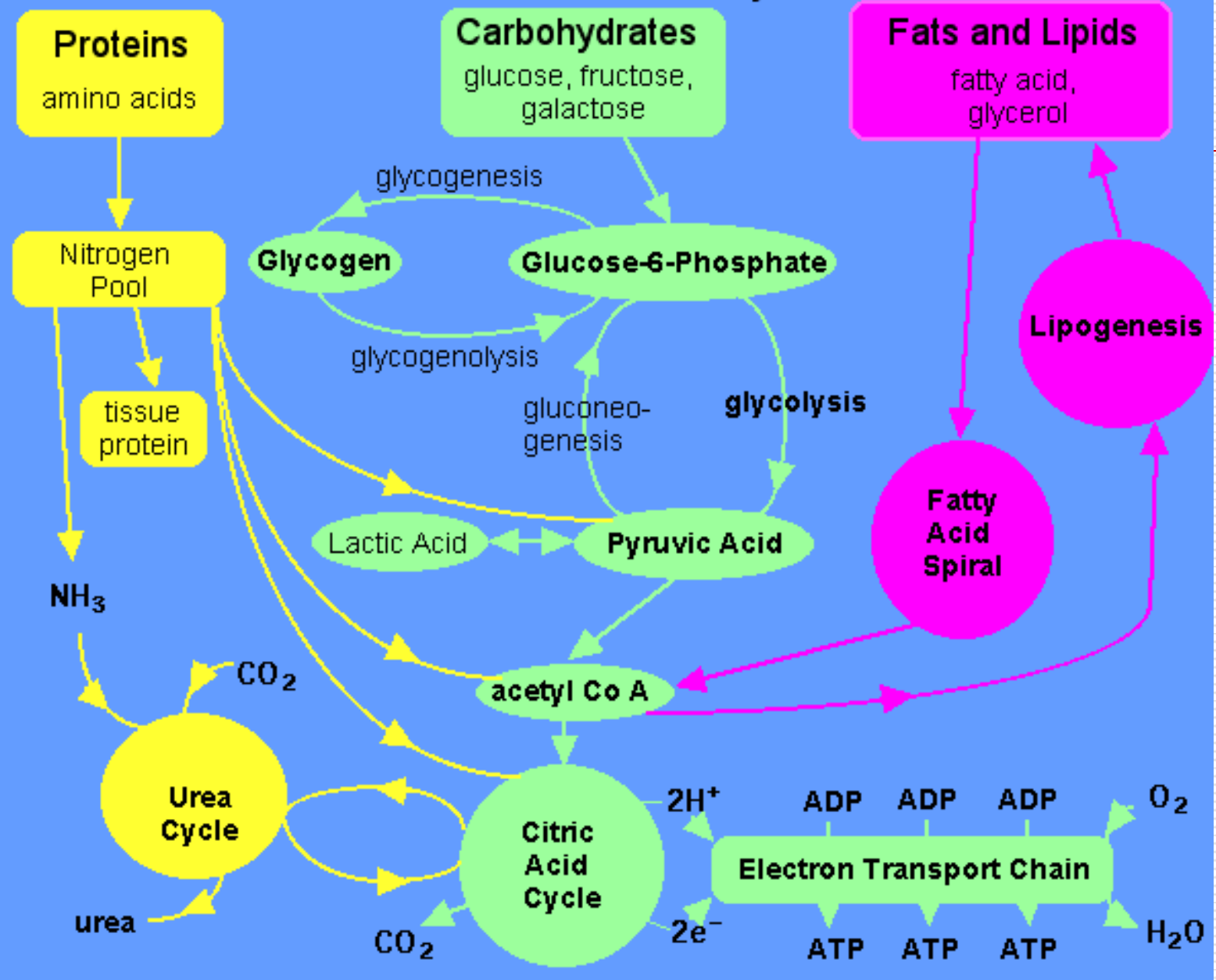


Lipids Metabolism

VLA 2017

11. 4. 2017

Metabolism Summary



Metabolism stages

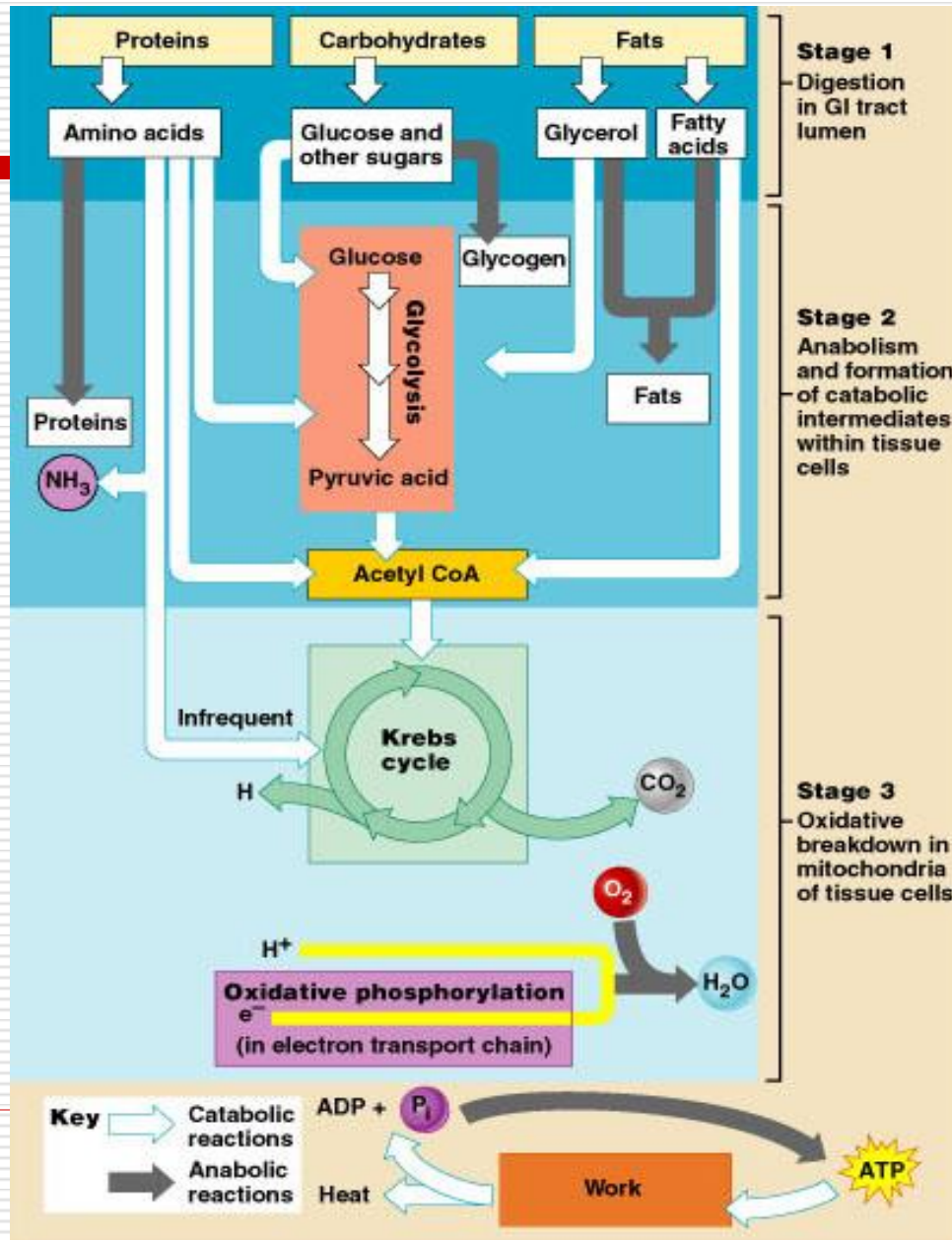
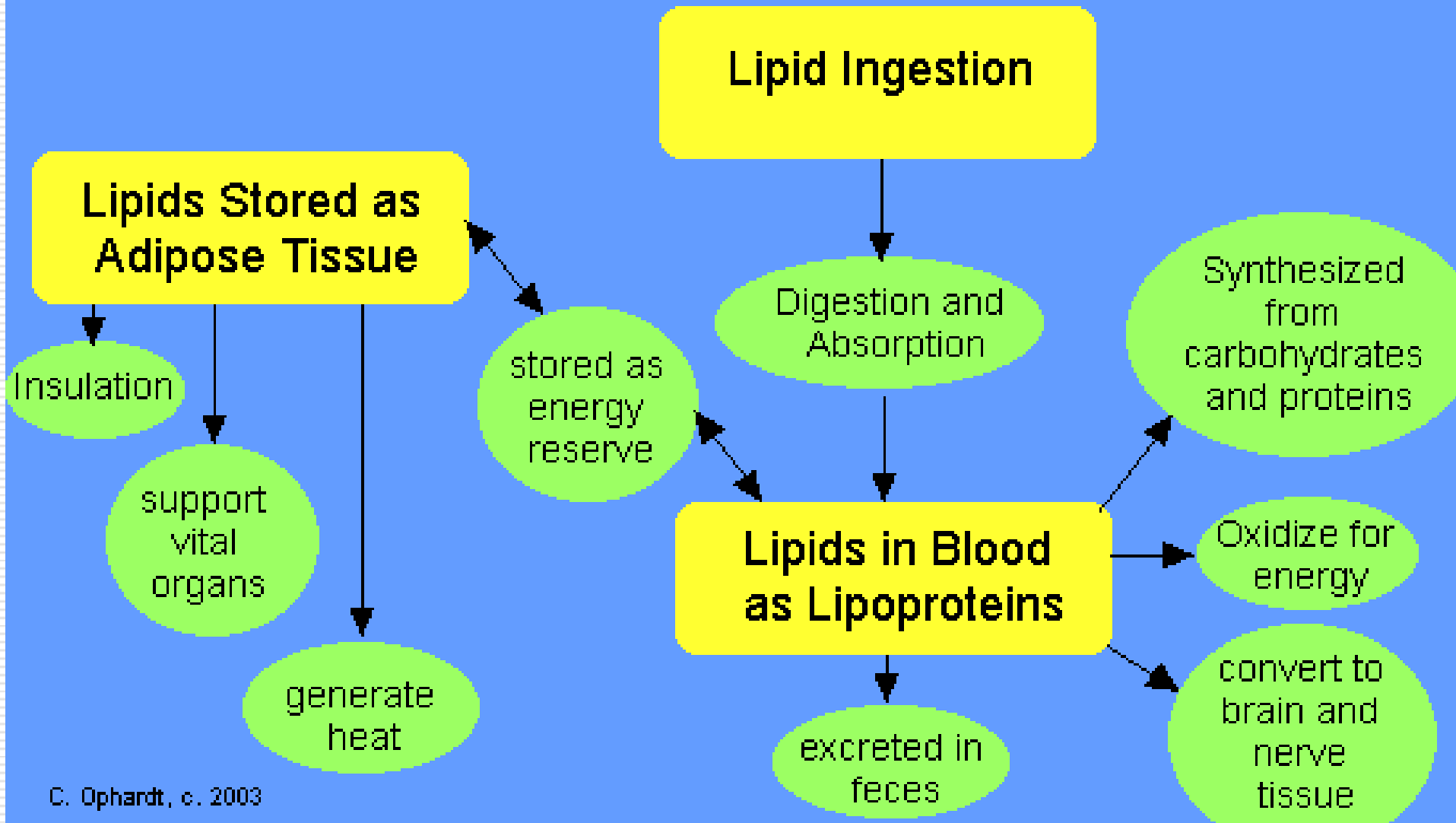


Figure 24.3

Complete oxidation – energy expenditure zisk

- Fatty acids: 9 kcal/g
 - Sugars: 4 kcal/g
 - Proteins: 4 kcal/g
-

Lipid Function and Metabolism Summary



Lipids as a energy reserve

- ❑ Most of body energy is formed by oxidation of sugars and lipids.
 - ❑ Sugars: quick source of energy
 - ❑ Lipids: energy reserve
 - ❑ Energy reserve of lipids is much higher compared to glycogen reserve
-

Lipids metabolism

- Most of lipids metabolism products is transported fo lymph as chylomicrones.
 - Lipids in chylomicrones are hydrolysed by plasmatic enzymes and absorbed by cells.
 - For energy formation only neutral lipids are oxidized
 - Lipids catabolism includes two distinct pathways:
 - Glycerol pathway
 - Pathway of fatty acids
-

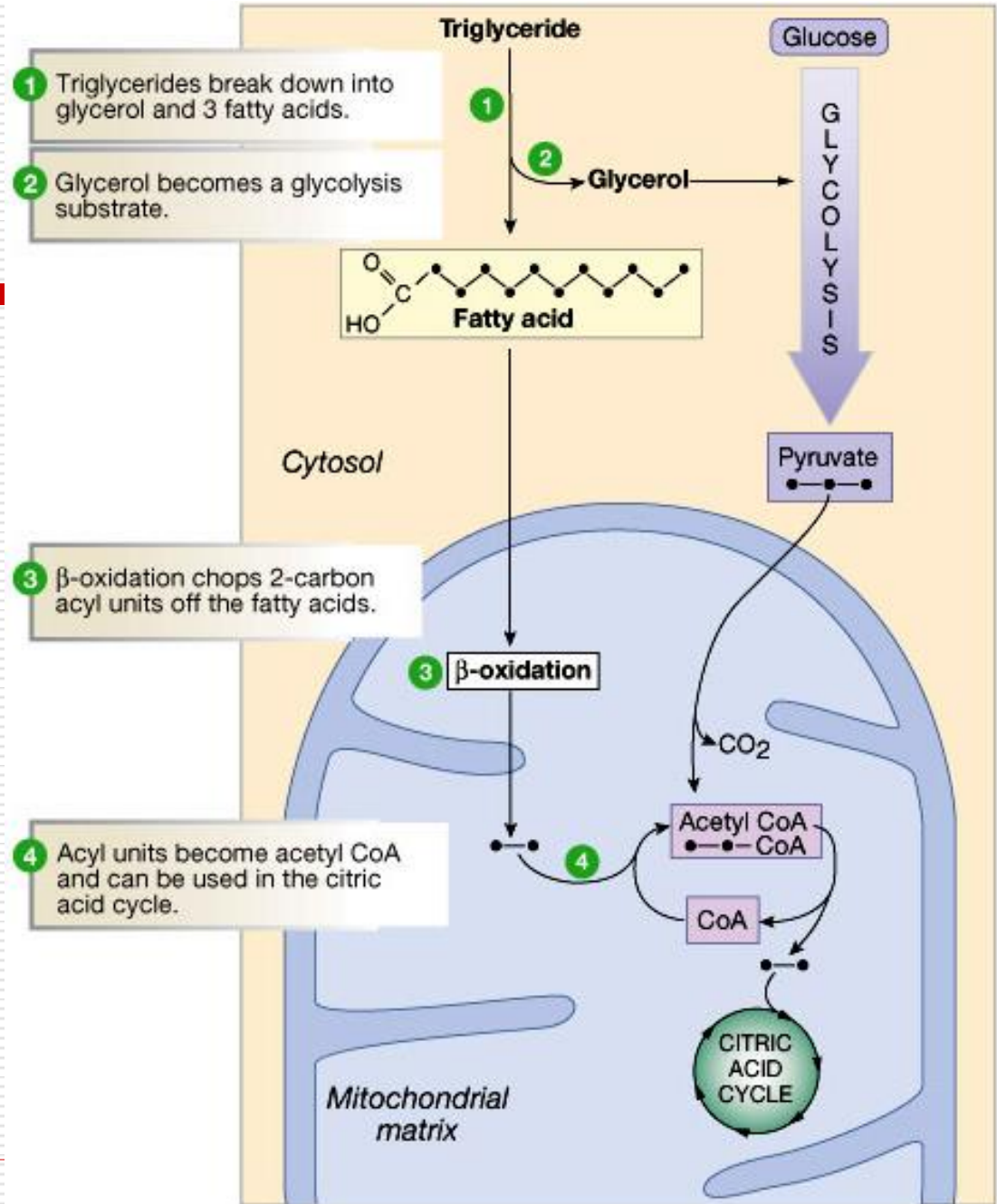
Fat Storage

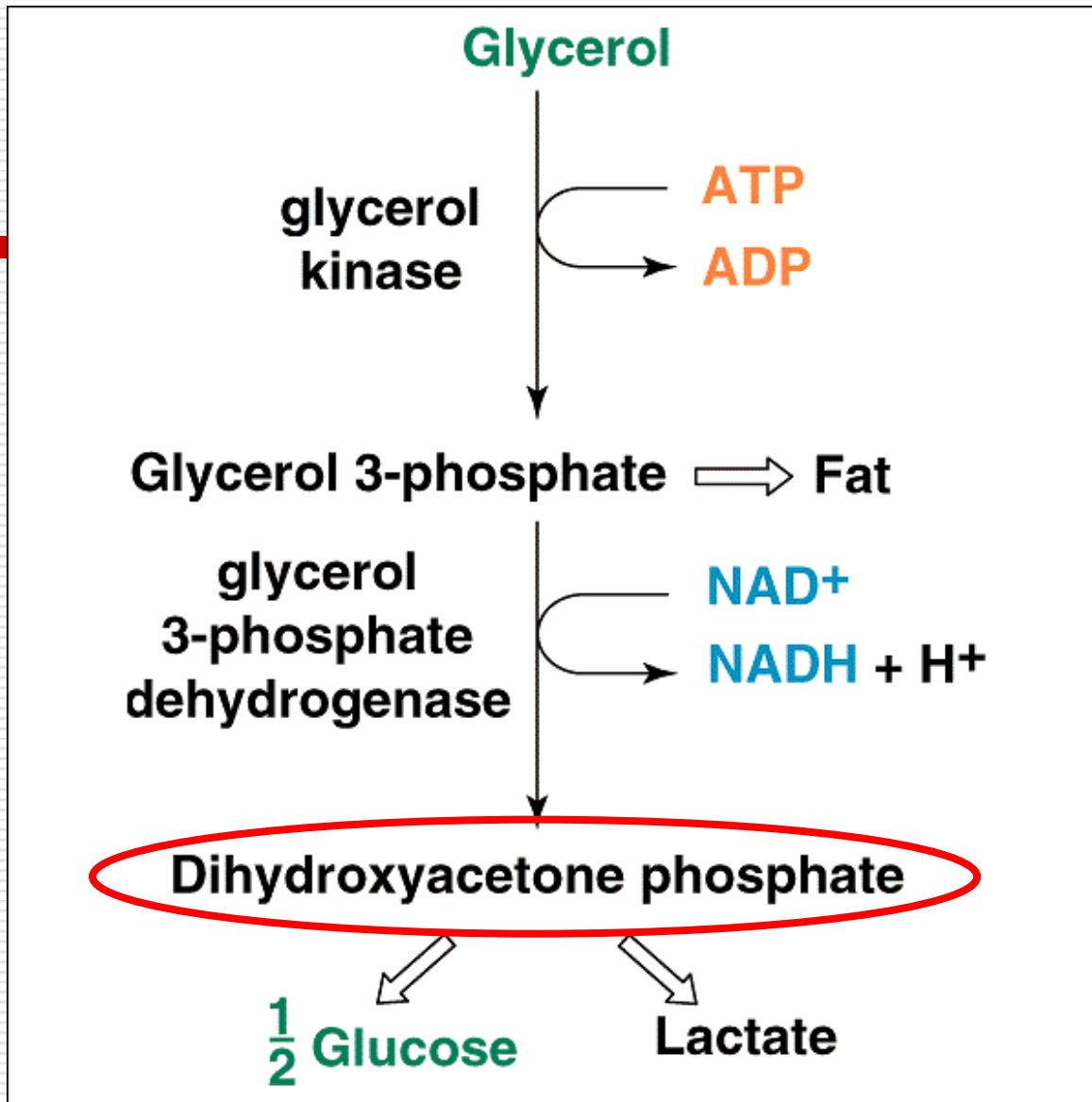
- **Mainly as triacylglycerols (triglycerides) in adipose cells**
- **Constitute 84% of stored energy**
 - Protein - 15%
 - Carbohydrate (glucose or glycogen) - <1%

Processing of Lipid Reserves: Overview

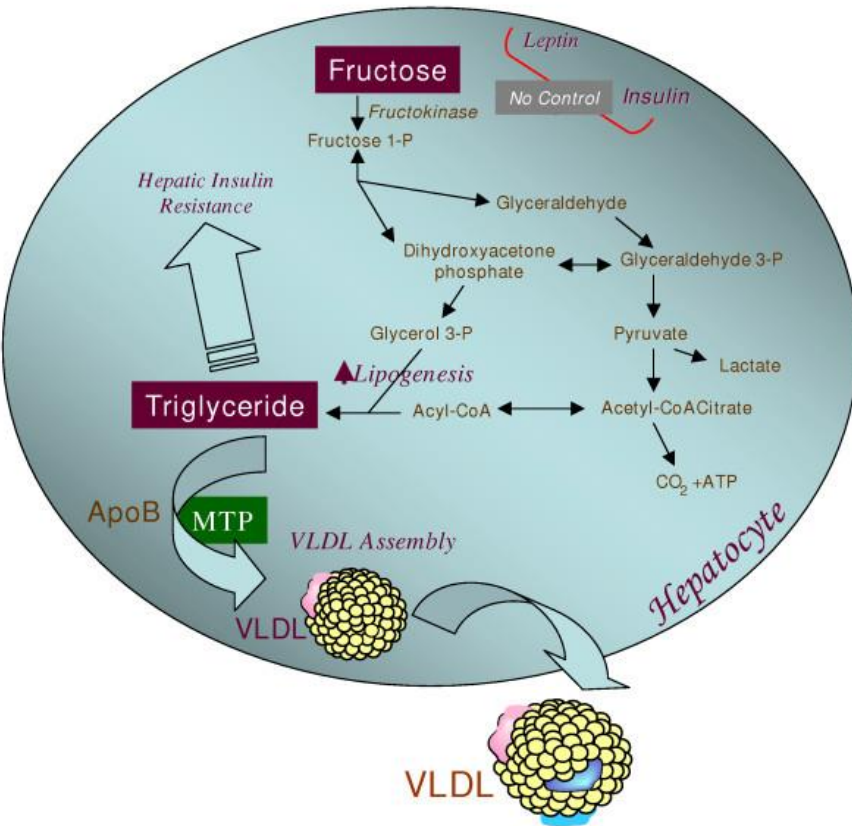
1. **Lipid Mobilization:**
In adipose tissue TAGs hydrolyzed to fatty acids plus glycerol
2. **Transport of Fatty Acids in Blood To Tissues**
3. **Activation of Fatty Acids as CoA Ester**
4. **Transport into Mitochondria**
5. **Metabolism to Acetyl CoA**

Lipolysis





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Hepatic fructose metabolism: A highly lipogenic pathway. Fructose is readily absorbed from the diet and rapidly metabolized principally in the liver. Fructose can provide carbon atoms for both the glycerol and the acyl portions of triglyceride. **Fructose is thus a highly efficient inducer of *de novo* lipogenesis.** High concentrations of fructose can serve as a relatively unregulated source of acetyl CoA. In contrast to glucose, dietary fructose does NOT stimulate insulin or leptin (which are both important regulators of energy intake and body adiposity). Stimulated triglyceride synthesis is likely to lead to hepatic accumulation of triglyceride, which has been shown to reduce hepatic insulin sensitivity, as well as increased formation of VLDL particles due to higher substrate availability, increased apoB stability, and higher MTP, the critical factor in VLDL assembly.

Lipolysis

Hormone
(Adrenalin, Glucagon, ACTH)

Receptor (7TM)

Activates
Adenylyl
Cyclase
ATP → c-AMP

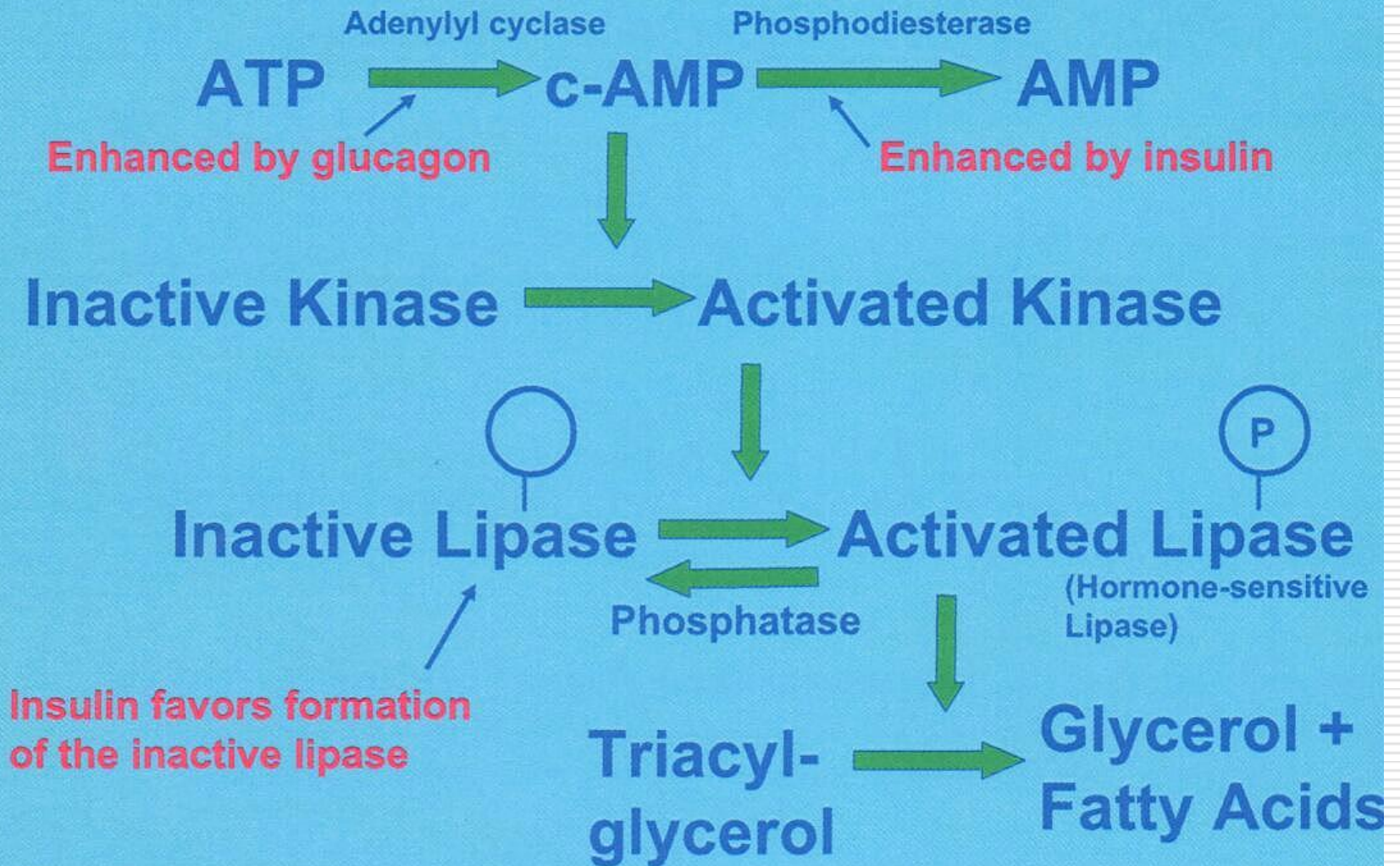
Activates lipase

Triacylglycerols → Glycerol +
Fatty acids

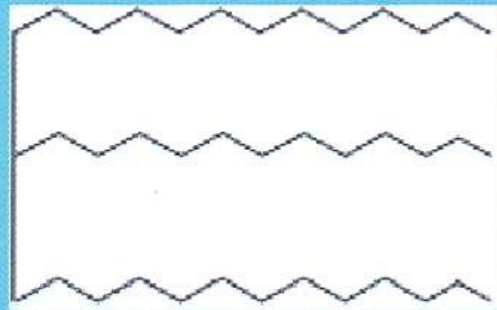
Blood

Adipose Cell

Insulin
blocks this
step



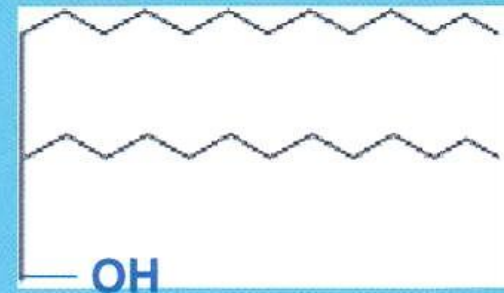
Acylglycerol Lipases



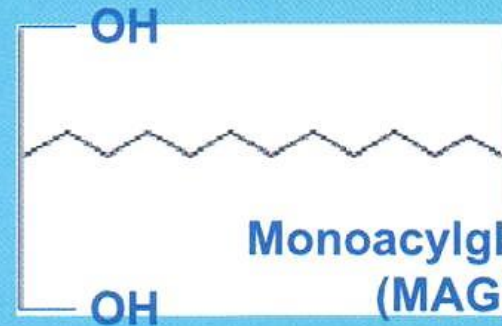
Triacylglycerol (TAG)

Triacylglycerol
Lipase

Diacylglycerol (DAG)

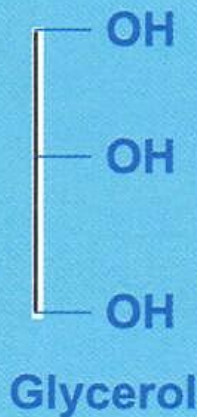


Diacylglycerol
Lipase



Monoacylglycerol
(MAG)

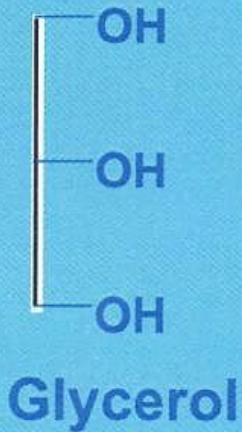
Monoacylglycerol
Lipase



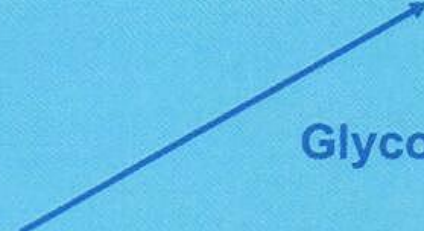
Glycerol

Fate of Glycerol

In Liver:

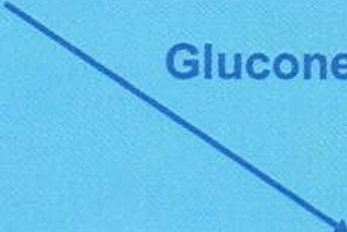


Dihydroxyacetone
Phosphate



Pyruvate

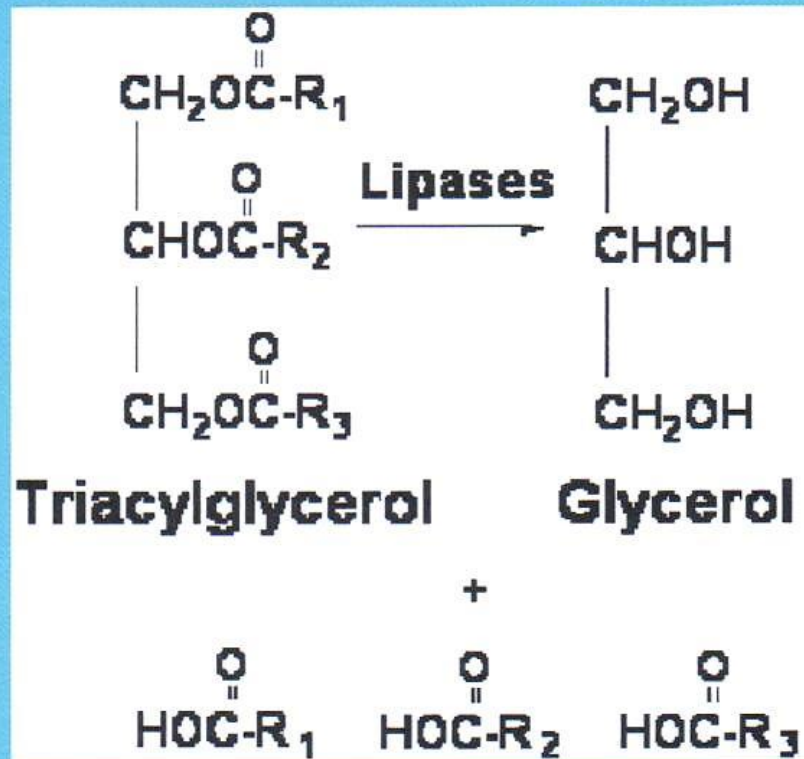
Glycolysis



Gluconeogenesis

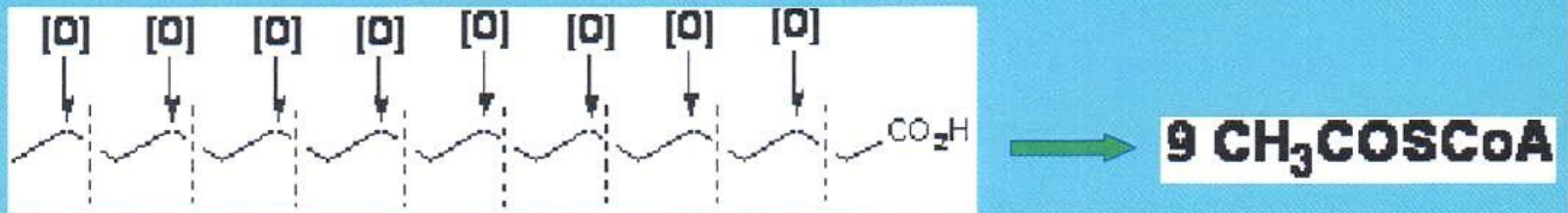
Glucose

Release of Fatty Acids from Triacylglycerols

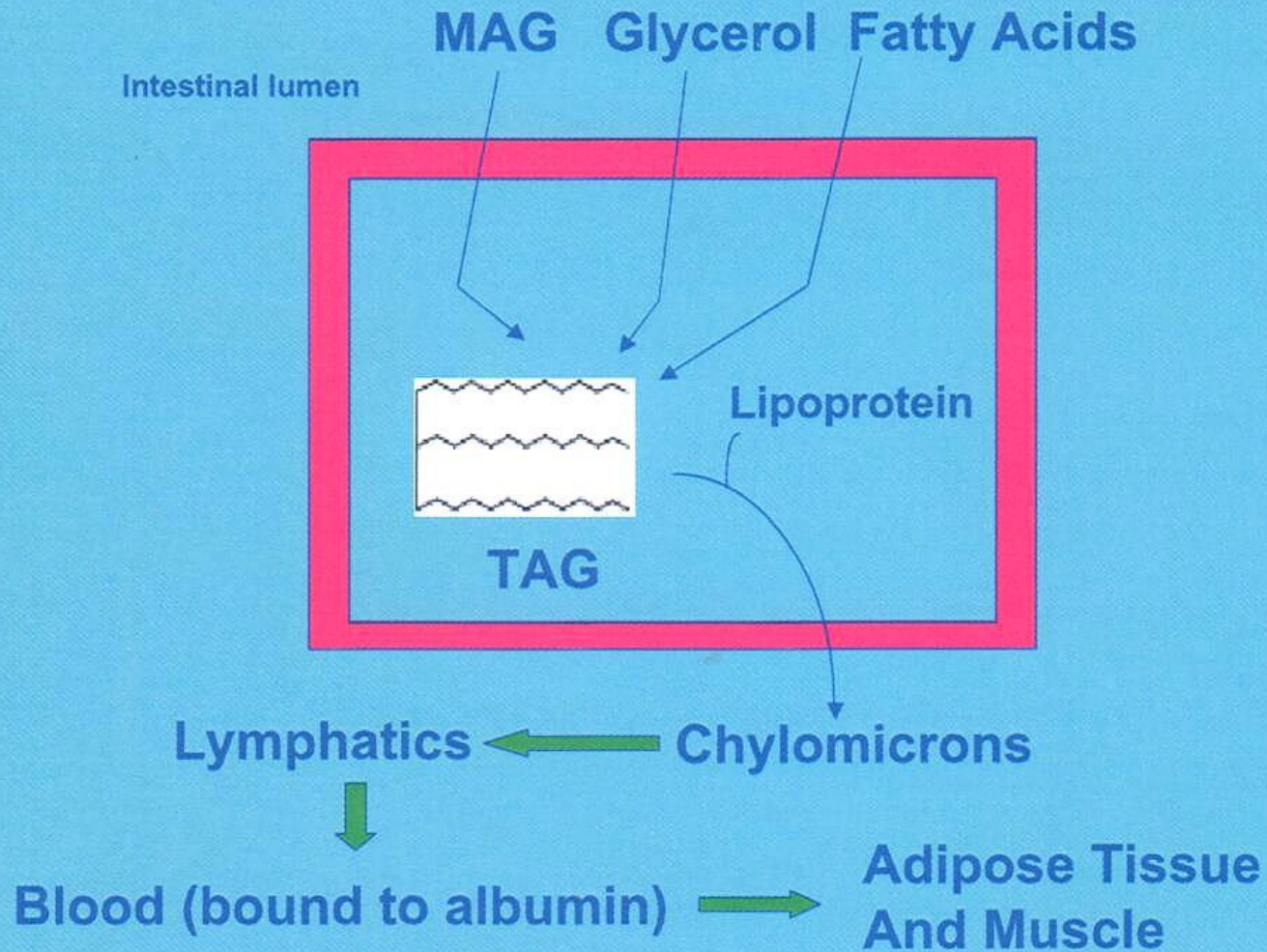


Beta Oxidation

- Cleavage of fatty acids to acetate in tissues
- Occurs in mitochondria



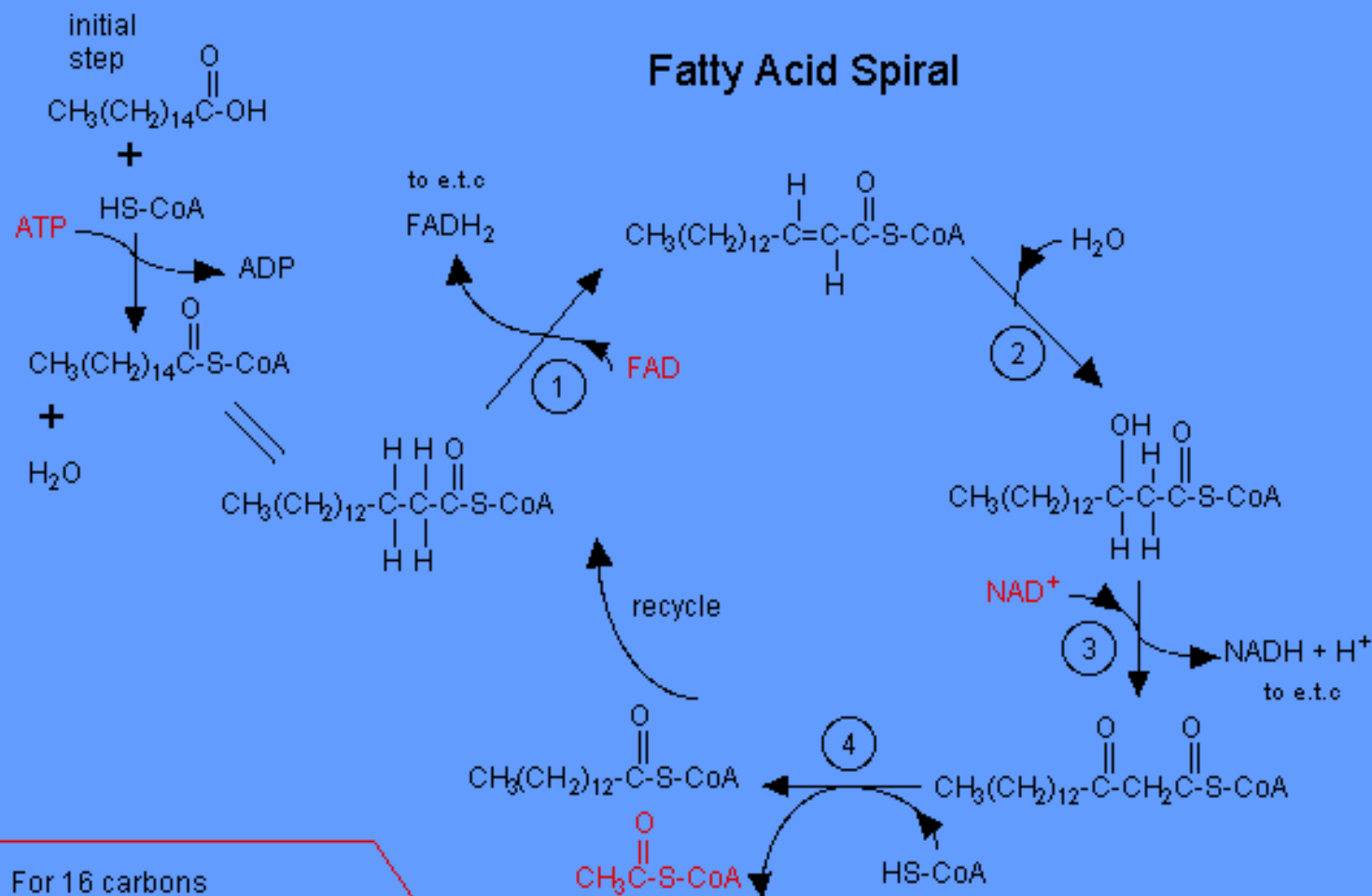
Epithelial Cell (Intestinal Wall)



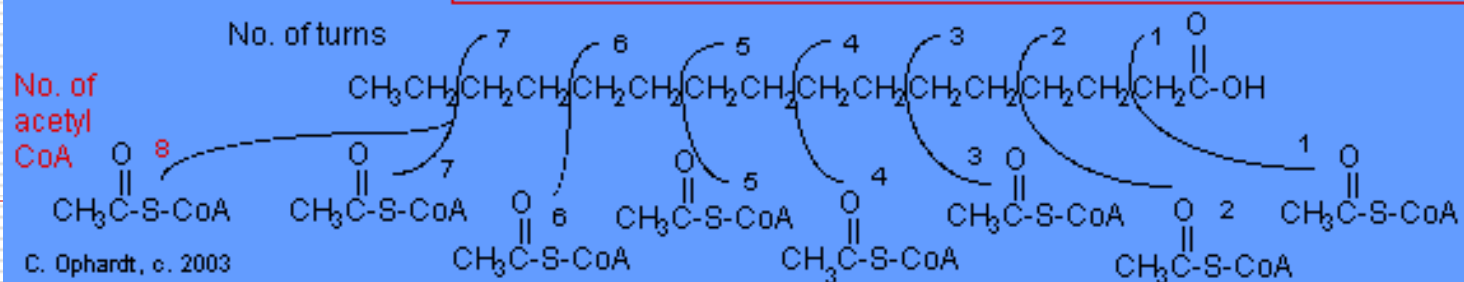
Steps in Beta Oxidation

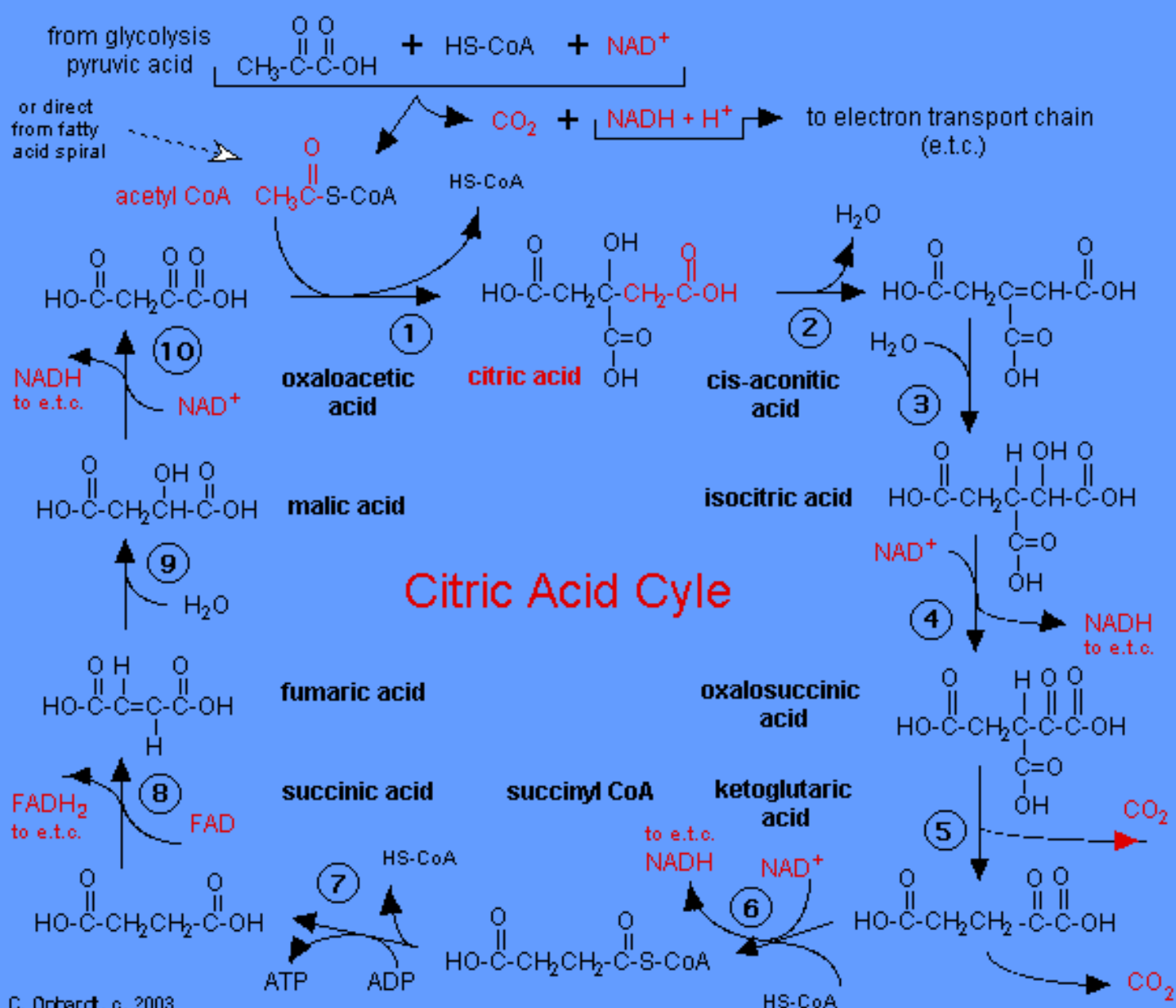
- **Fatty Acid Activation by Esterification with CoASH**
- **Membrane Transport of Fatty Acyl CoA Esters**
- **Carbon Backbone Reaction Sequence**
 - Dehydrogenation
 - Hydration
 - Dehydrogenation
 - Carbon-Carbon Cleavage (Thiolase Reaction)

Fatty Acid Spiral



For 16 carbons

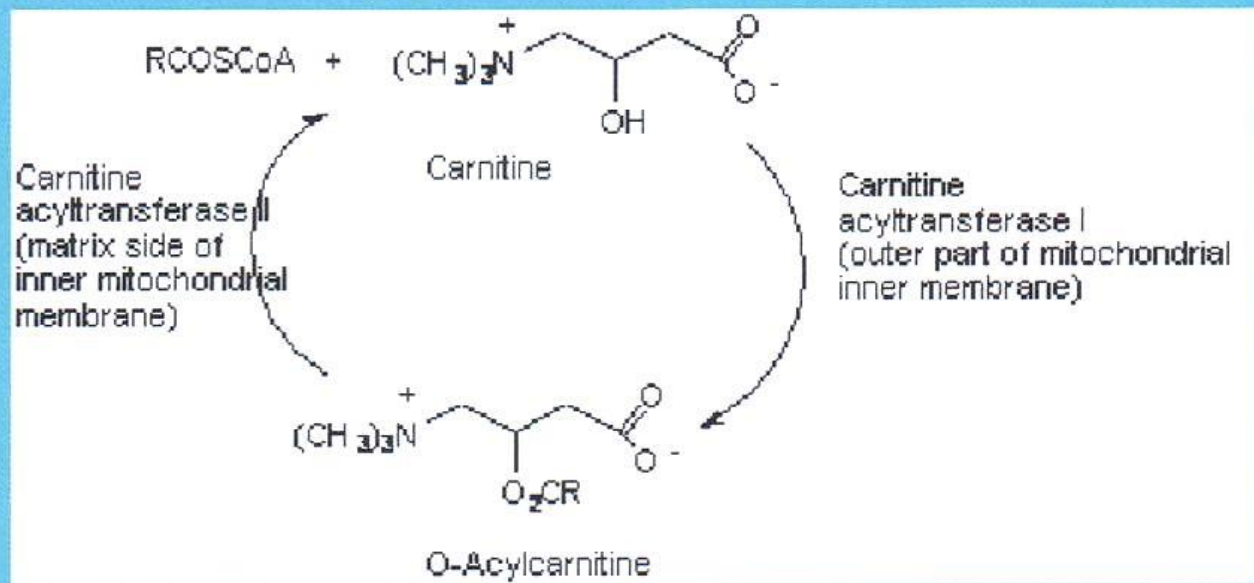




Acetyl CoA

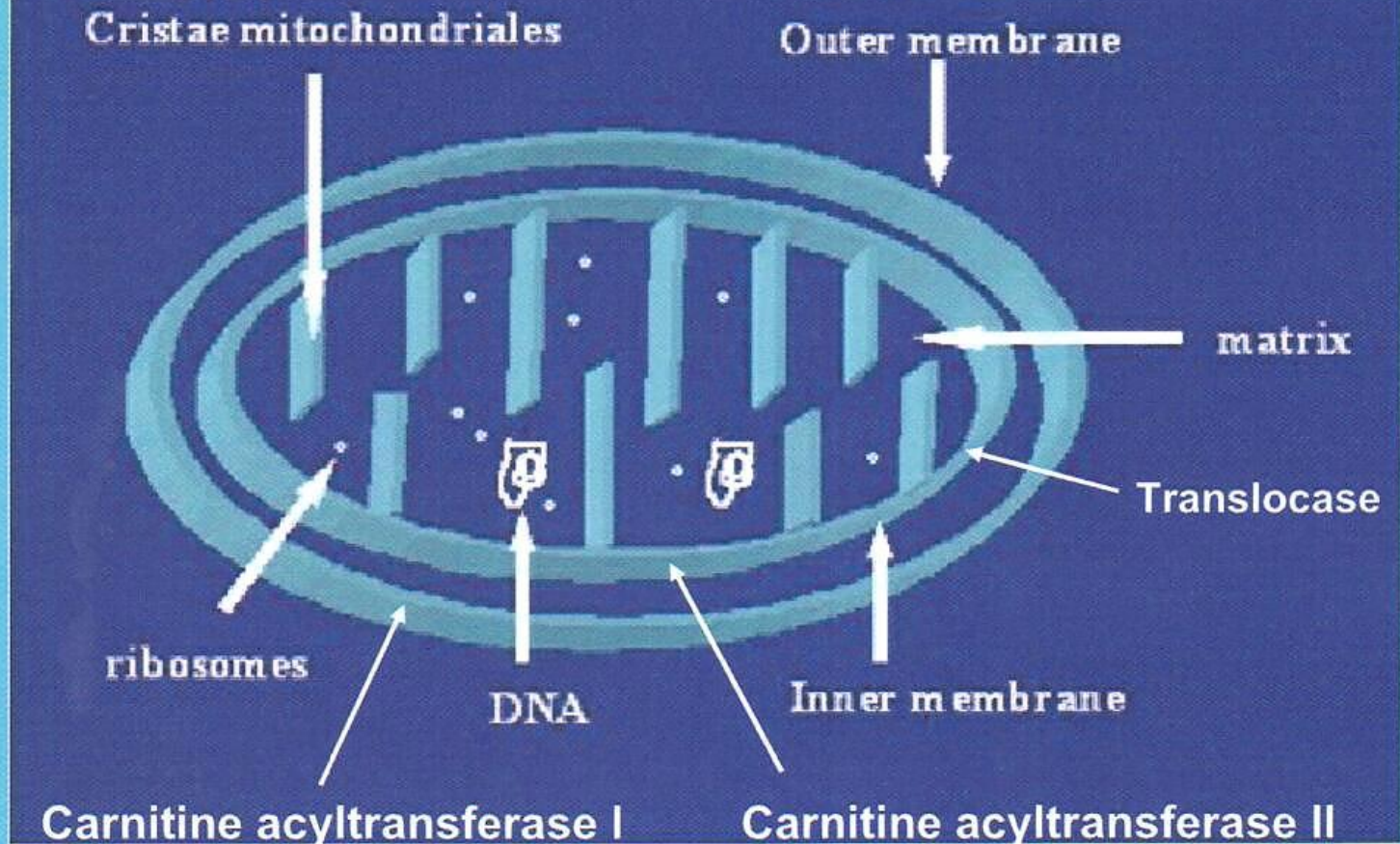
- Under aerobic conditions the end product of glycolysis is pyruvic acid. The next step is the formation of **acetyl coenzyme A** (acetyl CoA) - this step is technically not a part of the citric acid cycle, but is shown on the diagram on the top left.
 - Acetyl CoA, whether from glycolysis or the fatty acid spiral, is the initiator of the citric acid cycle. In carbohydrate metabolism, acetyl CoA is the link between glycolysis and the citric acid cycle.
 - The initiating step of the citric acid cycle occurs when a four carbon compound (oxaloacetic acid) condenses with acetyl CoA (2 carbons) to form citric acid (6 carbons).
 - The whole purpose of a "turn" of the citric acid cycle is to produce two carbon dioxide molecules. This general oxidation reaction is accompanied by the loss of hydrogen and electrons at four specific places. These oxidations are connected to the electron transport chain where many ATP are produced.
-

Membrane Transport of Fatty Acyl CoA Esters



↑
Transported across inner mitochondrial membrane by translocase

Mitochondrial Compartments



Ketone Bodies As Energy Sources

In liver

β -Hydroxybutyrate \longleftrightarrow Acetoacetate

Acetoacetate is major energy source in cardiac muscle and renal cortex; also in brain in starvation and diabetes

Succinyl CoA

β -Ketoacyl CoA transferase

Not found in liver

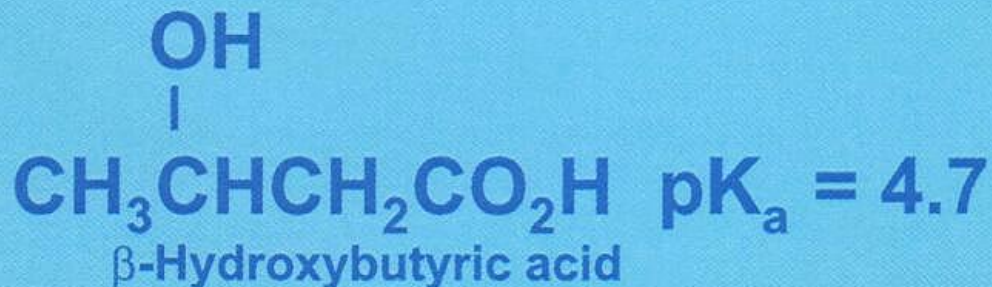
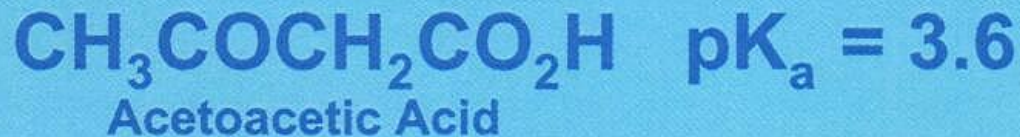
2 Acetyl CoA $\xrightleftharpoons{\text{Thiolase}}$ Acetoacetyl CoA

Succinate

Combines with oxaloacetate

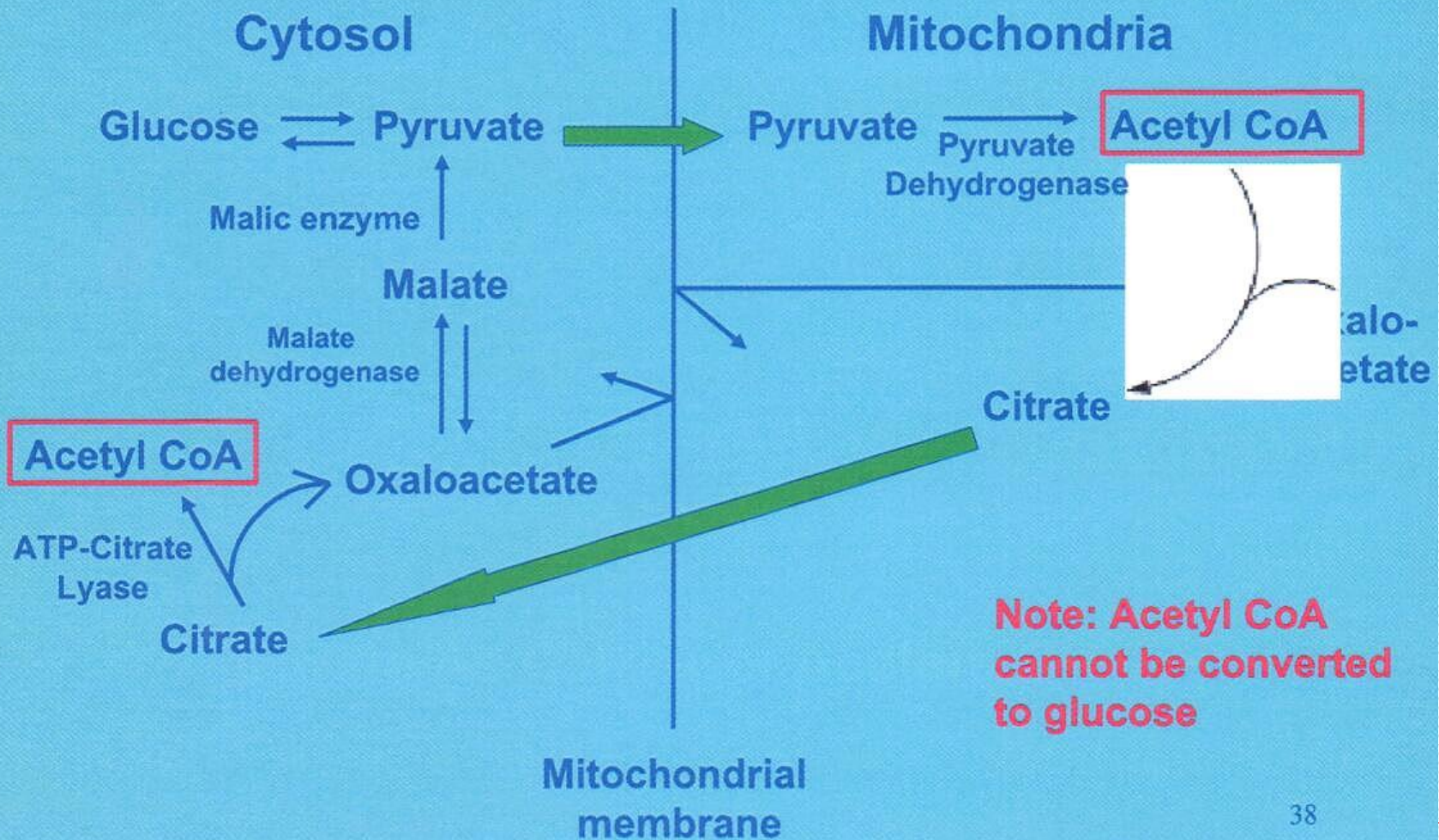
TCA Cycle

Metabolic Acidosis in Untreated Diabetes Mellitus



↑ Concentration of acetoacetic acid can result in metabolic acidosis (pH 7.1) → ↓ affinity of Hb for O₂.

Citrate As Carrier of Acetate Groups



Glycolysis

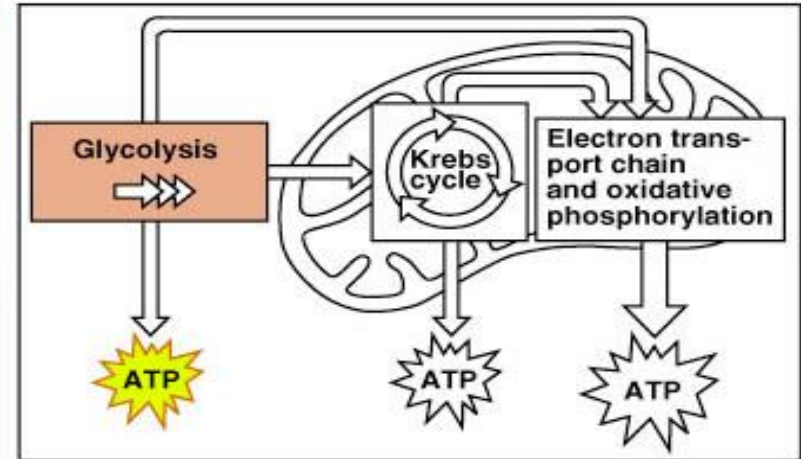
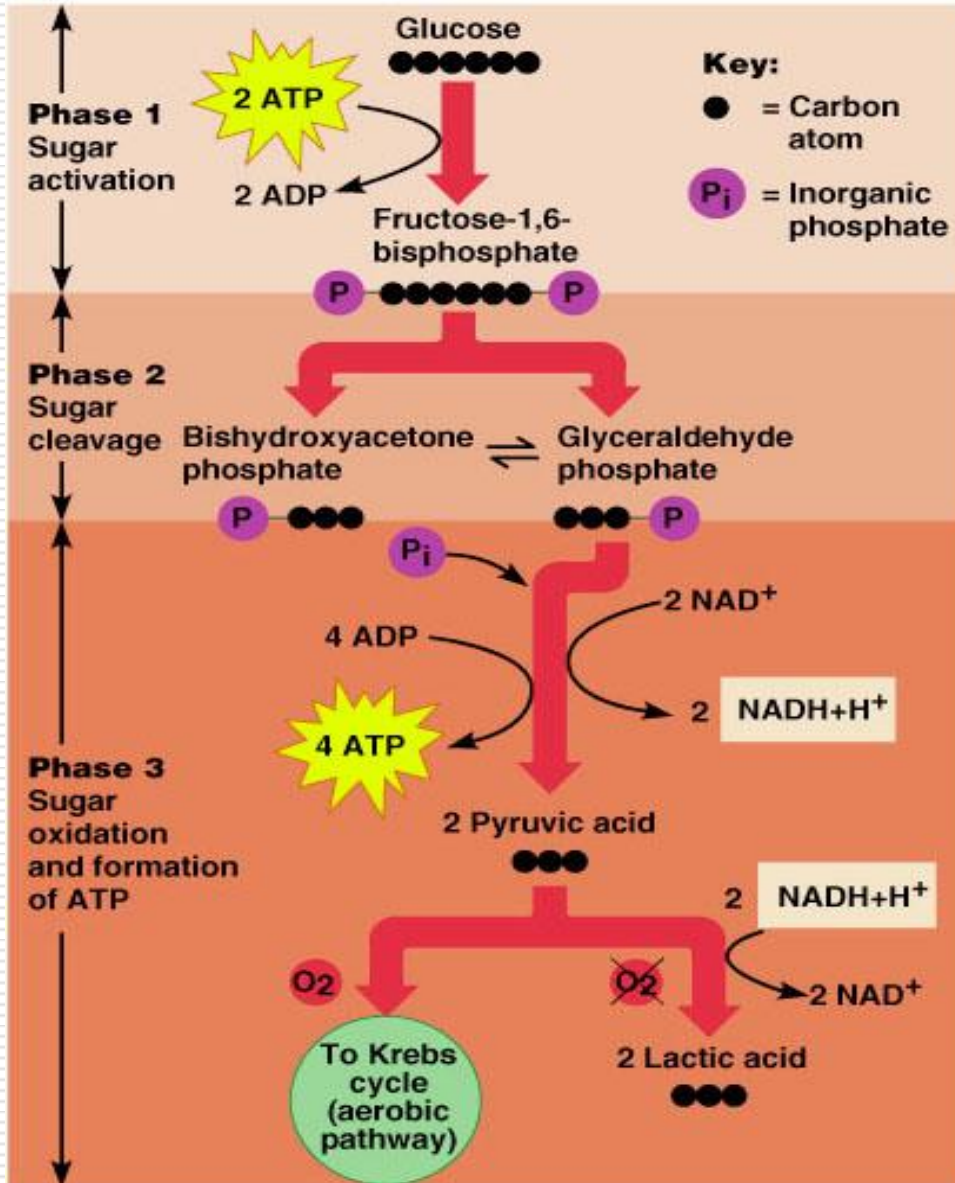
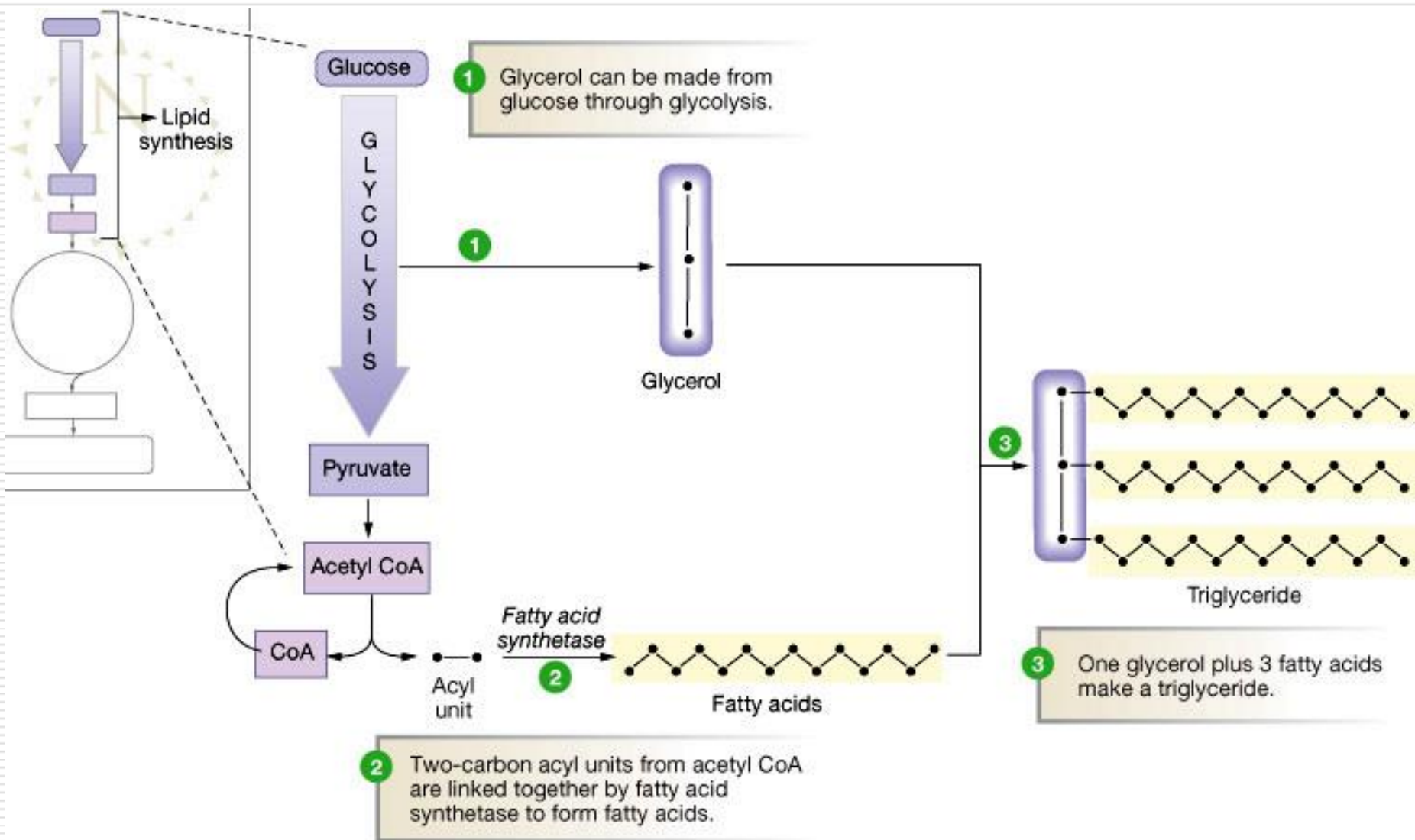


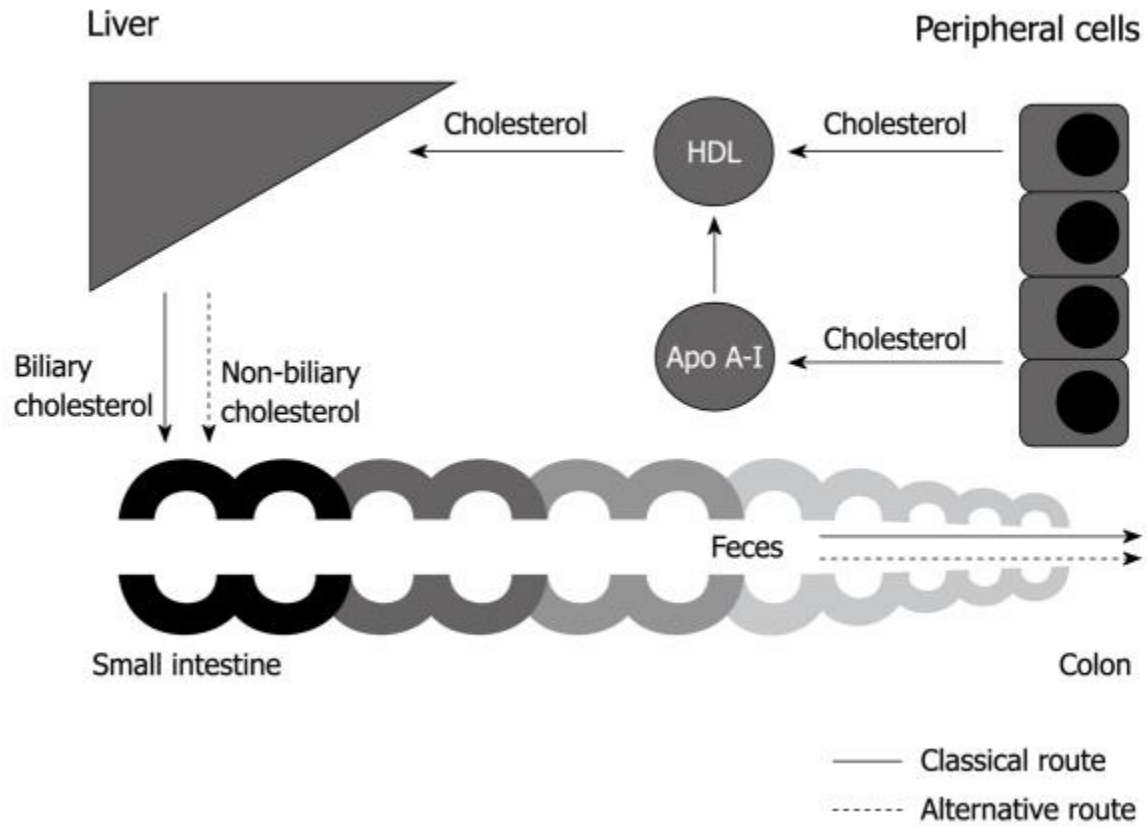
Figure 24.6

Lipids Synthesis

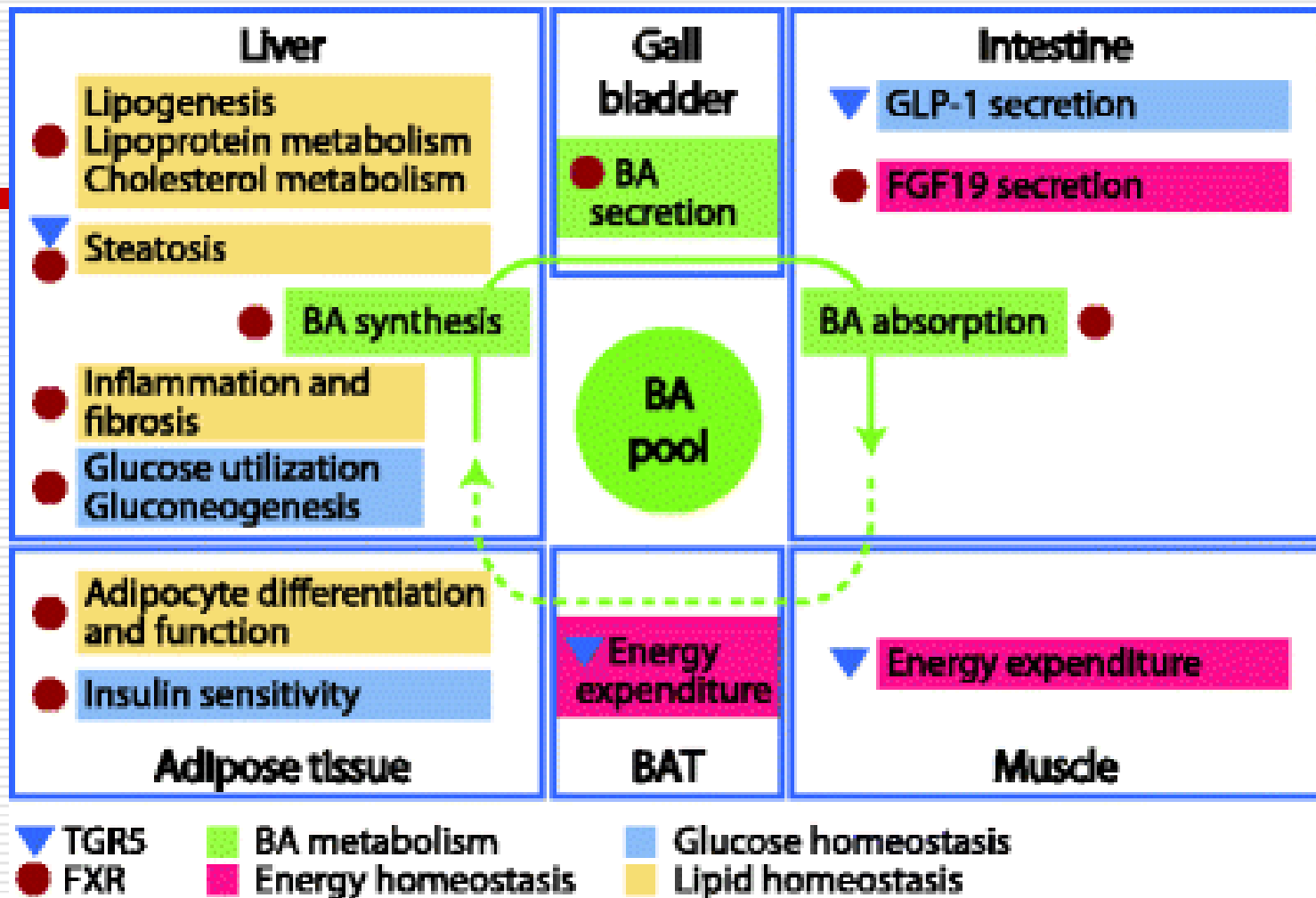


Functions of human plasma lipoproteins

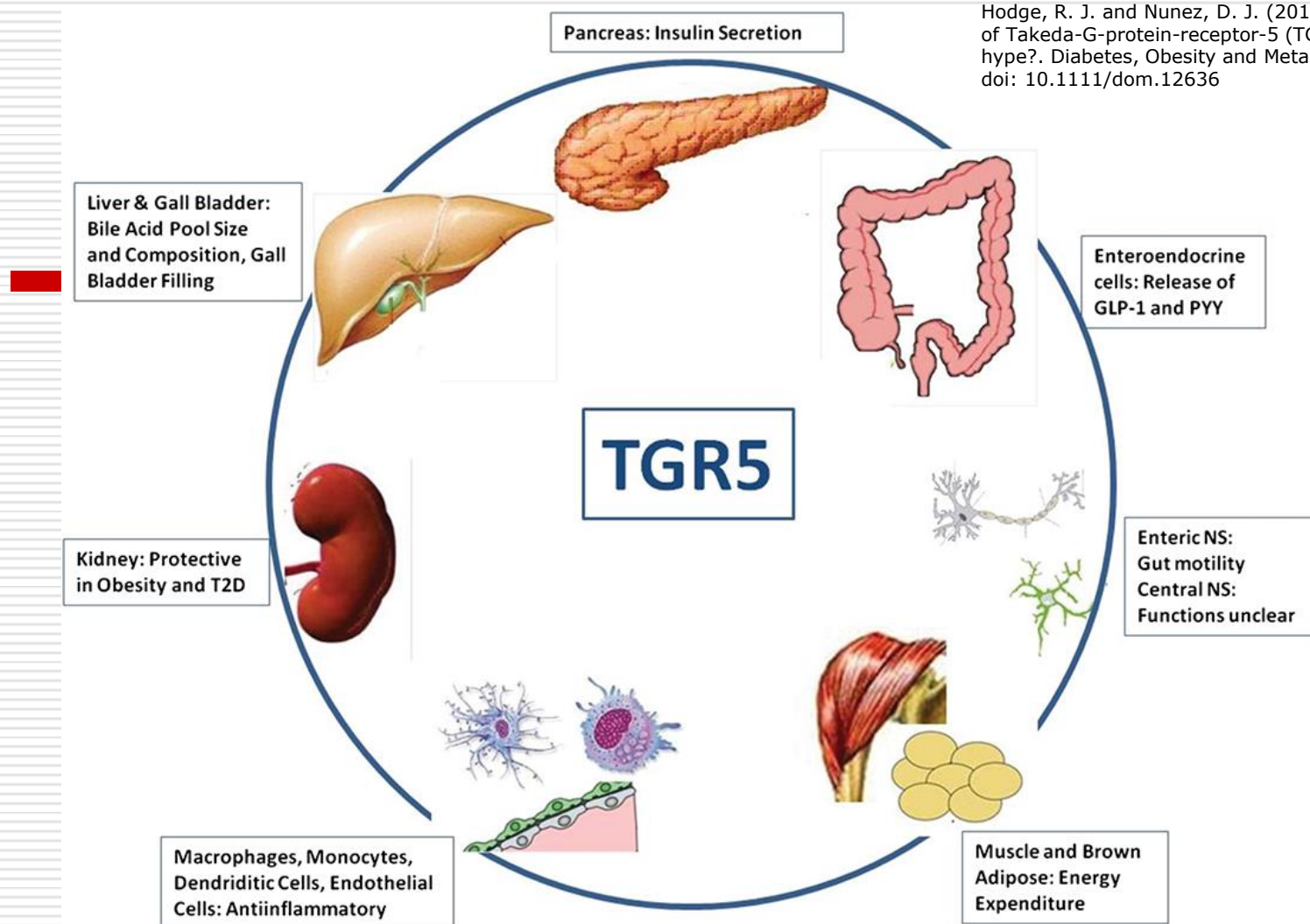
| Lipoprotein class | Origin | Function |
|----------------------------|-----------|--|
| Chylomicrons | Intestine | Transport lipids from intestine to liver and tissues |
| Very low density (VLDL) | Liver | Transport lipid from tissues to liver |
| Intermediate density (IDL) | VLDL | Precursor of LDL |
| High density (HDL 2 and 3) | Intestine | Remove cholesterol from tissues |



Cholesterol – the ways of excretion.
 Biliary and non-biliary cholesterol.

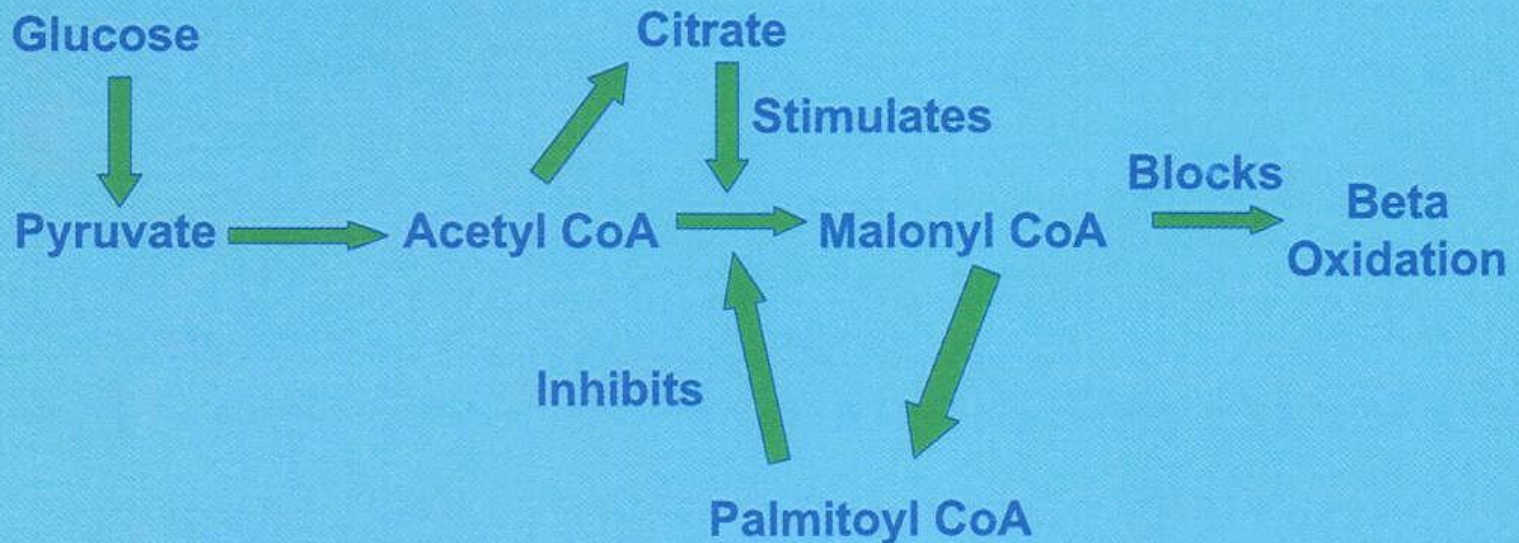


Functions of bile acids (BA) in regulation of BA, energy, glucose and lipid metabolism via farnesoid X receptor (FXR) and TGR5-mediated signaling pathways. BAT—brown adipose tissue; FGF—fibroblast growth factor; GLP-1—glucagon-like peptide 1



A wide range of Takeda-G-protein-receptor-5 (TGR5) effects. A variety of downstream effects has spawned intense interest in the therapeutic potential of TGR5 agonists for the treatment of metabolic and inflammatory diseases. GLP-1, glucagon-like peptide-1; NS, nervous system; PYY, peptide tyrosine tyrosine; T2D, type 2 diabetes.

Metabolite Regulation of Fatty Acid Synthesis and Breakdown



Tay-Sachs Disease

GM₂ (a ganglioside):

Ceramide - O - Glucose - Galactose - N-Acetylgalactose

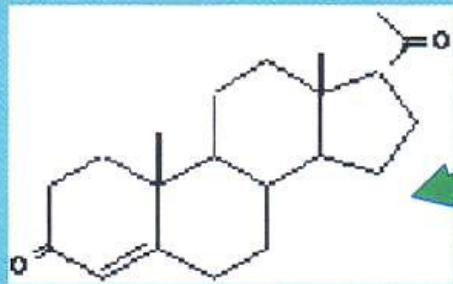
↑
**Hexoseaminidase A
catalyzes cleavage of this
glycoside linkage**

Autosomal recessive disorder characterized by deficiency
of hexoseaminidase A; accumulation of gangliosides in brain
Most prevalent in Jews from Eastern Europe

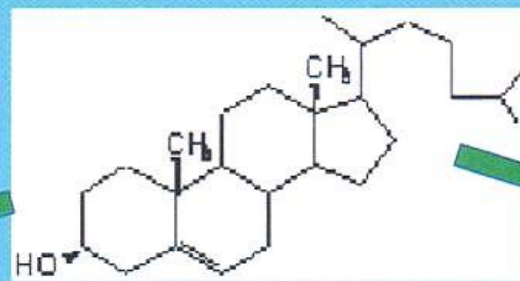
For further information see:

http://www.marchofdimes.com/professionals/681_1227.asp

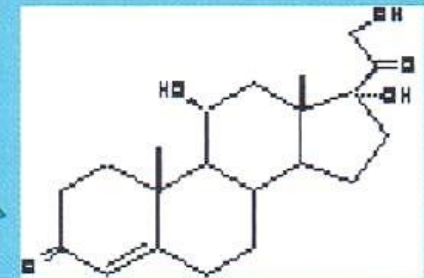
Transformations of Cholesterol: Steroid Hormones



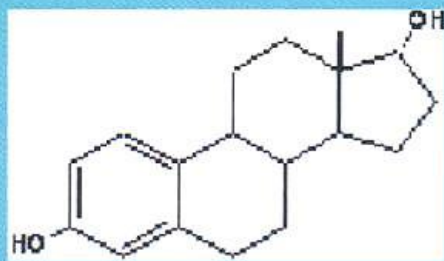
Progesterone



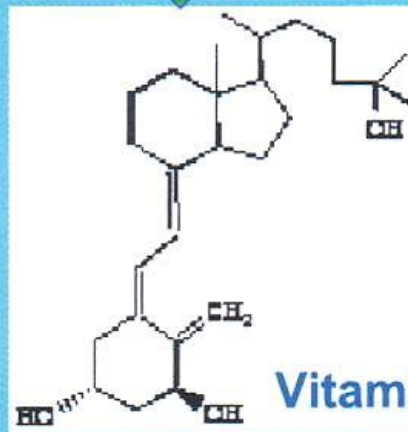
Cholesterol



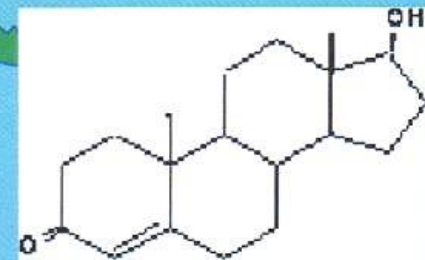
Cortisol



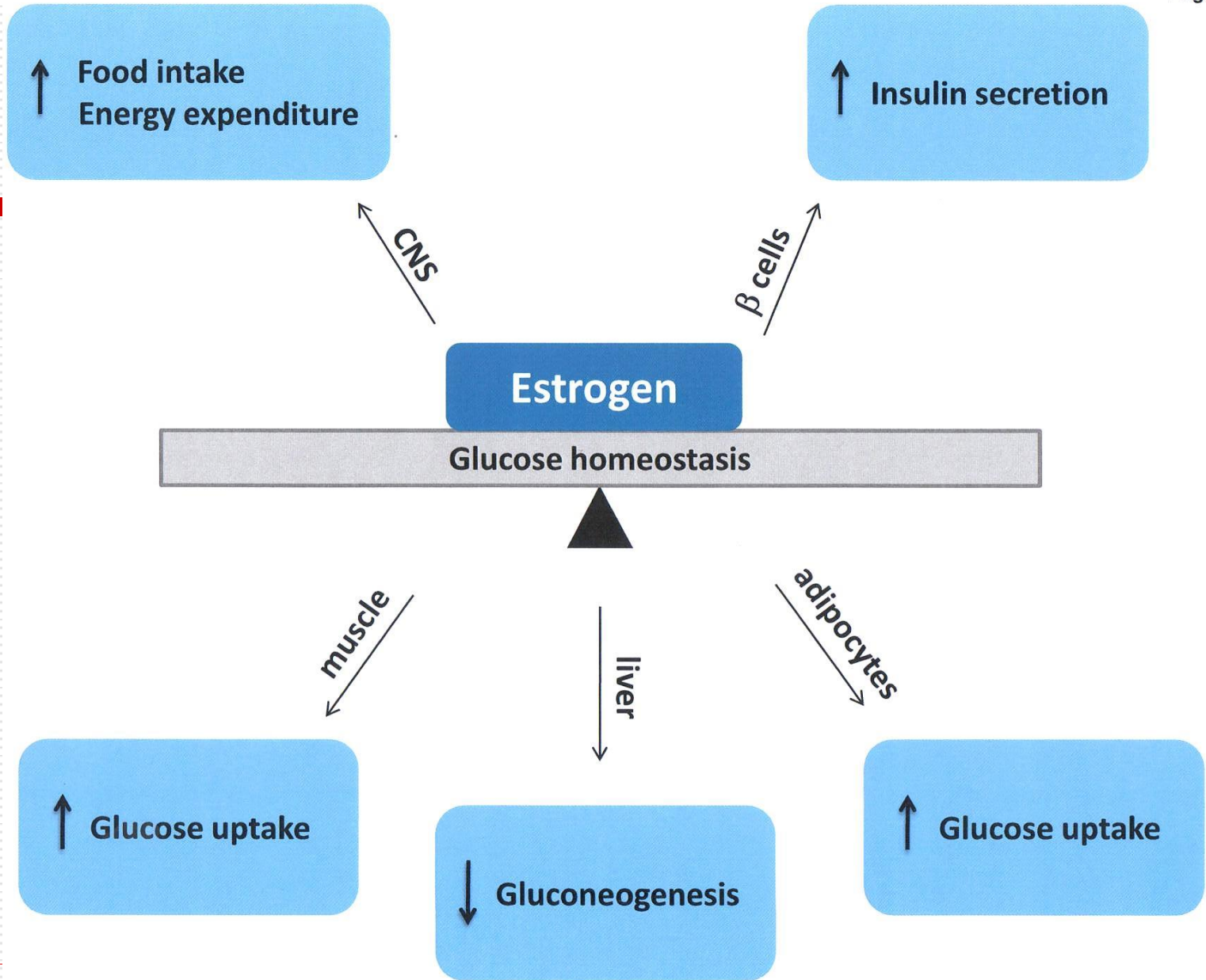
Estradiol



Vitamin D



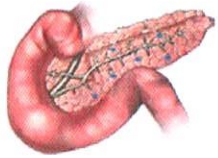
Testosterone



Estrogen deficiency



INSULIN RESISTANCE



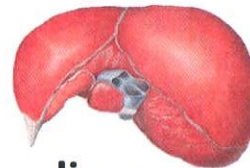
pancreatic β cells

Impaired insulin secretion



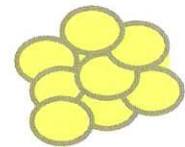
muscle

Impaired glucose uptake



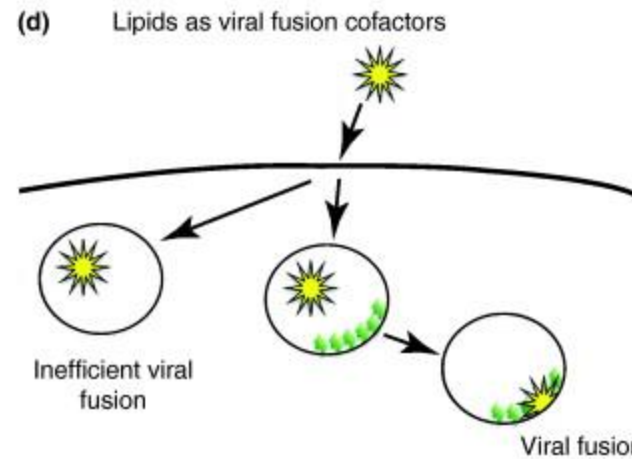
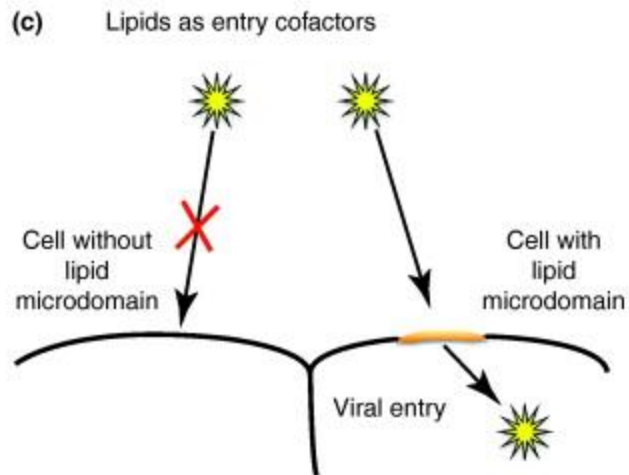
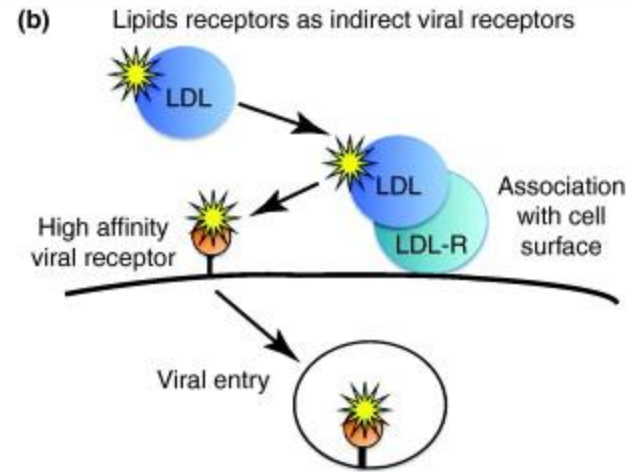
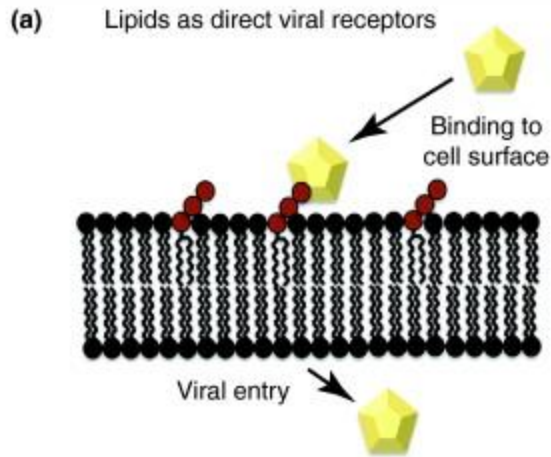
liver

Increased gluconeogenesis
Increased lipogenesis
TG accumulation
Increased VLDL production
Decreased insulin clearance



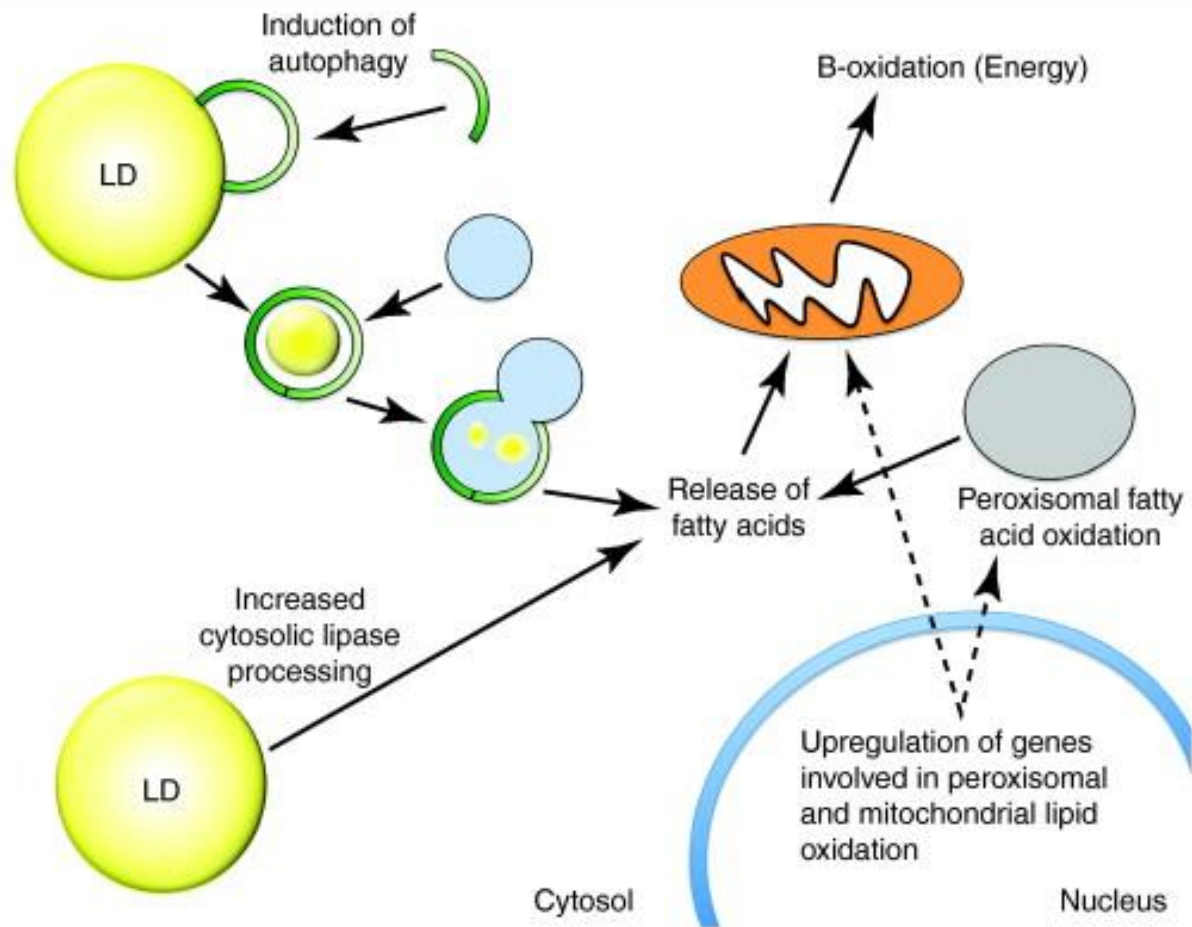
adipose tissue

Increased lipolysis
Increased adipocyte size
Inflammation



Lipid droplets

- Storage neutral lipids, i.e. triacylglycerols (TAG) and sterol esters (SE), are stored in the form of lipid droplets (LDs) in almost all eukaryotic cells.
 - LDs are dynamic subcellular organelles that not only govern the storage and turnover of lipids, but also function in membrane and lipid trafficking, protein storage and degradation, and even in the replication of hepatitis C virus.
 - All LDs comprise a core of storage neutral lipids which are wrapped by a monolayer of phospholipids with proteins embedded. LDs are believed to originate from the endoplasmic reticulum (ER), although the exact mechanism underlying their biogenesis remains to be determined.
-



Lipodystrophies

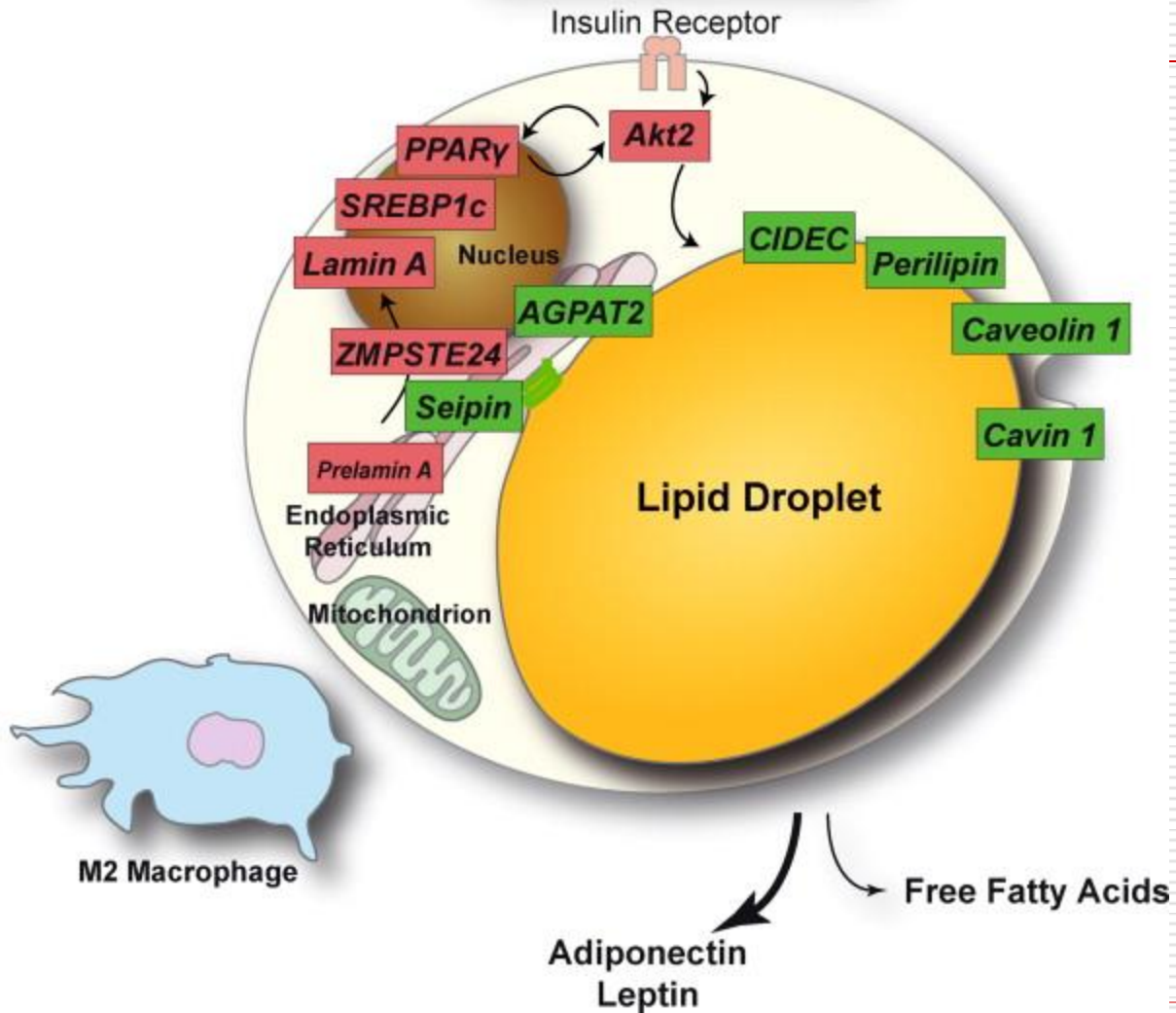
- ❑ Heterogenic group of diseases defined as **localised or generalised loss of body fat**.
 - ❑ If localised, usually related with **fat hypertrophy in other side of the body**.
 - ❑ Usually associated with sever metabolic changes including insulin resistance, dyslipidemia and glucose intolerance.

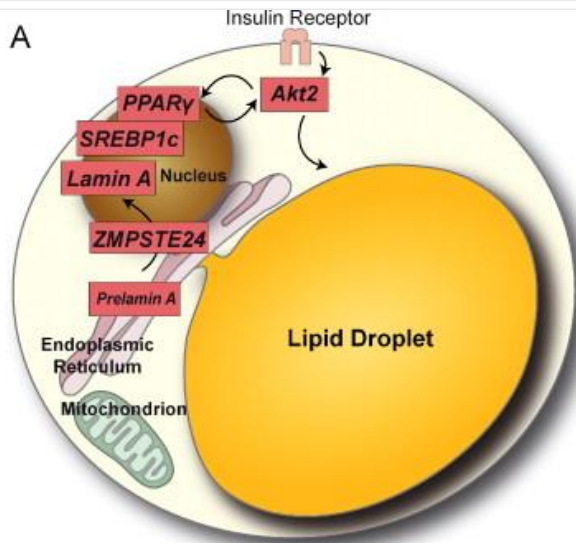
 - ❑ Different phenotypes:
 - ❑ **Familiar parcial lipodystrophy**, type Dunnigan (FPLD): fat reduction on the lower part of the body, hypertrophy on the upper part
 - ❑ **Barraquer-Simons** syndrome – reverse phenotype, milder metabolic changes

 - ❑ Problems on the level of:
 - ❑ adipogenesis, insulin sensitivity, TAGs storage, lipid droplets formation, oxidative stress and fat remodellation.
-

A

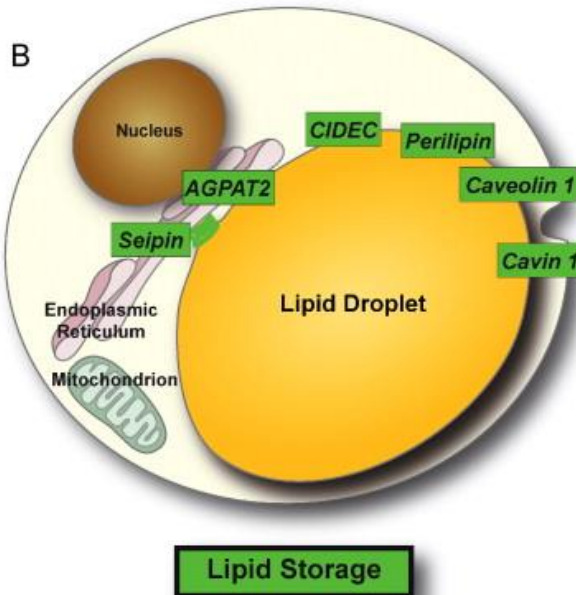
Healthy Adipose Tissue





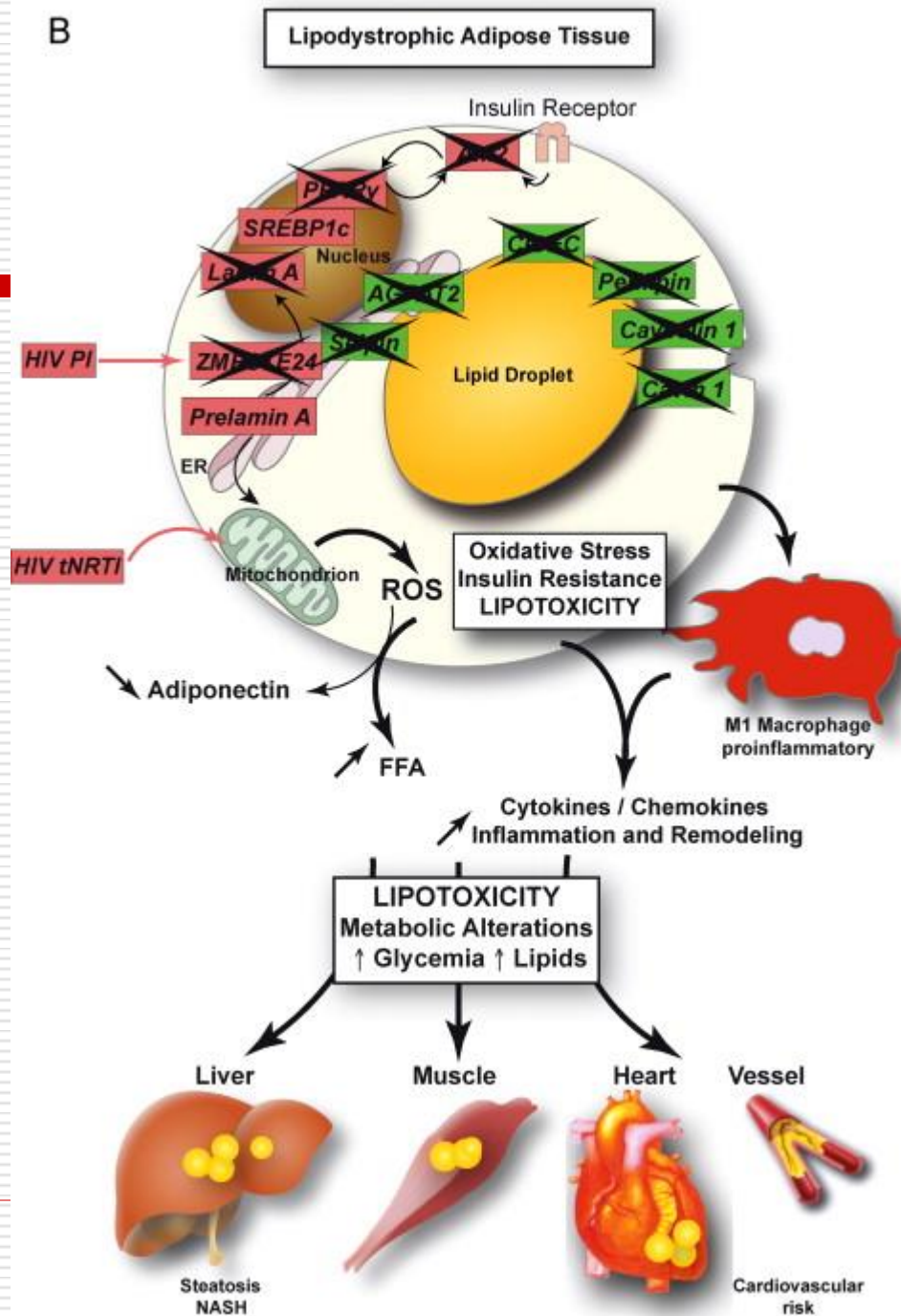
Cellular targets altered by mutations in lipodystrophies

A: proteins taking part in **adipogenesis** at the level of nuclear DNA and in insulin signal transduction pathway



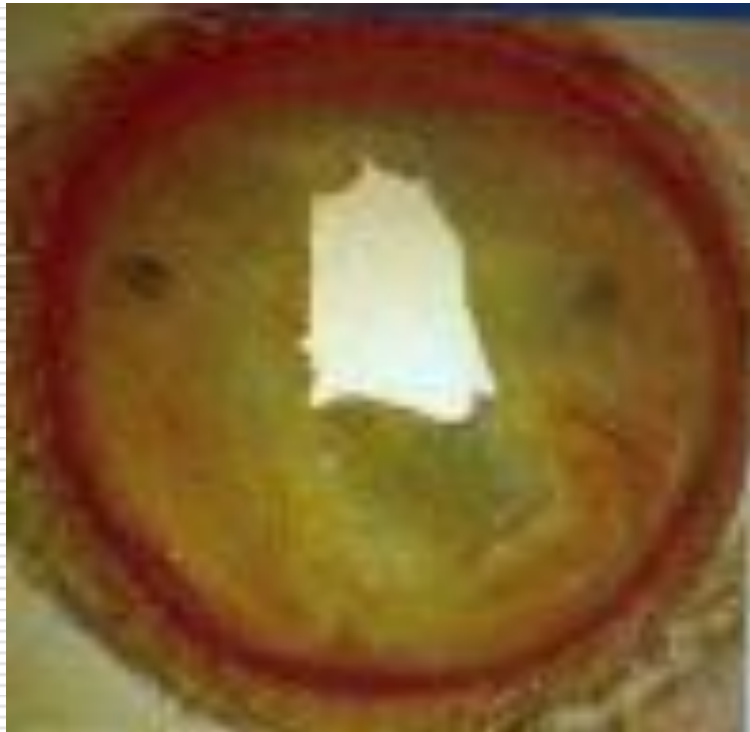
B: proteins of endoplasmic reticulum and lipid droplets during **fat storage**

B



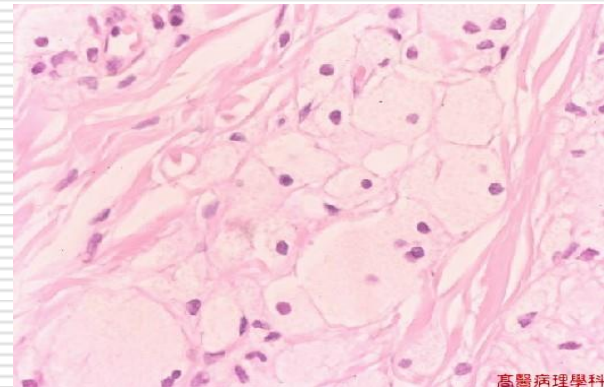
Hyperlipidemia Signs

- Atheroma- plaques in blood vessels



Hyperlipidemia signs

- Xanthoma- plaques or nodules composed of lipid-laden histiocytes (foamy cells) in the skin, especially the eyelids



Tendinous Xanthoma

Xanthoma deposits in tendon, commonly the Achilles



Corneal arcus

- Lipid deposit in cornea

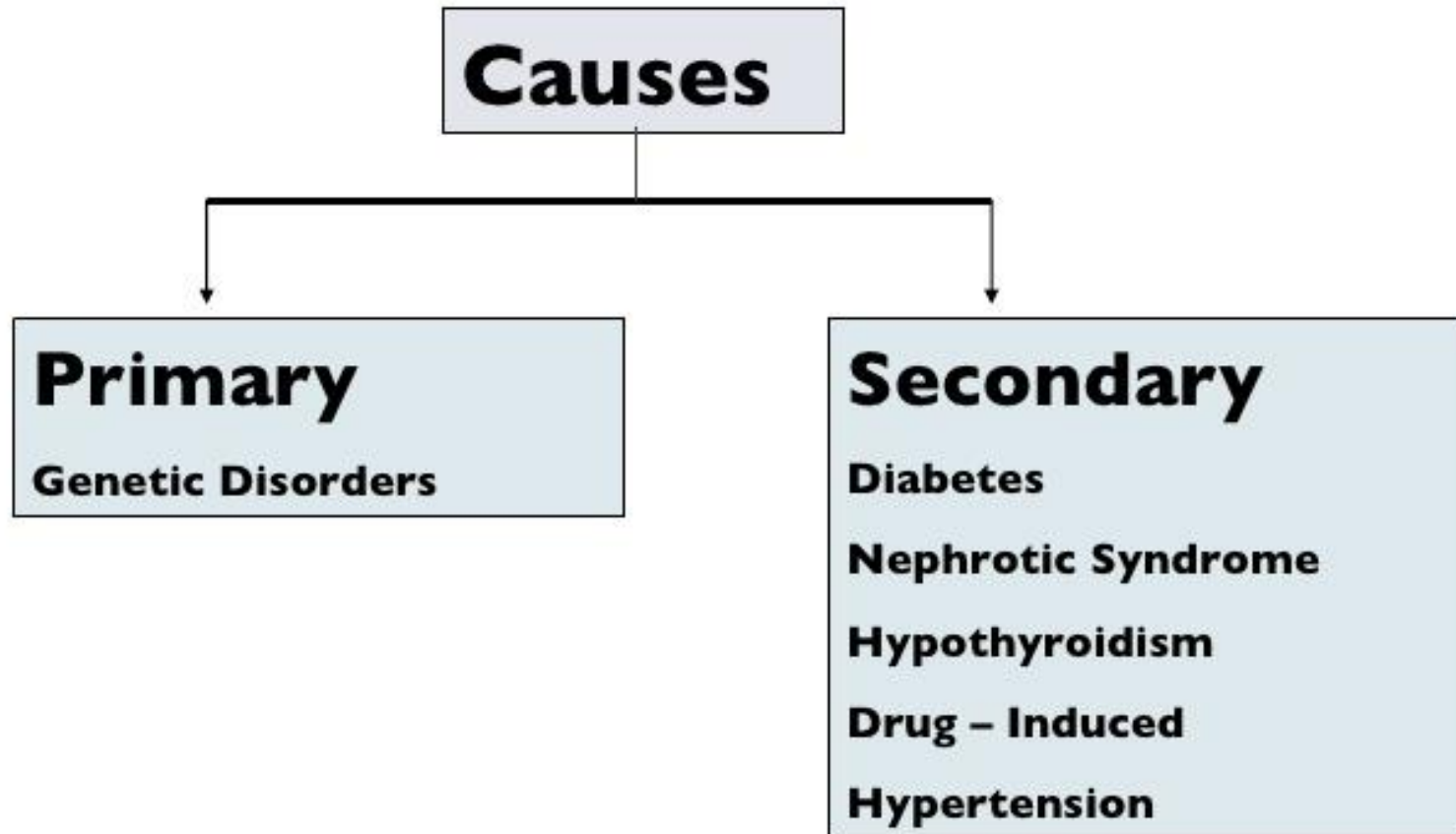


Dyslipidemia

- Disorder of Lipid & Lipoprotein Metabolism
- A common form of Dyslipidemia is characterized by three lipid abnormalities:
 - Elevated triglycerides,
 - Elevated LDL and
 - Reduced HDL cholesterol.
- Important Modifiable Risk Factor for CAD



Dyslipidemia



Secondary causes of Dyslipidemia

Selected Causes of Secondary Dyslipidemia

| | | |
|--|--|---|
| <p>Increased LDL cholesterol level</p> <p>Diabetes mellitus</p> <p>Hypothyroidism</p> <p>Nephrotic syndrome</p> <p>Obstructive liver disease</p> <p>Drugs</p> <p>Anabolic steroids</p> <p>Progestins</p> <p>Beta-adrenergic blockers (without intrinsic sympathomimetic action)</p> <p>Thiazides</p> | <p>Increased triglyceride level</p> <p>Alcoholism</p> <p>Diabetes mellitus</p> <p>Hypothyroidism</p> <p>Obesity</p> <p>Renal insufficiency</p> <p>Drugs</p> <p>Beta-adrenergic blockers (without intrinsic sympathomimetic action)</p> <p>Bile acid-binding resins</p> <p>Estrogens</p> <p>Ticlopidine (</p> | <p>Decreased HDL cholesterol level</p> <p>Cigarette smoking</p> <p>Diabetes mellitus</p> <p>Hypertriglyceridemia</p> <p>Menopause</p> <p>Obesity</p> <p>Puberty (in males)</p> <p>Uremia</p> <p>Drugs</p> <p>Anabolic steroids</p> <p>Beta-adrenergic blockers (without intrinsic sympathomimetic action)</p> <p>Progestins</p> |
|--|--|---|

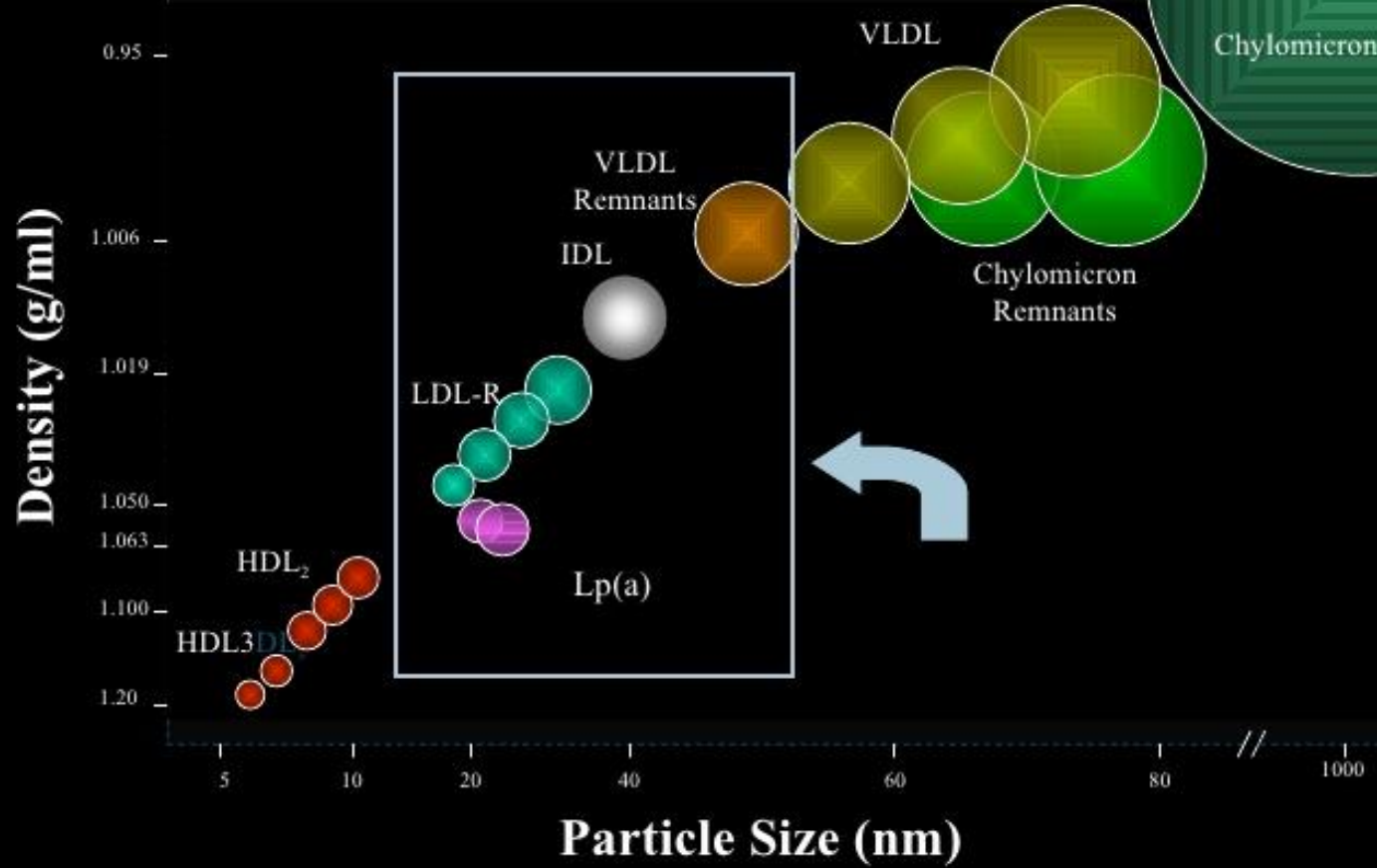
LDL=low-density lipoprotein; HDL=high-density lipoprotein.

Adapted with permission from Schaefer EJ. Diagnosis and management of lipoprotein disorders. In: Rifkind BM, ed. Drug

PRIMARY DYSLIPIDEMIA (Fredrickson's Classification)

| Type | Primary Lipid Elevation | Lipoprotein | Occurrence |
|-----------------|-------------------------|-----------------------|-------------|
| I | TG | Chylomicrons | Rare |
| II _a | C | LDL | Common |
| II _b | C, TG | LDL, VLDL | Most Common |
| III | C, TG | IDL | Rare |
| IV | TG | VLDL | Common |
| V | TG | VLDL, Chylomicrons | Rare |

Lipoprotein Particles



Genetic Causes of Dyslipidemia

- ◆ Type I – Familial Hyperchylomicronemia

 - Fasting triglycerides > 1000 mg/dl

 - Defect in lipoprotein lipase or apo CII

 - Not necessarily at increased risk of CAD

- ◆ Type II - Familial Hypercholesterolemia (type II)

 - LDL-C > 95th percentile for age and gender

 - CAD in men by 3rd or 4th decade

 - Defect in LDL receptor

 - Autosomal dominant inheritance

 - Prevalence 1:500

- ◆ Familial Defective apo B 100

 - Defective apo B alters LDLr handling

 - Previously undetectable from FH

Genetic Causes of Dyslipidemia

Type III – Hyperlipoproteinemia

Increased TC, VLDL, decreased HDL; Increased VLDL: TG

Defect in apo E results in increased concentration of remnant particles

Rare

Type IV – Familial Hypertriglyceridemia

Increased TC (due to VLDL), TG, decreased LDL, HDL

Results from hepatic overproduction of VLDL

Prevalence 1:100 – 1:50; Association with CAD not as strong as FH

Heterogeneous inheritance

Very sensitive to diet and EtOH

Type V

Increase in chylomicrons and VLDL

Rare

Genetic Causes of Dyslipidemia

Familial Combined Hyperlipidemia

Increased TC, LDL and/or triglycerides; decreased HDL

Most common genetic dyslipidemia: prevalence 1:50

Heterogenous inheritance

Accounts for 10-20% of patients with premature CAD

Defects in HDL Metabolism

Most often low HDL is secondary to other dyslipidemia

Not all associated with increased CAD risk (e.g. apo A_I_{Milano})

Tangier's Disease

CETP defects result in increased HDL

Thank you for your attention

