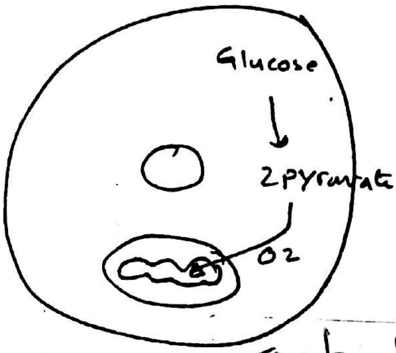
3Carboxyl يحوي

pter 19 : Krebs Cycle / Citric acid Cycle / TCA Cycle

Tricarboxlic acid

← ثاني مرحلة في تكسير الجلوكوز



6C
Glucose

$\downarrow$ Glycolysis — In Cytosol, NO O_2

2 pyruvate (2 ATP + 2NADH)
3C

مرحلة الوسطية
Mitochondria داخل

$2NAD^+ \rightarrow 2NADH$ — oxidative decarboxylation

$2CO_2$

$\downarrow$

2 Acetyl-CoA
2C

$\downarrow$

Oxaloacetate
4C

$\rightarrow$ Citric acid
6C

8-steps

Krebs Cycle for 2 acetyl-CoA
6 NADH
2 $FADH_2$
2 GTP = 2ATP
4 CO_2

$\rightarrow CO_2$

$\rightarrow CO_2$

1acetyl ل Krebs نواتج

$3NAD^+ \rightarrow 3 NADH$
In steps 3, 4, 8

1 FAD $\rightarrow$ 1 $FADH_2$
in step 6

1GTP = 1ATP
In step 5

2 CO_2 in steps 3, 4
(oxidative decarboxylation)

$\Downarrow$

Electron Transport chain
and Oxidative phosphorylation.

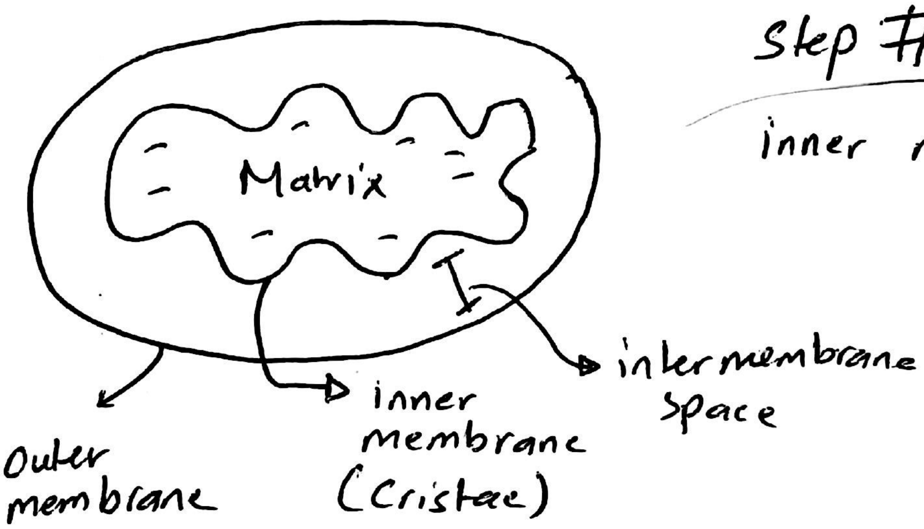
NADH $\rightarrow$ 2.5 ATP
$FADH_2 \rightarrow$ 1.5 ATP

* This Cycle is Amphibolic, means it works in

Anabolism → بناء

Catabolism → هدم

* All Enzymes of citric acid cycle found in the Mitochondrial Matrix, Except The enzyme that catalyze step #6, found in inner mitochodrial mem (Cristae)



* Sources of Acetyl-CoA that Enter Krebs Cycle:-

① Glucose (Carbohydrate)

② Fatty acids (Fat)

③ Amino-acids (proteins)

Jverall Reactions in TCA cycle.

3,4,8 → 3 NadH
6 → 1 FADH

- 4 Oxidation Steps = Steps 3, 4, 6, 8
- 1 Step produces GTP = step 5
- 2 Steps produce CO_2 = steps 3, 4

So,
steps 3, 4 ⇒ Oxidative-decarboxylation

$$* \quad \overset{\boxed{3C}}{\text{Pyruwate}} \xrightarrow[\text{NAD}^+ \;\to\; \text{NADH}]{\text{CoA} \;\searrow\;\nearrow\; CO_2} \overset{\boxed{2C}}{\text{Acetyl-CoA}}$$

pyruwate dehydrogenase Complex

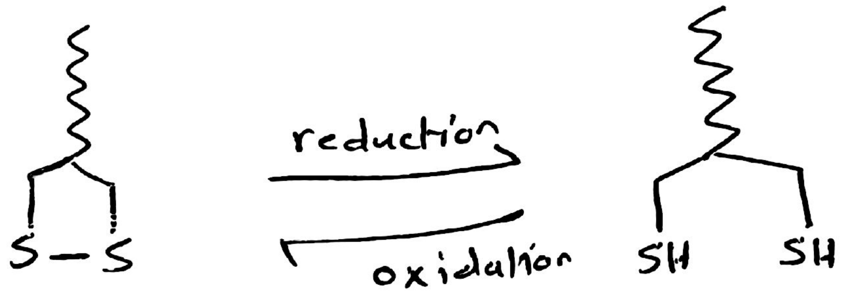
هذه الخطوة الوسطية تحدث في Mitochodrial Matrix

This Complex consist of :-

For Control
- pyruwate dehydrogenase Kinase (add Ⓟ)
- pyruwate dehydrogenase phosphatase (Remove Ⓟ)

تحول pyruwate الى Acetyl-CoA
- pyruwate dehydrogenase ----- B_1 TPP Coenzyme, يرتبط Non covalent
- Dihydrolipoyl transacetalase lys amide Bond lipoic acid, Covalent
- Dihydrolipoyl dehydrogenase --- FAD, Non-covalent

Lipoic acid, Cofactor required for Dihydrolipoyl transacetalase



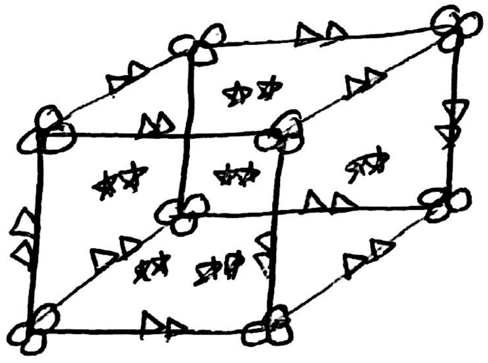
oxidized form
lipoamide
(No H+)

Reduced form
Dihydrolipoamide
(With H)

* This Complex need :-

Ⓝ NAD^+, Mg^+, lipoic acid, FAD, TPP, CoA

* This Complex Organized in Cube :-



* Dihydrolipoyl transacetalase

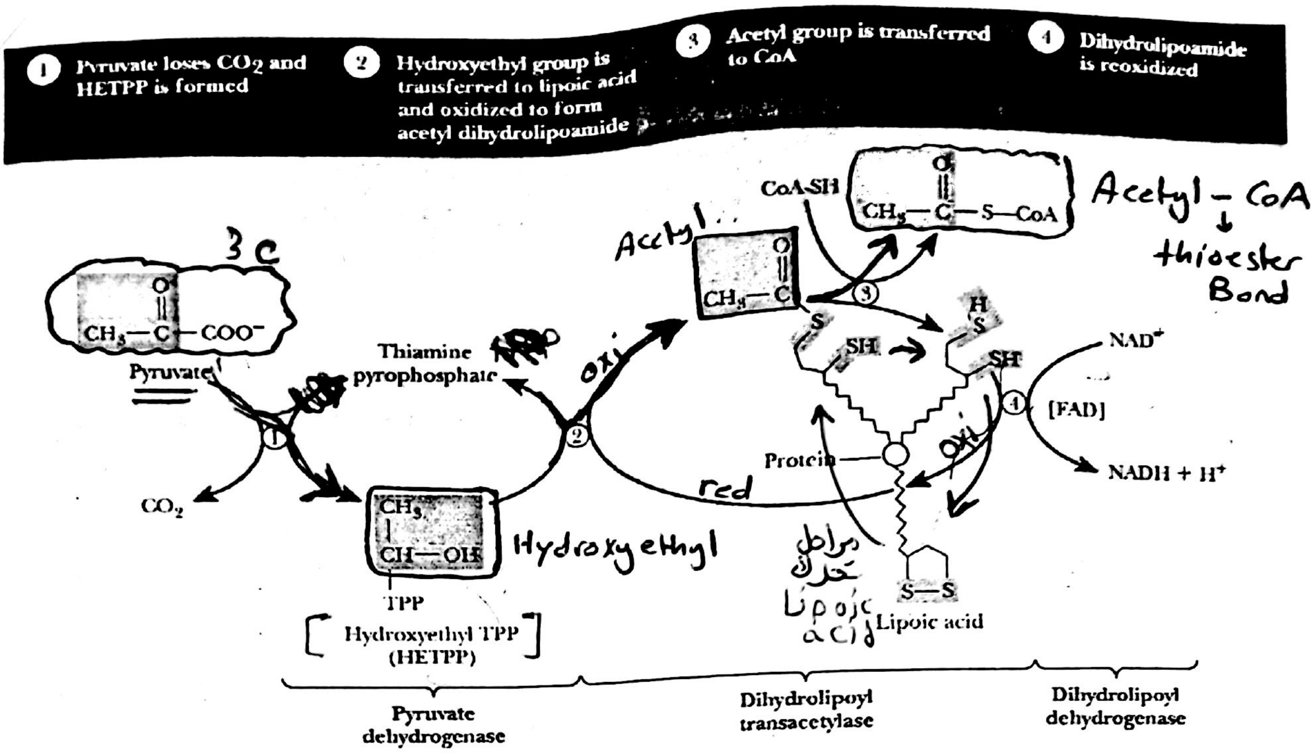
24 → ⚬⚬⚬ → 8
trimer on Corner

* pyruvate dehydrogenase

24 → ΔΔ → 12
dimer on Edges

* Dihydrolipoyl dehydrogenase

12 → ☆☆ → 6
dimer on faces

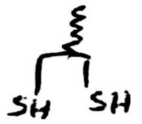


① CO2 removed from pyruvate to form Hydroxyethyl TPP

<< By pyruvate dehydrogenase / need TPP >>

② Hydroxyethyl TPP ——→ oxidation to Acetyl

lipoic acid ——→ Reduction



③ Co-A attach to Acetyl → Acetyl-CoA

<< by Dihydrolipoyl transacetalase which need lipoic acid >>

⇒ For this reaction to continue in further steps, lipoic acid should be oxidized form  and by the end of step 3 it's 

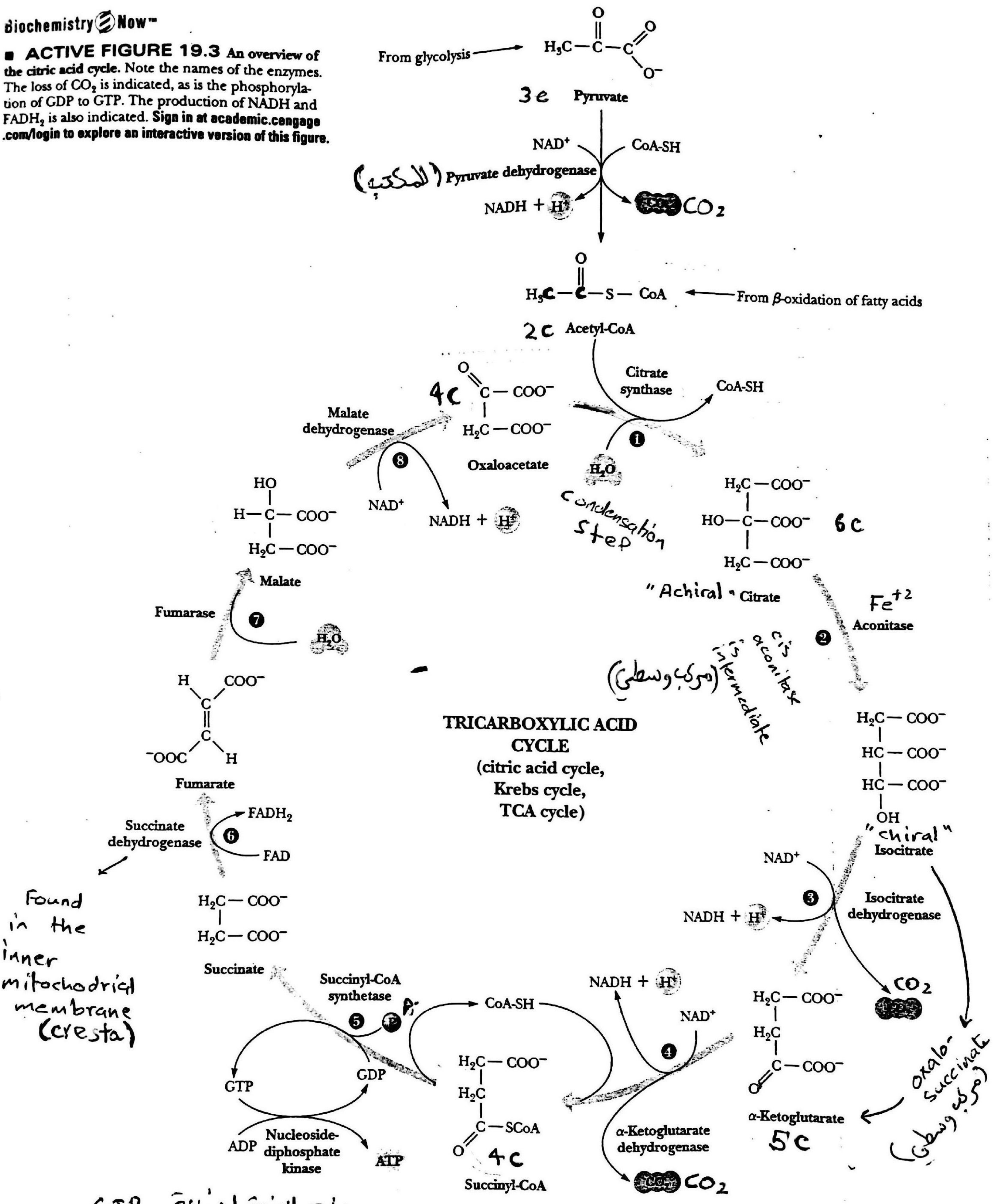
④ lipoic acid —oxidation→

NAD+ ——→ NADH

<< by dihydrolipoyl dehydrogenase which need FAD >>

Biochemistry Now™

■ **ACTIVE FIGURE 19.3 An overview of the citric acid cycle.** Note the names of the enzymes. The loss of CO_2 is indicated, as is the phosphorylation of GDP to GTP. The production of NADH and $FADH_2$ is also indicated. **Sign in at academic.cengage.com/login to explore an interactive version of this figure.**



GTP الطاقة اللازمة لصناعة
تأتي من تكسير
thioester
Bond
Succinyl — CoA

the
Only
reversible
Step

See Figure 19.4

* 8 steps :-

#1 :- acetyl - CoA + oxaloacetate → citrate
2C 4C 6C
+ H_2O « citrate synthase »

This is Condensation reaction.

#2 :- citrate $\xrightarrow{Fe^{+2}}$ Isocitrate
«achiral» «aconitase» «chiral»

(Isomerization)

Cis - acontase → intermediat in conversion of citrate to isocitrate.

#3 :-
6C
Isocitrate + NAD^+ $\xrightarrow{}$ CO_2 5C α-Ketoglutarate + NADH
« isocitrate dehydrogenase »

oxidative - decarboxylation

This step occur actuly as 2 step.

$$\text{Isocitrate} \xrightarrow[\text{NAD}^+ \curvearrowright \text{NADH}]{} \boxed{\text{oxalosuccinate}} \xrightarrow{\text{CO}_2} \alpha\text{ Ketogluterate.}$$

oxalosuccinate → intermediat in this step.

#4 :- (The only revesible step)

$$\alpha\text{-Ketogluterate} + \text{NAD}^+ \underset{\alpha\text{-ketogluterat dehydrogenas}}{\overset{\text{Co-A} \qquad \text{CO}_2}{\rightleftharpoons}} \text{Succinyl-CoA} + \text{NADH}$$

* Oxidative decarboxylation *

- it is <u>complex</u> exactly like pyruvate dehydrogenase.

* [TPP, Mg^{+2}, Co-A, FAD, NAD^+, Lipoic acid]

Step #5:-

$$\text{Succinyl-CoA} \xrightarrow{\text{GDP} \curvearrowright \boxed{\text{GTP}}} \text{Succinate}$$

« Succinyl CoA-Synthetase »

Synthase → no ATP

Synthatase → ATP

#6 :-

$$\text{Succinate} + \text{FAD} \xrightarrow[\text{succinat dehydrogenase}]{} \text{Fumarate} + FADH_2$$

- present in inner mitochondrial membran not in matrix
- this enzyme contain Iron but without heme, So called Non-heme Iron protein Or Iron-Sulfer protein

#7 :-

$$\text{Fumarate} + H_2O \xrightarrow{\text{« fumarase »}} \text{L-malat}$$

#8 :

$$\text{L-malate} + NAD^+ \xrightarrow[\text{malat dehydrogenase}]{} \text{oxaloacetat} + NADH$$

Note : 2 CO_2 are released in citric cycle.
You should know that these 2 carbon, not from $\boxed{\text{acetyl-COA}}$, it is from oxaloacetate

roducts of One pyruvate

Pyruvate

pyruvate Dehydrogenase Complex

→ CO_2
NADH

Acetyl-CoA

Krebs Cycle
3 NADH
1 $FADH_2$
1 GTP ≃ 1ATP
2 CO_2

* One Pyruvate gives
3 CO_2
4 NADH
1 $FADH_2$
1 GTP

= 12.5 ATP

- Products of One acetyl-CoA

Acetyl-CoA

Krebs Cycle
3 NADH
1 $FADH_2$
1 GTP = 1ATP
2 CO_2

= 10 ATP

each NADH → 2.5 ATP
each $FADH_2$ → 1.5 ATP

an you Calculate how many ATP produced from 1 glucose? ?

glycolysis → 2ATP
2NADH

give 2NADH خطوة برا ال cycl

6 NADH ← cycle
$2FADH_2$
2GTP

So 10 NADH → 25 ATP
$2\ FADH_2$ → 3 ATP
4 ATP

---

32 ATP ✓

Control on citric cycle :- Figure 19.8

on 4 steps
- → out side cycle (1) step
- → in cycle (3) steps

$$- \text{Pyruvate} + NAD^+ \xrightarrow[\text{“P.D complex”}]{} \text{acetyl-CoA} + NADH$$

if ↑ NADH
↑ ATP
↑ acetyl-CoA
} ⇒ -ve

How ?!.

active P. D $\xleftarrow[\text{phosphotase}]{}$ $\boxed{\text{P.D}}$-P

inactive .

Step #1

- acety CoA + oxaloacetat $\xrightarrow[\text{Citrate synthase}]{}$ Citrate

$$\left.\begin{array}{l}\uparrow \text{ATP} \\ \uparrow \text{NADH} \\ \uparrow \text{Citrate} \\ \uparrow \text{succinyl CoA}\end{array}\right\} \Longrightarrow -\text{ve}$$

Step #3

- Isocitrate $\xrightarrow[\text{isocitrate dehydrogenase}]{}$ α-ketoglutarate .

$$\left.\begin{array}{l}\uparrow \text{ATP} \\ \uparrow \text{NADH}\end{array}\right\} \Longrightarrow -\text{ve}$$

$$\left.\begin{array}{l}\uparrow \text{ADP} \\ \uparrow \text{NAD}^+\end{array}\right\} \Longrightarrow +\text{ve}$$

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Step #4

- α ketoglutarat ⟶ Succinyl CoA

α - ketoglutarate dehydrogenase.

↑ ATP
↑ NADH
↑ succinyl COA

} ⇒ -ve.

Comparsion :-

cell in resting state	cell in highly active state.
High ATP ↑	low ATP
Low ADP	High ADP ↑
So ATP/ADP **High**	So ATP/ADP low
High NADH ↑	NADH low
low NAD^+	NAD^+ High ↑
So $NADH/NAD^+$ High	So $NADH/NAD^+$ low

ATP/ADP ratio sometimes called the "Energy charge"

oxylate Cycle

This Cycle occurs only in plants the (happens inside glyoxysomes)
in Bacteria

NOT in Animals

* it enables the plant, Bacteria to produce glucose from Fatty acids (Fat)

⇓ when break

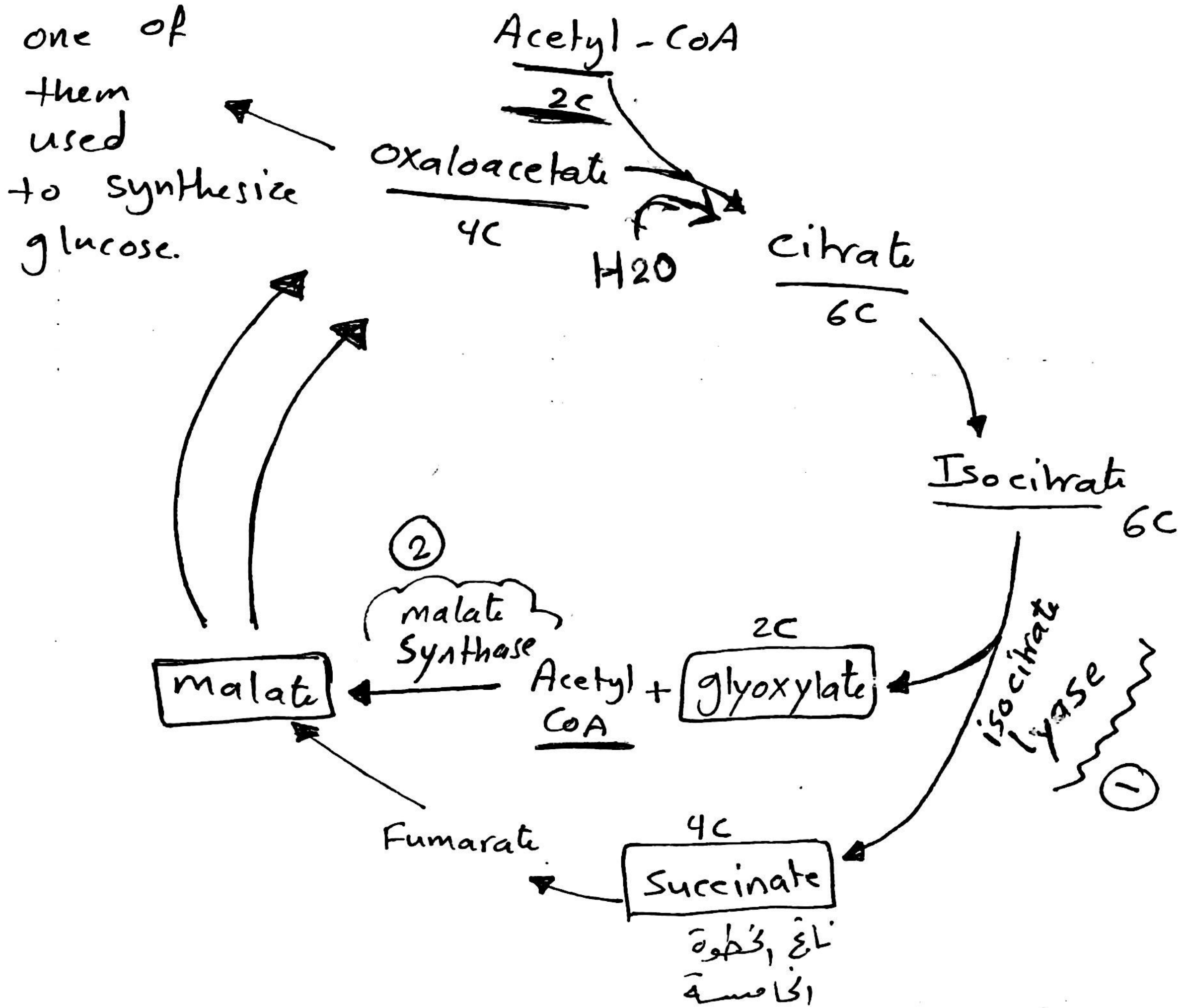
give Acetyl-CoA [product of Catabolism of F.A]

How this Can happen?

- we Know that we can Synthesize glucose from Oxaloacetate

But Oxaloacetate in Krebs Cycle, Not produced from acetyl-CoA, it already exist in Matrix and regenerated at the end

thats why we Can't Synthesize glucose from Acetyl-CoA in animal plant + Bacteria, there are 2 important enzymes (NOT found in animals)



* By this we bypass 2 oxidative decarboxylation steps (3, 4), So creating 4 carbon compound «oxaloacetate» can be drown off to make glucose without affecting the cycle.

* this is important in germinating Seeds

Seed contain Fatty acids (oils) $\xrightarrow[\text{to}]{\text{Broken}}$ Acetyl-CoA → Carbohydrate By Glyoxylate cycle

* also important in Bacteria

important Structural role

1. The citric acid cycle is the only metabolic pathway that can be used both as an anabolic and as a catabolic pathway.
   a. True
   b. False

   ANS: B

2. Which of the following statements concerning the citric acid cycle as the central metabolic pathway is true?
   a. It is involved in the metabolism of sugars and amino acids.
   b. It is involved in the metabolism of amino acids and lipids.
   c. It links anaerobic metabolism to aerobic metabolism.
   d. Many of its intermediates are starting points for synthesis of a variety of compounds.
   e. All of these are reasons why the citric acid cycle is considered to be the central pathway.

   ANS: E

3. The reaction of the citric acid cycle that does not take place in the mitochondrial matrix is the one catalyzed by:
   a. fumarase
   b. citrate synthase
   c. isocitrate dehydrogenase
   d. succinate dehydrogenase
   e. All of these reactions take place in the matrix

   ANS: D

4. The acetyl group is carried on lipoic acid as
   a. an alcohol.
   b. a thioester.
   c. a phosphoanhydride.
   d. an amide.

   ANS: B

5. Which of the following vitamins and enzyme cofactors are used by the pyruvate dehydrogenase complex during oxidative decarboxylation?
   a. Lipoic Acid.
   b. Niacin.
   c. Pantothenic Acid.
   d. Thiamine.
   e. All of these

   ANS: E

6. Which of the following is not a reaction occurring during oxidative decarboxylation of pyruvate?
   a. Removal of CO_2.
   b. Oxidation of an acetate group.
   c. Addition of Coenzyme A to a 2-carbon fragment.
   d. Reduction of NAD^+
   e. All of these

ANS: B

hich Coenzyme listed below is NOT associated with α-Ketoglutarale dehydrogenase complex?

a. TPP

b. lipoic acid

c. Biotin

d. NAD^+

ANS: C

Q8: The iron-ion, which is part of succinate dehydrogenase is bonded to heme

True False

ANS: False

Q9: when oxaloacetate react with acetyl-CoA to form Citrate

a. a new C-C bond is formed

b. an oxidative decarboxylation take place.

c. a dehydration reaction take place

d. a rearrangement take place.

ANS: A

Q10. Release of succinate from Succinyl-CoA Can be coupled with GTP synthesis because:-

a. The amide Bond between succinate and CoA has large $-\Delta G$

b. The thioester Bond Between Succinate and CoA has large $-\Delta G$

c. The link between succinate and CoA involve an acid anhydride compound, Just like GTP

d. CoA is a high energy

e. None - of these

ANS: B

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11: The Only difference between succinate and fumarate is the Geometry around there double bonds, one contains cis double Bond while the other contains Trans

True

False

ANS: False

Q: In the Conversion of Succinyl-CoA to Succinate
-12
GTP is produced from GDP, what is the source of phosphate added

a. ATP

b. ADP

c. Phosphoenolpyruvate

d. inorganic phosphate ion

ANS: D

Q! "Energy charge" in a cell is measure of
=13

a. ATP / NAD^+ ratio

b. ATP / NADH ratio

c. ATP / ADP ratio

d. NADH / NAD^+ ratio

e. NAD^+ / ADP ratio

ANS: C