Krebs Cycle

MED441
KING SAUD UNIVERSITY

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13
V1

Foundation Block - KSU

Color Index:

- Main text
- Important
- Notes
- Boys slides'
- Girls slides'
- Extra

Editing File

Objectives

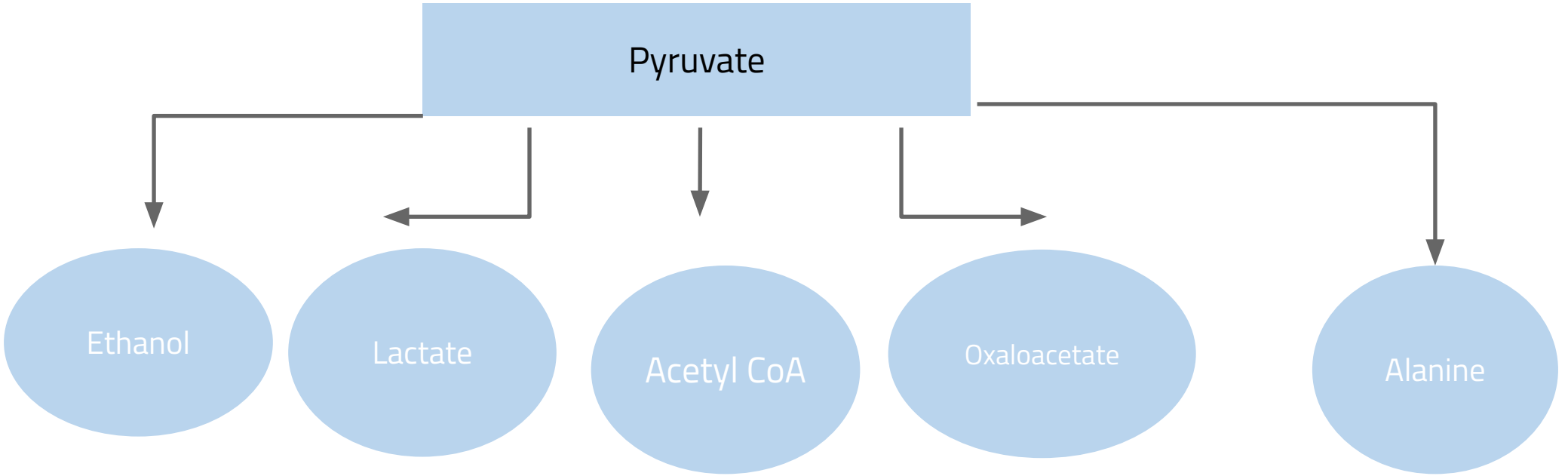
Oxidative Decarboxylation

- Recognize the various fates of pyruvate
- Define the conversion of pyruvate to acetyl CoA
- Discuss the major regulatory mechanisms for PDH complex
- Recognize the clinical consequence of abnormal oxidative decarboxylation reactions

Krebs Cycle

- Recognize the importance of Krebs cycle
- Identify various reactions of Krebs cycle
- Define the regulatory mechanisms of Krebs cycle
- Assess the energy yield of PDH reaction and Krebs cycle’s reactions

Fates of Pyruvate



Occurs in yeast and some bacteria (including intestinal flora)
Thiamine pyrophosphate-dependent pathway

Enzyme:
Lactate dehydrogenase

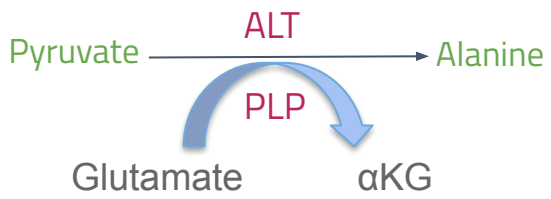
Found:
Anaerobic glycolysis

Enzyme:
PDH Complex inhibited by acetyl CoA

Found:
Krebs cycle

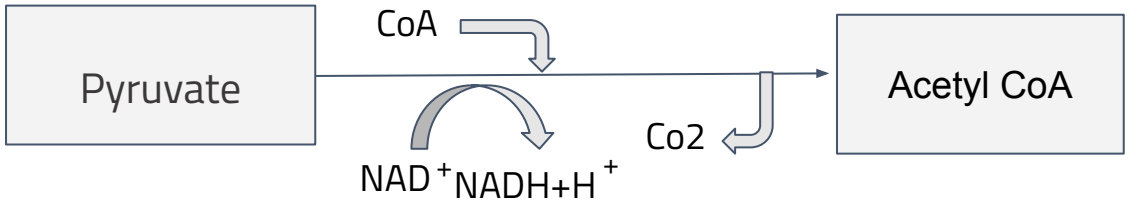
Enzyme:
Pyruvate Carboxylase

Found:
Gluconeogenesis
Krebs cycle



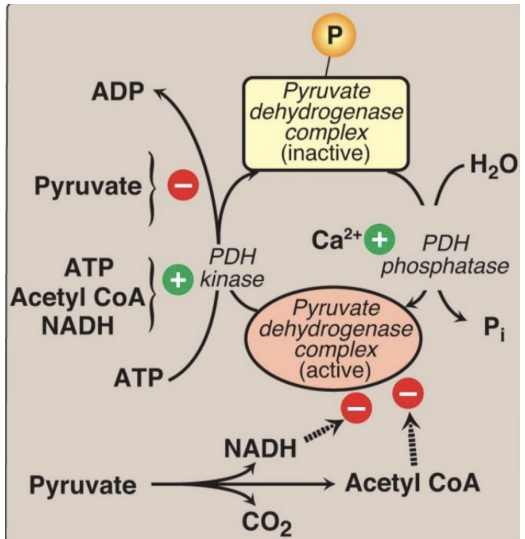
PDH Complex: Pyruvate Dehydrogenase Complex
PLP: Pyridoxal Phosphate (cofactor)
ALT: Alanine aminotransferase

Oxidative Decarboxylation of Pyruvate

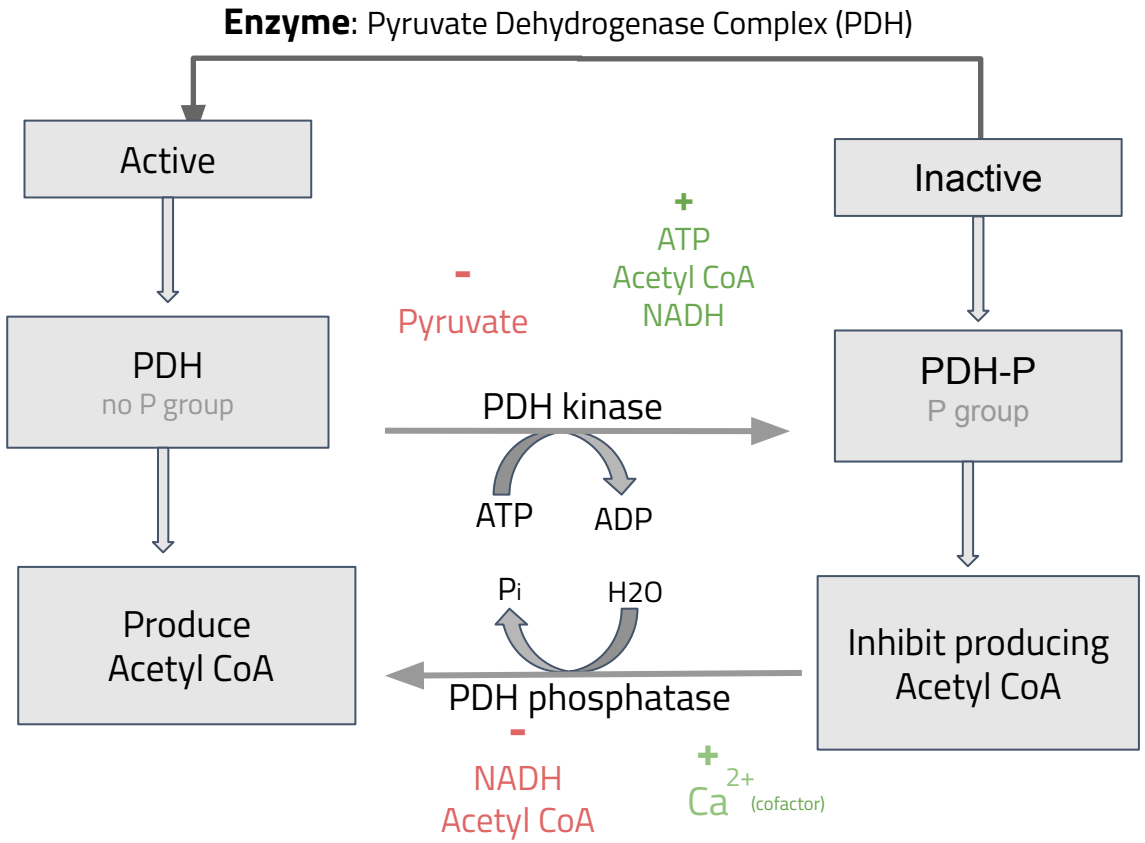


Enzyme: Pyruvate Dehydrogenase Complex (PDH)
Inhibitors: Allosteric Regulation: Acetyl CoA + NADH

- Irreversible
- energy producing
- 2 pyruvate produce 2 NADH = 6 ATP (1 NADH= 3 ATP)



PDH Complex: Covalent Regulation



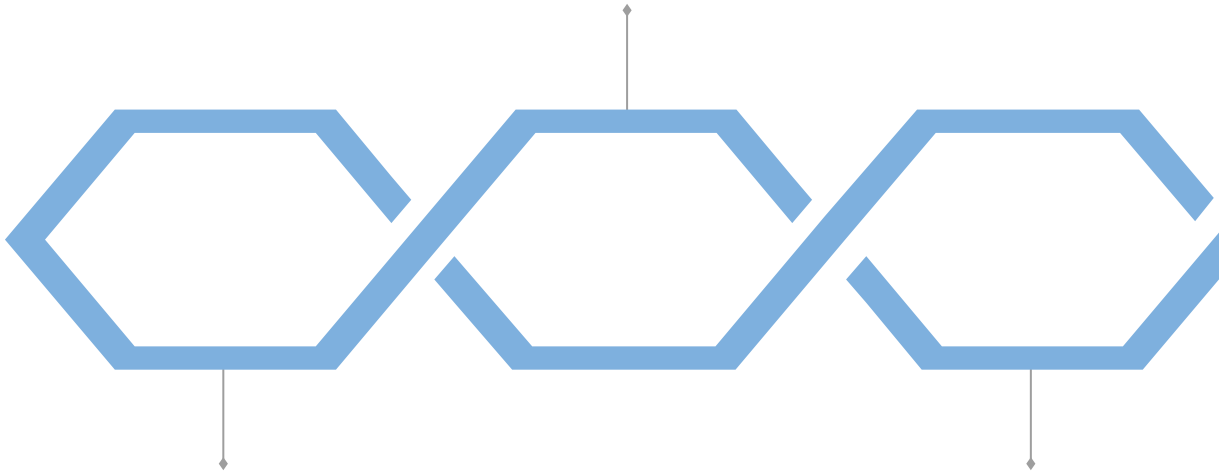
Team 439

Kinase= enzyme that adds phosphate group "phosphorylates"

Phosphatase = enzyme that removes phosphate group

PDH Reaction: Clinical application

Wernicke-Korsakoff
(encephalopathy-psychosis syndrome)
due to thiamine deficiency, may be seen especially with alcohol abuse.



Deficiencies of thiamine (vitamin B1) or niacin (vitamin B3) can cause serious CNS problems. WHY?
Brain cells are unable to produce sufficient ATP if the PDH complex is inactive.

PDH complex deficiency is the most common biochemical cause of congenital lactic acidosis.

Tricarboxylic Acid Cycle: Krebs Cycle

01 **Final common pathway for oxidation**

02 **Exclusively in mitochondria**

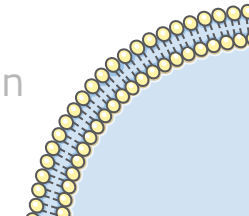
03 **Major source for ATP** 24 ATP

04 **Mainly catabolic with some anabolic features** (amphibolic)

05 **Synthetic reactions (anabolic features):**

- **Glucose from amino acids**
- **Nonessential amino acids**
- **Fatty acids**
- **Heme**

an iron-containing compound which forms part of hemoglobin

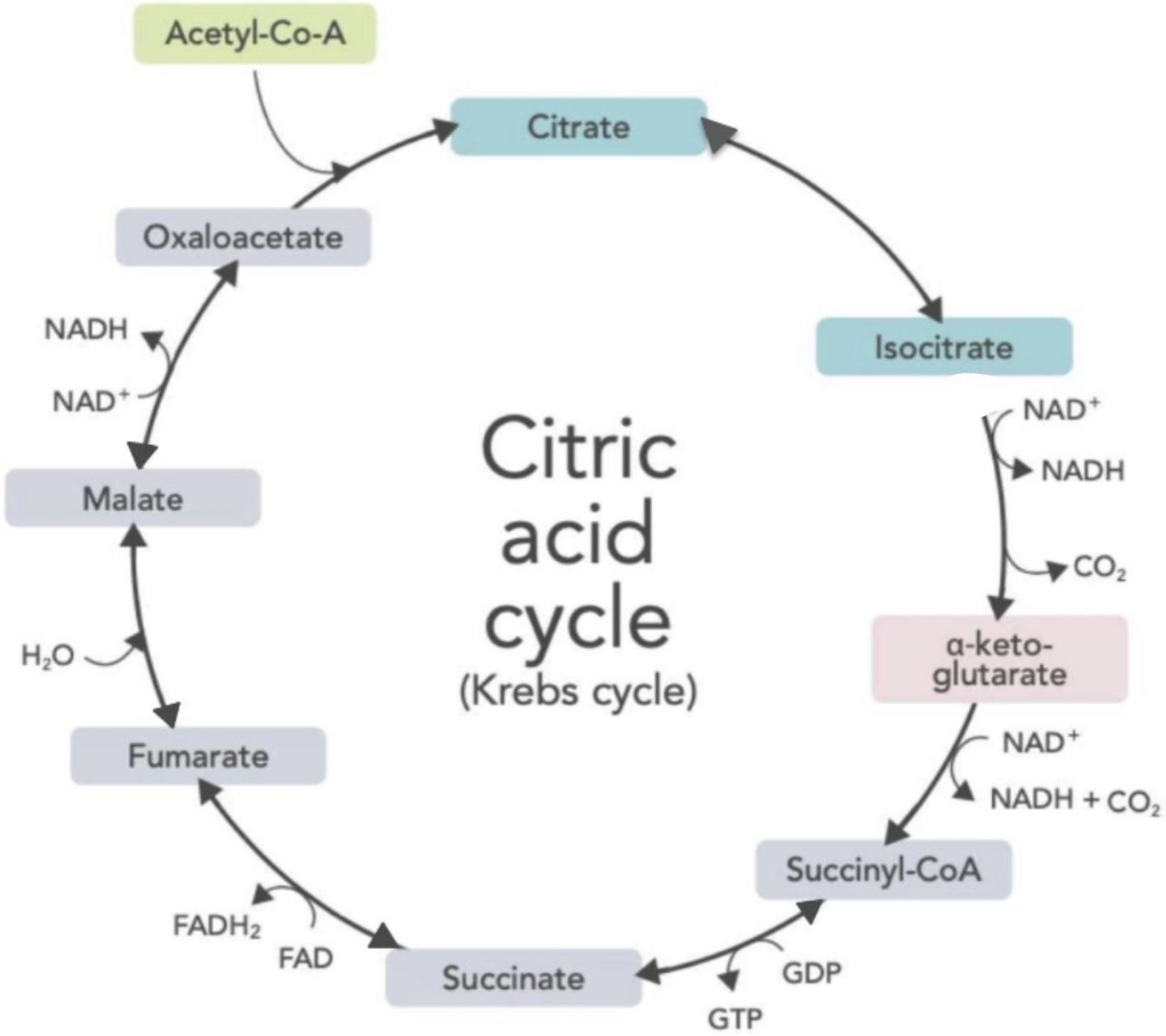


Krebs Cycle: overview

-helpful video

-helpful video

شرح بالعربي



OBJ Team 439:
Mnemonic to memorize the products of krebs cycle: Citrate Is Krebs Starting Substrate For Making Oxaloacetate

C = Citrate
I = Isocitrate
K = a-Ketoglutarate
S = Succinyl CoA
S = Succinate
F = Fumarate
M = Malate
O = Oxaloacetate

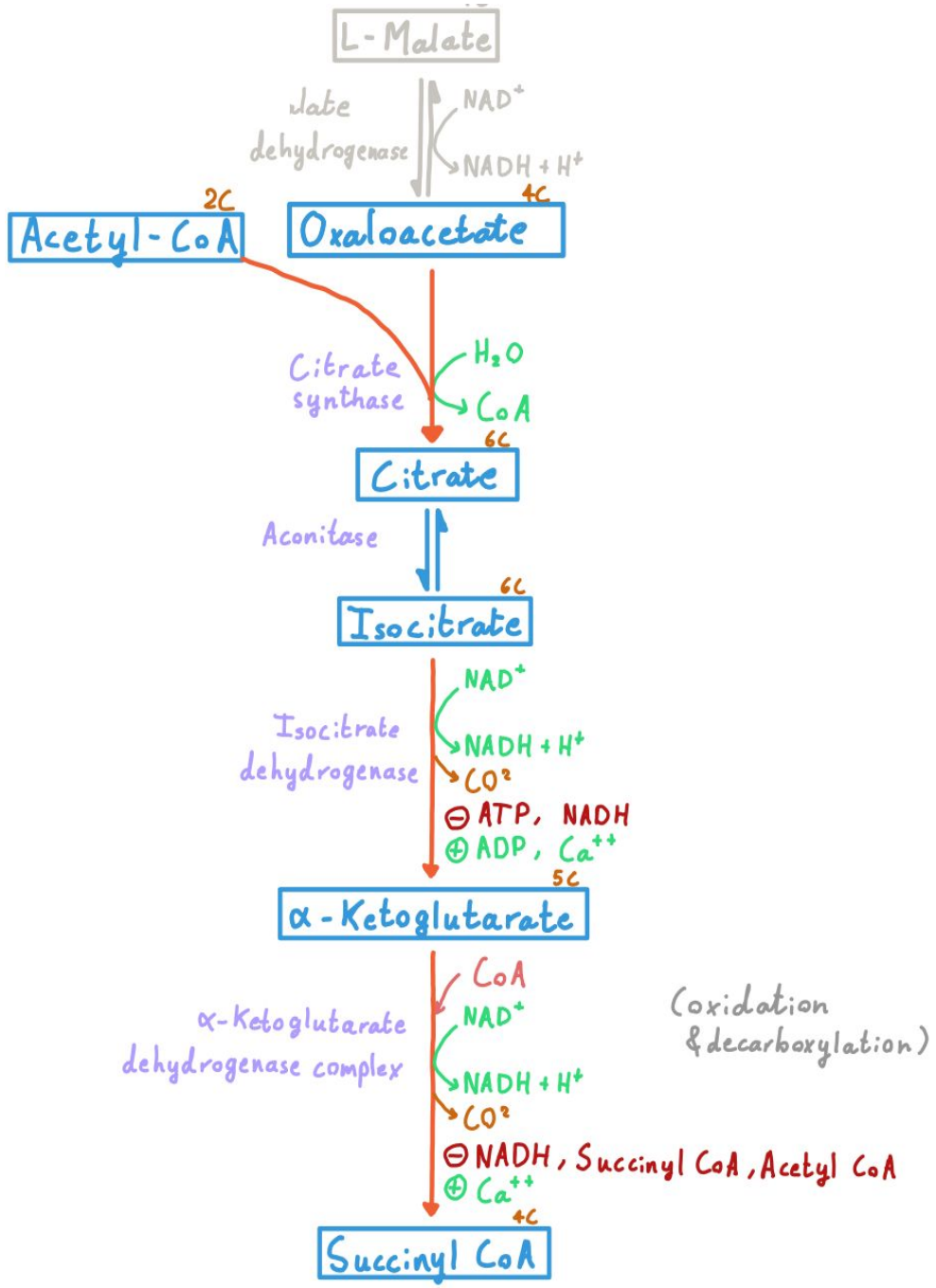
Krebs cycle (1)

1. Acetyl CoA (2C) (from pyruvate) + Oxaloacetate (4C) → Citrate (6C)
   (oxaloacetate from cycle, pyruvate carboxylase or fatty acids oxidation)
   - **Enzyme**: Citrate synthase
   - **In**: H_2O
   - **Out**: CoA

2. Citrate ⇄ Isocitrate (isomerase reaction)
   - **Enzyme**: Aconitase

3. Isocitrate (6C) → α-Ketoglutarate (5C)
   - **Enzyme**: Isocitrate dehydrogenase
   - **Regulation**:
     (-) ATP, NADH
     (+) ADP, Ca^{++} (Cofactor)

4. α-Ketoglutarate (5C) → Succinyl CoA (4C)
   - **Enzyme**: α-Ketoglutarate dehydrogenase complex
   - **In**: CoA, NAD^+
   - **Out**: CO_2, NADH + H^+
   - **Regulation**:
     (-) NADH, Succinyl CoA
     (+) Ca^{++}



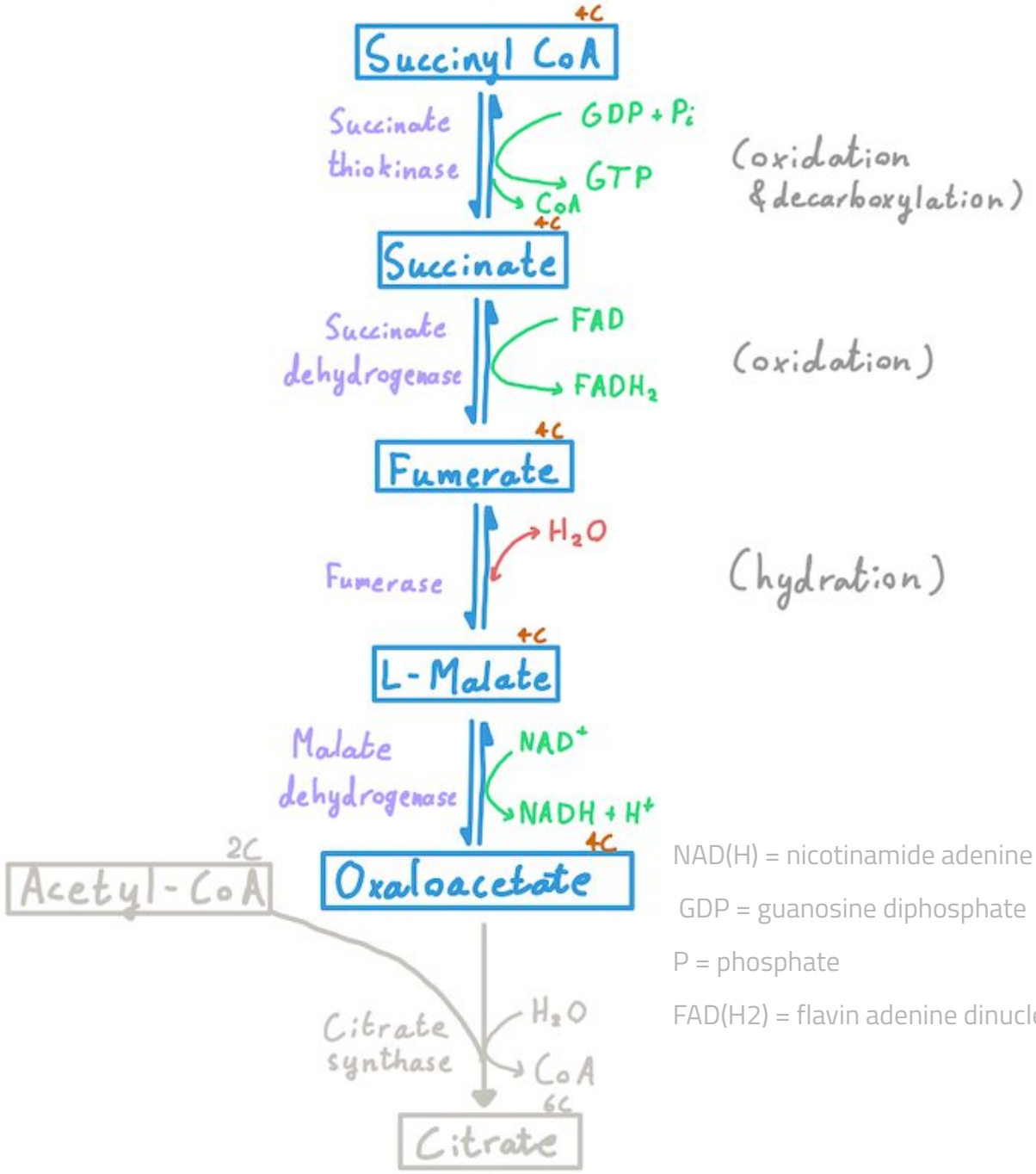
Krebs cycle (2) and (3)

5. Succinyl CoA ⇄ Succinate
   - **Enzyme**: Succinate thiokinase
   - **In**: GDP + P_i
   - **Out**: GTP, CoA
   - Note: this is the only substrate level phosphorylation in krebs cycle

6. Succinate ⇄ Fumarate
   - **Enzyme**: Succinate dehydrogenase
   - **In**: FAD
   - **Out**: $FADH_2$

7. Fumarate ⇄ Malate (L-Malate)
   - **Enzyme**: Fumarase
   - **In**: H_2O

8. Malate (L-Malate) ⇄ Oxaloacetate
   - **Enzyme**: Malate dehydrogenase
   - **In**: NAD^+
   - **Out**: NADH + H^+



NAD(H) = nicotinamide adenine dinucleotide

GDP = guanosine diphosphate

P = phosphate

FAD(H2) = flavin adenine dinucleotide.

ATP production by complete glucose oxidation

Aerobic glycolysis	2 ATP 2 NADH → 6 ATP 2+6 = **8 ATP**
Oxidative decarboxylation (preparation)	per pyruvate: 1 NADH → 3 ATP 3x2 = **6 ATP**
Krebs cycle	per pyruvate: 3 NADH → 9 ATP 1 $FADH_2$ → 2 ATP 1 GTP → 1 ATP 12x2 = **24 ATP**
Total	8 + 6 + 24 = **38 ATP**

Note:

1 GTP = 1 ATP

1 NADH = 3 ATP

1 $FADH_2$ = 2 ATP

Regulation of oxidative decarboxylation & krebs cycle

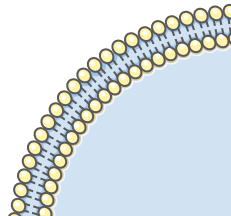
- PDH complex & krebs cycle are both **up-regulated** in response to **decrease** in the ratio of:
  - ATP : ADP
  - NADH : NAD^+

- Krebs cycle activators:
  - ADP
  - Ca^{++}

- Krebs cycle inhibitors:
  - ATP
  - NADH

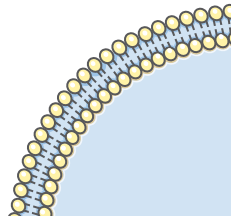
Note:

Krebs cycle AKA **TCA cycle** (tricarboxylic acid cycle) AKA **Citric acid cycle**



Take home messages

- Pyruvate is oxidatively decarboxylated by PDH to acetyl CoA inside the mitochondria
- Krebs cycle: Final common pathway for the oxidation of carbohydrates, fatty acids and amino acids
- Occurs in the mitochondria, Aerobic.
- Mainly catabolic, with some anabolic reactions
- The complete oxidation of one glucose molecule results in a net production of 38 ATP molecules



step	reactant	product	enzyme	CO_2	ATP	NADH	$FADH_2$
Glycolysis (cytosol)	D-glucose	Glucose 6-phosphate	Hexokinase (all tissues) or Glucokinase (liver)	_	-1	_	_
	Glucose 6-phosphate	Fructose 6-phosphate	Phosphoglucos isomerase	_	_	_	_
	Fructose 6-phosphate	Fructose 1,6-bisphosphate	Phosphofructokinase-1 (PFK-1)	_	-1	_	_
	* Fructose 1,6-bisphosphate * Dihydroxyacetone phosphate	*(glyceraldehyde 3-phosphate+Dihydroxyacetone phosphate) *(glyceraldehyde 3-phosphate)	* Aldolase A * Triose phosphate isomerase	_	_	_	_
	2 (glyceraldehyde 3-phosphate)	2 (1,3-bisphosphoglycerate)	glyceraldehyde 3-phosphate dehydrogenase	_	_	2(1)= 2	_
	2 (1,3-bisphosphoglycerate)	2 (3-phosphoglycerate)	Phosphoglycerate kinase	_	2(1)= 2	_	_
	2 (3-phosphoglycerate)	2 (2-phosphoglycerate)	Phosphoglycerate mutase	_	_	_	_
	2 (2-phosphoglycerate)	2 (2-phosphoenolpyruvate)	Enolase	_	_	_	_
	2 (2-phosphoenolpyruvate)	2 (pyruvate)	Pyruvate kinase (PK)	_	2(1)= 2	_	_
Oxidative decarboxylation (mitochondria)	2 (pyruvate)	2 (acetyl CoA)	Pyruvate dehydrogenase complex (PDH)	2(1)= **2**	_	2(1)= 2	_
Krebs cycle [TCA cycle] (mitochondria)	2 (acetyl CoA) + 2 H_2O + 2 (Oxaloacetate)	2 (citrate)	Citrate synthase	_	_	_	_
	2 (citrate)	2 (isocitrate)	Aconitase	_	_	_	_
	2 (isocitrate)	2 (α- ketoglutarate)	Isocitrate dehydrogenase	2(1)= **2**	_	2(1)= 2	_
	2 (α- ketoglutarate)	2 (succinyl CoA)	αKG dehydrogenase	2(1)= **2**	_	2(1)= 2	_
	2 (succinyl CoA)	2 (Succinate)	Succinate thiokinase	_	2(1)= 2	_	_
	2 (Succinate)	2 (fumarate)	Succinatedehydrogenase	_	_	_	2(1)= 2
	2 (fumarate)	2 (malate)	fumerase	_	_	_	_
	2(malate)	2 (oxaloacetate)	Malate dehydrogenase	_	_	2(1)= 2	_

Quiz

Q1: What is the step of Krebs cycle that include substrate level phosphorylation?

A	Isocitrate → a-ketoglutarate	B	Succinyl CoA → Succinate	C	Succinate → Fumarate	D	Malate → Oxaloacetate

Q2:TCA cycle activators are:

A	ADP,Ca2+	B	ATP,NADH	C	FADH2,ADP	D	ADP,NADH

Q3:PDH kinase is inhibited by:

A	ATP	B	NADH	C	Pyruvate	D	Acetyl CoA

Q4: How many ATPs produced per $FADH_2$?

A	1	B	2	C	3	D	4

Q5: Succinyl CoA

A	activates isocitrate dehydrogenase	B	inhibits isocitrate dehydrogenase	C	activates a-Ketoglutarate dehydrogenase complex	D	inhibits a-Ketoglutarate dehydrogenase complex

Answer Key: 1) B 2) A 3) C 4) B 5) D

Q6:What are the irreversible steps in TCA cycle?

Q7:What is the most common biochemical cause for congenital lactic acidosis?

Q8:Enumerate the fates of pyruvate?

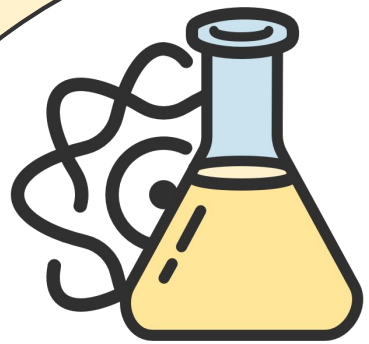
Q9:What is the cofactor for PDH phosphatase?

A6:
Acetyl CoA + Oxaloacetate→ Citrate
Isocitrate → a-Ketoglutarate
a-Ketoglutarate → Succinyl CoA

A7:
PDH complex deficiency

A8:
Ethanol, Lactate,Acetyl CoA, Oxaloacetate and Alanine

A9: Ca2+



Biochemistry 441

Girls

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Wareef Almousa
Joud Alangari
Fay Alluhaidan
Sarah Alhamlan
Arwa Almobeirek
Jumana AL-qahtani
Latifa Alkhdiri
Alanoud Alhaider
Futoon Almotairi
Manal Aldhirgham
Raaoum Jabor
Norah alawlah
Shahad Helmi
Rand Aldajani

Khalid Alhamdi - Leader

Ahmed Alayban
Sultan Alosaimi
Abdullah Alomran
Bassam Alghizzi
Ibrahim Aljurayyan
Mohammed Almutairi
Turki Alkhalifa
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