Biochemistry

Title = Lipid metabolism-L(2)
Lec no =15
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وقل رب زدني علما

Lipid metabolism lecture 2 of 3

Lipolysis, fatty acid oxidation and ketone bodies

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Lipids metabolism	1. Fatty acids metabolism a. Fatty acid synthesis b. Fatty acid catabolism 2. Cholesterol synthesis 3. Eicosanoids synthesis from fatty acids

Adipose tissues and energy stores

- Types of adipose tissue
  - *White adipose tissue:* mainly concerned with energy storage
    - Has very few mitochondria
    - TAG makes 80% of it
  - *Brown adipose tissue:* involved in thermogenesis
    - Numerous mitochondria, cytochromes → brown colour
    - Important in new-borns and hibernating animals

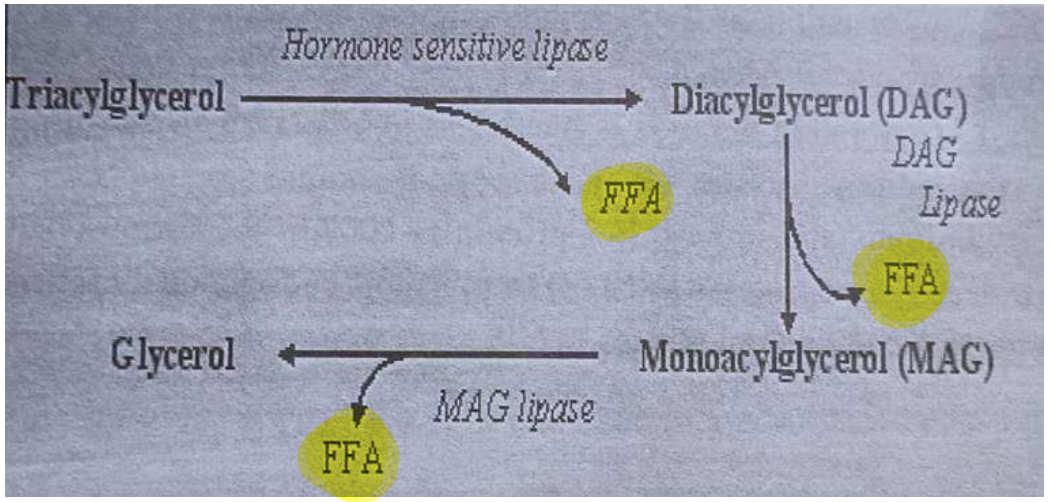
- Thermogenesis
  - Process in which heat is liberated by uncoupling oxidation from phosphorylation → energy is released as heat
    - Occurs due to presences of uncoupling protein (thermogenin)

Process of mobilization of stored fats

بدل يتخزن الـ (Fat) في الـ (subcuteneous) بتتحرك وبتظهر في الدم

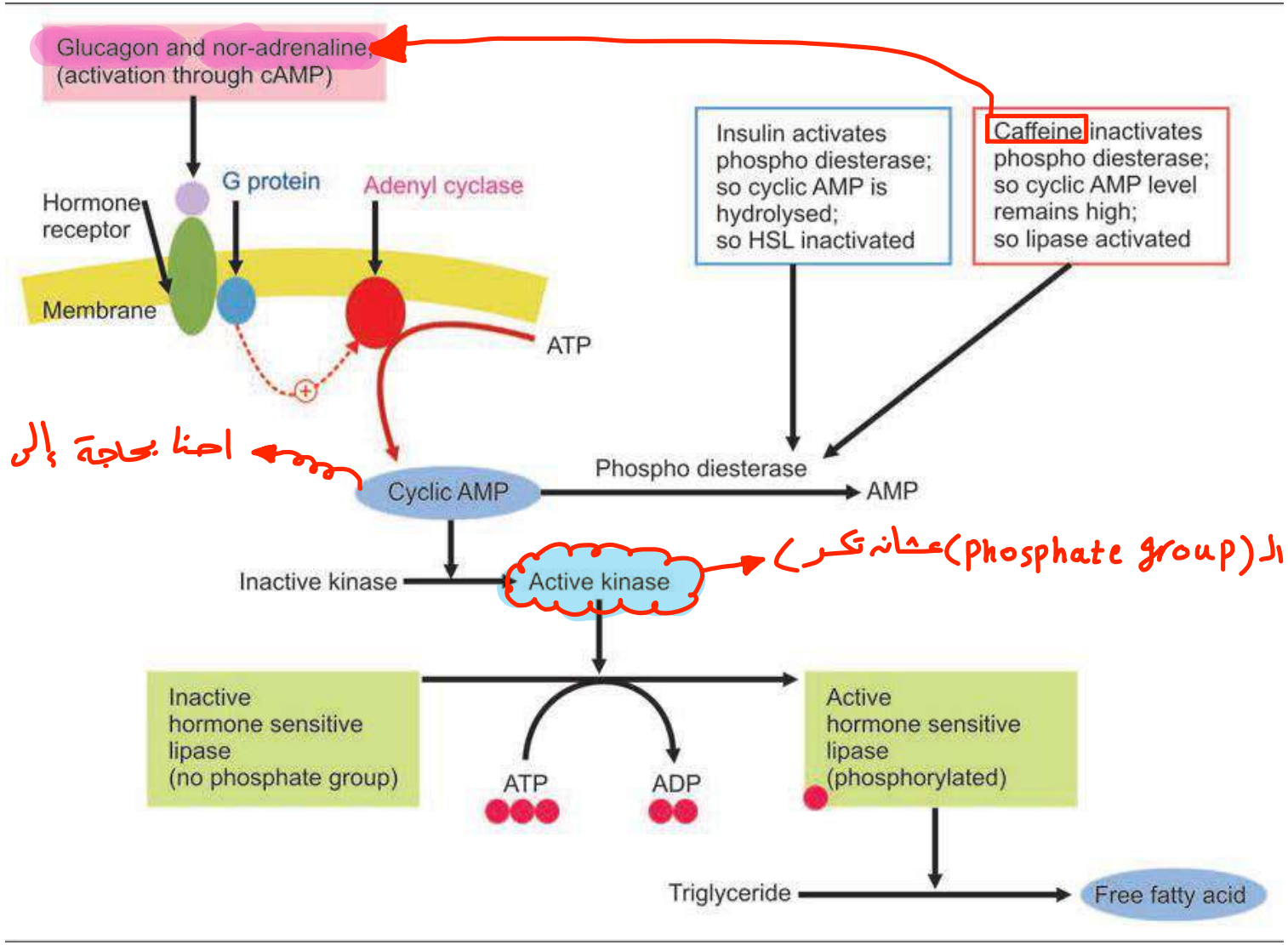
- **Lipolysis:** process of appearance of FAs in blood during fasting is due to mobilization of fat stores
- This is via hydrolytic release of FAs from glycerol in TAG (3 FA, 1 Glycerol) ممكن تتحول (glucose) منها بالـ (Gluconeogenesis) وبعدين تحرق
- Initiated by hormone sensitive lipase (removes FAs from carbon 1 and/or carbon 3 of TAG) (بكسر الـ (TAG))
- Additional lipases remove the remaining FAs from diacylglycerol or monoacylglycerol

(لما تكسر الـ (TAG) رح تحصل على طاقة منه:)



HSL is active in a phosphorelated form
- activated by Glucagon
- inhibited by insulin

Regulation of hormone sensitive lipase



احنا بحاجة إلى (cyclicAMP) عشانه (HSL) الـ

(أنت محتاجة عشانه تضيف الـ(Phosphate group) عشانه تكسر)

الـ (Glycerol) اللي بطلع ما بتقدر تستغله إلا عن طريق (Glycerol Kinase) اللي بعمله (Activation) بالـ (Gluconeogenesis)

- Fatty acids are stored in adipose tissue as TAG
- TAG are the major fuel storage reserve.
- Lipolysis is the hydrolysis of stored TAG in adipose tissue into glycerol and FA

glycerol

Liver is the only organ that contain a glycerokinase
Other tissues can not metabolize glycerol
Glycerol phosphate is formed in liver to form TAG or can be converted to DHAP (gluconeogenesis)

FFA

FFA are released to blood and carried by albumin to the tissues where it is oxidized for energy

Fatty acids oxidation (تكسير الـ (FA))

- The main pathway for FA oxidation is present in the **mitochondria** and known as **β-oxidation**
  (التكسير يصير على (C - β))

- **Other specified pathways are:**
  - α-oxidation of FA
  - ω-oxidation

(أحوال أصعب منه (β) لكنه لهم استخدام في بعض الأحيان)

β-oxidation of fatty acids

- **Site:**

All cells containing mitochondria (it isn't happens in the RBCs)

• Remember sites of: Glycolysis in cytosol / gluconeogenesis (جزء كبير في الـ cytosol) بس في منه بالـ (mitochondria)

FA Synthesis in cytosol / Krebs cycle and β-oxidation in mitochondria / Oxidative phosphorelation Mitochondria

- **Steps:**

Several enzymes, known collectively as **"FA oxidase"** are found in the mitochondrial matrix adjacent to citric acid cycle

(Acetyl CoA) تنتج

(Krebs cycle) بتروح على

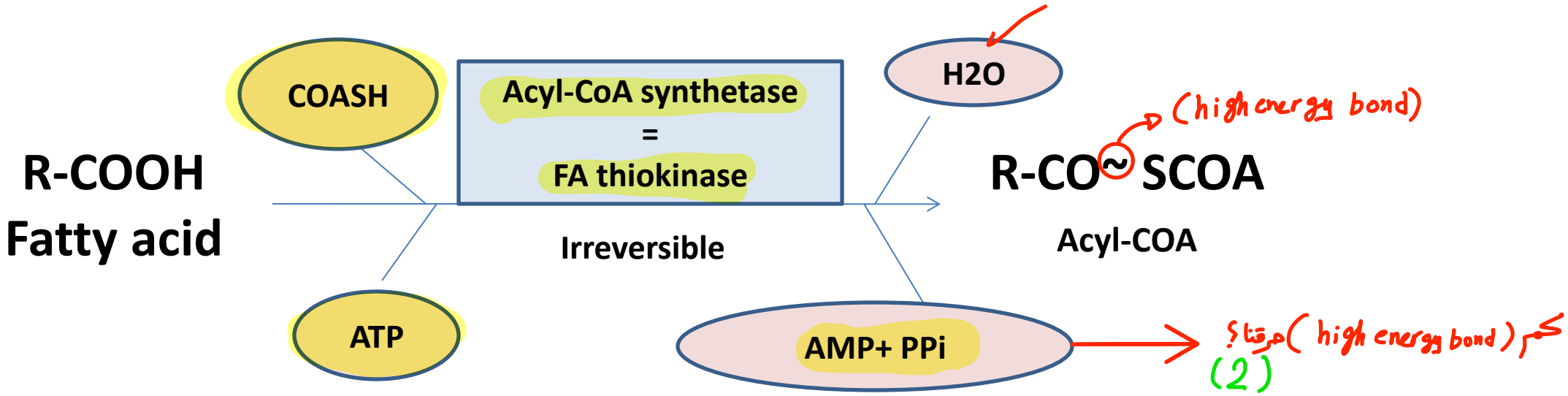
Steps:

1- Activation of FA to acyl-CoA

2-Transport of acyl-CoA through mitochondrial membrane by the **carnitine shuttle**

3-Oxidation of acyl-CoA inside the mitochondrial matrix

1- Activation of FA



Coenzyme required: CoASH

Energy required:

ATP which converted into AMP & PPi (pyrophosphate)

The PPi is hydrolyzed by inorganic pyrophosphatase with the loss of further high-energy phosphates

So, **the total loss, two "high" energy phosphates**.

Fate of activated FAs

- لما تعمل (β-oxidation) بتنتج كثير طاقة.

- If energy charge of cell is low
  - Activated acyl coA will be moved to mitochondrial matrix by carnitine shuttle
    → **FA oxidation** (β-oxidation) → ATP Synthesis

- If energy charge of cell is high (ما بحتاج أصنع ATP)
  - FA synthesis is favoured → movement of activated acyl coA is inhibited and it is used for TAG or membrane lipid synthesis in cytosol

(بكونه صار له (inhibited) الـ (β-oxidation))

2- Transport of acyl-CoA through the inner mitochondrial membrane

- After activation of FA to fatty acyl-CoA,:
  - short & medium chain FA (shorted then 12C) can penetrate the inner mitochondrial membrane for oxidation without any shuttle
  - Transport of long chain acyl-CoA **requires** the presence of **carnitine**. They are transported through the membrane as **acyl-carnitine**.

Carnitine (β-hydroxy-γ-trimethylammoniumbutyrate), $\{(CH_3)_3N^+-CH_2-CH(OH)-CH2-COO\}^-$ is present in all tissues & in excess in muscle

مش مطلوب معرفته

- **Carnitine acyl (palmitoyl)transferase-1 (CAT-1 or CPT-1),** present in the outer mitochondrial membrane, converts the long chain acyl-CoA to **acylcarnitine**

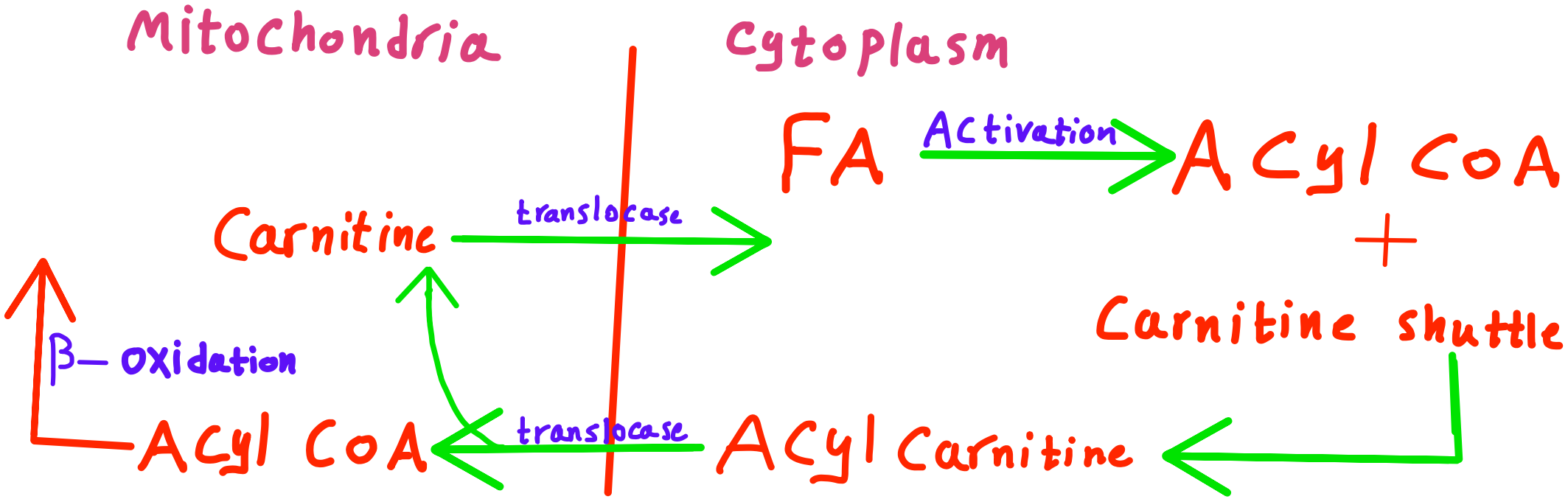
- Acylcarnitine is able to penetrate the inner membrane and gain access to the **β** –oxidation

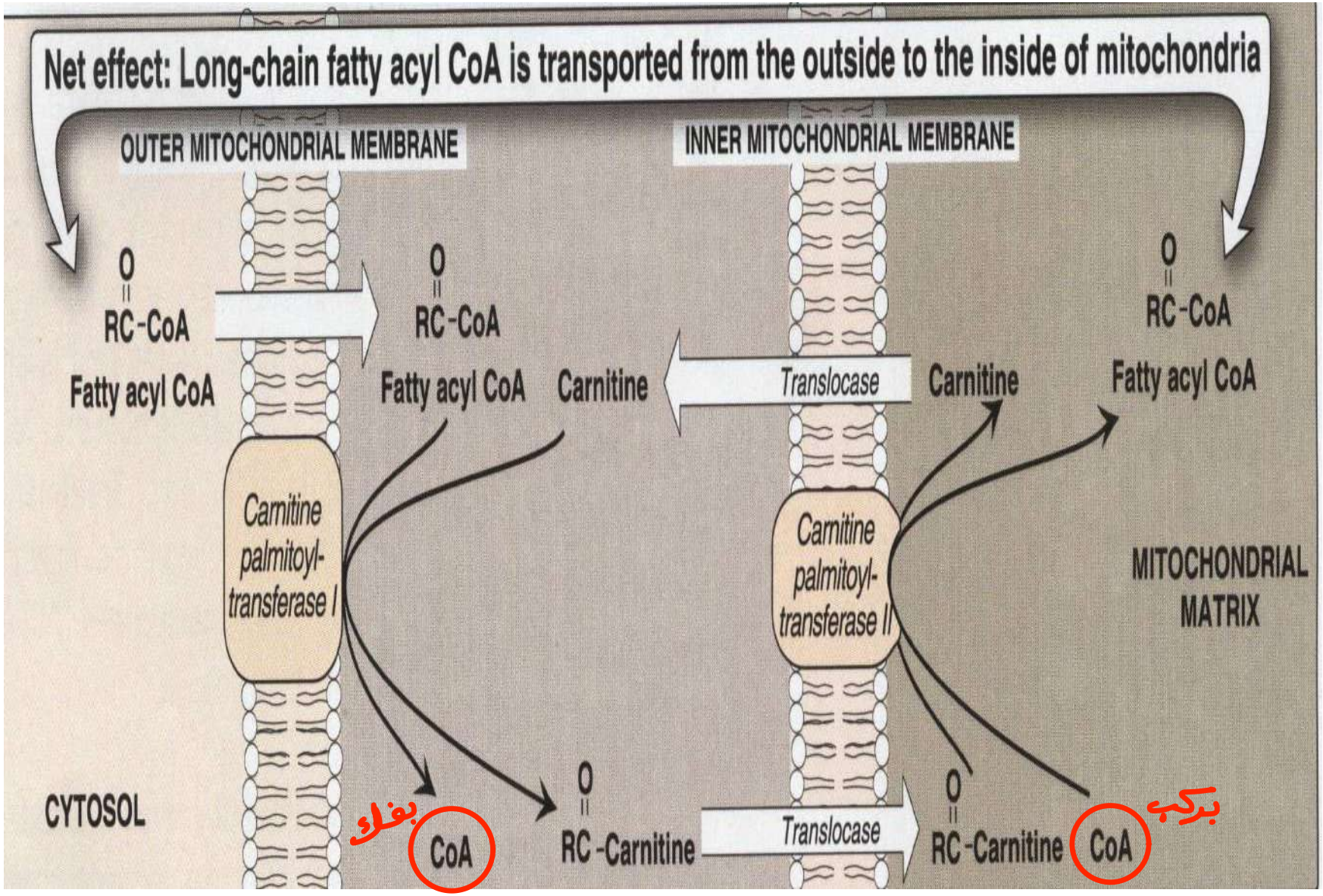
- Carnitine-acylcarnitine translocase acts as an inner membrane exchange transporter

- Acylcarnitine is transported in exchange with Carnitine

- Acylcarnitine then reacts with CoA, catalyzed by **carnitine acyl (palmitoyl)transferase-2 (CAT-2 or CPT-2),** and located on the inside of the inner membrane

- Acyl-CoA is reformed in the mitochondrial matrix (mitosome) and carnitine is liberated


Mitochondria
Cytoplasm
FA
Activation
Acyl CoA
+
Carnitine shuttle
Carnitine
translocase
β– oxidation
Acyl CoA
translocase
Acyl Carnitine


Net effect: Long-chain fatty acyl CoA is transported from the outside to the inside of mitochondria
OUTER MITOCHONDRIAL MEMBRANE
INNER MITOCHONDRIAL MEMBRANE
O
RC-CoA
Fatty acyl CoA
Carnitine palmitoyl-transferase I
Translocase
Carnitine palmitoyl-transferase II
MITOCHONDRIAL MATRIX
CYTOSOL
RC-Carnitine
CoA
يفك
يركب

– Short and medium fatty acids are found in milk and butter
(milk product)

Info about carnitine shuttle

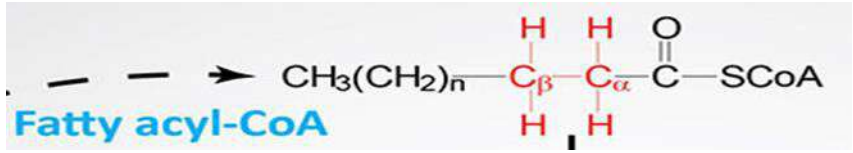
- Carnitine is primarily found in meat
- It can also be synthesized from amino acids lysine and methionine
  - Happens in liver and kidney
  - Does not happen in skeletal muscles or heart (totally dependent on exogenous carnitine or that distributed in blood)
- **Malonyl coA** inhibits CAT-1 preventing entry of long chain acyl groups from entering inner mitochondrial membrane → turn FA oxidation off
- Short and medium chain FA can cross inner mitochondrial membrane **without** shuttle
  - Their oxidation is not dependent on carnitine or inhibited by malonyl coA

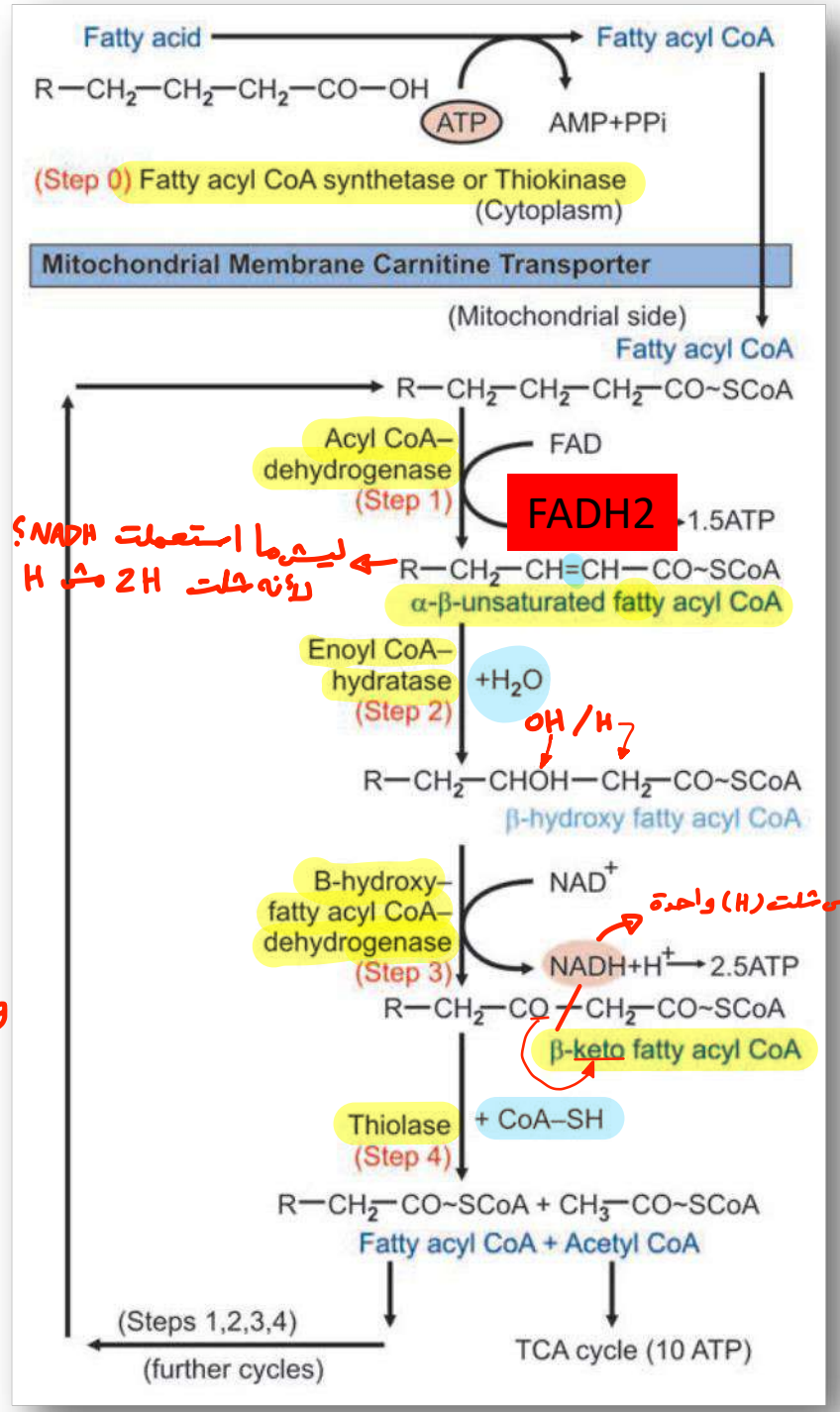
3-Oxidation of acyl-CoA

- The process is multi-cyclic
  - each cycle catalyzes removal of two carbons (from carboxyl end of acyl coA) as **active acetate (acetyl coA)**
    - & two reduced coenzymes are formed (**FADH2 & $NADH+H^+$**)

- Active acetate are oxidized in citric acid cycle to 2 CO2

- Reduced coenzymes produced by **β-oxidation and citric acid cycle are oxidized by electron transport chain (ETC) for synthesis of ATP**





* آخر خطوة بالتكسير برجع للأساسي (4C) والتي تتفكك إلى (2 Acetyl CoA)

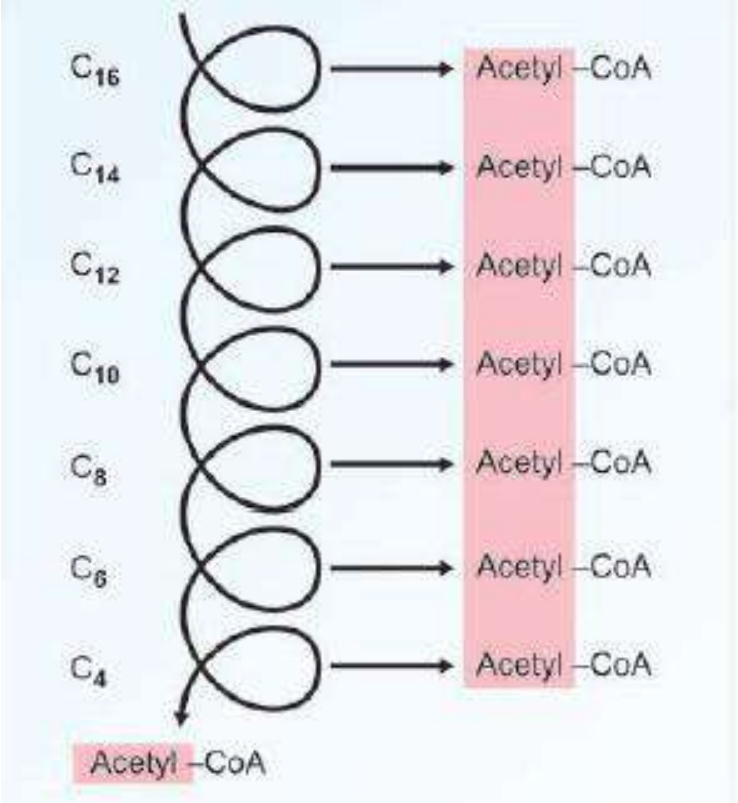
ولا تحتاج إلى دورة أخرى

16C

When one molecule of palmitate undergoes beta-oxidation, the net reaction is:

Palmitoyl CoA		8 Acetyl CoA
+ 7FAD		+ $7FADH_2$
+ $7NAD^+$	⟶	+ 7NADH
+ $7H_2O$		+ $7H^+$
+ 7HSCoA		7 cycles

ليش (7) عشانه



* لما تحسب عدد الدورات / NAD/FAD : ....

بتعتمد عدد الكربونات في الـ (FA) على (2) ثم تطرح (1)

على هذه الفكرة (سؤال، سؤالين، 3 أسئلة) في الإمتحان

سؤال في الإمتحان: احسب عدد الـ (ATP) الناتج من تكسير (TAG) المكون من (3palmitate and Glycerol) عن طريق الـ (β-oxidation) على النظام الجديد على افتراض أنه الـ (Glycerol) سينتج (DHAP) في (Gluconeogenesis)؟

1) تكسر الـ (TAG) إلى (1 Glycerol / 3 palmitate) واللتي لا تحتاج إلى طاقة ولا تنتجها

2) الـ (Glycerol) سيدخل في (Gluconeogenesis) فيستهلك (1 ATP) ليتوقف عند (DHAP)

3) كل (palmitate) الـ (Activation) يستهلك (2 ATP)، وهو رح يدخل في (7 cycles) وينتج (8 AcetylCoA)، (7 NADH)، (7 $FADH_2$) و (7 $FADH_2$ = 10.5 ATP / 7 NADH = 17.5 ATP)

الـ (8 AcetylCoA) سيدخلوا في (Krebs cycle) لينتج كل واحد منهم (10 ATP) = 8 X (80 ATP)

∴ الـ (palmitate) الواحد = 108 - 2 = 106، ولا ننا نتعامل مع (3 palmitate) نضرب الحاصل بـ (3) = 318

- لا ننسى الـ (-1 ATP) من الـ (Glycerol)

الحصلة:-

318 - 1 = 317

- بالنسبة للـ (Glycerol) إذا كانه من (1 TAG) فإنه من الممكن أنه يصرف في خيارين:

1) أنه ينتج (DHAP) فيستهلك (1 ATP) ويتوقف.

2) أنه لا يتوقف ويدخل في (Glycolysis) فينتج (1 ATP) (1ATP from Gluconeogenesis, and 2ATP from glycolysis)

- إذا استخدمنا (2 Glycerol) فإنه:

إذا انتج (Glucose) سيستهلك (2 ATP)

إذا انتج (Glucose) ثم عمل له (Glycolysis) سينتج (0 ATP) zero

Calculation of energy yielded from complete oxidation of FA (e.g. palmitic acid):

- Palmitic acid is C16, saturated FA
- Palmitic acid is activated to palmityl-CoA = (-2 ATP).
- Complete oxidation of palmityl-CoA gives **8** mol of acetyl-CoA (16/2 = 8) through **7** β oxidation cycles.
- Each turn of β oxidation gives FADH2 & NADH+H+ which by respiratory chain give 5 ATP (old system), 4 (new system)
- So 7 cycles x 5 ATP = 35 ATP (old) or
- 7 cycles x 4 ATP = 28 ATP (new)

- Each acetyl-CoA by citric acid cycle gives **12** ATP (old system),
- so 8 acetyl-CoA x 12 ATP= **96** ATP (old system)
- The total gain : 96 + 35 = 131 ATP (old system)
- The net gain : 131- 2 = **129** ATP (old system)

Exam question: what is total net energy of complete oxidation of a fatty acid with 18 carbons (for example) ∴120ATP

New system

8 acetyl CoA × 10	=	80 ATP
7 $FADH_2$ × 1.5	=	10.5 ATP
7 NADH × 2.5	=	17.5 ATP
Gross total	=	108 ATP
Net yield	**= 108–2 = 106 ATP**	

Importance of β oxidation:

- 1- source of energy during fasting
- 2- source of acetyl-CoA which can be converted to other important compounds as cholesterol and acetyl choline

Regulation of β oxidation:

(1) feeding status:

free / nonesterfide : بقدروا يعملوك شومبك

- Fasting increases lipolysis →release of FFA from adipose tissue → ↑↑ FA in tissues → stimulation of β oxidation

- CHO feeding → ↑ insulin → inhibition of lipolysis in adipose tissue → ↓↓ FFA in tissues → inhibition of β oxidation

Regulation of beta oxidation

- **Rate limiting step** of beta oxidation is formation of fatty acyl carnitine (catalysed by CAT1)
- Malonyl coA (1st intermediate of synthesis of FA) allosterically inhibits CAT1
- **In fed state:**
  - ↑ insulin/glucagon ratio → fatty acid synthesis is promoted in liver (insulin activates acetyl coA carboxylase) → ↑ malonyl coA → inhibition of CAT1 → ↓ beta oxidation
- **In starvation:**
  - ↓ insulin/glucagon ratio → glucagon inhibits acetyl coA carboxylase → ↓ malonyl coA → release inhibition of CAT1 → ↑ beta oxidation
- Hormone sensitive lipase is activated by phosphorylation (glucagon)
  - Its activity is low when insulin levels are high

(2) Energy needs by cells:

(Coenzymes for dehydrogenases in β-oxidation) يعني بكونه ماعندهم القدرة أنهم يشتغلوا كـ

- ↑↑ ATP → ↓↓ respiratory chain → FADH2 and NADH+H+ remain reduced → inhibition of DH "dehydrogenases" of β oxidation

- ↓↓ ATP & ↑ ADP and Pi → ↑↑ respiratory chain so, FAD& NAD+ are oxidized → stimulation of DH of β oxidation

Notes:

- Oxidation of FA supplies **NADH** and **ATP** **required for gluconeogenisis** and supplies **excess acetyl CoA.**

عندك كثير فرح تكبير (Pyrovate) منه التحويل له
(Pyrovate) وبتحول منه (Oxalo acetate) إلى

- Acetyl CoA allosterically activates pyruvate carboxylase and inhibits pyruvate dehydrogenase. **This directs pyruvate towards gluconeogenesis rather than oxidation.**

(Oxaloacetate) بعطيك

(Acetyl CoA) ما بدنا ننتج

- **If FA oxidation is inhibited, gluconeogenesis is inhibited.**

(لأنه لو ما جبت طاقة ركيت بدي أصنع جلوكوز، الإشي اللي بده طاقة)

- pyrovate decarboxilase gives Acetyl CoA

Oxidation of FA with an odd number of C atoms:

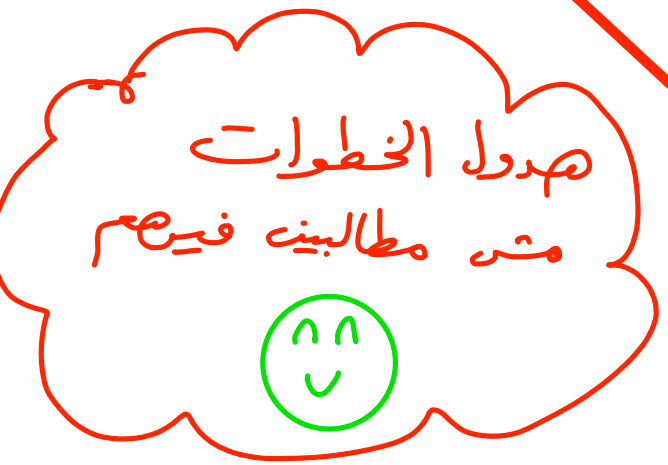
- Odd chain FA are oxidized by β oxidation producing acetyl-CoA but only at the last step one **propionyl-CoA** (3C) is produced

- Propionyl CoA can be converted to methyl malonyl CoA which is converted to succinyl-CoA → citric acid cycle → oxaloacetate → glucose

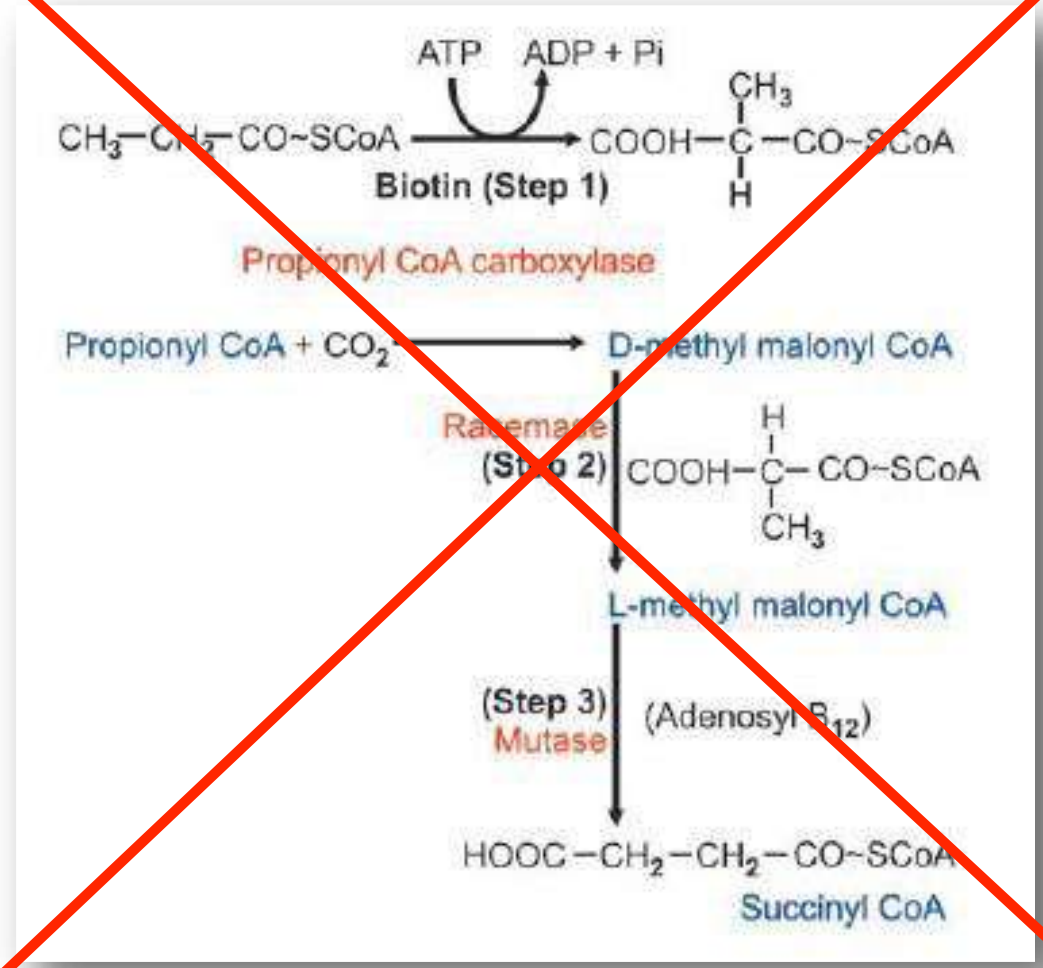
This is the only mechanism by which Fatty acids are converted to glucose

- 3 C units from odd chain FA are glucogenic

- Cow's milk contains significant quantity of odd chain FAs



Metabolism of propionyl-CoA



Metabolic disorders of FA oxidation:

- These include deficiency of carnitine, CPT1, CPT2 and acyl CoA dehydrogenase
  - → impairment of FA oxidation, fasting hypoglycemia (due to decreased gluconeogenesis as well as increased uptake of glucose by muscles and heart), muscle weakness , and fatty liver, finally produce coma and death

المشكلة أنه الـ (gluconeogenesis) مش شغال — فأنت بعد عندك مشكلة بس بخلصت الـ (Glycogen stores)

- Patients with deficiency of carnitine, CPT1, or CPT2 should avoid prolonged fasting & may benefit from the ingestion of fats rich in medium chain fatty acids

لأنه بقوتوا على الـ(mitochondria) بدون (shuttle)

α-oxidation of FA

- It is a **minor** pathway for the oxidation of FA that have methyl group in the β carbon , e.g. phytanic acid (found in animal and milk fats)
- The site of oxidation is the peroxisome of brain and liver mainly
- **α-oxidation occurs in the α- position because the** β carbon is occupied by a methyl group
- **The α carbon is oxidized and removed as CO2, now the methyl group is at the α position (no energy produced, no coA needed) and the** β carbon is free to undergo β oxidation **forming propionyl-CoA in the last turn**

لأنك كسرت كربونه وحدة
فأنت حولت منه even
إلى odd

فعفه رح تضل تعمل
(β-oxidation) لهيك لحد متكونه عندك امكانية تعمل

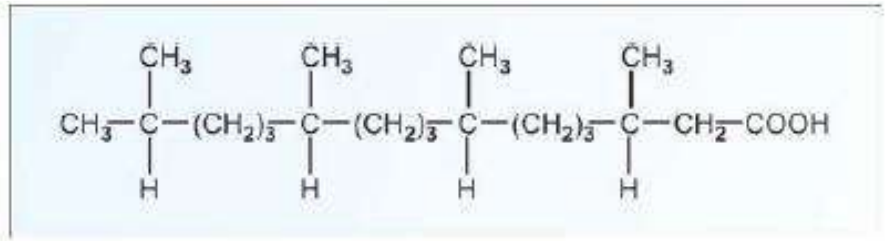


Fig. 11.12. Phytanic acid

لكنه ممكن تجيب

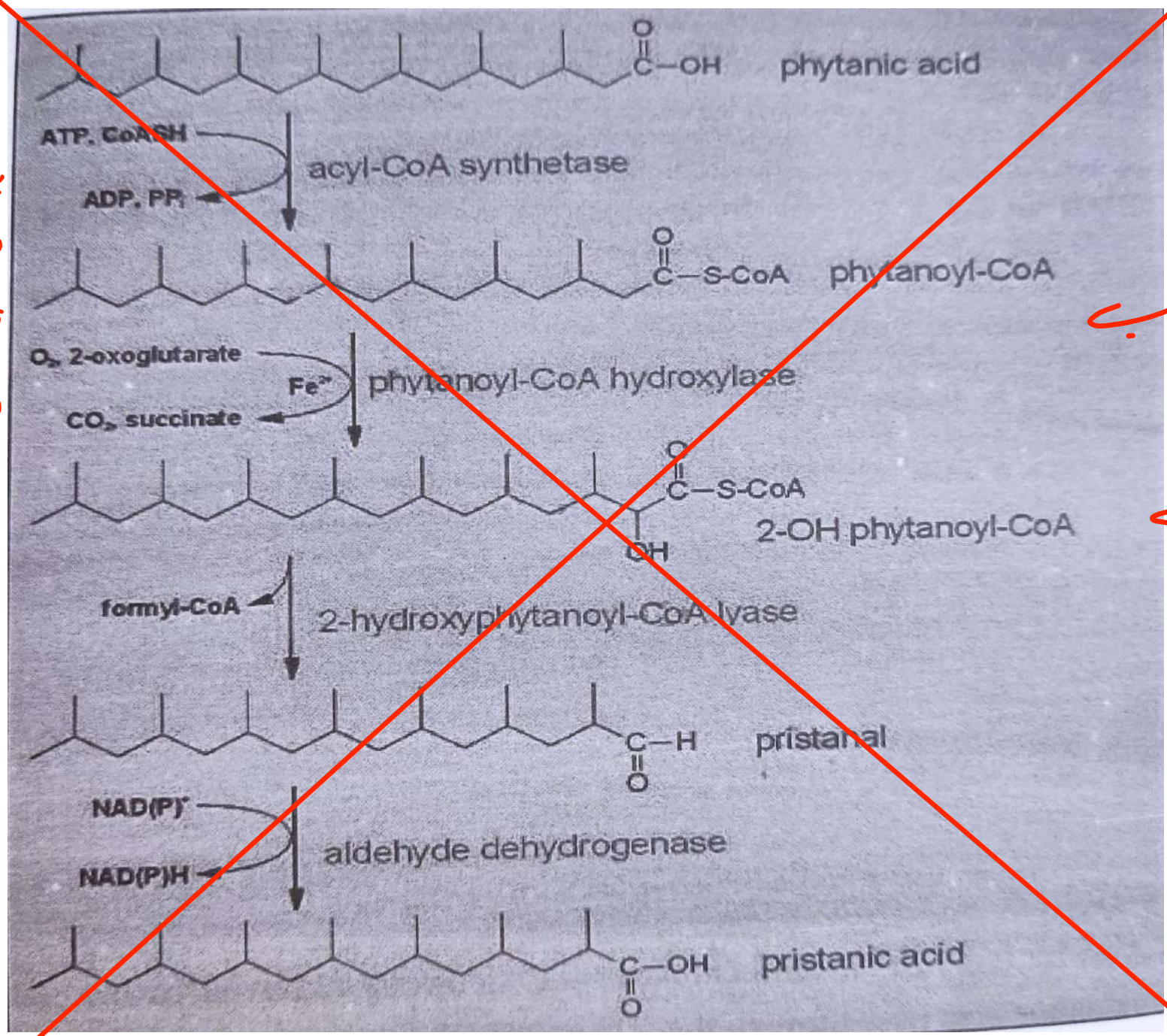
بالإمتحان صورة ويقلك أنه

هذا هو (FA) وأنت لازم

تنتبه للـ (methyl group)

وتعرف لحالك أنها

(α-oxidation of FA)



مش مطالب

بالخطوات

*Refsum's disease:

- Rare autosomal recessive disorder
- Defect in alpha oxidation
- Due to congenital deficiency of enzyme system of **α-oxidation leading to accumulation of large amounts of phytanic acid in the brain, liver and blood**

Symptoms

– **Polyneuropathy, cerebellar ataxia, deafness (الصمم) and blindness (العمى) occur at young age**

Treatment: dietary restriction to halt disease progression (لوقف)

(phytanic acid) يقلل تناول ال

(سؤال في الإمتحان)

- ***Ataxia*** *is a neurological sign consisting of lack of voluntary coordination of muscle movements that can include gait abnormality, speech changes, and abnormalities in eye movements. Ataxia is a clinical manifestation indicating dysfunction of the parts of the nervous system that coordinate movement, such as the cerebellum.*

ω-oxidation

- It is a minor pathway for FA oxidation
- Site : in the liver endoplasmic reticulum (involves cytochrome p-450)

- The oxidation occurs at the terminal methyl group (**ω carbon)→ formation of a dicarboxylic acid**

- **The dicarboxylic acid is oxidized from both ends by β oxidation liberating acetyl-CoA**

- **It ends with the formation of adipic acid (C6) which is excreted in urine.**

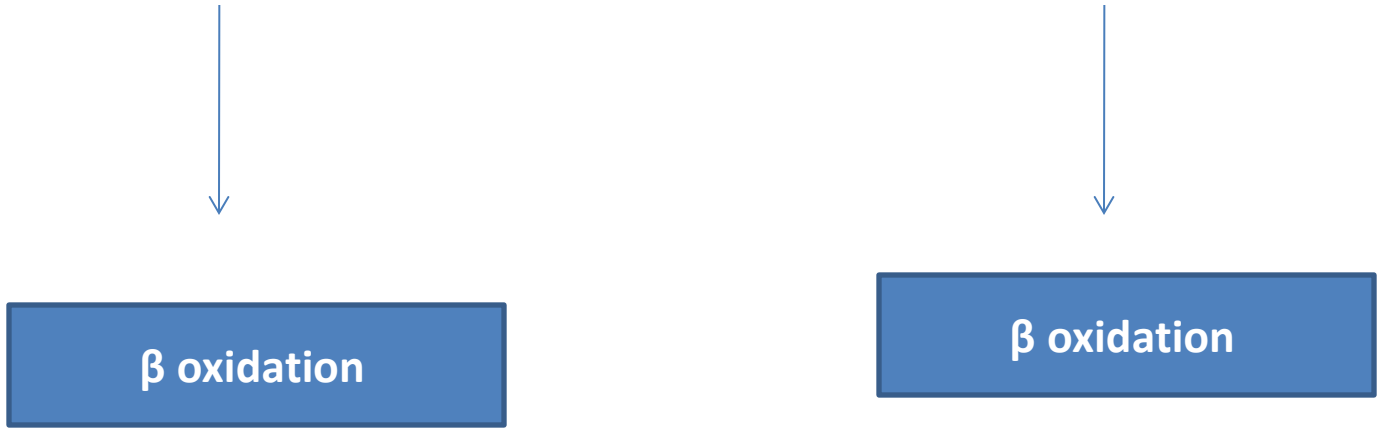
ا ل (oxidation) بصير على الجهتين فبعمل (Dicarboxylic acid) فبدل ميكونه عندك (carboxyl group) على جهة

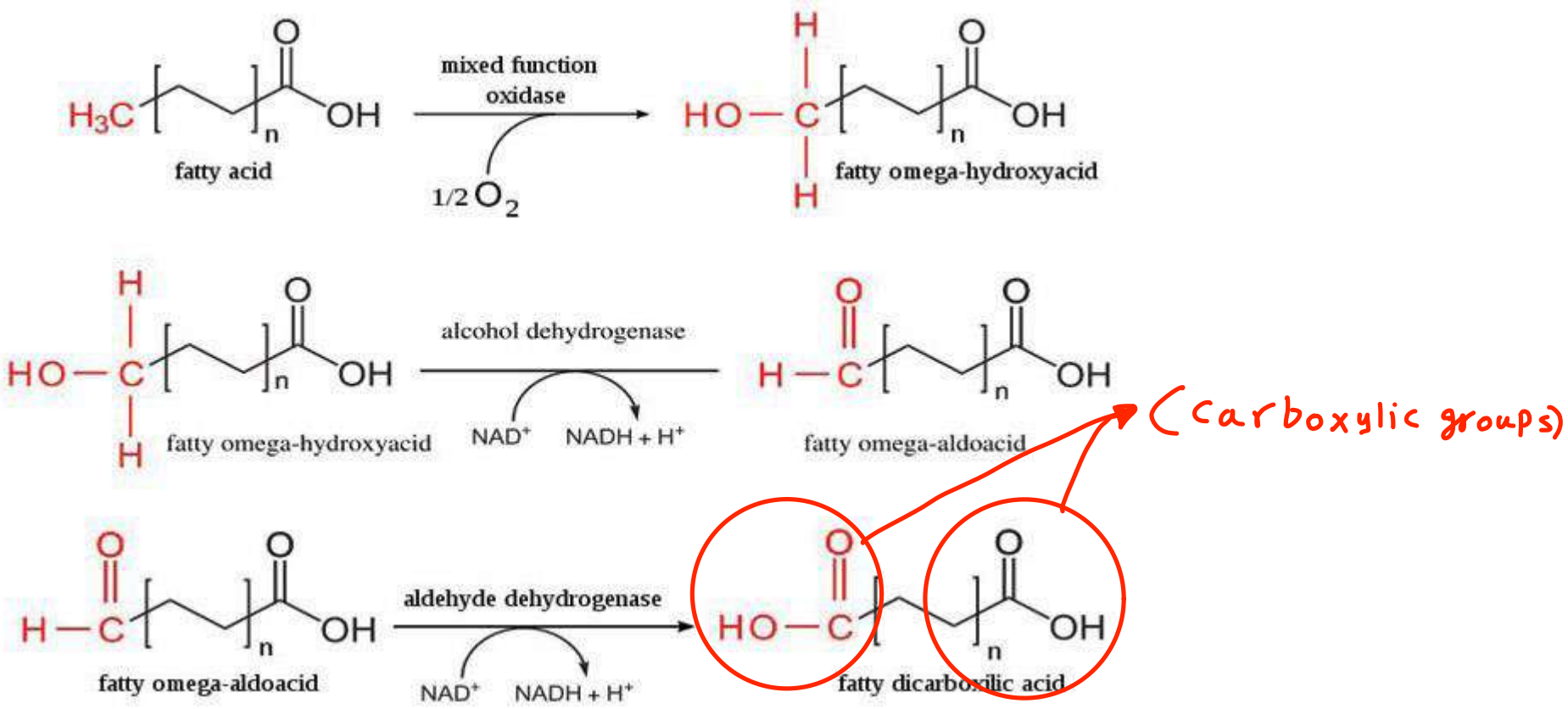
و (methyl group) على جهة و بصير عندك (carboxyl group) على الجهتين، فبتقدر تستعمل الجهتين وتعمل (β-oxidation)

* (ω-oxidation) ما اله أي أهمية طالما يكون الـ(β-oxi) شغال كويس

- It occurs to average chain length FA (10-14 C).
- It produces acetyl-CoA faster. (لأنه بيشتغل β-oxidation بشكل أسرع)

HOOC-CH2-CH2----------CH2-CH2-COOH





Omega oxidation is upregulated when beta oxidation is defective as is seen with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

جاي عليهم حالات بالإمتحان

Introduction- ketone bodies (هيه ٣ حغلات)

- Acetoacetate, β-hydroxyl butyrate & acetone are collectively called ketone bodies
- **Ketogenesis**: formation of ketone bodies (occurs in liver)
- **Ketolysis**: utilization of ketone bodies as fuel (occurs in extrahepatic tissues)
- Under normal conditions, production of ketone bodies is at relatively low rate

أنت مش محتاج الهم لأنه بالعادة عندك جلوكوز ولو مافي جلوكوز المفروض يكونه عندك (FA)

- Increased ketone bodies is known as **ketosis** while high blood level is known as **ketonemia**

Metabolism of ketone bodies

- Fats are burned in the fire of carbohydrates
  - Acetyl coA formed from FAs enters Krebs → oxidised only when oxaloacetate is present (oxaloacetate comes mainly from CHO)

- During starvation and DM, acetyl coA takes the alternate fate of formation of ketone bodies (ketogenesis)
  - This allows **heart** and skeletal muscle (to some extent, increased use in fasting) to use ketone bodies (ketolysis) as major source of energy → preserving limited glucose supply for brain and RBCs

- Ketone bodies are water soluble (فيهم ينزلوا بالـ(urine/ بمرضه السكري بنقدر نقيسهم جوا الـ(urine)
  - Transported across inner mitochondrial membrane, blood brain barrier and cell membranes
    - » Used as fuel for a variety of tissues including CNS
    - » Preferred substrates for aerobic heart and muscles (to some extent, increased use in fasting)

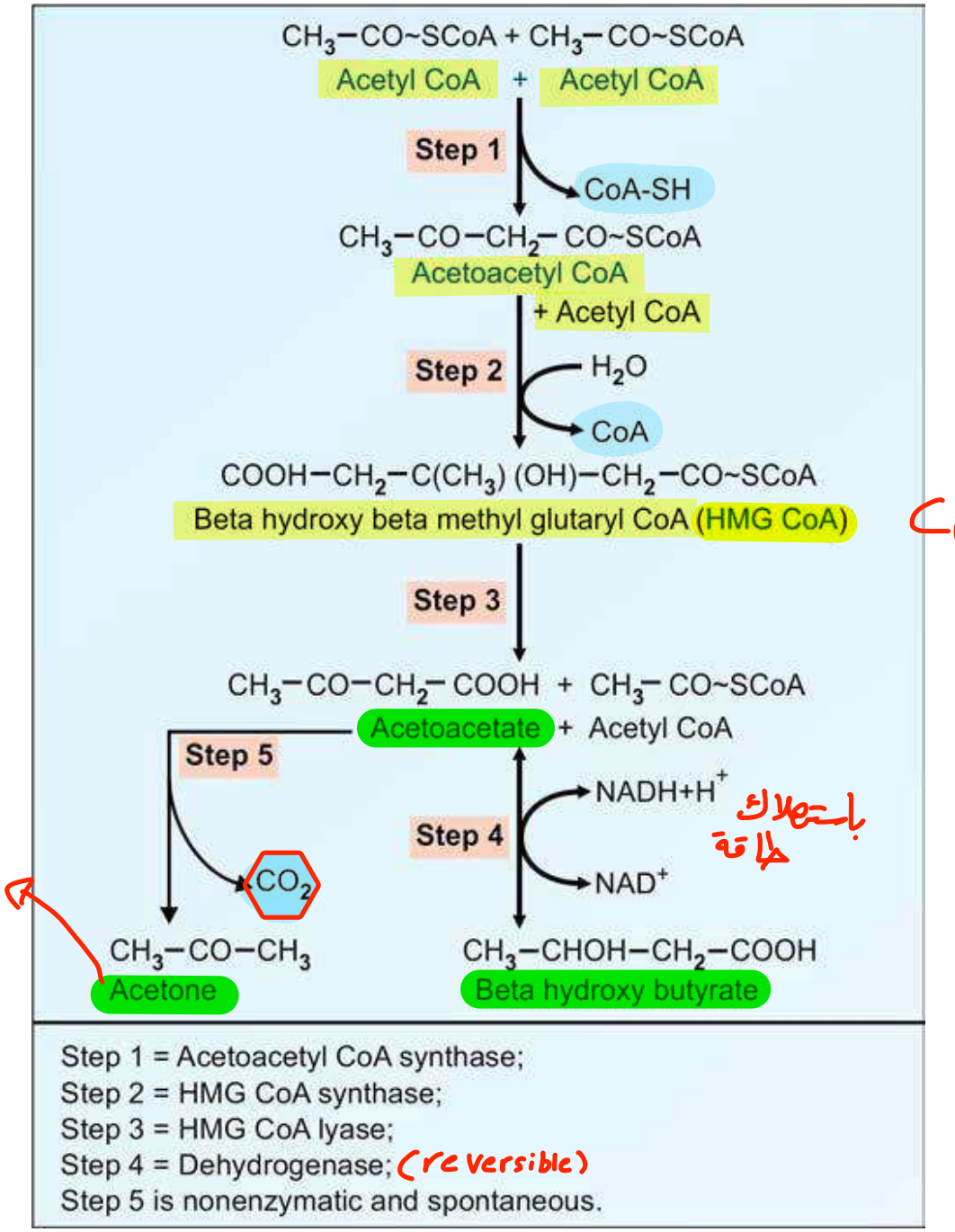
Ketogenesis

- Acetoacetate is primary ketone body
- Synthesised **exclusively** in liver **mitochondria**
- 4 Steps:
  - Condensation
  - Production of HMG coA
  - Lysis
  - Reduction
  - Spontaneous decarboxylation

Produce acetone

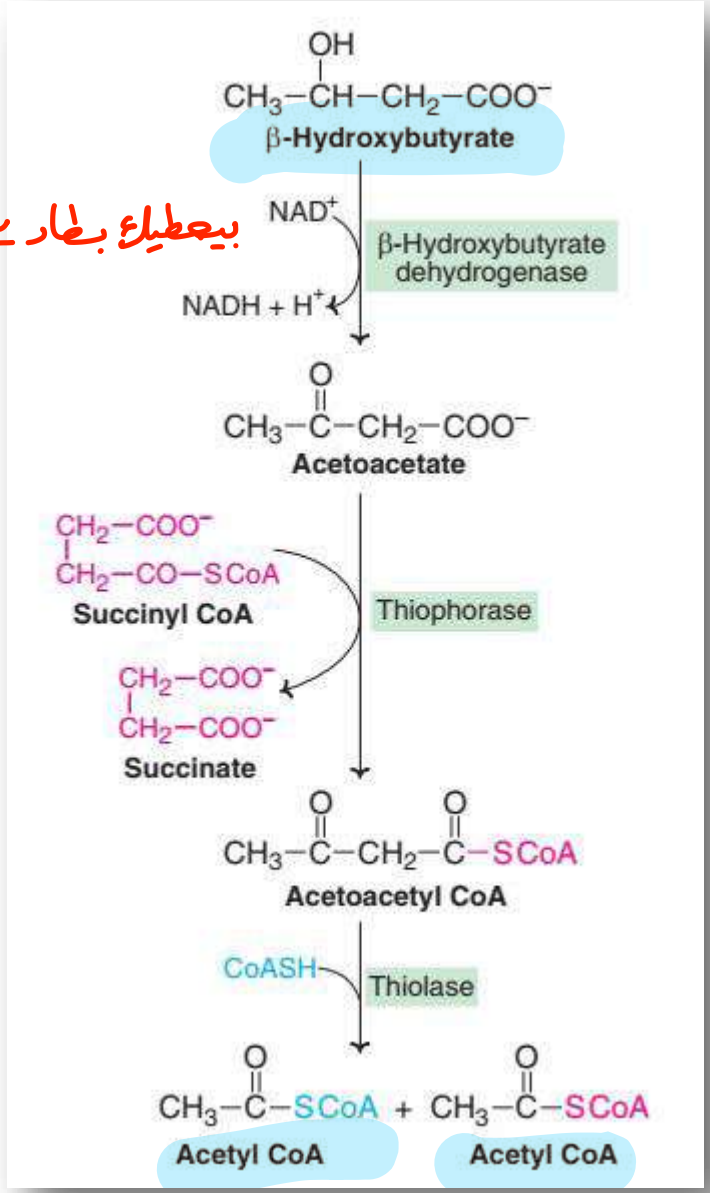
له رائحة قوية بتشمها عند المرضى سكري

HMG coA synthase is rate limiting step in synthesis of ketone bodies and is present in significant quantities only in liver

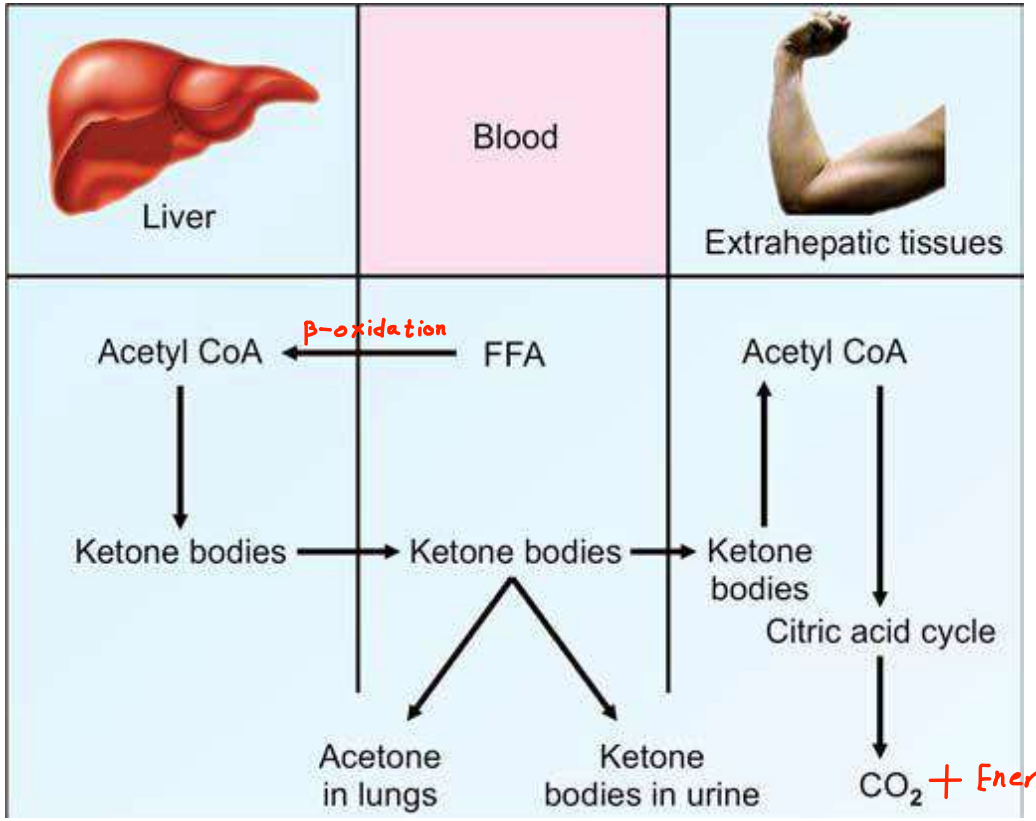


Ketolysis

- Ketone bodies are formed in liver but utilized in extrahepatic tissues
- Heart muscle, renal cortex sometimes prefer ketone bodies to glucose as fuel
- Muscle can also utilize ketone bodies



Fate of ketone bodies



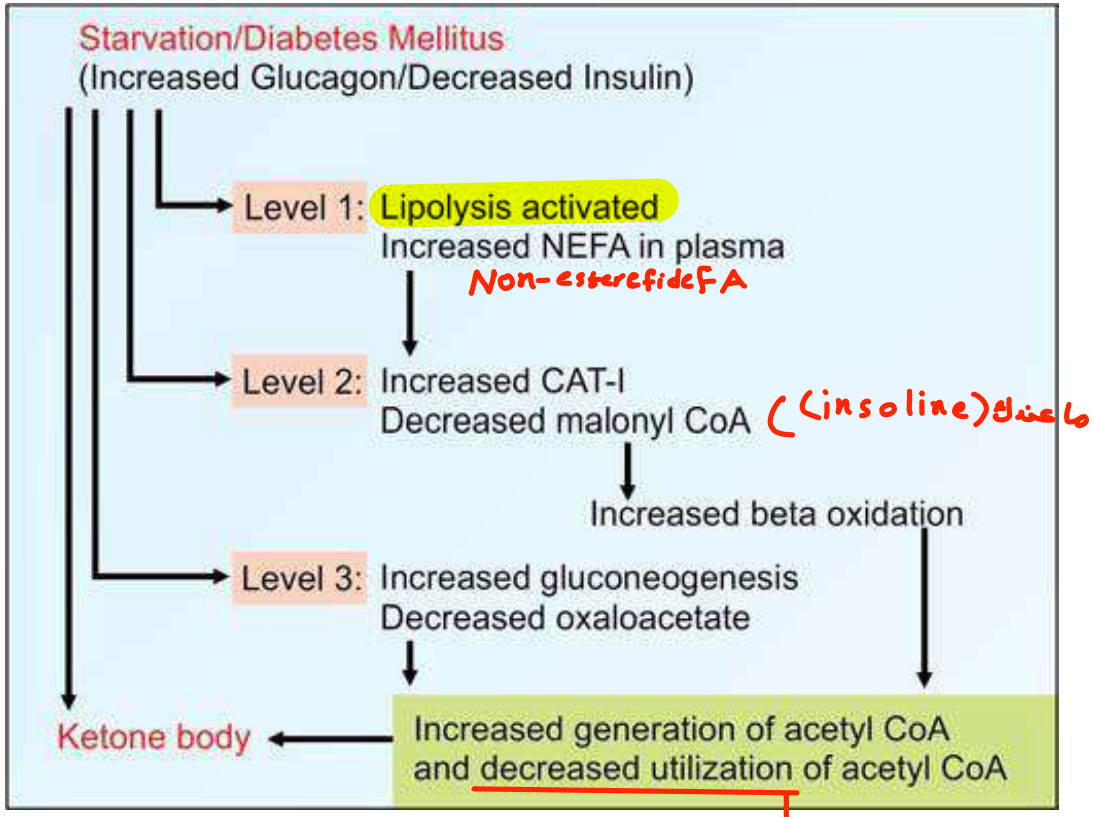
Ketosis

- Causes
  - **Uncontrolled DM:** most common cause of ketosis
    - » Glucose is plenty but **deficiency of insulin** → accelerated lipolysis → increased acetyl coA
      - Enhanced gluconeogenesis restricts oxidation of acetyl coA in TCA as there is less oxaloacetate
  - **Starvation:** dietary supply of glucose reduced → oxaloacetate channelled to gluconeogenesis, increased lipolysis to provide fuel, excess acetyl coA converted to ketone bodies
    - Hyperemesis in pregnancy may also lead to starvation like condition → ketosis
      الحامل اللي بتستفرغ كتير

- Explanation of ketogenesis
  - Starvation and DM: glucagon is increased →
    - Inhibits glycolysis
    - Activates gluconeogenesis
    - Activates lipolysis
    - Decreases malonyl coA (يعتمد على الـ insoline)
    - Stimulates ketogensis (high glucagon/ insulin ratio is ketogenic)

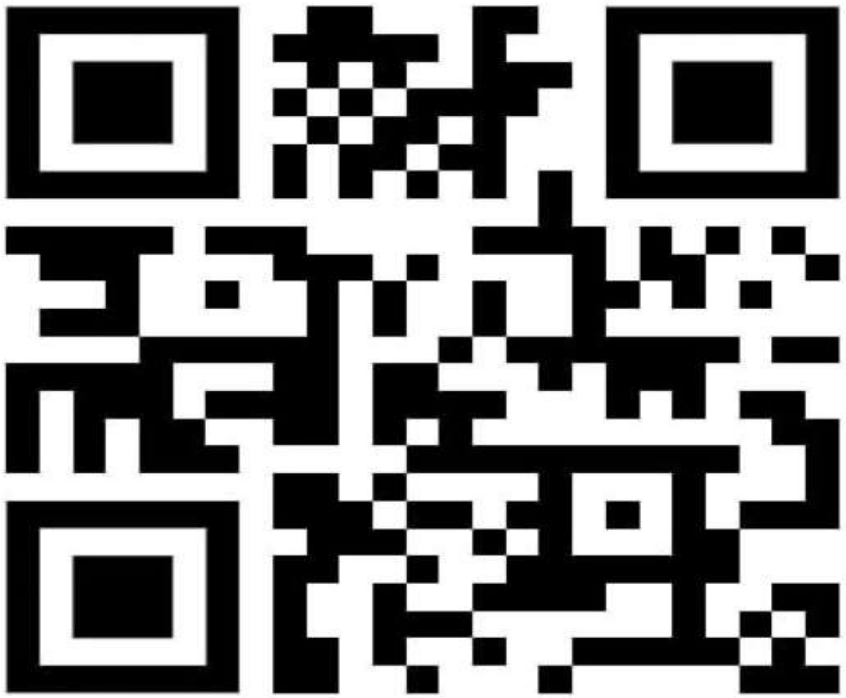
Insulin has opposite effect

Ketosis



Salient Features of Ketosis

1. **Metabolic acidosis.** Acetoacetate and beta-hydroxy butyrate are acids. When they accumulate, metabolic acidosis results. (see Chapter 29).
2. **Reduced buffers.** The plasma bicarbonate is used up for buffering of these acids.
3. **Kussmaul's respiration.** Patients will have typical acidotic breathing (see Chapter 24) due to compensatory hyperventilation.
4. **Smell of acetone** in patient's breath.
5. **Osmotic diuresis** induced by ketonuria may lead to dehydration.
6. **Sodium loss.** The ketone bodies are excreted in urine as their sodium salt, leading to loss of cations from the body.
7. **Dehydration.** The sodium loss further aggravates the dehydration.
8. **Coma.** Hypokalemia, dehydration and acidosis are contributing for the lethal effect of ketosis.



ستجدون في هذا الرابط قناة التلغرام للنادي الطبي الذي
سيتم تحميل جميع اعمال الفريق العلمي واخبار الكلية وكل
شيء مهم حتى تتمكنوا من معرفة كل شيء عن طريق تلجرام