لجان الدفعات

BIOCHEMISTRY

MORPHINE ACADEMY

By Maryam Alhasan

Lipid metabolism

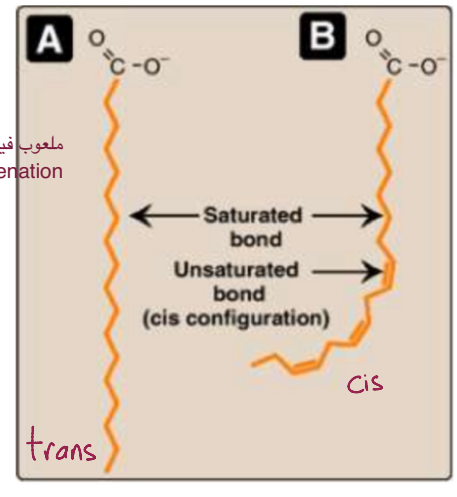
- الاحماض الدهنية او الدهون بشكل عام ، عندي الزيوت موجودة عشكل liquid ، وزيوت عشكل solid
- اشي saturated واشي unsaturated
- اشي short chain واشي long chain

- الfatty acid chain بتفرق معنا اذا كان فيها double bond او ما فيها

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

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



ملعوب فيها صارلها hydrogenation

- شو بختلف عندي لما يكون trans ولا cis ؟ الstability

- وجود الdouble bond يعني unsaturation بقلل الmelting temperature
- يعني بدل ما تكون الmelting point الها 20 ممكن تصير مثلا 10 او 5
- يعني ايش 10او 5 ؟ يعني عالroom temperature بتكون liquid
- اما لما تكون 20 وعندي ال15 room temperature فحتكون solid

- الشغلة التانية الlength كل ما كانت اطول بتكون الmelting point الها اعلى

- اغلب الfatty acids النباتية اللي مش ملعوب فيها ، بتكون بالcis configuration

Chain length of fatty acids

الproperties الهم بتختلف حسب:
الlength of chain
والsaturation

- 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.

Fatty acids with chain lengths of four to ten carbons are found in significant qantities in 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)

زيت حيل ← Palmitic acid
Solid ← Stearic acid
liquid ← double bond فيه Oleic acid
بعرفوا 2 ب

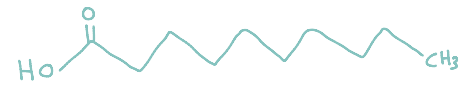
Precursor of prostaglandins

Essential fatty acids

مثلا :

Capric acicd

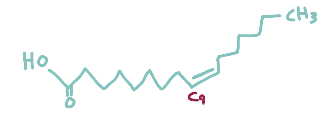
10:0
عدد الكربونات
عدد الunsaturation (عدد الdouble bonds)



مثال تاني :

Palmitoleic acid

16:1(9)
16 carbons
One double bond
الdouble bond على carbon رقم 9



شايفين الkink اللي صارت ، هاي مهمة لما يكون عندي unsaturation بالphospholipids حكينا الfluidity بتزيد

Essential fatty acids

ما بقدر اصنعهم داخل الجسم

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

منحتاجهم لحماية الكلى ، والمعدة من التقرحات , وبالكلى بتوفر الblood supply
deficiency المناسب بحيث ما يصير عندي
او نقص تروية ، يعني بتعمل vasodilation وبتزيد كمية الدم اللي رايحة لkidney

داخل الجسم بقدر اضيف بس one unsaturation, معناته بحصلهم من الdeit

الlinoleic acid منصنع منه arachidonic acid اللي هو موجود بالاكل كمان بس هو مش essential طالما الlinoleic acid عم بحصله من deit

الomega 3 ، شايفين الlinlenic acid عبارة عن 18 كربونة وفي عندي 3 unsaturation على 9 ،12,15 هاد هو الomega 3 الموجود عندي من رقم 15ل18 اللي هو 3carbons هاد الomega 3 , عنا اشي omega 6 زي linoleic acid فـ18 ناقص 12 يعني 6 carbons وكمان arachidonic acid برضو 20 ناقص 14 يساوي 6 , وهدول كلهم عبارة عن essential fatty acids

De novo synthesis of fatty acids

Cytosol
Mainly in

- 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 → Acetyl CoA, Acetoacetyl CoA
  - Ketone bodies
  - Certain amino acids → Acetyl CoA, Acetoacetyl CoA

- 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

يعني عشان اصنع carbon 16 كم acetyl CoA بدي ؟ 16 تقسيم 2 يعني 8 بدي
بحط وحدة acetyl CoA و 7 من malonyl CoA اللي هي بتتصنع من acetyl CoA
بحتاج ATP و NADPH , طبعا قلنا وين في عندي fatty acid synthesis, cholesterol synthesis اي شي بحتاج NADPH بكميات كبيرة

هلا اول خطوة لازم نسويها الacetyl CoA بنتج من الpyruvate جوا mitochondria ، فأول خطوة لازم اطلعه لبرا فبحوله بالoxaloacetate والacetyl CoA
بعديها بالcondensation بحولهم لcitrate والcitrate بطلعه مرة تانية وبكسره

1. translocation of citrate from the mitochonderion to the cytosol

- 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.

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

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

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

- الacetyl CoA عندي ياها عادة بتتصنع بالmitochondria ، الCoA ابدا ما بتطلع من خلال الmembrane , عنا 2 membranes الouter membrane والinner membrane , الouter ما عنا مشكلة فيه بطلع كل المركبات ، لكن الinner ما بمرق ولاشي لازم اشي يمرقه الacetyl CoA بما انها الCoA ما بتمرق معناها لازم تكون على شكل معين حتى ندخلها او نطلعها من الmitochondria

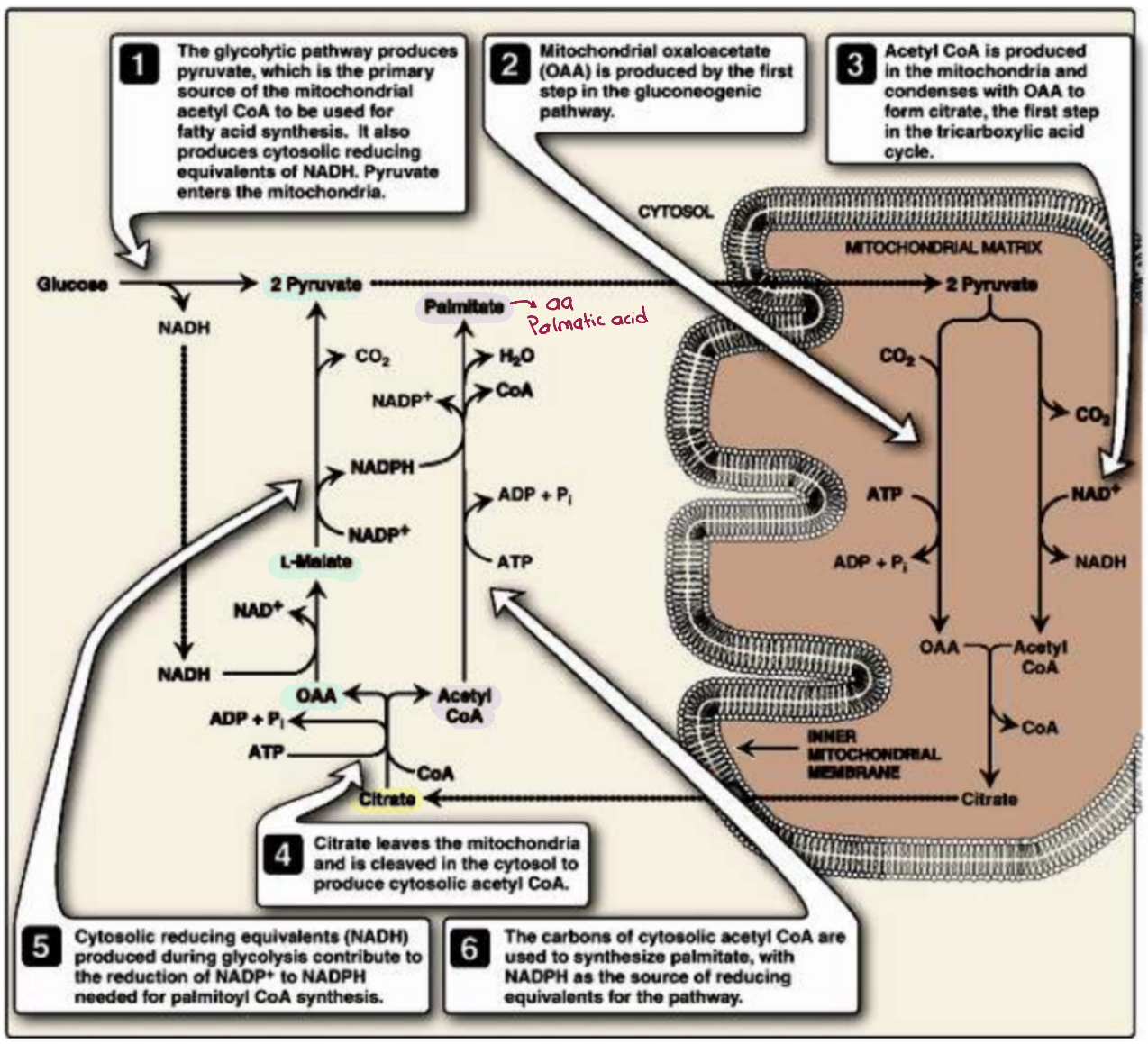
- اول اشي هي فعليا بدايات الkrebs cycle , الkrebs cycle انا كان عندي الpyruvate ممكن احوله لacetyl CoA بالpyruvate dehydrogenase enzyme ، وممكن احوله بالpyruvate carboxylase enzyme لoxaloacetic acid اللي هو oxaloacetate, وهدول التنين لما برتبطوا مع بعض بتحولو لcitrate

- هلا احنا عنا الkrebs cycle مربوطة مع كمية الNADH وكمية الطاقة الموجودة عندي بالخلية ، مجرد انه الglycolysis كان عندي very active يعني استعملت قد ما قدرت من الglucose ، الglucose هاد رح يطلعلي كميات هائلة من NADH ، ومنها بطلع ATP , لما ترتفع كمات ATP لدرجات كتير كبيرة بروح بوقف ETC اللي هي electron transport chain اللي هي عملية الoxidative phosphorylation للNADH تحويلها لATP , هلا الNADH ببلش يتراكم يتكون بكميات اكبر ، بروح عالisocitrate dehydrogenase enzyme وبعمله inhibition, طبعا هاد اللي بحول لalpha ketoglutarate فهاد ببلش يتراكم isocitrate والcitrate,

- هلا الcitrate ببلش يطلع من mitochondria على الCytosol وهناك بATP citrase lyase enzyme ببلش يكسره مرة تانية لacetyl CoA وoxaloacetate ، وهيك انا برجع للacetyl CoA
- الacetyl CoA بستعملها بصناعة الfatty acids
- والoxaloacetate برجع بحولها لmalate وبعدين لpyruvate والpyruvate برجع للmitochondria بتحول لacetyl CoA او oxaloacetate والcycle بتضلها شغالة

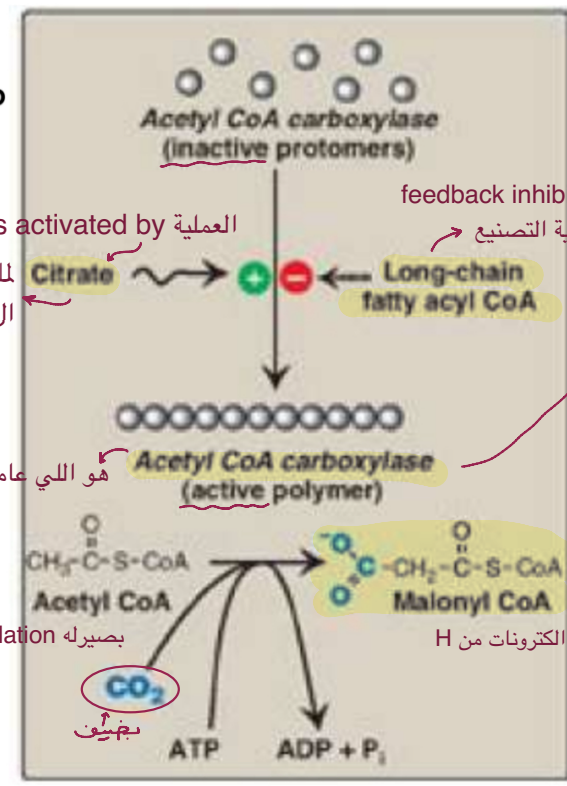
- كم بحتاج pyruvate لأحولها لOAA ؟ وحدة لكل cycle وكل مرة بطلع منها acetyl CoA

Source of cytosolic Acetyl coA



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.



ال palmatic acid عبارة عن 16:0 , يعني 16 كربونة يعني 8 acetyl CoA

1 acetyl CoA — 7 malonyl CoA

feedback inhibition بعمل
بوقف عملية التصنيع

لما يرتفع بال mitochondria ويطلع عناعال Cytosol بحفز عملية ال polymerization لل [acetyl CoA polymerase enzyme]

Active form

هو اللي عامل regulation وهو ال key enzyme

اهم واحد بكل ال processes
يعني كل ال fatty acid synthesis
فيها 2 enzymes هاد
وال fatty acid synthase enzyme

بصيرله carboxylation

ال carbon بتجيب الكترونات من H

متذكرين ال pyruvate carboxylase كان بده biotin , ال OH بنعمل عليه carboxylation بعدين برجع مرة تانية بنقلها لـ acetyl CoA وبحولها لـ malonyl CoA

من كتر ال ATP وقفت ال krebs cycle , فال ATP موجودة بكميات كبيرة من عمليات ال metabolism لل glucose

Regulation of acetyl CoA carboxylase

Dimer is active
Monomer is inactive

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.

dephosphorylation هو اللي بعمل → inactive بصير phosphorylation لما يصيرله

Long-term regulation of acetyl CoA carboxylase:

carbohydrates كتير

↑ carbs ↑ enzyme ↑ fat

- 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.

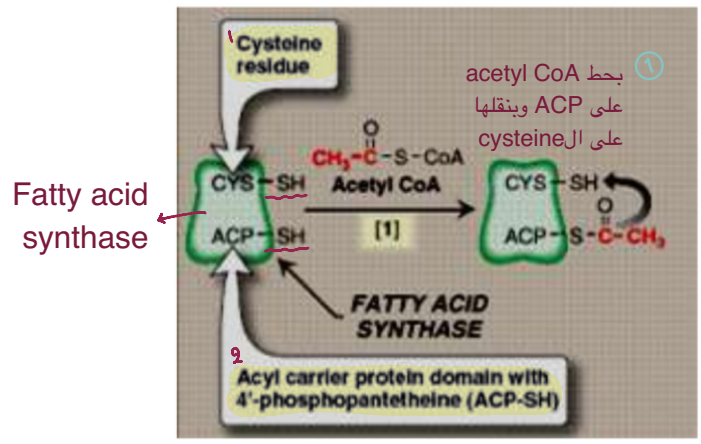
↓ carbs
Ketogenic diet أو
(مثل اللي بعنهم مشاكل بالوزن)

هلا بدنا نبلش نبني fatty acids ونكون ال16 كربونة

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 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

منبدأ بوحدة acetyl CoA والباقي malonyl CoA



عشان احول acetyl CoA لmalonyl CoA بدي 1ATP

7 in 1

Steps of fatty acid synthesis

عنده 7 domains كل واحد اله catalytic activity معينة

[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

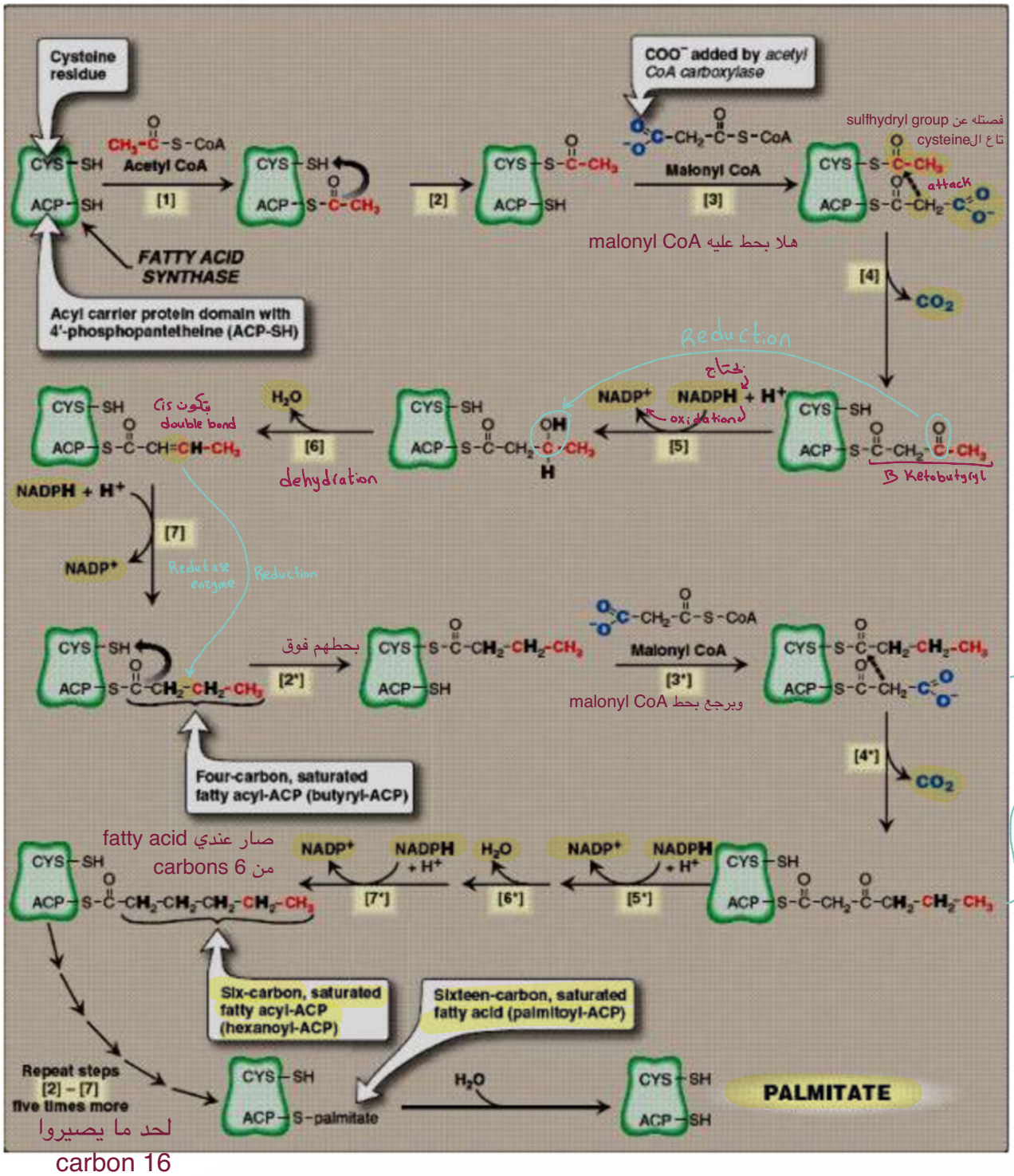
[4] The malonyl group loses the HCO_3 originally added by CoA carboxlyase, facilitating its nucleophilic attack of thioester bond linking the acetyl group to the cysteine residue The result is a four-carbon unit attached to the ACP

[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.

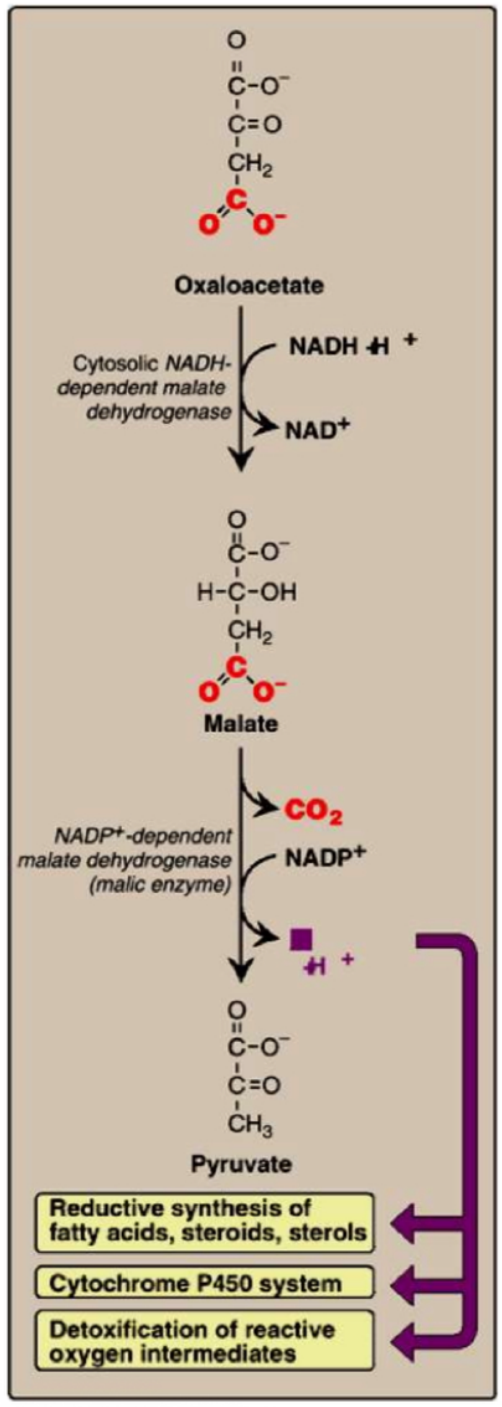
[7] A second reduction step occurs. Domain: Enoyl-ACP reductase

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



هاي العملية بدي 2 NADH لكل مرة

بتتكرر العملية



- بقدر اطوله اكتر ؟ اه ، بالendoplasmic reticulum والmitochondria , بقدر اطوله كمان كربونتين لحد 18
- وبقدر احط فيه unsaturation ؟ اه ، one saturation
- الlinoleic و linolenic اللي همه polyunsaturated, ما بقدر اصنعهم لانهم essential

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.

it can produce it's own fatty acids كمصدر للطاقة ولكن fatty acids حالة خاصة لانه اصلا ما بستهلك

- 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.

مسؤول عن عملية unsaturation

- 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.

double bond بعمل

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

اكتر من وحدة فيهم

ممكن اصنعه من linolic acid

بقدر اصنعهم بالجسم	ما بقدر اصنعهم لازم من diet
Oleic acid	[Arachidonic acid]
Palmitoleic acid	Linoleic acid
	Linolenic acid

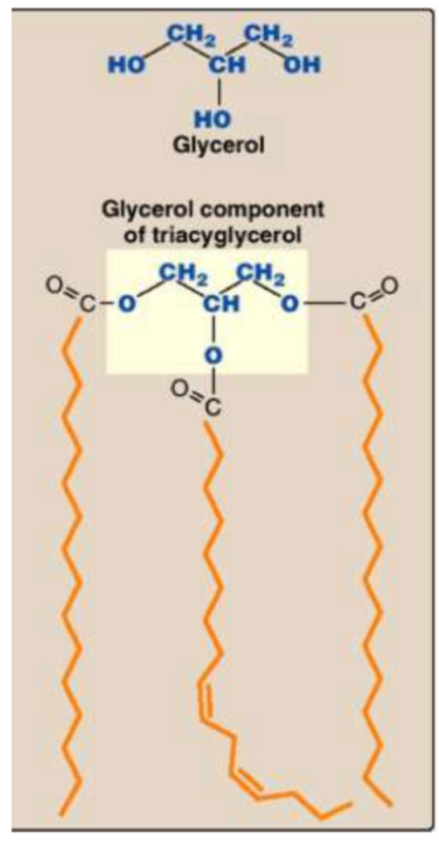
هو acidic in nature ما بقدر اخزنه as it is , لازم
اربطه مع glycerol عشكل triglycerides عشان اقدر

هلا بدي اركب fatty acids على triglycerides

اخزنه بال cytosol of adipose tissue وممكن عملية
التصنيع بال adipose tissue و mammary glands
للستات المرضعات وممكن كمان بال liver

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



Solid → fat (Saturated بكونوا)

liquid → oil (mainly unsaturated)

لأنه melting Point إلها دخل بال Saturation and unsaturation

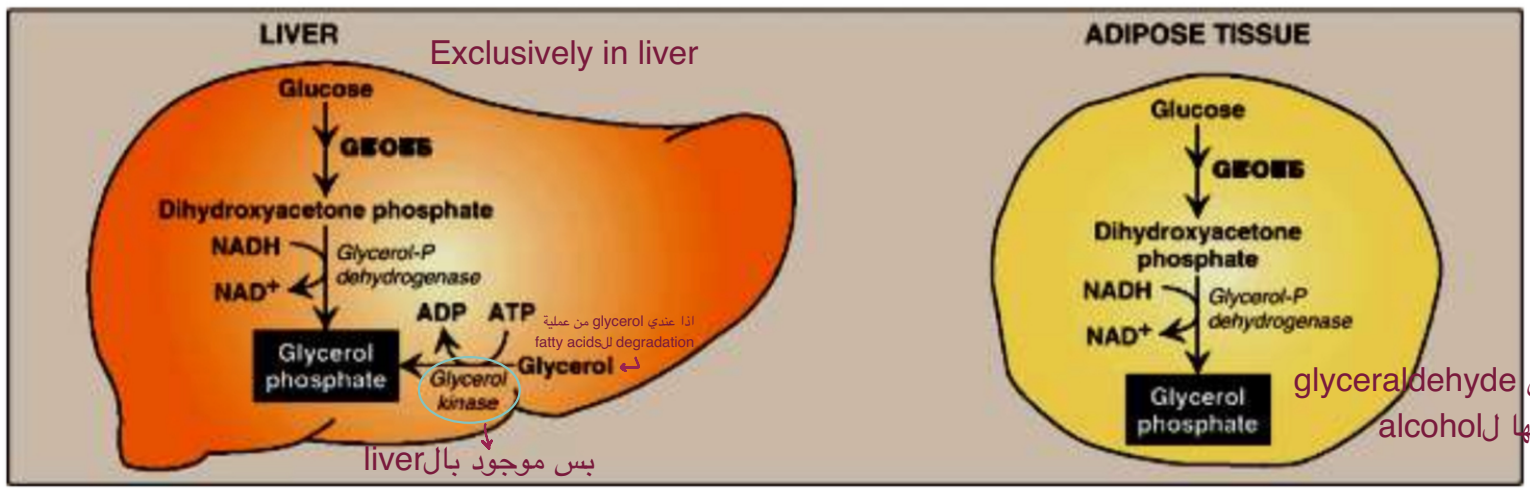
Storage of TAG

ما بكون حوليه water

- 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

ممكن احصل عالglycerol من glucose metabolism



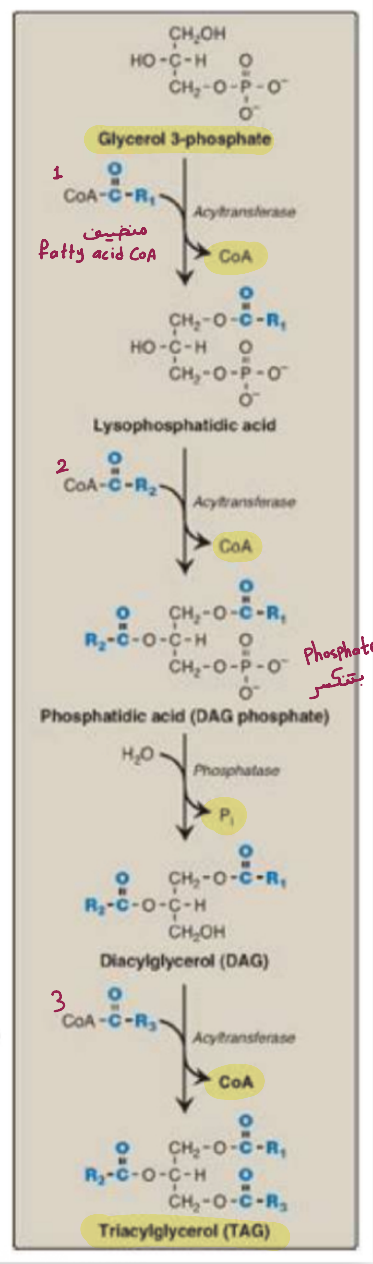
Synthesis of triacylglycerol

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

لازم اعمل activation عشكل fatty acid 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.

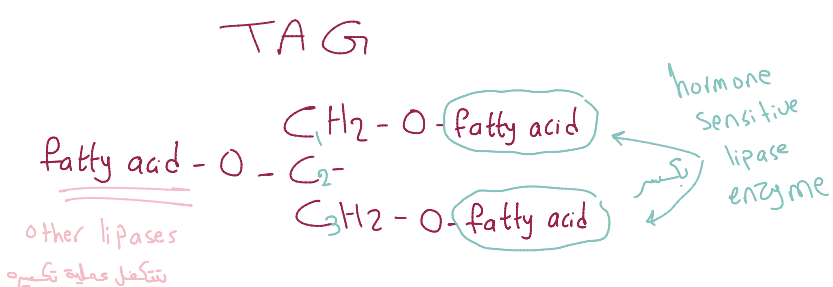
اذا بضل بالliver بصير عندي fatty liver , فبعمله packaging وبطلعه برا



ممكن يعمل circulating اذا في muscle بدها triglycerides او organs بتحتاج اله للحصول عالطاقة وممكن الadipose tissue تاخد منه وتخزن، فالعملية حسب الorgan اللي رايحله ، بتحول وقتها لLDL, HDL, ... المهم it will circulate in blood والtissue اللي بحتاجه رح ياخد منه

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.



2 fatty acyl glycerol المركب اللي بضل هو

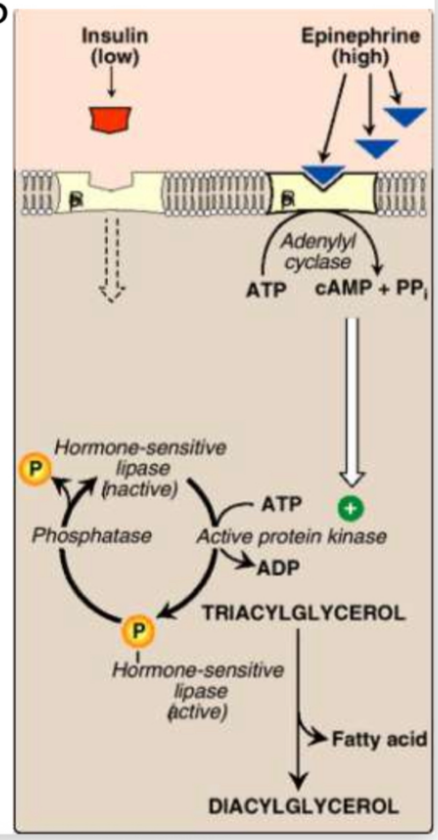
- هلا العملية العكسية ، انه انا هلا جعانة عندي شوية الجلوكوز اللي ضلو انا خزنت كلشي خبيت كلشي وخلصت من كل الglucose اللي اخدته بالdiet تبعي ، يا حولته لfat يا خزنته يا خبيته glycogen او استعملته بالglycolysis او صنعت بروتينات
  فهلا صارلي اربع خمس ساعات بدون اكل ، برجع بستعمل الاشياء اللي خبيتها للحاجة
- الglycogen وgluconeogenesis, هدول حكينا عنهم بس للbrain و RBCs
- باقي الخلايا بروحو عالfat
- الregulation اله fasting (جعانة فبسكر fats)

Mobilization of stored fat

متذكرين لما كنا نحكي عن glycogen synthase وphosphorylase , كنا نحكي انه بعمل phosphorylation للتنين, والphosphorylase بصير active والsynthase بصير inactivate, هدول نفس الاشي

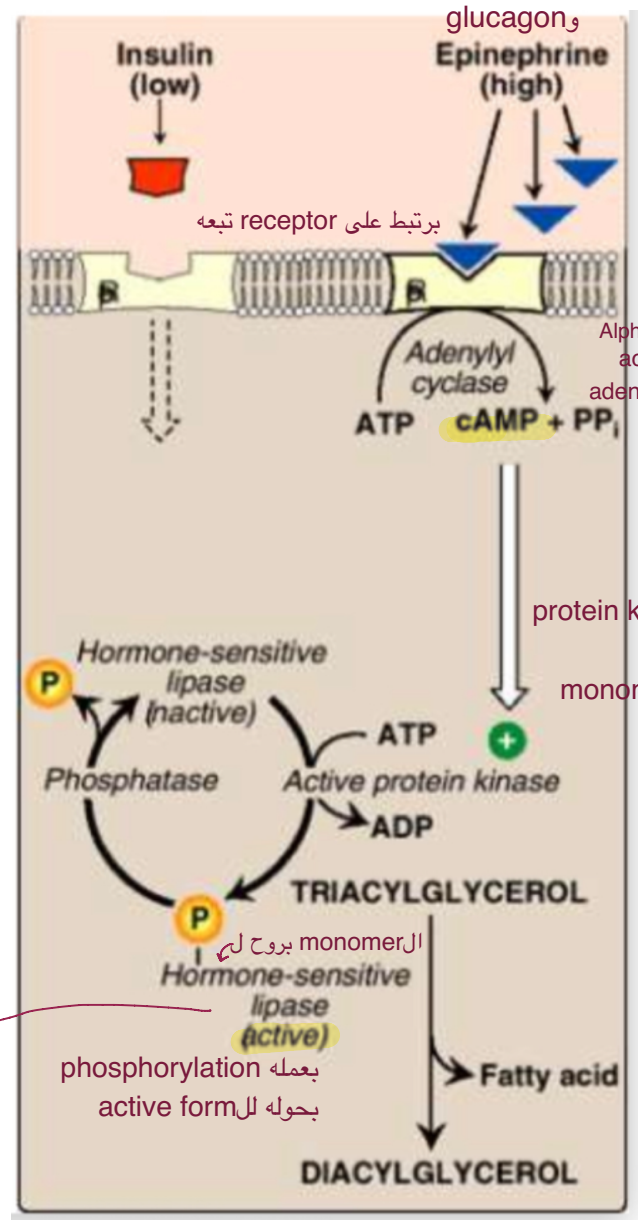
1. Activation of hormone-sensitive lipase (HSL): This enzyme is activated when phosphorylated by a 3',5'-cyclic AMP-dependent protein kinase in the adipocyte upon binding of hormones (like epinephrine) to receptors on the cell membrane, and activation of adenylate cyclase

- 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)



ال insulin بشيل
ال phosphate عن التنين ،
فبرجع ال lipase لـ inactove
و carboxylase لـ active

بكسر ال phosphate



ال glucagon بعمل phosphorylation وبالتالي
hormone sensitive lipase لـ activation
ول carboxylase بصير inactive

بكسر fatty acids الي على TAG
وبحوله لـ Diacylglycerol او بعد هيك
لـ monoacylglycerol
او fatty acyl glycerol 2

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.

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.

من albumin لل tissue بحولها لـ fatty acyl CoA وبعد هيك بدخلها mitochondria عشان اعملها beta oxidation

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

الطريقة الوحيدة للتخلص منه يروح عال liver ، بعمله phosphorylation وبعدين بـ dehydrogenase enzyme بتحول لـ glyceraldehyde 3 phosphate ، يا بكمل metabolism glycolysis يا برجع بصنع منه glucose , هون منصنع منه glucose

للعلم lipolysis is coupled with gluconeogenesis ، الطاقة اللي بتطلع بستهلكها لانتاج جلوكوز لل gluconeogenesis ال organss اللي ما بتقدر تستهلك fatty acids هي brain aand RBCs

بتم بالmitochondria فانزيماتها كلها بالmitochondria لكل
cells ما عدا barin والRBCs اصلا ما عندها mitochondria

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.

عشان اقدر ادخله لحوله لي

- 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.

حكينا outer membrane بمرق كلشي
الinner ما بمرق اشي الا بواسطة carnitine

عملية الtransportation in mitochondria will require amino acids ، طبعا هو عبارة عن gama amino acid , متذكرين كنا نحكي عن alpha amino acids
في اشي اله codon واشي ما اله ، ، هاد الgama amino acid ما اله codon ، وظيفته عملية transportation للfatty acids

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

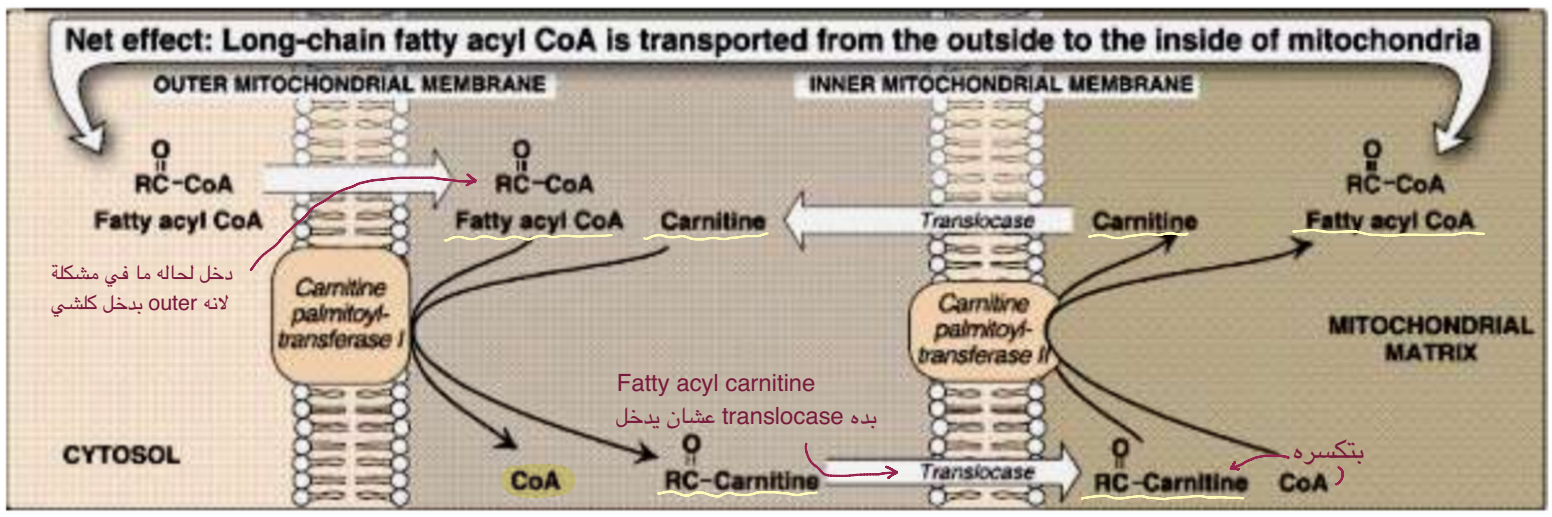
موجود عالouter membrane
من جوا الreaction بصير

2. The acylcarnitine is transported into the mitochondrion in exchange for free carnitine by carnitine-acylcarnitine translocase.
3. 2 Carnitine palmitoyltransferase II (CPT-II) catalyzes the transfer of the acyl group from carnitine to CoA in the mitochondria matrix, thus regenerating free carnitine.

موجود على inner
اله beta oxidation ويبدا عملية fatty acyl CoA حتى يرجعلي ياه

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



ال carnitine بحتاجوه الناس اللي بلعبوا رياضة، اللي عندهم ضعف عضلات ، اللي ببنوا عضلات ...
حتى يزيدوا من efficiency لاستعمال الfat , حتى يحصلوا على كم اكبر من الطاقة لعضلاتهم

ال fatty acid اللي بصنعه بال cytosol عشان ما يدخل عال mitochondria ويفوت يصيرله degradation , احنا قلنا ما عنا عمليات بناء وعملية هدم شغالين مع بعض ، فلما ال malonyl CoA يرتفع بال cytosol بعمل inhibition ل CPT وبالتالي بوقف عملية دخوله لل mitochondria, فما في عندي degradation و synthesis بنفس الوقت

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.

1 حيوانية اكتر
2 اكتر مستهلك لل carnitine 97%
اول شي بدخل fatty acids لل mitochondria
ال carnitine بشبك معها وممكن يطلعها من خلال kidney

Carnitine deficiencies

بكون في نقص بالdiet تبعه
او مشكلة بالliver اللي بصنعه

- 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

عنا dialysis الfluid والblood للمريض وعندي membrane بالنص بينهم

صوديوم
بوتاسيوم
كالسيوم
مغنيسيوم .. بديش يطلعو من الجسم

الcreatinine وurea
ما بدي ياهم
بطلعو برا

- 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.

matrix of mitochondria داخل

عكس عملية الsynthase

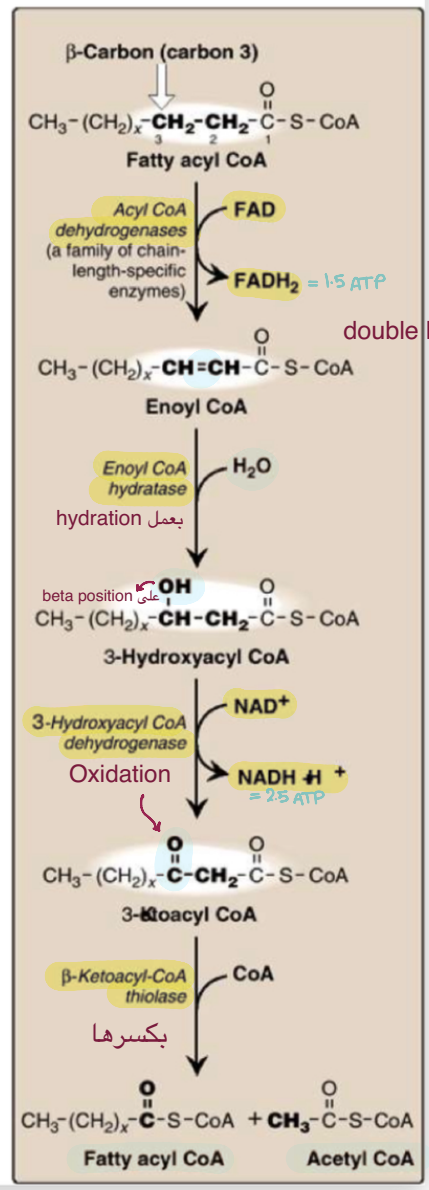
Reactions of β-oxidation

1 Very long chain fatty acyl dehydrogenase enzyme
2 Long chain fatty acyl dehydrogenase enzyme
3 Medium chain fatty acyl dehydrogenase enzyme
4 Short chain fatty acyl dehydrogenase enzyme

- 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.

activation بعمله
اللي بحول pyruvate لoxaloacetate
وبصنع منه glucose

it's coupled with lipolysis عشان هيك



double bond بتكون

هون الpalmatic acid كسرته ل8 acetyl CoA

8 Acetyl CoA * 10 ATP (Krebs cycle) = 80 ATP

7 NADH * 2.5 = 17.5 ATP

7 FADH2 * 1.5 = 10.5 ATP

= 108 ATP

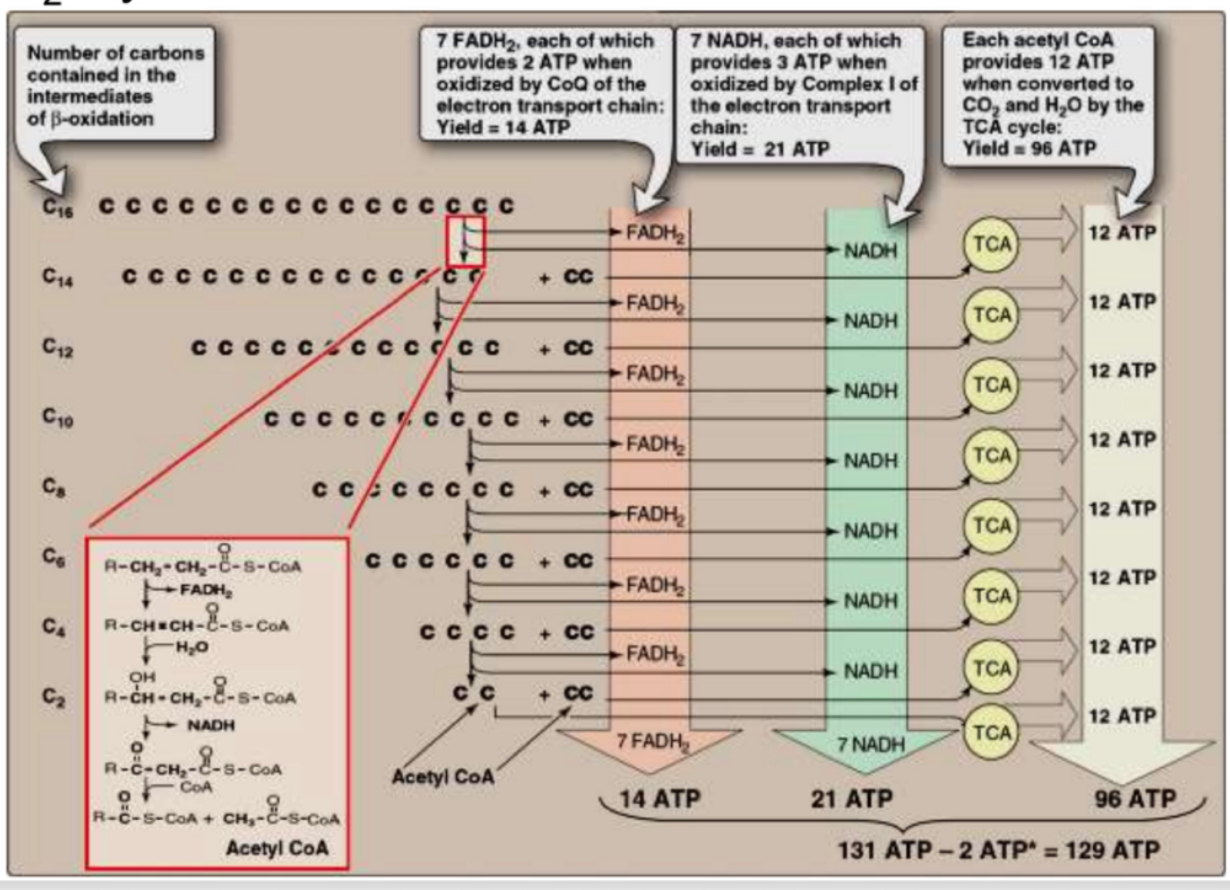
من تكسير 1 Fatty acid

لـ 3 Fatty acids و بضرب 3 * 108 = 324 ATP

(1TAG) ←

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 يعني لازمني defected genes 2
  - 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). لانه مش قادر اكسر fat فبكسر glucose
- Treated by a carbohydrate-rich diet. اكتر مشكلة ممكن تصير
- 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

لانه في الshort والmedium chain

ممكن كمان الcystic fibroses يتضررو، لانه معتمدين عليه

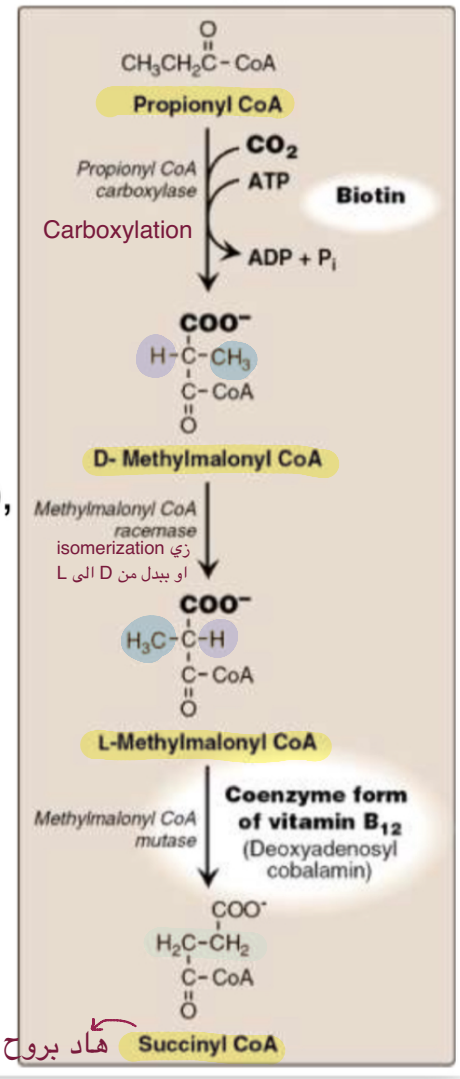
اللي عنده viral infection واخد aspirin, بصير damage للliver كامل ،

Oxidation of fatty acids with an odd number

لما يكون مش 16,18 ....
مثلا 17 كربونة

- 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.

بصير accumulation لmethlmalonic acid



هاد بروح Krebs cycle

عنا كتير من amino acids كانت تنتهي بـsuccinyl CoA او propionyl CoA , ارجعولهم

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)

هون double bond جاهزة

خسرت 1 من FADH2 بالprocess كلها (يعني بطلع طاقة اقل ب1.5)

اكتر من double bond

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

لحد ما يضل one double bond بوديها لـ3,2- enoyl CoA

اول شي بكون double bond على carbon 2 and 3 (عملية تكسير beta oxidation)

بعدين بعمل رقم 3 بعمل hydration بدخل H2O

بعدين بعمل oxidation

بعدين بكسر ، وبرتبط CoA جديدة

عملية الoxidation الاولى بتطلع FADH2 والoxidation التاني بتطلع NADH

هاد مهم عشان اشوف unsaturated بطلعلي طاقة اكتر ولا اقل

Oxidation in the peroxisome

مثلا brain بصنع لحد 24 كربونة

اول شي الperoxisomes بعملوا shortening , بعدين بصير beta oxidation ، وبدخل mitochondria

- 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.

الولد بكون مصاب والبنت حاملة المرض فهو منتشر بالmales اكتر

اذا كان في مشكلة بالperoxisomes بتراكم very long chains ← بتضر liver Kidney Brain

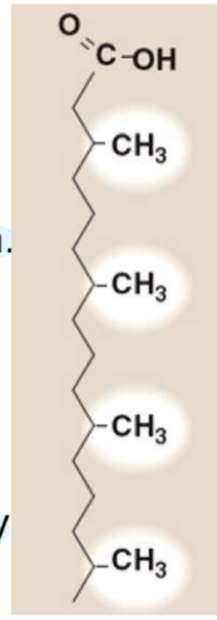
α-Oxidation of fatty acids

ما بزبط اعملها beta oxidation
فبعمل alpha

موجود بالقمح ، شعير ...

- 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.

يعني بدي 2 genes عشان يكون عنده deficiency لهاد الenzyme

- **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

عملية التصنيع تبعها تتم فقط بالliver

Ketone bodies

مش منيح للناس الطبيعية يكون عندهم

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

1 2

مش glutarate

3- Acetone

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

بقدر يستعمل ketone bodies

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

الliver بصنع بس ما بقدر يكسر

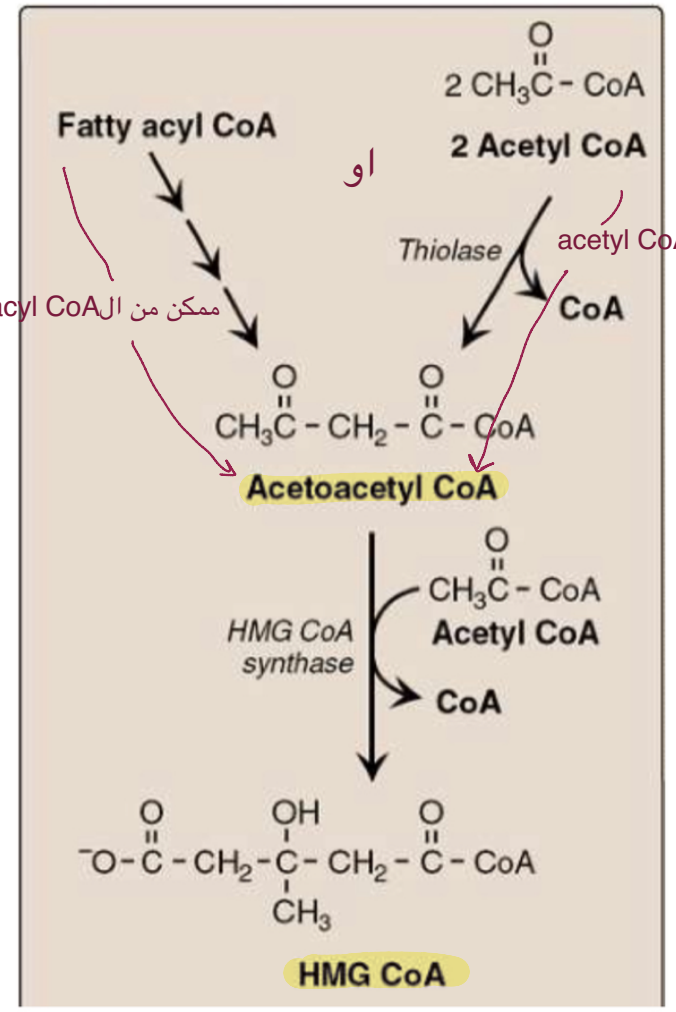
- The liver lacks the ability to degrade ketone bodies, and so synthesizes them specifically for the peripheral tissues.

مين ما عنده Krebs cycle ؟ RBCs
فما بقدر يستخدم ketone bodies

الاشخاص اللي ممكن يصير معهم ketone bodies ؟
١ الType 1 diabetes
٢ حالات الstarvation
٣ الناس اللي عندهم vomiting for long time
٤ اللي عندهم diarrhea
٥ والناس اللي عالketogenic diet

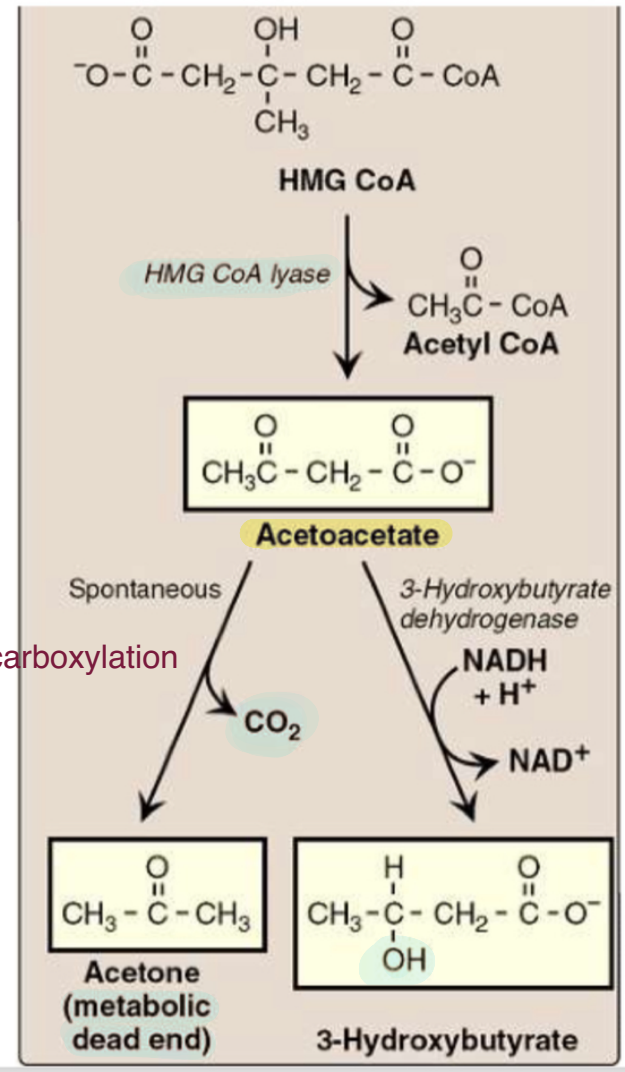
شو صار عنا اشياءء بس بالliver ؟
عملية phosphorylation للglycerol
تصنيع الktone bodies
الurea cycle
وكمان شوي رح نحكي عن تصنيع bile

Synthesis of ketone bodies by the liver



fatty acyl CoA ممكن من ال

acetyl CoA 2 بجمع

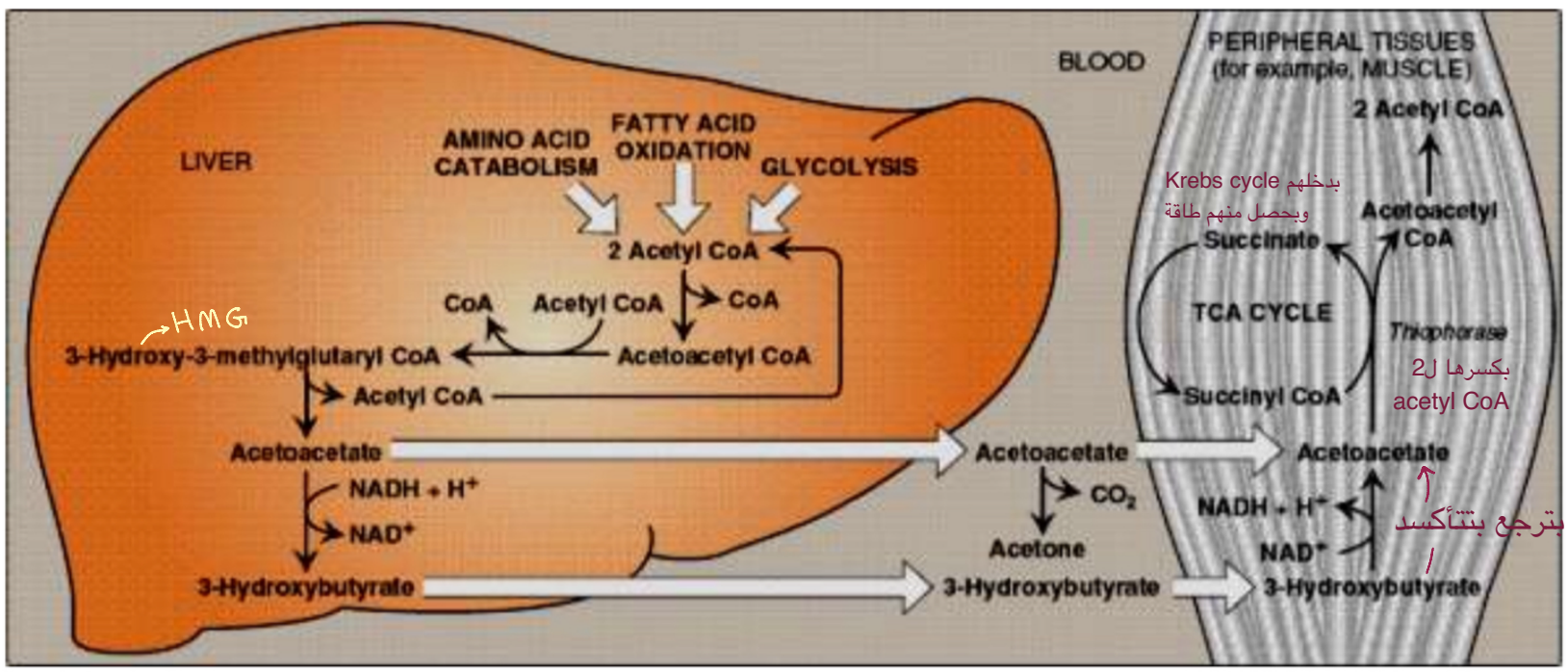


Decarboxylation

هو volatile ويطلع من الدم عن طريق النفس

Synthesis of ketone bodies by the liver

الacetoacetate كم بطلع طاقة ؟ ATP 20



HMG

بترجع بتتأكسد

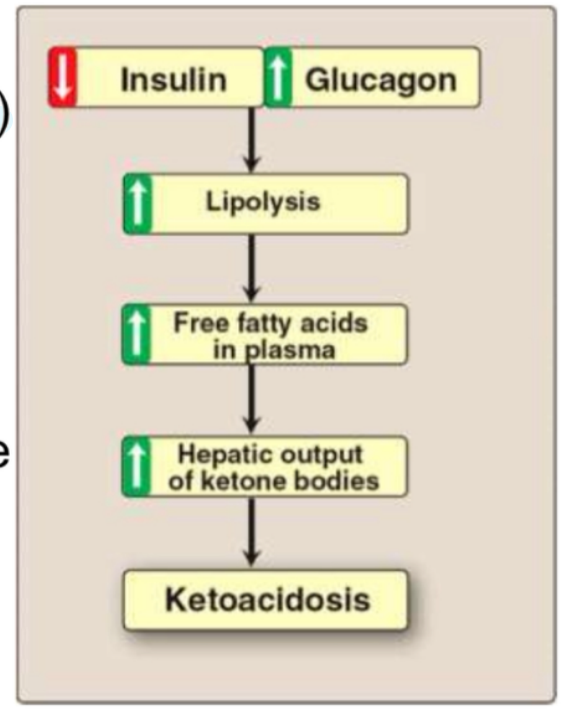
Ketoacidosis

- 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).

ببلش يرتفع بالدم بروح عالurin وبسحب معه صوديوم فممكن الواحد كمان يصير معه hyponatremia

- 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

لما يدخل acetyl CoA لل krebs cycle ال NADH
كميات كبيرة عن تنتج ، فهاد بعمل depletion للNAD+



الدكتورة بسلايد alpha oxidation و oxidation of unsaturated كانت ترسم عاللوح فممكن هدول الصورتين قراب من اللي رسمته اذا بدكم تشوفو