Lipid metabolism

By raneem Al-syouf

- سؤالات / اسئلة
- كلام الدكتورة
- فيديوهات شرح
- تلخيص

best luck ★

Fatty acids
Saturation of fatty acids

- Fatty acid chains (with no double bonds or one or more double bonds that are always in the cis configuration) and this causes fatty acid to kink at that position

trans configuration is very toxic

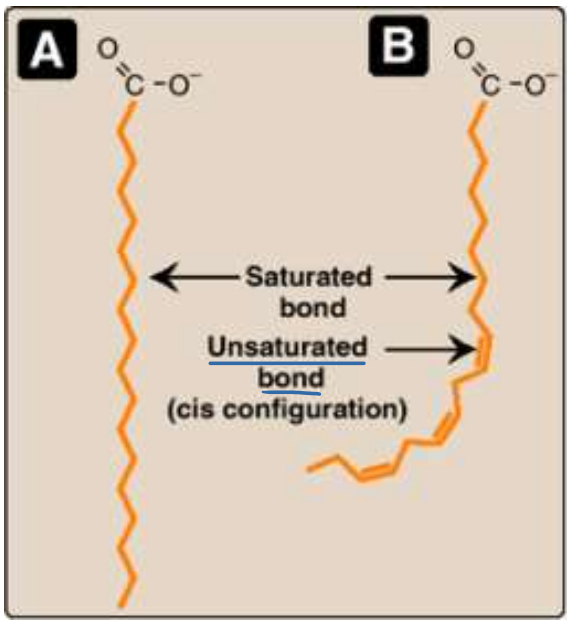
- Addition of double bond decreases the melting temperature (T_m) of a fatty acid, whereas increasing the chain length increases the T_m

double bonds ↑
melting point ↓

عكسية

Chain length ↑
melting point ↑

طردية



carboxyl group

hydrocarbon

Chain length of fatty acids

number of carbons : number of double bonds

- The number before the colon indicates the number of carbons in the chain, and those after the colon indicate the numbers and positions of double bonds

ω-6

- For example, arachidonic acid, 20:4(5, 8, 11, 14), is 20 carbons long ana double bonds (between carbons 5-6, 8-9, 11-12, and 14-15). The carbon to which the carboxyl group is attached (carbon 2) called the α-carbon, carbon 3 is the β-carbon. The carbon of the terminal methyl group is called ω-carbon regardless of the chain length

- Arachidonic acid is referred to as an ω-6 while linolenic acid, 18:3(9,12,15), is an ω-3 fatty acid.

ω-3 — مضافات الثلاث

Arachidonic acid = omega 6

linolenic acid = omega 3

Fatty acids with chain lengths of four to ten carbons are found in significant qantities in milk (4-10) milk

Structural lipids and triacylglycerols contain primarily fatty acids of at least sixteen carbons.

COMMON NAME	STRUCTURE
Formic acid	1
Acetic acid	2:0
Propionic acid	3:0
Butyric acid	4:0
Capric acid	10:0
Palmitic acid	16:0
Palmitoleic acid	16:1(9)
Stearic acid	18:0
Oleic acid	18:1(9)
Linoleic acid	18:2(9,12)
α-Linolenic acid	18:3(9,12,15)
Arachidonic acid	20:4(5, 8,11,14)
Lignoceric acid	24:0
Nervonic acid	24:1(15)

16C

16:1(9) → في double bond

Precursor of prostaglandins

Essential fatty acids

Essential fatty acids

body can't synthesis it

- Two fatty acids are dietary essentials in humans:
  - Linoleic acid, which is the precursor of arachidonic acid, the substrate for prostaglandin synthesis
  - omega 3 (ω-3)
    Linolenic acid, the precursor of other ω -3 fatty acids important for growth development
  - omega 3
    A deficiency of linolenic acid rest decreased vision and altered learning behaviors
  - Arachidonic acid becomes essential if linoleic acid is deficient in the diet.

منطقي لأنه لو مش موجود lindeic acid
الجسم مارح يصنع arachidonic acid

cytosol)

De novo synthesis of fatty acids in

- liver
- lactating mammary glands
- Adipose tissues

- In humans, fatty acid synthesis occurs primarily in the **liver** and **lactating mammary glands** and, to a lesser extent, in **adipose tissue**.
- The process incorporates carbons from acetyl CoA into the growing fatty acid chain, using ATP and reduced nicotinamide adenine dinucleotide phosphate (NADPH).

- Acetyl-CoA → carbon source
- ATP → energy
- NADPH → reducing power

- Production of cytosolic acetyl CoA
- First acetate units is transferred from mitochondrial acetyl CoA to the cytosol. Mitochondrial acetyl CoA is produced by:
  - The oxidation of pyruvate
  - The catabolism of fatty acids
  - Ketone bodies
  - Certain amino acids

Students often confuse NADH with NADPH.

Remember:

- NADPH → synthesis
- NADH → ATP production

- The coenzyme A portion of acetyl CoA cannot cross the mitochondrial membrane and only the acetyl portion is transported to the cytosol. It does so in the form of citrate produced by the condensation of oxaloacetate (OAA) and acetyl CoA

Acetyl-CoA + OAA → citrate

Concept	High-Yield Fact
Fatty acid synthesis location	⭐ Cytosol
β-oxidation location	⭐ Mitochondria
Transport molecule	Citrate
Reducing agent	NADPH
Major organ	Liver
Shuttle enzyme	ATP citrate lyase

Easy Memory Trick

“Fat is made in the cytosol, but acetyl CoA needs a citrate taxi.”

https://youtu.be/nBFSz63T1c0?si=5pFJ5kYgCGMvr15P

the regulation part 18:00 minute

1. translocation of citrate from the mitochonderion to the cytosol

A

- The translocation of citrate from the mitochonderion to the cytosol, where it is cleaved by **ATP-citrate lyase** to produce cytosolic acetyl CoA and OAA, occurs when the mitochondrial substrate concentration is high. A lot of Acetyl-CoA + energy (ATP)

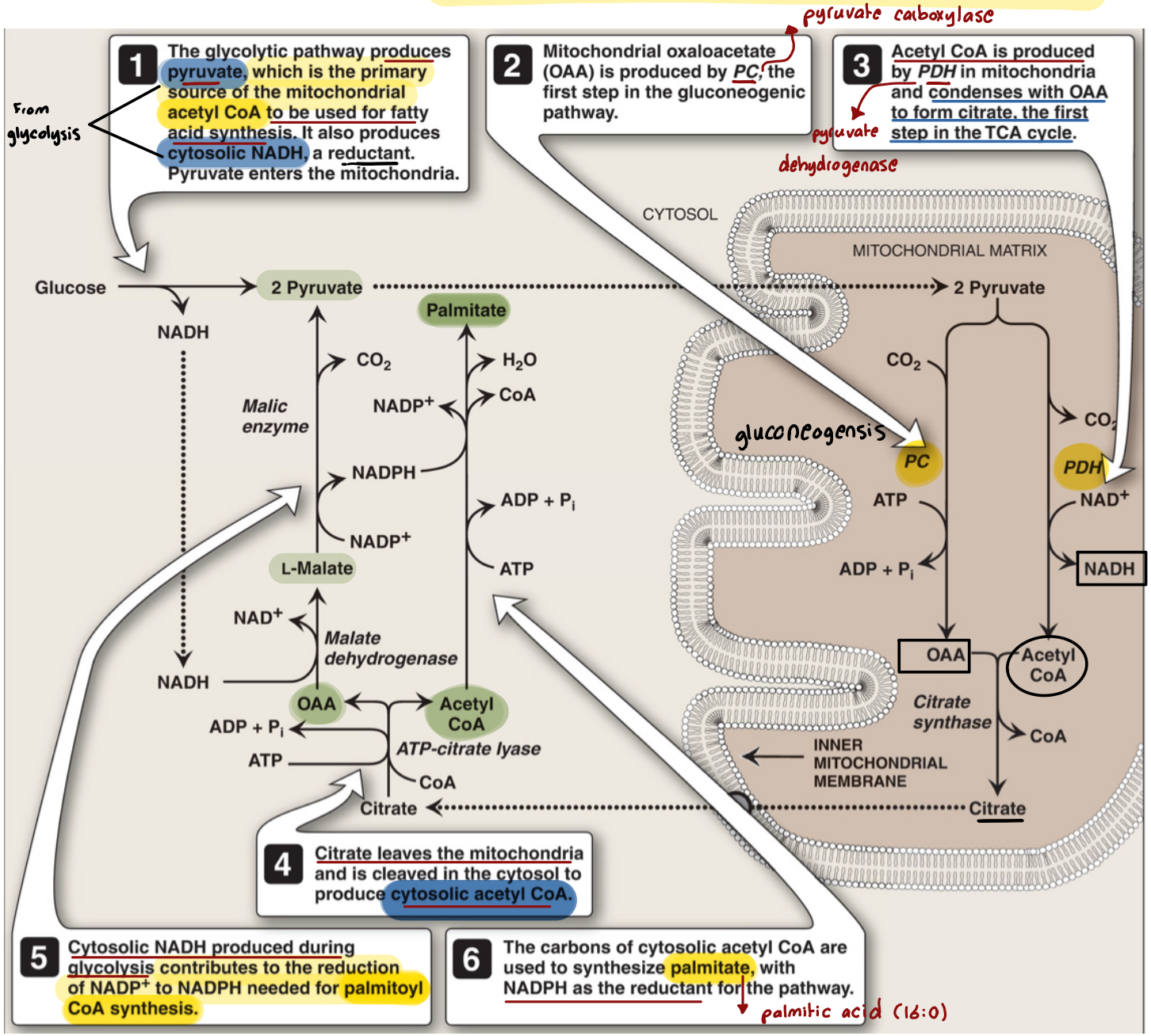
- This is observed when isocitrate dehydrogenase is inhibited by the presence of large amounts of ATP. causing citrate and isocitrate to accumulate. مخزنهم fat نصنع ← I don't need glycolysis ATP ↑ منطق

- A large amount of ATP is needed for fatty acid synthesis

- The increase in both ATP and citrate enhances this pathway.

(+) ATP
(+) citrate
activate fatty acids synthesi

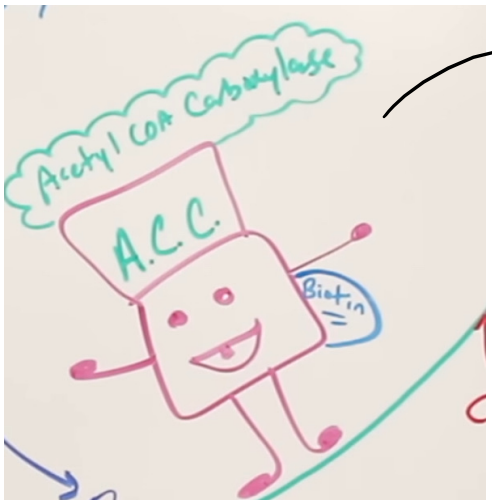
Source of cytosolic Acetyl coA



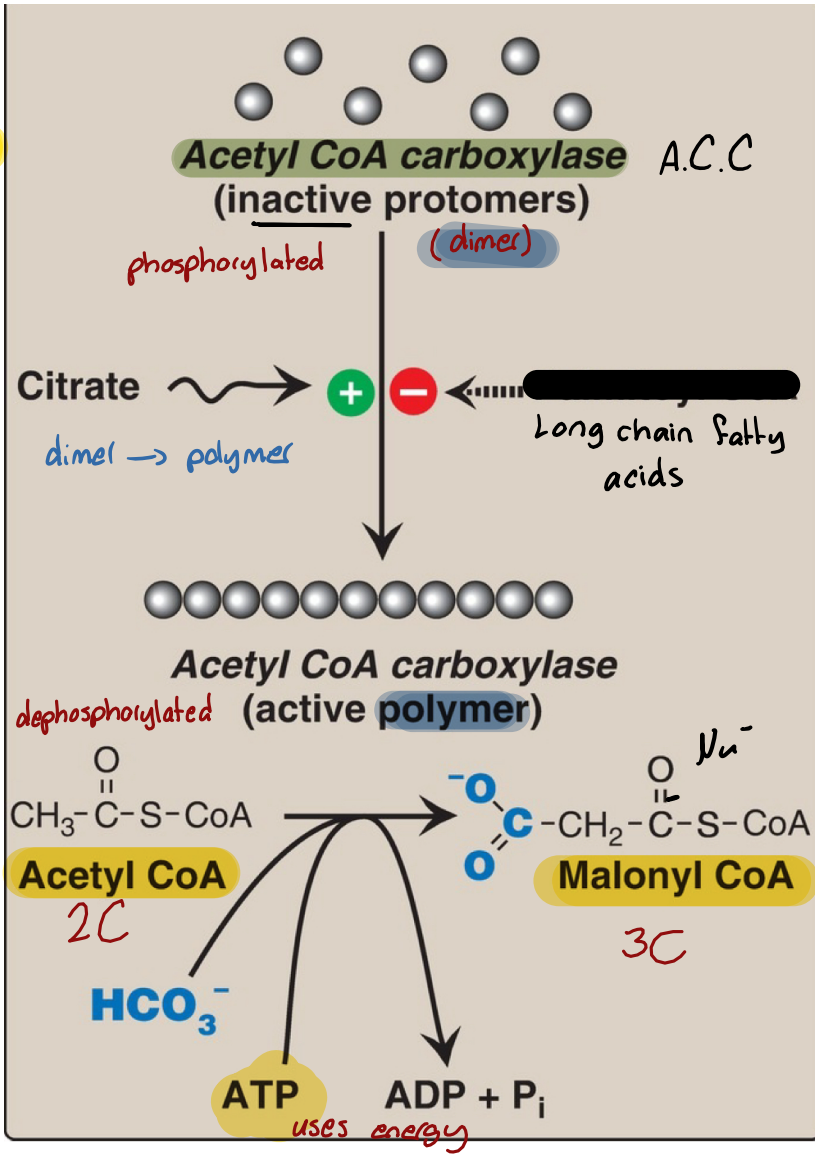
+ CO_2

2. Carboxylation of acetyl CoA to form malonyl CoA

- The carboxylation of acetyl CoA to form malonyl CoA is catalyzed by acetyl CoA carboxylase and requires HCO_3^- and ATP and biotin coenzyme.



I am active when dephosphorylated bc I donate my (P) and that energize me !!



Regulation of acetyl CoA carboxylase

long term

short term

Short-term regulation of acetyl CoA carboxylase:

- This carboxylation is both the rate-limiting and the regulated step in fatty acid synthesis
- The acetyl CoA carboxylase is a dimer. Which is allosterically activated by citrate by polymerizing it.
- The enzyme can be allosterically inactivated by
  - Long-chain fatty acyl CoA (the end product of the pathway), which causes its depolymerization. back to dimer
  - Reversible phosphorylation in the presence of epinephrine and glucagon (inhibited) inactive
- In the presence of insulin, Acetyl CoA carboxylase is dephosphorylated and, so activated.

Long-term regulation of acetyl CoA carboxylase:

Fed state
insulin ↑
ATP ↑
glucose ↑
citrate ↑

- Prolonged consumption of high-calorie, high-carbohydrate diets causes an increase in acetyl CoA carboxylase synthesis, thus increasing fatty acid synthesis. "logic"
- Conversely, a low-calorie diet or fasting causes a reduction in fatty acid synthesis by decreasing the synthesis of acetyl CoA carboxylase.

bc its the limiting eating step

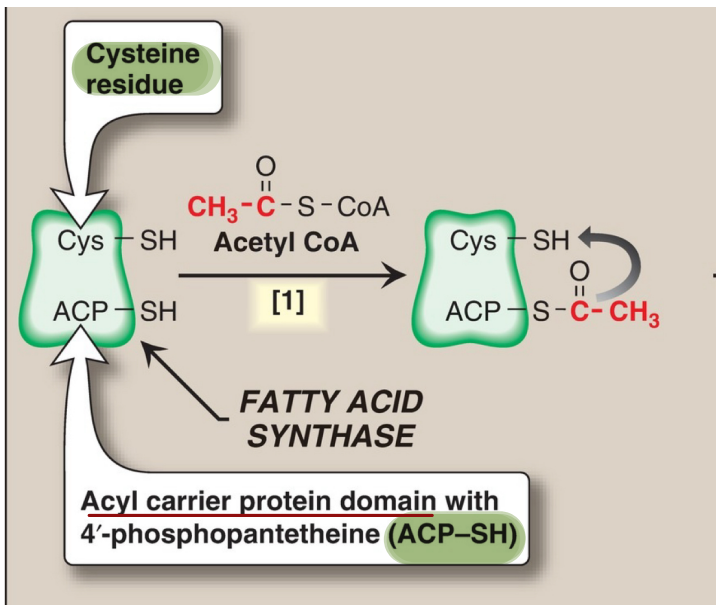
https://youtu.be/iKcvb1IihcM?si=hLy6ucuqrKlGMFBG

7 in 1

Fatty acid synthase

- The remaining series of reactions of fatty acid synthesis is catalyzed by the multifunctional, dimeric enzyme, fatty acid synthase.

- Each fatty acid synthase monomer is a multicatalytic polypeptide with 7 seven different enzymatic activities plus a domain that covalently binds a molecule of 4'-phosphopantetheine, carries acetyl and acyl units on its terminal thiol (-SH group) during fatty acid synthesis



Steps of fatty acid synthesis

[1] A molecule of acetate is transferred from acetyl CoA to the -SH group of the ACP. Domain: Acetyl CoA-ACP acetyltransacylase

[2] This two-carbon fragment is transferred to the holding site, the thiol group of a cysteine residue on the enzyme.

[3] The now-vacant ACP accepts a three-carbon malonate from malonyl CoA. Domain: Malonyl CoA-ACP-transacylase

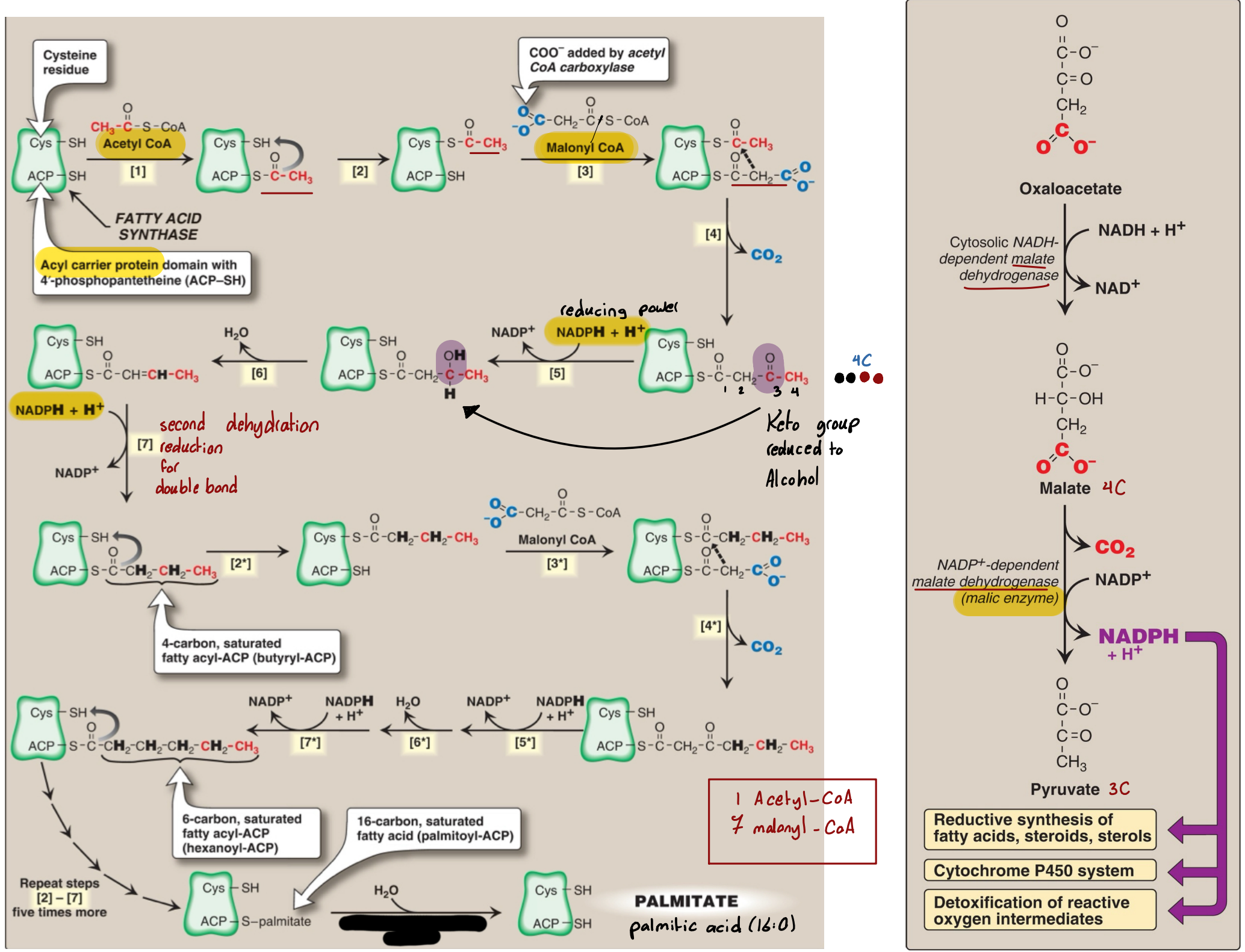
[4] The malonyl group loses the HCO_3 originally added by CoA carboxlyase, facilitating its nucleophilic attack of thioester bond linking the acetyl group to the cysteine residue The result is a four-carbon unit attached to the ACP carbon growing step 4C = step 4

[5] The keto group is reduced to an alcohol. Domain: 3-Ketoacyl ACP reductase. the reducing power is NADPH → $NADP^+$

[6] A molecule of water is removed to introduce a double bond. Domain: 3-Hydroxyacyl-ACP dehydratase. dehydration

[7] A second reduction step occurs. Domain: Enoyl-ACP reductase

- At the end, Palmitoyl thioesterase cleaves the thioester bond, producing a fully saturated molecule of palmitate (16:0).


Cysteine residue
Acetyl CoA
[1]
COO⁻ added by acetyl CoA carboxylase
Malonyl CoA
[3]
[2]
FATTY ACID SYNTHASE
Acyl carrier protein domain with 4′-phosphopantetheine (ACP–SH)
[4]
CO2
reducing power
NADPH + H+
NADP+
[5]
4C
H2O
[6]
NADPH + H+
NADP+
[7]
second dehydration reduction for double bond
Keto group reduced to Alcohol
Malonyl CoA
[3*]
[2*]
[4*]
CO2
4-carbon, saturated fatty acyl-ACP (butyryl-ACP)
[5*]
[6*]
[7*]
6-carbon, saturated fatty acyl-ACP (hexanoyl-ACP)
16-carbon, saturated fatty acid (palmitoyl-ACP)
Repeat steps [2] – [7] five times more
S–palmitate
PALMITATE
palmitic acid (16:0)
1 Acetyl-CoA
7 malonyl-CoA
Oxaloacetate
Cytosolic NADH-dependent malate dehydrogenase
NADH + H+
NAD+
Malate 4C
NADP+-dependent malate dehydrogenase (malic enzyme)
CO2
NADP+
NADPH + H+
Pyruvate 3C
Reductive synthesis of fatty acids, steroids, sterols
Cytochrome P450 system
Detoxification of reactive oxygen intermediates

All of the following stimulate fatty acids synthesis except:

phosphorylations of the key : الجواب كان enzyme

Acetyl-CoA carboxylase

Steps of fatty acid synthesis ترتيبهم

oleic acid 18C the body can synthesis it from palmitate

Further elongation of fatty acids

- Palmitate can be further elongated by the addition of two-carbon units in the endoplasmic reticulum (**ER**) and **the mitochondria**. These organelles use separate enzymatic processes.

- The brain has additional elongation capabilities allowing it to produce the very-long-chain fatty acids (up to 24 C) that are required for synthesis of brain lipids.
  - can synthesis its own fatty acids
  - up to 24 C

- Enzymes present in the **ER** are responsible for desaturating fatty acids (that is, adding cis double bonds). Termed **mixed-function oxidases**, the desaturation reactions require NADH and O_2.

  ER desaturation = adding cis double bonds

- We must have the polyunsaturated linoleic and linolenic acids provided in the diet.

acidic in nature

Storage of fatty acids as components of triacylglycerols

- Mono-, di-, and triacyiglycerols consist of one, two, or three molecules of fatty acids are esterified to a molecule of glycerol through their carboxyl groups, resulting in a loss of negative charge and formation of 'neutral fat"
  - Fatty acid at C1 is usually saturated
  - Fatty acid at C2 is usually unsaturated C2
  - Fatty acid at C3 can be either

saturated unsaturated

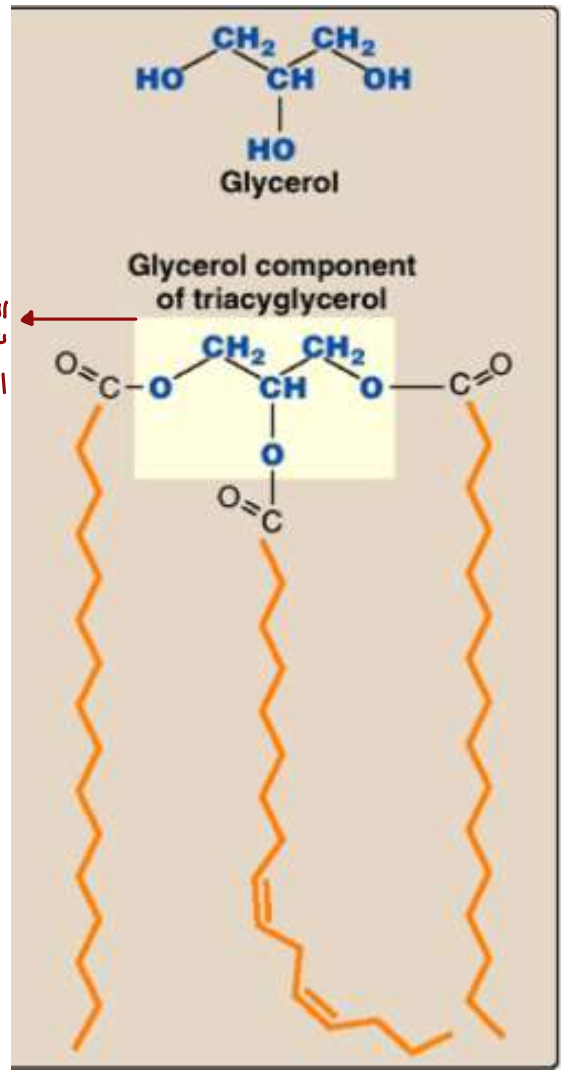
un saturated مقطعين 2

الهدف تخليه neutral

- If a species of acylglycerol is solid at room temperature, it is called a "fat", if liquid, it is called an "oil"

solid → fat

liquid → oil



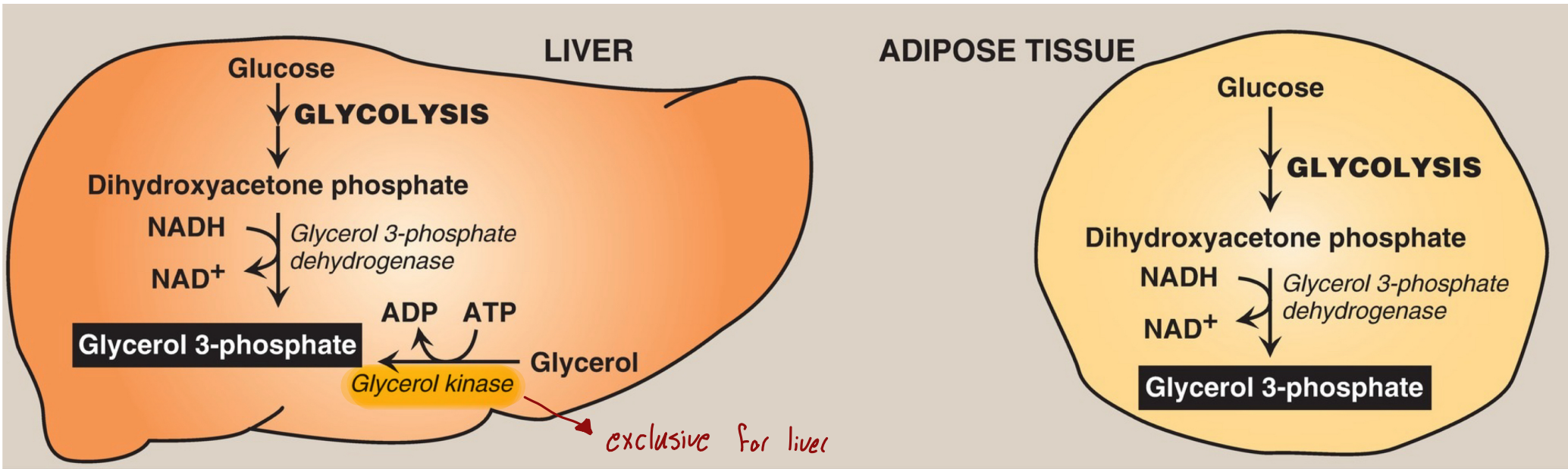
glycerol kinase موجود

exclusively in liver

Storage of TAG

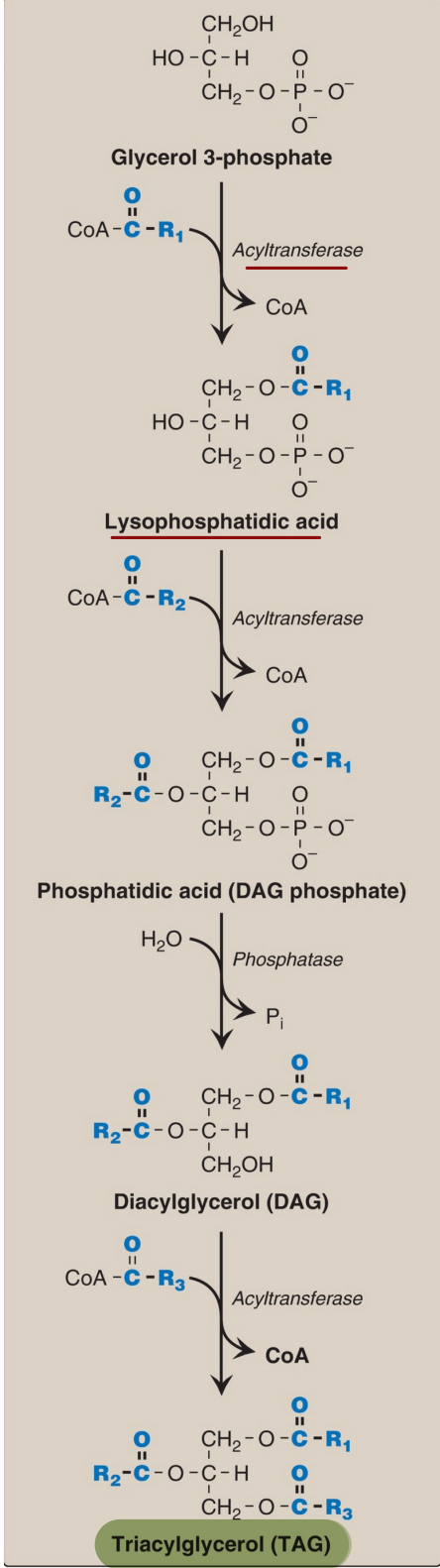
- TAGs are slightly soluble in water and cannot form stable micelles so they coalesce within adipocytes to form oily droplets that are nearly anhydrous. تلتحم
- They act as the major energy reserve of the body. TAG

- Production of glycerol 3P intermidiate of glycolysis



Synthesis of triacylglycerol

- Synthesis of glycerol-3-phosphate from glucose during glycolysis in liver and adipose tissue
- Conversion of a free FA to its activated form (CoA)
- TAG is synthesized
- Different fates of TAG in the liver and adipose tissue
  - In adipose tissue, TAG is stored in the cytosol of the cells in a nearly anhydrous form.
  - In liver, most are exported, packaged with cholesteryl esters, cholesterol, phospholipid, and protein (apolipoprotein B-100) to form lipoprotein particles called very low density lipoproteins (VLDL). VLDL are secreted into the blood where they mature and function to deliver the endogenously-derived lipids to the peripheral tissues.



Mobilization of stored fat

- Release of fatty acids from TAG
  - This process is initiated by hormone-sensitive lipase, which removes a fatty acid from carbon 1 and/or carbon 3 of the TAG.
  - Additional lipases specific for diacylglycerol or monoacylglycerol remove the remaining fatty acids.

on carbon 2

إذا fats بدي اكسر متى

Fasting state

Mobilization of stored fat

Active when phosphorylated

1. Activation of hormone-sensitive lipase (HSL): This enzyme is activated when phosphorylated by a 3',5'-cyclic AMP-dependent protein kinase in the adipocyte upon binding of hormones (like epinephrine) to receptors on the cell membrane, and activation of adenylate cyclase

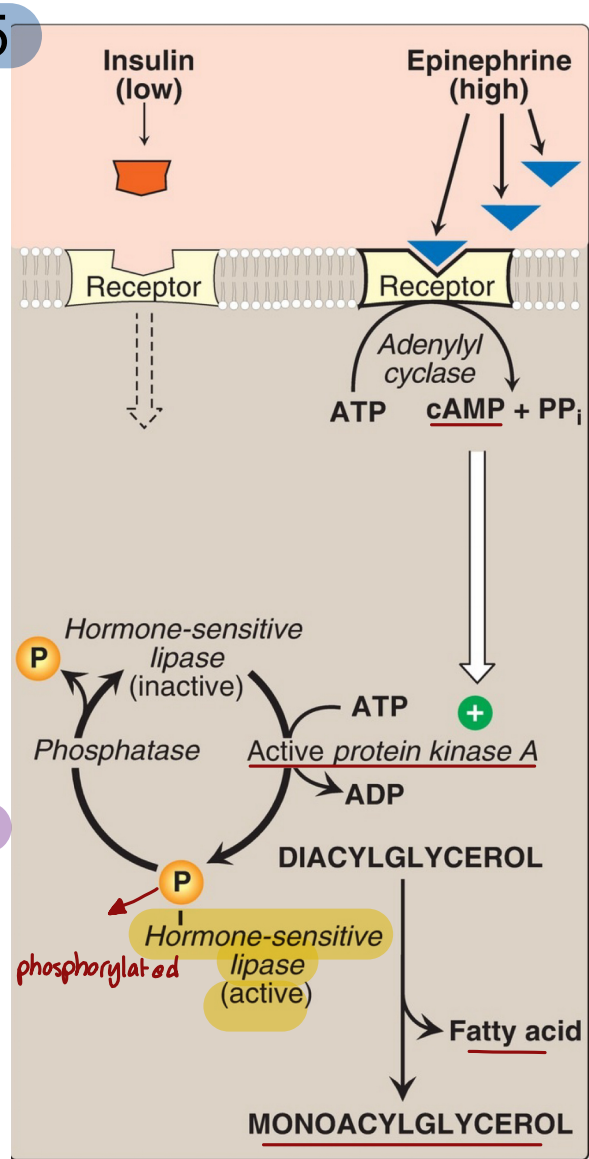
Fasting state

ATP → cAMP ✓

- The process is similar to that of the activation of glycogen phosphorylase :
  - Because acetyl CoA carboxylase is inhibited upon phosphorylation, when the cAMP-mediated cascade is activated. fatty acid synthesis is turned off when TAG degradation is turned on.
  - In the presence of high plasma levels of insulin and glucose, HSL is dephosphorylated (inactive)

(Fed state)

logic bc we want to store the fat not degrade it



Meaning:

If glucose is already present/bound, the enzyme becomes less responsive to AMP.

So even if AMP tries to activate it:

- activation is blocked
- glycogen breakdown decreases

Regulation

glycogen → glucose

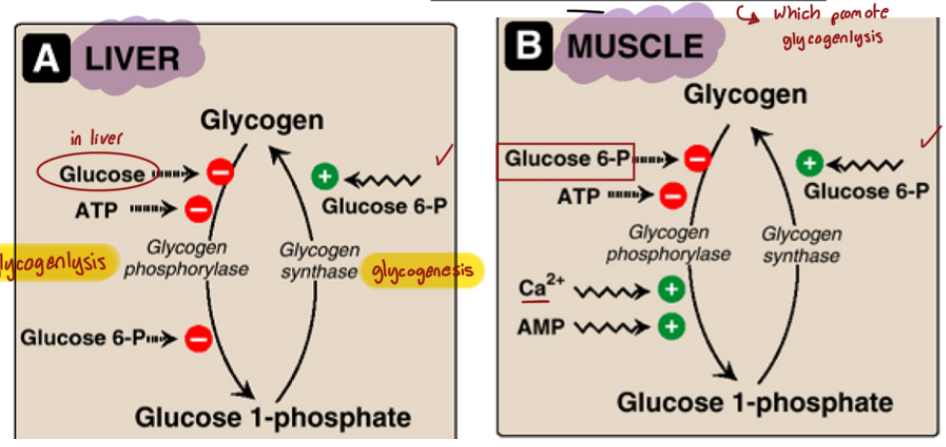
inactive form (dephosphorylated)

- when muscle glycogen phosphorylase b is bound to glucose, it cannot be allosterically activated by AMP

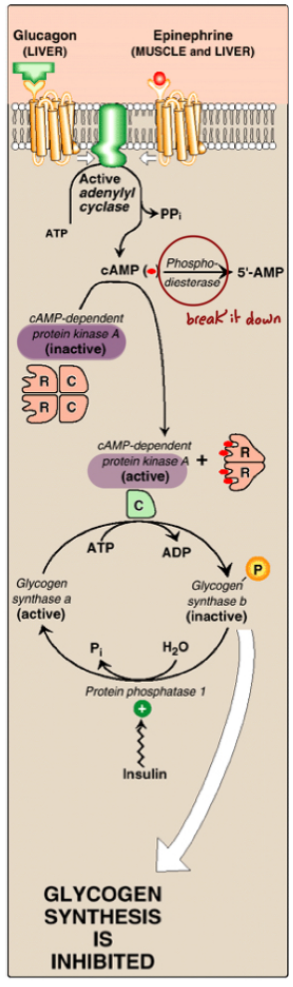
(glycogen phosphorylase)

- In the muscle, insulin indirectly inhibits the enzyme by increasing the uptake of glucose, leading to an increased level of glucose 6-phosphate-a potent allosteric inhibitor of glycogen phosphorylase

Allosteric inhibitor



which promote glycogenlysis



glycogen phosphorylase
+
hormone sensitive lipase

Active when phosphorylated

I am active when dephosphorylated bc I donate my (P) and that energize me !!

↳ Acetyl-CoA → malonyl-CoA
promote fatty acids synthesis
(Fed state)

so when cAMP active
(fasting state)
TAG degradation active

A.C.C should be inhibited
(phosphorylated)

Mobilization of stored fat

Fate of glycerol:

It cannot be metabolized by **adipocytes** because they **lack glycerol kinase**. Rather, glycerol is transported through the blood to the liver, where it can be phosphorylated, which can be used to form TAG in the liver; or can be converted to DHAP that can participate in glycolysis or gluconeogenesis.

only liver

Fate of fatty acids:

The free fatty acids move through the cell membrane of the adipocyte, and immediately bind to albumin in the plasma, enter cells, get activated to their CoA derivatives, and are oxidized for energy. (ATP)

Active transport of fatty acids across membranes is mediated by a membrane fatty acid binding protein

plasma free fatty acids cannot be used for fuel by **erythrocytes** (RBCs), which have no mitochondria, or by the **brain** because of the impermeable BBB

https://youtu.be/q1Xtk1bgPvE?si=mqkZ5ST0WYC3BEEp

شرح ناري

β-Oxidation of fatty acids

to have ATP (energy)

except: RBCs, brain

اطلع طاقة الحتز من unsaturated

- The major pathway for catabolism of saturated fatty acids is a mitochondrial pathway called β-oxidation, in which two-carbon fragments are successively removed from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and FADH2.
- Transport of long-chain fatty acids (LCFA) into the mitochondria:
- After LCFA enters a cell, it is converted to the CoA derivative by long-chain fatty acyl CoA synthetase (thiokinase) in the cytosol.

LCF Acyl-CoA synthetase (thiokinase)

- Because β-oxidation occurs in the mitochondria matrix, the fatty acid must be transported from the cytosol across the mitochondrial inner membrane by a specialized carrier, Carnitine.

LCFA translocation

1. An acyl group is transferred from the cytosolic CoA to carnitine by carnitine palmitoyltransferase I (CPT-I), an enzyme associated with the outer mitochondrial membrane, to form acylcarnitine, and regenerates free CoA

2. The acylcarnitine is transported into the mitochondrion in exchange for free carnitine by carnitine-acylcarnitine translocase.

3. Carnitine palmitoyltransferase II (CPT-II) catalyzes the transfer of the acyl group from carnitine to CoA in the mitochondria matrix, thus regenerating free carnitine.

Fatty acids synthesis

cytosol

fatty acids degradation (oxidation)

mitochondria

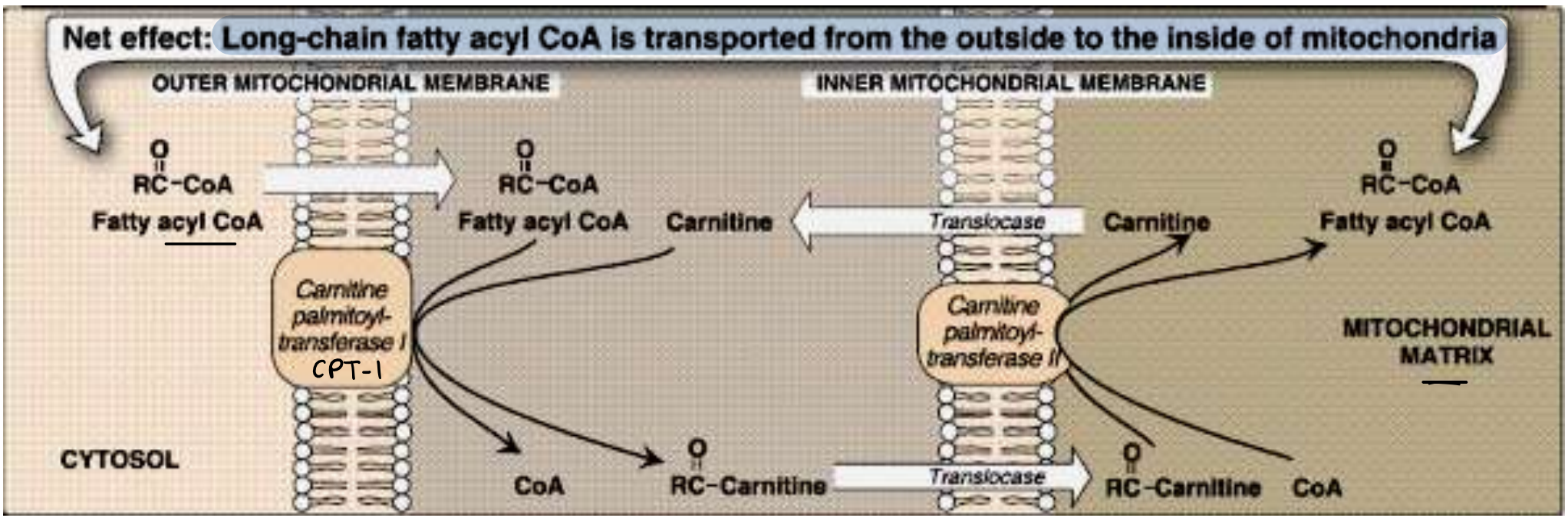
Beta oxidation
Fat degradation
Fasting

Inhibitor of the carnitine shuttle

logic bc it promote
Fatty acid synthesis

- Malonyl CoA inhibits CPT, thus preventing the entry of long-chain acyl groups into the mitochondrial matrix.

- When fatty acid synthesis is occurring in the cytosol (as indicated by the presence of malonyl CoA), the newly made palmitate cannot be transferred into the mitochondria and degraded



NOT synthesized in skeletal or heart muscle.

Carnitine ← Lysine, methionine

- **Sources:**
  - from the diet (meat, diary products, nuts), synthesized from the amino acids lysine and methionine by an enzymatic pathway found in the liver and kidney but not in skeletal or heart muscle.
  - these tissues are totally dependent on carnitine provided by hepatocytes or the diet, and distributed by the blood.
    (**Skeletal muscle** contains 97% of all carnitine in the body)
- **Additional functions:**
  - The carnitine system also allows the export from the mitochondria of branched-chain acyl groups (such as those produced during the catabolism of the branched-chain amino acids).
  - The carnitine system is involved in the trapping and excretion via the kidney of acyl groups that cannot be metabolized by the body.

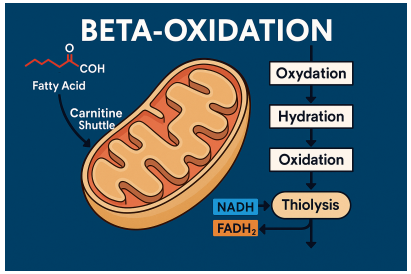
Carnitine deficiencies

- result in a decreased ability of tissues to use LCFA as a metabolic fuel, can also cause the accumulation of toxic amounts of free fatty acids and branched-chain acyl groups in cells.

- Secondary carnitine deficiency occurs for many reasons:

1) in patients with **liver disease** causing decreased synthesis of carnitine
2) individuals suffering from **malnutrition** or those on strictly vegetarian diets
3) in those with an **increased requirement** for carnitine as in pregnancy, severe infections, burns, or trauma
4) in those undergoing **hemodialysis**, which removes carnitine from the blood

- Congenital deficiencies in one of the components of the carnitine palmatoyltransferase system, in tubular reabsorption of carnitine, or a deficiency in carnitine uptake by cells, can also cause carnitine deficiency.



Reactions of β-oxidation

F.a synthesis لـ عكس خطوات

- It consists of a sequence of four reactions that result in shortening the fatty acid chain by two carbons.

[1] oxidation that produces FADH2

[2] hydration step

[3] a second oxidation that produces NADH

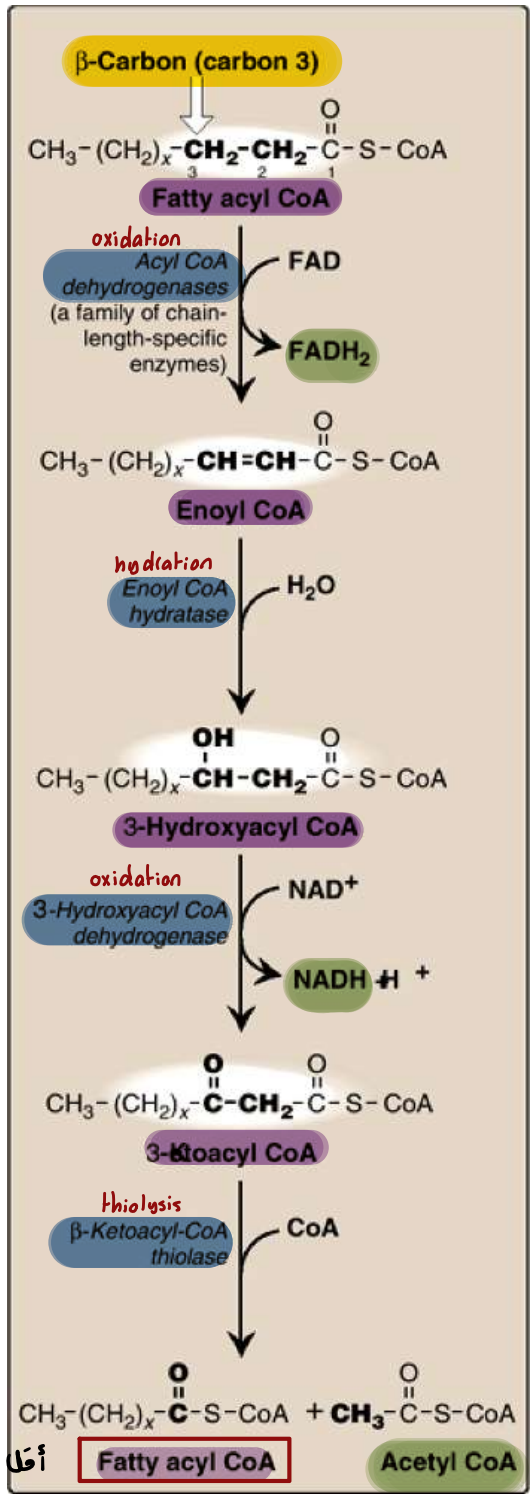
[4] Thiolytic cleavage that releases a molecule of acetyl CoA.

- These four steps are repeated for saturated fatty acids of even numbered carbon chains (n16), each cycle producing an acetyl group plus one NADH and one FADH2

- The final thiolytic cleavage produces two acetyl groups.

- Acetyl CoA is a positive allosteric effector of pyruvate carboxylase, thus, linking fatty acid oxidation and gluconeogenesis.

pyruvate → oxaloacetate



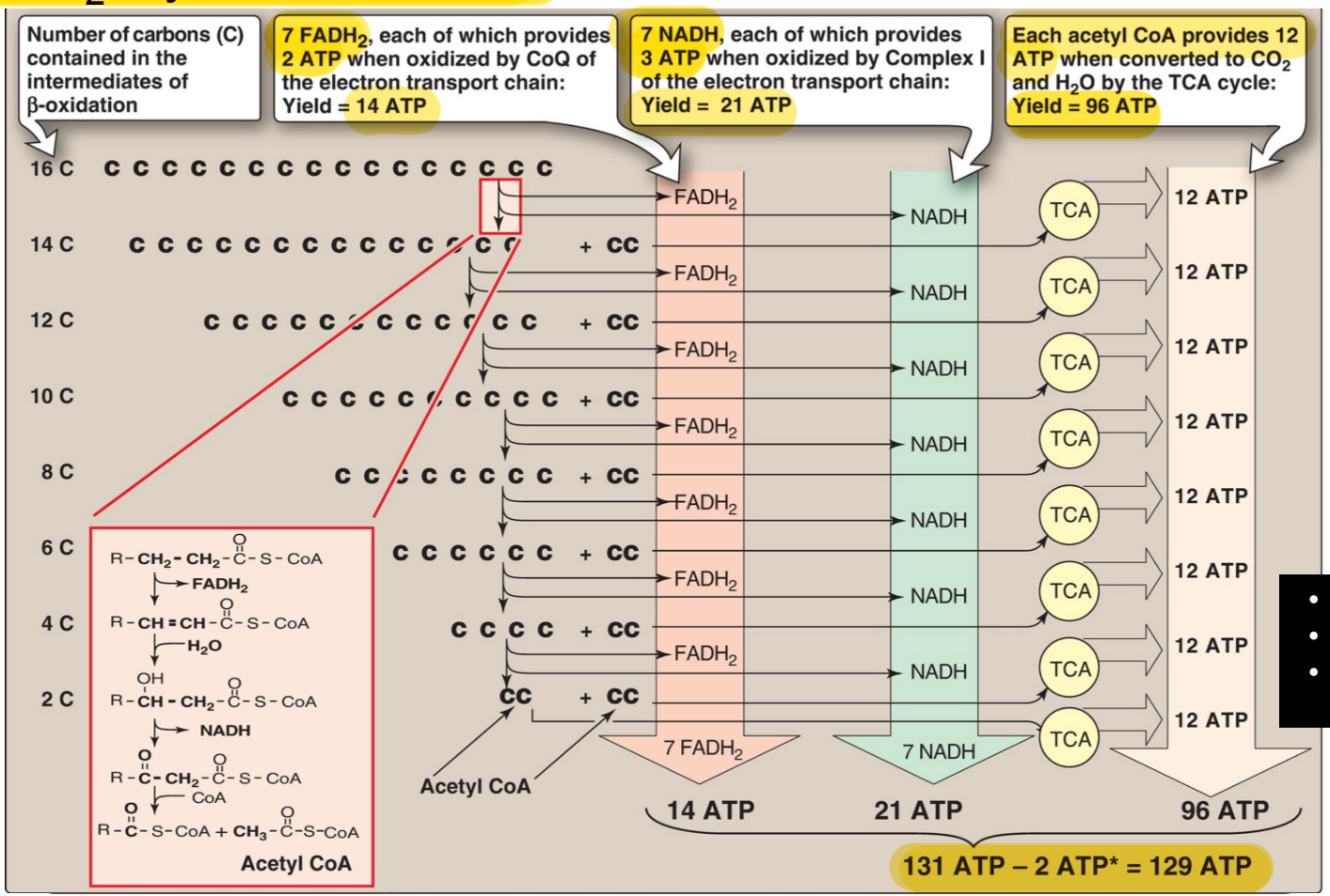
أعلى بكربونتين

Every cycle produces one acetyl-CoA, except the last cycle, which produces **two**. Therefore, acetyl-CoA = cycles + 1.

🧠 Palmitate (16-carbon FA) → **7 cycles** → 8 acetyl-CoA

Energy yield from fatty acid oxidation

- The energy yield from the oxidation pathway is high.
- For example, the oxidation of a molecule of palmitoyl CoA to CO_2 and H_2O yields 131 ATP



1 $FADH_2$ → 2 ATP
1 NADH → 3 ATP
1 Acetyl-CoA → 12 ATP

palmitoyl-CoA
131 ATP

palmitoyl
129 ATP

- Number of **acetyl-CoA molecules** = $\frac{n}{2}$
- Number of **β-oxidation cycles** = $\frac{n}{2} - 1$
- Each cycle produces **1 NADH** and **1 $FADH_2$**

The number of Acetyl coA produced by myristyl coA (14:0) oxidation is:

1. 5
2. 6
3. 7
4. 4
5. 8

3

How many Acetyl-CoA and NADPH molecules are produced from the beta-oxidation of capric acid (a 10-carbon fatty acid)?

Answer : (5,4)

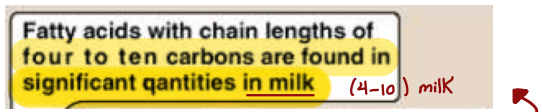
كم NADH , acetyl coA ينتج من 18 كربونة

9 , 8 NADH

Acetyl-CoA

Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency

- In mitochondria, there are four fatty acyl CoA dehydrogenase species, each of which has a specificity for either short-, **medium-**, long-, or very-long-chain fatty acids.
- MCAD deficiency is:
  - an autosomal, recessive disorder
  - one of the most common inborn errors of metabolism.
  - causes a decrease in fatty acid oxidation and severe hypoglycemia (no full energetic benefit from fatty acids and so must now rely on glucose).
- Treated by a carbohydrate-rich diet.
- Infants are particularly affected by MCAD deficiency, because they rely for their nourishment on milk, which contains primarily MCADS
- MCAD dehydrogenase deficiency has been identified as the cause of sudden infant death syndrome (SIDS) or Reye's syndrome



Reye's syndrome : viral infection

↳ liver disease
viral infection + Aspirin
complete liver damage

جابت هاد وكان بدها ايش الخطأ كان من ضمن الخيارات

Treated by a protein-rich diet.

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  - one of the most common inborn errors of metabolism.
  - causes a decrease in fatty acid oxidation and severe hypoglycemia (no full energetic benefit from fatty acids and so must now rely on glucose).
- Treated by a carbohydrate-rich diet.
- Infants are particularly affected by MCAD deficiency, because they rely for their nourishment on milk, which contains primarily MCADS
- MCAD dehydrogenase deficiency has been identified as the cause of sudden infant death syndrome (SIDS) or Reye's syndrome

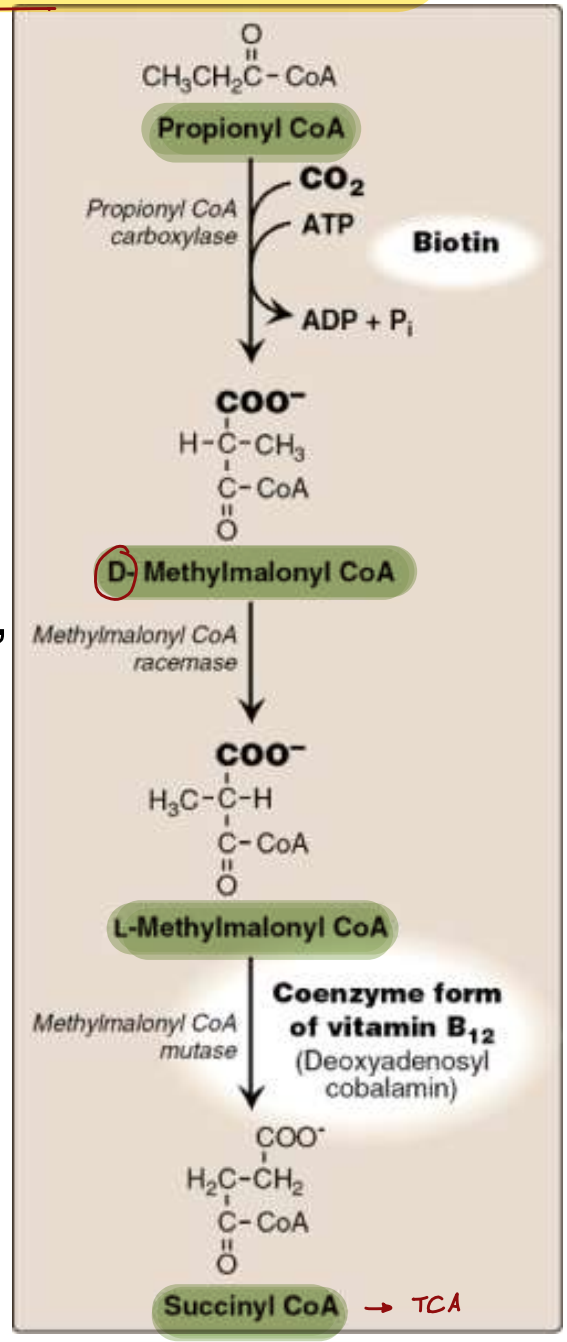
Acetyl-CoA NADH $FADH_2$ وكم يطلع 15 17 16 تجيب سؤال
carbons

Oxidation of fatty acids with an odd number

- It oxidizes two carbons at a time (producing acetyl CoA) until the last three carbons (propionyl CoA).
- (Propionyl CoA is also produced during the metabolism of certain amino acids)
- This compound is carboxylated to methylmalonyl CoA by propionyl CoA carboxylase (requires biotin), which is then converted to succinyl CoA by methylmalonyl CoA mutase (requires vitamin B12). (Succinyl CoA can enter TCA cycle)
- A genetic error in the mutase or vitamin B12 deficiency causes methylmalonic acidemia and aciduria in addition to developmental retardation.

(3C)

+ CO_2



methylmalonic acidemia
+
Aciduria

} mental retardation

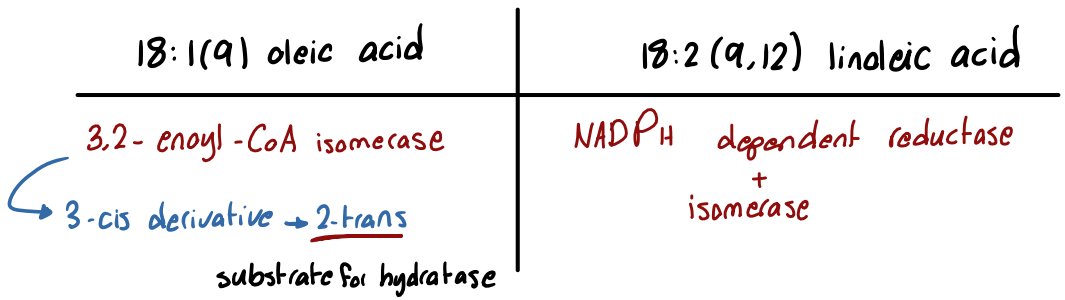
less ATP

Oxidation of unsaturated fatty acids

- The oxidation of unsaturated fatty acids provides less energy than that of saturated fatty acids because they are less highly reduced and, therefore, fewer reducing equivalents can be produced from these structures.

- Oxidation of monounsaturated fatty acids, such as 18:1(9) (oleic acid) requires one additional enzyme, **3,2-enoyl CoA isomerase** (converts the 3-cis derivative obtained after three rounds of p-oxidation to the 2-trans derivative that can serve as a substrate for the hydratase)

- Oxidation of polyunsaturated fatty acids, such as 18:2(9,12) (linoleic acid) requires an NADPH-dependent reductase in addition to the isomerase.



destroys fat

Oxidation in the peroxisome

hydrogen peroxide H_2O_2 — soma "body"

20 or more

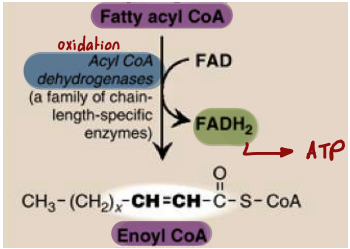
- Very-long-chain fatty acids (VLCFA), twenty carbons long or longer, undergo a preliminary β-oxidation in peroxisomes. The shortened fatty acid is then transferred to a mitochondrion for further oxidation.

- In contrast to mitochondrial β-oxidation, the initial dehydrogenation in peroxisomes is catalyzed by an FAD-containing acyl CoA oxidase.

- The $FADH_2$ produced is oxidized by molecular oxygen, which is reduced to H_2O_2. The H_2O_2 is reduced to H_2O by catalase

- The genetic defects Zellweger (cerebrohepatorenal) syndrome (a defect in peroxisomal biogenesis in all tissues) and X-linked adrenoleukodystrophy (a defect in peroxisomal activation of VLCFA) lead to accumulation of VLCFA in the blood and tissues.

β-oxidation mitochondria



First step

dehydrogenase

β-oxidation in peroxisome

Fatty Acyl - CoA

FAD - containing acyl - CoA oxidase

$FADH_2 + O_2$ → (oxidized by molecular oxygen) toxic H_2O_2 → (reduced catalase) H_2O

zellweger syndrome

(cerebrohepatorenal) → peroxisome biogenesis → brain, liver, kidney

males

- X-linked (adrenoleukodystrophy)

↳ defect in peroxisomal activation of VLCFA

accumulate

High-yield exam summary

Mitochondria	Peroxisomes
Oxidize short-, medium-, and long-chain fatty acids	Begin oxidation of VLCFAs
First enzyme: acyl-CoA dehydrogenase	First enzyme: acyl-CoA oxidase
$FADH_2$ enters ETC and makes ATP	$FADH_2$ reduces O_2 directly
No H_2O_2 produced	H_2O_2 produced
No catalase role	Catalase converts H_2O_2 to H_2O

A common MCQ point is:

Which organelle performs initial oxidation of very-long-chain fatty acids?

Answer: Peroxisomes.

Another favorite question:

Which enzyme detoxifies the H_2O_2 generated during peroxisomal β-oxidation?

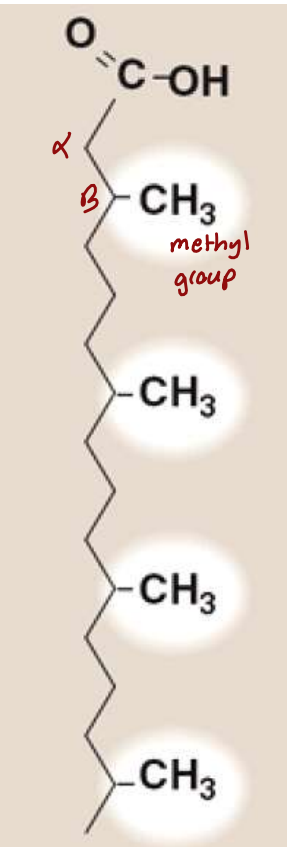
Answer: Catalase.

https://youtu.be/rMeFqABWbIs?si=Sgr6oCDwfNeBwu29

α-Oxidation of fatty acids

- The branched-chain fatty acid (phytanic acid) is not a substrate for acyl CoA dehydrogenase due to the methyl group on its third carbon
- Instead, it is hydroxylated at the α-carbon by **fatty acid α - hydroxylase**.
- The product is decarboxylated and then activated to its CoA derivative, which is a substrate for the enzymes of β-oxidation.
- **Refsum disease** is a rare, autosomal recessive disorder caused by a deficiency of α-hydroxylase. Leading to the accumulation of phytanic acid in the plasma and tissues.
- The symptoms are primarily neurologic, that treated by dietary restriction to halt disease progression

يوقف



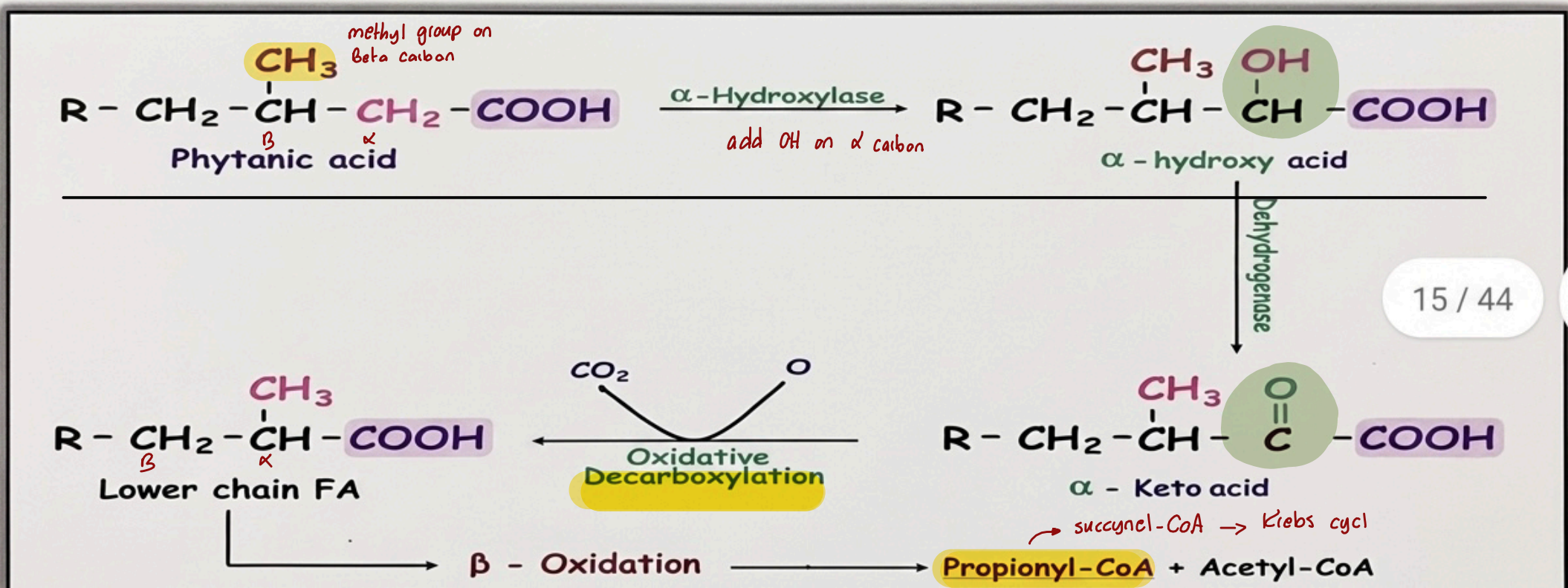
Exam tip

A common question is:

"Which fatty acid requires α-oxidation before β-oxidation?"

Answer: Phytanic acid

α-Oxidation of Fatty Acids



Ketone bodies

produce Ketone bodies

- Liver mitochondria can convert acetyl CoA derived from fatty acid oxidation into the ketone bodies, acetoacetate and 3-hydroxy-butyrate. + Acetone

الوحيد إلي يقدر يصنعهم بس ما يستخدمهم

موجود بنفس مريض السكري

RBCs can't utilize Ketone bodies

- Peripheral tissues possessing mitochondria can oxidize 3-hydroxybutyrate to acetoacetate, which can be reconverted to acetyl CoA, thus producing energy for the cell.

3-hydroxybutyrate → acetoacetate

وظيفته سوات *

- Unlike fatty acids, ketone bodies can be utilized by the brain and, therefore, are important fuels during a fast.

- The liver lacks the ability to degrade ketone bodies, and so synthesizes them specifically for the peripheral tissues.

Key exam point

Liver = produces ketone bodies but cannot use them.

Question 33 / 56

The organ that can't utilize ketone bodies during long fasting is

1. Adipose tissue use
2. Heart muscle use
3. Brain use
4. Liver
5. Skeletal muscles use

4

Which of the following is nether utilize fatty acid nor ketone bodies

1-brain can utilize Ketone bodies

2-liver can utilize Fatty acids

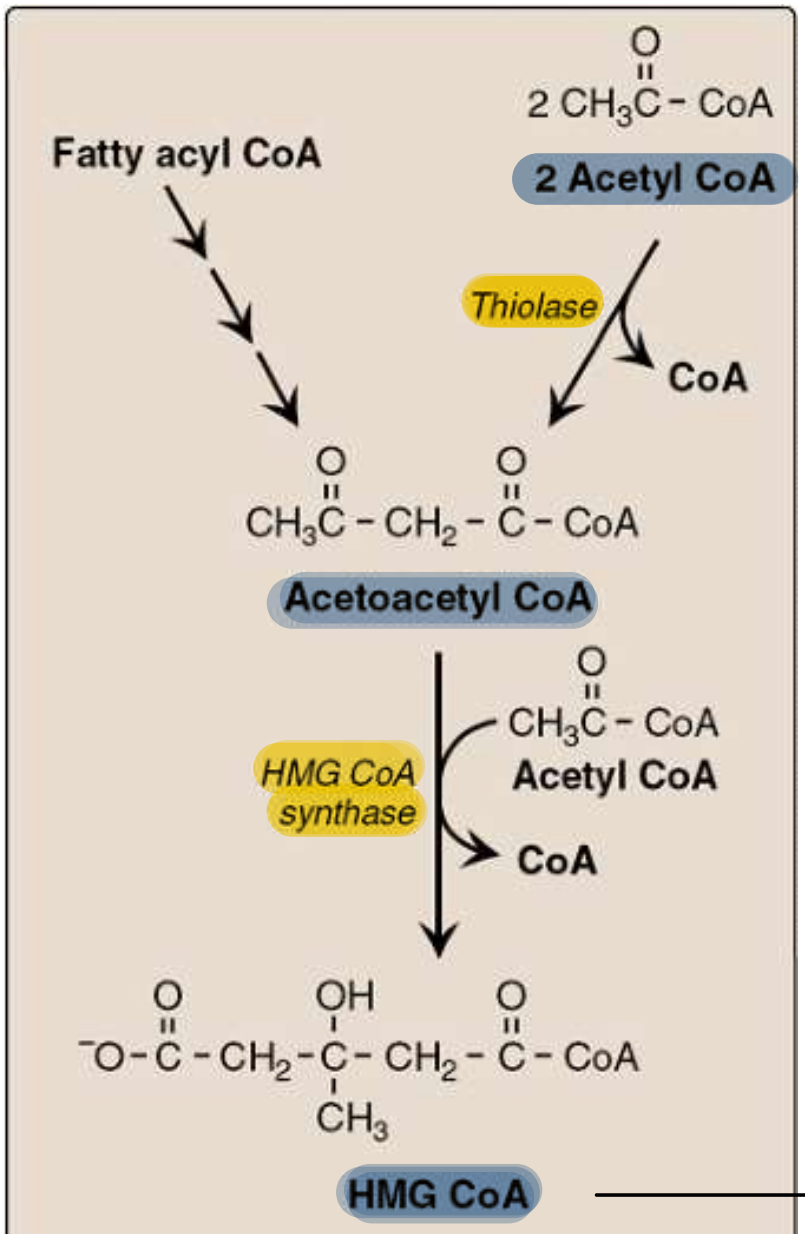
3-RBC can't utilize neither bc it lacks mitochondria

4-all

5-two choice

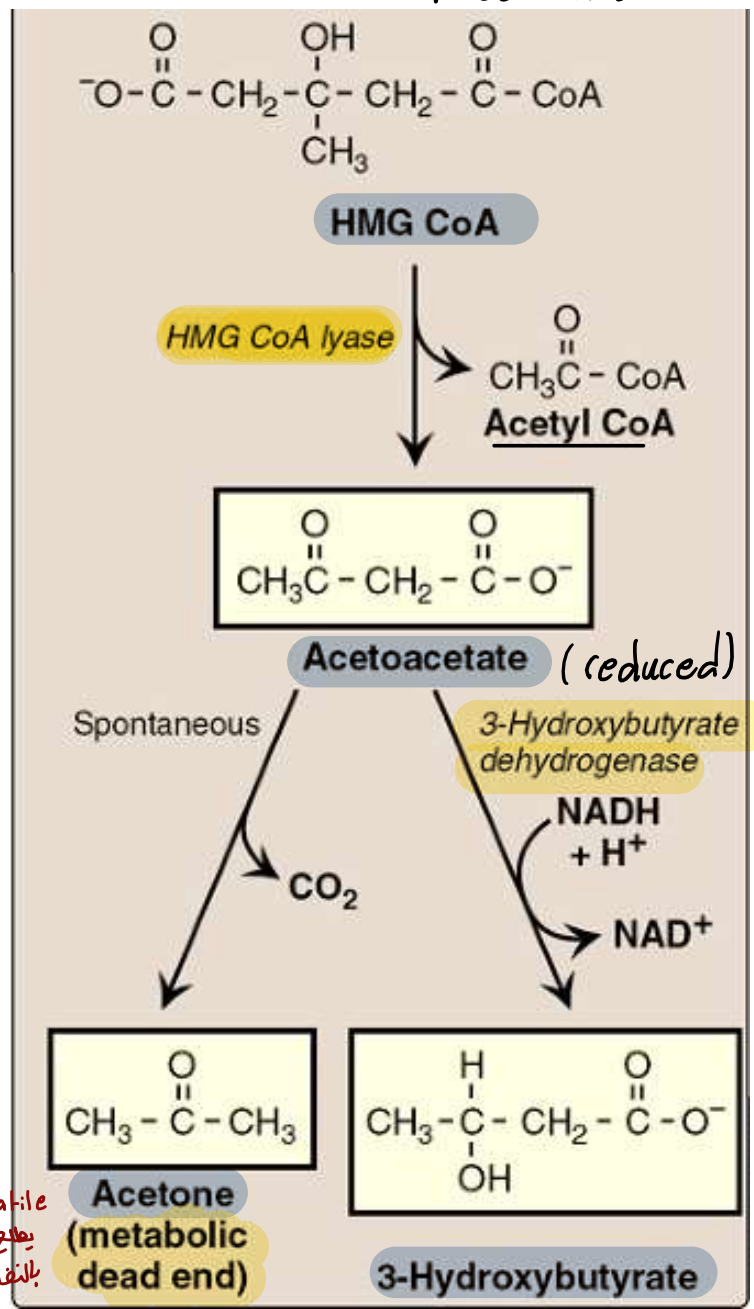
https://youtu.be/-UR1HFz78kc?si=n3ynoK4DR-IGfIj0

Synthesis of ketone bodies by the liver



لهون نفس خطوات تصنيع الـ cholesterol

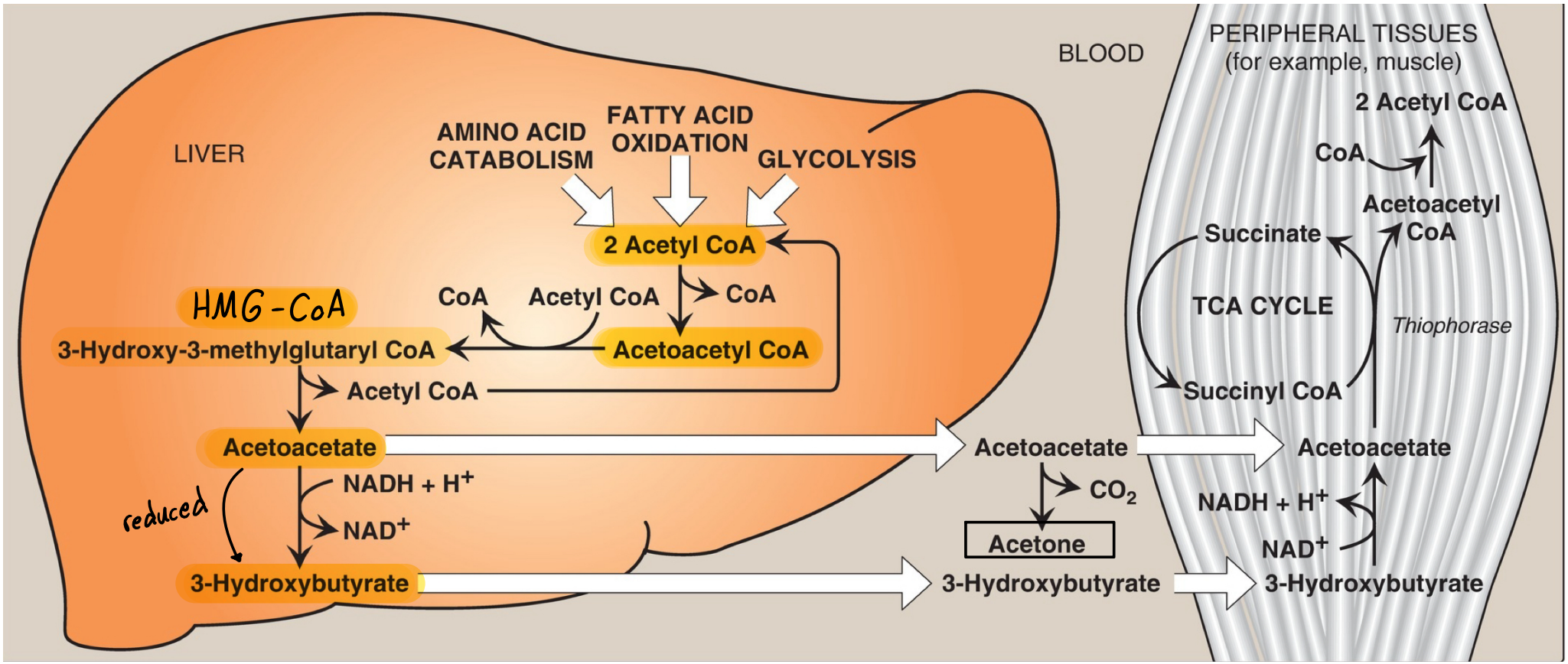
mitochondria



Synthesis of ketone bodies by the liver

مين بيعيرهم Ketone bodies ؟! ☆

1- diabetes mellitus patients
2- starvation
3- vomiting
4- diarrhia



Ketoacidosis

- Ketoacidosis occurs when the rate of formation of ketone bodies is greater than their rate of use, as seen in cases of uncontrolled, type 1 (insulin-dependent) diabetes mellitus.

little to no insulin ↓

- their levels begin to rise in the blood (ketonemia) and eventually in the urine (ketonuria).

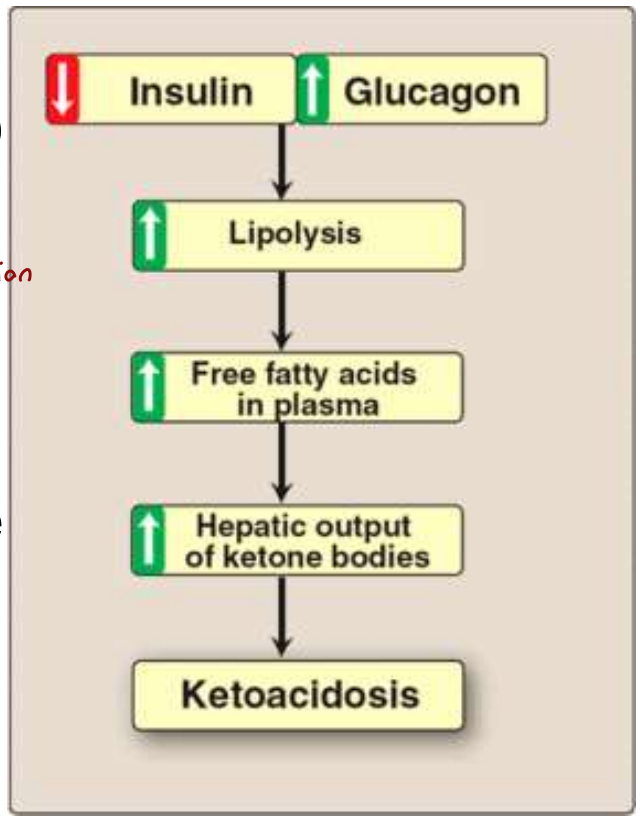
Ketones in blood and urine

- In such individuals, high fatty acid degradation produces excessive amounts of acetyl CoA. ↑

Beta oxidation

NADH ↑
$FADH_2$ ↑

- It also depletes the NAD^+ pool and increases the NADH pool, which slows the TCA cycle



When their production exceeds their utilization:

- Ketones accumulate in blood → **ketonemia**
- Ketones appear in urine → **ketonuria**
- Blood pH falls → **ketoacidosis**

In humans, fatty acid synthesis occurs primarily in the **liver** and **lactating mammary glands** and, to a lesser extent, in **adipose tissue**.

- The translocation of citrate from the mitochonderion to the cytosol, where it is cleaved by **ATP-citrate lyase** to produce cytosolic acetyl CoA and OAA, occurs when the mitochondrial substrate concentration is high.

- Palmitate can be further elongated by the addition of two-carbon units in the endoplasmic reticulum (**ER**) and **the mitochondria**. These organelles use separate enzymatic processes.

Fate of glycerol:

It cannot be metabolized by **adipocytes** because they **lack glycerol kinase**. Rather, glycerol is transported through the blood to the liver, where it can be phosphorylated, which can be used to form TAG in the liver; or can be converted to DHAP that can participate in glycolysis or gluconeogenesis.

- plasma free fatty acids cannot be used for fuel by **erythrocytes**, which have no mitochondria, or by the **brain** because of the impermeable BBB

(**Skeletal muscle** contains 97% of all carnitine in the body)

- Secondary carnitine deficiency occurs for many reasons:

1) in patients with **liver disease** causing decreased synthesis of carnitine
2) individuals suffering from **malnutrition** or those on strictly vegetarian diets
3) in those with an **increased requirement** for carnitine as in pregnancy, severe infections, burns, or trauma
4) in those undergoing **hemodialysis**, which removes carnitine from the blood

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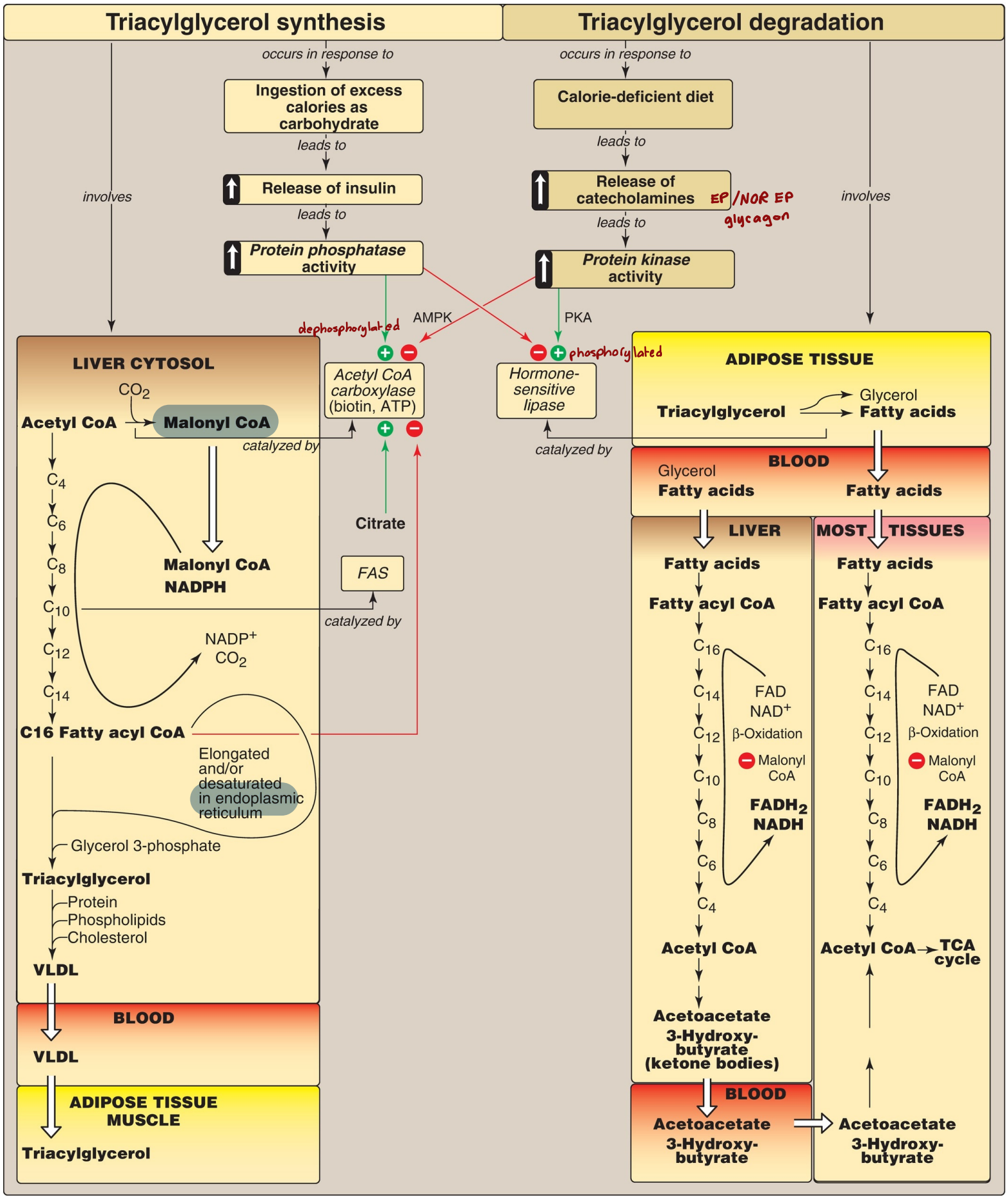
quiz yourself


Triacylglycerol synthesis
Triacylglycerol degradation
occurs in response to
Ingestion of excess calories as carbohydrate
leads to
Release of insulin
leads to
Protein phosphatase activity
occurs in response to
Calorie-deficient diet
leads to
Release of catecholamines
EP/NOR EP
glycagon
leads to
Protein kinase activity
involves
involves
dephosphorylated
AMPK
PKA
phosphorylated
Acetyl CoA carboxylase (biotin, ATP)
Hormone-sensitive lipase
catalyzed by
catalyzed by
LIVER CYTOSOL
CO2
Acetyl CoA
Malonyl CoA
C4
C6
C8
C10
C12
C14
C16 Fatty acyl CoA
Malonyl CoA
NADPH
NADP+
CO2
Citrate
FAS
catalyzed by
Elongated and/or desaturated in endoplasmic reticulum
Glycerol 3-phosphate
Triacylglycerol
Protein
Phospholipids
Cholesterol
VLDL
BLOOD
VLDL
ADIPOSE TISSUE
MUSCLE
Triacylglycerol
ADIPOSE TISSUE
Triacylglycerol
Glycerol
Fatty acids
BLOOD
Glycerol
Fatty acids
Fatty acids
LIVER
Fatty acids
Fatty acyl CoA
C16
C14
C12
C10
C8
C6
C4
FAD
NAD+
β-Oxidation
Malonyl CoA
FADH2
NADH
Acetyl CoA
Acetoacetate
3-Hydroxy-butyrate
(ketone bodies)
BLOOD
Acetoacetate
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MOST TISSUES
Fatty acids
Fatty acyl CoA
C16
C14
C12
C10
C8
C6
C4
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Acetyl CoA
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