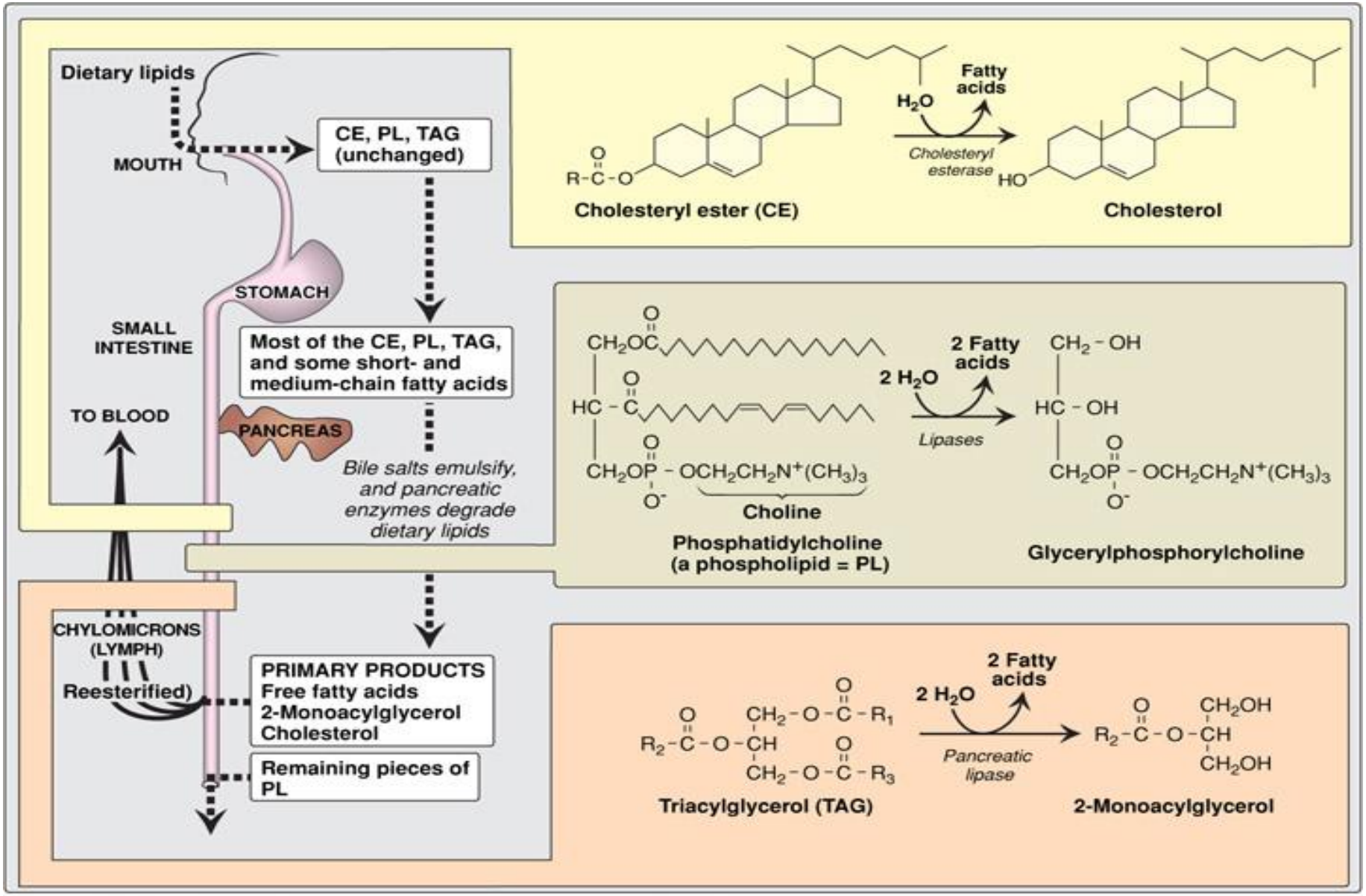
CHY2026: General Biochemistry

Lipid Metabolism

Lipid Digestion



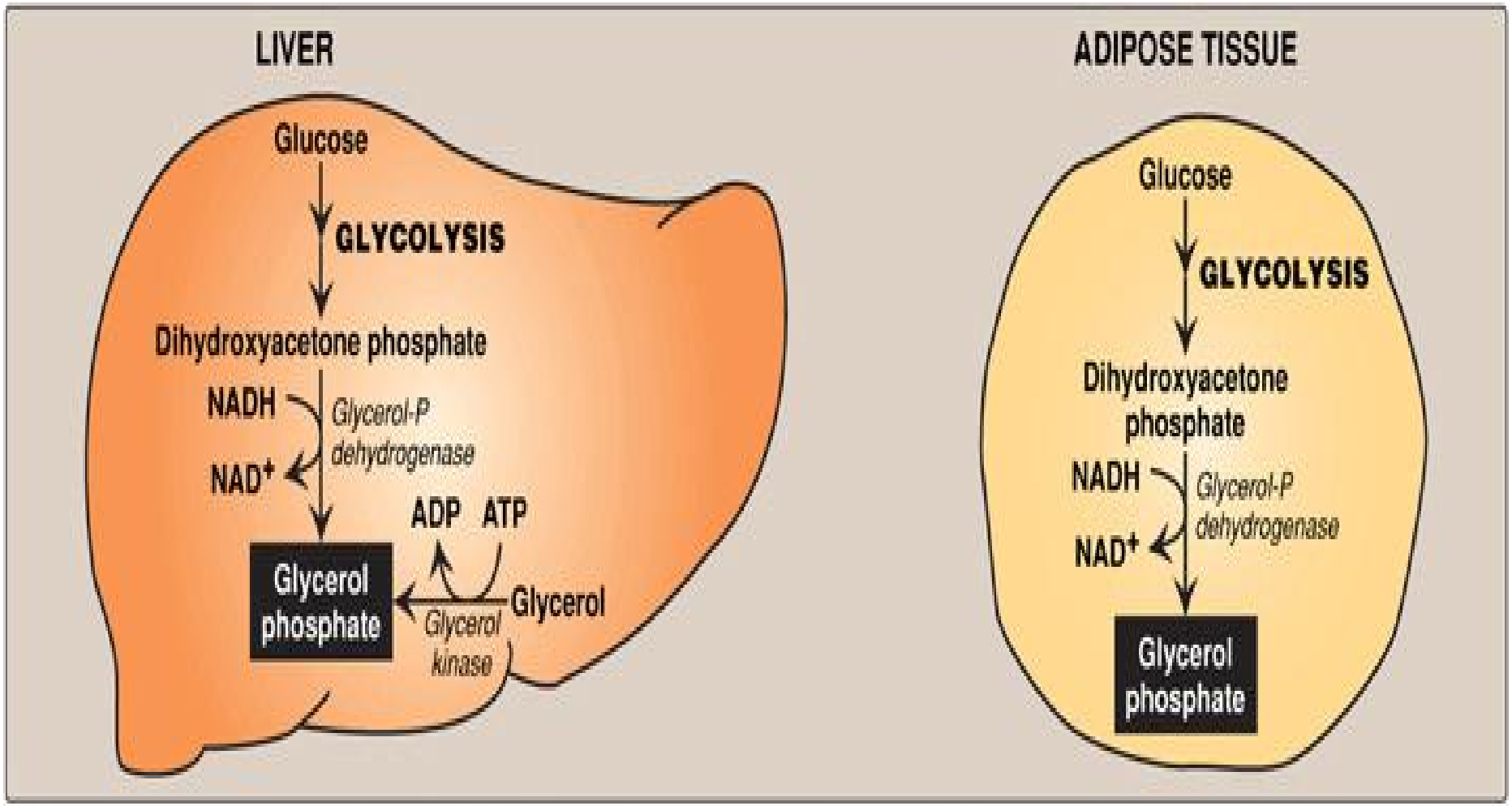
Lipid Metabolism

- Fats (triglycerides) are high metabolic energy molecules
- Fats yield 9.3 kcal of energy (carbohydrates and proteins – 4.1 kcal)
- They are the best heat producers when compared to the other macromolecules i.e. carbohydrates and proteins. The significant difference is due to the long hydrocarbon chain
- When we consume more calories than what is being utilized, the excess energy is stored as fats
- Due to their hydrophobic and inert properties, fats can be stored for very long periods

Lipid Metabolism

- Fats can also be stored in large amounts
- Carbohydrates can be stored **(glycogen)** to a limited extent – and is broken down first to release energy
- Proteins cannot be stored

Production of glycerol phosphate (precursor of triacylglycerol)



Lipid Metabolism

- Fats are stored as **triaclyglycerols** in the fat cells **(adipose tissue)**
- These molecules coalesce to form large globules that are able to occupy most of the cell volume
- The liver and adipose tissue are the sites for metabolic activity of fats
- Triacylglycerols are hydrophobic in nature and unreactive
- They can therefore be stored extracellularly
- They will not react with other cellular components

Lipid Metabolism

- Because triacylglycerol is insoluble in water they must be emulsified to fatty acids and glycerol **(enzymes necessary for digestion are water soluble)**
- The emulsified form can then be digested and absorbed in the intestines
- Free fatty acids can move through the cell membrane of the adipocytes into the plasma
- Proteins (albumin) help to transport the fatty acids and glycerols (2-monoacylglycerol) in the blood
- In order for fatty acids to be used as fuel, they must undergo β-oxidation

Lipid Metabolism

- The reaction occurs in the mitochondrial matrix
- Erythrocytes which have no mitochondria cannot use fatty acids as fuel
- The brain also does not use fatty acid as fuel due to an impermeable blood brain barrier

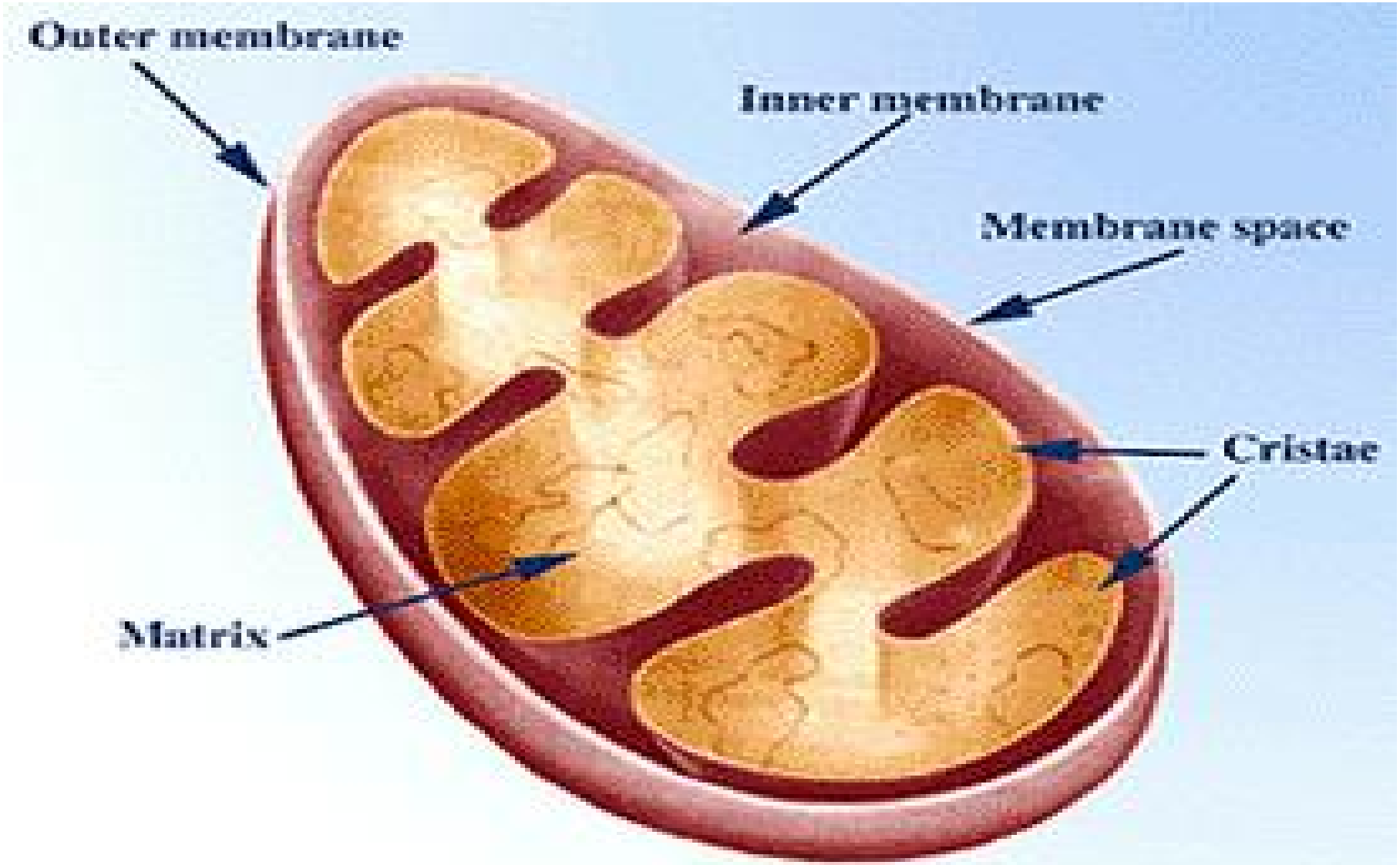
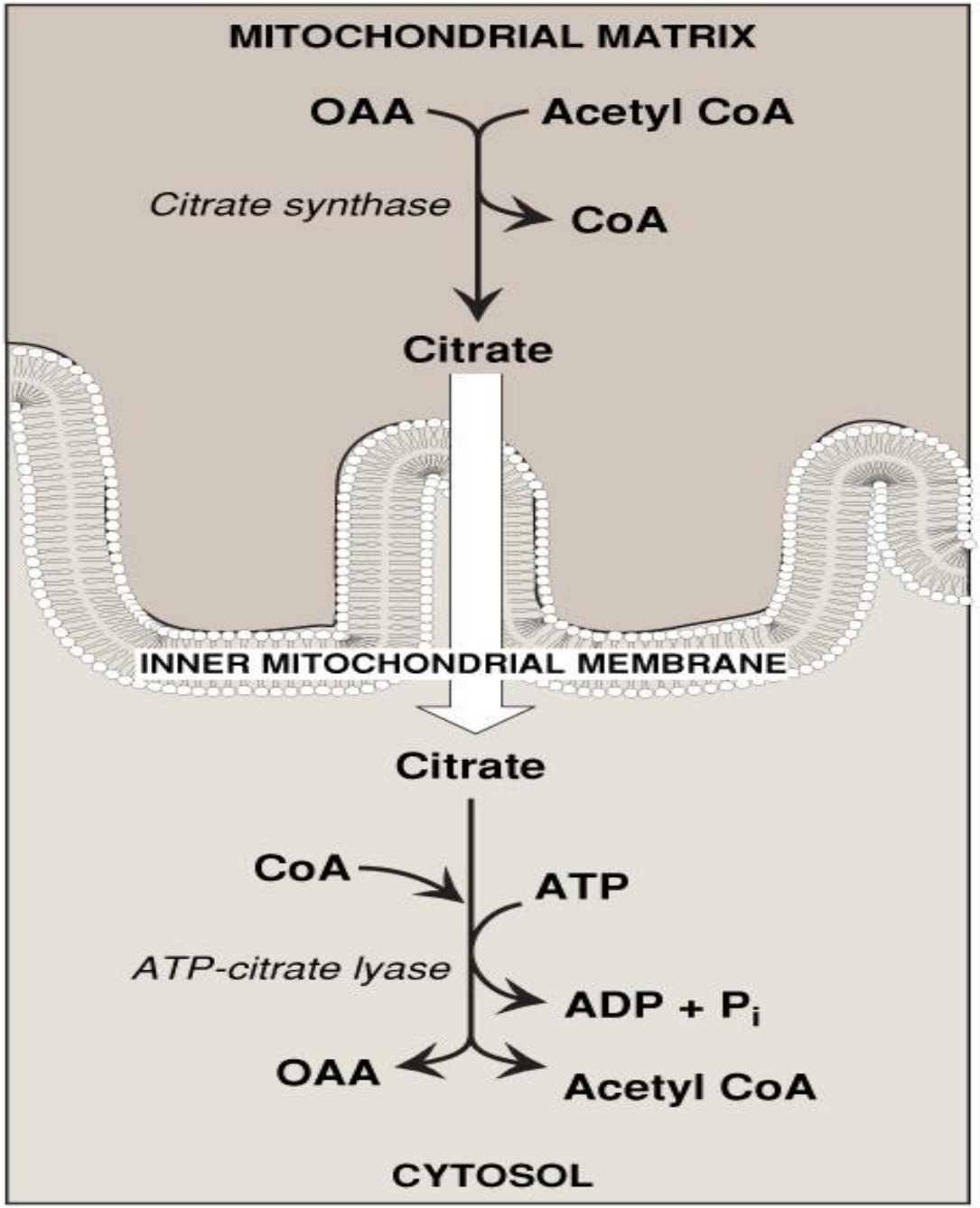


Fig. 1. Schematic of mitochondria.

Fatty Acid Synthesis

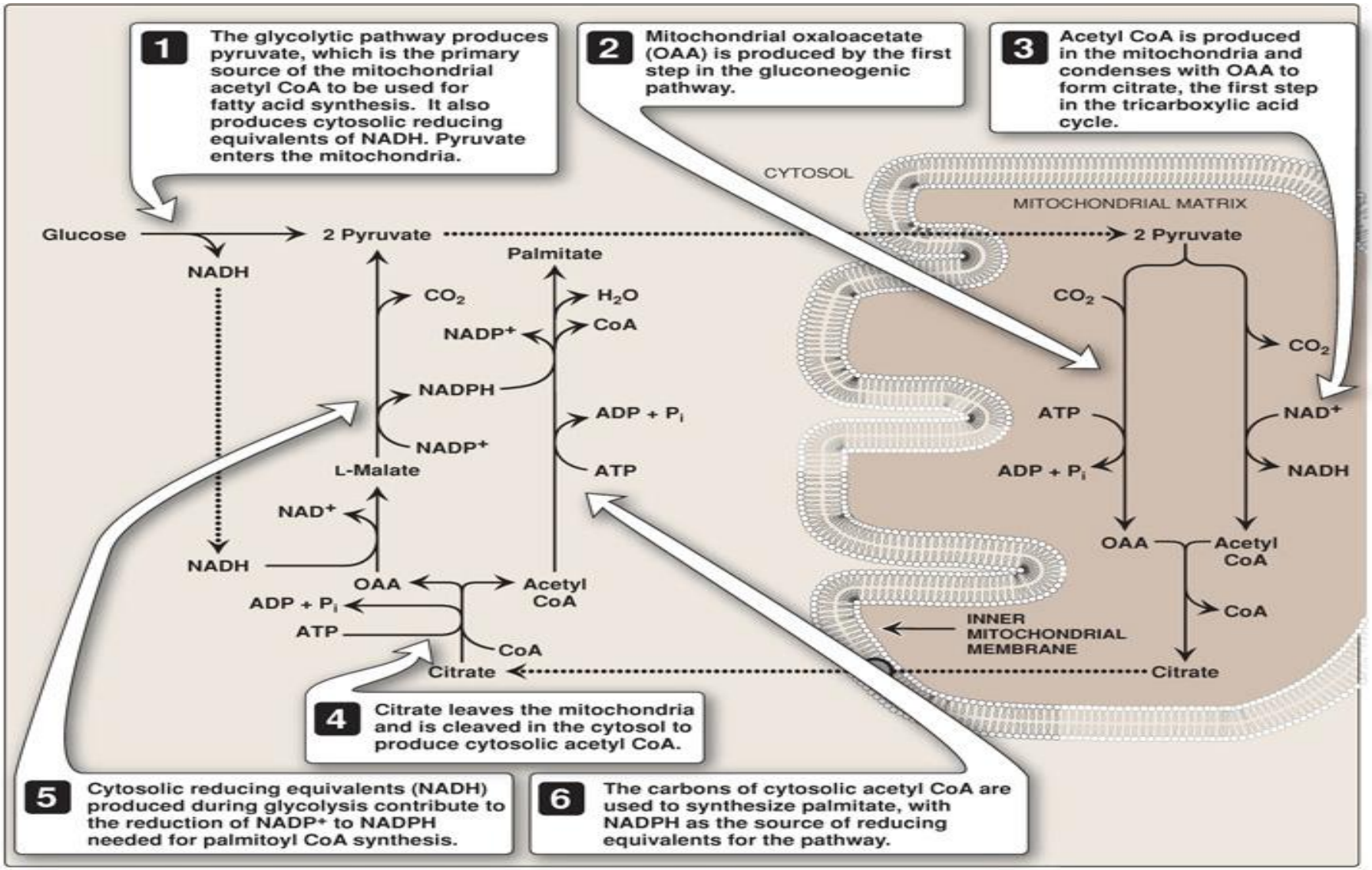
- A large proportion of fatty acid used by the body is from dietary source
- Carbohydrates and proteins obtained from the diet can also be converted to fatty acid
- the synthesis occurs in the liver and lactating mammary glands
- Acetyl CoA formed in the mitochondria is transported across the membrane into the cytosol
- However the acetyl CoA must first be converted to citrate and then once in the cytosol, the citrate is converted to acetyl CoA



Fatty Acid Synthesis

- The acetyl CoA then acts as substrate for palmitate
- Palmitate acts as precursor for other long chain fatty acids
- Examples of some fatty acids derived from palmitate include stearate, oleate and linoleate

Interrelationship between glucose metabolism and palmitate synthesis



β-Oxidation of Fatty Acids

- This is a catabolic reaction for fatty acids
- It involves the complete combustion of fatty acids to CO_2 and H_2O and ultimately the generation of ATP
- The reaction involves 2 key steps

1. The sequential oxidation of all the carbons in the fatty acid to acetyl CoA
2. The acetyl CoA is channeled into the TCA cycle where it is oxidized

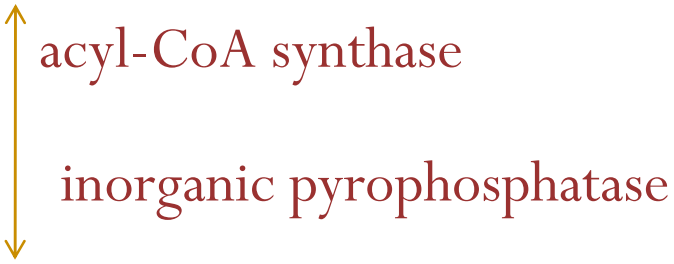
β-Oxidation of Fatty Acids

- Both reactions produce molecules that can generate ATP via oxidative phosphorylation
- ***The formation of acetyl CoA via β-oxidation serves mainly as a precursor for biosynthetic reactions***. It is also a secondary fuel source
- Acetyl CoA may also be converted to ketone bodies
- These ketone bodies are water soluble and are able to cross the blood brain barrier
- **They can serve as fuel for the brain and other tissues when glucose becomes unavailable**

β-Oxidation of Fatty Acids: *Mechanism*

(a) The fatty acid is first converted to fatty acyl-CoA

Long chain fatty acids + CoA + ATP (needed so forward rxn. is favoured)



fatty acyl-CoA + ADP + P_i

E.g. The fatty acid palmitic acid is converted to palmitoyl-CoA

The reaction occurs in the outer mitochondrial membrane

β-Oxidation of Fatty Acids: Activation of Fatty Acids

(b) Because β-oxidation occurs in the mitochondria matrix. The Co-A derivative must be transported across the inner mitochondrial membrane. However the membrane is impermeable to free fatty acids and Co-A derivatives, therefore specialized carriers called **carnitine**, transport the molecule from the cytosol into the mitochondrial matrix. This process is referred to as the **activation of fatty acids**

The fatty acyl-CoA then becomes attached to carnitine forming fatty acyl-carnitine (catalyzed by carnitine acyl transferase I)

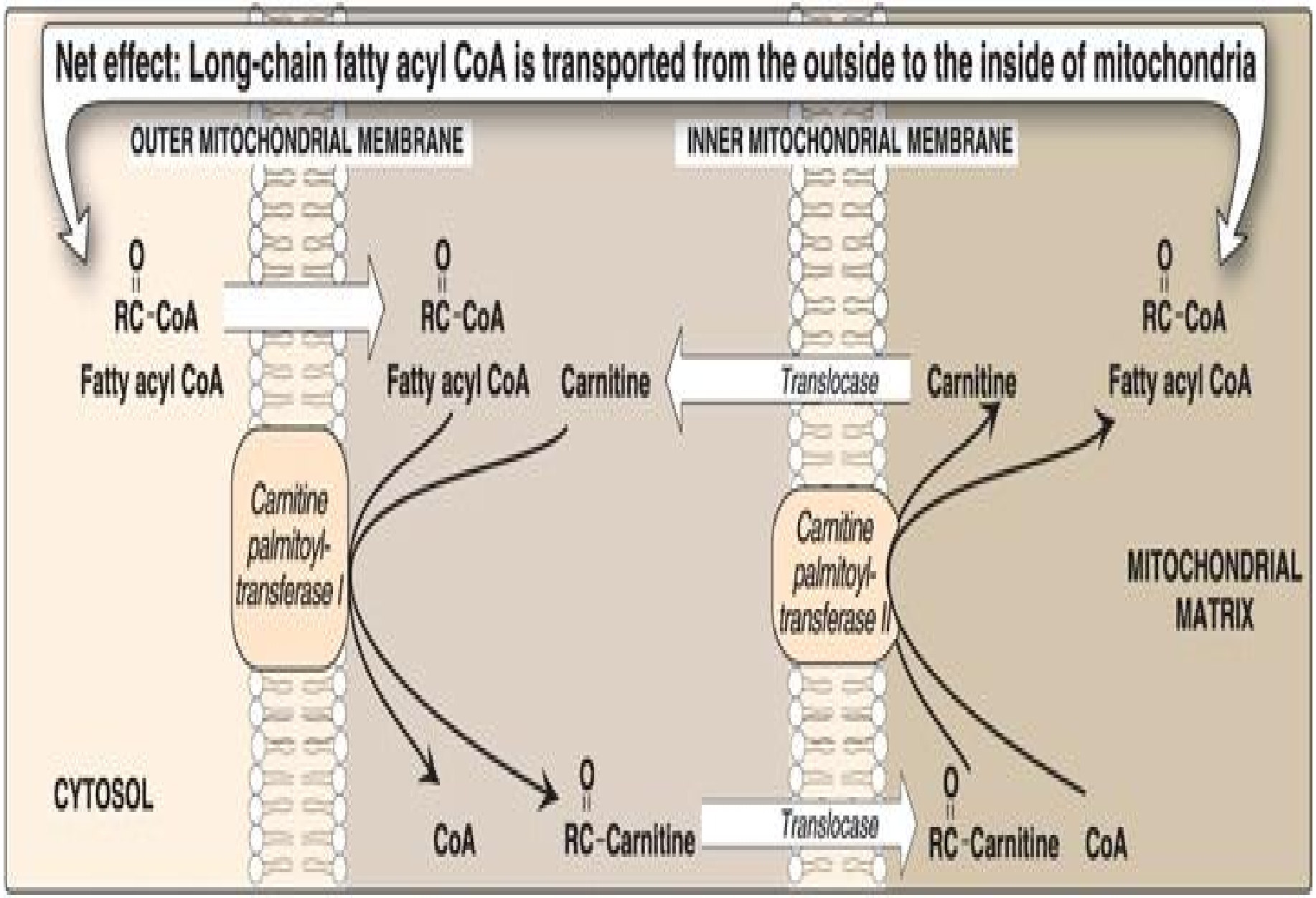
The fatty acyl-carnitine is carried across the inner mitochondrial membrane by a specific transporter

β-Oxidation of Fatty Acids

(c) The fatty acyl group is transferred from the carnitine to intramitochondrial coenzyme A by carnitine acyl transferase II

This enzyme therefore regenerates fatty acyl-CoA and carnitine and release them inside the matrix

The carnitine then reenters the space between the inner and outer mitochondrial membrane via a acyl-carnitine transporters

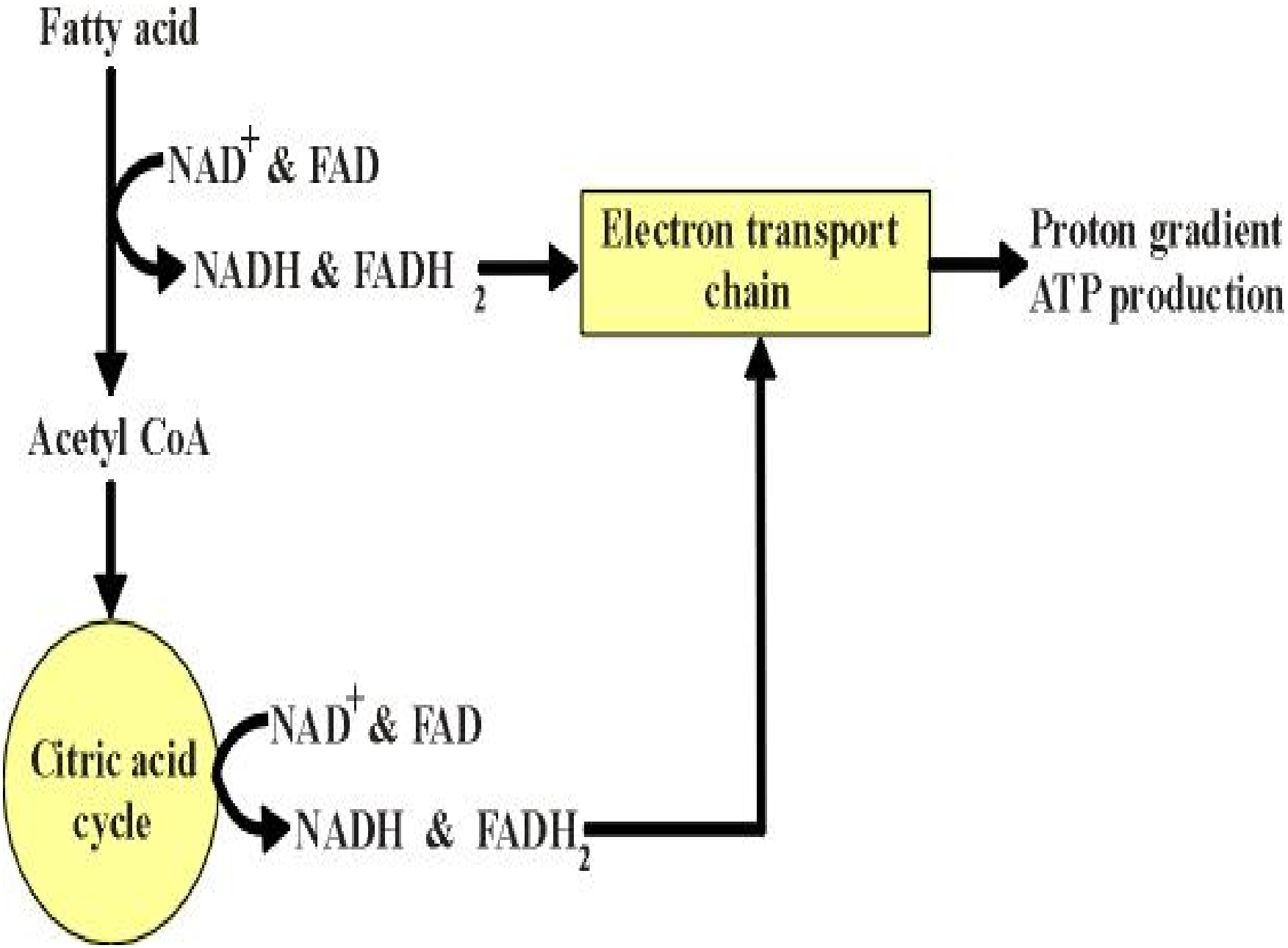


β-Oxidation of Fatty Acids

- The β-oxidation of fatty acids result in a consecutive shortening of the chain by 2 carbon atoms
- These 2 carbon atoms are used to form acetyl CoA
- The long chain fatty acids will be broken down to produce many acetyl CoA molecules
- NADH and $FADH_2$ are other products of the reaction

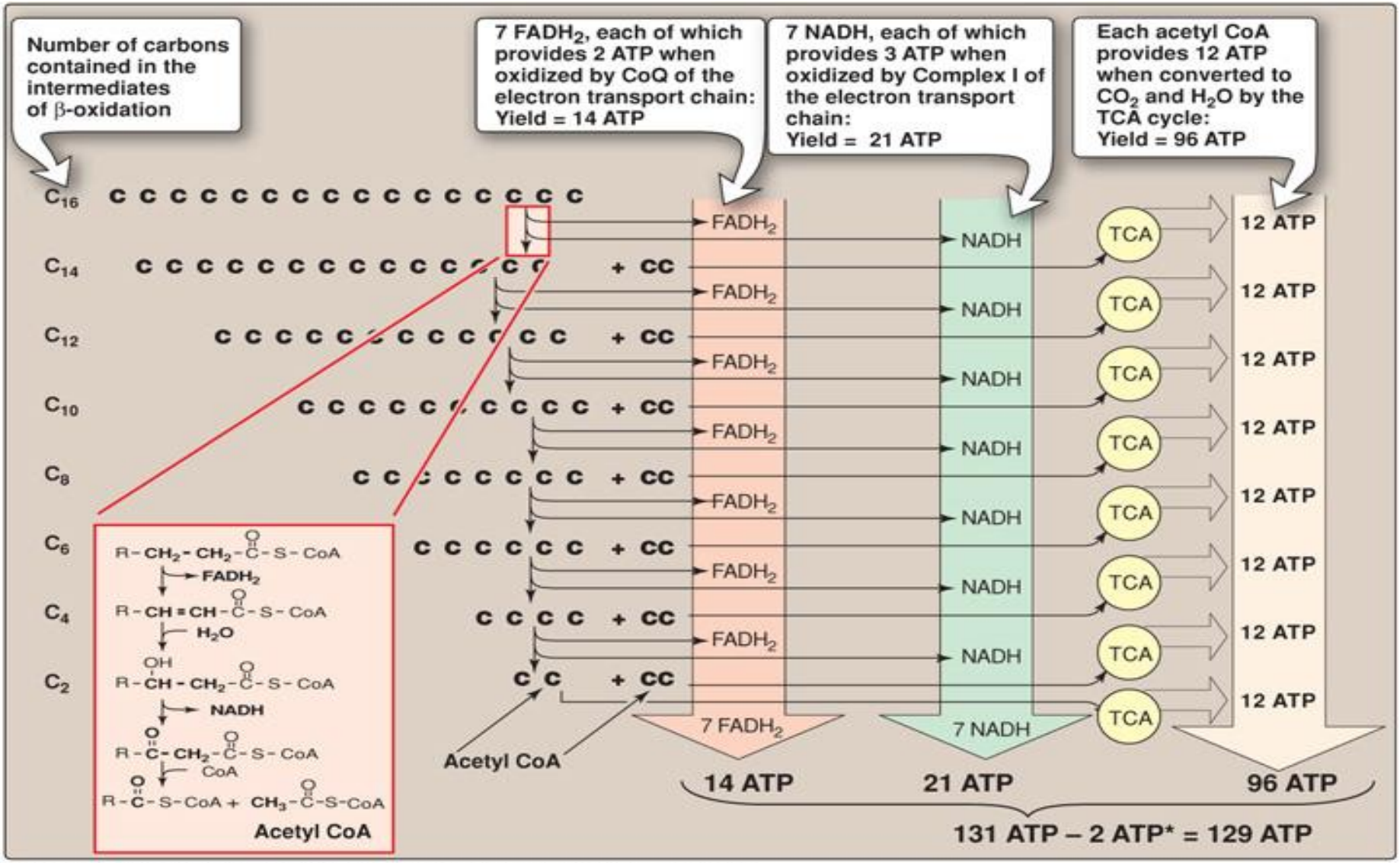
β-Oxidation of Fatty Acids

- The acetyl CoA formed can be channeled into the TCA cycle and be incorporated in gluconeogenesis
- The acetyl CoA formation therefore links fatty acid metabolism with glucose metabolism
- The complete oxidation of one acetyl CoA molecule yields 12 molecules of ATP (taking also into consideration NADH and $FADH_2$ produced)
- For example, palmitic acid contains 16 carbon atoms
- During the β-oxidation process, the fatty acid will yield 8 molecules of acetyl CoA thus producing 96 molecules of ATP

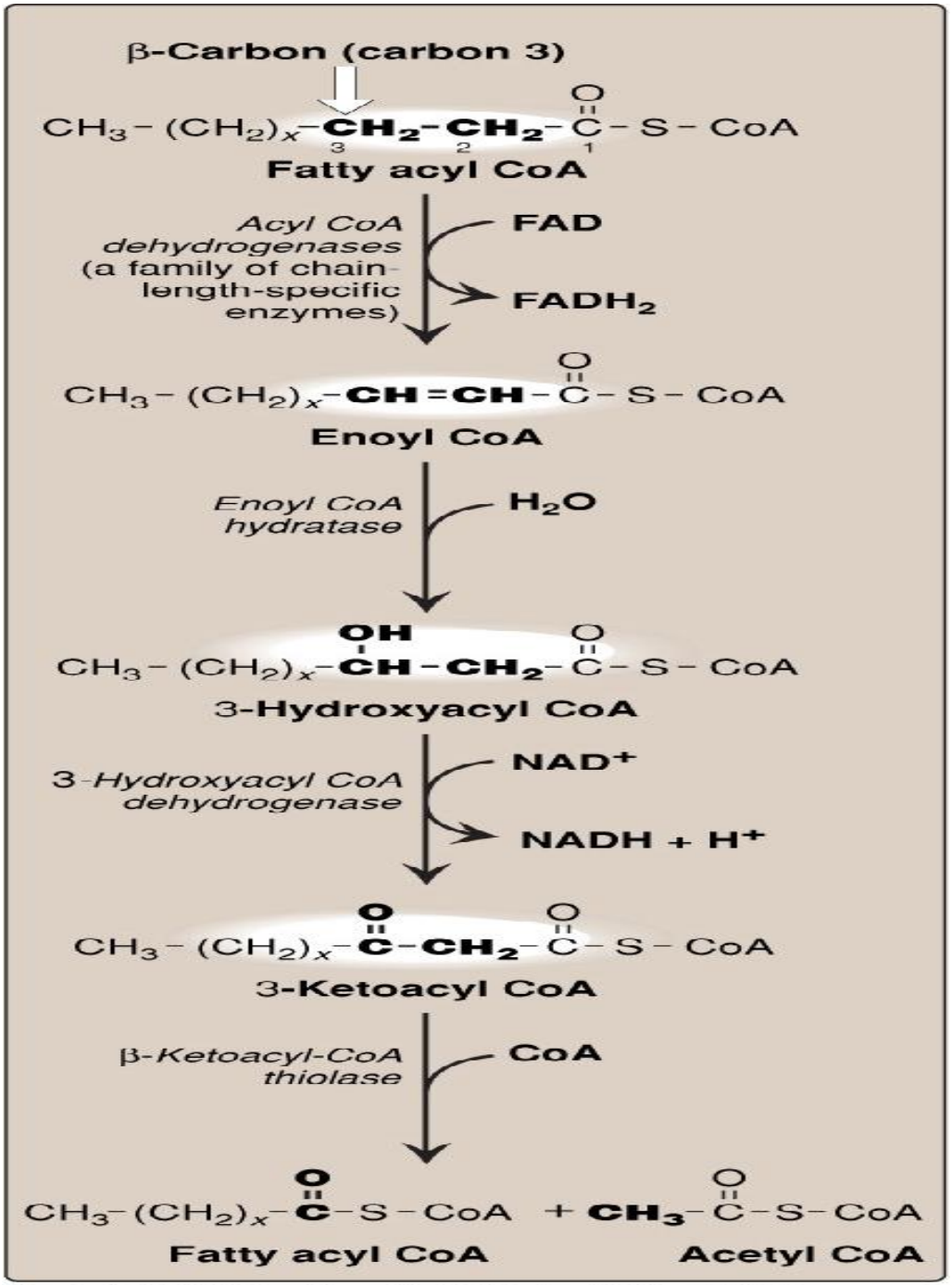


http://www.dentistry.leeds.ac.uk/biochem/lecture/faox/intro.gif

β-Oxidation of Fatty Acids



- Reactions involved in the formation of acetyl CoA from fatty acyl CoA



β-Oxidation of Fatty Acids

- Therefore the number of ATP molecules produced are as follows

8 molecules of acetyl Co A = 96 ATP

7 molecules of FADH2 = 14 ATP

7 molecules of NADH = 21 ATP

131 ATP

2 ATP was used in the process, therefore the total amount of ATP = 129

Carnitine

- Carnitine can be obtained from the diet (meat products)
- It can also be synthesized from the amino acids lysine and methionine by a reaction pathway that occurs in the liver and kidney
- The heart and skeletal muscle depends on carnitine that is endogenously made or acquired in the diet and transported in the blood
- Skeletal muscle contains 97% of all carnitine in the body
- A deficiency in carnitine results in an inability of long chain fatty acids to be used as fuels

Carnitine

- This may occur in persons with

  Liver disease (unable to make carnitine)

  Malnourished (protein deficiency)

  Strict vegetarian (meat is a good source of carnitine)

  Undergoing haemodialysis (removes carnitine from blood)

  An increased demand for carnitine e.g. Burn victims, severe infection etc.

Ketogenesis

- This is the formation of ketone bodies
- Ketone bodies include 3 substances
  1. acetoacetate
  2. D-3-hydroxybutyrate (predominant ketone body)
  3. acetone
- Ketone bodies are formed when fat breakdown predominates (i.e. there is a ↓ in carbohydrate breakdown)

Ketogenesis

- In such a situation the acetyl CoA is not fed into the TCA cycle – this is because the [oxaloacetate] is lowered
- The acetyl CoA undergoes a different fate, i.e. to form ketone bodies
- Decreased [oxaloacetate] also occurs during fasting and in diabetes as this molecule is used to generate glucose **(gluconeogenesis)**

Ketogenesis - mechanism

- Ketogenesis occurs in the liver and kidney mitochondria
- The acetoacetate and D-3-hydroxybutyrate that are formed, diffuse from the liver mitochondria into the blood where it is transported to peripheral tissues
  - They are then reconverted to acetyl CoA **(Ketolysis)** which can be oxidized by the TCA cycle
  - Therefore they act as a source of energy
- Acetone cannot be further metabolized

Ketogenesis

- The brain is able to use ketone bodies as an energy source during prolonged period of fasting…starvation
- Ketone bodies are soluble in polar solvents and as such do not need protein to aid in transportation as the lipids
- When the [ketone body] > the rate of usage then increased concentration becomes evident in the blood **(ketonemia)** and urine **(ketonuria)**
- In addition the smell of acetone is detected on the breath of the individual