Fatty acid Catabolism (Oxidation)

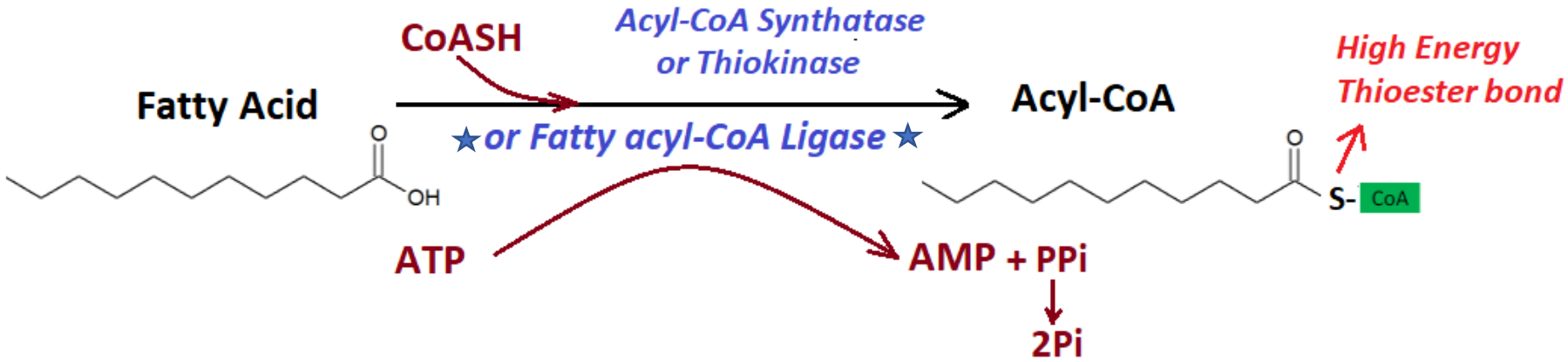
- Fatty acids are an Important source of energy used mainly by Liver and Muscles but NOT brain or RBCs
- Fatty acids are stored as Triglyceride in adipocytes where each 3 fatty acids are esterified to one molecule of glycerol
- During fasting or starvation; body cells increase Utilization (استخدام) of fatty acids as source of energy, so triglycerides are hydrolyzed by hormone sensitive lipase/DAG and MAG lipases to release free fatty acids, which then carried in blood by albumin to body tissue
- Fatty acids (Fat) store more energy than carbohydrate or protein (fat is a long term energy storage)
- Fat is the major storage form of energy (most of your energy is stored as fat)
- Carbohydrate release energy quickly but not a major form of energy storage (maximum 500 mg of glucose is stored as glycogen)

يعني معظم الطاقة اللي انتا مخزنها بجسمك مخزنة على شكل دهون مش كربوهيدرات
الدهون وزنها خفيف وفيها طاقة عالية
افضل الك تحمل بجسمك كيلوغرام دهون من انك تحمل كيلوغرام كربوهيدرات لانو
كيلوغرام الدهون بحتوي على اكثر من ضعف الطاقة الموجودة بكيلوغرام الكربوهيدرات

Fatty acid Catabolism

- First step in fatty acid catabolism called **Activation:**

binding the fatty acid carboxyl-head to CoA by thioester bond



عند حساب ال ATP تعتبر
ان ال Activation step
تستهلك 2ATP

ATP→AMP + 2Pi = 2ATP→2ADP +2Pi

2ATP تكافئ اسهلاك

Note: Acyl-CoA is a general name FA-CoA

Palmitate (16:0) → Palmitoyl-CoA Stearate (18:0) → Stearyl-CoA Acetate (2:0) → Acetyl-CoA

The Activation Step

Long Chain Fatty acids (LCFA)

Location: outer Mitochondrial membrane at Cytosolic Side

in the Cytosol

من جهة السيتوبلازم

Short and Medium chain Fatty acids such as Milk Fat

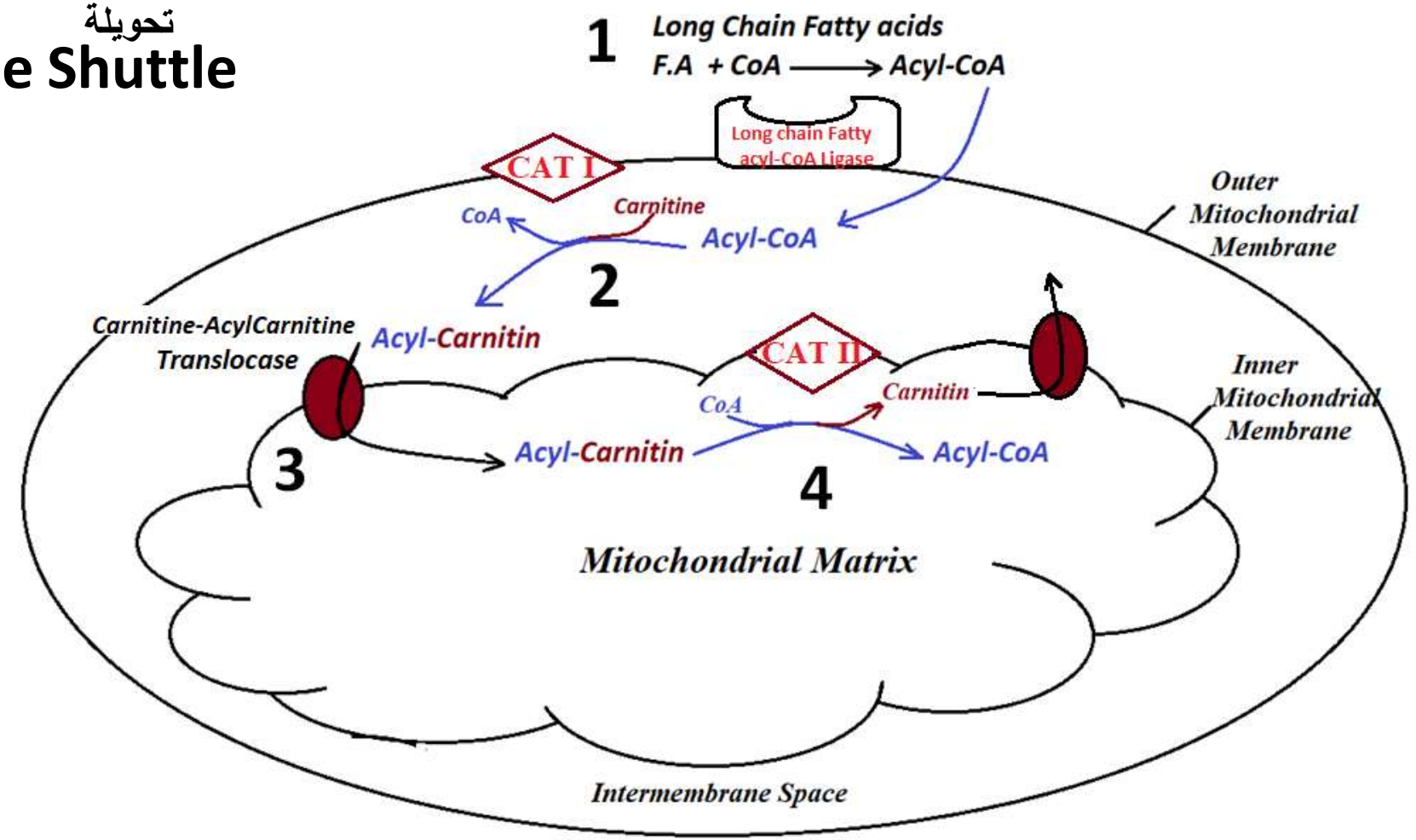
Location: Mitochondial Matrix

- **The rest of steps occur in the mitochondrial matrix, So Long chain Acyl-CoA should be transported to mitochondrial matrix**
- **BUT, the inner mitochondrial membrane is impermeable (غير منفذ) to long chain Acyl-CoA!! What we do???**

تحويلة

What we do?? Carnitine Shuttle

1. LCFA is activated in the cytosol forming Acyl-CoA
2. Long chain Acyl-CoA cross the outer mitochondrial membrane to the intermembrane space
3. ***CAT-I*** remove CoA and bind Carnitine forming Acyl-Carnitine
4. Acyl-Carnitine cross the inner membrane by special carrier called ***Carnitine-AcylCarnitine Translocase (Antiporter)***
5. In the matrix ***CAT-II*** remove Carnitine and bind CoA forming long chain Acyl-CoA in the matrix



CAT-I: Carnitine-Acyl Transferase I also called Carnitine Palmitoyl Transferase I (CPT I)

CAT-II: Carnitine-Acyl Transferase II also called Carnitine Palmitoyl Transferase II (CPT II)

تحويلة

This process called **Carnitin Shuttle** required only for catabolism of long chain fatty acids and it's the rate limiting step of catabolism of long chain fatty acids

Genetic Deficiency of CAT-I and CAT-II

Deficiency of CAT-I:

- Affect mainly Liver
- Low energy production during fasting; inhibiting gluconeogenesis leading to sever hypoglycemia, coma (غيبوبة)

Q: Expect what will happen if someone has carnitine deficiency or Carnitine-Acyl-Carnitine Translocase genetic deficiency?

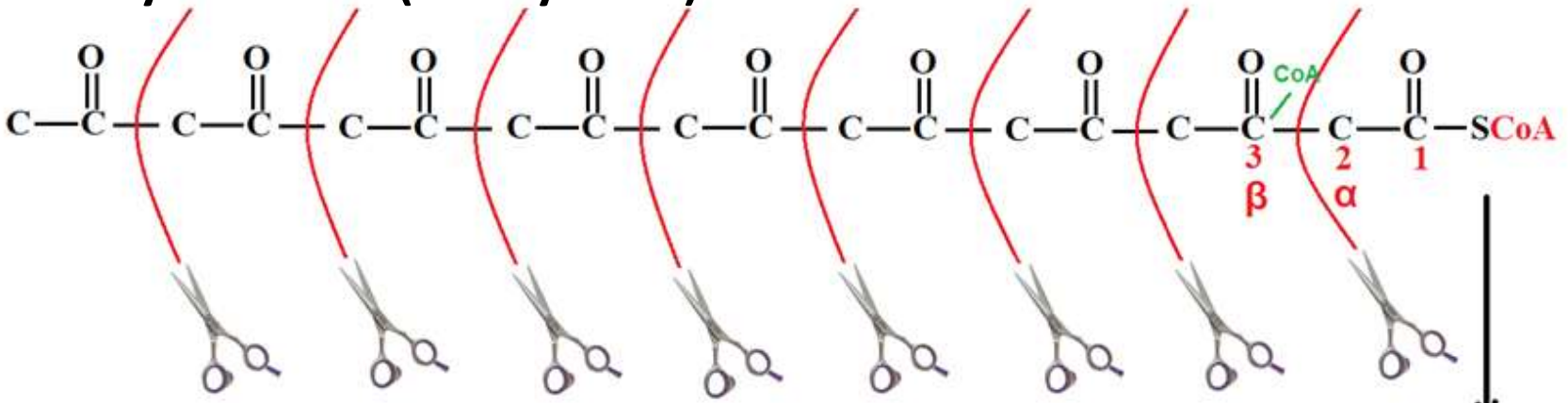
Deficiency of CAT-II

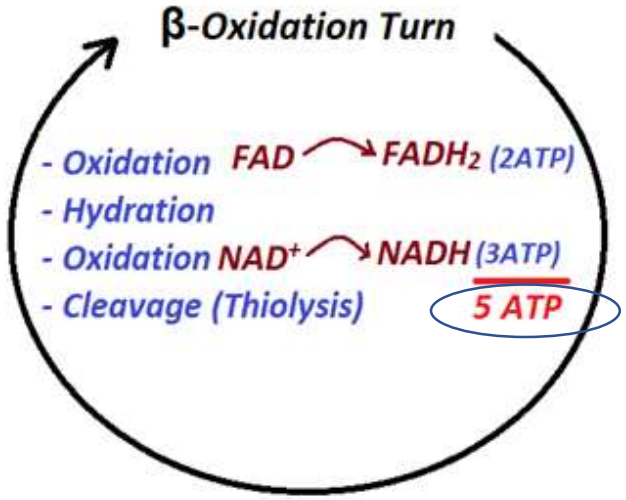
- affect heart or Skeletal muscle
- Leads to Cardiomegaly (تضخم عضلة القلب) and muscle weakness

Treatment:

- Avoidance (الامتناع عن) of fasting
- Diet with high carbohydrate and low fat
- Short and medium chain fatty acids such as Milk fat that does not need CAT transport system

The process of catabolism of Acyl-CoA in the Mitochondrial Matrix called β-oxidation turns of Cycles For Acyl-CoA 18C (Stearyl-CoA)





Acetyl-CoA

TCA Cycle

3 NADH x 3 = 9 ATP

1 $FADH_2$ x 2= 2 ATP

1 GTP = 1 ATP

12 ATP

Each Round of β-Oxidation produce One $FADH_2$, One NADH, One Acetyl-CoA, and a Fatty Acyl-CoA Shortened by Two Carbons

Each Acetyl-CoA Released in Matrix is Oxidized in the Citric Acid Cycle.

Q: calculate the net ATP produced from catabolism of Palmitic acid (16:0)??

# of Acetyl-CoA = $\frac{16}{2} = 8\ x12 = 96$

# of turns = $\frac{16}{2} - 1 = 7\ x\ 5 = 35$

Net = 96 + 35 = 131 – (2ATP)??

For Activation

لا تنساهم

# of Acetyl-CoA = $\frac{\#\ of\ Carbons}{2} = \frac{18}{2} = 9\ x\ 12 = 108\ ATP$

# of β-Oxidation Turns = $\frac{\#\ of\ Carbons}{2} - 1 = \frac{18}{2} - 1 = 8\ x\ 5 = 40\ ATP$

Total = 108 + 40 = 148 ATP

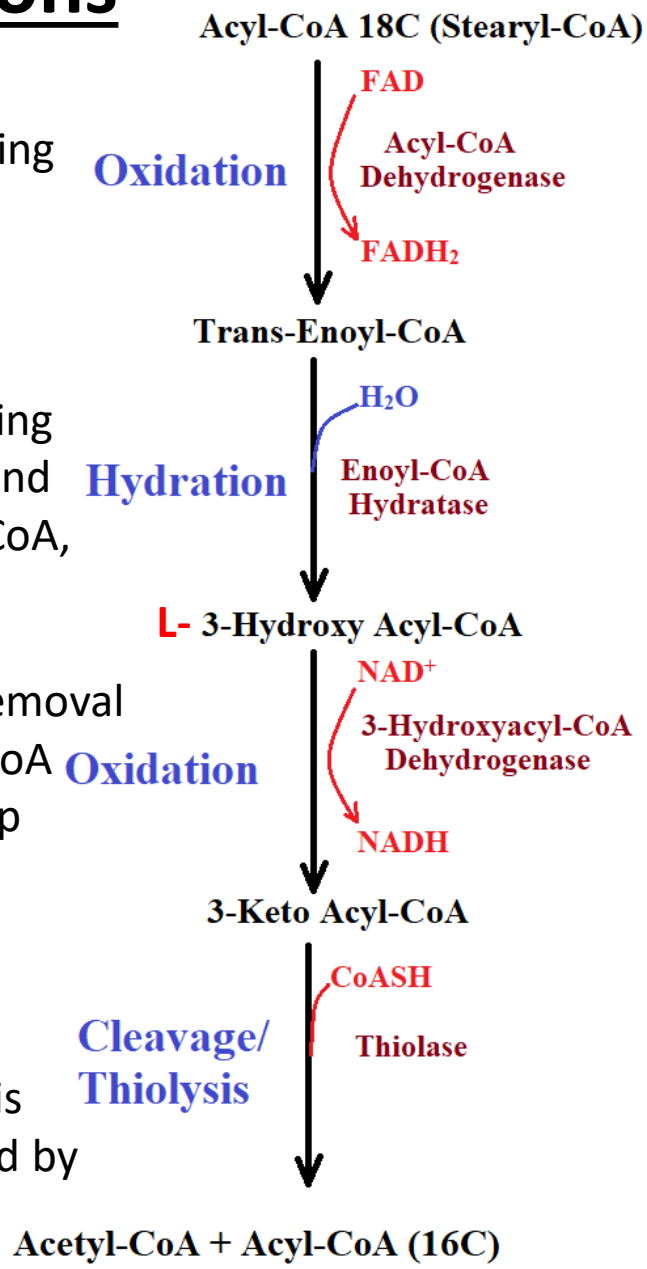
β-Oxidation Reactions

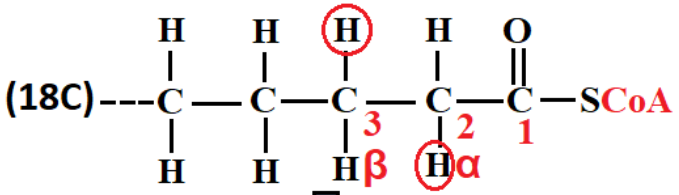
1. Dehydrogenation "Oxidation": Removal of 2H from C2 and C3 forming ***Trans***-enoyl-CoA (FAD is reduced to $FADH_2$), this step catalyzed by **Acyl-CoA Dehydrogenase**

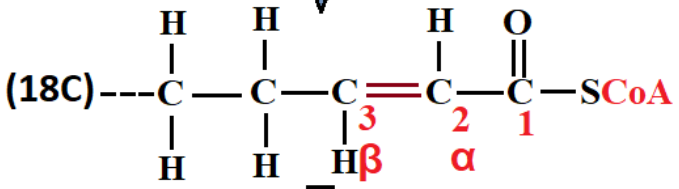
2. Hydration (اضافة ماء): addition of H_2O breaking the double bond (OH added to C3 and H to C2) forming **L**-3-Hydroxy Acyl-CoA, this step is catalyzed by **Hydratase**

3. Dehydrogenation "Oxidation": Removal of 2H from C3 forming 3-Ketoacyl-CoA (NAD^+ is reduced to NADH), this step catalyzed by **3-Hydroxyacyl-CoA Dehydrogenase**

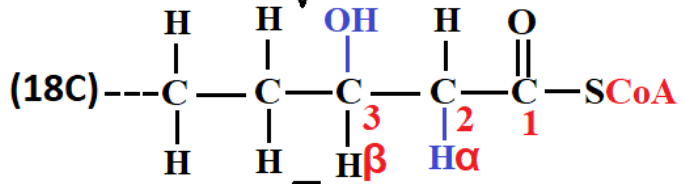
4. Thiolytic Cleavage (تكسير): release 2C as Acetyl-CoA and the remaining (المتبقية) Acyl is bonded to CoA; this step is catalyzed by **Thiolase**



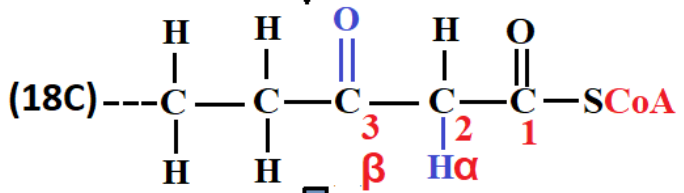


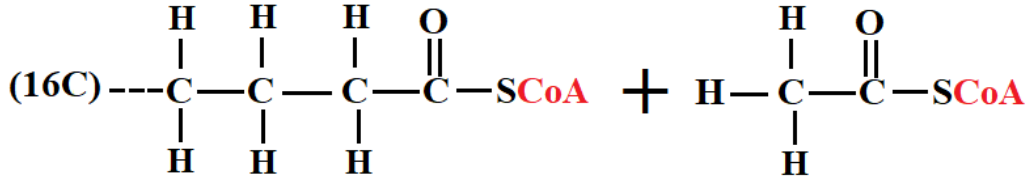


تكونت رابطة ثنائية
نوعها Trans



نوعه L





Notes:

الانزيم المسؤول عن كل خطوة يكون خاص لطول معين من الاحماض الادهنية

Each step in the β-oxidation cycle is catalyzed by enzymes specific to particular chain length; for example we have 4 Acyl-CoA dehydrogenases for the first step

- Very long chain Acyl-CoA dehydrogenase
- Long chain Acyl-CoA dehydrogenase
- **Medium chain Acyl-CoA dehydrogenase (MCAD)**
- Short chain acyl-CoA dehydrogenase

امراض وراثية

MCAD deficiency is the most common inborn errors of β-Oxidation 1:14000 birth; result in decreased ability to oxidize medium chain fatty acids which accumulate and appears in the urine

عدم القدرة

Symptoms: Severe hypoglycemia, sudden infant death syndrome (SIDS) because milk contains mainly MCFA

الامتناع عن

Treatment: avoid fasting, high Carbohydrate diet

VLCFA: very long chain fatty acids
LCFA: long chain fatty acids
MCFA: medium chain fatty acids
SCFA: short chain fatty acids

Q: for Catabolism of stearic acid (18:0):

a. **How many acetyl-CoA produced?** 9 Acetyl-CoA

b. **How many beta-oxidation cycles required?** 8 β-oxidation cycles

c. **The Net ATP produced when completely oxidized to CO_2 and H_2O?**
(9 acetyl-CoA x 12ATP) + (8 cycles x 5ATP) – (2ATP for activation) = 146 ATP

a. **Total CoASH required??** فصلهم 9 CoASH required (1 for activation and 8 for 8 β-oxidation cycles)

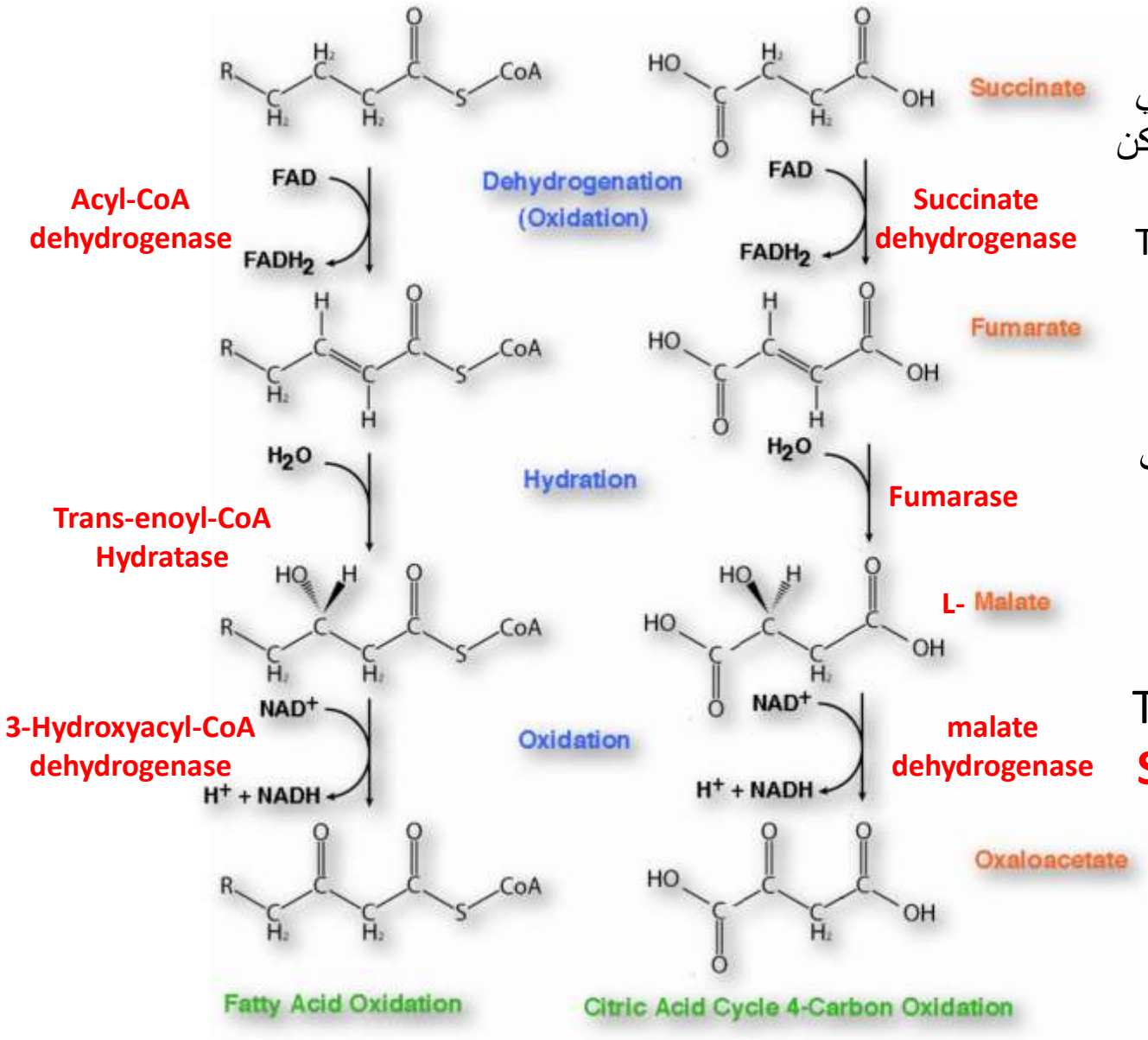
b. **How many water molecules required??** 8 H2O molecules

c. **How many NADH produced in β-Oxidation?** 8 NADH

d. **How many $FADH_2$ produced in β-Oxidation?** 8 $FADH_2$

Q: Calculate ATP results from complete oxidation of Palmitic acid?
Q: Calculate ATP result from complete oxidation of Palmitoyl-CoA?

Reactions 1, 2, and 3 in β-oxidation resembles steps 6,7, and 8 in TCA cycle



ملاحظة: الرابطة الثنائية التي تكونت بالخطوة الاولى نوعها Trans وهي تتكون بشكل مؤقت كمركب وسطي ثم تتكسر بالخطوة الثانية بالتالي لا يمكن اعتبارها Trans Fat

Trans Fat: unsaturated fatty acid with Trans double bond

ذكرنا سابقا ان الرابطة الثنائية الموجودة بالاحماض الدهنية غير المشبعة تكون عادة Cis

لكن هنا الرابطة الثنائية لم تكن اصلا موجودة انما تكونت كمركب وسطي اثناء التكسير

To calculate ATP result from complete oxidation of

Saturated fatty acid with Even number of carbon

(8.5 x # of carbons) – 7 *

من زميلكم عبدالرحمن بني ياسين*

حالات خاصة

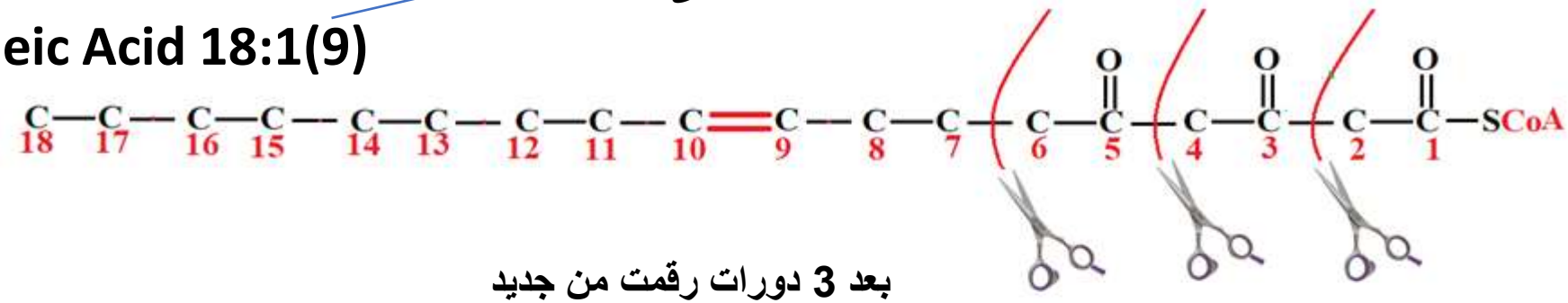
Unsaturated Fatty acids

= at C9 (Odd carbon)

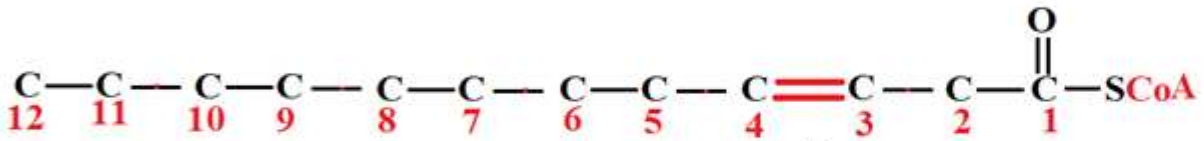
= at C12 (Even carbon)

رابطة ثنائية على كربونه فردية

Oleic Acid 18:1(9)



بعد 3 دورات رقمت من جديد



$12:1^{\Delta 3}$

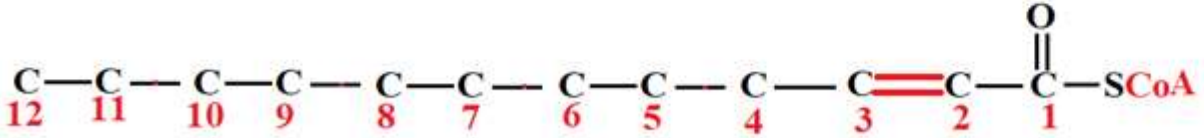
First oxidation step will not occur

Oxidation ما بتعرف عليها Acyl-CoA dehydrogenase

حل المشكلة

نقل

3,2-enoyl-CoA Isomerase: Transfer the double bond from *cis*C3=C4 to *trans*C2=C3



$12:1^{\Delta 2}$

Continue
Hydration
Oxidation
Cleavage

مقابل كل = على كربونه فردية رح تخسر $FADH_2$ بالتالي بنقص 2ATP

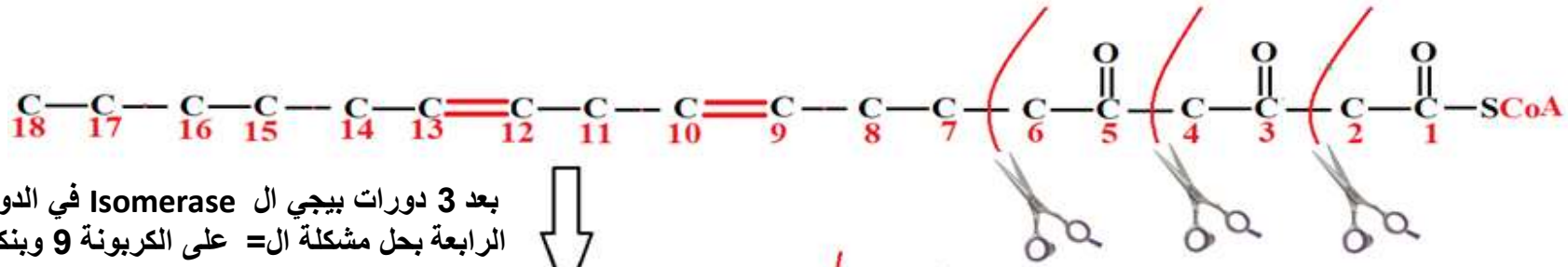
Q: which give me more energy; Saturated or Unsaturated fatty acids??

Saturated; more oxidation steps→ more $FADH_2$ →more ATP

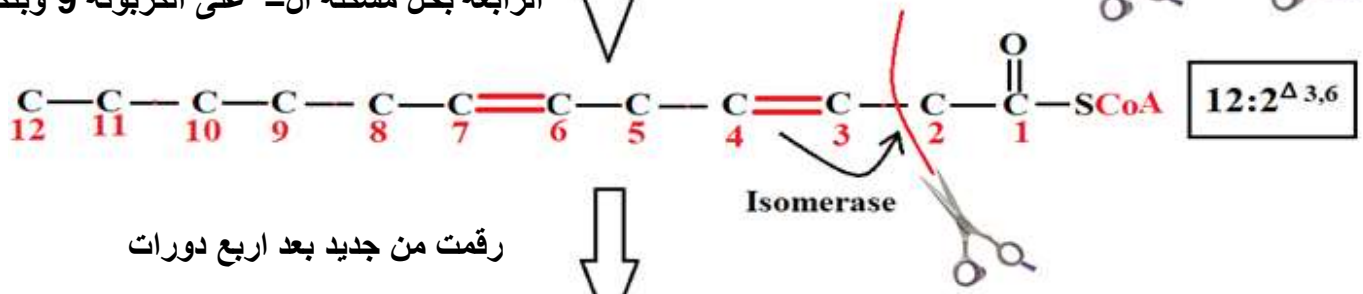
رابطة ثنائية على كربونه زوجية

Linoleic Acid 18:2(9,12)

حالات خاصة



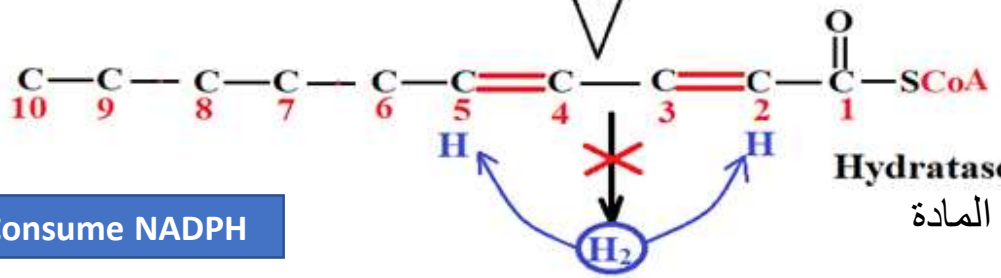
بعد 3 دورات بيجي ال Isomerase في الدورة الرابعة بحل مشكلة ال= على الكربونة 9 وبنكمل



12:2$^{\Delta 3,6}$

رقمت من جديد بعد اربع دورات

10:1$^{\Delta 4}$



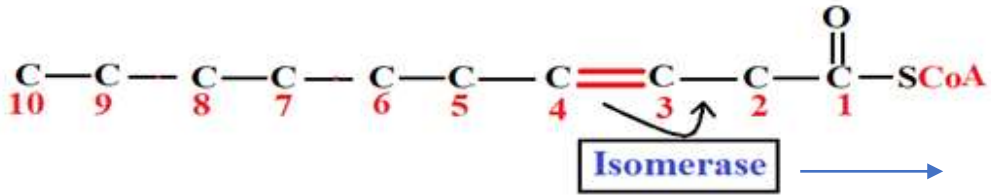
10: 2$^{\Delta 2,4}$

Hydratase can NOT work
ما بتعرف على المادة

= at odd C → Isomerase
= at even C → Reductase + Isomerase

Consume NADPH

NADPH-dependant 2,4-dienoyl-CoA Reductase: break double bond C2=C3 & C4=C5 form new = C3=C4



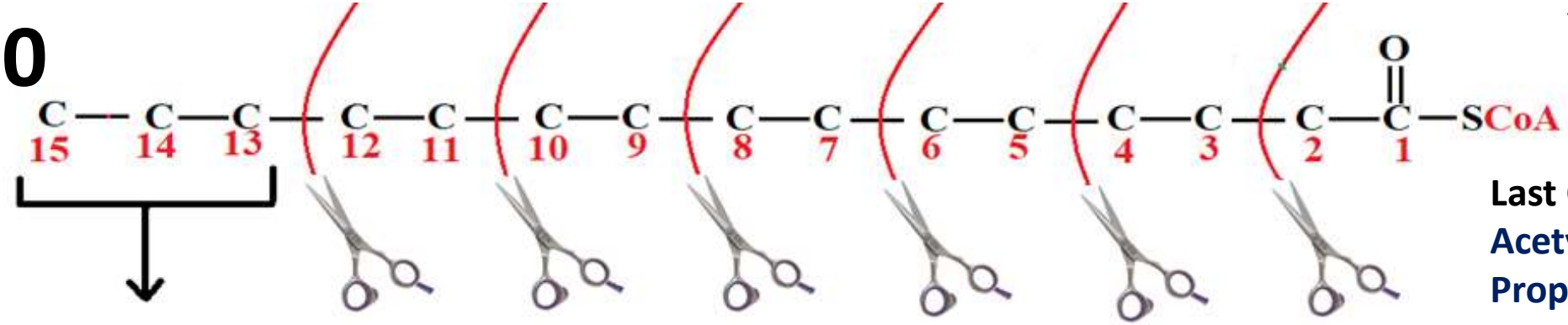
10: 1$^{\Delta 3}$

بعد هيك بتكمل عادي

Fatty acids with Odd number of Carbons (rare 10% of Dietary fatty acids)

حالات خاصة

15:0

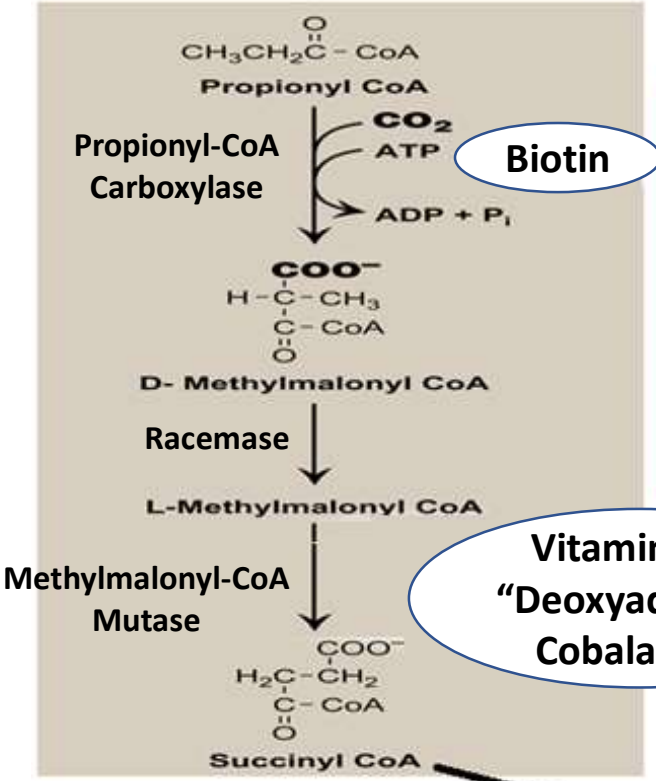


تنتج

Last Cycle will yield:-

Acetyl-CoA (2C)

Propionyl-CoA (3C)



# of Acetyl-CoA = $\frac{\text{\# of Carbons - 3}}{2}$

# of β-Oxidation turns = $\frac{\text{\# of Carbons - 3}}{2}$

Vitamin B12 "Deoxyadenosyl Cobalamin"

Glucose

Oxaloacetate

TCA Cycle

1GTP 1FADH$_2$ 1NADH

Q: Vitamin B12 deficiency will accumulate ……..

Note:

Heritable (الوراثي) Methylmalonic academia and aciduria can result from:

- **Mutase deficiency**
- **Deficiency of the enzyme that convert vitamin B12 to the it's active form**

- Vitamin B12 deficiency result in accumulation of Methylmalonic acid in the blood and urine→ ***Methylmalonic academia and aciduria*** also there will be accumulation of odd carbon fatty acids in the cell membrane of neurons leading to neurological manifestation (مشاكل في الجهاز العصبي)

High methyl-Malonyl-CoA can be used to detect Vitamin B12 deficiency

Note:

Heritable (الوراثي) Methylmalonic academia and aciduria can result from:

- ***Mutase deficiency*** either absent (مش موجود), deficient (ناقص) or has reduced affinity for its coenzyme
- Deficiency of the enzyme that convert vit B12 to the it's active form

Symptoms: Metabolic acidosis & Growth retardation

Note:

- You know that we cannot synthesize Glucose from Acetyl-CoA, so fatty acids with even number of carbon cannot be precursor for glucose because they are catabolized totally to acetyl-CoA
- Fatty acids with odd number of carbon, the last 3C atoms only can be used to synthesize Glucose because they are released as propionyl-CoA then converted to succinyl-CoA (TCA cycle intermediate)

Ketone Bodies (Ketoacids)

They are molecules synthesized in the **Liver Mitochondria**, from **Acetyl-CoA** (Precursor المادة الاولية)

- Normally Ketone Bodies synthesized at Low Rate (less than 20mmolar) بالوضع الطبيعي تصنع بكميات قليلة

يزداد صناعتها بشكل كبير في حالات:

1. Starvation **Low insulin High Glucagon (low Insulin/Glucagon ratio)**
2. Uncontrolled Diabetes (Low Insulin), mainly Type I Diabetes

In this cases:

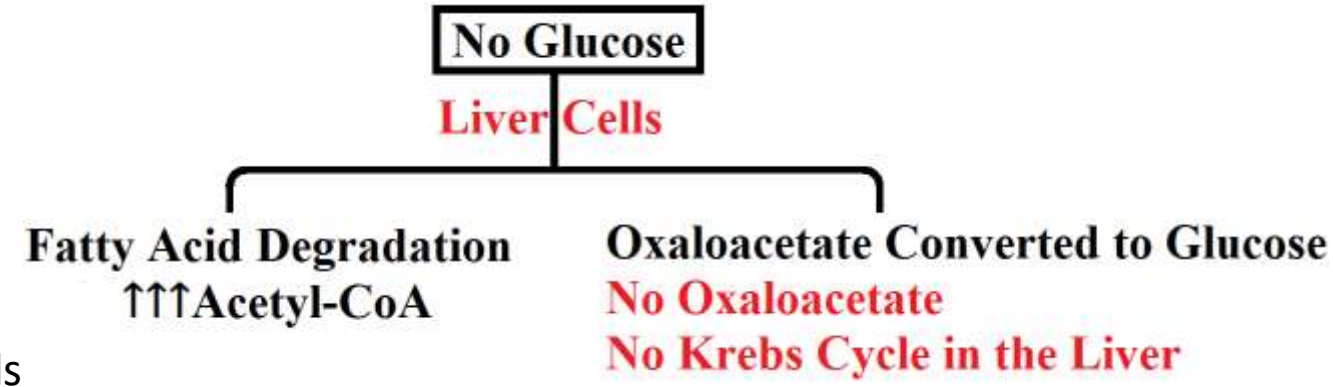
liver cells catabolize fatty acids to Acetyl-CoA, but this Acetyl-CoA cannot go through TCA cycle because of low Oxaloacetate level

Acetyl-CoA will accumulate **trapping CoA with it**

(Remember first step in TCA cycle free CoA from acetyl)

Now if CoA is trapped then we cannot catabolize fatty acids

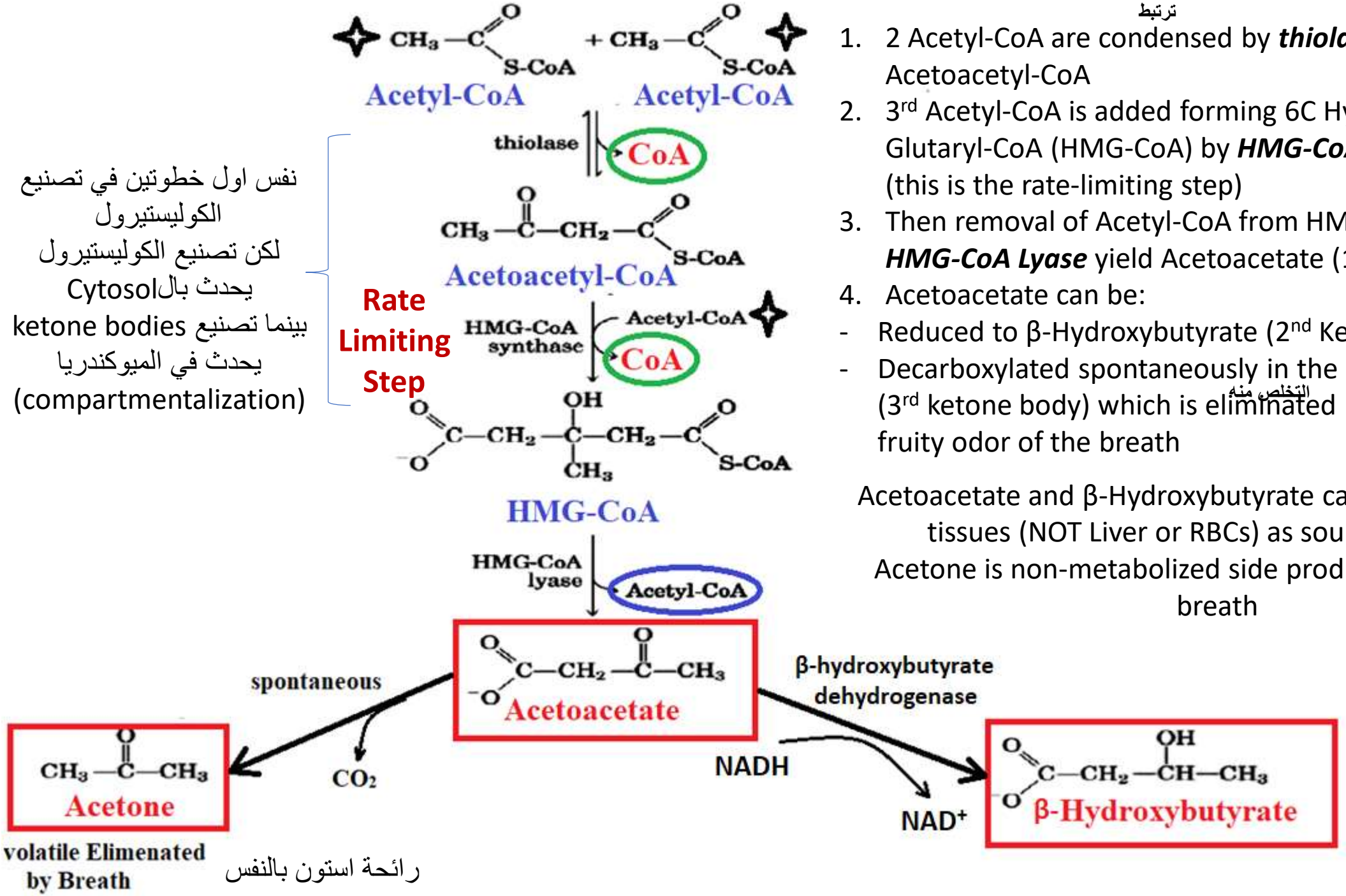
وسلامتك شو الحل؟؟



So, Acetyl-CoA accumulate (يتراكم) in the liver and Can NOT go through TCA Cycle

Solution: Synthesize Ketone Bodies (Ketogenesis)

تحرير CoA هو هدف الكبد الوحيد من تصنيع ketone bodies



نفس اول خطوتين في تصنيع الكوليستيرول
لكن تصنيع الكوليستيرول يحدث بالCytosol
بينما تصنيع ketone bodies يحدث في الميوكندريا (compartmentalization)

رائحة استون بالنفس

ترتبط

1. 2 Acetyl-CoA are condensed by ***thiolase*** forming Acetoacetyl-CoA
2. 3rd Acetyl-CoA is added forming 6C Hydroxy-Methyl-Glutaryl-CoA (HMG-CoA) by ***HMG-CoA synthase*** (this is the rate-limiting step)
3. Then removal of Acetyl-CoA from HMG-CoA by ***HMG-CoA Lyase*** yield Acetoacetate (1st Ketone body)
4. Acetoacetate can be:

- Reduced to β-Hydroxybutyrate (2nd Ketone body)
- Decarboxylated spontaneously in the blood to Acetone (3rd ketone body) which is eliminated (التخلص منه) by breath giving fruity odor of the breath

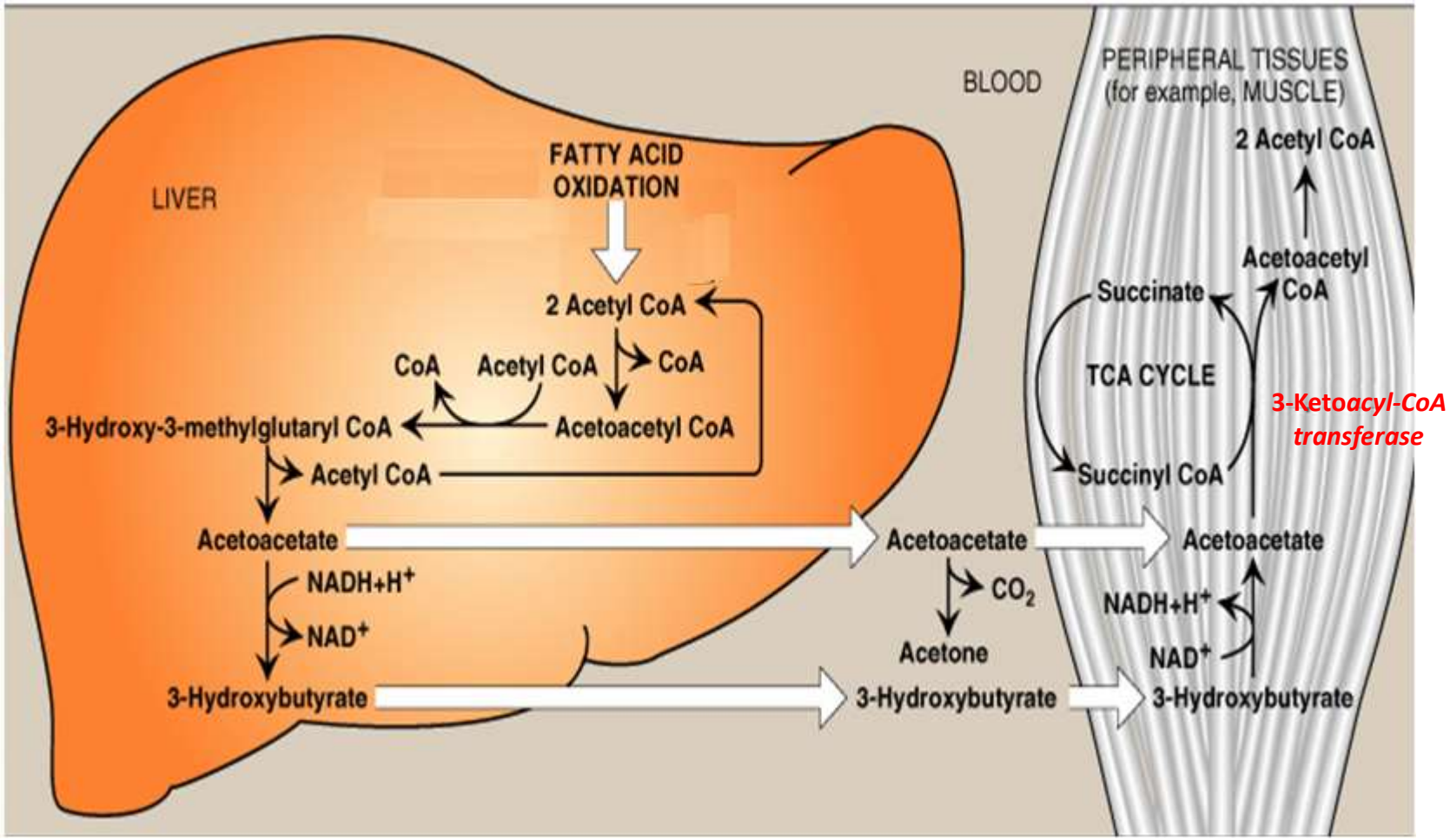
Acetoacetate and β-Hydroxybutyrate can be used by body tissues (NOT Liver or RBCs) as source of energy
Acetone is non-metabolized side product eliminated by breath

Peripheral tissues such as muscles and brain can use Ketone body as source of energy, they are **water soluble** and can be transported in blood without the need of carrier protein

Actually heart/skeletal muscles prefer ketone bodies as a source of energy, that's why we synthesize then at low rate under normal physiological conditions

3-Keto*acyl-CoA transferase* is a Mitochondrial enzyme not found in the liver so, Liver and cell that lack mitochondria (RBCs) cannot use Ketone body as source of energy

الكبد يصنع ketone bodies لكن لا يستطيع استخدامهم كمصدر للطاقة



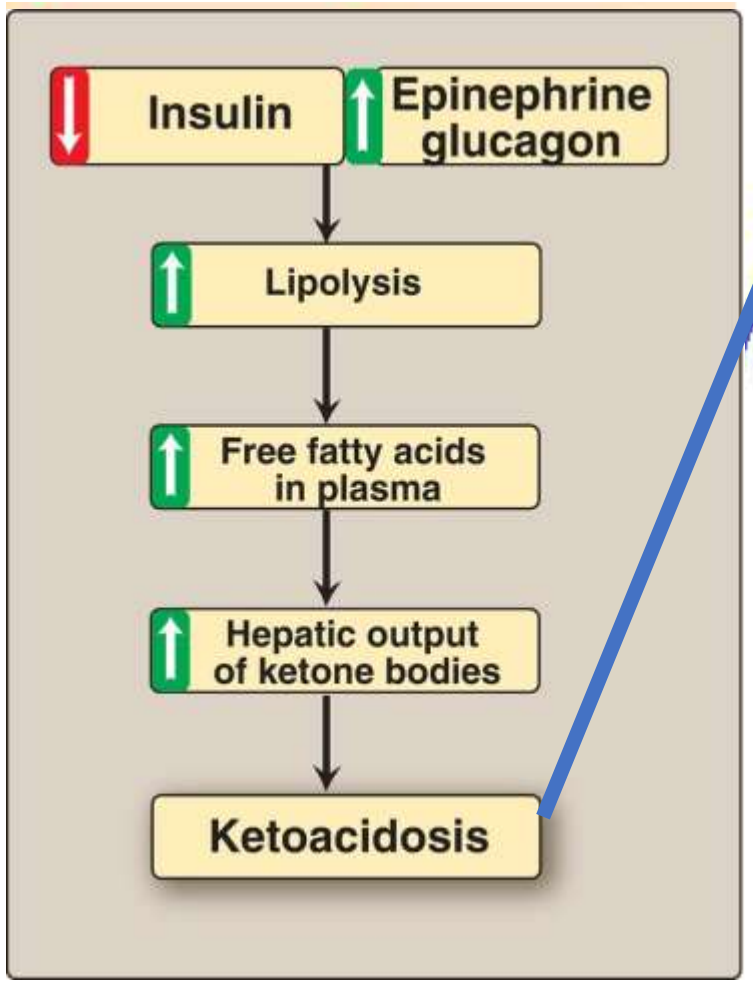
Brain Prefer Glucose as energy source, but in case of starvation, Brain use Ketone bodies as sources of energy why?

ketone Bodies في حالة المجاعة الدماغ يتاقلم يستخدم كمصدر للطاقة بجانب / بدلا من glucose وذلك لتقليل عملية تكسير البروتينات في الجسم

In body tissues:

3-Hydroxybutyrate is oxidized to Acetoacetate, then acetoacetate converted in the Mitochondria to Acetoacetyl-CoA by enzyme called **3-Keto*acyl-CoA transferase (Thiophorase)*** (Succinyl-CoA is the source of CoA)

Then Acetoacetyl-CoA is cleaved by thiolase to 2Acetyl-CoA to be used in Krebs cycle; this process called ***Ketolysis***



Increased Excretion in Urine
loss of Sodium in urine
Loss of water
Dehydration جفاف
Coma غيبوبة
Death

In Starvation or **Diabetus Mellitus** low insulin/Glucagon ratio and increased Epinephrine increase the rate of Lipolysis (Hydrolysis of TAG) consequently the synthesis of Ketone bodies increase in the liver
Ketone bodies are water soluble molecules they will increase in the blood and Urine (Ketonemia/Ketonuria)
Since ketone bodies are acids and increased in the plasma they will ↓pH of the blood (Ketoacidosis)

ملاحظة

في خلايا الكبد

في الوضع الطبيعي: Fatty Acids —β-Oxidation→ Acetyl-CoA —TCA→ CO_2 (الناتج النهائي)

في حالة starvation or uncontrolled diabetes: Fatty Acids —β-Oxidation→ Acetyl-CoA → *Ketone Bodies* (الناتج النهائي)

في حال سألك بالامتحان عن ATP الناتجة من تكسير F.A في الكبد في حالة Starvation او Diabetes نحسب فقط ال ATP الناتجة من ال β-Oxidation

Palmitic acid → 7 Cycles x 5 = 35 - 2