

# **Amphibolic nature of Krebs Cycle**

**How what we are is what we eat**

- In aerobic organisms, the citric acid cycle is **an amphibolic pathway, one that serves in both catabolic and anabolic processes.**
- Since the citric acid does both synthesis (anabolic) and breakdown (catabolic) activities, it is called an **amphibolic pathway**
- **The citric acid cycle is amphibolic (i.e it is both anabolic and catabolic in its function).**
- **It is said to be an AMPHIBOLIC pathway, because it functions in both degradative or catabolic and biosynthetic or anabolic reactions (amphi = both)**

**A central metabolic pathway or amphibolic pathway is a set of reactions which permit the interconversion of several metabolites, and represents **the end of the catabolism** and **the beginning of anabolism****

- The KREBS CYCLE or citric acid cycle is a series of reactions that degrades acetyl CoA to yield carbon dioxide, and energy, which is used to produce NADH, H<sup>+</sup> and FADH.
- The KREBS CYCLE **connects the catabolic pathways that begin with the digestion and degradation of foods in stages 1 and 2 with the oxidation of substrates in stage 3 that generates most of the energy for ATP synthesis.**
- **The citric acid cycle is the final common pathway in the oxidation of fuel molecules. In stage 3 of metabolism, citric acid is a final common catabolic intermediate in the form of acetylCoA.**
- **This is why the citric acid cycle is called a central metabolic pathway.**

# Anaplerosis and Cataplerosis

**Anaplerosis** is a series of enzymatic reactions in which metabolic intermediates enter the citric acid cycle from the cytosol.

**Cataplerosis** is the opposite, a process where intermediates leave the citric acid cycle and enter the cytosol.

In muscle, anaplerosis is important for increasing citric acid throughput during periods of exercise.

There is some evidence that anaplerosis is required for a glucose-induced rise in mitochondrial ATP production.

Some amino acids (the building blocks of proteins) enter and leave the citric acid cycle through anaplerosis and cataplerosis.

# Subway Analogy

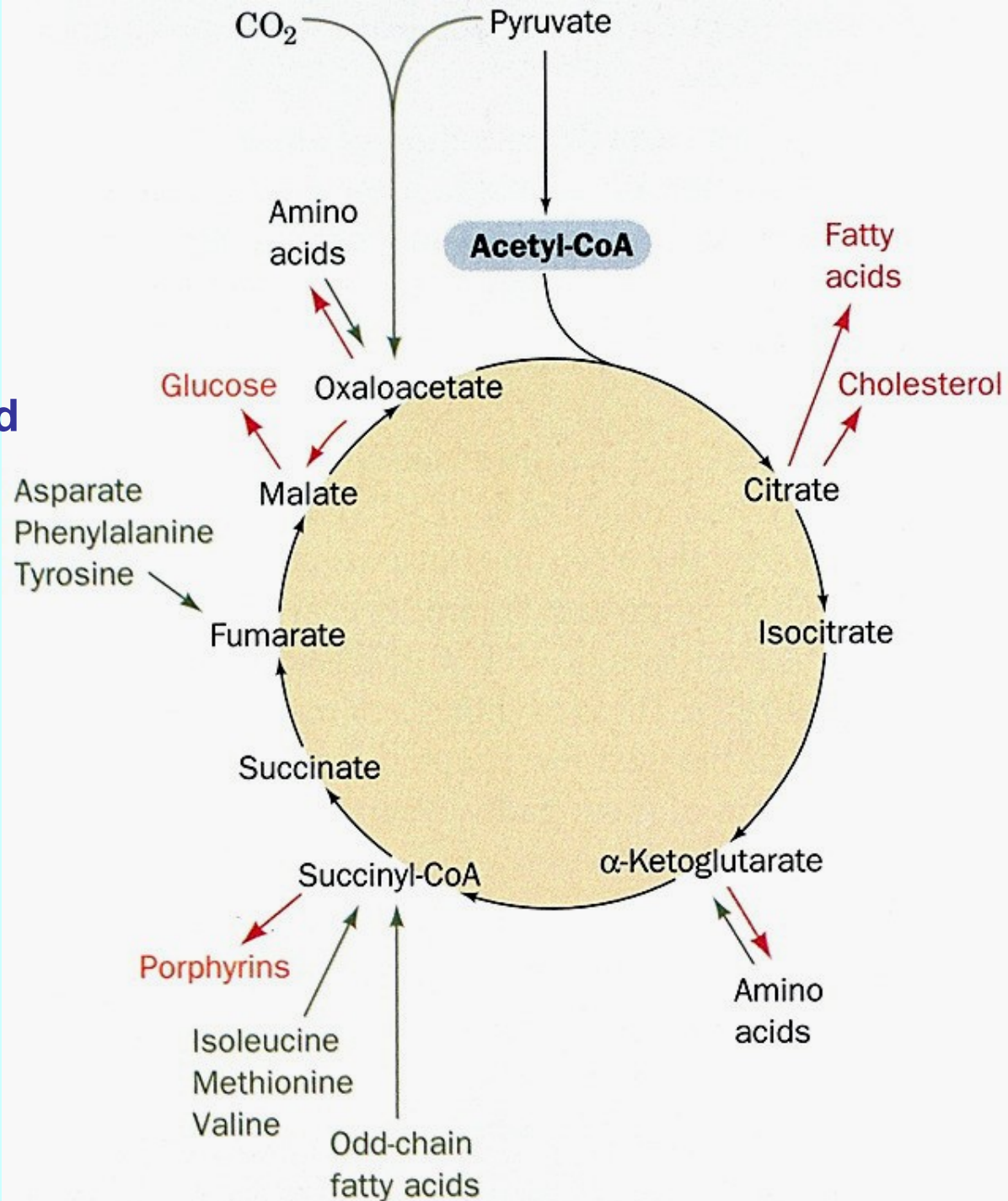
Citric Acid Cycle is like a subway system:

- Acetyl-CoA is like people getting on at station A
- NADH is like people getting off at station B
- Intermediates are like the subway cars
- **Anaplerosis is like adding cars to the system**
- **Cataplerosis is like removing cars to use for spare parts**

# Krebs Cycle is Amphibolic

- **Contains both catabolic and anabolic reactions.**
- **Catabolic**
  - Energy from oxidation of acetyl CoA is stored in reduced coenzymes.
- **Anabolic**
  - Several intermediates are precursors in biosynthetic pathways.

Diagram of the citric acid cycle, indicating positions at which intermediates are drawn off for use in **anabolic pathways (red arrows)** and points where **anaplerotic reactions replenish depleted cycle intermediates (dark green arrows)**.

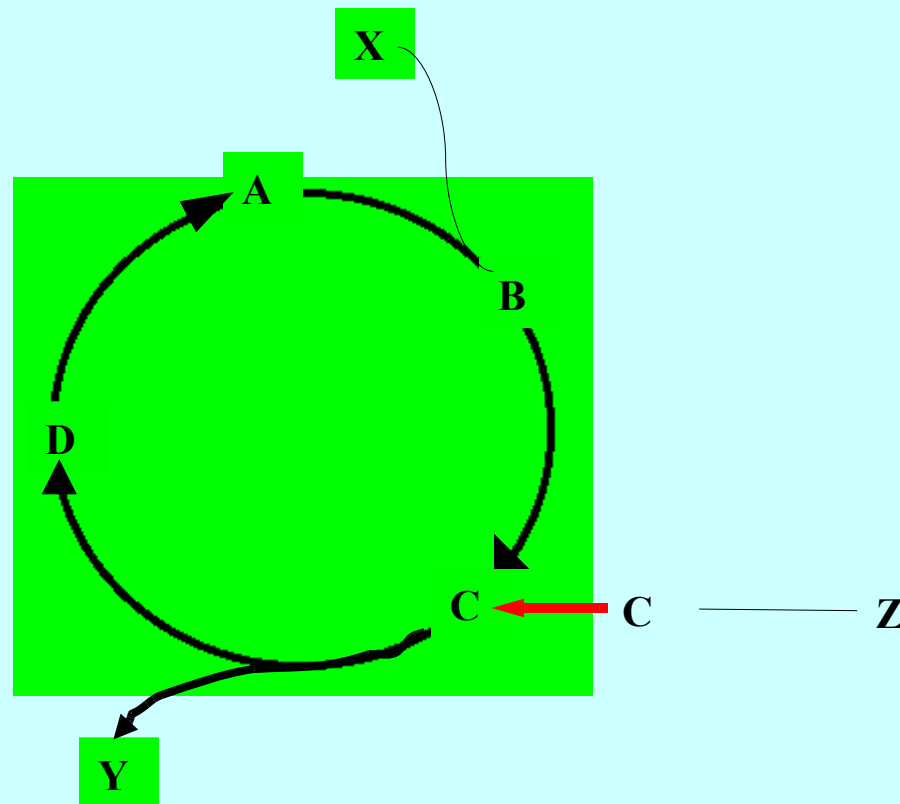




## Citric acid cycle intermediates are always in flux.

Intermediates are brought for degradation in..... reactions; i.e reactions that replace cyclic intermediates.

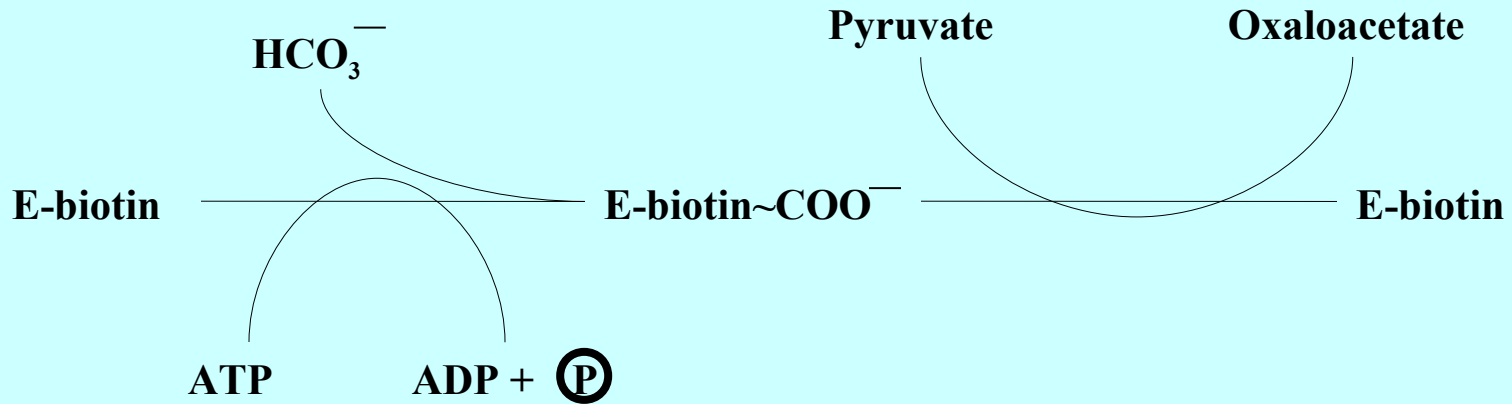
**Anaplerotic pathways are a set of metabolic reactions which replenish the central metabolic pathway**



- The reaction catalyzed by pyruvate carboxylase that replenishes **oxaloacetate** to the TCA cycle is a good example of an **anaplerotic, or “filling up,” reaction.**
- $\text{pyruvate} + \text{CO}_2 + \text{ATP} + \text{H}_2\text{O} \rightarrow \text{oxaloacetate} + \text{ADP} + \text{P}_i + 2 \text{H}^+$
- This reaction assures that there is sufficient oxaloacetate for condensation with acetyl CoA. In fact, acetyl CoA stimulates pyruvate carboxylase.
- This reaction is most important, especially in liver and kidney.

# ANAPLEROTIC REACTION

- Pyruvate carboxylase



Acetyl-CoA

# The anaplerotic, or “filling up” reaction that connects pyruvate to the Krebs cycle

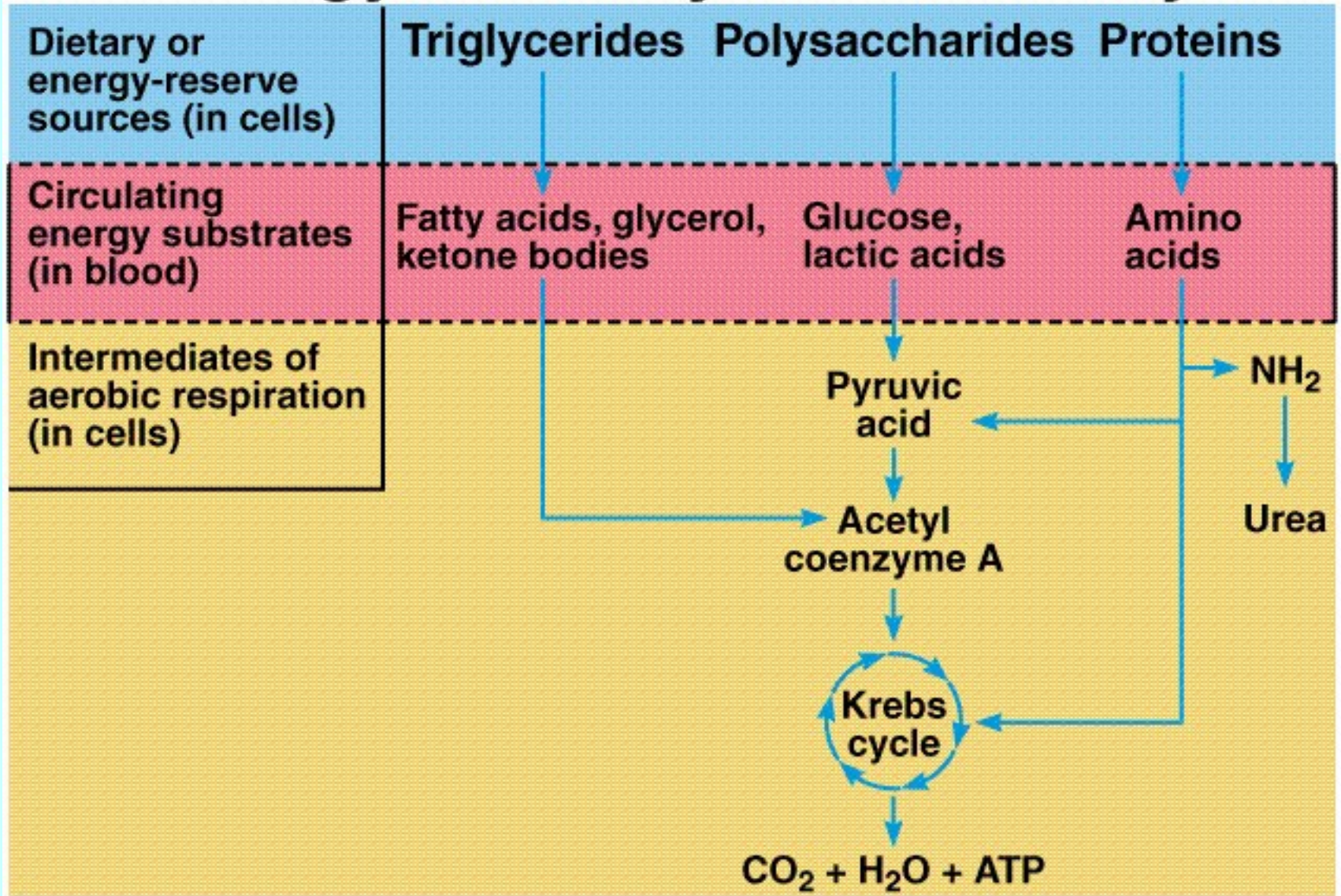
table 16-2

## Anaplerotic Reactions

Reaction	Tissue(s)/organism(s)
$\text{Pyruvate} + \text{HCO}_3^- + \text{ATP} \xrightleftharpoons{\text{pyruvate carboxylase}} \text{oxaloacetate} + \text{ADP} + \text{P}_i$	Liver, kidney
$\text{Phosphoenolpyruvate} + \text{CO}_2 + \text{GDP} \xrightleftharpoons{\text{PEP carboxykinase}} \text{oxaloacetate} + \text{GTP}$	Heart, skeletal muscle
$\text{Phosphoenolpyruvate} + \text{HCO}_3^- \xrightleftharpoons{\text{PEP carboxylase}} \text{oxaloacetate} + \text{P}_i$	Higher plants, yeast, bacteria
$\text{Pyruvate} + \text{HCO}_3^- + \text{NAD(P)H} \xrightleftharpoons{\text{malic enzyme}} \text{malate} + \text{NAD(P)}^+$	Widely distributed in eukaryotes and prokaryotes

- **Other important anapleurotic reactions include the anapleptic reactions that are sources of succinyl CoA**
- **Succinyl CoA is formed from fatty acids with an odd-number of carbon atoms via propionyl CoA.**
- **Succinyl CoA is also formed from propionyl CoA generated in the breakdown of the branched chained amino acids isoleucine, methionine, and valine**
- Oxidation of odd-chain fatty acids leads to production of **succinyl-CoA** from propionyl CoA.
- Transamination and deamination of amino acids leads to production of  **$\alpha$ -ketoglutarate and oxaloacetate.**

# Energy Pathways in the Body

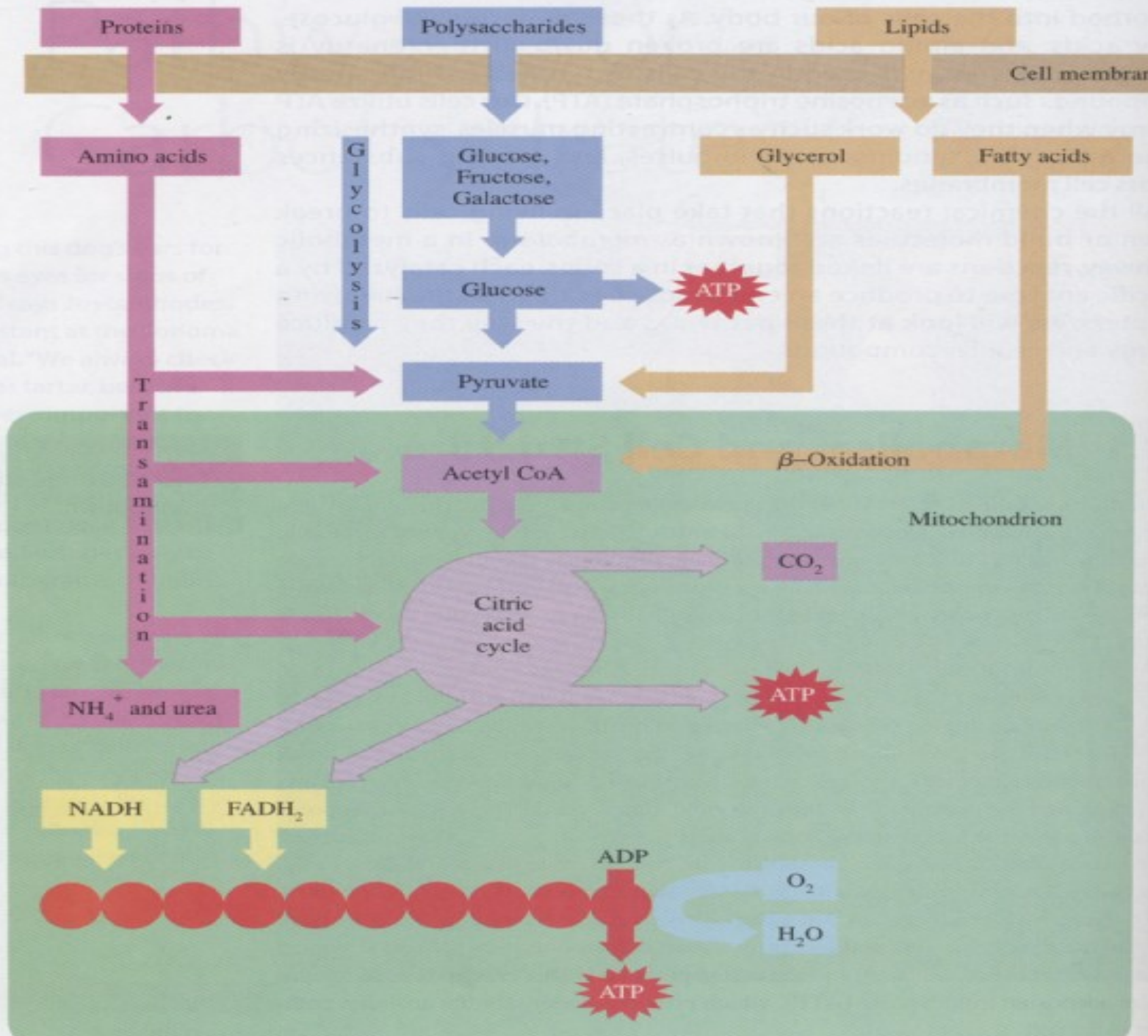




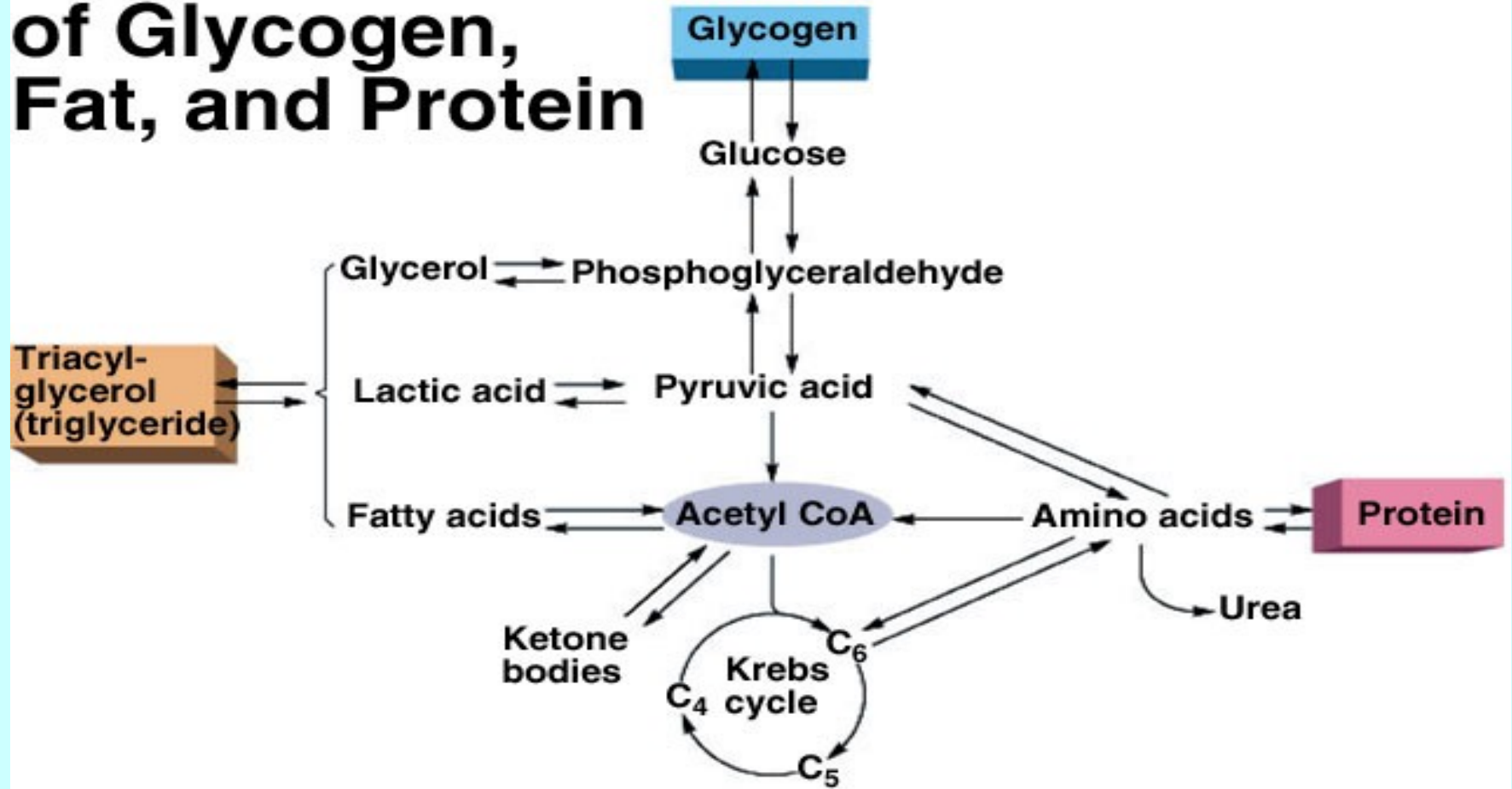
**Stage 1**  
Digestion and hydrolysis

**Stage 2**  
Degradation and some oxidation to smaller molecules

**Stage 3**  
Oxidation to  $\text{CO}_2$ ,  $\text{H}_2\text{O}$  and energy for ATP synthesis

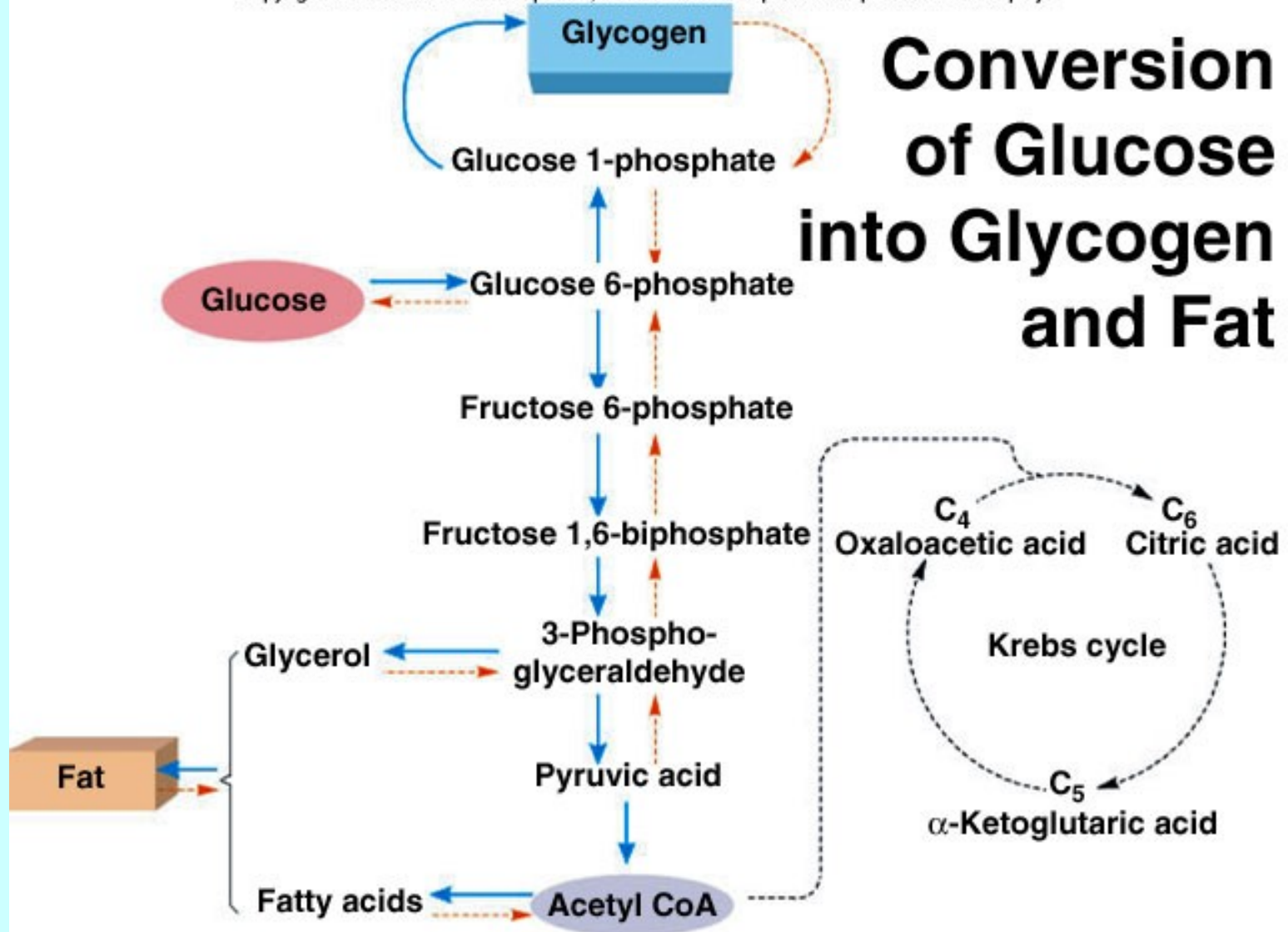


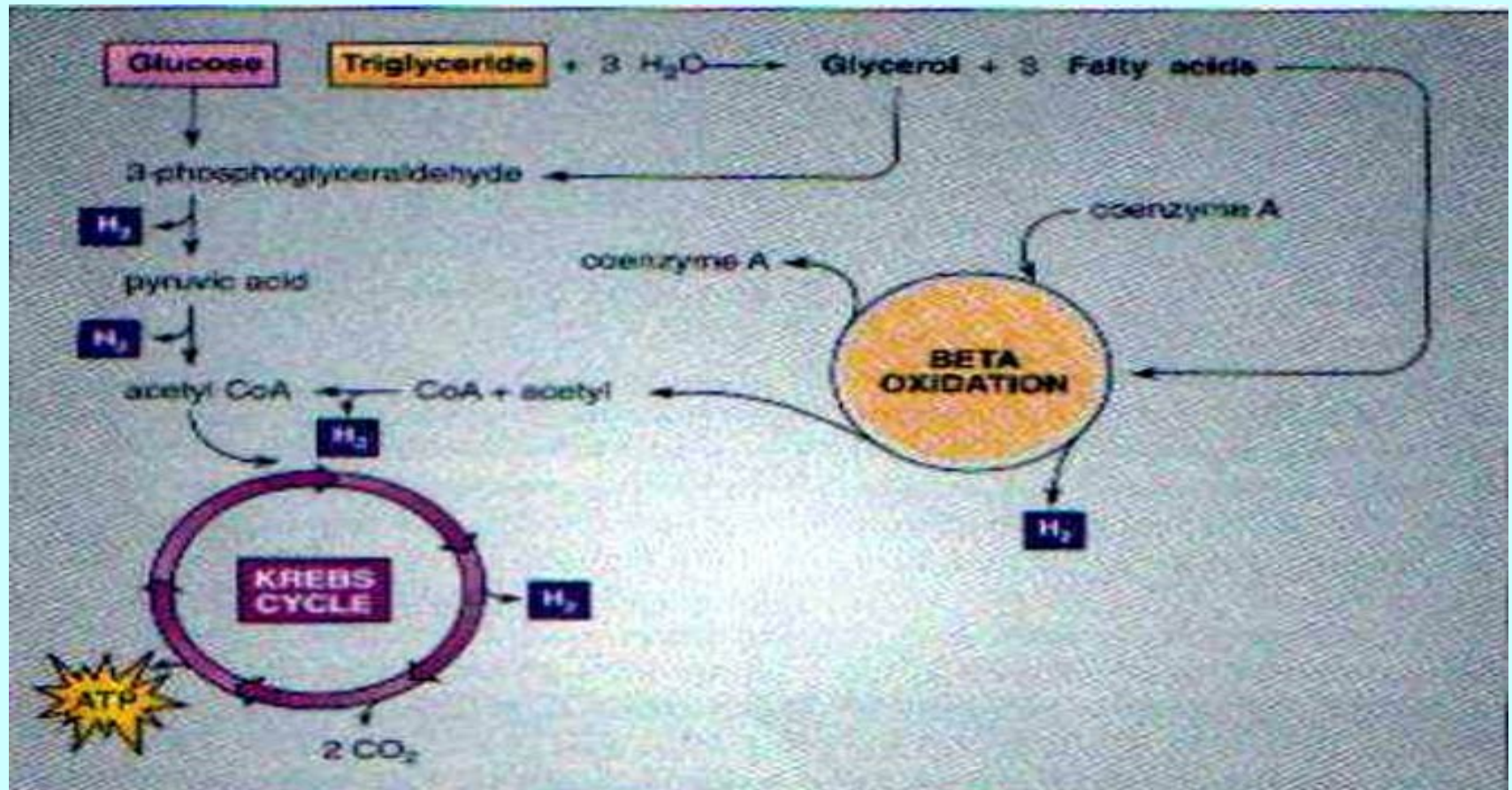
# Interconversion of Glycogen, Fat, and Protein





# Conversion of Glucose into Glycogen and Fat





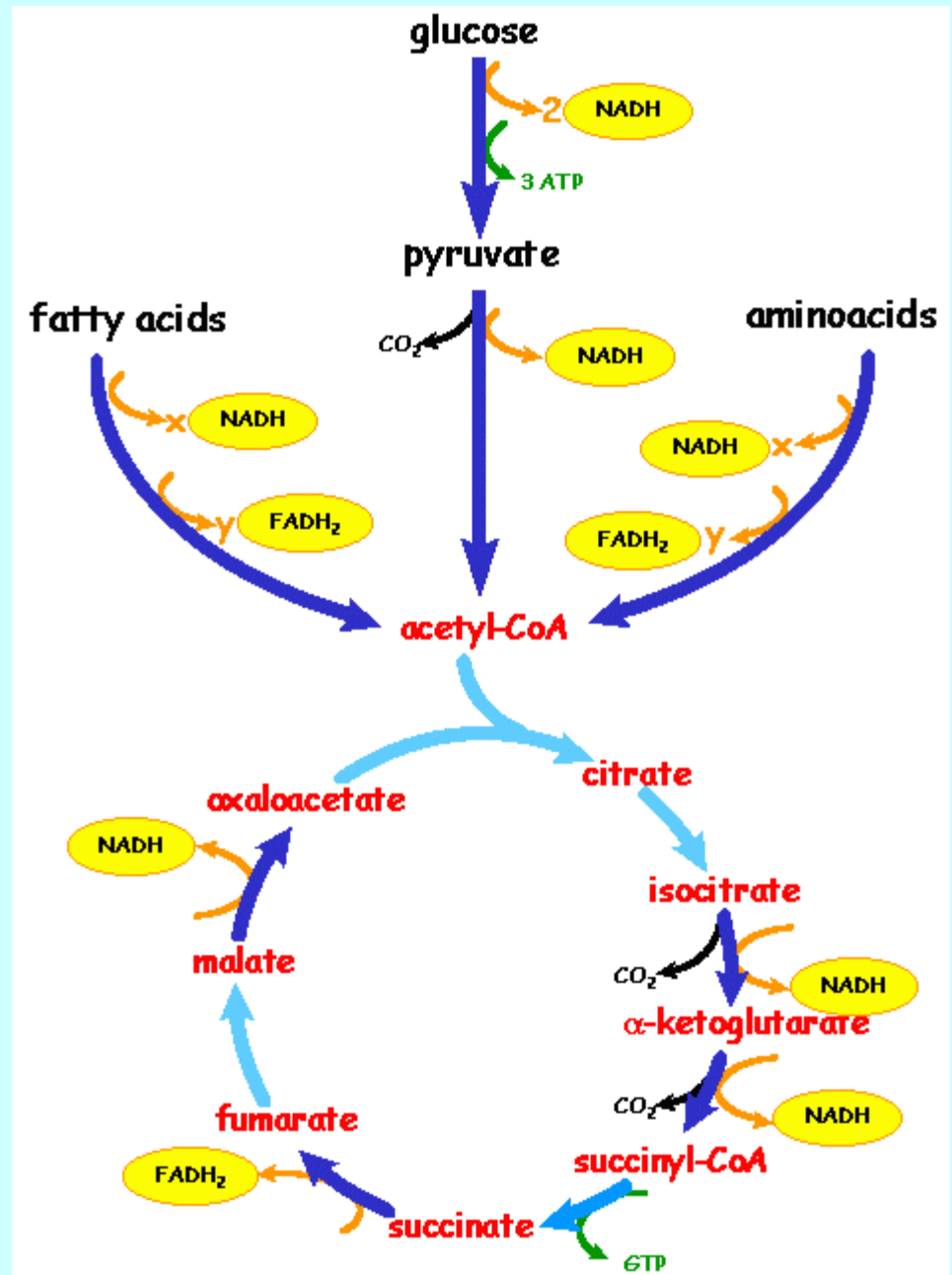
Fats breakdown  
and feed  
into the TCA Cycle

Breaking down fat for energy produces acetyl CoA, which feeds directly into the citric acid cycle

**Both fatty acids (from lipids) and amino acids (from proteins) form**

**ACETYL CoA**

**which enter the Citric Acid Cycle for continuation of their degradation or catabolism**

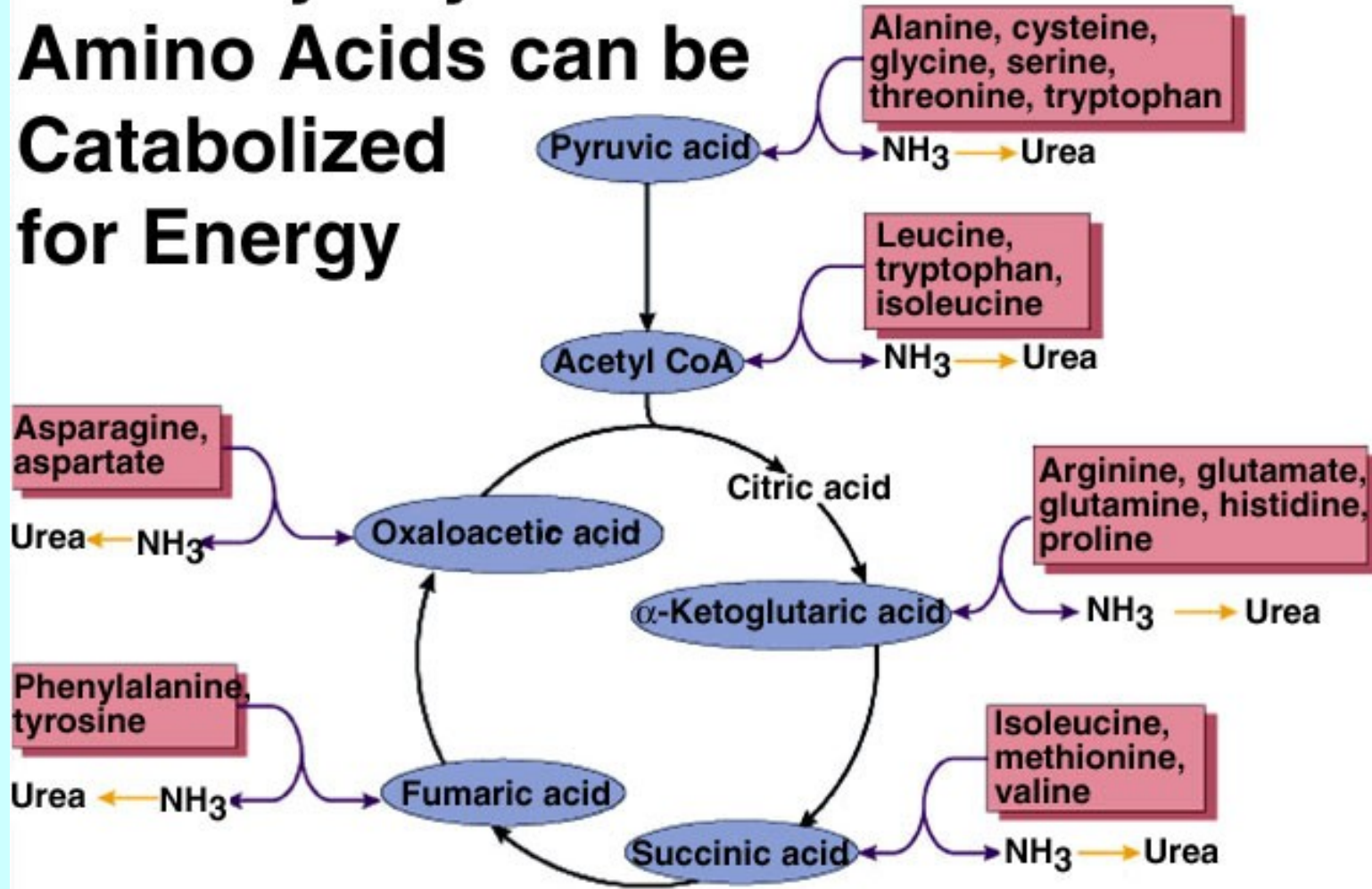


- **Protein may serve an excellent sources of nutrient energy**
- **Catabolism of amino acids provides:**  
succinate, oxaloacetate, fumarate,  $\alpha$ -ketoglutarate.
- pyruvate (from glycolysis)
- acetyl CoA stimulates pyruvate carboxylase

- **Proteins can also be broken down to feed into the citric acid cycle and generate energy**
- Under extreme starvation in animals or during senescence in plants polypeptides are cleaved to amino acids, amino group is cleaved off of amino acid forming an organic acid that can enter the citric acid cycle

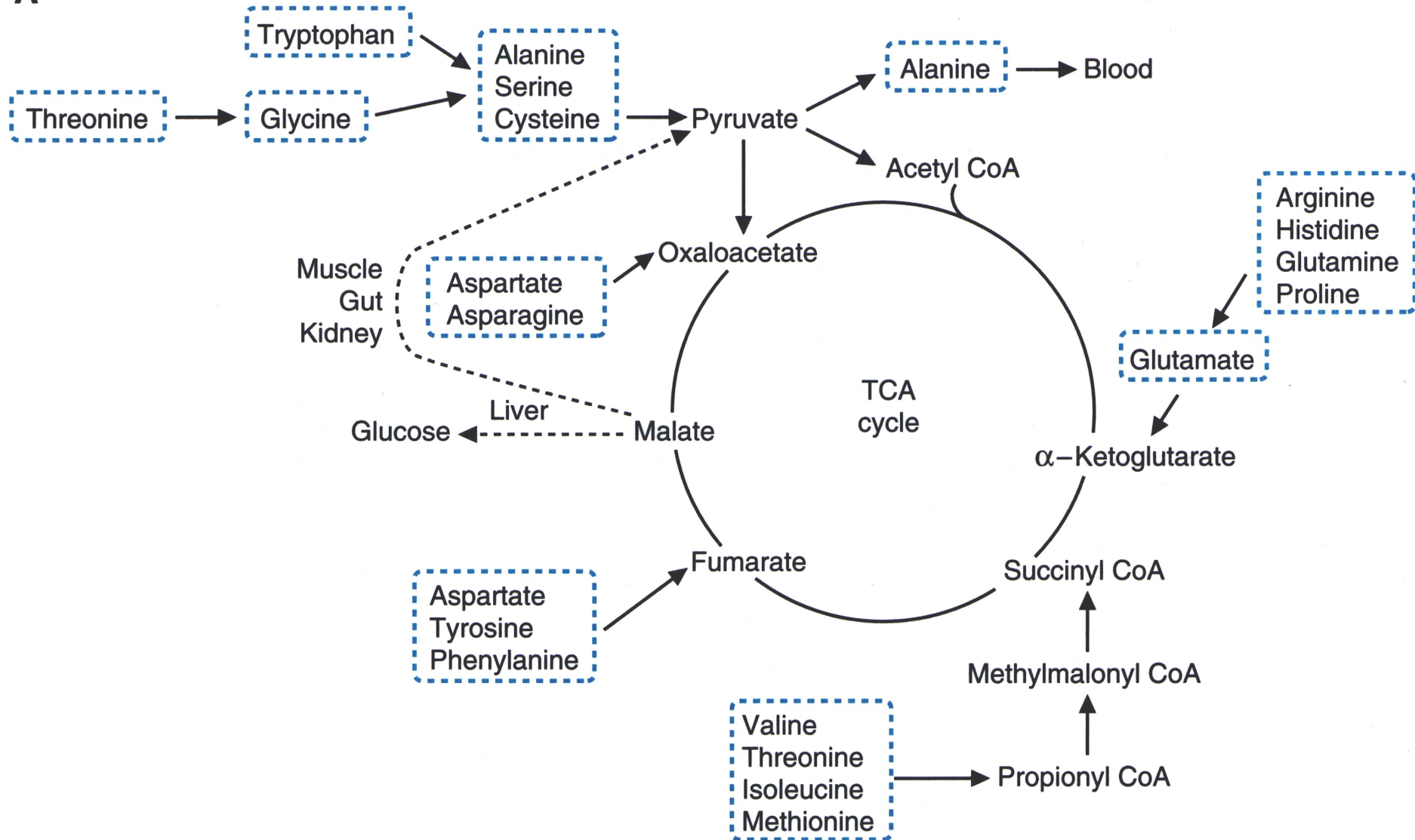


# Pathways by which Amino Acids can be Catabolized for Energy



# Degradation of amino acids that produce pyruvate or intermediates of the TCA cycle are shown at the points at which they enter the TCA.

A

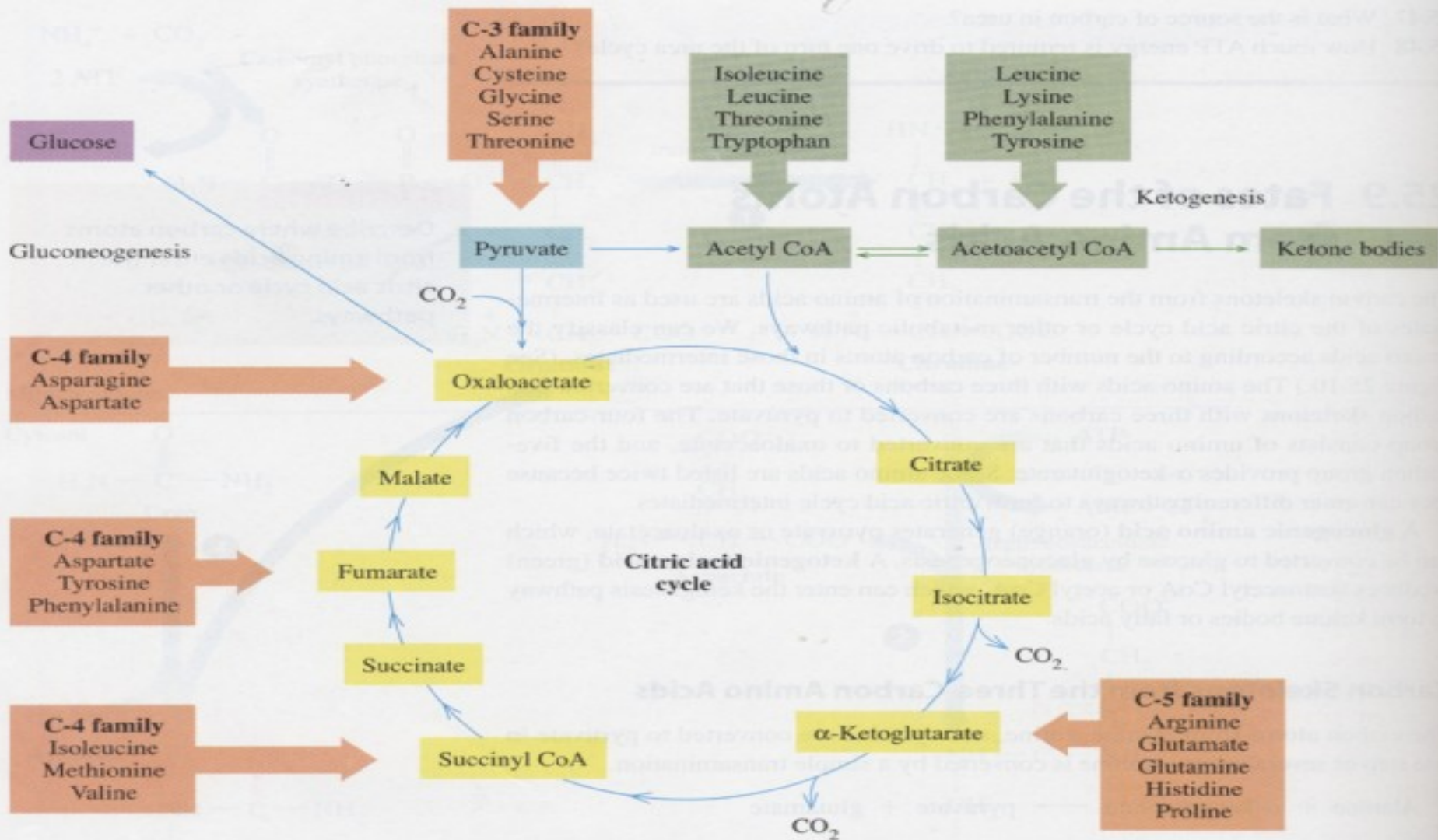


- The strategy followed by the cell in the catabolism of amino acids is to convert all twenty common amino acids into one of the following seven compounds useful in gluconeogenesis or the citric acid cycle.
- **acetylCoA**
- **acetoacetyl CoA**
- **pyruvate**
- **oxaloacetate**
- **fumarate**
- **succinyl CoA**
- **alphaketoglutarate**
- **Most of the metabolic pathways of the body are channeled through these seven molecules.**

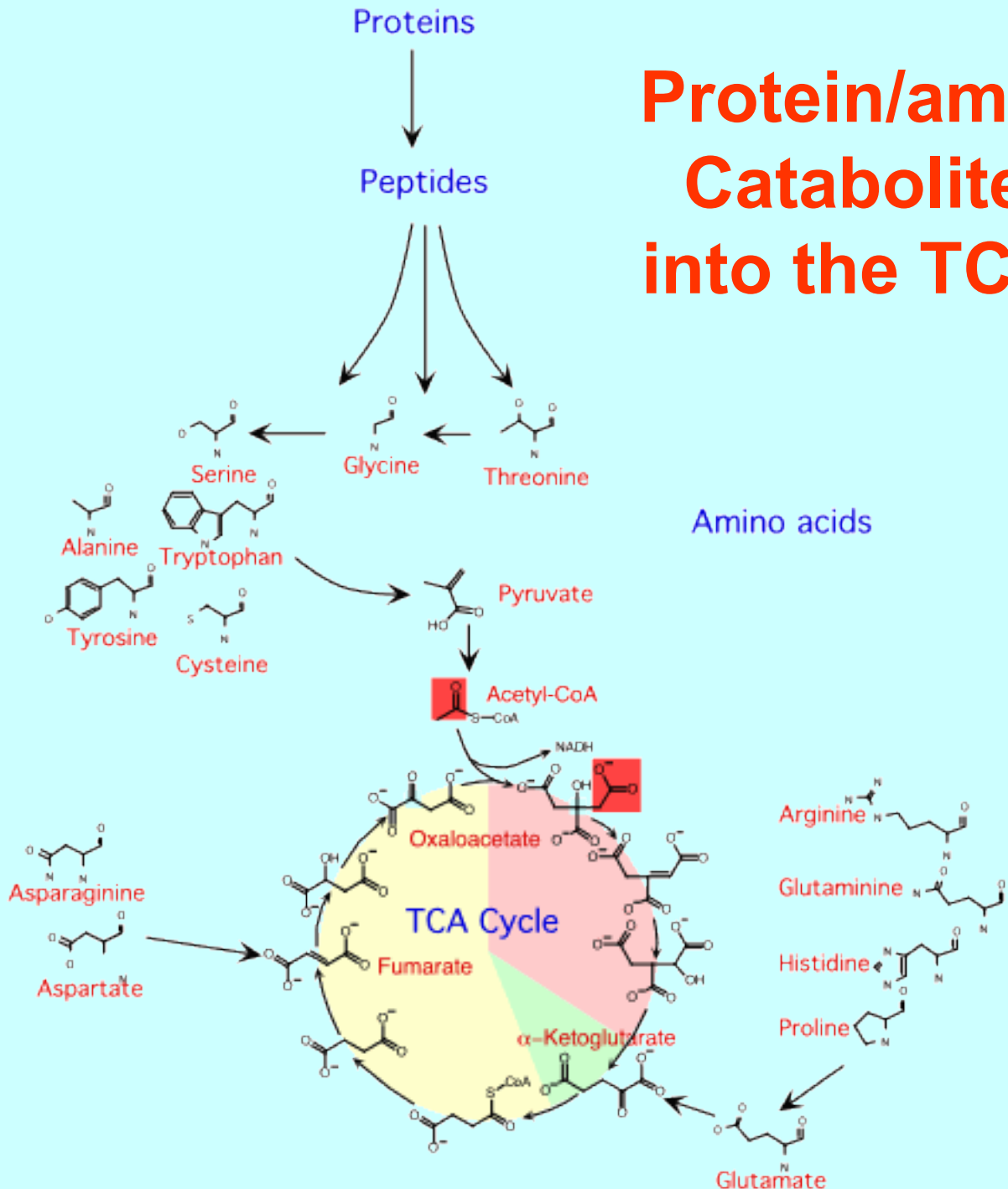


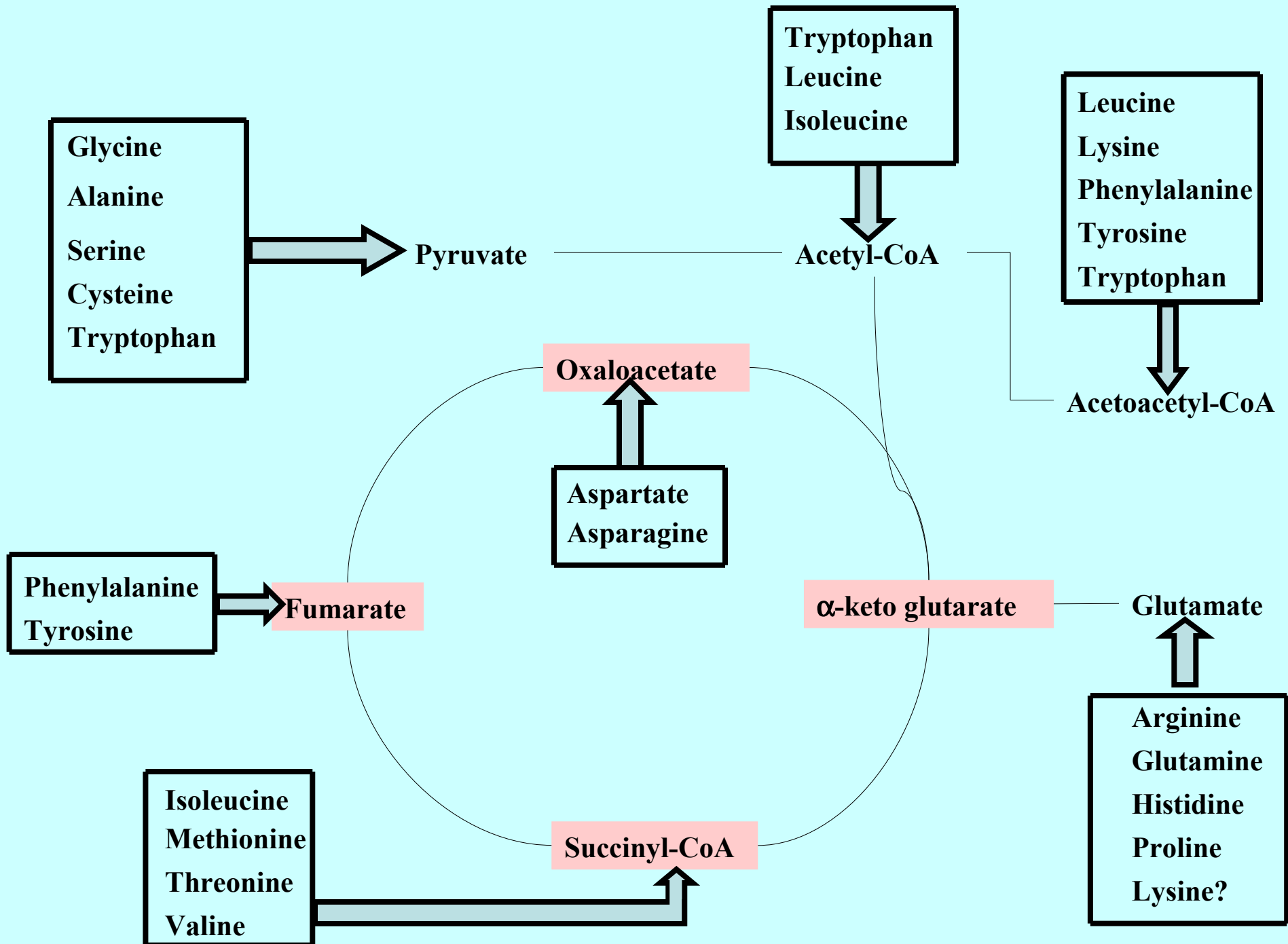
- The great importance of the two slides above resides in the fact that they highlight some of the molecules that are the major players in metabolism in the body.
- These two slides indicate the position of these molecules in the citric acid cycle, and emphasize that the KREBS CYCLE is indeed **a central metabolic pathway, and an amphibolic pathway; which has BOTH a catabolic and an anabolic role.**

Carbon atoms from degraded amino acids are converted to the intermediates of the citric acid cycle or other pathways. **Glucogenic amino acids** (orange boxes) produce carbon skeletons that can form glucose, and **ketogenic amino acid** (green boxes) can produce ketone bodies.



# Protein/amino acid Catabolites feed into the TCA Cycle

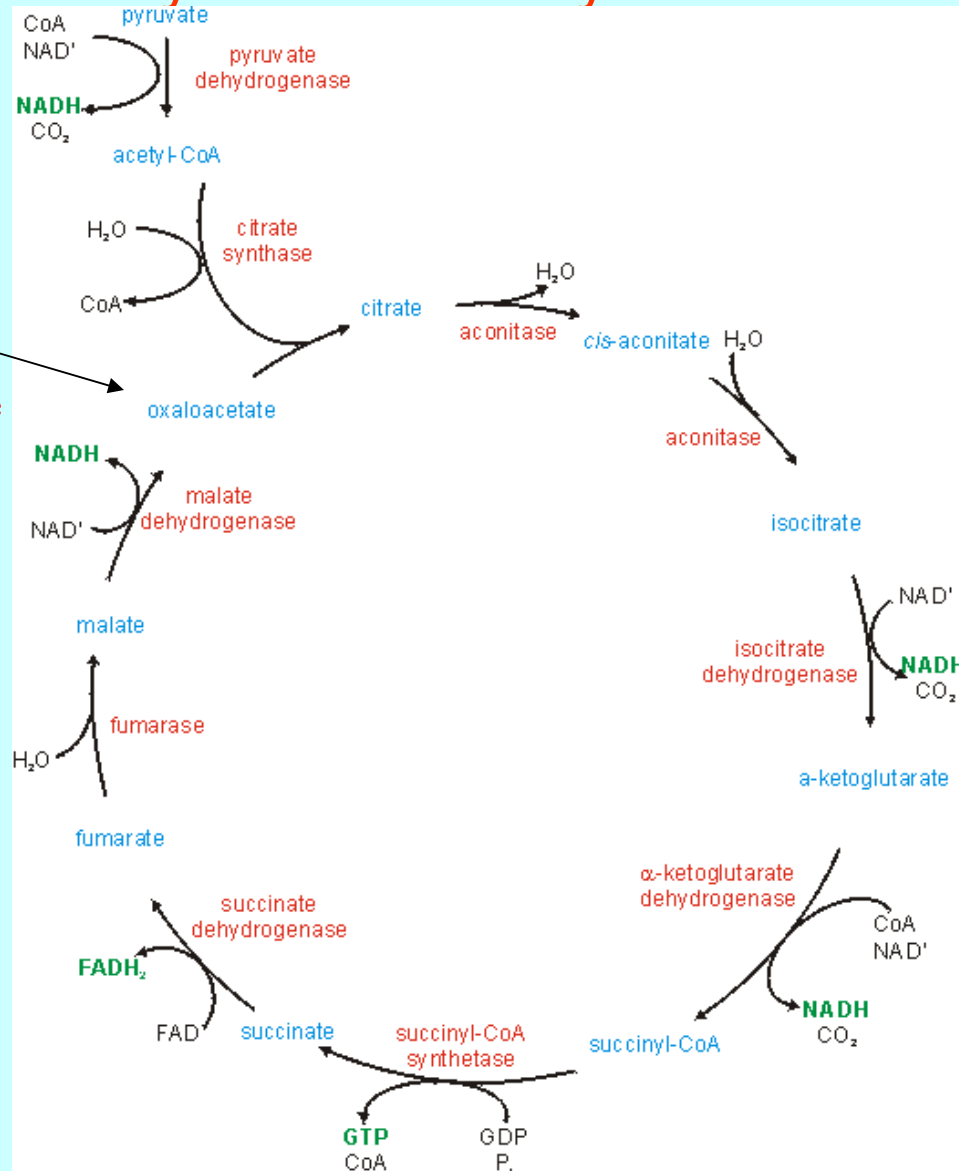




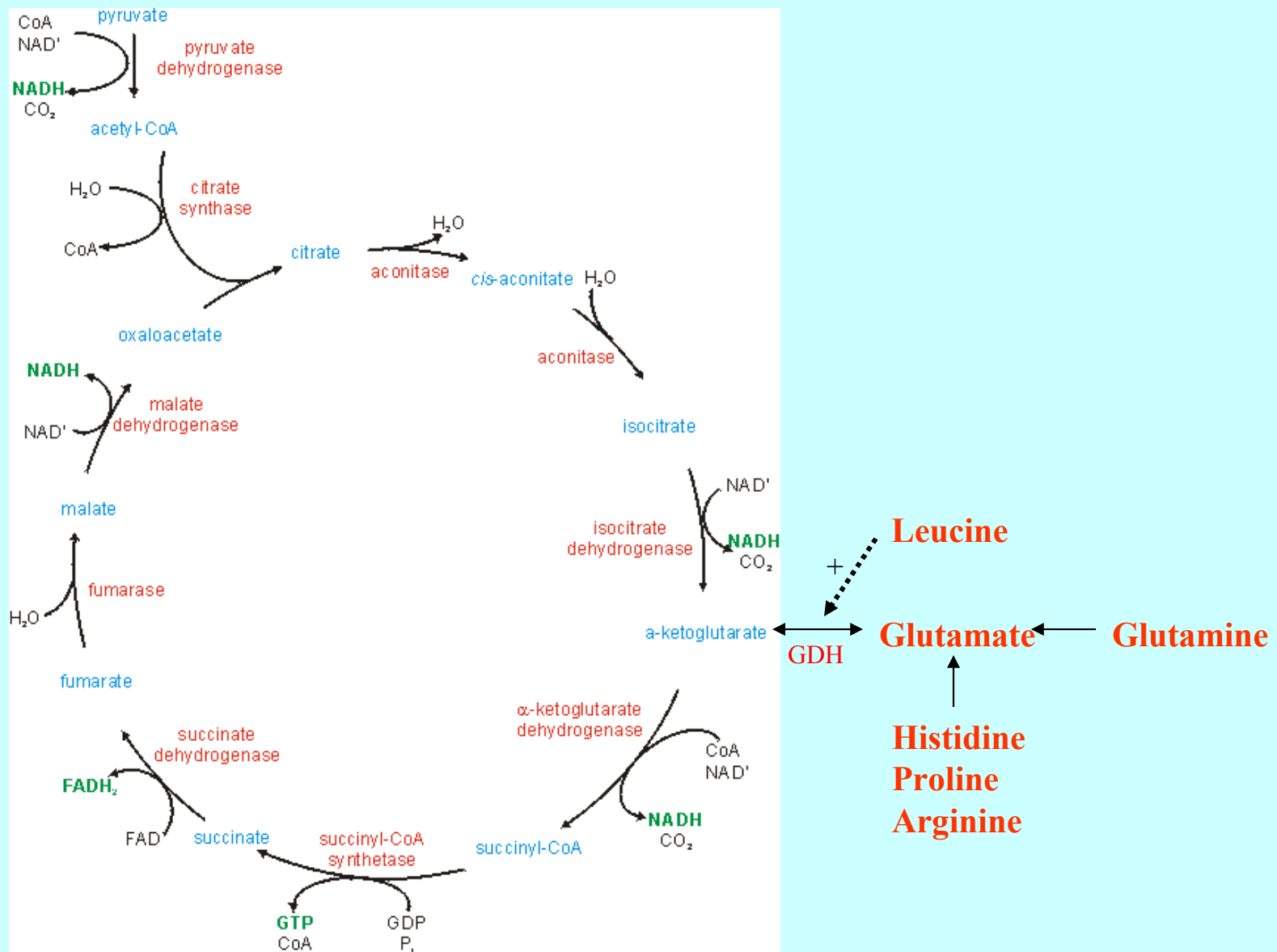
# Anaplerosis Involving Amino Acids entering the citric acid cycle from the cytosol

**Pyruvate**

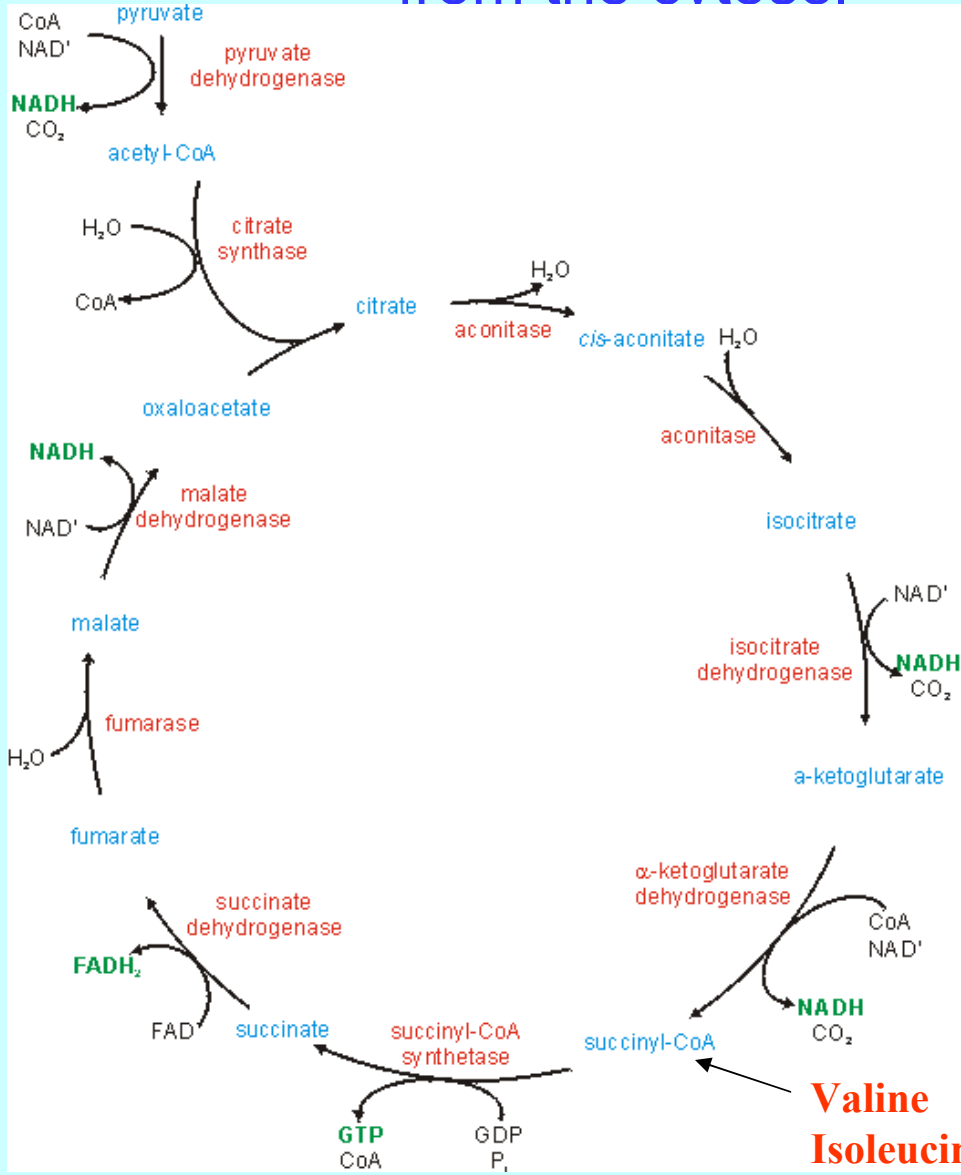
pyruvate  
carboxylase



# Anaplerosis Involving Amino Acids entering the citric acid cycle from the cytosol

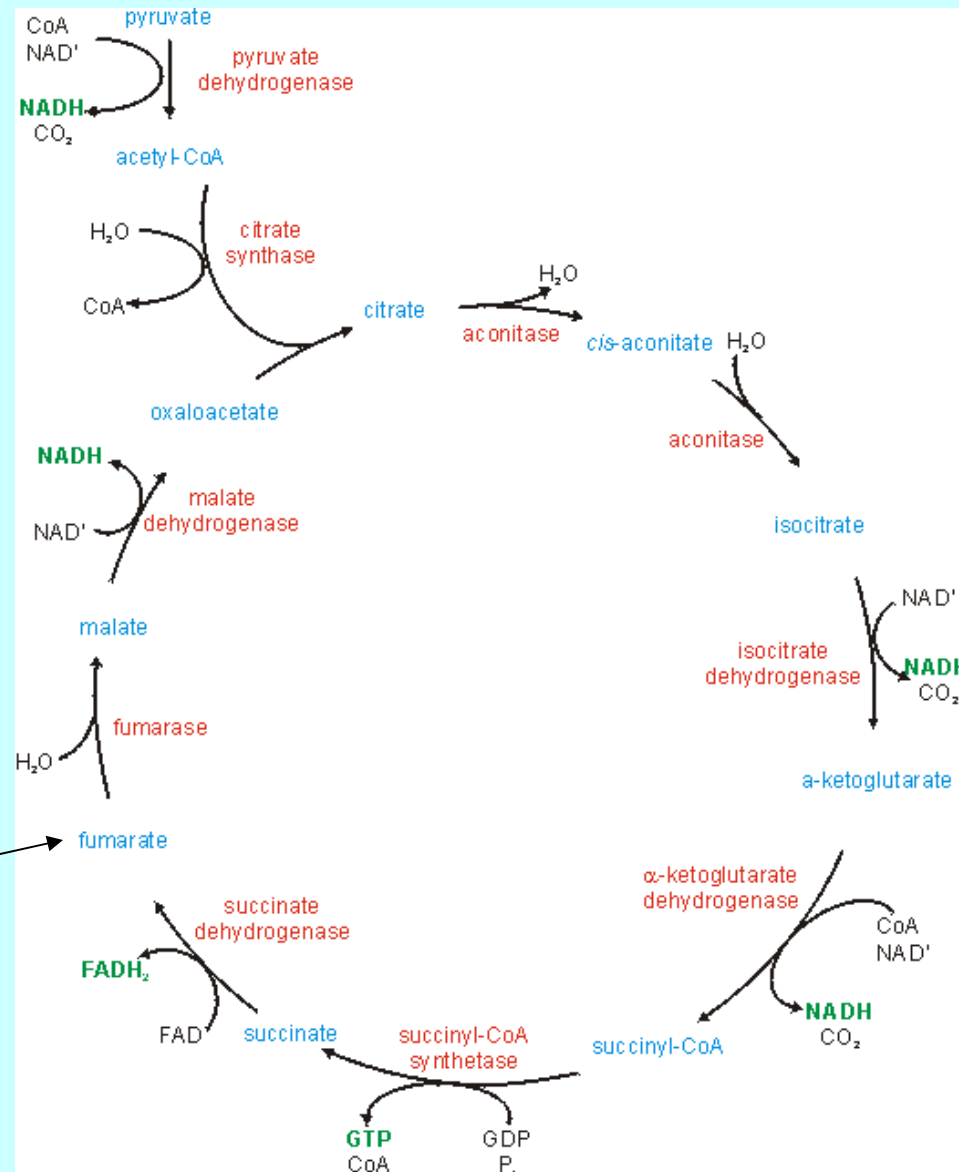


# Anaplerosis Involving Amino Acids entering the citric acid cycle from the cytosol



**Valine**  
**Isoleucine**  
**Methionine**

# Anaplerosis Involving Amino Acids entering the citric acid cycle from the cytosol



**Phenylalanine**  
**Tyrosine**



# Anaplerosis Involving Amino Acids entering the citric acid cycle from the cytosol

