The module: Metabolism

Session 4 Lecture 2

Fuel storage & lipid metabolism

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For more discussion, questions or
cases need help please post to the session group

Learning outcomes (LO)

- Describe the major energy stores in 70kg man. LO1
- Describe the reactions involved in glycogen synthesis and breakdown. LO2
- Compare the function of liver and muscle glycogen. LO3
- Explain the clinical consequences of glycogen storage diseases. LO4
- Describe the various classes of lipids. LO5
- Explain why triacylglycerols can be used as efficient energy storage molecule in adipose tissue. LO6
- Describe how dietary triacylglycerols are processed for storage or to produced energy. LO7
- Describe how fatty acid degradation differs from fatty acid synthesis. LO8
- Describe the central role of acetyl-coA in metabolism. LO9

LO1 Energy storage in man

- 70kg man

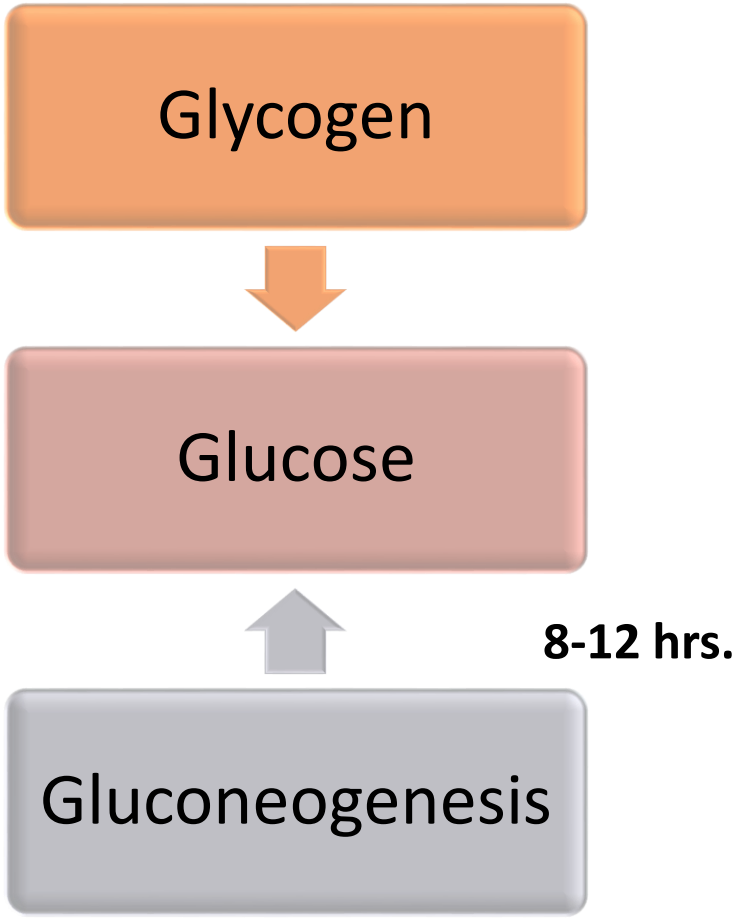
Substance (type of fuel)	Weight of the body(kg)	Energy produced(kj)
Triacylglycerol	**15**	**600,000**
Glycogen	0.4	4000
Muscle protein	6	100,000

- 135kg man

Triacylglycerol	**80**	**3,000,000**
Glycogen	0.4	4000
Muscle protein	6	100,000

LO2

Glucose storage (glycogen metabolism)

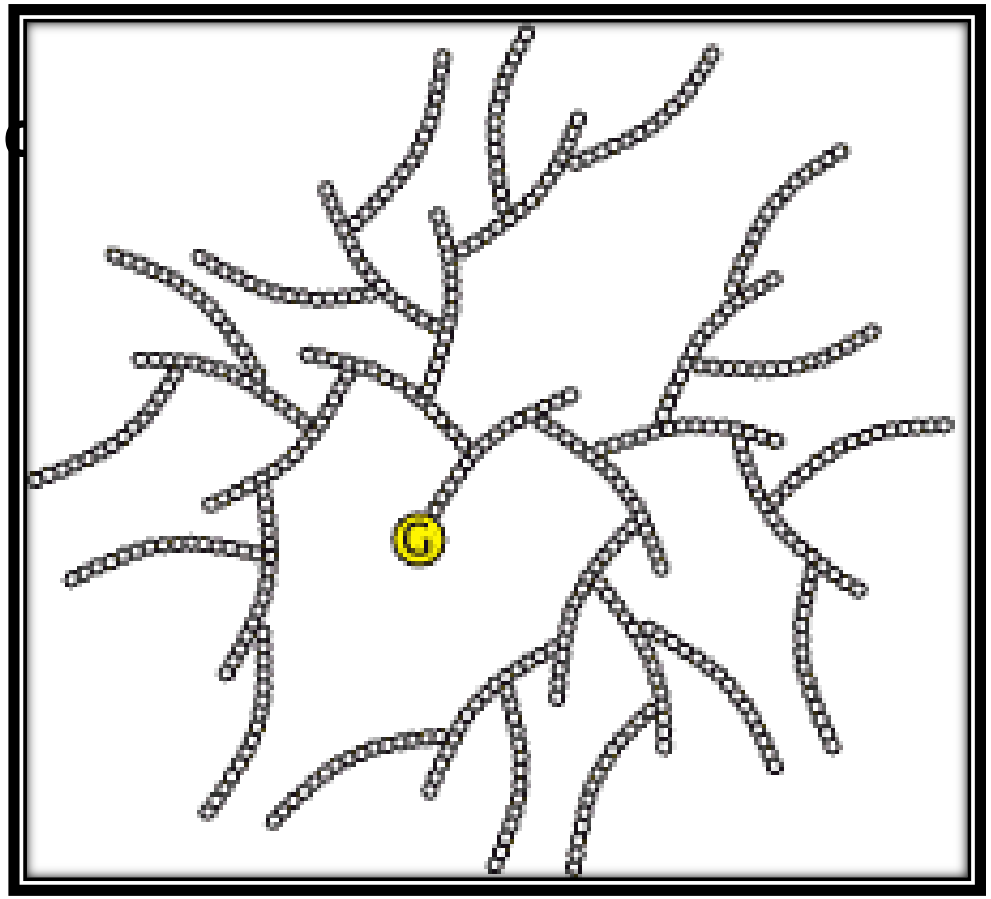


- **Glycogen is a highly branched polymer of glucose residues linked together by glycosidic bonds.**
- **Glycogen is a large molecule, that is stored in granules in liver and skeletal muscle.**

LO2
Glucose storage (glycogen metabolism)

- **Glycogen is a readily mobilized storage form of glucose. It is a very large, branched polymer of glucose residues**

Why?

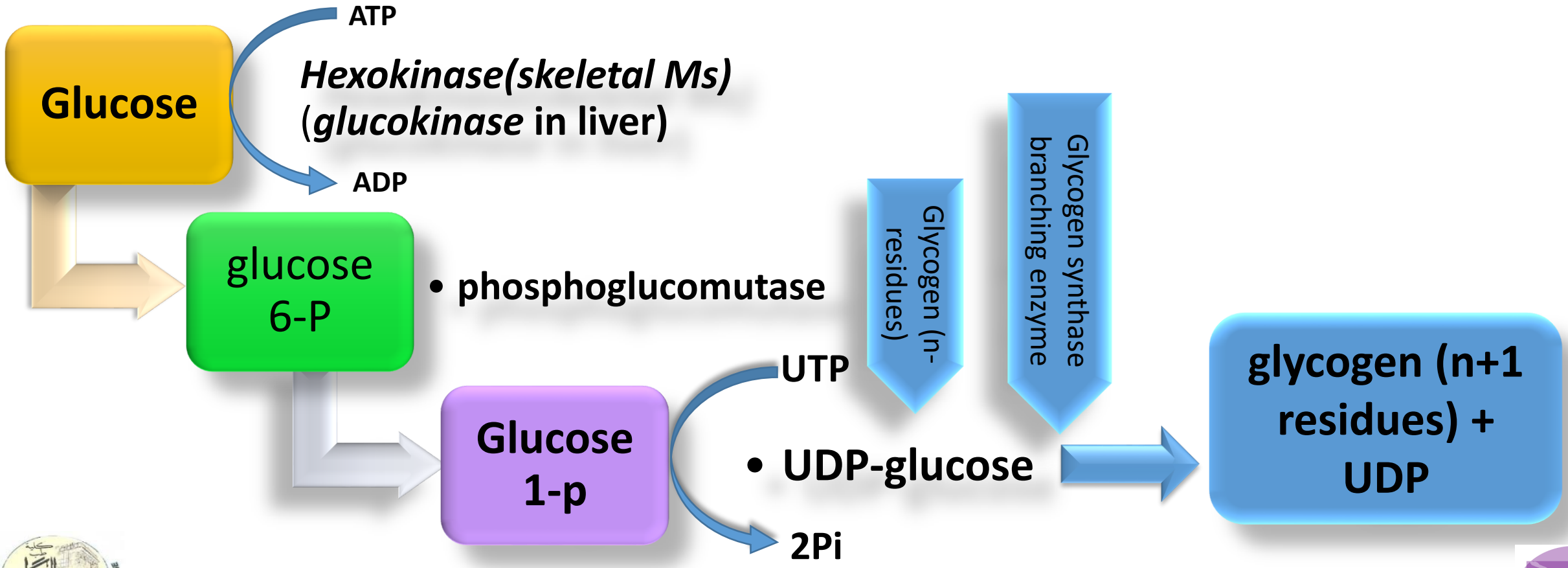


LO2

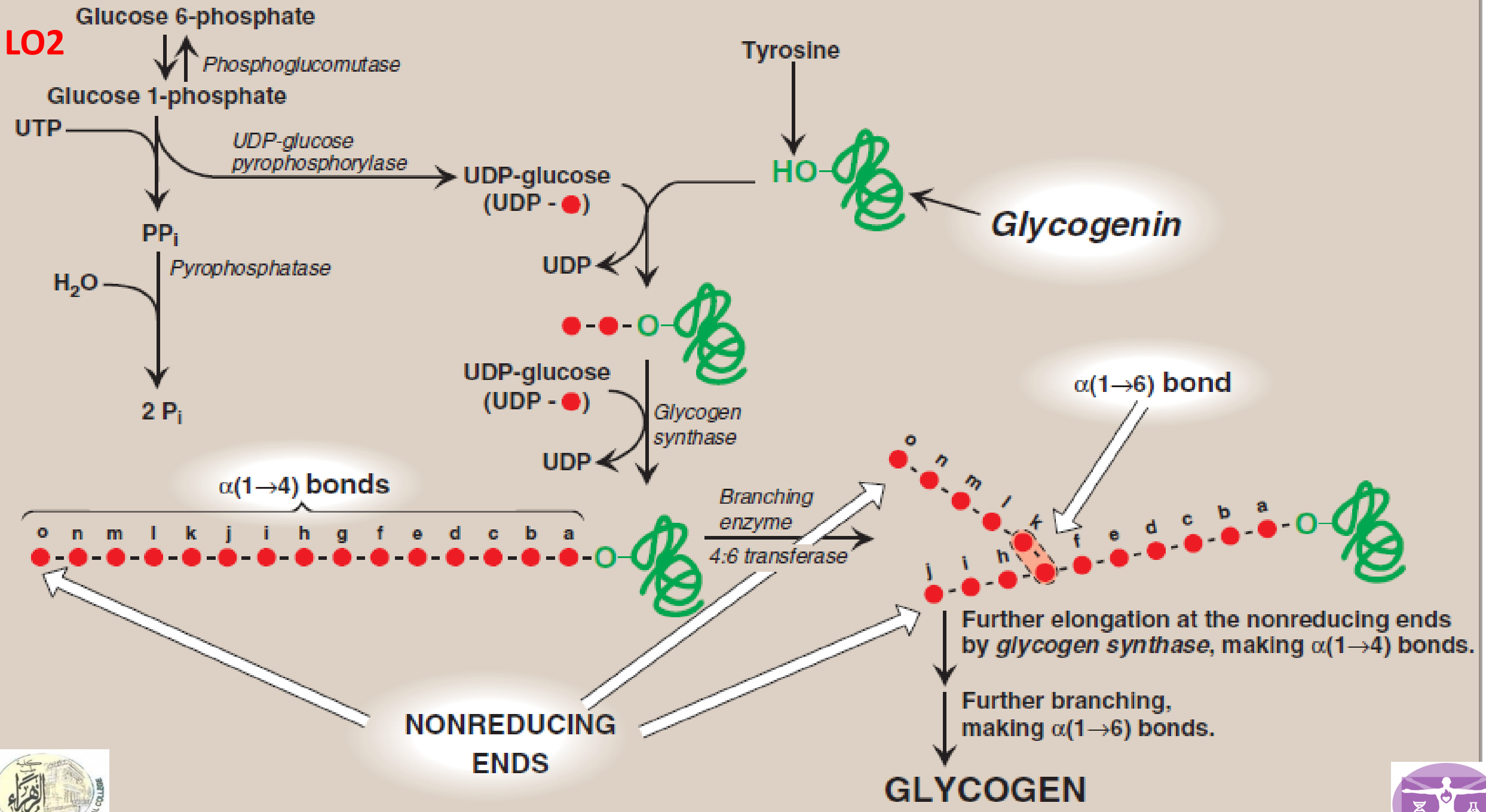
- The liver can store up to ~100g glycogen while skeletal muscle can store up to ~300g glycogen.
- Abnormal storage of glycogen (excessive or inadequate) is seen in a number of clinical conditions known collectively as the glycogen storage diseases.

LO2

Glycogen synthesis (glycogenesis)



LO2


Glucose 6-phosphate
Phosphoglucomutase
Glucose 1-phosphate
UTP
UDP-glucose pyrophosphorylase
PPi
H2O
Pyrophosphatase
2 Pi
UDP-glucose (UDP - ●)
UDP
Tyrosine
HO
Glycogenin
UDP-glucose (UDP - ●)
UDP
Glycogen synthase
α(1→4) bonds
o n m l k j i h g f e d c b a
Branching enzyme
4:6 transferase
α(1→6) bond
Further elongation at the nonreducing ends by glycogen synthase, making α(1→4) bonds.
Further branching, making α(1→6) bonds.
NONREDUCING ENDS
GLYCOGEN

Glycogen degradation (glycogenolysis)

LO2,LO3

*Exercise stimulate the degradation → muscle glycogen

*Fasting, stress(e.g fight, flight) degraded → liver glycogen

LO2,LO3

Glycogen degradation (glycogenolysis)

- **Three steps in the degradation process :**

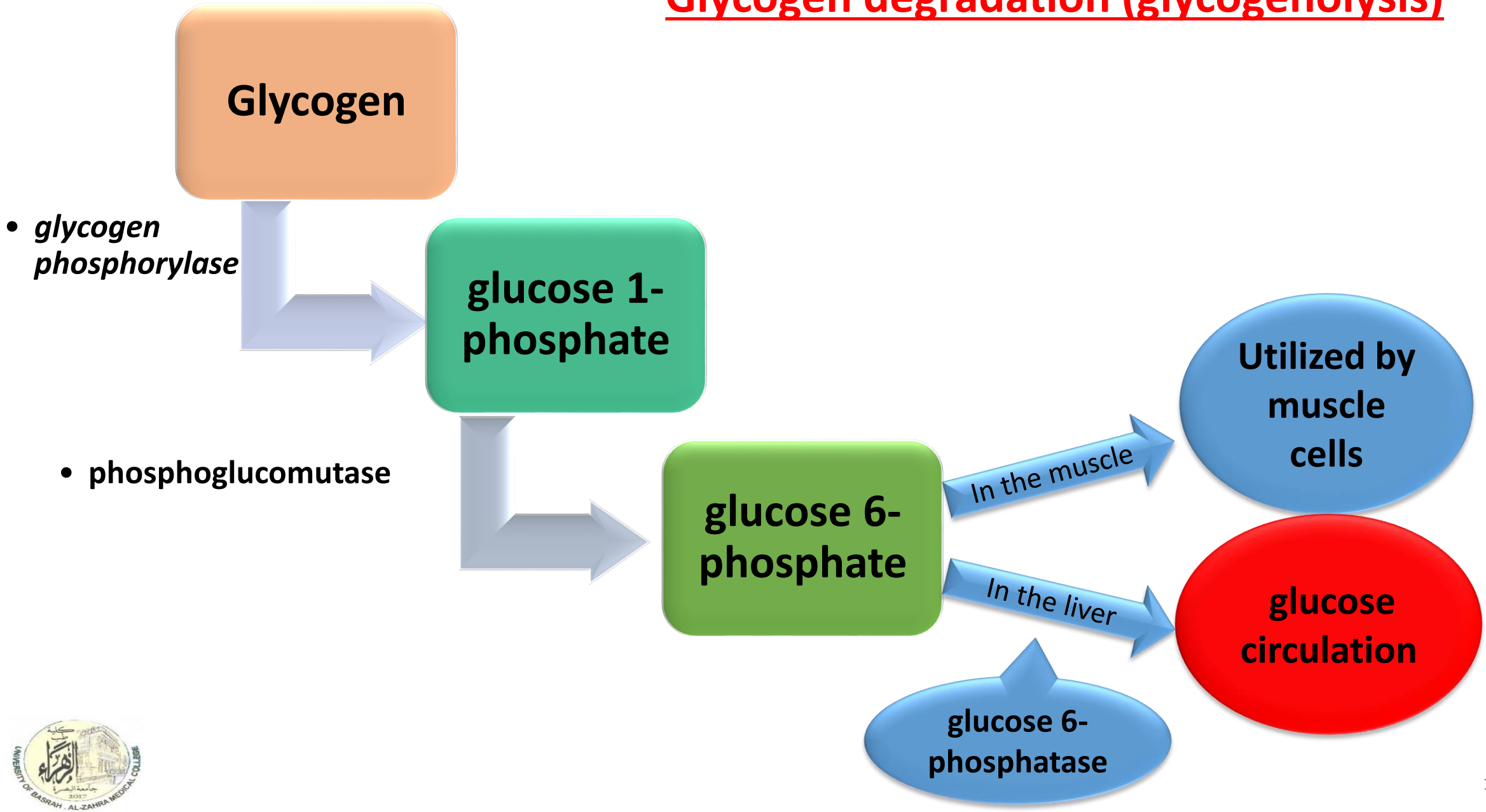
1- **Phosphorolysis** **(glycogen phosphorylase)**

2- **Glycogen remodeling** **debranching enzyme-(transferase and alpha 1-6 glucosidase)**

3- **Glucose 1- phosphate conversion to G6P** **(phosphoglucomutase)**

LO2,LO3

Glycogen degradation (glycogenolysis)



LO3

Glycogen metabolism

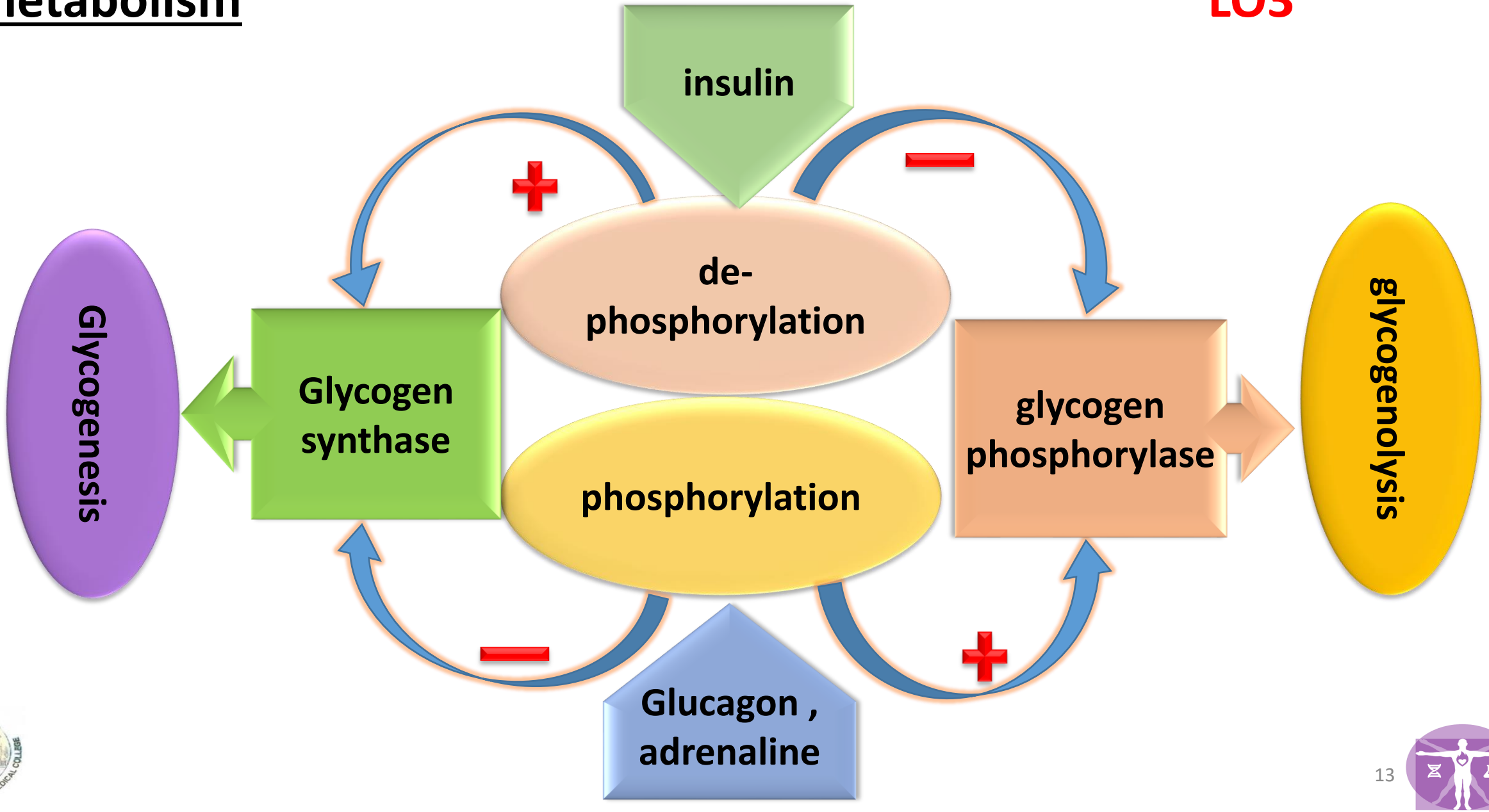
- **Glycogen metabolism is regulated by controlling the activities of enzymes catalyzing irreversible reactions (glycogen synthase and glycogen phosphorylase):**

1-Allosteric control (AMP activates phosphorylase)

2-Covalent modification (reversible phosphorylation) in response to hormone levels

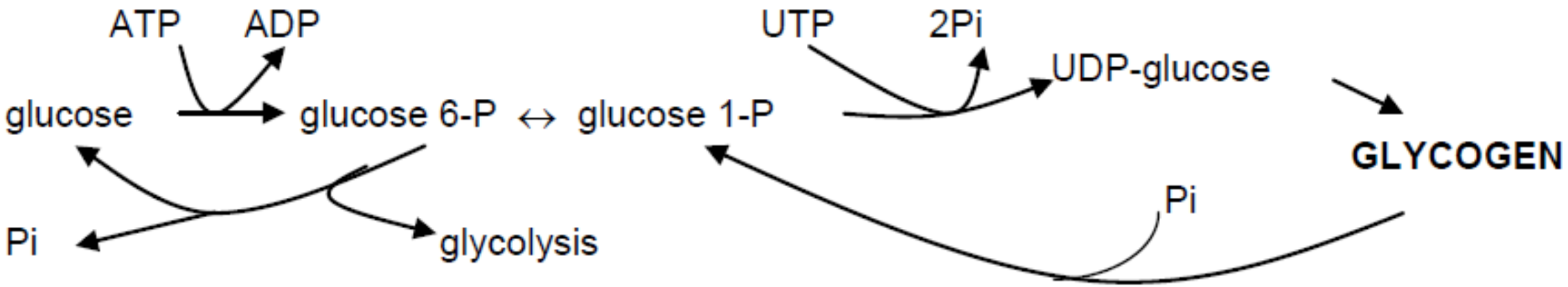
Regulation of glycogen metabolism

LO3



Lo3

Overview of glycogen metabolism



LO4
Glycogen storage diseases

A number of inherited disorders of glycogen metabolism

abnormality in one or other of the enzymes of glycogen metabolism.

increased or decreased amounts of glycogen which may cause:

tissue damage if excessive storage.

fasting hypoglycaemia (low blood glucose).

poor exercise tolerance.

glycogen structure may be abnormal.

usually liver and/or muscle are affected

LO4

Glycogenosis	Causes of disorder
Type 1	Deficiency of glucose-6-phosphatase
Type II	Deficiency of lysosomal alpha 1→4 and 1→6 glucosidase
Type III	Absence of debranching enzyme
Type IV	Absence of branching enzyme
Type V	Absence of muscle phosphorylase
Type VI	Deficiency of liver phosphorylase
Type VII	Deficiency of phosphofructokinase in muscle and erythrocytes
Type VIII	Deficiency of liver phosphorylase kinase

LO5
Lipid metabolism

- **Lipids are a structurally diverse group of important compounds that are generally insoluble in water (hydrophobic) but are soluble in organic solvents.**
- **There is no general formula but most only contain C, H and O (phospholipids also contain P and N).**

LO5

Classes of lipids

Fatty acid derivatives

- **Fatty acids** - fuel molecules.
- **Triacylglycerols** - fuel storage and insulation
- **Phospholipids** - components of membranes and plasma lipoproteins
- **Eicosanoids** - local mediators

Hydroxy-methyl- glutaric acid derivatives

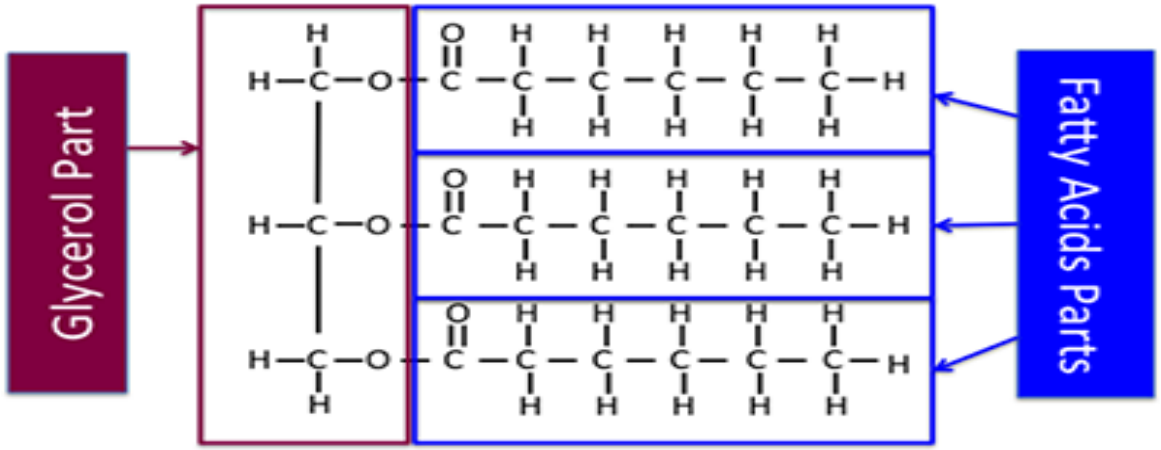
- **Cholesterol** membranes and steroid hormone synthesis
- **Cholesterol esters** - cholesterol storage
- **Bile acids and salts** — lipid digestion

Vitamins

- **A, D, E and K.**

LO6
Triacylglycerols

- Triacylglycerols are the major dietary and storage lipid in the body. They consist of three fatty acids esterified to glycerol
- Triacylglycerols are hydrophobic and are stored in an anhydrous form in a highly specialized storage tissue (adipose tissue)



LO6

- They function largely as a store of fuel molecules (fatty acids and glycerol) for :

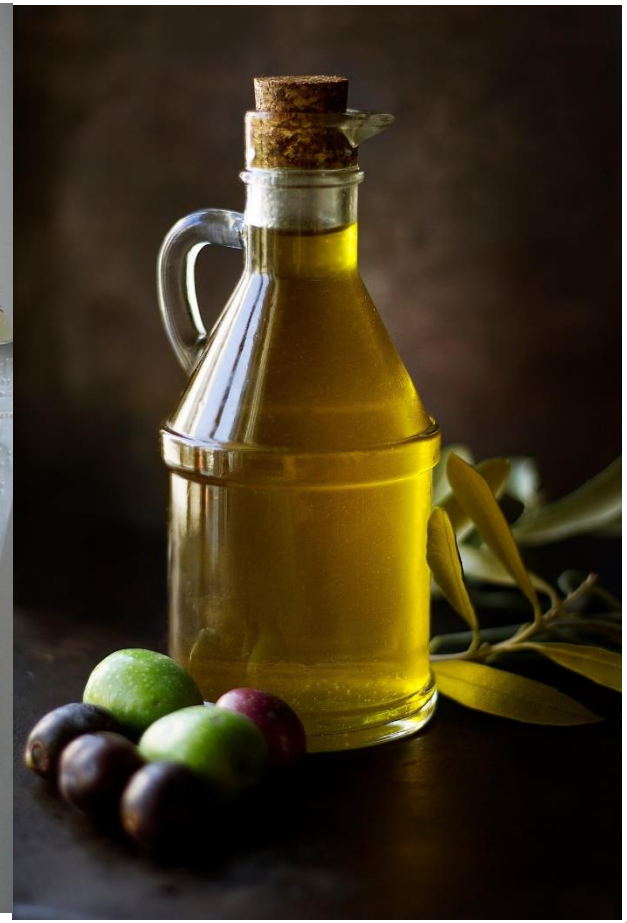
* prolonged aerobic exercise.

* stress situations such as starvation and during pregnancy.

- Storage is under hormonal control being promoted by insulin and reduced by glucagon, adrenaline, cortisol, growth hormone and thyroxine

LO7
Stage 1 metabolism of triacylglycerols

- **The major dietary lipids are triacylglycerol (butter, ghee, margarine, vegetable oils).**



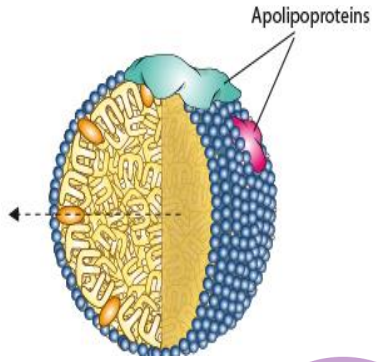
Types of TG

LO6,7

1-Exogenous :

main component of the diet , pancreatic Lipase will hydrolyzed TG to monoglycerides and 2 fatty acid.

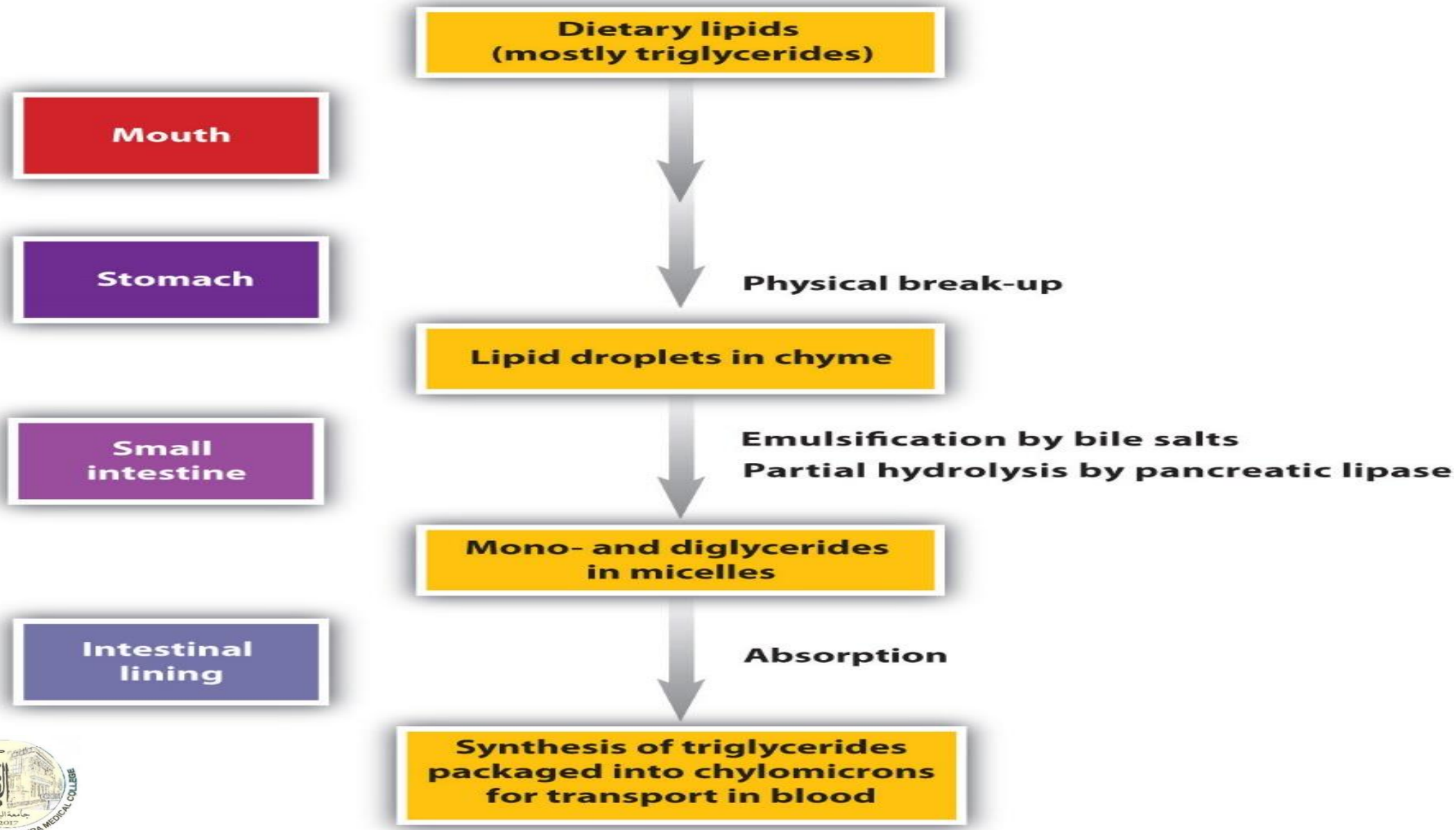
These absorbed and TG resynthesized in the mucosal cell and incorporated in structure called "Chylomicron"



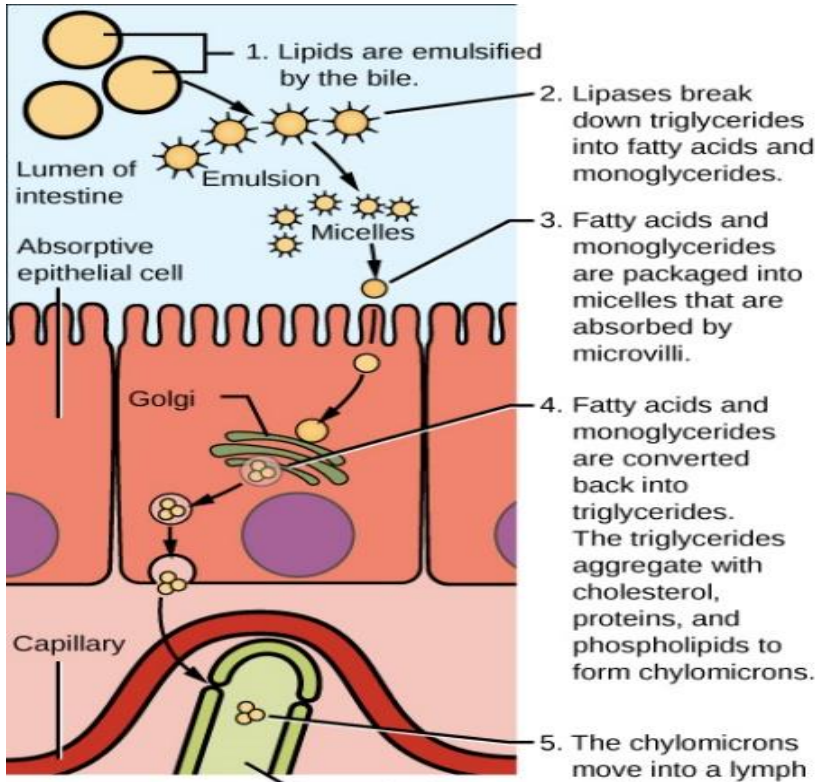
Which release into intestinal lymph and reach systemic circulation through the thoracic duct .

Dietary TG metabolism

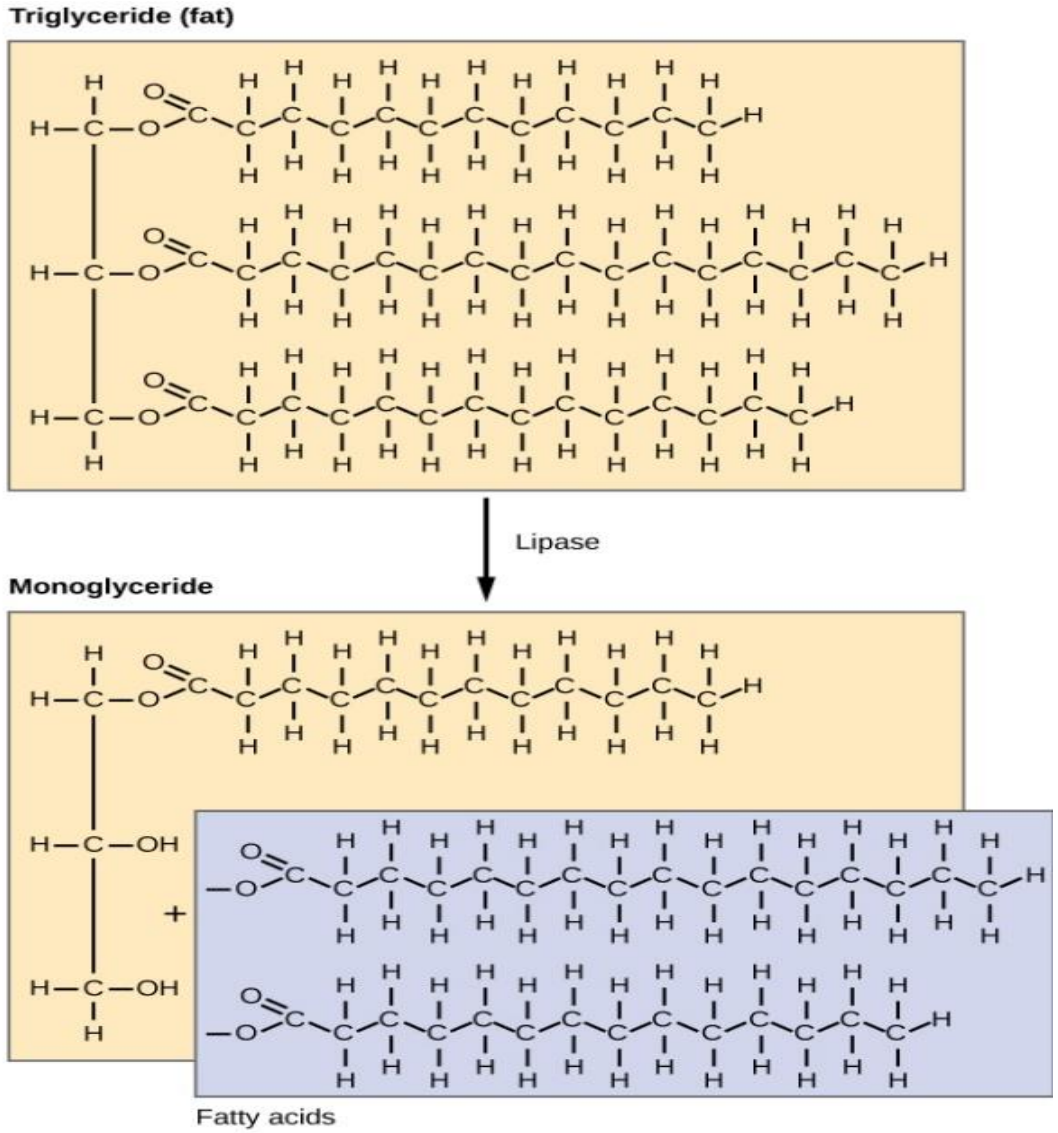
LO7



LO7


1. Lipids are emulsified by the bile.
2. Lipases break down triglycerides into fatty acids and monoglycerides.
3. Fatty acids and monoglycerides are packaged into micelles that are absorbed by microvilli.
4. Fatty acids and monoglycerides are converted back into triglycerides. The triglycerides aggregate with cholesterol, proteins, and phospholipids to form chylomicrons.
5. The chylomicrons move into a lymph capillary, which transports them to the rest of the body.
Lumen of intestine
Emulsion
Micelles
Absorptive epithelial cell
Golgi
Capillary
Lymphatic capillary

(a)


Triglyceride (fat)
Lipase
Monoglyceride
Fatty acids

(b)

LO6,7

2)Endogenous:

the liver is the major site for synthesis from glycerol and 3 fatty acids which incorporated into Lipoproteins(VLDL) and release into the circulation to utilized by peripheral tissue as energy source or stored in adipose tissue.

LO7

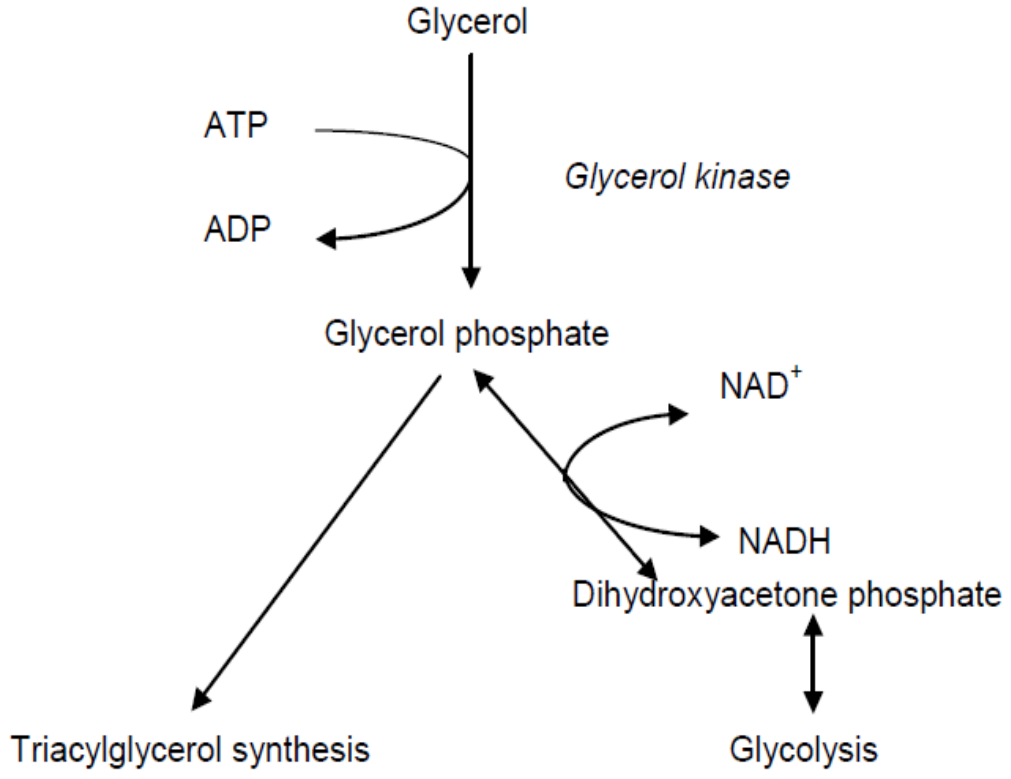
Glycerol metabolism

- **Glycerol derived from the hydrolysis of dietary triacylglycerol enters the blood stream and is transported to the liver where it is metabolized :**

1-Oxidized(glycolysis)

2-Converted to glucose

3-TG synthesis



LO8

Fatty acids

A. Carboxylic acids

Name	Number of carbons : Number of double bonds; Position of double bonds
Formic acid	1 : 0
Acetic acid	2 : 0
Propionic acid	3 : 0
Butyric acid	4 : 0
Valerianic acid	5 : 0
Caproic acid	6 : 0
Caprylic acid	8 : 0
Capric acid	10 : 0
Lauric acid	12 : 0
Myristic acid	14 : 0
Palmitic acid	16 : 0
Stearic acid	18 : 0
Oleic acid	18 : 1; 9
Linoleic acid	18 : 2; 9,12
Linolenic acid	18 : 3; 9,12,15
Arachidic acid	20 : 0
Arachidonic acid	20 : 4; 5,8,11,14
Behenic acid	22 : 0
Erucic acid	22 : 1; 13
Lignoceric acid	24 : 0
Nervonic acid	24 : 1; 15

Not contained in lipids

$HOOC—CH_2—CH_2—CH_2—CH_2—CH_3$

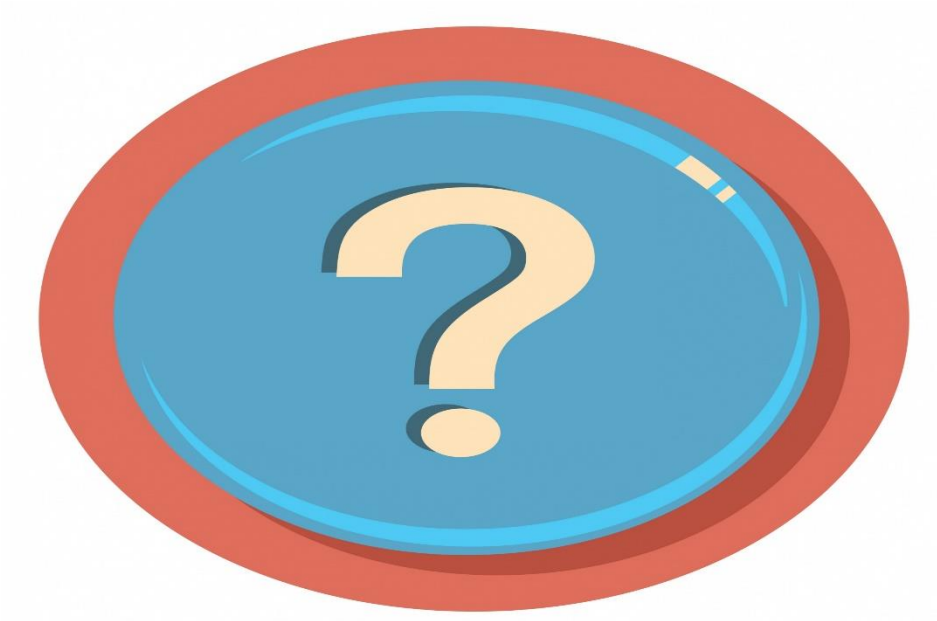
Caproic acid

Essential in human nutrition

LO8

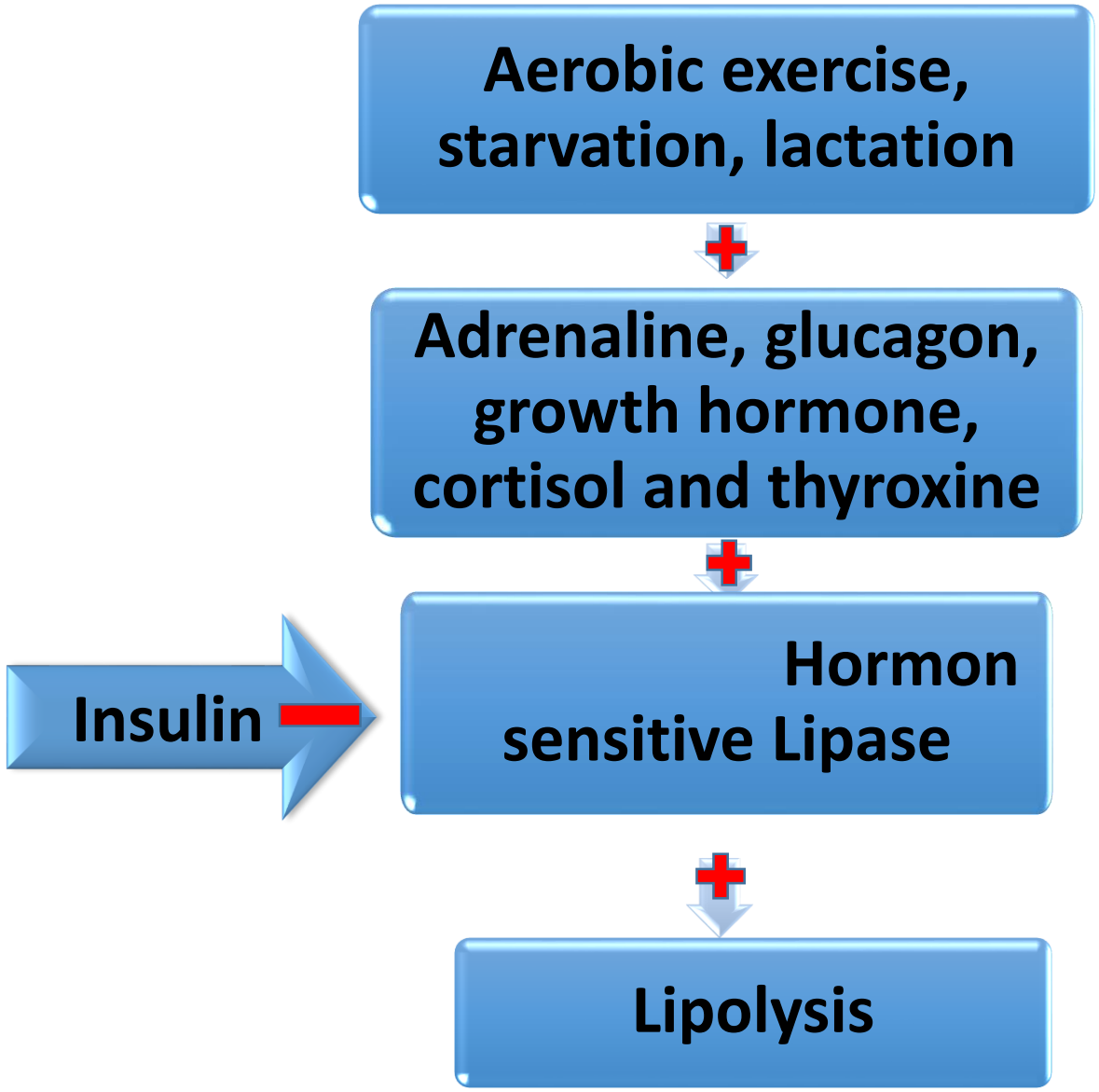
Fatty acids are ideal source for energy storage.

WHY ???



LO8

stage 2 Catabolism of fatty acids



LO8

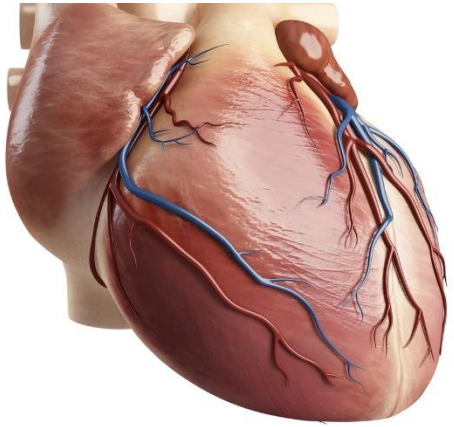
The fatty acids

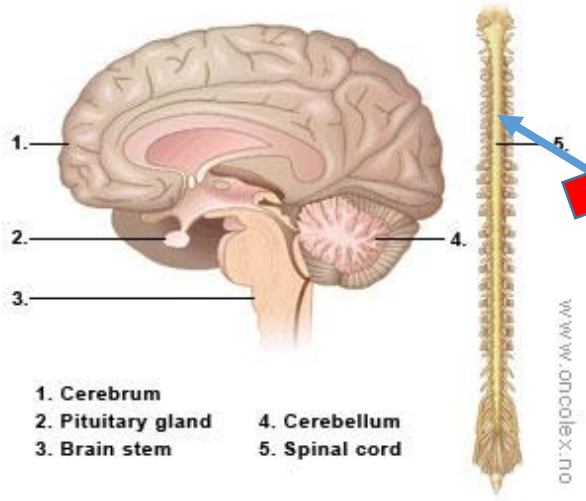
- carried to tissues via the blood stream bound non-covalently to albumin.
- The albumin-bound fatty acids are variously called non-esterified fatty acids (NEFA) or free fatty acids (FFA).

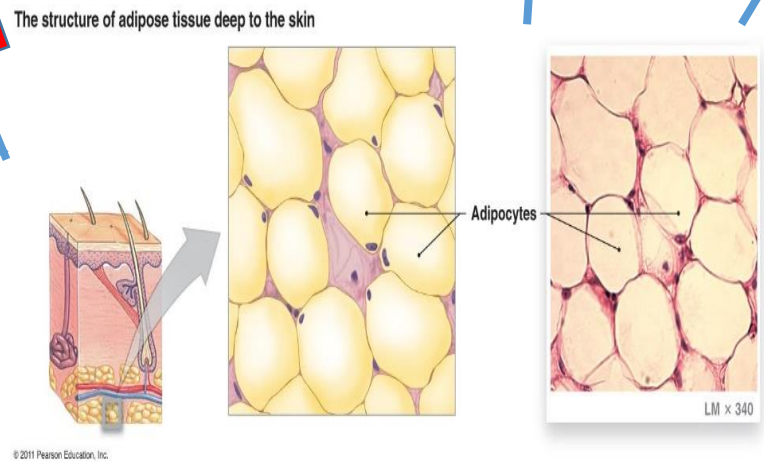
The glycerol

- transported in the blood to the liver where it may be oxidised, converted to glucose or used in the synthesis of triacylglycerols

LO8




1.
2.
3.
4.
5.
1. Cerebrum
2. Pituitary gland
3. Brain stem
4. Cerebellum
5. Spinal cord
www.oncolex.no


The structure of adipose tissue deep to the skin
Adipocytes
LM × 340
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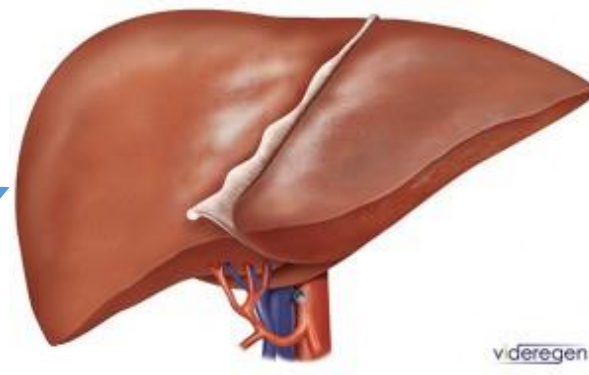
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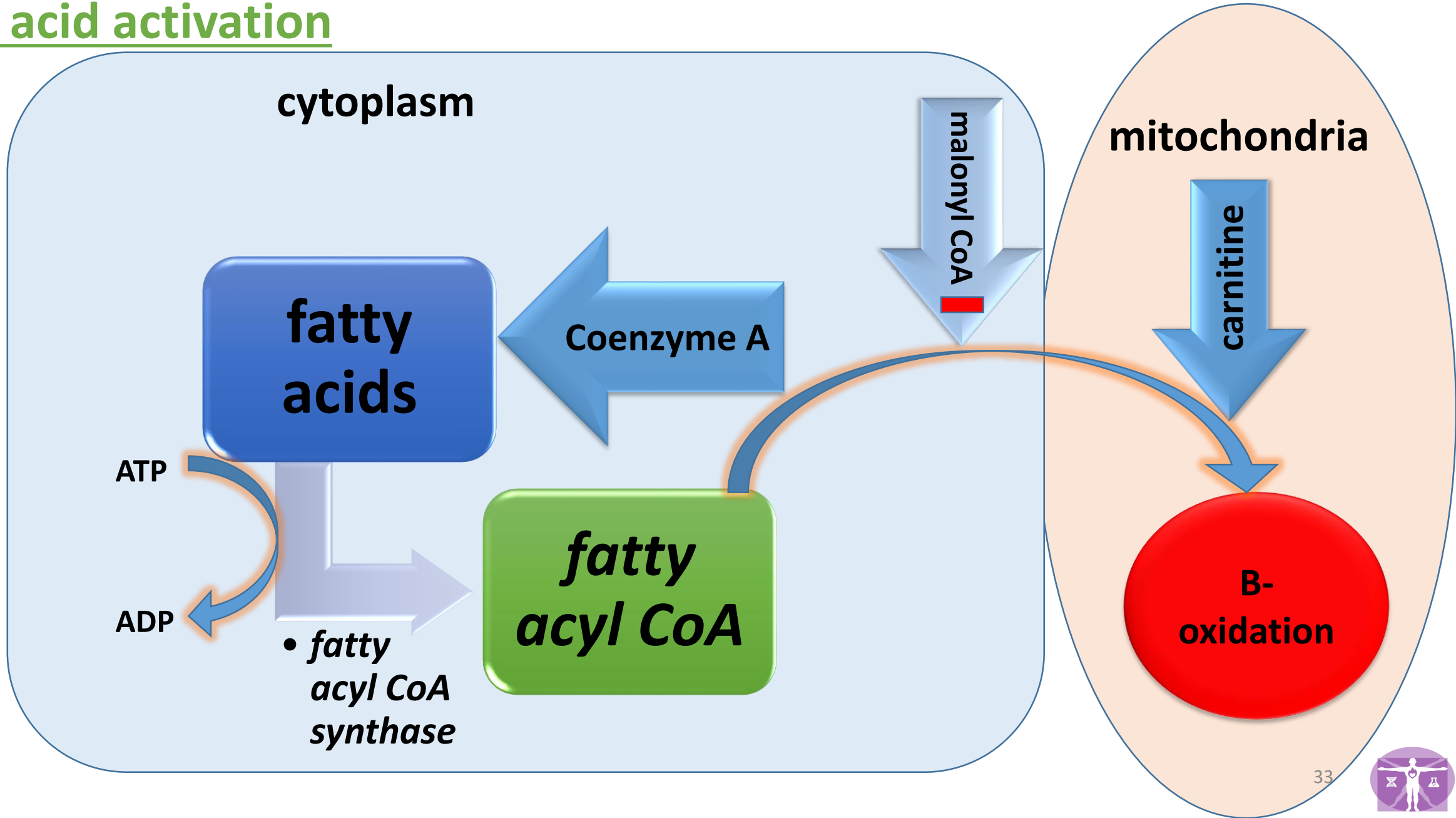
LO8

- The process by which fatty acids are oxidized to release energy is known as B-oxidation and it occurs in mitochondria.

LO8

Fatty acid activation



LO8

Fatty acid oxidation

- **The only step in the fatty acid oxidation that requires ATP is the first step and it is irreversible step because the PPi is hydrolyzed by the pyrophosphatase enzyme to yield two inorganic phosphates.**

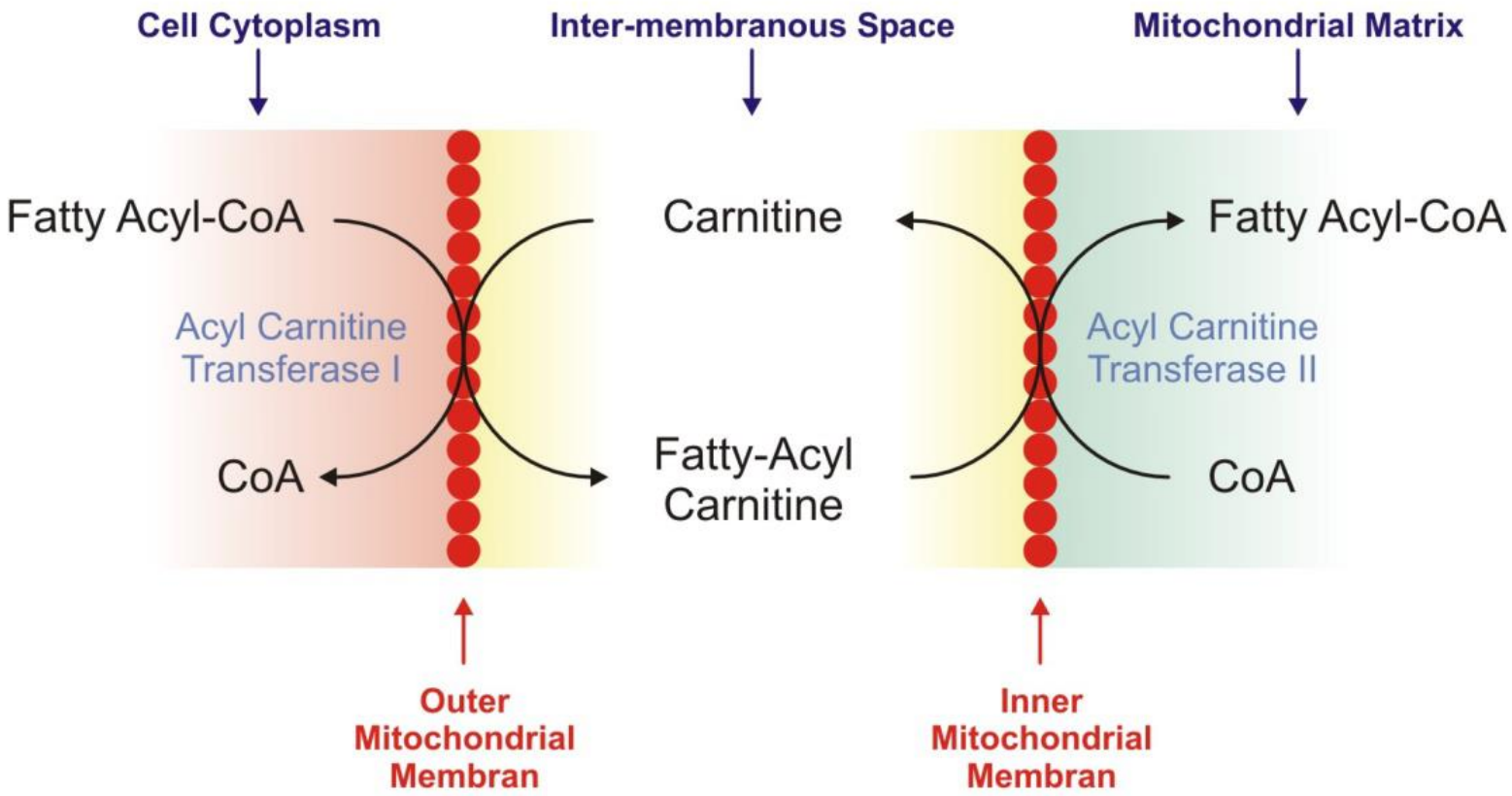
LO8

Fatty acid oxidation

- The subsequent steps in the oxidation of the fatty acids occur in the mitochondrial matrix. Since the mitochondrial membrane is impermeable to acyl-CoA, therefore a special mechanism is required for the transport of acyl-CoA from the cytoplasm to the mitochondrial matrix .

- This mechanism involves a compound called Carnitine, and the process is known as carnitine shuttle.

LO8


Cell Cytoplasm
Inter-membranous Space
Mitochondrial Matrix
Fatty Acyl-CoA
Acyl Carnitine Transferase I
CoA
Carnitine
Fatty-Acyl Carnitine
Fatty Acyl-CoA
Acyl Carnitine Transferase II
CoA
Outer Mitochondrial Membran
Inner Mitochondrial Membran

LO8
Fatty acid oxidation

- A number of patients have been discovered with a defective mitochondrial fatty acid transport system.
- They suffer from :

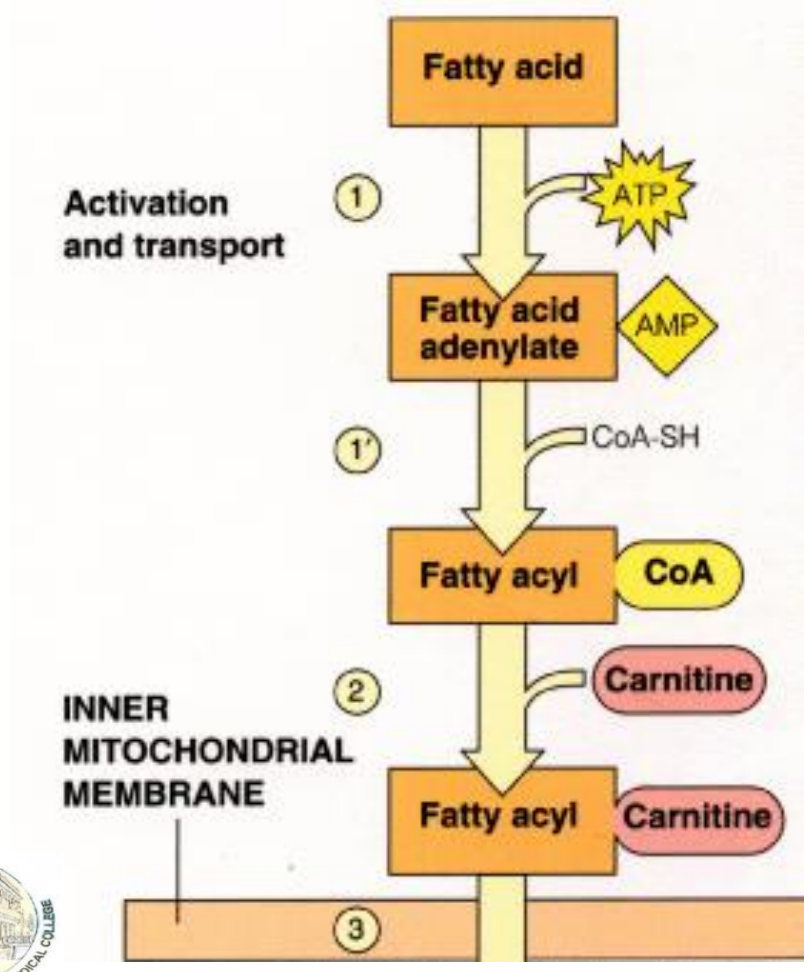
1. poor exercise tolerance and
2. have unusually large amounts of triacylglycerols in their muscle cells.

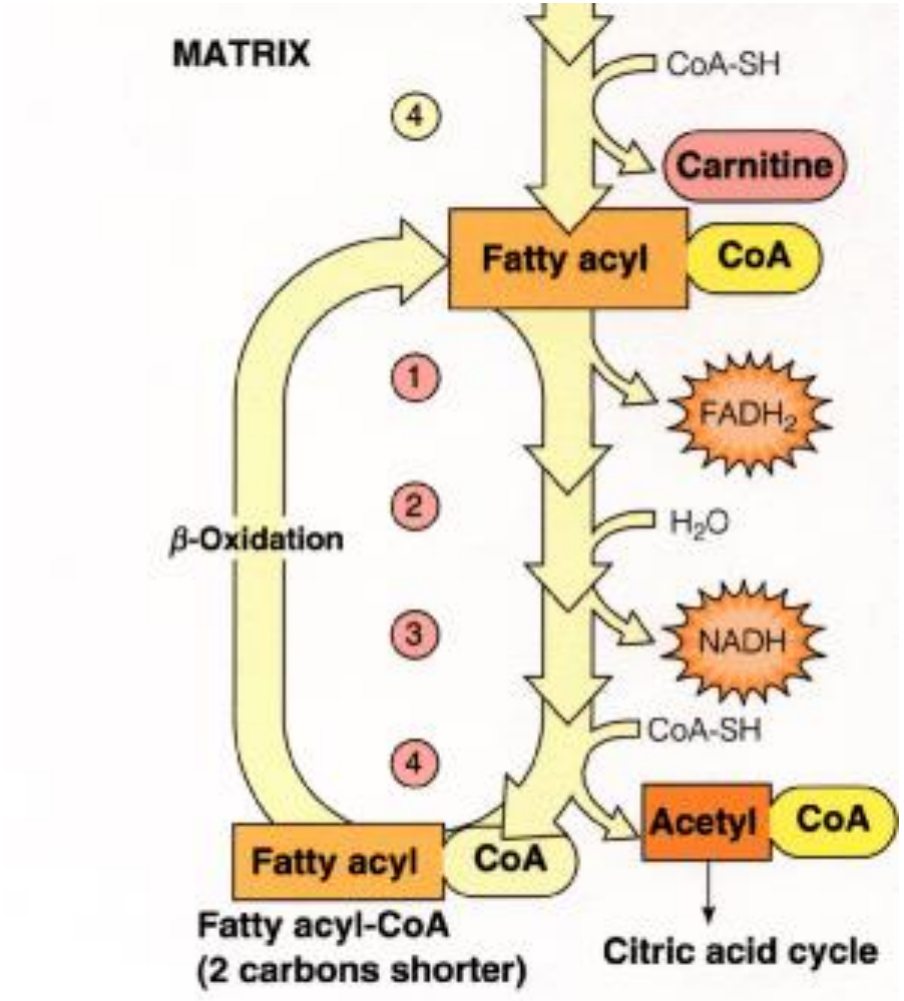
LO8

WHAT ARE THE SOURCES OF CARNITINE IN THE BODY

LO8

B-oxidation of fatty acids





From Mathews and van Holde: *Biochemistry 2/e.* © The Benjamin/Cu

LO8,9

Fatty acid synthesis :

- In mammal fatty acid synthesis occur primarily in the liver & lactating mammary glands & to lesser extent in adipose tissue.

- The primary metabolic substrate for synthesis of fatty acid is Acetyl CoA which is generated from the catabolism of carbohydrate, aminoacids &fatty acids.

LO8

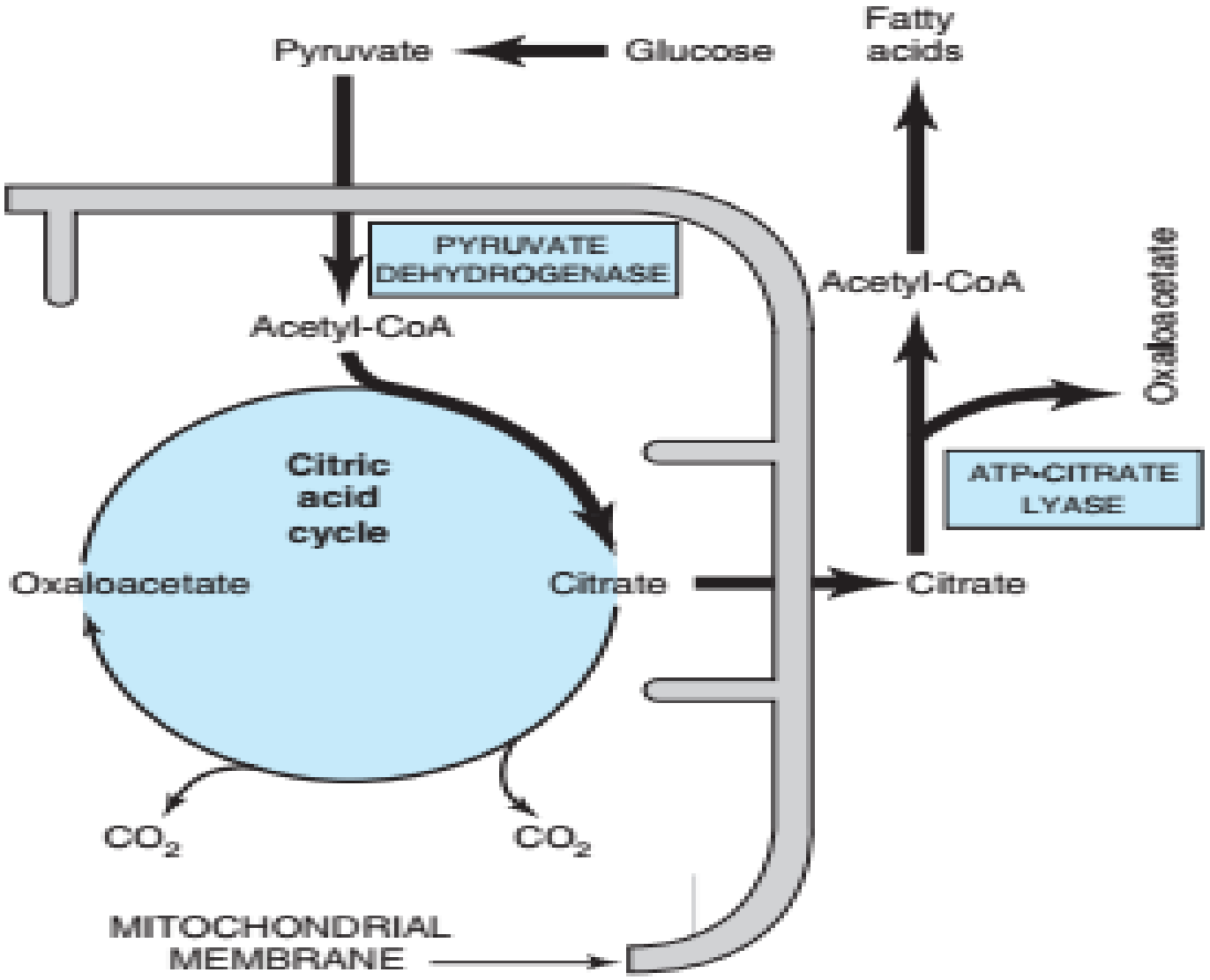
Fatty acids synthesis

Should be considered in three phases :

1. Transportation of acetyl CoA.
2. Formation of malonyl CoA.(rate limiting step)
3. Fatty acid synthase multienzyme complex.

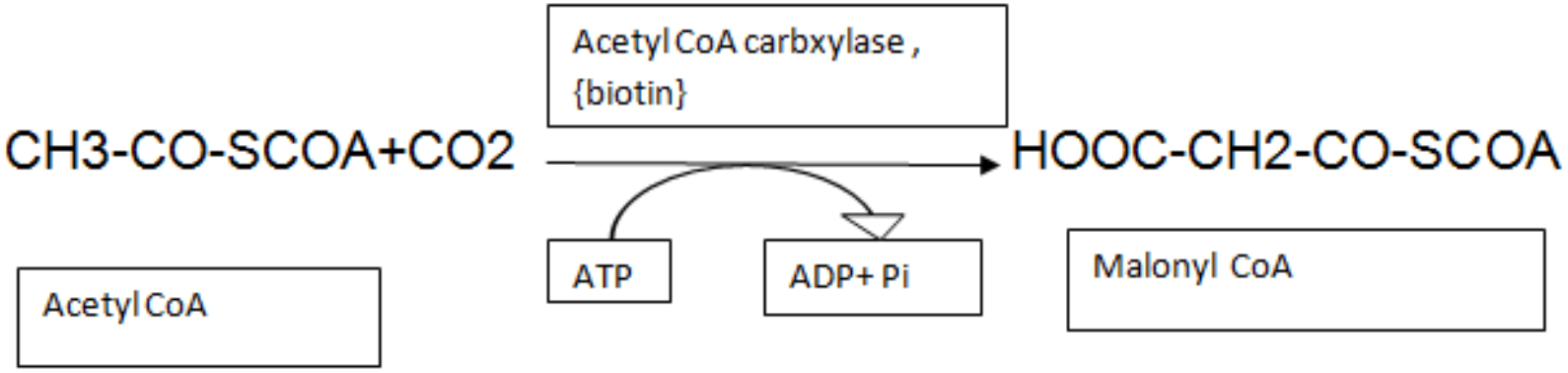
LO8

Fatty acid synthesis (transportation of Acetyl-CoA)



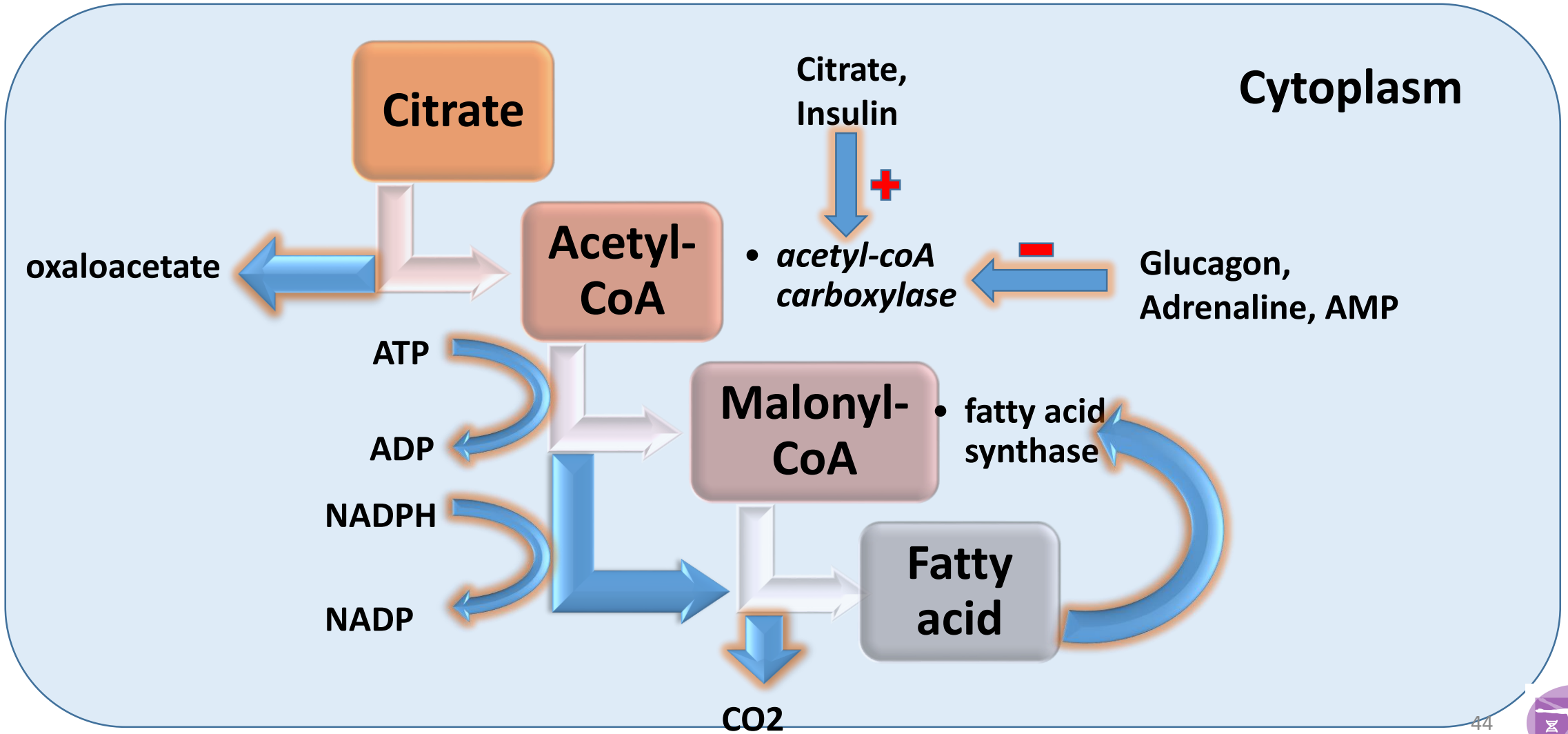
LO8

Fatty acid synthesis(formation of malonyl CoA)



LO8

Fatty acid synthesis (lipogenesis)

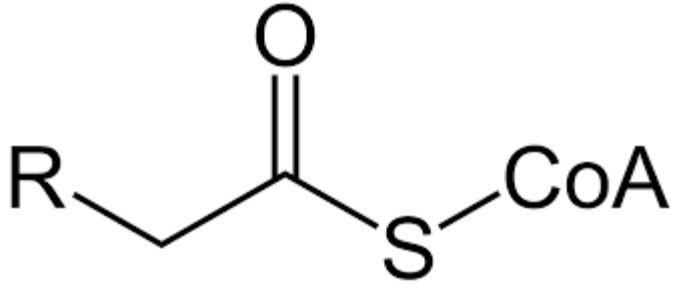


LO8

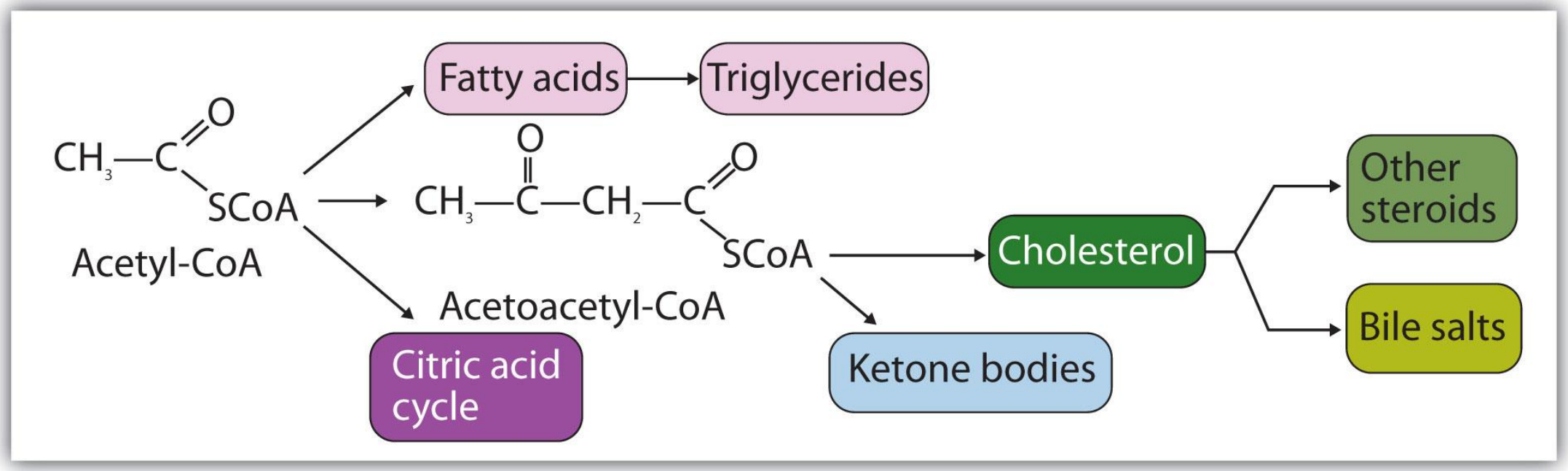
- Conversion to fatty acids and esterification to triacylglycerols for storage in adipose tissue is the fate of most of the dietary carbohydrate and protein consumed in excess of requirements.
- These processes are important clinically as excessive lipid synthesis and storage is the cause of obesity and associated problems such as type 2 diabetes and atherosclerosis.
- The process is stimulated by insulin and inhibited by the anti-insulin hormones glucagon and adrenaline

LO9
Acetyl-coA

- Acetyl-coA is produced by the catabolism of fatty acids, sugars, alcohol and certain amino acids and can be oxidized via stage 3 of catabolism.
- It is also an important intermediate in lipid biosynthesis.
- The major site of lipid synthesis in the body is the liver (some in adipose tissue) and most lipids (not polyunsaturated fatty acids) can be synthesized



LO9
Acetyl Co-A



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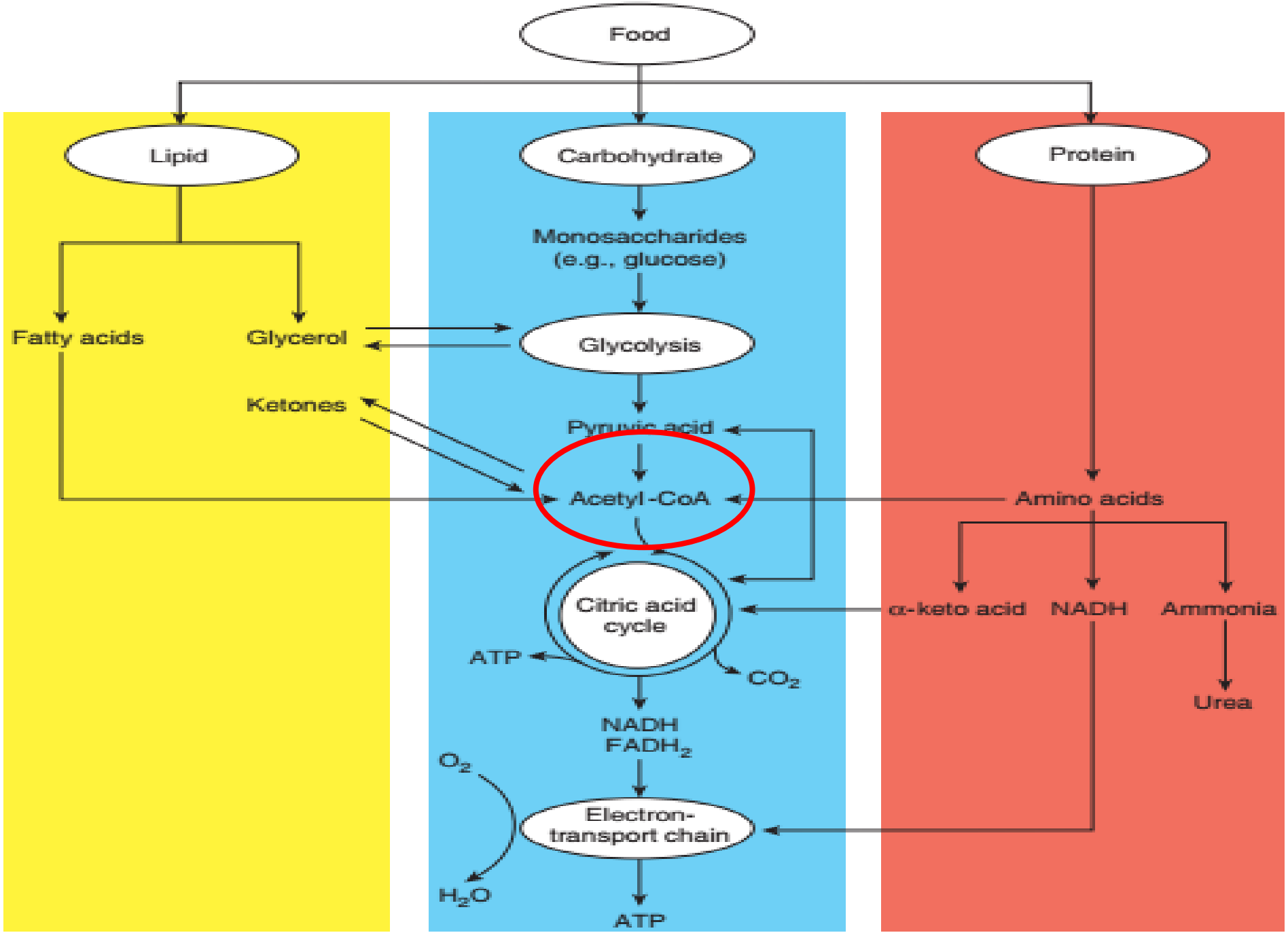
Food
Lipid
Carbohydrate
Protein
Monosaccharides
(e.g., glucose)
Fatty acids
Glycerol
Glycolysis
Ketones
Pyruvic acid
Acetyl-CoA
Amino acids
Citric acid
cycle
α-keto acid
NADH
Ammonia
ATP
CO_2
Urea
NADH
$FADH_2$
O_2
Electron-
transport chain
H_2O
ATP


Thank
You