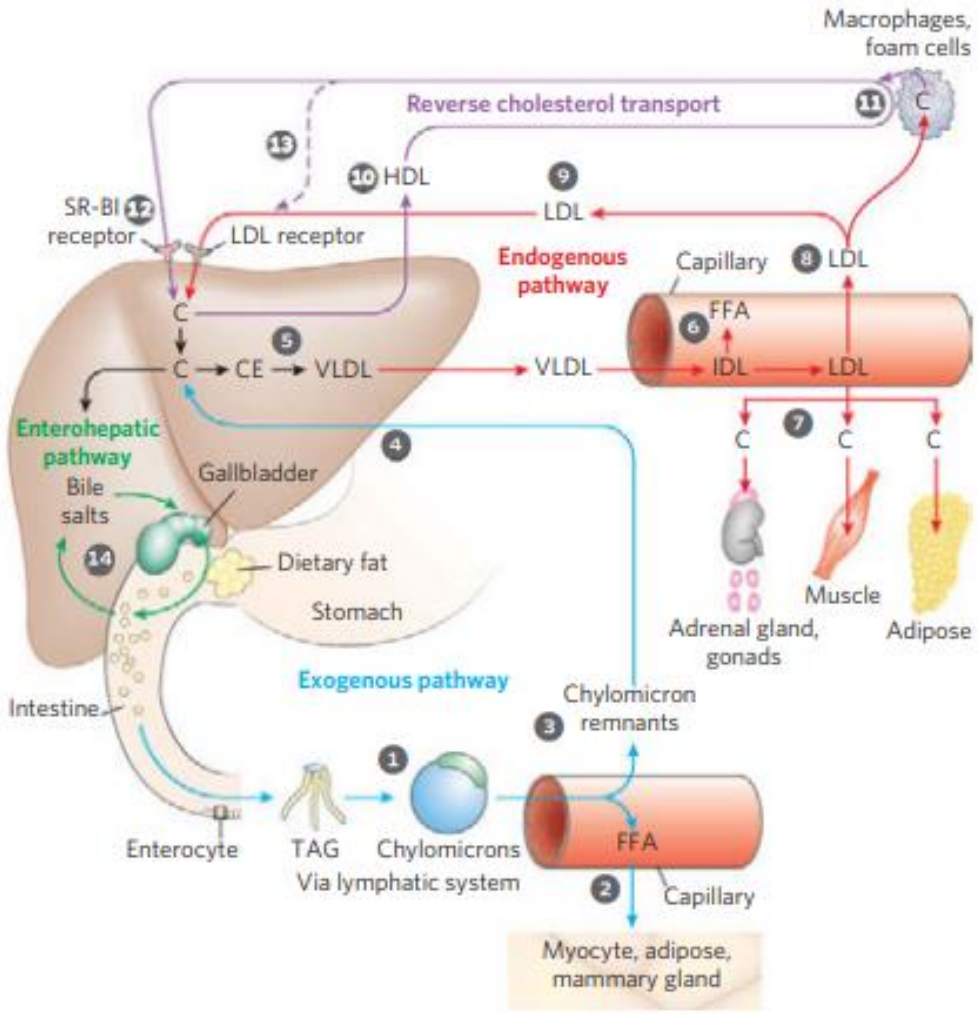
Fatty acyl–CoA

CoA-SH



Exogenous pathway: dietary lipids are packaged into chylomicrons;
Triacylglycerol content is released by lipoprotein lipase to adipose and muscle tissues during transport through capillaries.
Chylomicron remnants (containing largely protein and cholesterol) are taken up by the liver.

Bile salts produced in the liver aid in dispersing dietary fats, and are then reabsorbed in the enterohepatic pathway



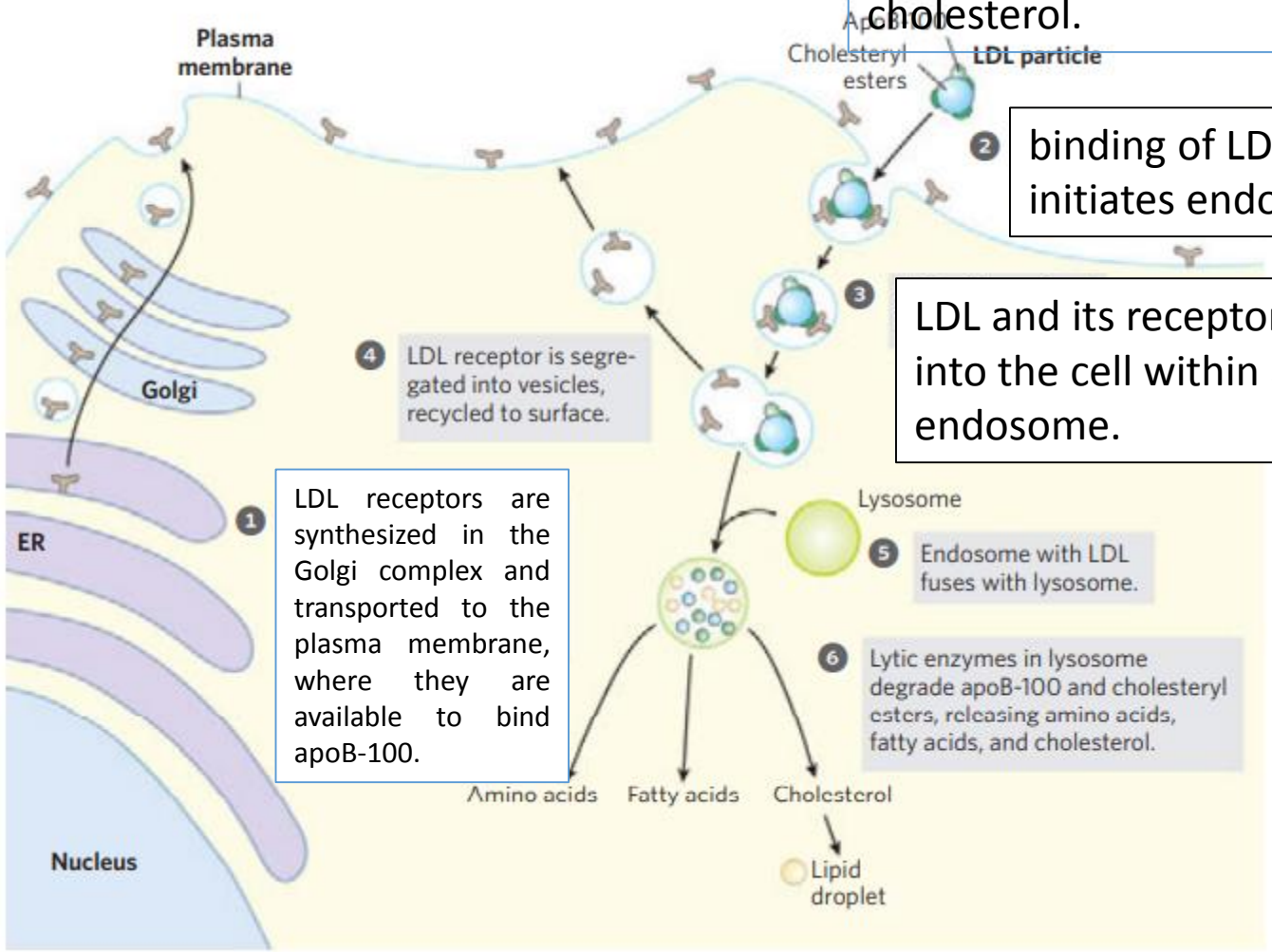
In the endogenous pathway lipids synthesized or packaged in the liver are delivered to peripheral tissues by VLDL.

VLDL gradually are converted into LDL, which deliver cholesterol to extrahepatic tissues or returns to the liver.

Excess cholesterol in extrahepatic tissues is transported back to the liver as HDL

C: cholesterol;
CE: cholesteryl ester

Each LDL particle in the bloodstream contains apoB-100, which is recognized by LDL receptors present in the plasma membranes of cells that need to take up cholesterol.



The endosome fuses with a lysosome, which 6 contains enzymes that hydrolyze the cholesteryl esters, releasing cholesterol and fatty acids into the cytosol. The apoB-100 protein is also degraded to amino acids that are released to the cytosol. ApoB-100 is also present in VLDL, but its receptor-binding domain is not available for binding to the LDL receptor; conversion of VLDL to LDL exposes the receptor-binding domain of apoB-100.

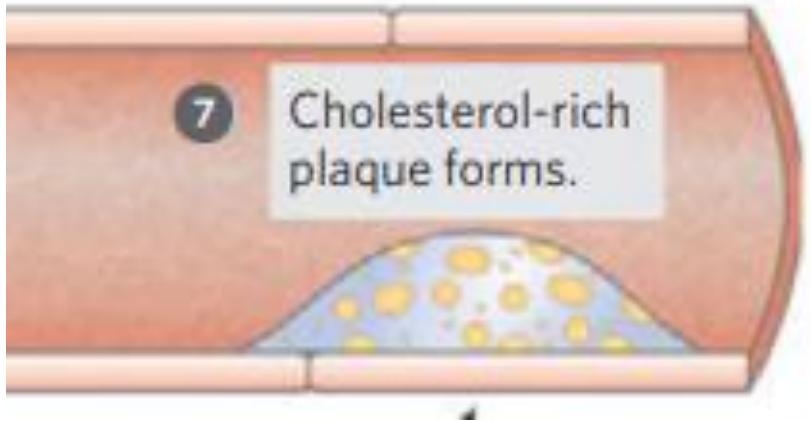
Familial hypercholesterolemia (FH)

Genetic disease

Mutations in the LDL receptor that prevent the normal uptake of LDL by liver and peripheral tissues

Defective LDL uptake is very high blood levels of LDL (and of the cholesterol it carries)

Individuals have a greatly increased probability of developing atherosclerosis, a disease of the cardiovascular system in which blood vessels are occluded by cholesterol-rich plaques



Niemann-Pick type-C (NPC) disease

A defect in lipid storage, in which cholesterol is not transported out of the lysosomes and instead accumulates in lysosomes of liver, brain, and lung, bringing about early death.

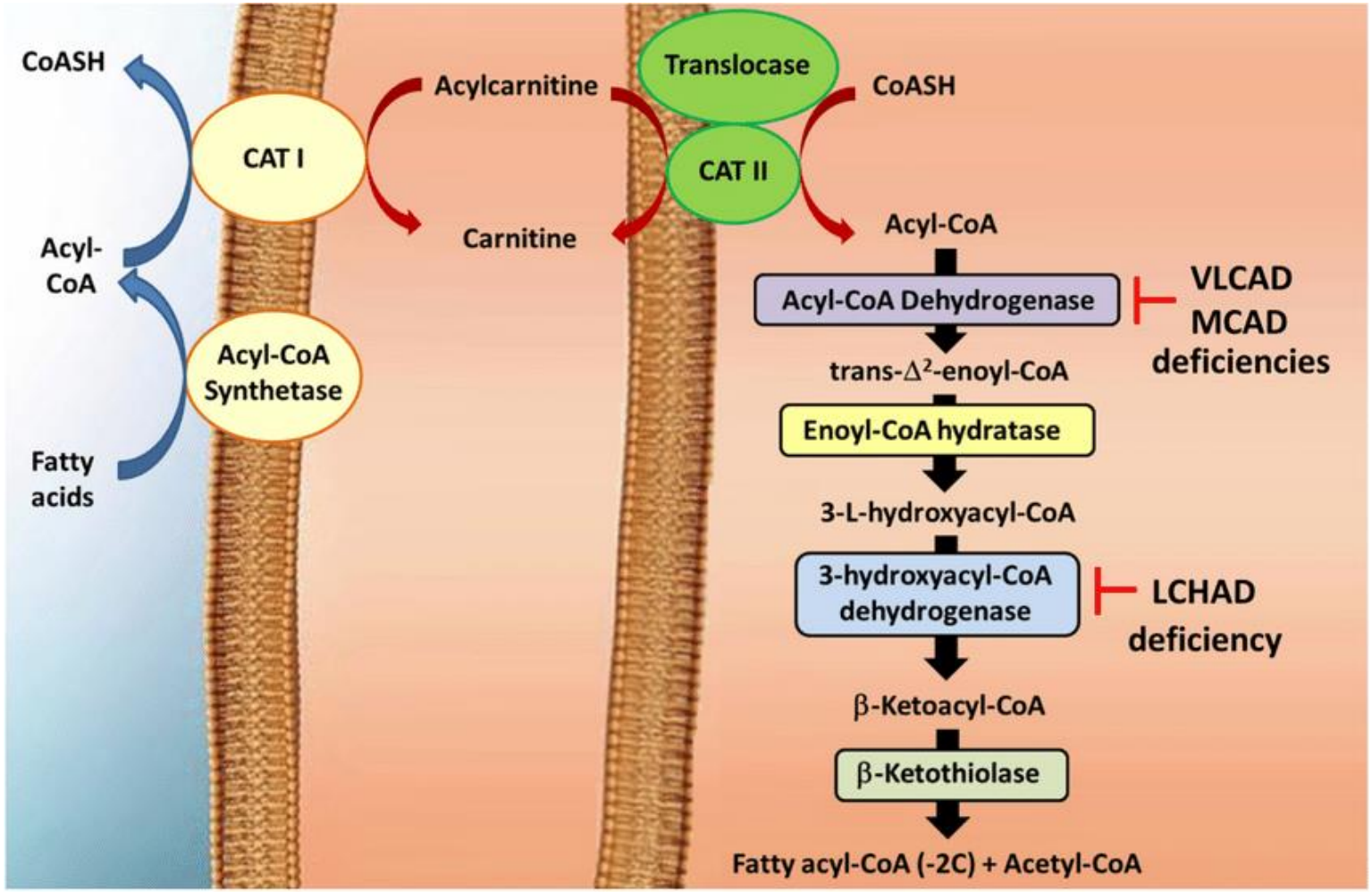
Mutation in either of two genes (NPC1, NPC2) essential to moving cholesterol out of the lysosome and into the cytosol, where it can be further metabolized

NPC1 encodes a transmembrane lysosomal protein. NPC2 encodes a soluble protein.

These proteins act in tandem to transfer cholesterol out of the lysosome and into the cytosol for further processing or metabolism

Genetic Defects in Fatty Acyl–CoA Dehydrogenases Cause Serious Disease

Mitochondrial beta-oxidation of long and very long-chain fatty acids.
The fatty acids are initially converted to fatty acyl-CoA and then are transported into the mitochondrial matrix by the actions of carnitine acyltransferase I (CAT I), carnitine acyltransferase II (CAT II) and carnitine–acylcarnitine translocase. Once in the mitochondrial matrix, fatty acyl-CoA are oxidized producing acetyl-CoA for the Krebs cycle.



VLCAD - Very Long-Chain Acyl-CoA Dehydrogenase (C12-C16)

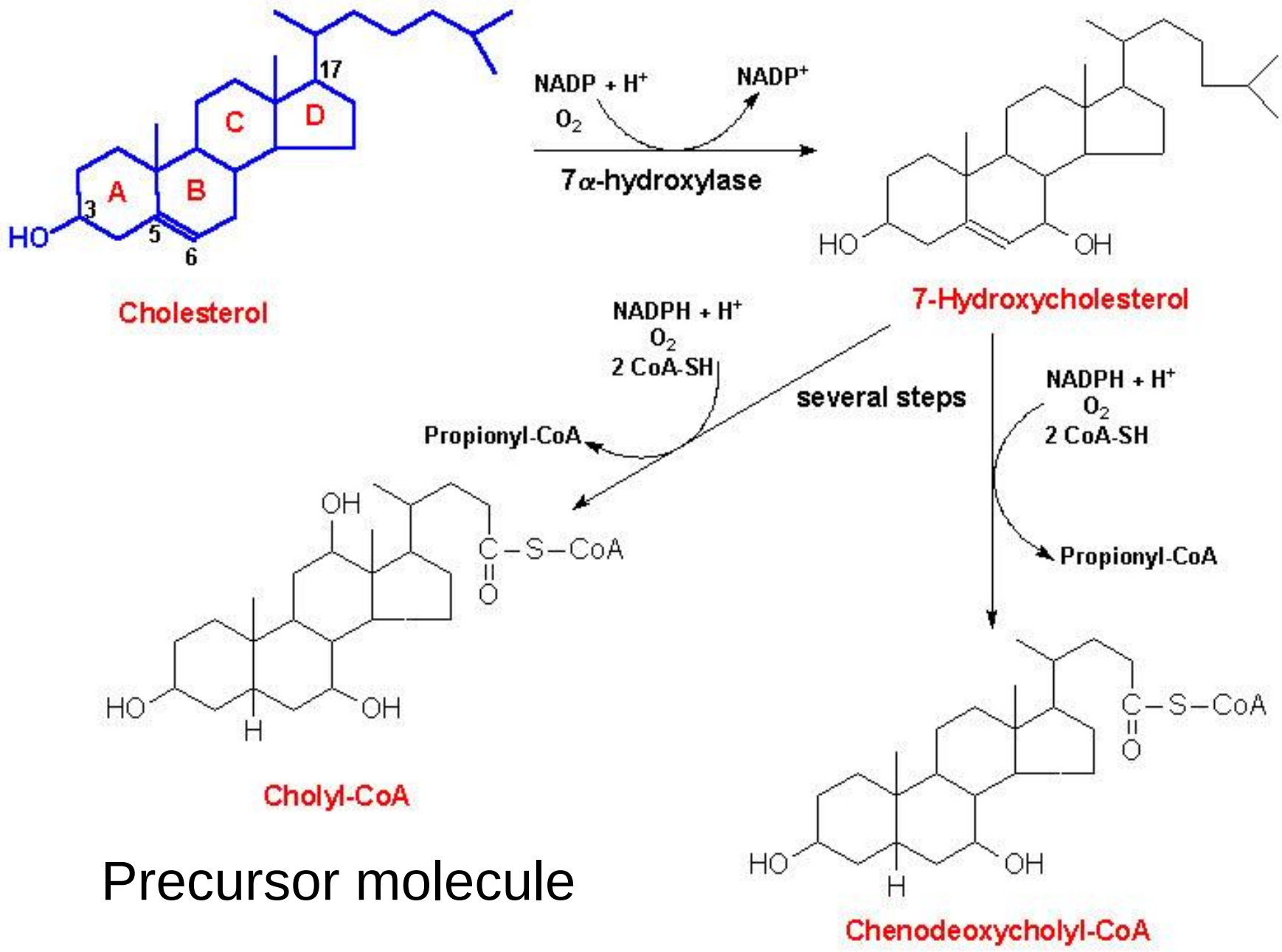
LCAD - Long-Chain Acyl-CoA Dehydrogenase (C8-C16)

MCAD - Medium-Chain Acyl-CoA Dehydrogenase (C4-C12)

SCAD - Short-Chain Acyl-CoA Dehydrogenase (C4-C6)

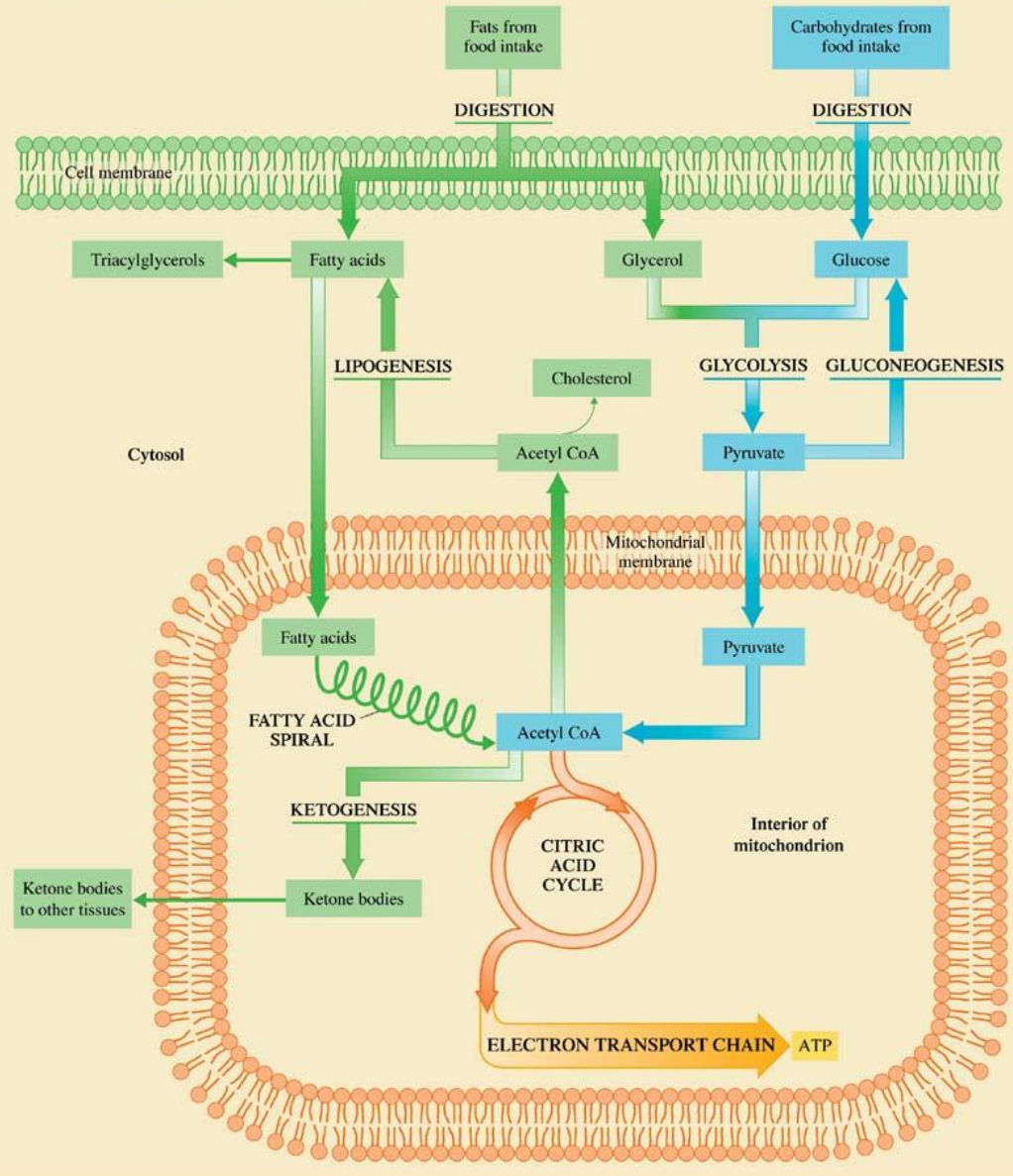
LCHAD-Long-chain 3-hydroxyacyl-CoA dehydrogenase

Enzyme deficiency	Gene	Clinical phenotype	Laboratory findings
Carnitine transporter	OCTN2	Cardiomyopahty, skeletal myopathy, sudden death	Decreased total and free carnitines
Long-chain fatty acid transporter	FATP1-6	Acute liver failure in childhood requiring liver transplantation	Reduced intracellular C_{14}-C_{18} fatty acids, reduced fatty acid oxidation
Carnitine palmitoyl transferase-I	CPT-I	Liver failure, skeletal myopathy, and sudden death	Normal or increased free carnitine
Carnitine translocase	CACT	Chronic progressive liver failure	Normal or decreased free carnitine,

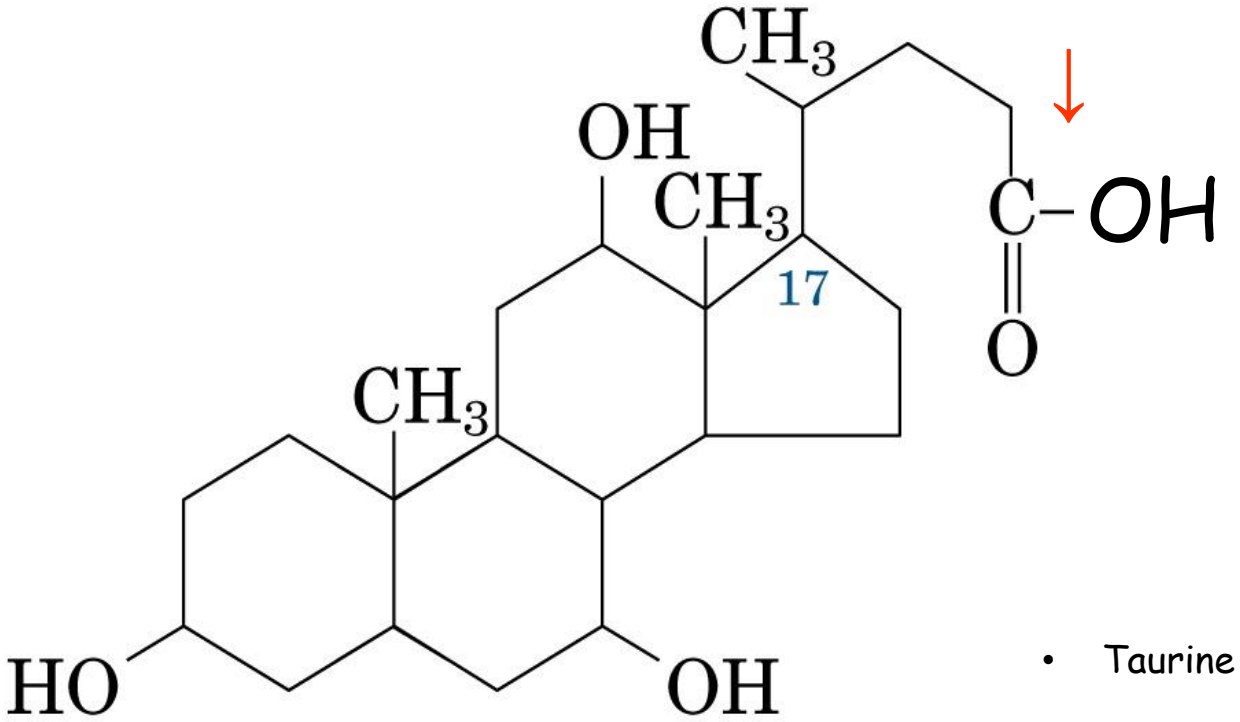


Precursor molecule

Interrelationships Between Carbohydrate and Lipid Metabolism



Bile salts: cholic acid + taurine o glycine



- Taurine is an amine with a sulfonic group

Taurocholic acid: R—COOH + $NH_2—CH_2—CH_2—SO_3^-$

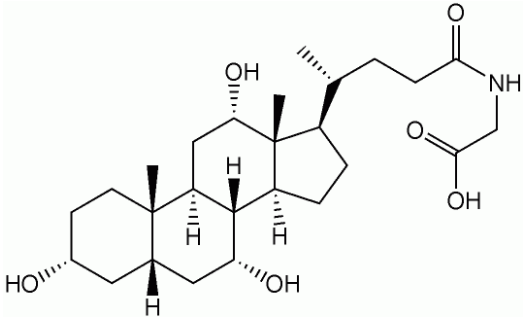
taurine

Glycocholic acid R—COOH + $NH_2—CH_2—COO^-$

glycine

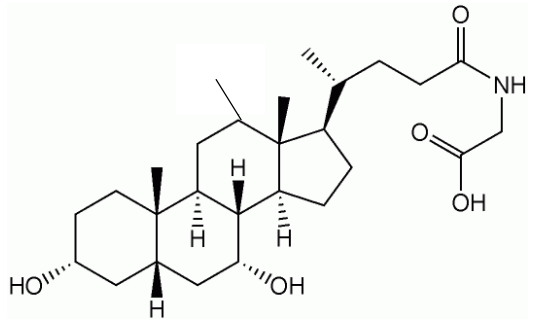
PRIMARY BILE SALTS

24 carbon atoms

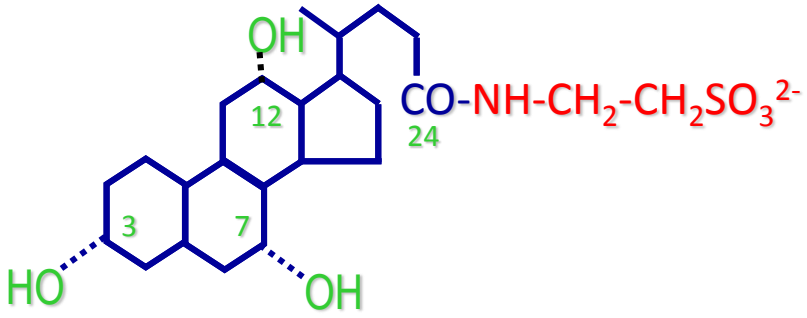


Glycocholic acid

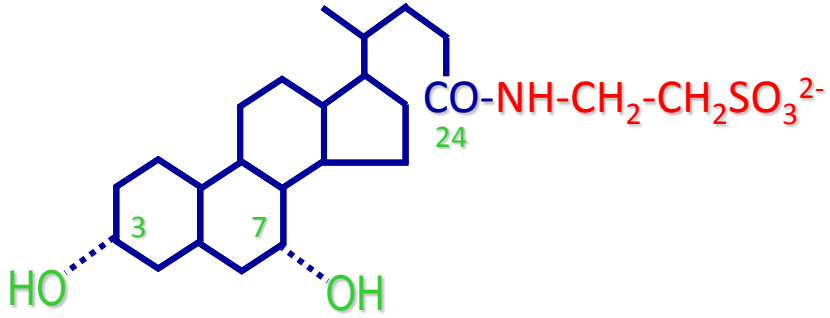
LIVER



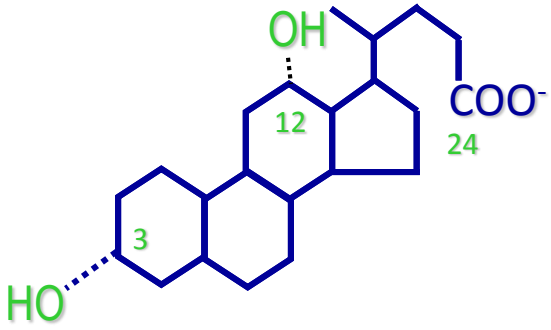
Glycochenodeoxycolic acid



Taurocholic acid



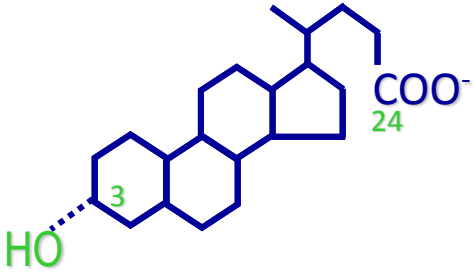
Taurochenodeoxycolic acid



Deoxycholic acid

SECONDARY BILE SALTS

Intestin



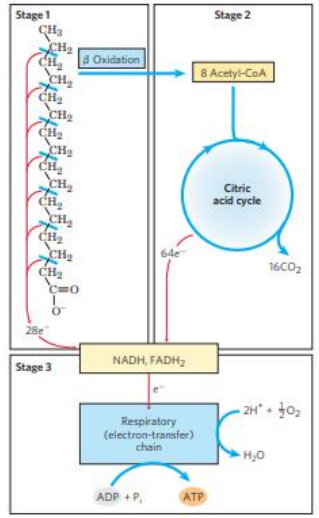
Lithocholic acid

Ketone Bodies

Humans
Other mammals

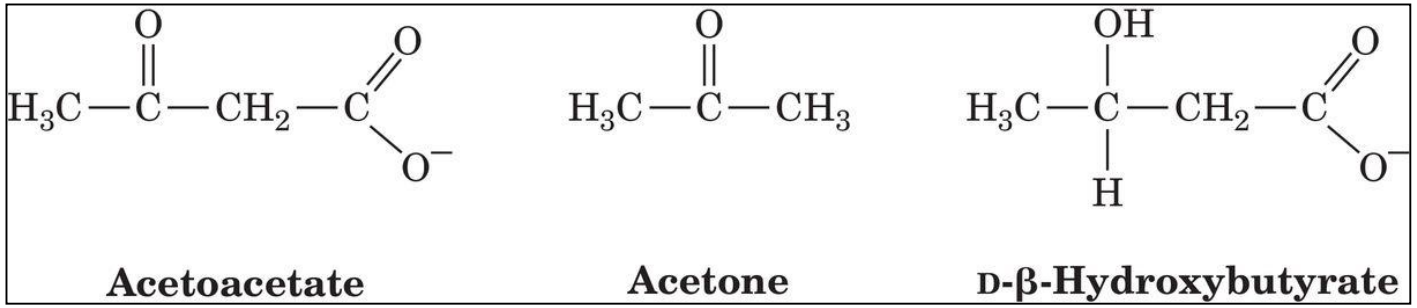
• Acetyl-CoA products **in liver** from β-oxidation can be converted to ketone bodies and exports to other tissues

Acetyl-CoA formed in the liver(mitochondrion) during oxidation of fatty acids can be oxidated in Krebs cycle (stage 2)



They are called “bodies”.
The term usually applied to insoluble particles, but these compounds are soluble in blood and urine.

Ketone Bodies

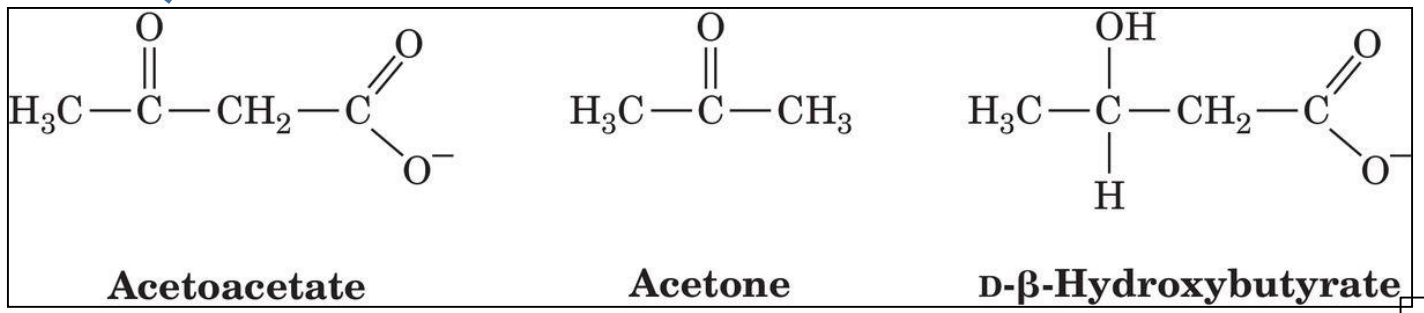


Important metabolic fuels for heart and muscle,

transported by the blood to other tissues
(skeletal and heart muscle and renal cortex)

converted to acetyl-CoA and oxidized in the citric acid cycle

Energy



produced in smaller quantities than the other ketone bodies, is exhaled

The production and export of ketone bodies from the liver to extrahepatic tissues allows continued oxidation of fatty acids in the liver when acetylCoA is not being oxidized in the citric acid cycle

The brain, which preferentially uses glucose as fuel, can adapt to the use of ketone bodies when glucose is unavailable.

(lipids cannot cross the blood-brain barrier)

Ketogenesis:

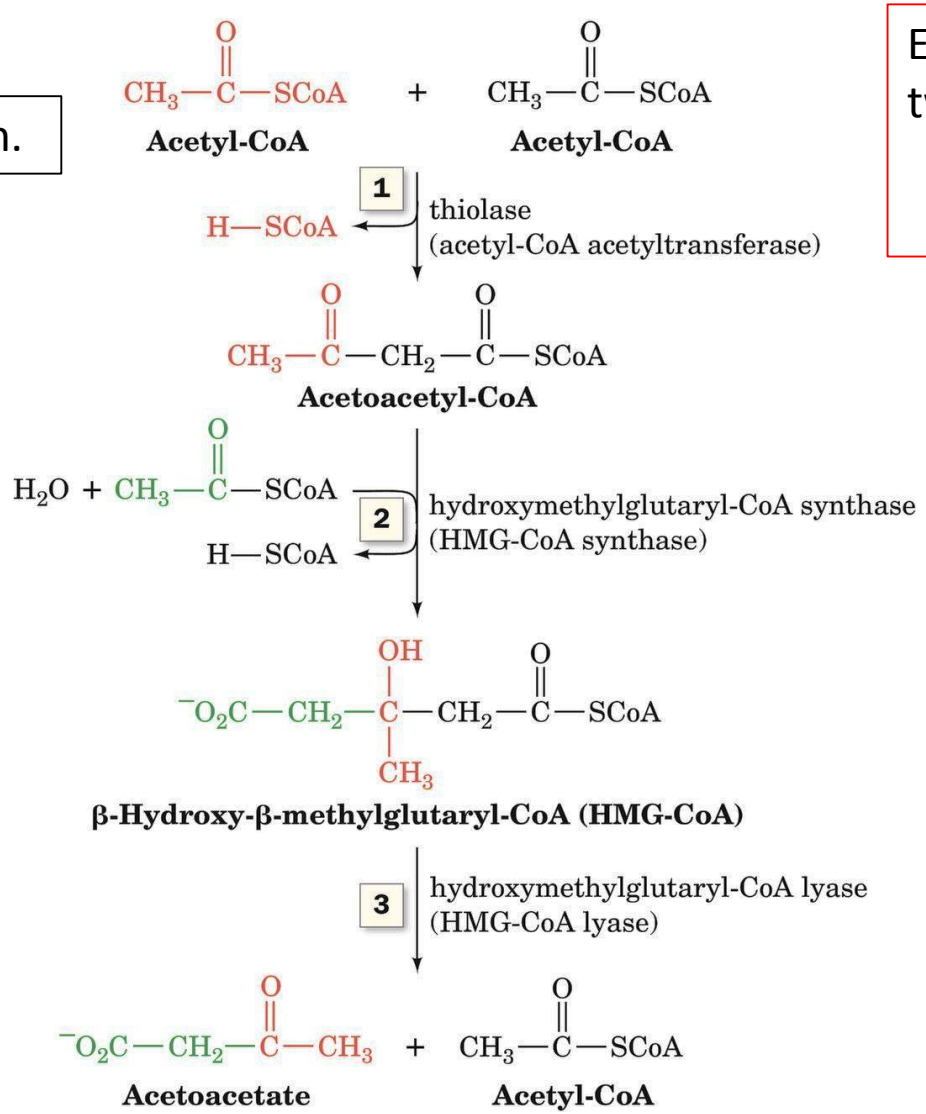
The first step in the formation of acetoacetate, (liver)

1

Enzymatic condensation of two molecules of acetyl-CoA,

catalyzed by thiolase

Reversal of the last step of β oxidation.



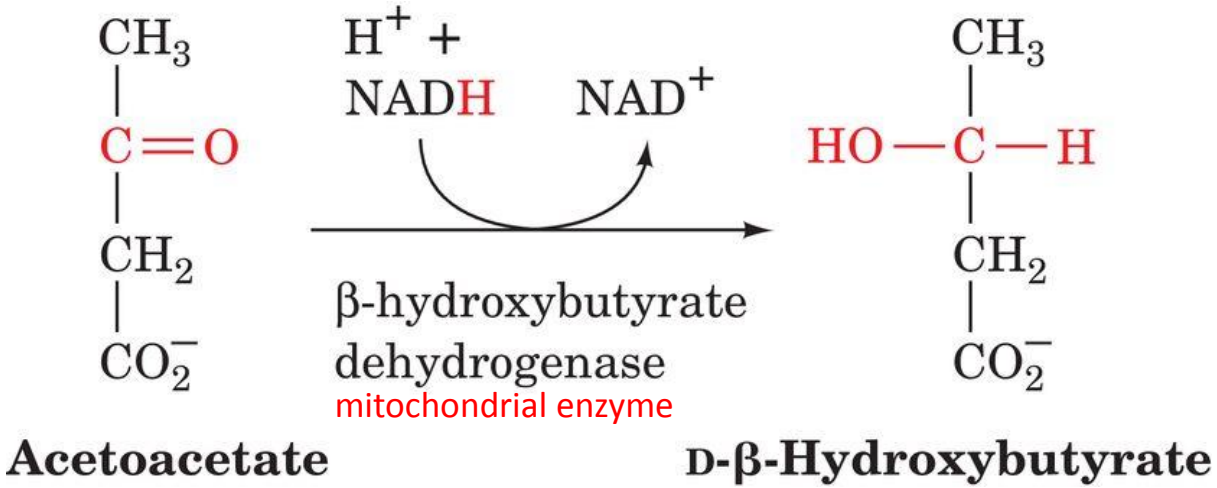
2

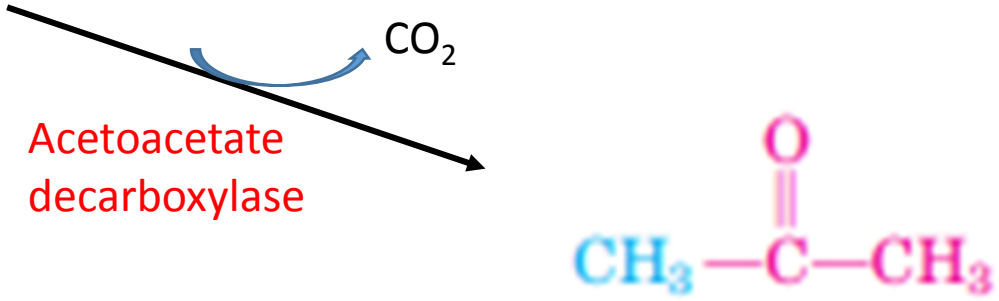
The acetoacetyl-CoA then condenses with acetyl-CoA to form HMG-CoA

3

HMG-CoA is cleaved to free acetoacetate and acetyl-CoA.

Acetoacetate is reduced to D-β-hydroxybutyrate by D-β-hydroxybutyrate dehydrogenase





In healthy people, acetone is formed in very small amounts from acetoacetate,

- Spontaneously

People with untreated diabetes produce large quantities of acetoacetate

↓

blood contains significant amounts of acetone (Ketosis).

↓

Acetone is volatile and imparts a characteristic odor to the breath,

↓

useful in diagnosing diabetes.

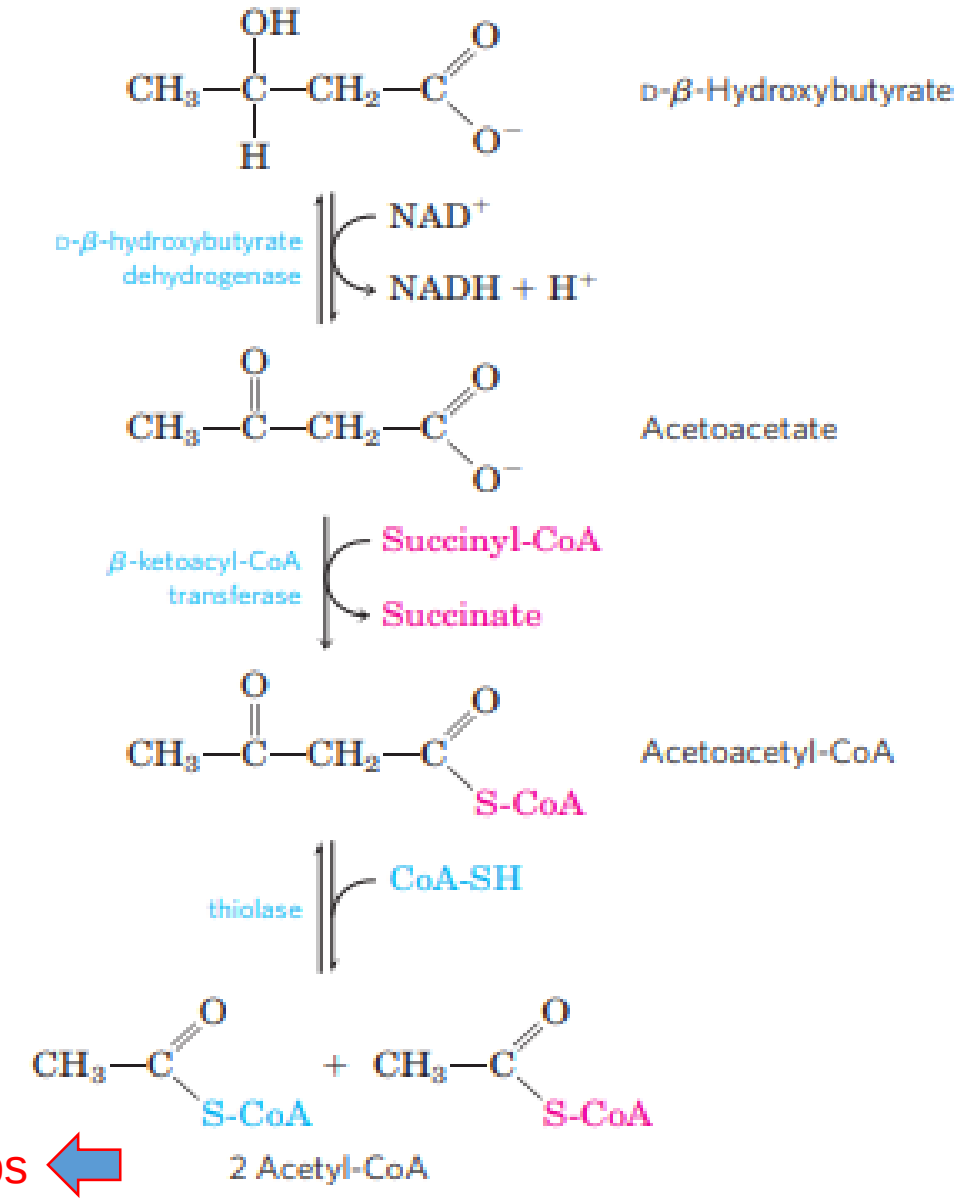
Extrahepatic tissues,

1. D-β-hydroxybutyrate is oxidized to acetoacetate

2. Acetoacetate is activated to its coenzyme A ester by transfer of CoA from succinylCoA, an intermediate of the citric acid cycle in a reaction catalyzed by β-ketoacyl-CoA transferase, also called thiophorase.

3. AcetoacetylCoA is then cleaved by thiolase to yield two acetylCoAs, which enter the citric acid cycle.

Ketone bodies are used as fuels in all tissues except liver, which lacks thiophorase.



Ciclo di Krebs

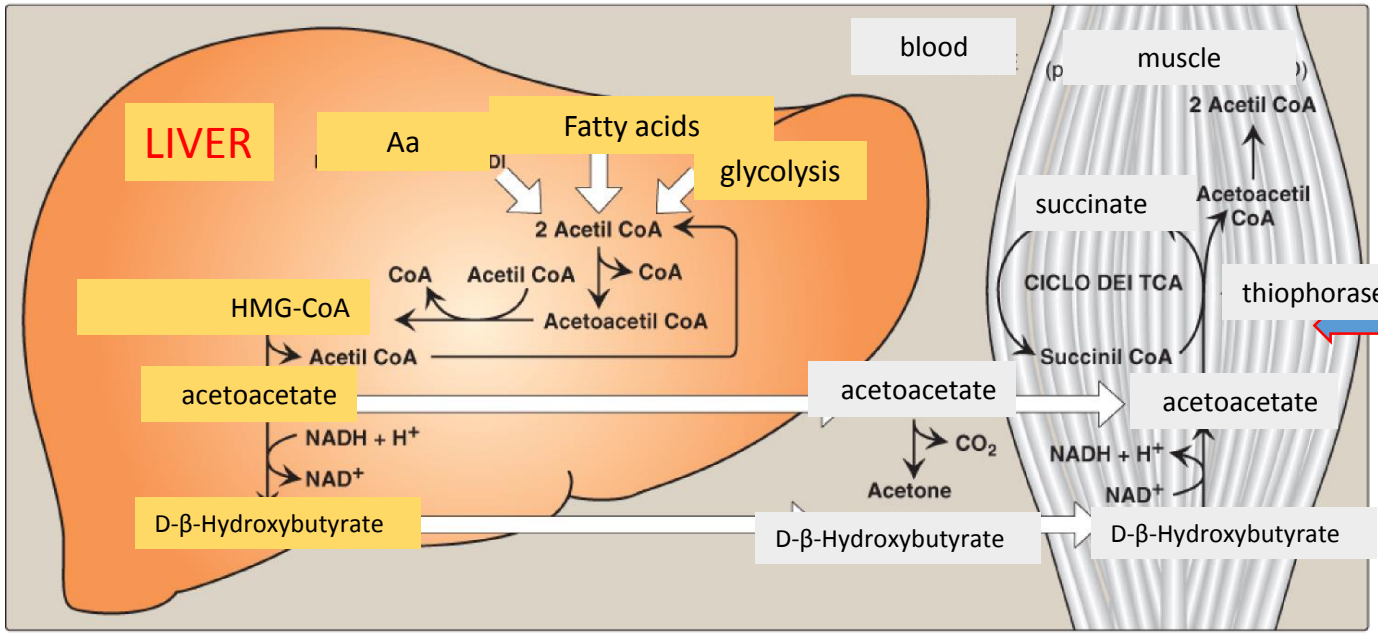
Ketone Bodies to Acetyl-CoA

Liver not uses ketone bodies

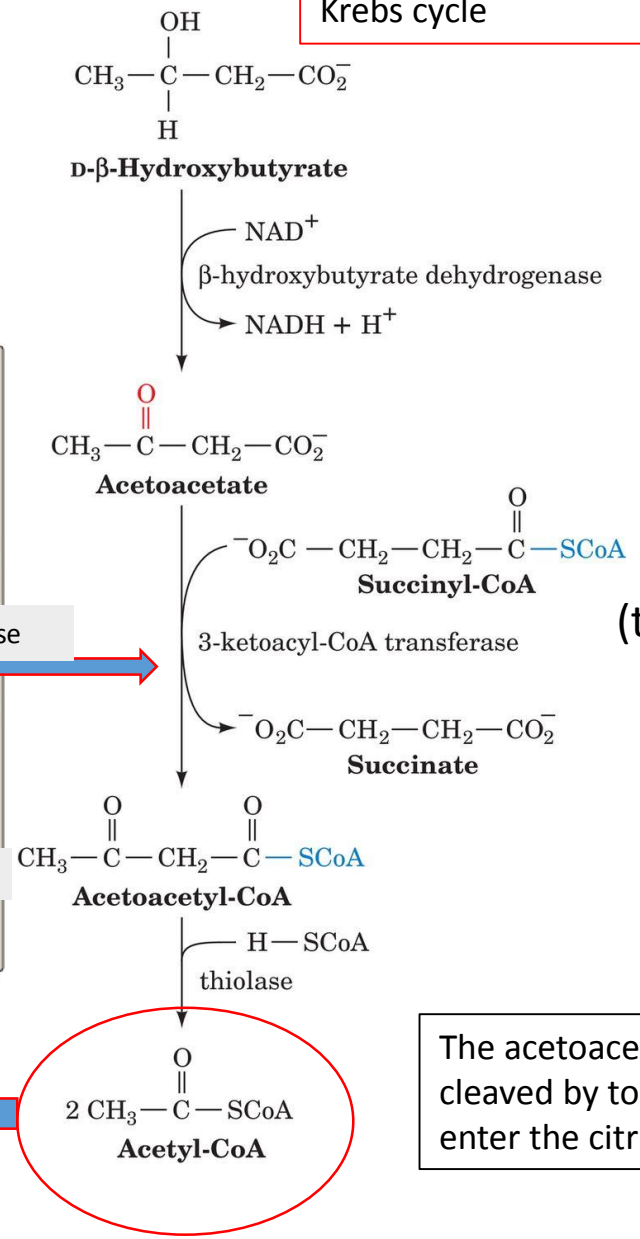
use as fuels

LIVER release ketone bodies in blood that reach peripheric tissue.

Ketone bodies are reconverted into 2 Acetil-CoA molecules



The acetoacetate is activated to its coenzyme A ester by transfer of CoA from succinyl. CoA (intermediate of Krebs cycle



(thiophorase).

Liver lacks

The liver is therefore a producer of ketone bodies for the other tissues, but not a consumer.

Ciclo di Krebs

The acetoacetyl-CoA is then cleaved by to yield two , which enter the citric acid cycle.

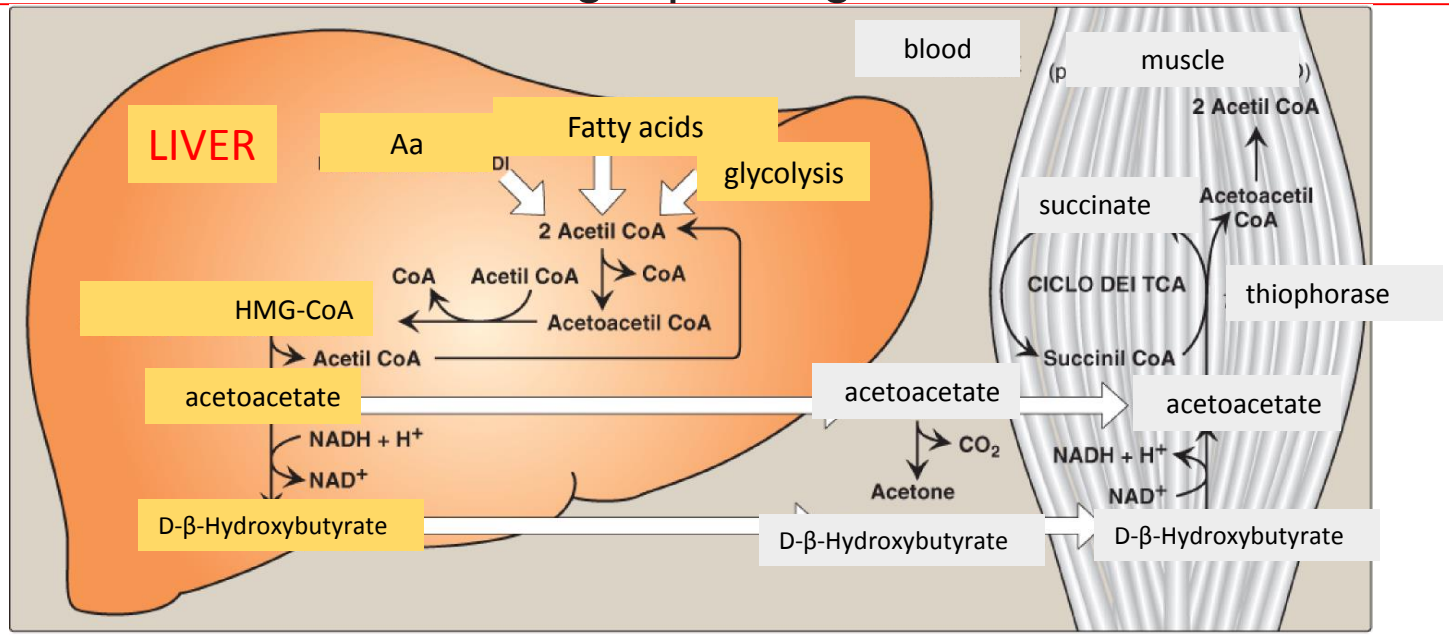
Ketone bodies come out of hepatocytes.

They enter the circulation and are absorbed by tissues such as the brain, heart and skeletal muscle.

They are sources for the Krebs cycle and produce greater amounts of metabolic energy.

Heart, muscles and adrenal cortex mainly use acetoacetate instead glucose.

Brain mainly uses glucose
but brain uses the ketone bodies following a prolonged fast



Under normal conditions and with a balanced diet,

Ketone bodies are produced in small quantities

(acetyl-CoA is used by the citric acid cycle).

Ketone bodies are produced in excess during fasting and in diabetes.

Prolonged fasting -> increased gluconeogenesis
-> increased β- oxidation

accumulation of acetyl-CoA

Increased Ketone bodies

-During a prolonged fast
- Untreated diabetes mellitus

overproduction of ketone bodies

LIver

↑ GLUCONEOGENESIS

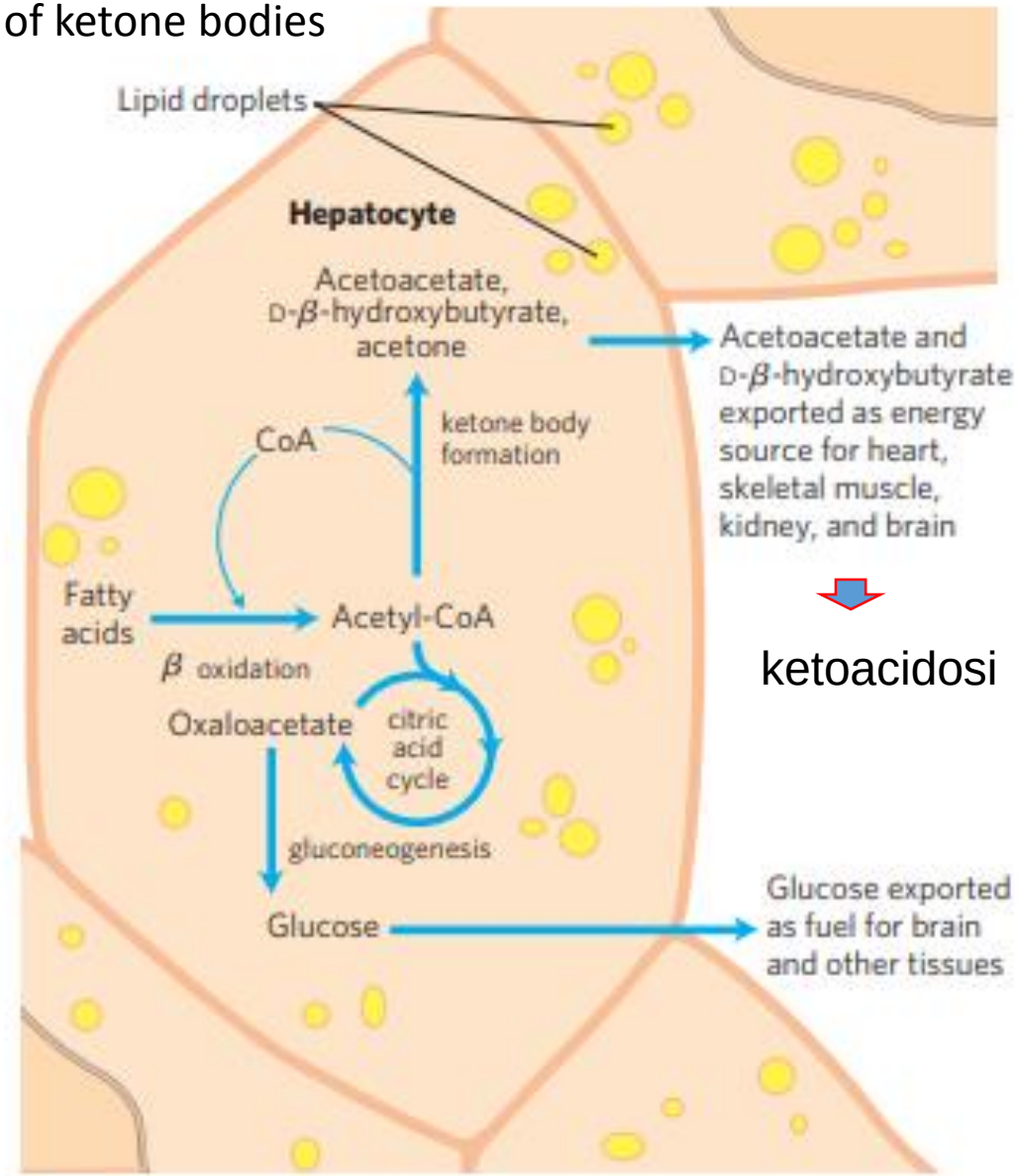
AcetylCoA not enters the cycle because oxalacetate is subtracted for gluconeogenesis

↓KREBS cycle

↓oxidation of acetyl units
↑ Acetyl-CoA

↑Ketogenesis

lead
to, with several
associated medical problems.



ketoacidosi

https://www.youtube.com/watch?v=ppqpUVaasNc