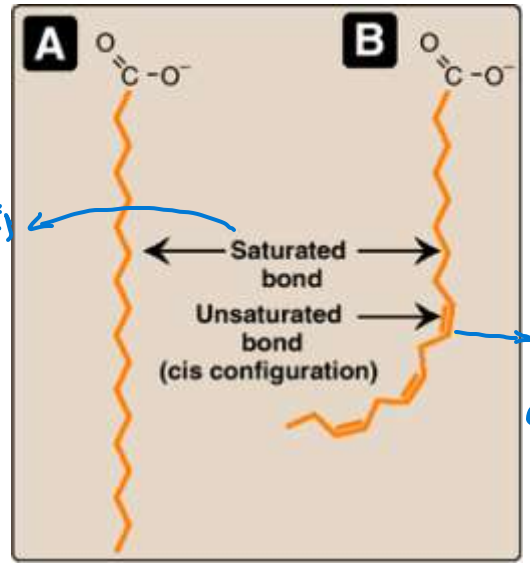
Lipid metabolism

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
  التواء
  ← trans fatty acid more toxic
- Addition of double bond decreases the melting temperature (T_m) of a fatty acid, whereas increasing the chain length increases the T_m
  ← Tm saturation fatty acid > Tm unsaturated



melting point عالي

less interaction → high fluidity at room temperature

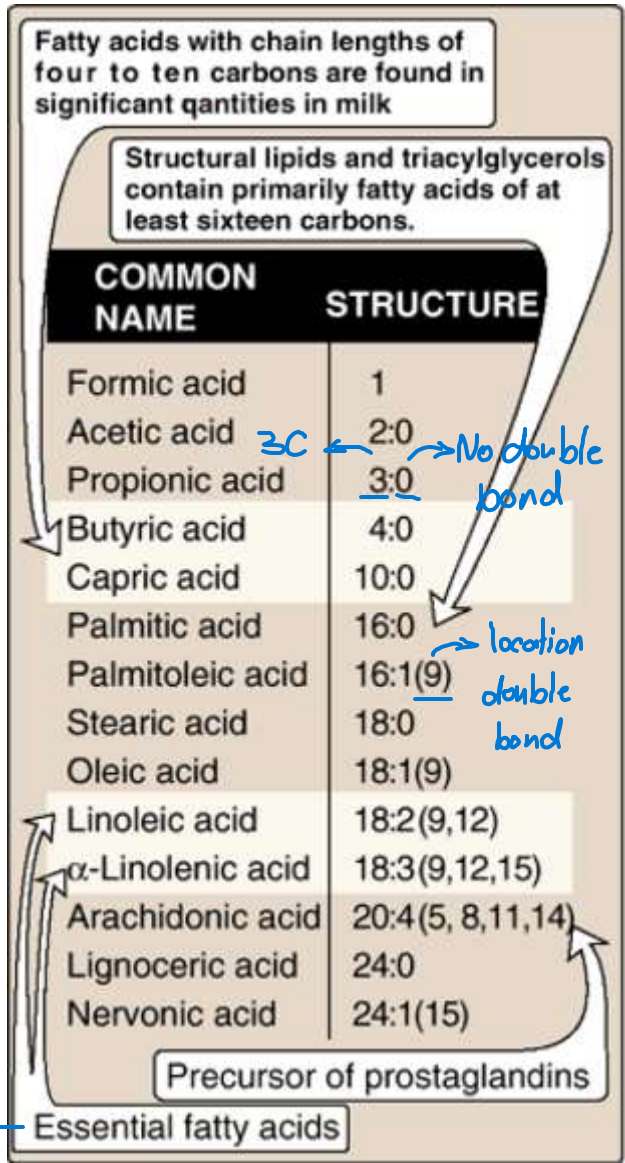
hydrocarbon + COOH
↓
fatty acid

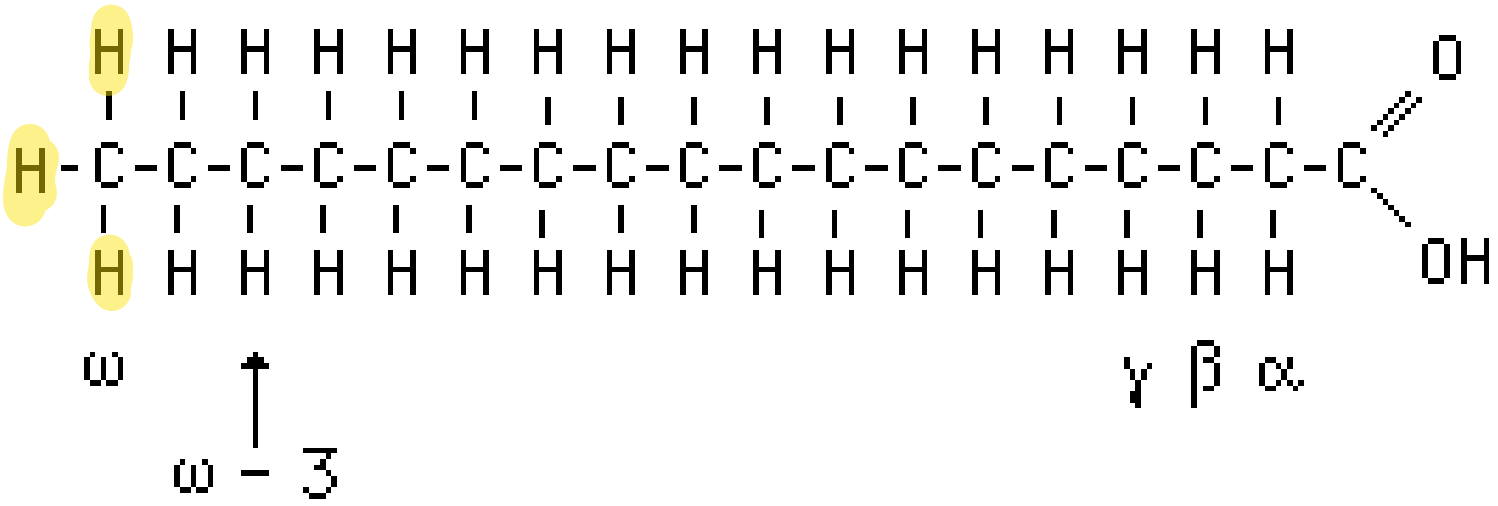
Chain length of fatty acids

- 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

- 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

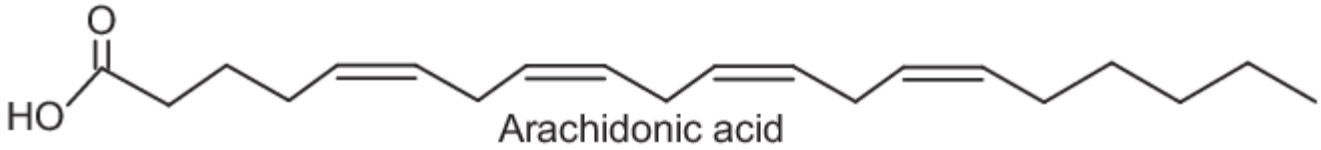
- Arachidonic acid is referred to as an ω-6 while linolenic acid, 18:3(9,12,15), is an ω-3 fatty acid.





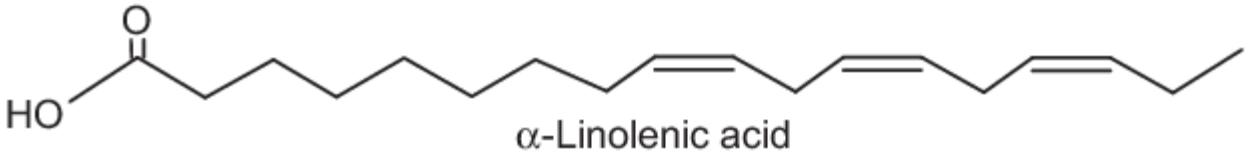
Arachidonic acid, 20:4(5, 8, 11, 14) is an ω-6 fatty acid → [20 minus 14=6].

α-linolenic acid, 18:3(9,12,15), is an ω-3 fatty acid → [18 minus 15=3].



Arachidonic acid

ω-6 fatty acid



α-Linolenic acid

ω-3 fatty acid

Essential fatty acids

linoleic acid

α- linoleic acid

- Two fatty acids are dietary essentials in humans:
  - Linoleic acid, which is the precursor of arachidonic acid, the substrate for prostaglandin synthesis

    inflammatory midiator
  - Linolenic acid, the precursor of other ω -3 fatty acids important for growth development
  - A deficiency of linolenic acid rest decreased vision and altered learning behaviors
  - Arachidonic acid becomes essential if linoleic acid is deficient in the diet.

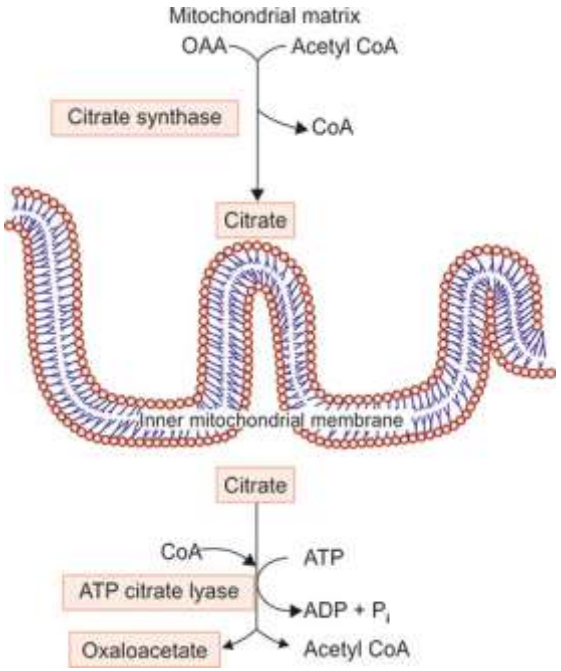
    ناقص

De novo synthesis of fatty acids

- 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).

- 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

- 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



1. translocation of citrate from the mitochonderion to the cytosol

→ to form fat

- 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.

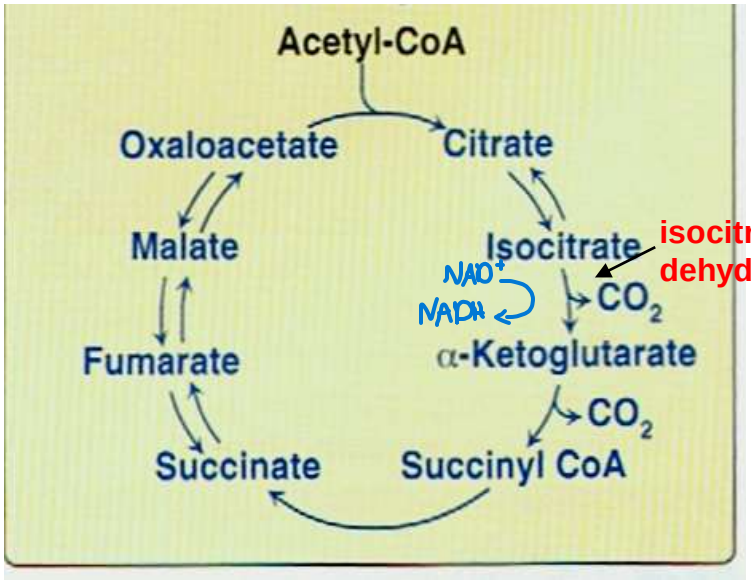
need large amount of NADPH

(Acetyl CoA + ATP) بعد الأكل

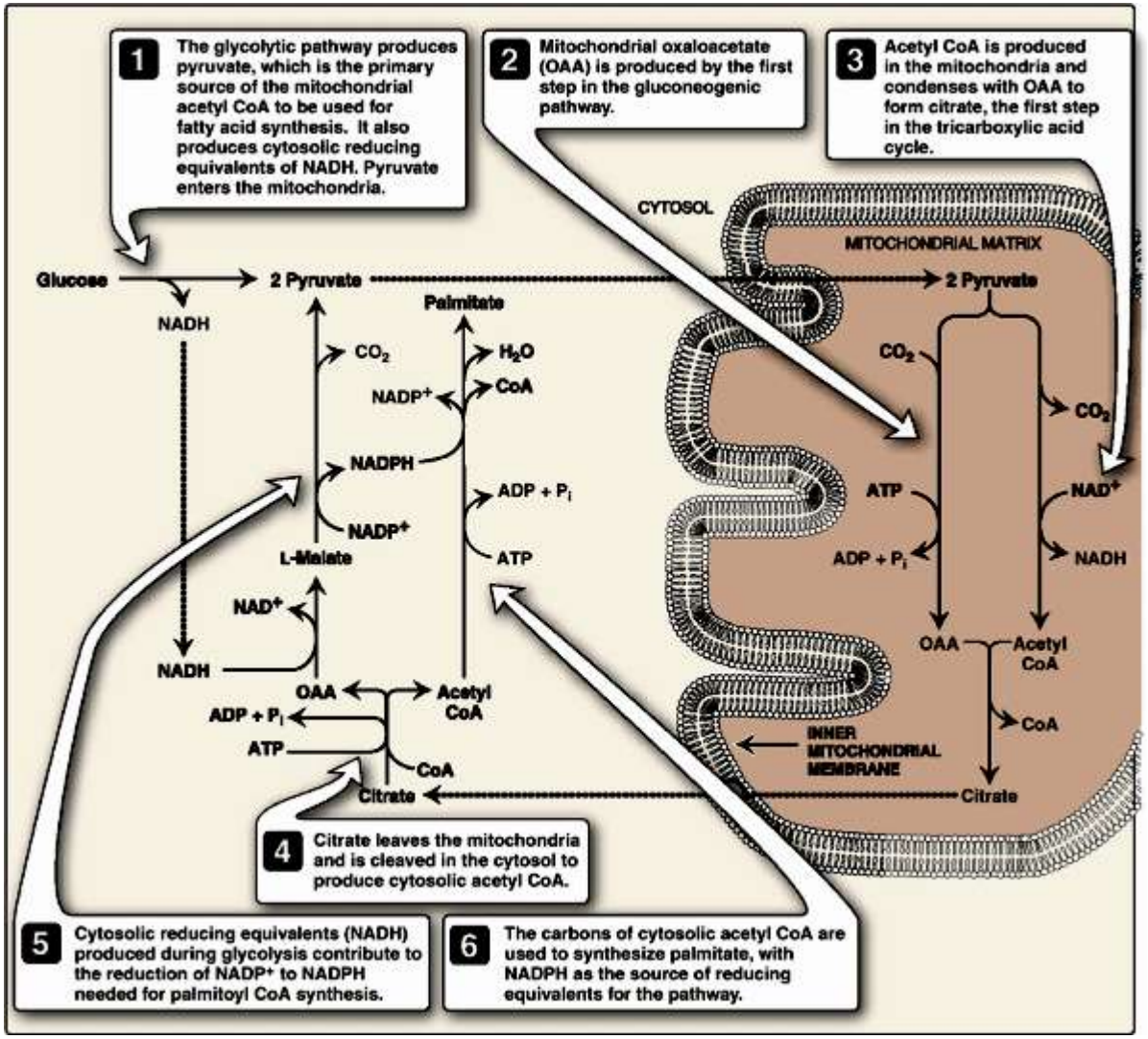
- This is observed when isocitrate dehydrogenase is inhibited by the presence of large amounts of ATP. causing citrate and isocitrate to accumulate. → cytosole → fatty acid

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

- The increase in both ATP and citrate enhances this pathway. → fatty acid produce



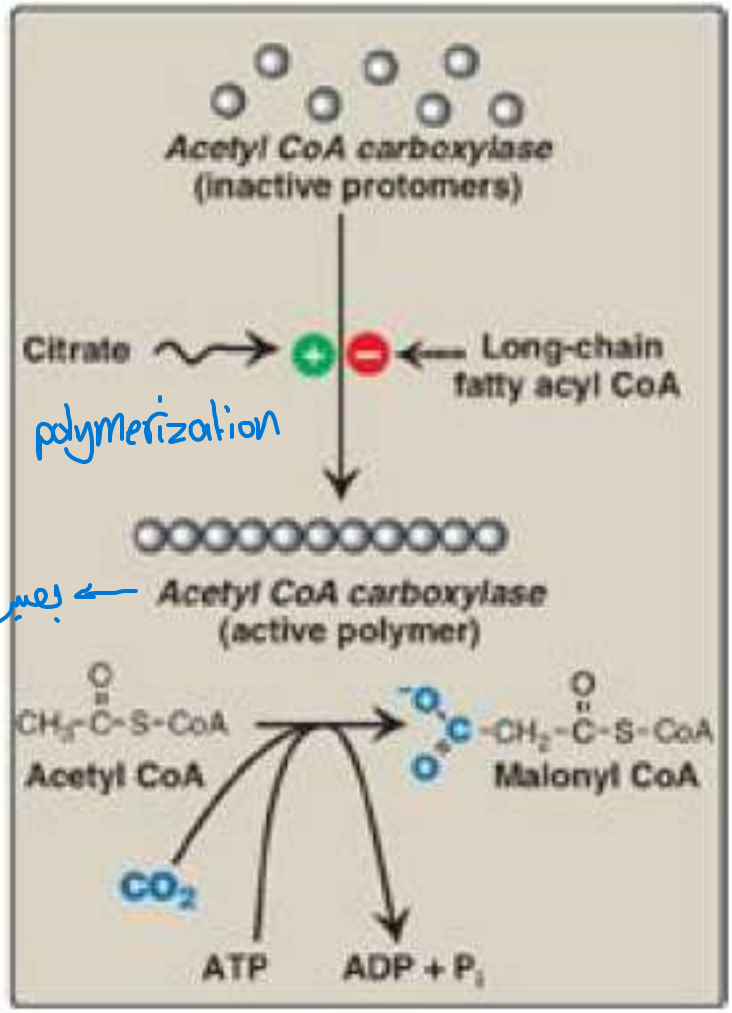
Source of cytosolic Acetyl coA



2. Carboxylation of acetyl CoA to form malonyl CoA

activation ← acetyl CoA عشان أعمل

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

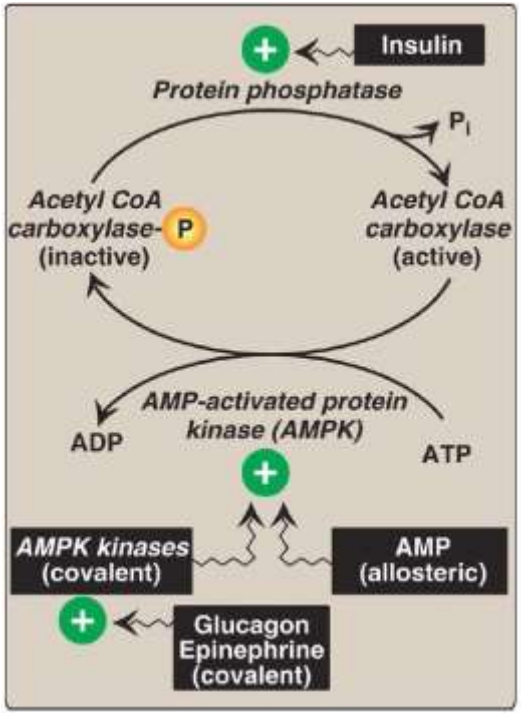


← بعمل إلكتروفيلي جيد

Regulation of acetyl CoA carboxylase

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.
  - Reversible phosphorylation in the presence of epinephrine and glucagon
- In the presence of insulin, Acetyl CoA carboxylase is dephosphorylated and, so activated.



Long-term regulation of acetyl CoA carboxylase:

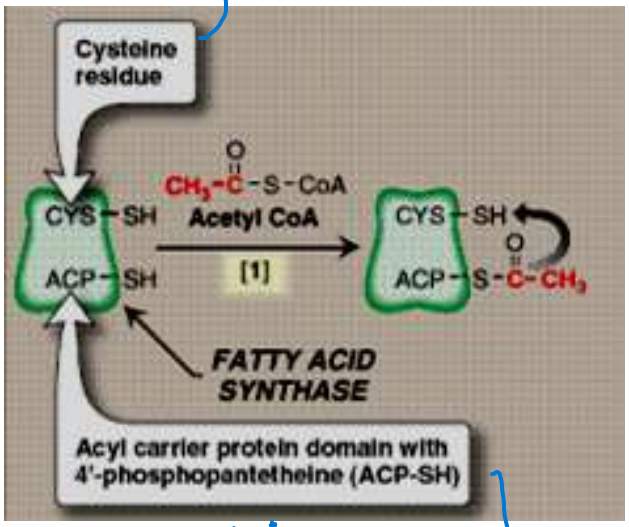
- Prolonged consumption of high-calorie, high-carbohydrate diets causes an increase in acetyl CoA carboxylase synthesis, thus increasing fatty acid synthesis.
- Conversely, a low-calorie diet or fasting causes a reduction in fatty acid synthesis by decreasing the synthesis of acetyl CoA carboxylase.

Fatty acid synthase → activation for seven reaction

- 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 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

يحمل الأسيتيل في البداية ثم السلسلة أثناء التكوين



يحمل الوحدات أثناء التفاعل

خطوات تصنيع الحمض الدهني داخل FAS:

الخطوة	ما يحدث	الإنزيم/الدومين
1	تحميل Acetyl-CoA على ACP	**Acetyl-CoA–ACP acetyltransferase**
2	نقل الأسيتيل إلى السيستئين (Cys)	داخل الإنزيم
3	تحميل Malonyl-CoA على ACP	**Malonyl-CoA–ACP transferase**
4	تفاعل تكاثف (Condensation): تكوين سلسلة 4C	**β-Ketoacyl synthase**
5	اختزال الكيتون إلى كحول	**3-Ketoacyl-ACP reductase**
6	نزع الماء (Dehydration)	**3-Hydroxyacyl-ACP dehydratase**
7	اختزال الرابطة المزدوجة	**Enoyl-ACP reductase**

تتكرر هذه الدورة **7 مرات** لإنتاج سلسلة كربونية مكونة من 16 ذرة كربون.

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

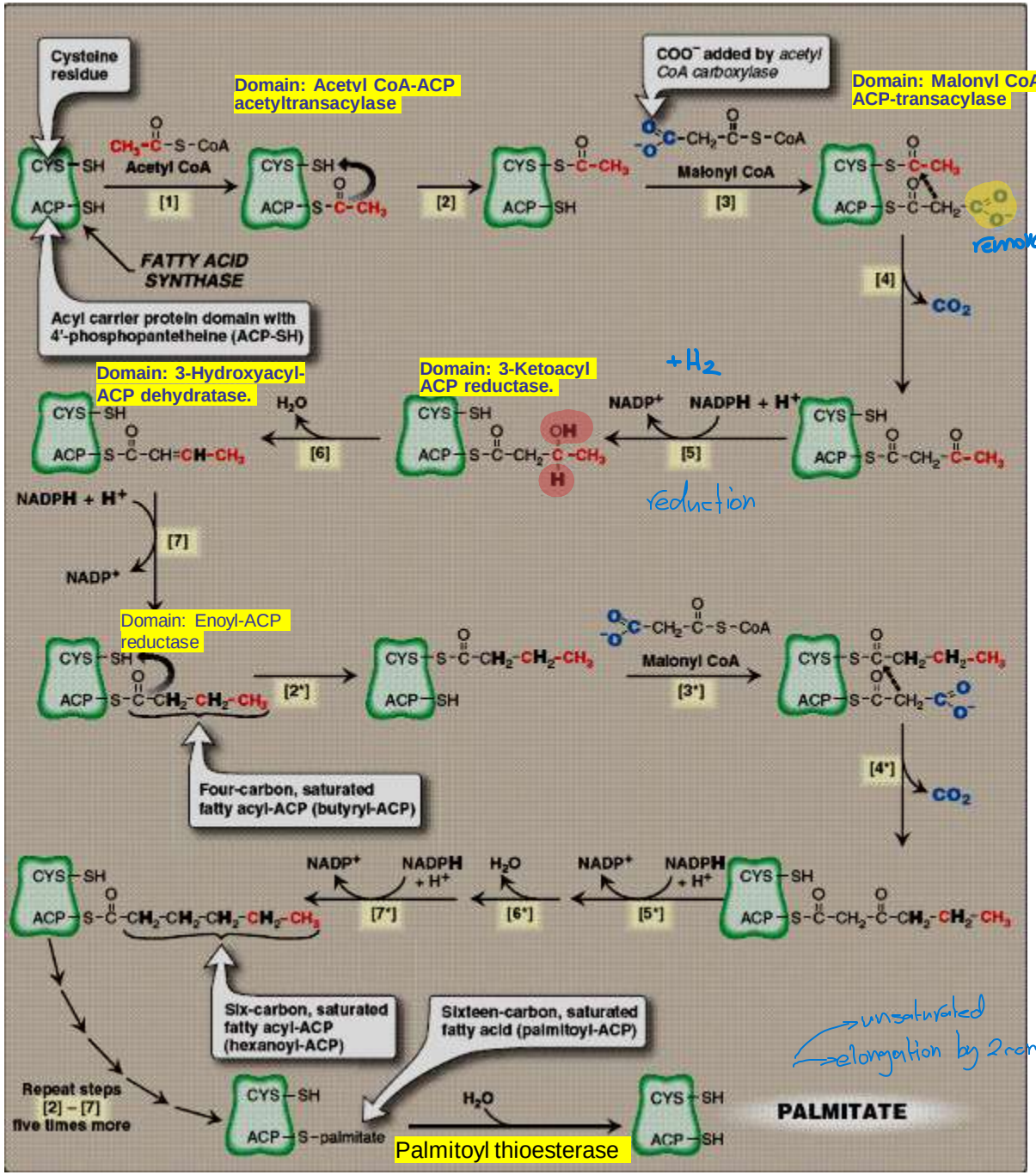
[4] The malonyl group loses the HCO_3 originally added by CoA carboxlyase, facilitating its nucleophilic attack of thioester bond linking the acetyl group to the cysteine residue The result is a four-carbon unit attached to the ACP

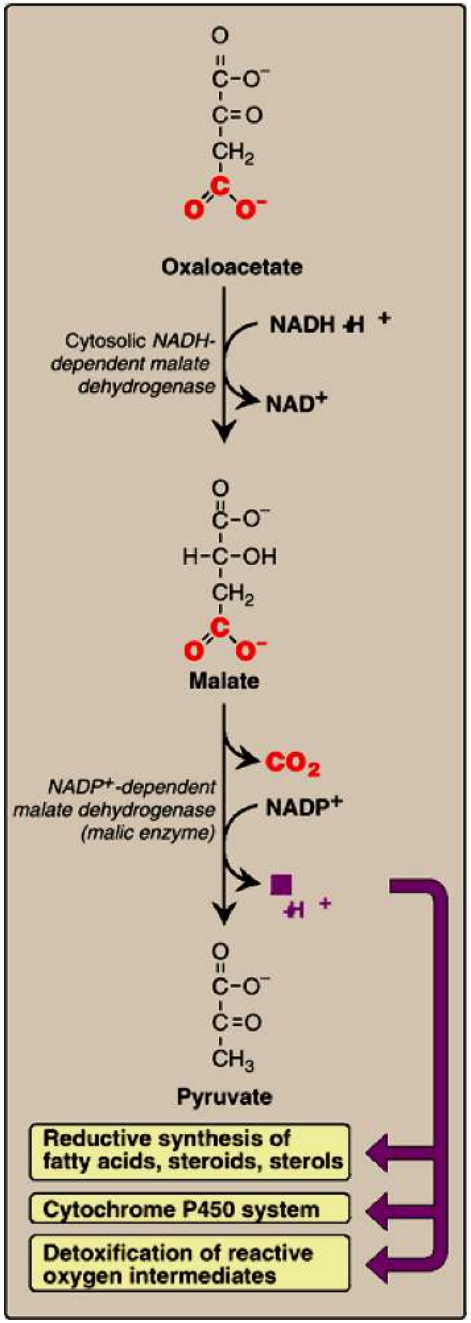
[5] The keto group is reduced to an alcohol. Domain: 3-Ketoacyl ACP reductase.

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

[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
Domain: Acetyl CoA-ACP acetyltransacylase
COO⁻ added by acetyl CoA carboxylase
Domain: Malonyl CoA-ACP-transacylase
Acetyl CoA
Malonyl CoA
[1]
[2]
[3]
[4]
CO2
remove
FATTY ACID SYNTHASE
Acyl carrier protein domain with 4'-phosphopantetheine (ACP-SH)
Domain: 3-Hydroxyacyl-ACP dehydratase.
Domain: 3-Ketoacyl ACP reductase.
+H2
H2O
NADP+
NADPH + H+
[5]
[6]
reduction
[7]
Domain: Enoyl-ACP reductase
[2']
[3']
[4']
Four-carbon, saturated fatty acyl-ACP (butyryl-ACP)
[5']
[6']
[7']
Six-carbon, saturated fatty acyl-ACP (hexanoyl-ACP)
Sixteen-carbon, saturated fatty acid (palmitoyl-ACP)
unsaturated
elongation by 2 carbon
Repeat steps [2] – [7] five times more
Palmitoyl thioesterase
PALMITATE


Oxaloacetate
Cytosolic NADH-dependent malate dehydrogenase
NADH + H+
NAD+
Malate
NADP+-dependent malate dehydrogenase (malic enzyme)
CO2
NADP+
+H+
Pyruvate
Reductive synthesis of fatty acids, steroids, sterols
Cytochrome P450 system
Detoxification of reactive oxygen intermediates

Further elongation of fatty acids

وين بصير عنا الاستطالة

- 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.

- 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.

لـ fatty acid وهيدين عشان يصير عنا رابطة ثنائية في

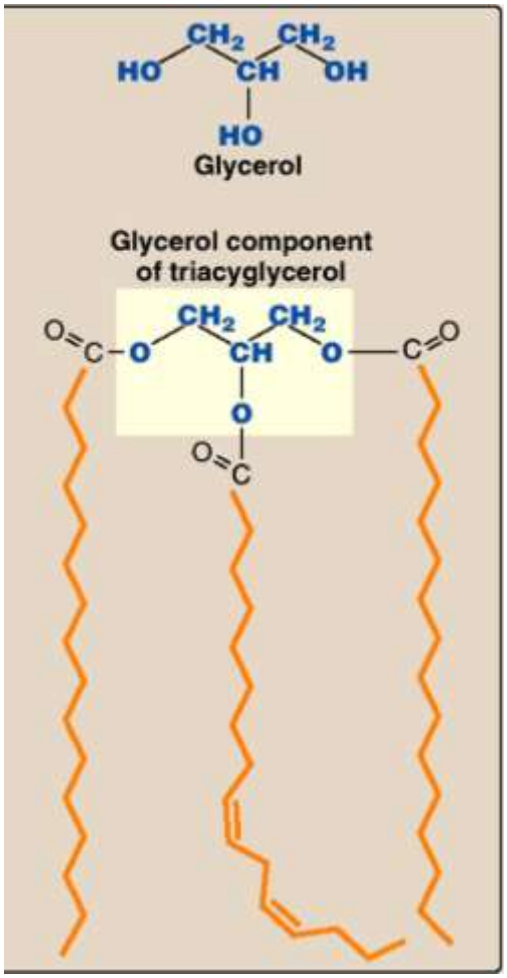
- We must have the polyunsaturated linoleic and linolenic acids provided in the diet.

ما بنقدر نحل unsaturated بالجسم

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
  - Fatty acid at C3 can be either (saturated, unsaturated)

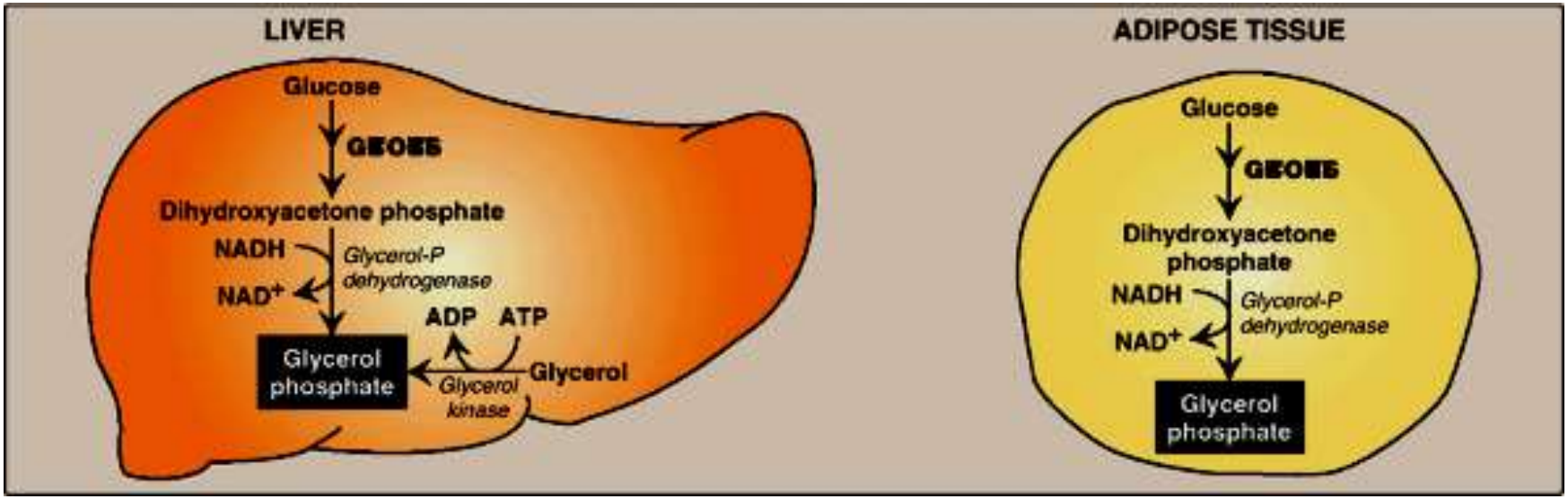
- If a species of acylglycerol is solid at room temperature, it is called a "fat", if liquid, it is called an "oil"



Storage of TAG

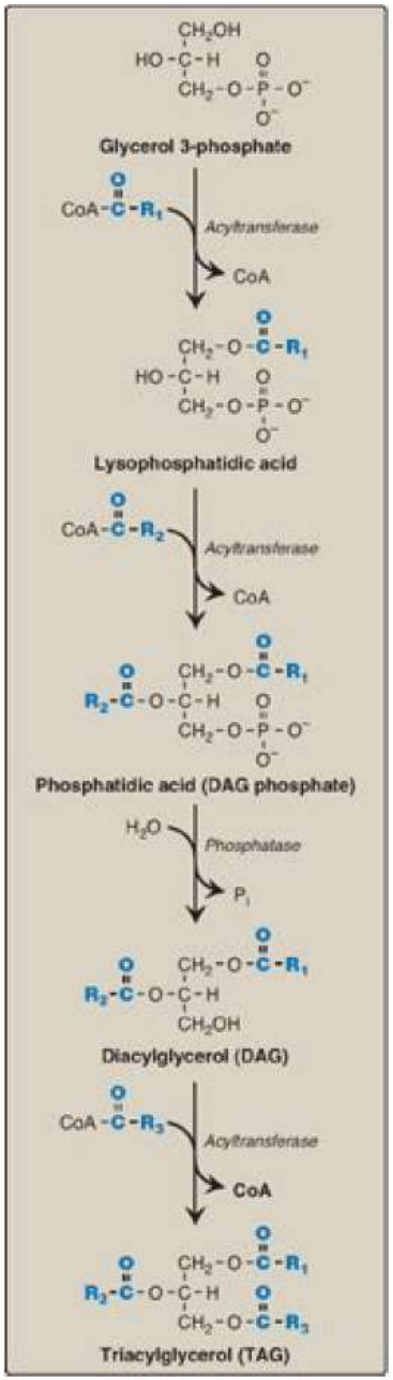
- TAGs are slightly soluble in water and cannot form stable micelles so they coalesce within adipocytes to form oily droplets that are nearly anhydrous.
- They act as the major energy reserve of the body.

- Production of glycerol 3P



Synthesis of triacylglycerol

- Synthesis of glycerol phosphate from glucose during glycolysis in liver and adipose tissue
- Conversion of a free FA to its activated form (CoA)
  ↳ Acyl-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.



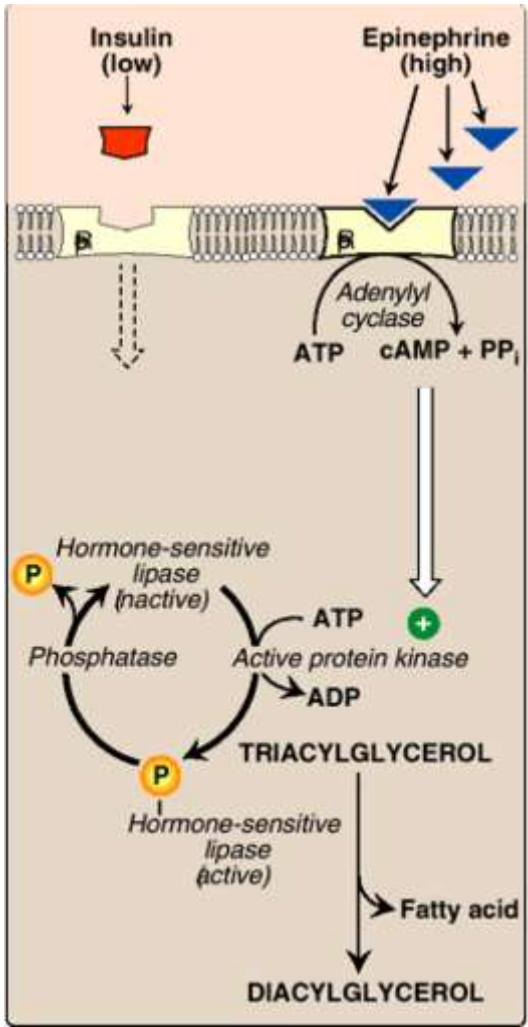
Mobilization of stored fat

- Release of fatty acids from TAG → degradation TAG to glycerol and FA
  - 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. at carbon 2

Mobilization of stored fat

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

- 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)



🔁 تلخيص الوظائف الرئيسية لـ DHAP:

المسار	دور DHAP
Glycolysis	وسيط ينتج من شطر Fructose 1,6-BP
Lipogenesis	يتحول إلى G3P ← لتكوين ثلاثي الغليسريد
Gluconeogenesis	يُستخدم لإعادة تصنيع الجلوكوز
إنتاج الطاقة	يمكن تحويله إلى G3P ← يدخل في سلسلة إنتاج ATP

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.

↳ dihydroxyacetone phosphate

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.

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**, which have no mitochondria, or by the **brain** because of the impermeable BBB

β-Oxidation of fatty acids

- 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.
- 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

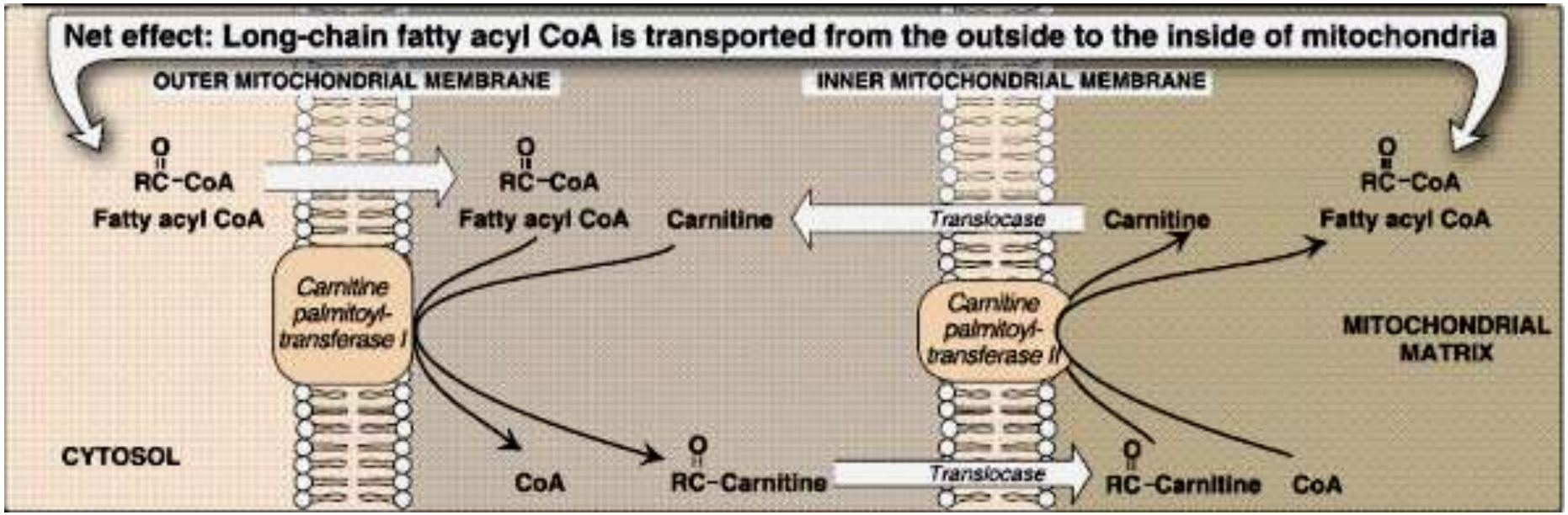
2. The acylcarnitine is transported into the mitochondrion in exchange for free carnitine by carnitine-acylcarnitine translocase.

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.

Inhibitor of the carnitine shuttle

- 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



Carnitine

- **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

- 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 + H_2O

[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

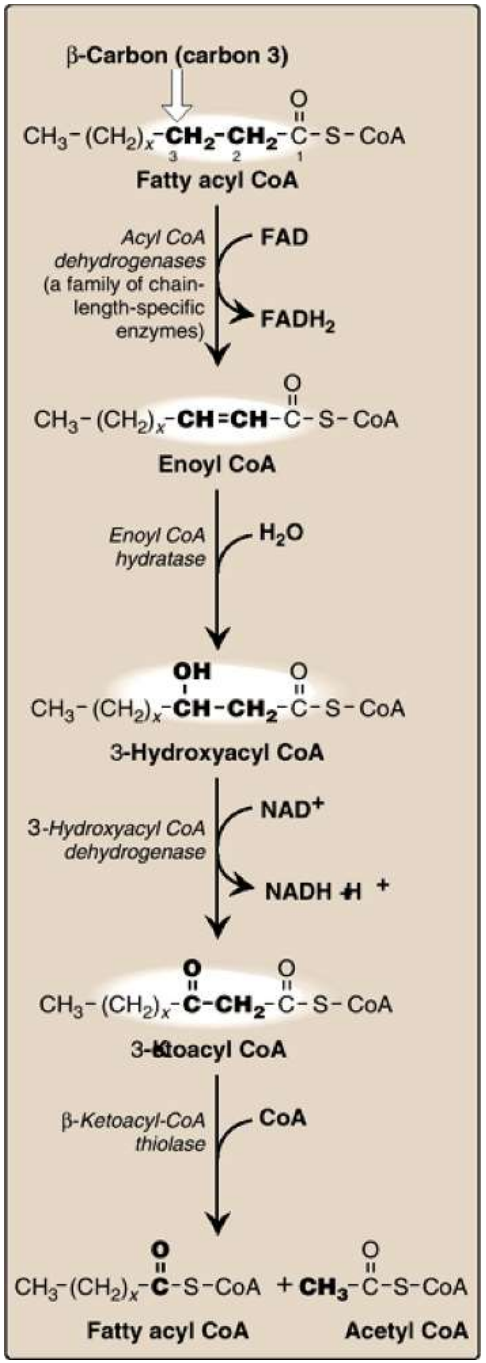
- The final thiolytic cleavage produces two acetyl groups.

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

يعمل تنشيط لهذ الإنزيم

pyruvate → OAA

F.A breakdown



Palmitoyl CoA

Domain: Enoyl-ACP reductase

Domain: 3-Hydroxyacyl-ACP dehydratase.

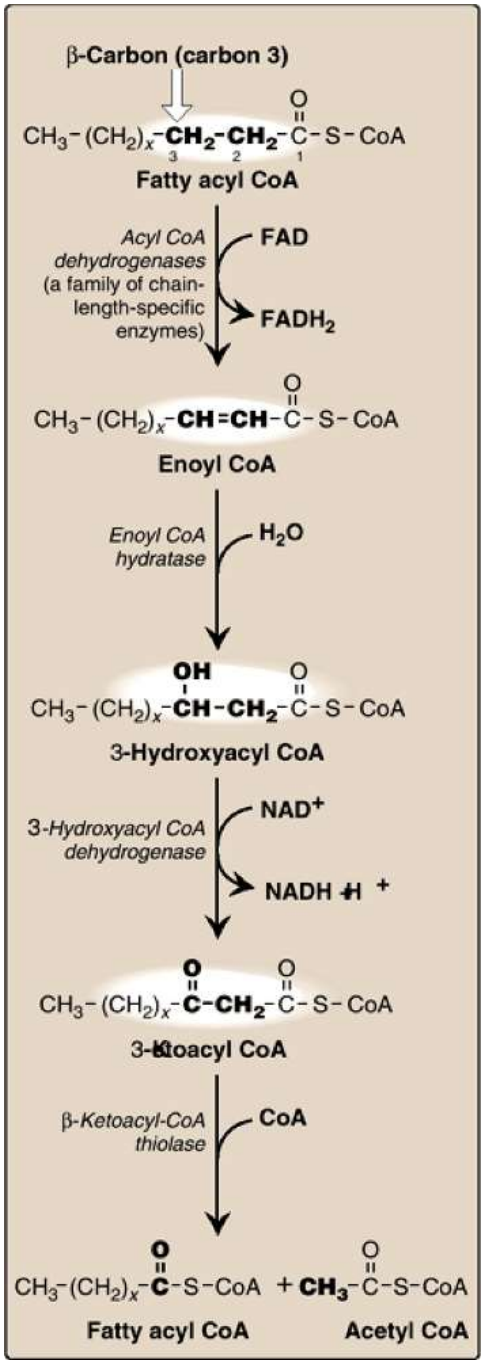
Domain: 3-Ketoacyl ACP reductase.

malonyl CoA + Acetyl CoA

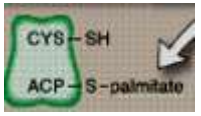
F.A synthesis

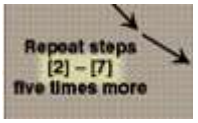
F.A breakdown

Produce energy

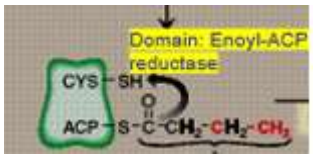


Palmitoyl CoA



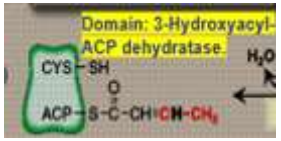


Domain: Enoyl-ACP reductase

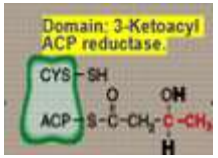


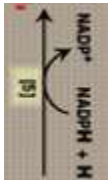
Requires energy

Domain: 3-Hydroxyacyl-ACP dehydratase.

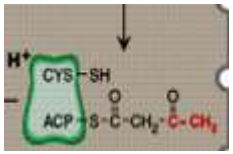


Domain: 3-Ketoacyl ACP reductase.





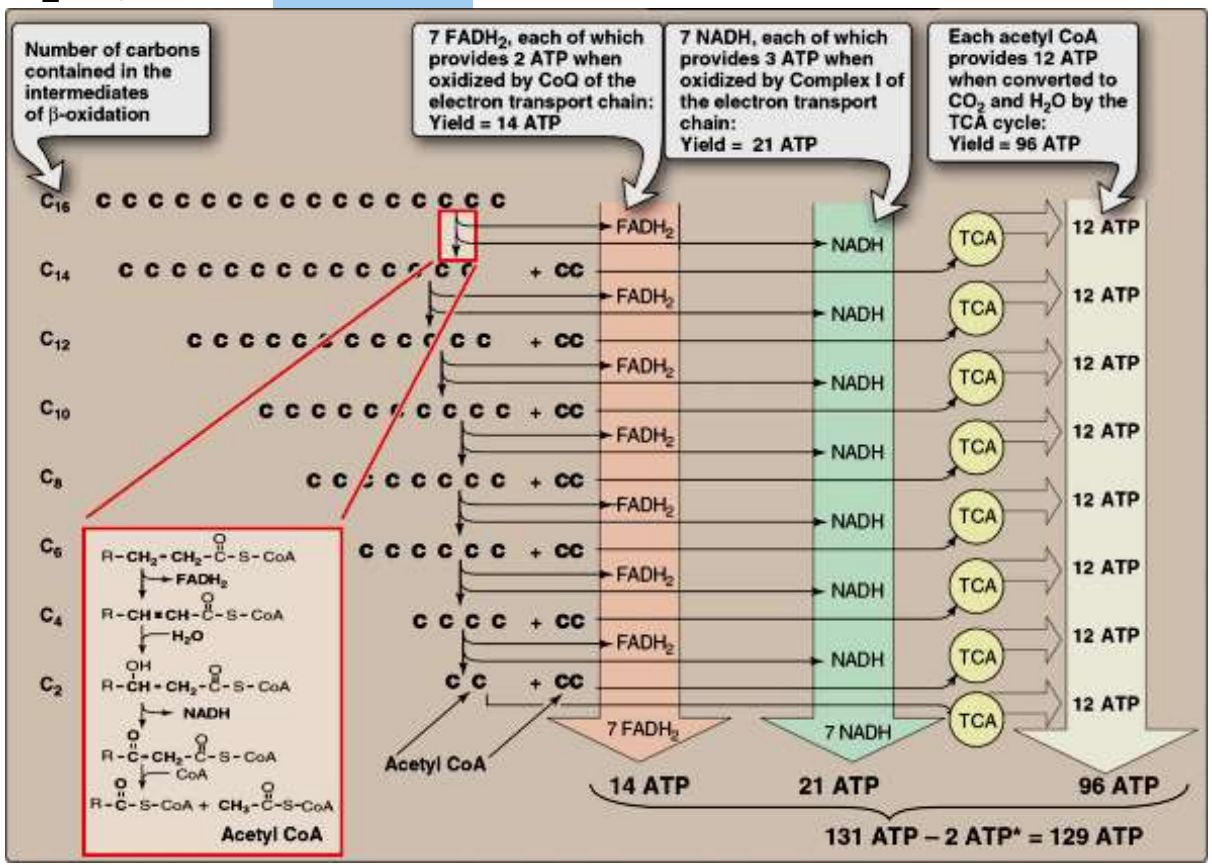
malonyl CoA + Acetyl CoA



F.A synthesis

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



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

يحل محل فردي من الالكترونات ② عمليات الأيض لاتحاض أحيائية معينة FA ① propiony CoA الحصرين

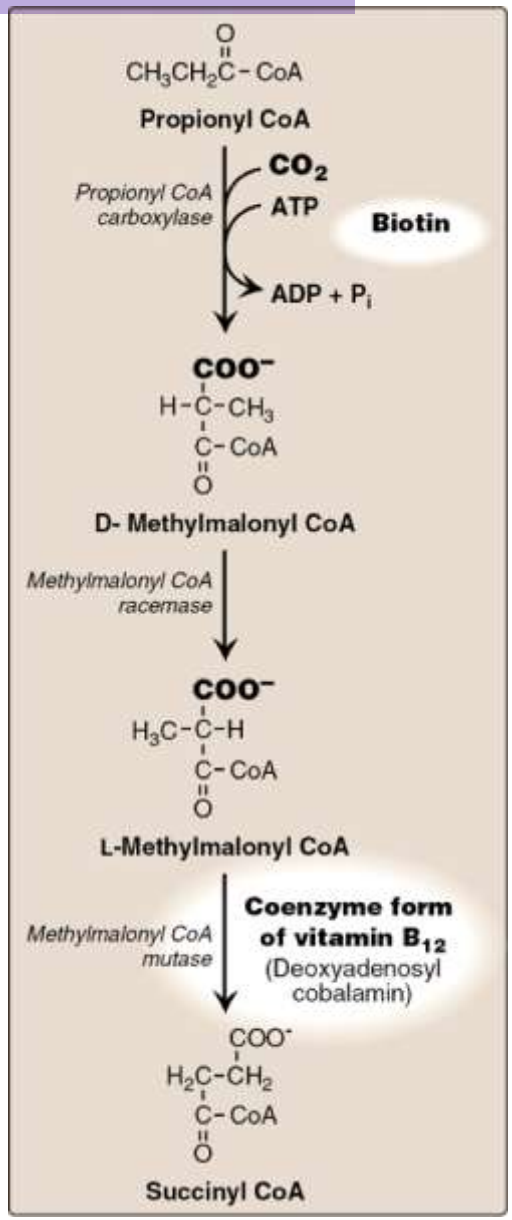
Oxidation of fatty acids with an odd number

- 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)

دورة كريس

- A genetic error in the mutase or vitamin B12 deficiency causes methylmalonic acidemia and aciduria in addition to developmental retardation.

تأخر في النمو

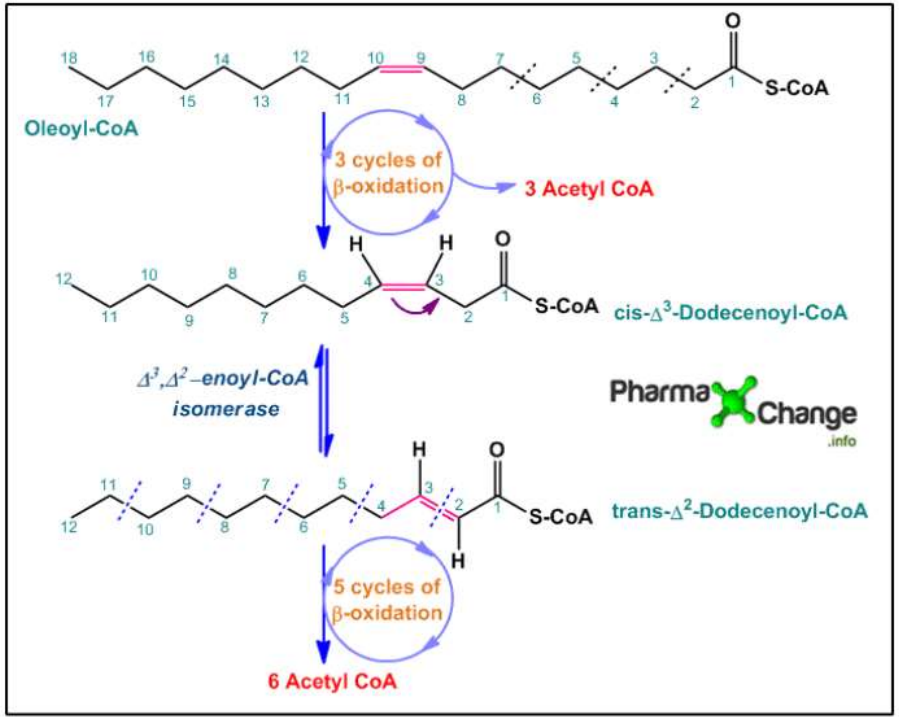


Oxidation of unsaturated fatty acids

- 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. → ↓ NADH

→ why ?!

- 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)



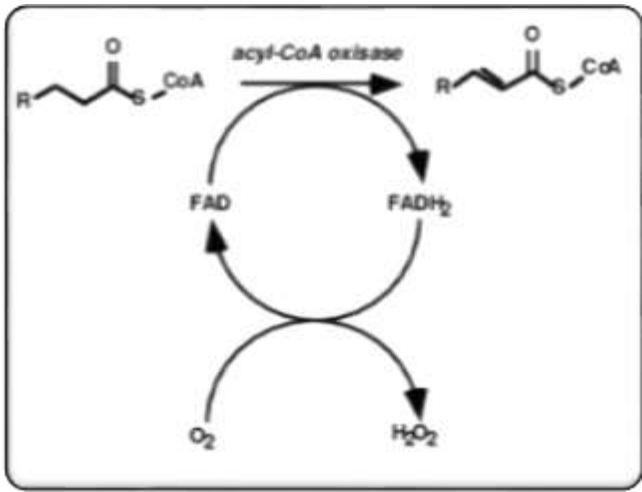
Oxidation in the peroxisome

- 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

خلل في التكوين

- 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.

خلل في النقل



Peroxisomal Disorders

- 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.

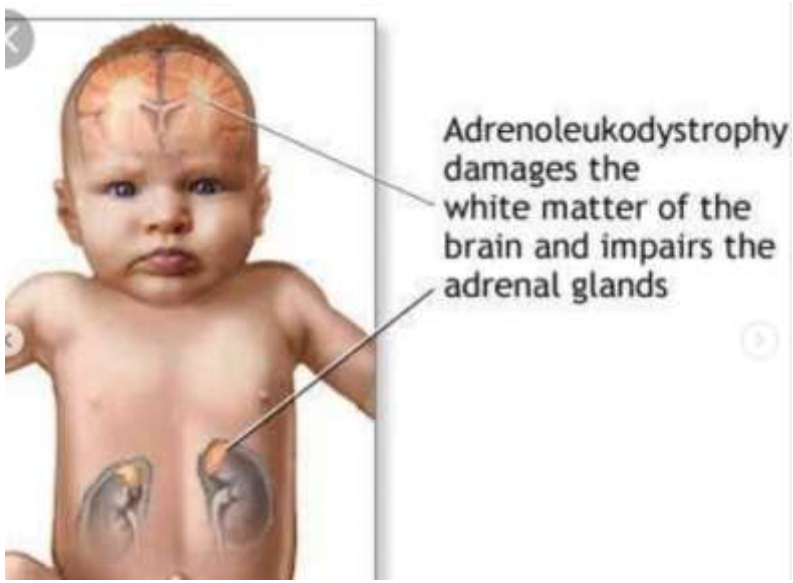
Zellweger Syndrome Cerebro-hepato-renal syndrome

Clinical signs

- Typical and easily recognized dysmorphic facies.
- Progressive degeneration of Brain/Liver/Kidney, with death ~6 mo after onset.
- Hypotonic, seizures and poor feeding
- Distinctive facies.
- Retinal dystrophy,
- hearing loss, severe DD

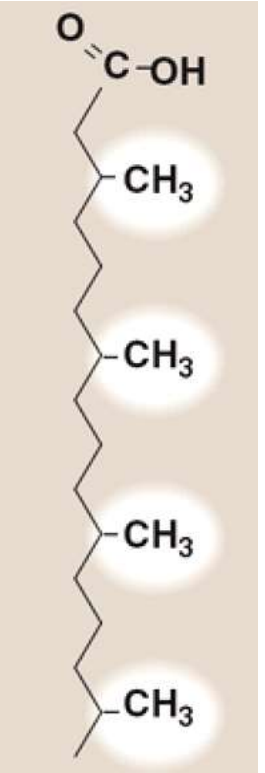
Diagnosis

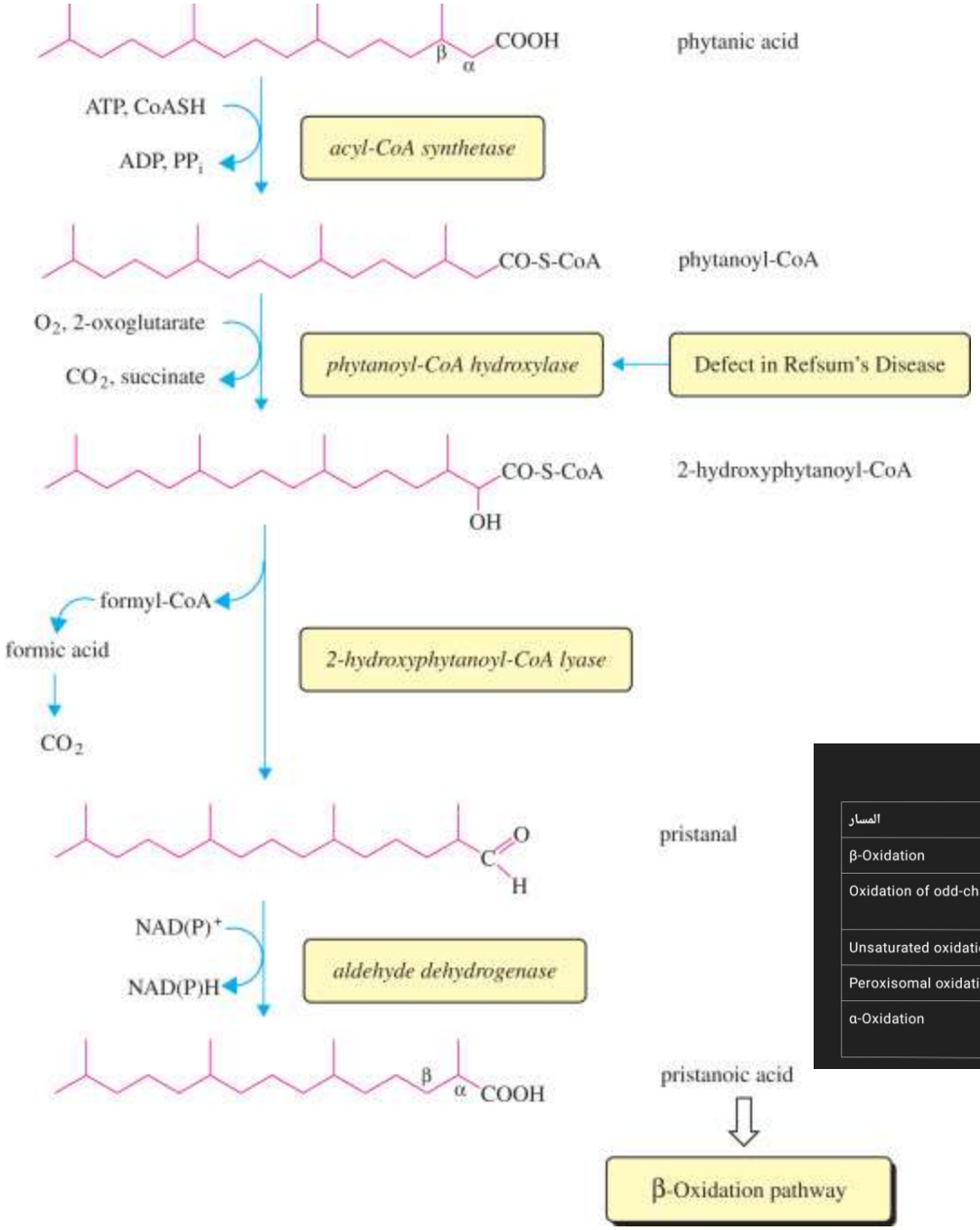
- Biochemical, serum Very Long Chain Fatty Acids- VLCFAs
- Gene test



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





✅ **الخلاصة:**

المسار	متى يستخدم؟	ملاحظات
β-Oxidation	الأحماض الدهنية العادية	مصدر رئيسي للطاقة
Oxidation of odd-chain	أحماض بعدد فردي	ينتج Propionyl-CoA → Succinyl-CoA
Unsaturated oxidation	أحماض غير مشبعة	طاقة أقل، يتطلب إنزيم إضافي
Peroxisomal oxidation	VLCFA (≥ C20)	أول خطوة تنتج H_2O_2
α-Oxidation	أحماض متفرعة	مثل Phytanic acid، مهم للدماغ

CASE STUDY

PHYSIOLOGY

ZELLWEGER SYNDROME

REFSUM DISEASE

ADRENOLEUKO.

RECAP

SUMMARY

ZELLWEGER SYNDROME

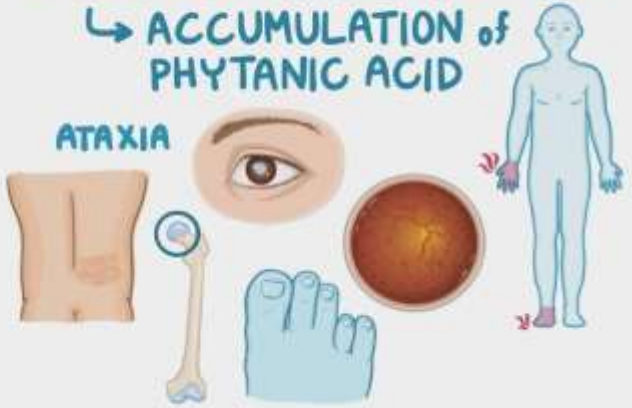
* MUTATION in PEX GENES
  - ↳ DEFECT in FORMATION of PEROXISOMES
    - ↳ BUILDUP of:
      - ~ VLCFAs
      - ~ BRANCHED CHAIN FATTY ACIDS
      - ~ AMINO ACIDS
      - ~ TOXIC SUBSTANCES
    - ↳ DEFICIENCY of PLASMALOGENS

EARLY DEATH

REFSUM DISEASE

* DEFECT in α-OXIDATION
  - ↳ ACCUMULATION of PHYTANIC ACID

ATAXIA



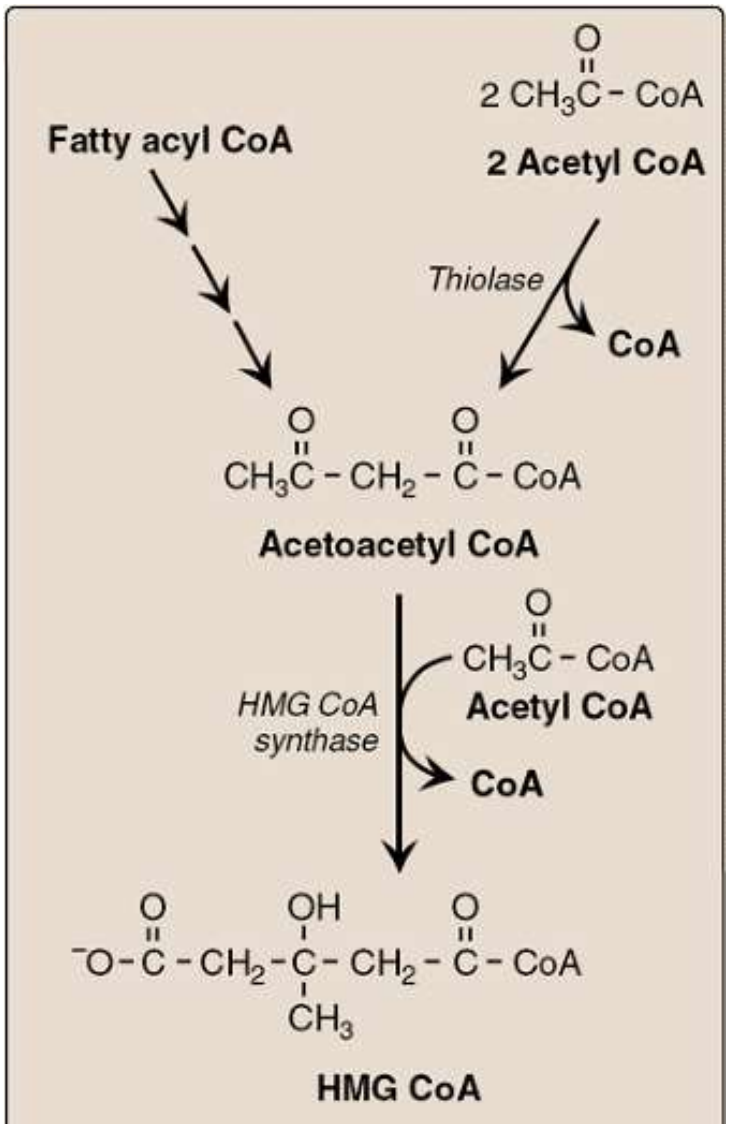
ADRENOLEUKODYSTROPHY

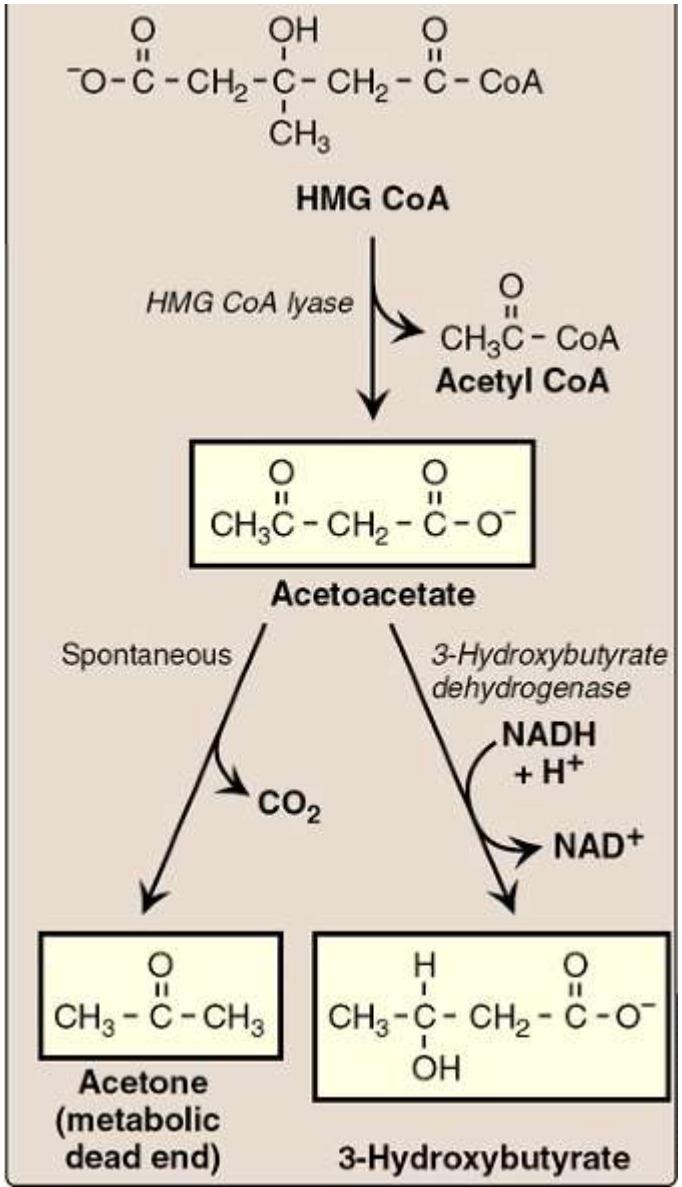
* MUTATION in ABCD1 GENE
  - ↳ DEFICIENCY in ALD PROTEINS
    - ↳ ADRENAL INSUFFICIENCY
    - ↳ TESTICULAR DYSFUNCTION
    - ↳ NERVOUS SYSTEM DEMYELINATION

Ketone bodies

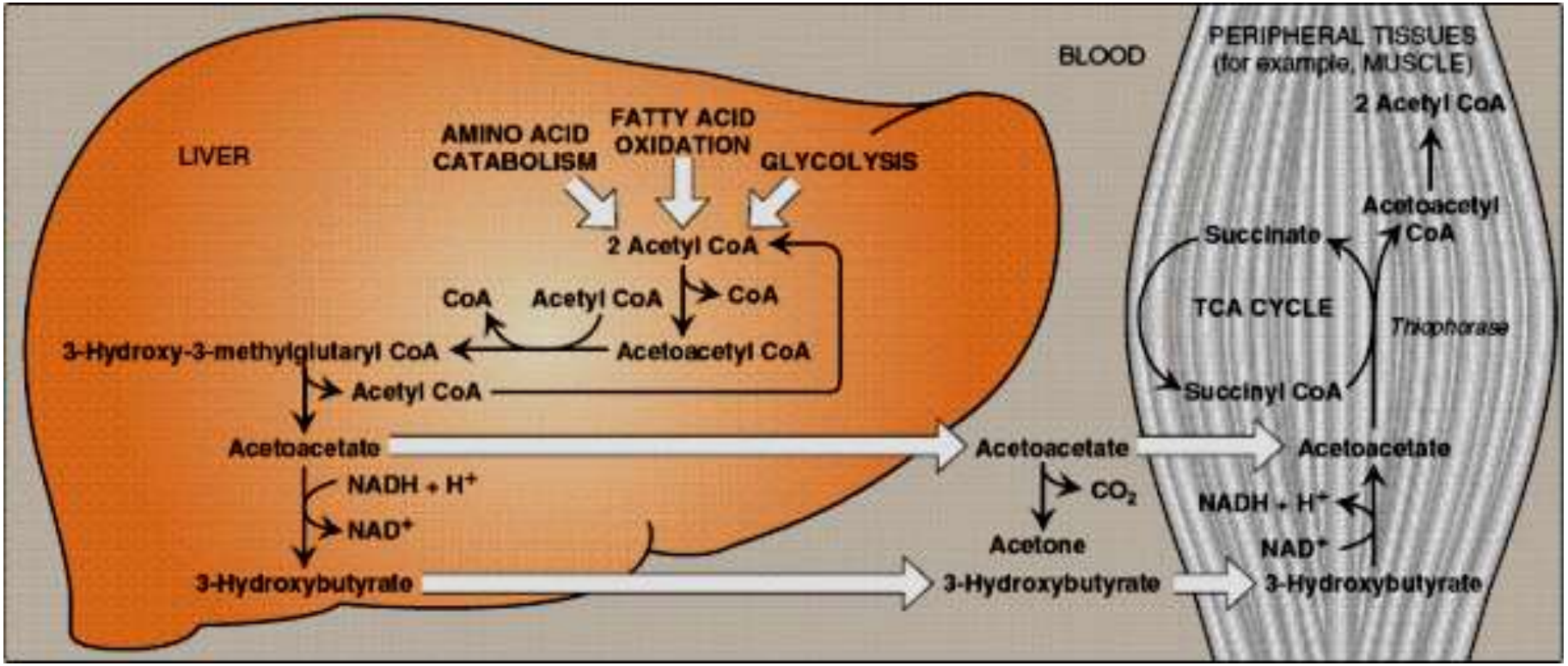
- Liver mitochondria can convert acetyl CoA derived from fatty acid oxidation into the ketone bodies, acetoacetate and 3-hydroxy-butyrate.
- Peripheral tissues possessing mitochondria can oxidize 3-hydroxybutyrate to acetoacetate, which can be reconverted to acetyl CoA, thus producing energy for the cell.
- 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.

Synthesis of ketone bodies by the liver





Synthesis of ketone bodies by the liver



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.
- their levels begin to rise in the blood (ketonemia) and eventually in the urine (ketonuria).
- In such individuals, high fatty acid degradation produces excessive amounts of acetyl CoA.
- It also depletes the NAD^+ pool and increases the NADH pool, which slows the TCA cycle