Citric Acid Cycle

Specific learning objectives

- Steps of TCA cycle
- Significance - final common oxidative pathway
- Amphibolic role of TCA cycle
- Regulation
- Inhibitors of TCA cycle

Stages of Oxidation of Foodstuffs

First Stage - Primary metabolism.

Digestion in the gastrointestinal tract

Converts the macromolecules into small units.

Second Stage - Secondary or intermediary metabolism.

Products of digestion are absorbed, catabolized & ultimately oxidized to CO_2 in TCA cycle.

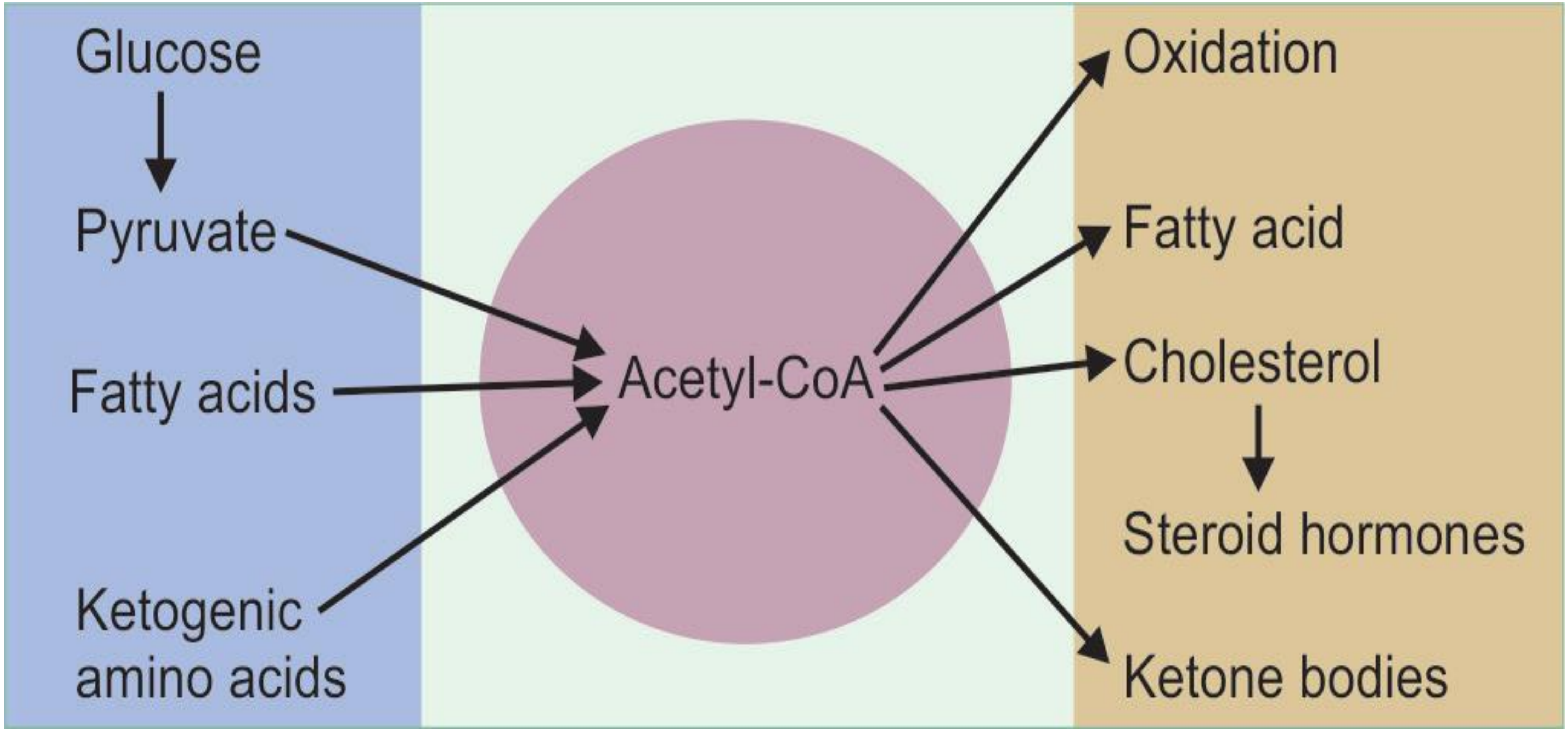
NADH and FADH2 are generated.

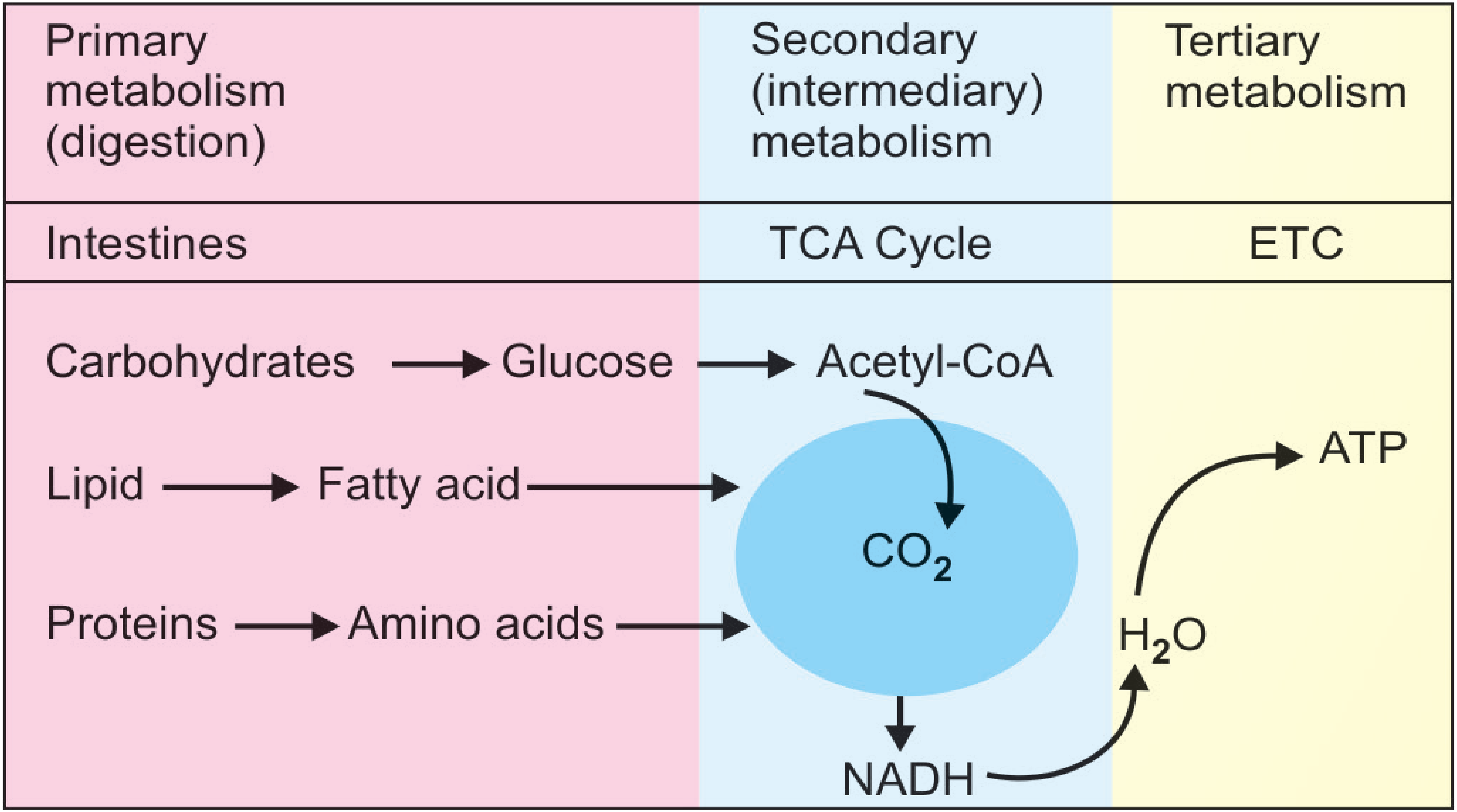
Third Stage - Tertiary metabolism or **internal respiration**

Reduced equivalents enters Electron transport chain or Respiratory chain,

Energy is released as ATP.

Sources and utilization of acetyl-CoA





Primary metabolism (digestion)
Secondary (intermediary) metabolism
Tertiary metabolism
Intestines
TCA Cycle
ETC
Carbohydrates
Glucose
Acetyl-CoA
Lipid
Fatty acid
Proteins
Amino acids
CO_2
NADH
H_2O
ATP

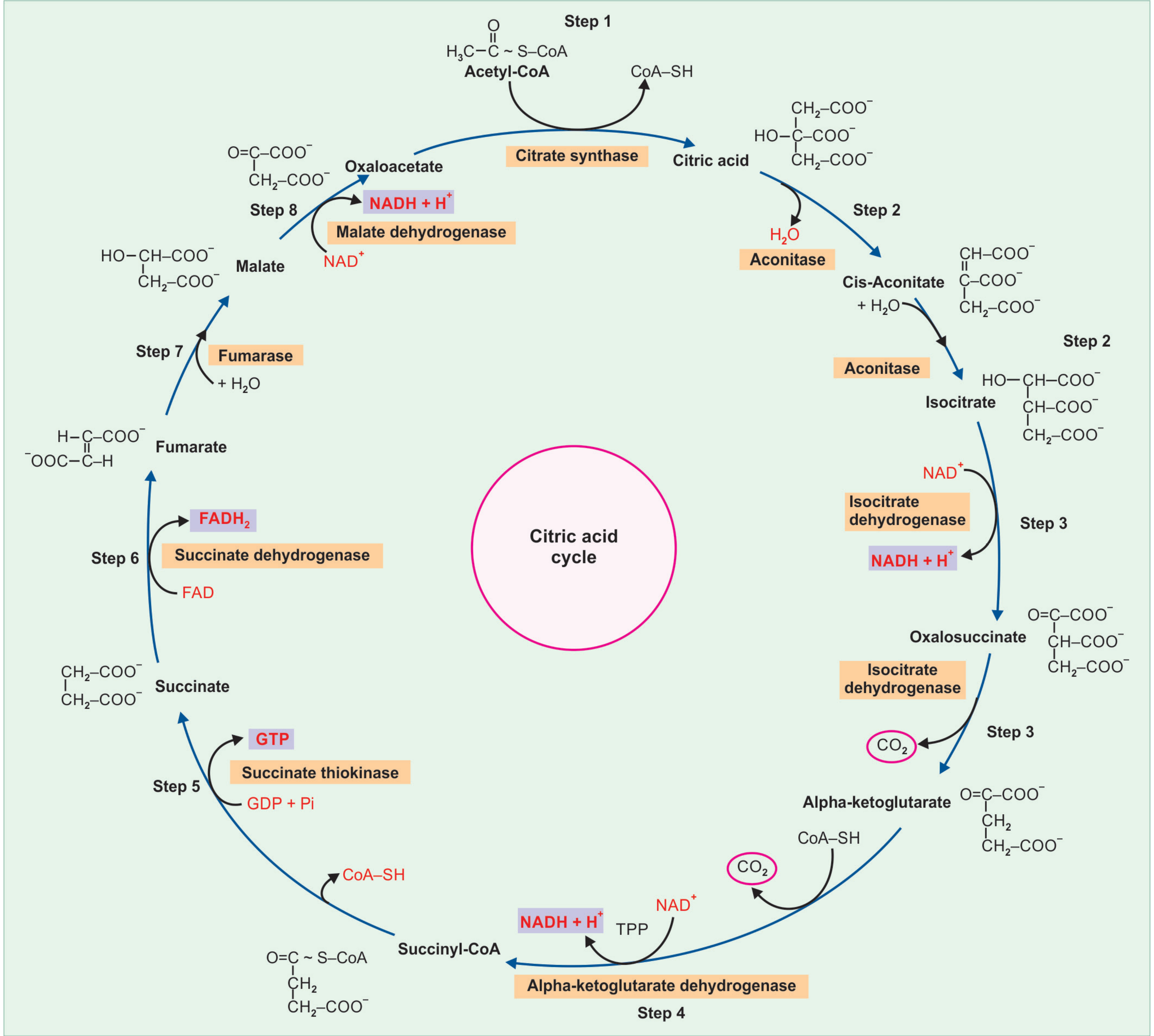
Tricarboxylic acid cycle/ Krebs cycle/ Citric acid cycle

Site: Mitochondria

Functions

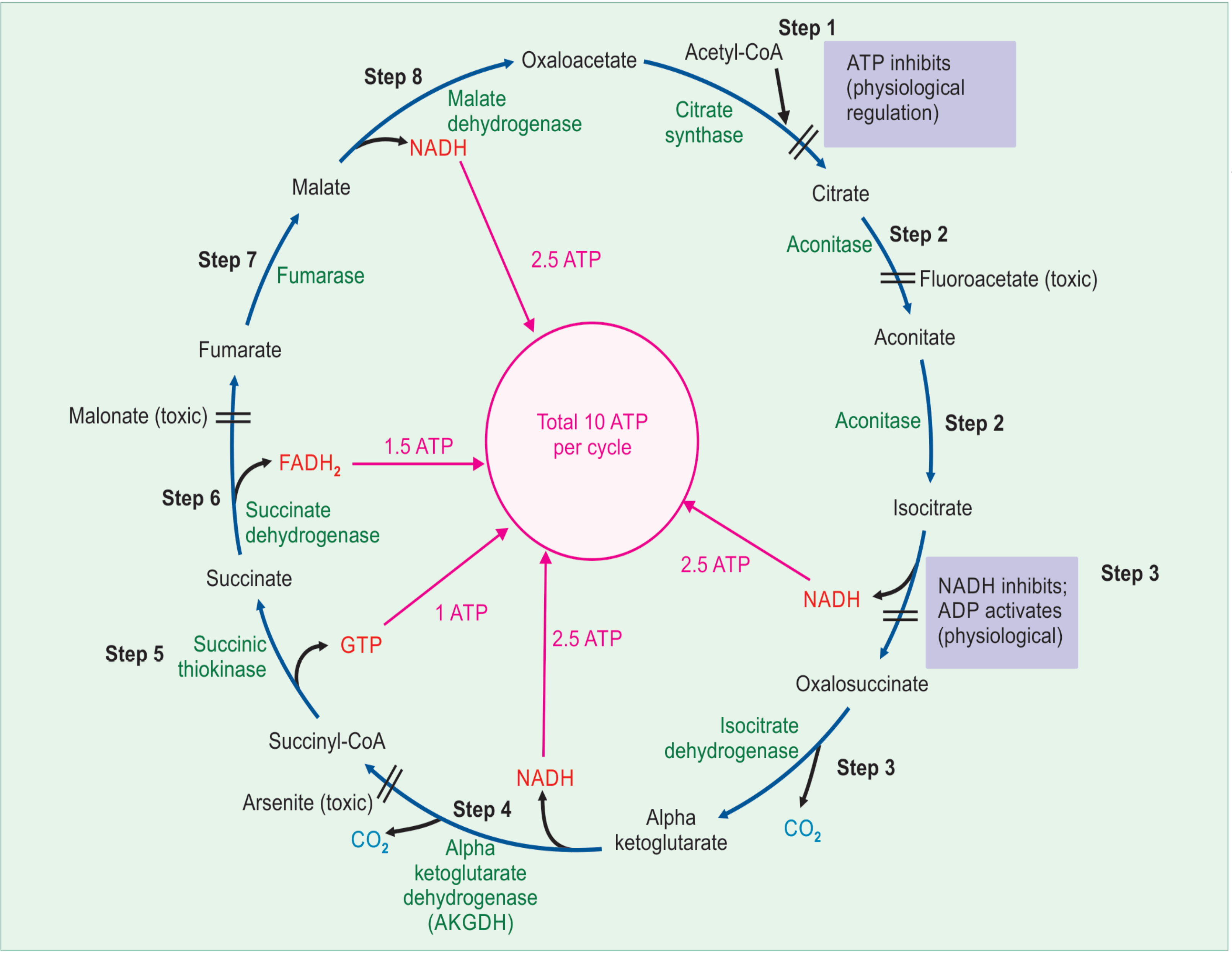
- Final common oxidative pathway Acetyl CoA to CO_2
- Source of reduced coenzymes – substrate for respiratory chain
- Amphibolic role
- Precursors for amino acid and nucleotide synthesis
- Controls key enzymes of other pathways

Sir Hans Krebs



Mnemonic: CCis IO αS² FMO

Mnemonic: Citrate Is Krebs Starting Substrate For Making OAA



Physiological regulatory steps :

- Citrate synthase is physiologically inhibited by ATP.
- ICDH is inhibited by NADH and activated by ADP.

Steps where energy is trapped :

- Marked with the coenzyme and the number of ATP generated during that reaction.

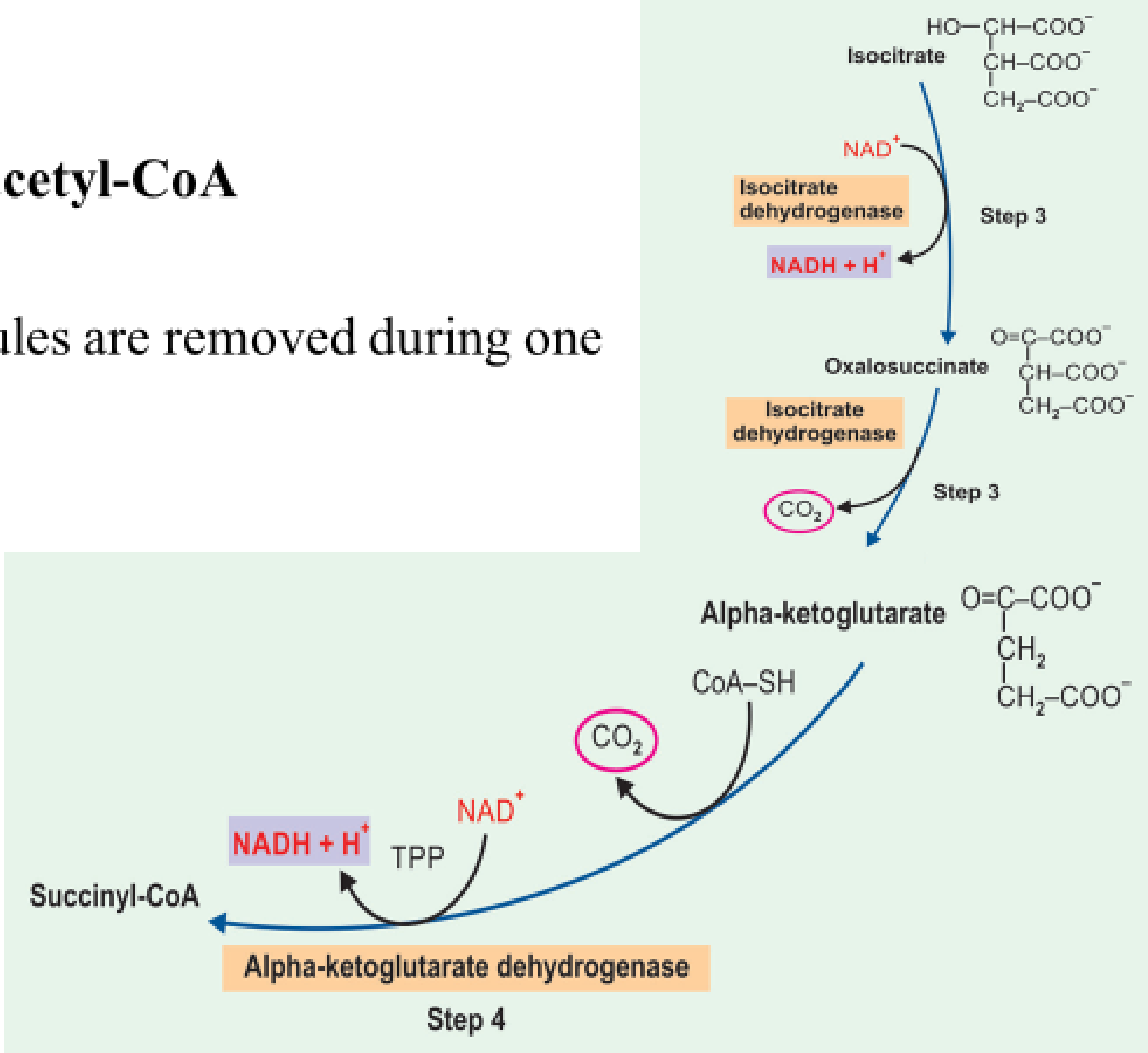
<u>Total 10 ATPs are generated during 1 cycle.</u>

Significance

1. Complete oxidation of acetyl-CoA
2. ATP generation
3. Final common oxidative pathway
4. Integration of major metabolic pathways
5. Fat is burned on the wick of carbohydrates
6. Excess carbohydrates are converted as neutral fat
7. No net synthesis of carbohydrates from fat
8. Carbon skeletons of amino acids finally enter the citric acid cycle
9. Amphibolic pathway
10. Anaplerotic role

1. Complete oxidation of acetyl-CoA

- Two carbon dioxide molecules are removed during one turn of citric acid cycle



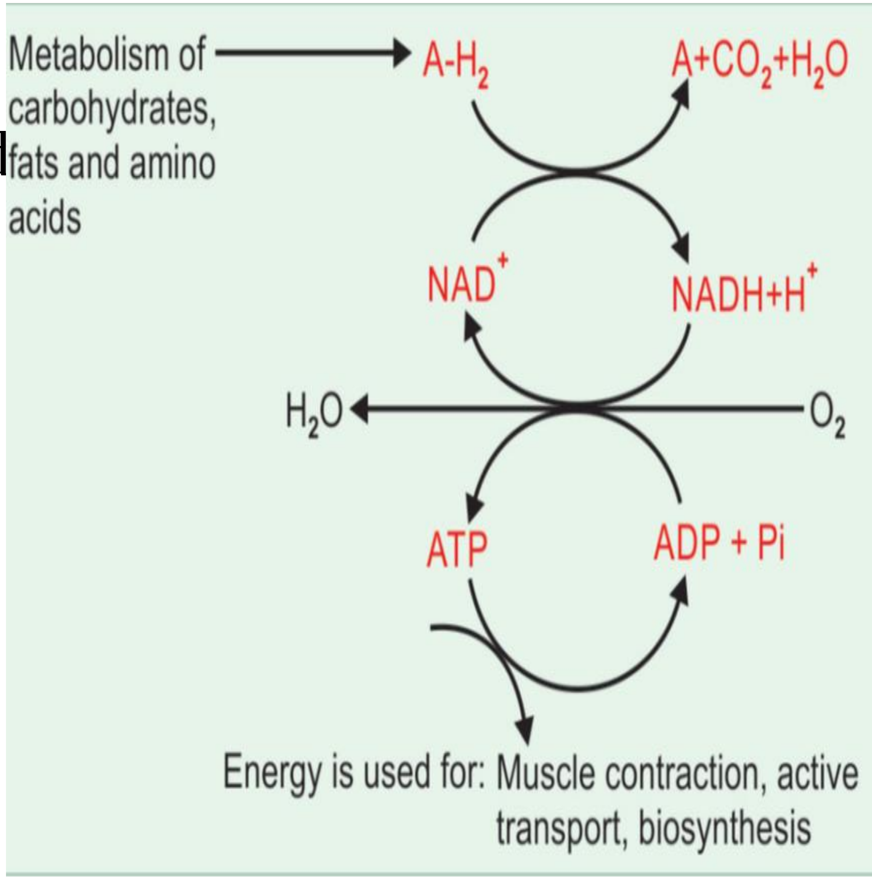
2. ATP Generation Steps of Citric Acid Cycle

STEP NO	REACTIONS NO.	CO-ENZYME	ATPs GENERATED
3	Isocitrate → alpha ketoglutarate	NADH	2.5
4	Alpha ketoglutarate → succinyl CoA	NADH	2.5
5	Succinyl CoA → Succinate	GTP	1
6	Succinate → Fumarate	FADH2	1.5
8	Malate → Oxaloacetate	NADH	2.5
		Total	**10**

3. Final common oxidative pathway

All major ingredients in foodstuffs are finally oxidized through TCA cycle

All biochemical processes use ATP for meeting energy needs



4. Integration of major metabolic pathways

CHO – glycolysis- pyruvate – PDH – Acetyl CoA – TCA

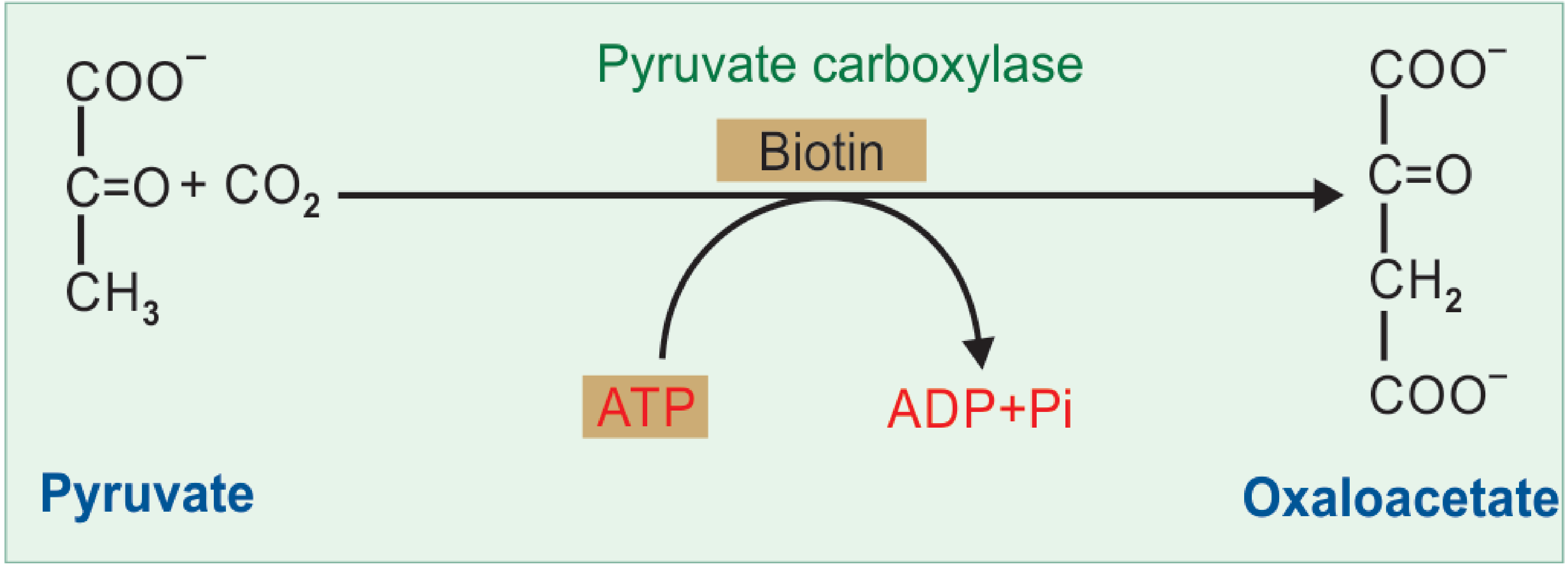
FA – Beta oxidation – Acetyl CoA – TCA

Glucogenic Aminoacids – Transamination – TCA

Ketogenic Aminoacids – Acetyl CoA -TCA

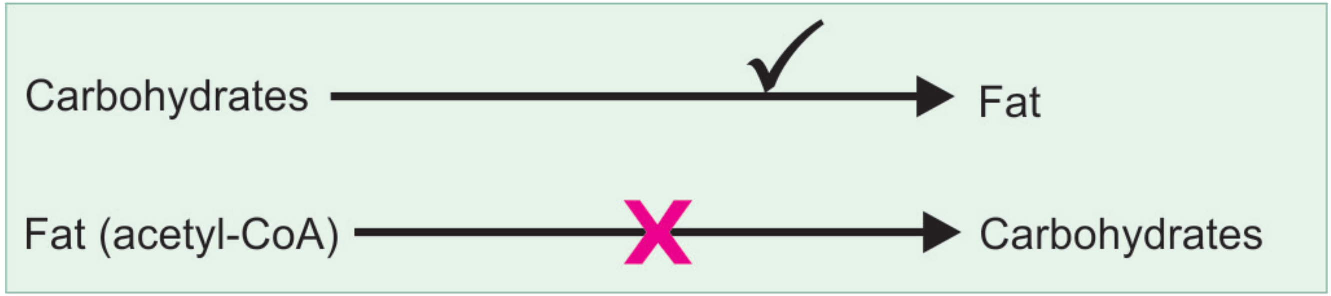
5. Fat is burned on the wick of carbohydrates

- Oxidation of fat (Acetyl CoA) needs oxaloacetate
- Oxaloacetate is regenerated and is the true catalyst
- Major source of OAA is pyruvate (carbohydrate)



6. Excess carbohydrates are converted into neutral fats and deposited in adipose tissue

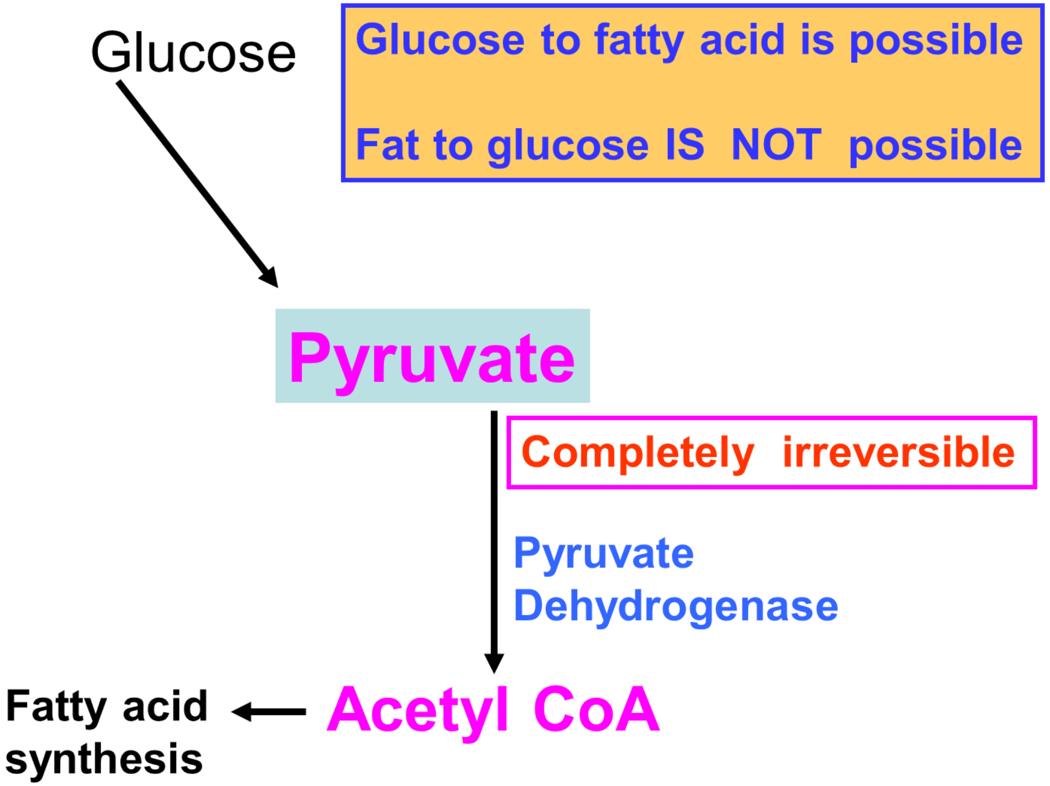
- Fat cannot be converted to glucose



7. No net synthesis of carbohydrates from fat

Acetyl CoA is completely oxidised to CO_2,

thus cannot be used for gluconeogenesis



8. Carbon skeletons of amino acids finally enter the citric acid cycle

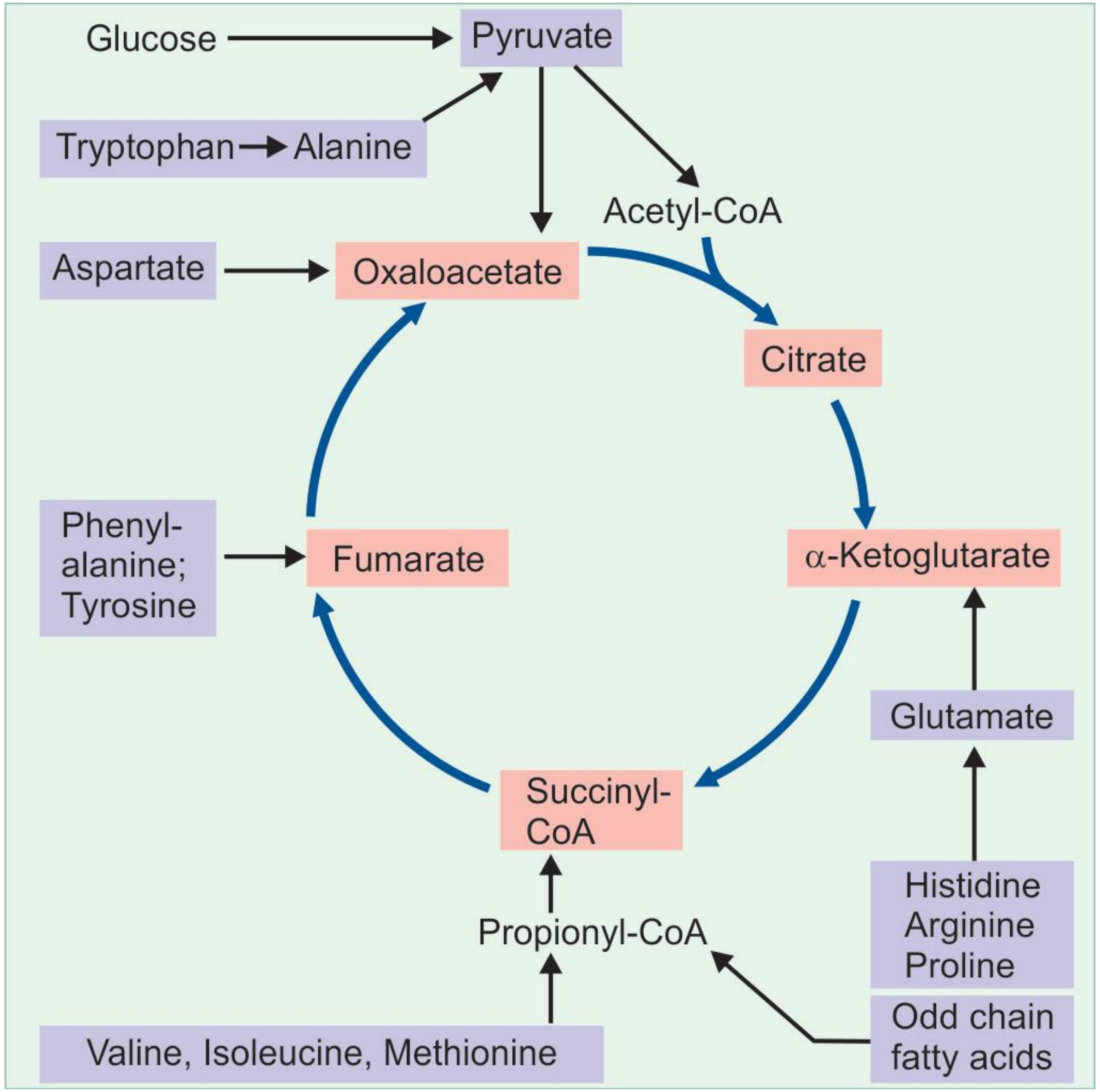
Glucogenic Aminoacids – Transamination – TCA cycle intermediates

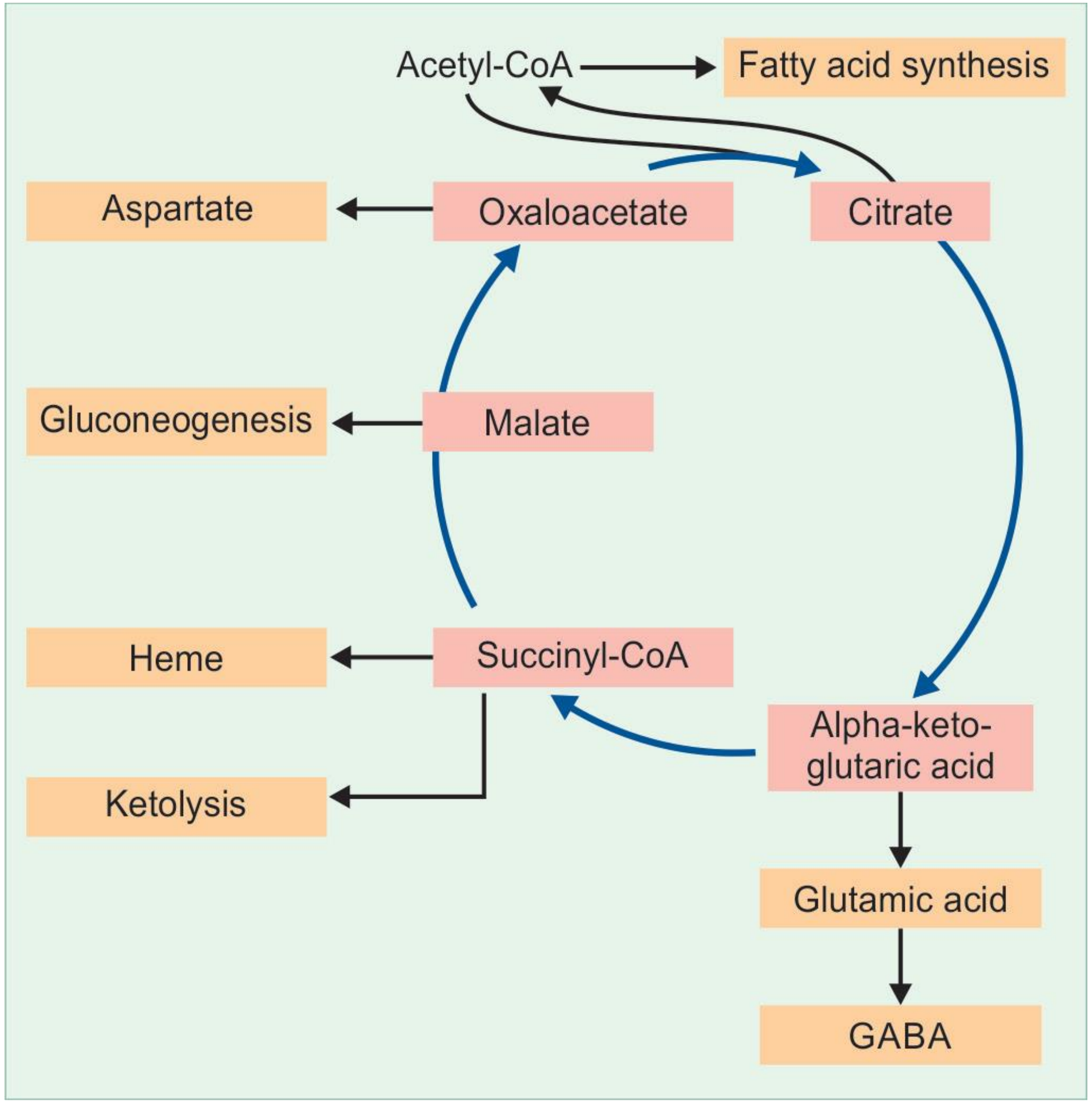
Ketogenic Aminoacids – Acetyl CoA –TCA cycle / ketone body formation

9. Amphibolic pathway = Catabolic + Anabolic

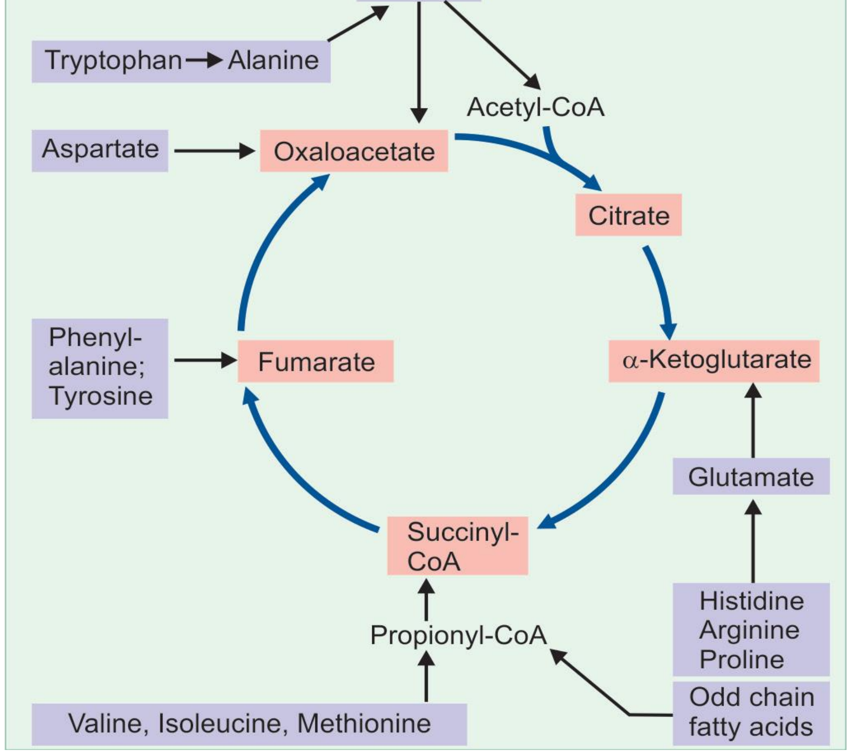
Continuous influx and efflux of 4-C units from TCA cycle - Metabolic traffic circle

Influx & efflux of TCA cycle intermediates.





• **10. Anaplerotic role (Filling up reactions)**



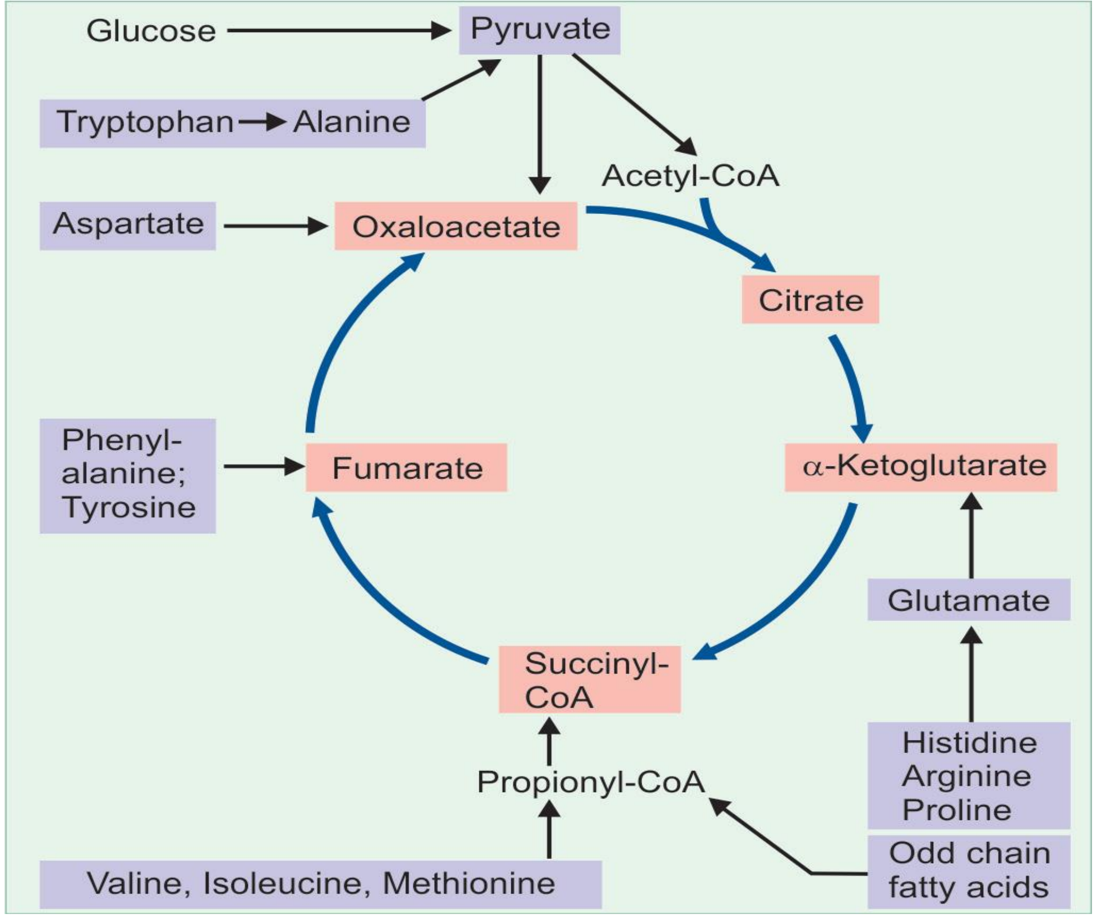
Reactions which deplete TCA cycle intermediates are ***Cataplerotic*** reactions and those which replenish them are ***Anaplerotic*** reactions

TCA cycle is the source of precursors for biosynthetic pathways

- Succinyl CoA used for Heme synthesis
- Oxaloacetate used for Aspartate synthesis

To counterbalance this **Cataplerotic loss** and keep up the concentration of 4C units **Anaplerotic or influx or filling up or replenishing** reactions are important

Anaplerotic reactions



- Pyruvate carboxylase enzyme : pyruvate to **oxaloacetate**
- NADP+ dependent malic enzyme : pyruvate to **malate**
- Aspartate to **oxaloacetate**
- Glutamate to **alpha keto glutarate**
- Glutamine, histidine, arginine, proline to glutamate – **alpha keto glutarate**
- Valine, isoleucine, methionine, threonine to propionyl CoA - **Succinyl CoA**
- Phenylalanine, tyrosine, urea cycle - **Fumarate**
- Ketogenic aminoacids leucine, lysine, isoleucine, tryptophan, phenylalanine, tyrosine - **Acetyl CoA**

Regulation of citric acid cycle

- *Low cellular energy – TCA cycle operates faster*
- *Major regulatory factor is the flux of acetyl CoA into TCA cycle from PDH reaction*

  Covalent modification: Phosphorylated enzyme is inactive

    PDH kinase inactivates and PDH phosphatase activates pyruvate dehydrogenase
- Allosteric enzyme activators and inhibitors
- ATP/ADP and NADH/ NAD+ ratio
- Coenzymes and Cofactors

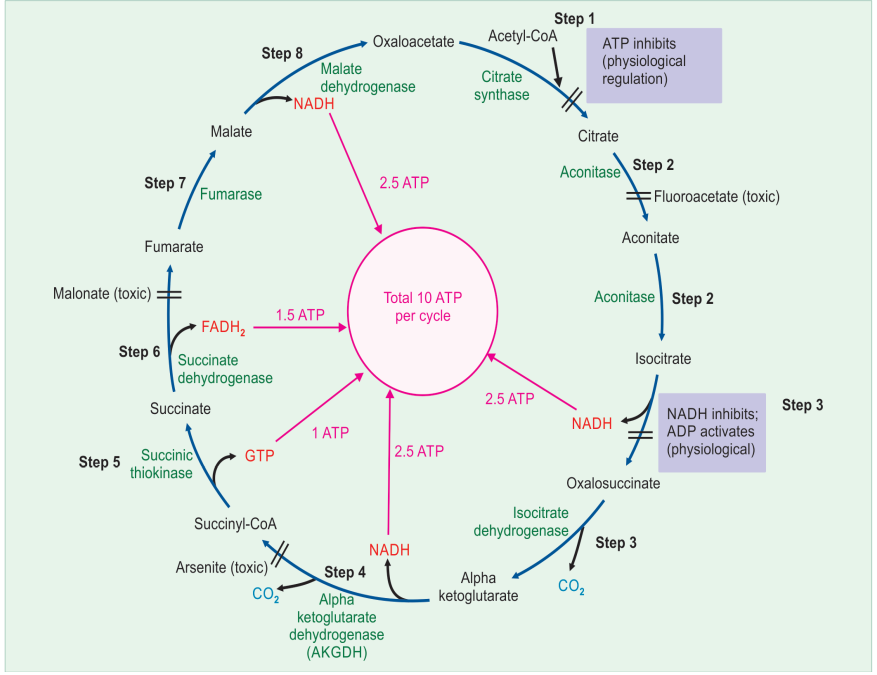
    ICDH needs NAD+

    AKGDH needs TPP, CoA, FAD, NAD+ and lipoamide

    Succinate DH needs FAD

    Malate DH needs NAD+
- Mg, Mn, Ca , Pi are required

Regulation of citric acid cycle



1. *Citrate and citrate synthase*

    ATP inhibits citrate synthase.

    Citrate inhibits PFK, the key enzyme of glycolysis.

2. *Availability and cellular need of ATP* : TCA cycle is tightly coupled to the respiratory chain providing ATP.

    Citrate Synthase:- Inhibited by citrate; ATP

    Hypoxia inhibits ETC, NADH and FADH2 accumulates – inhibits TCA cycle

3. *Isocitrate Dehydrogenase:*- Inhibited by NADH

4. *α-KG Dehydrogenase* :- Inhibited by succinyl Co-A and NADH.

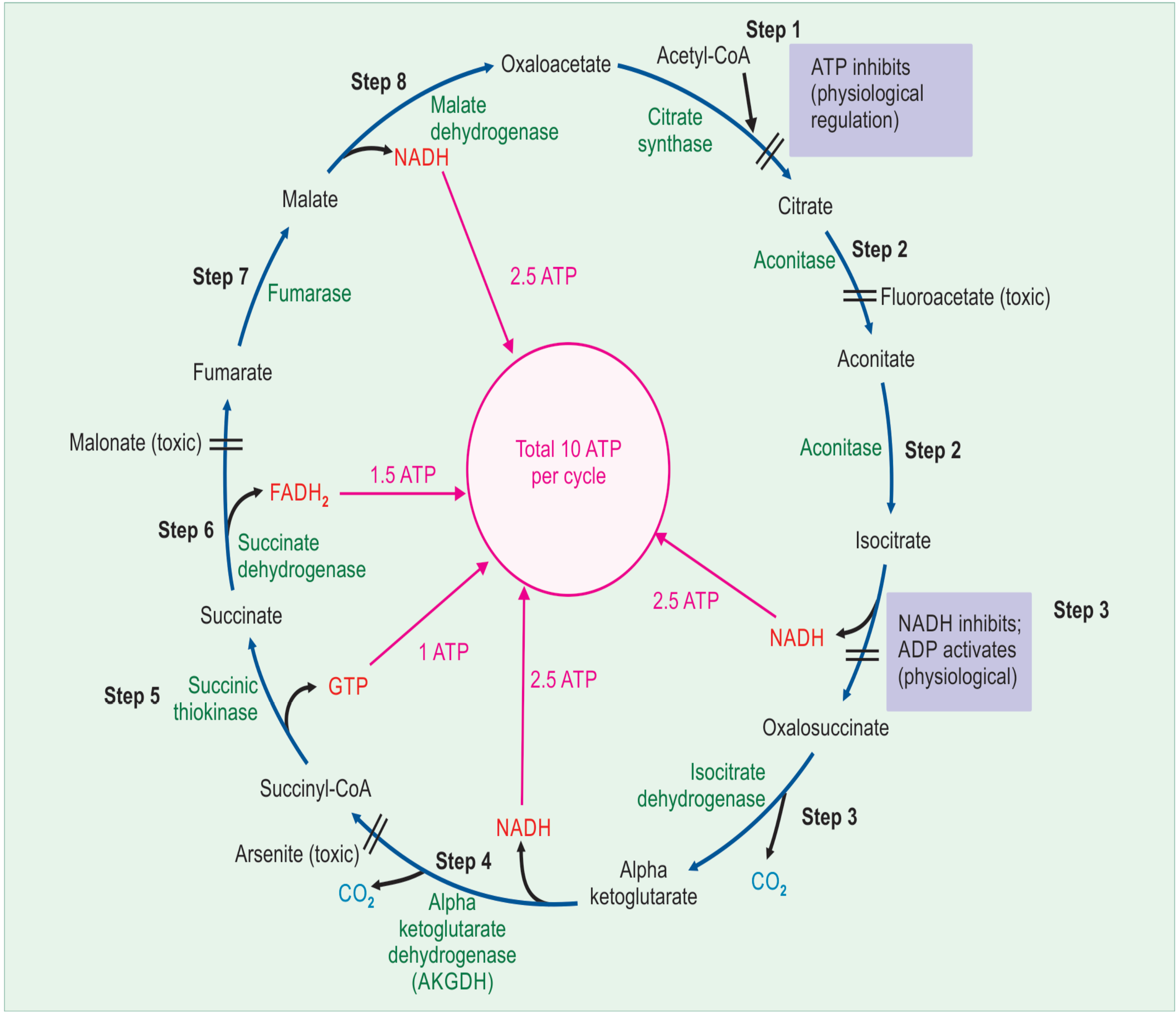
5. *Availability of oxaloacetate* – regenerated from succinate – decides speed of TCA cycle.

Inhibitors of TCA Cycle

Heavy metal ions like arsenite, arsenate, mercury inhibits TCA cycle

- Fluoroacetate : inhibits Aconitase - Non-competitive type
- Arsenite : inhibits α-KGDH - non-competitive type
- Malonate : inhibits SuccinateDH - competitive type

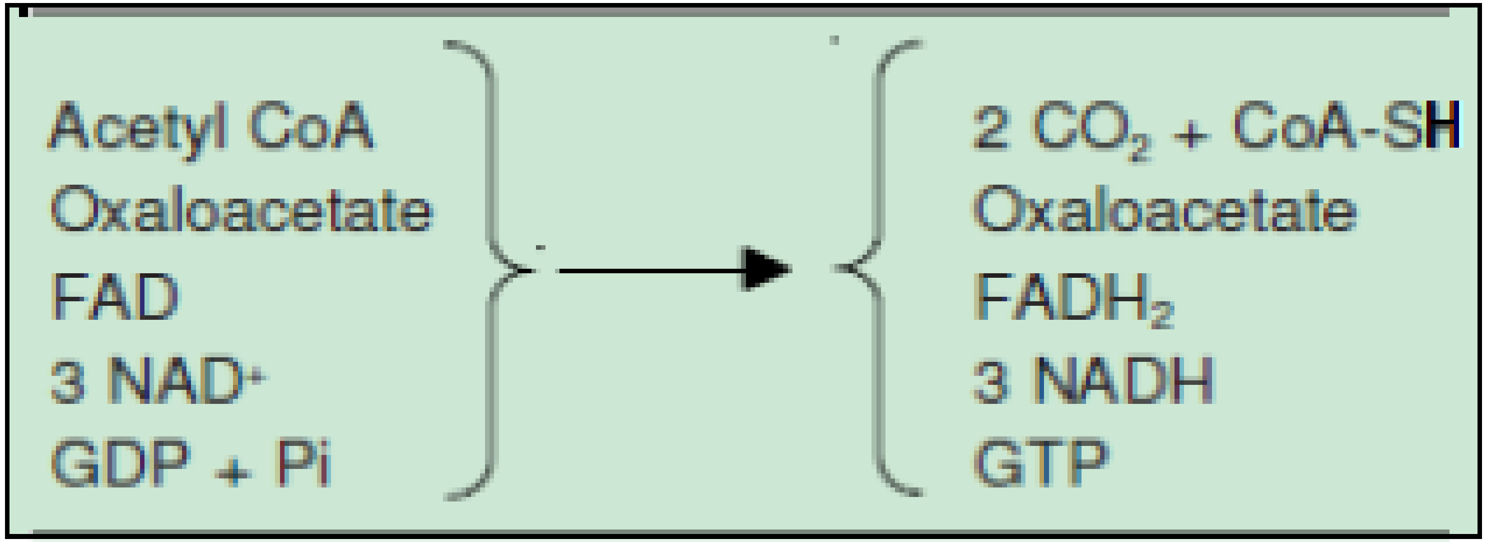
Malonate has structural similarity to succinate



Metabolic Defects of Oxidative Metabolism

Enzymes	Reactions catalysed	Abnormalities
Pyruvate dehydrogenase	Pyruvate →acetyl CoA	Lactic acidosis, Neurological disorders
Acyl CoA-dehydrogenase	Fatty acyl CoA → alpha, beta- unsaturated fatty acyl CoA	Organic aciduria, glutaric aciduria, acidosis, hypoglycemia. Electron flow from FAD → CoQ is affected
Pyruvate carboxylase	Pyruvate →Oxaloacetate	Oxaloacetate needed for sparking TCA cycle is deficient. Lactic acidosis, hyperammonemia and hyperalaninemia

Summary of Bioenergetics



1.**Free energy** is a measure of the energy available to perform useful work.

2.ΔG can predict the direction of a chemical reaction.

3.Chemical reactions can be **coupled** which allows an energetically unfavorable reaction to proceed to conclusion.

4.ΔG measured under physiological conditions may be different from that at a standard state.


thank you