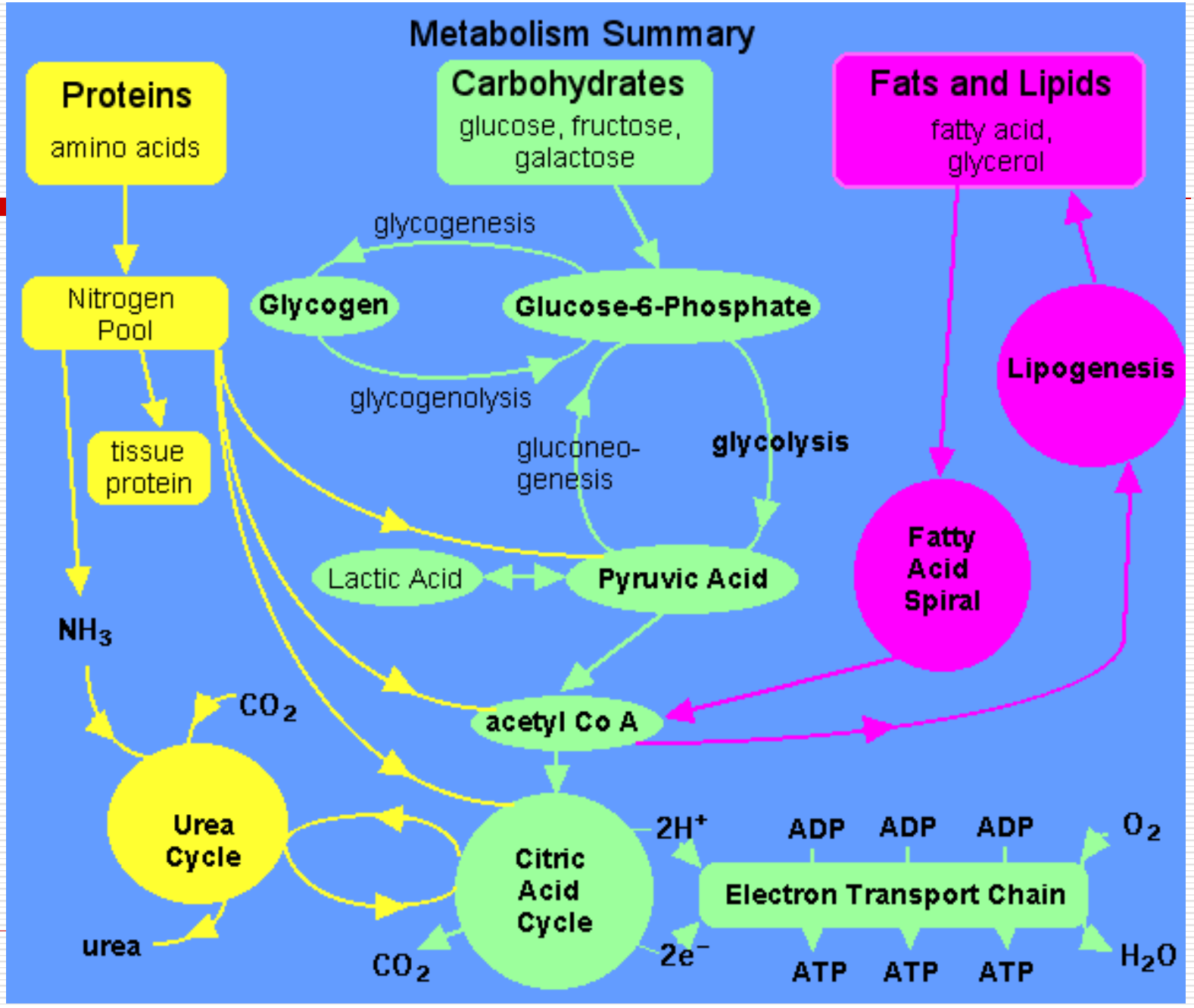
Lipids Metabolism

VLA 2019

2. 4. 2019


Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e−
ATP ATP ATP
H2O

Metabolism stages

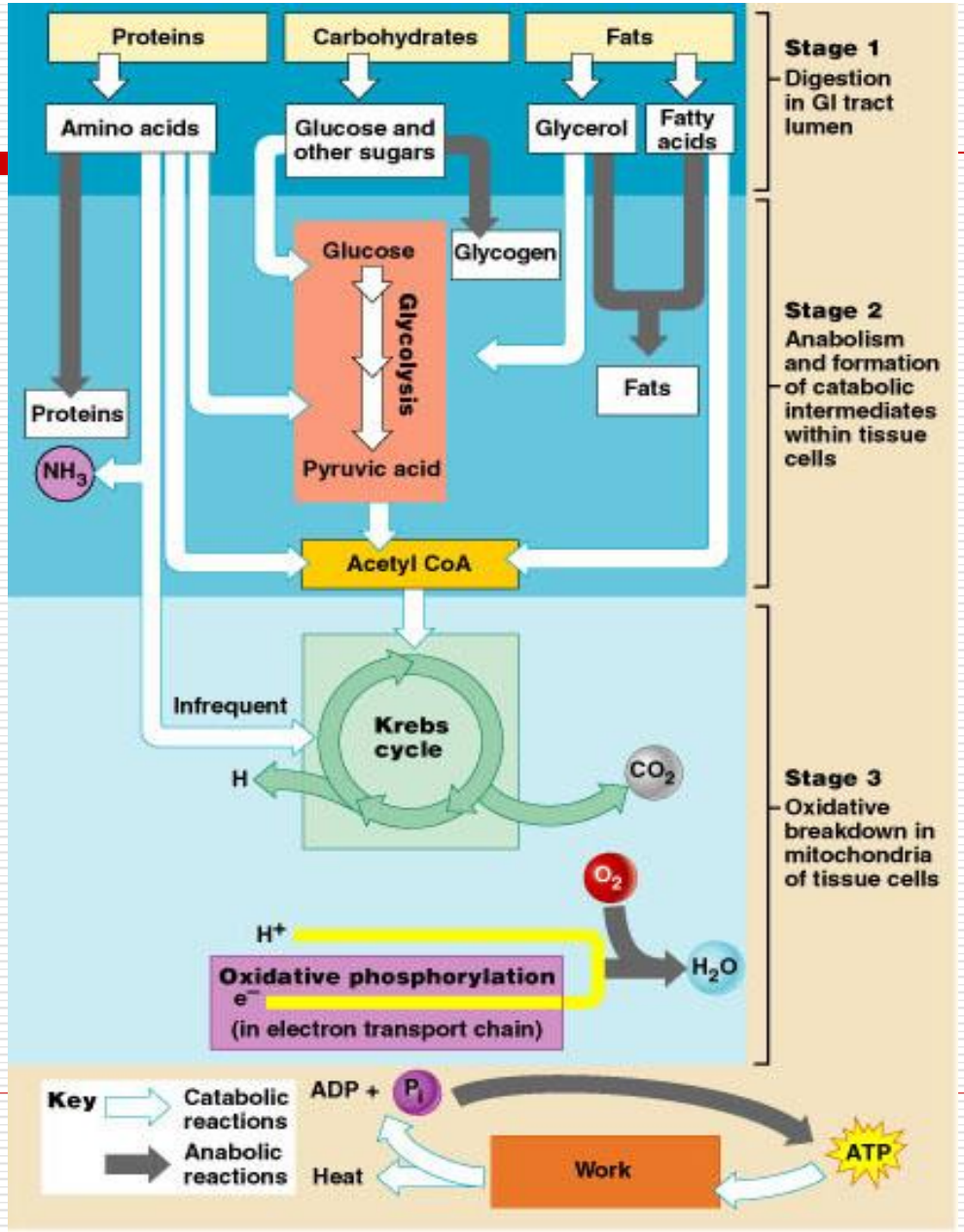
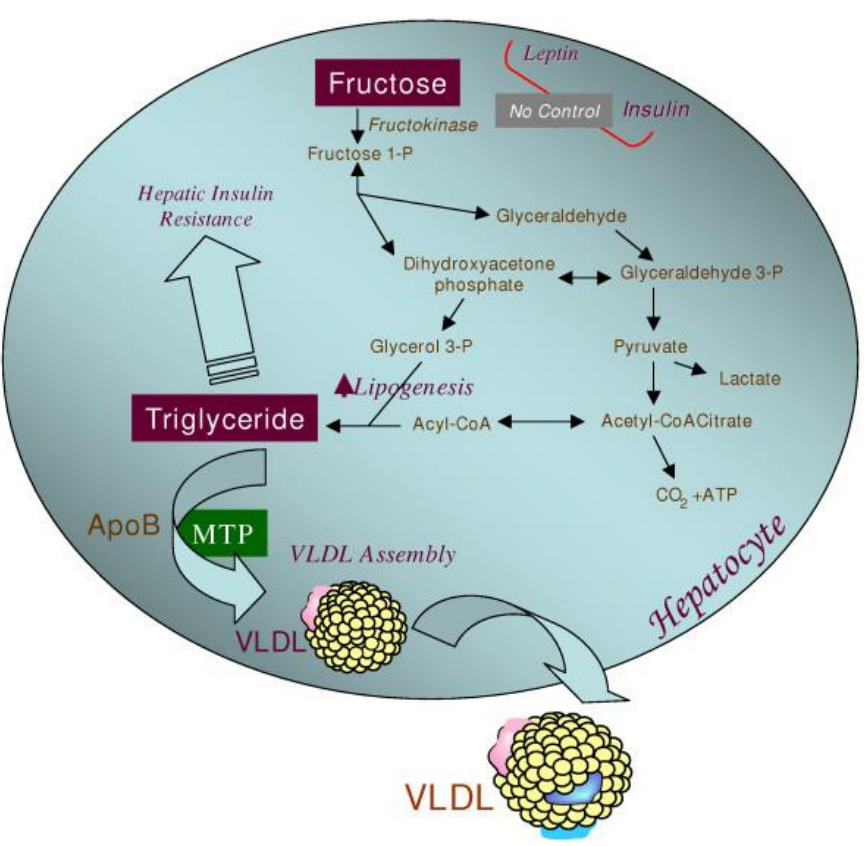


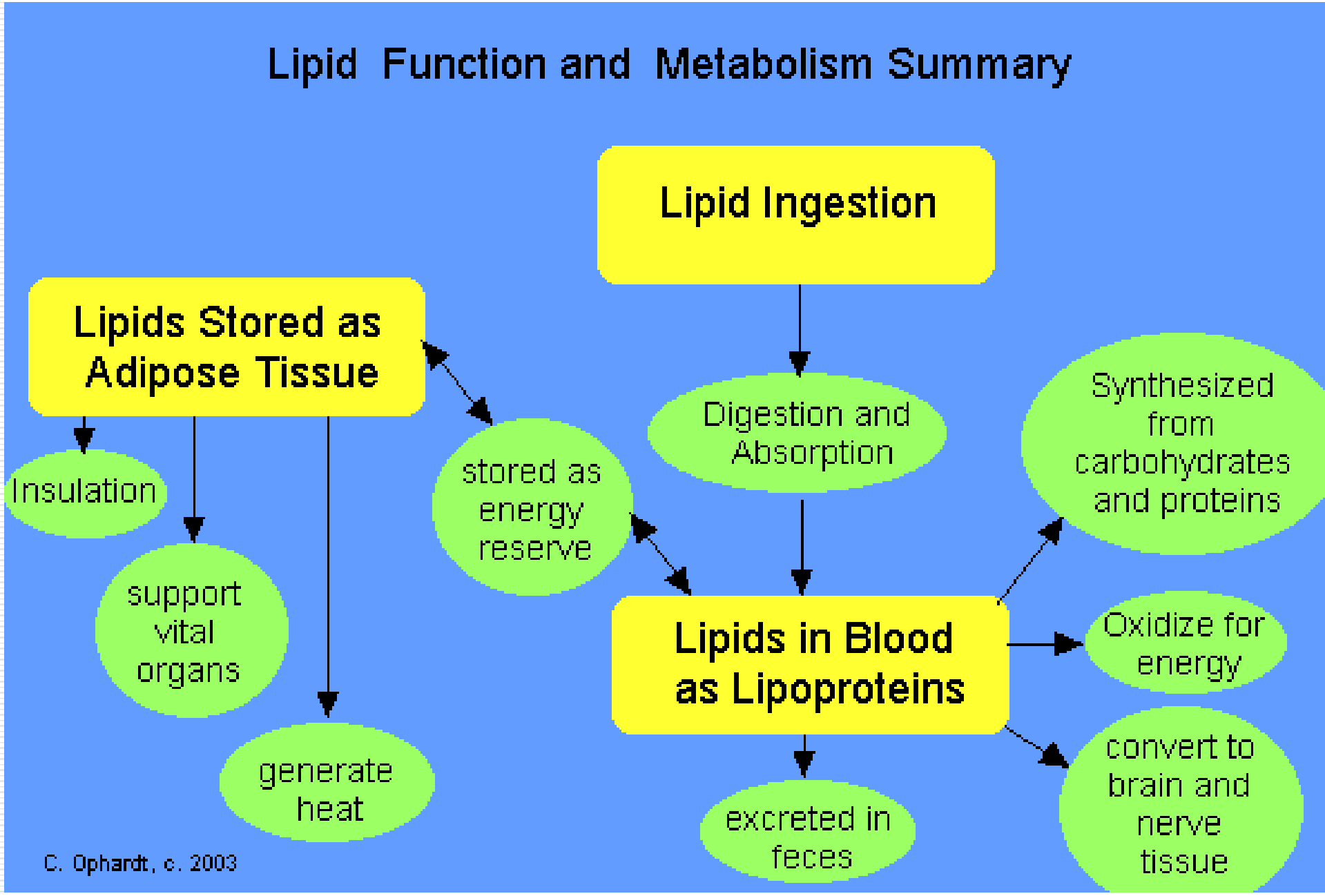
Figure 24.3

Complete oxidation – energy expenditure zisk

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



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 (microsomal triglyceride transfer protein** , the critical factor in VLDL assembly.

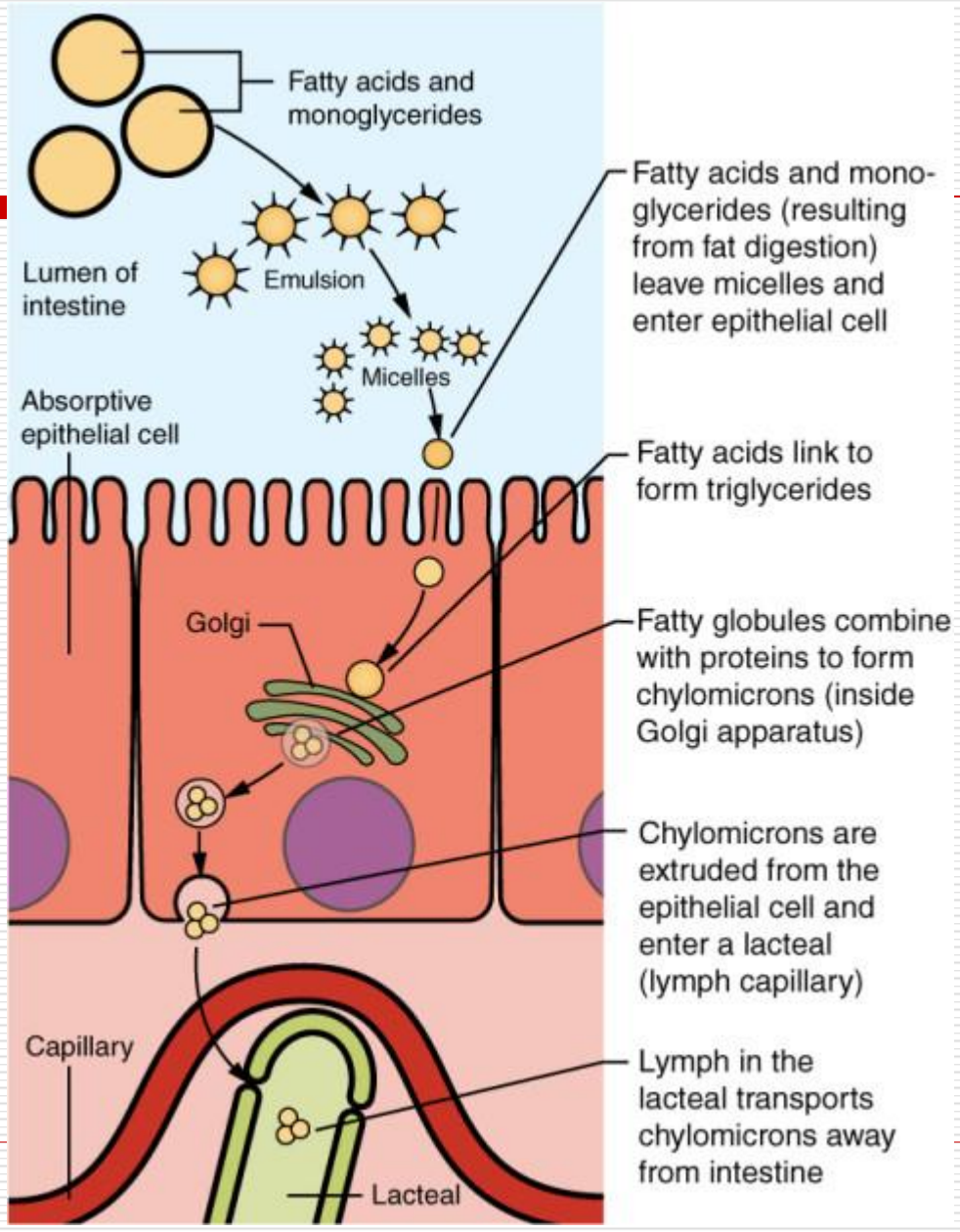

Lipid Function and Metabolism Summary
Lipid Ingestion
Lipids Stored as Adipose Tissue
Digestion and Absorption
Synthesized from carbohydrates and proteins
Insulation
stored as energy reserve
support vital organs
Lipids in Blood as Lipoproteins
Oxidize for energy
generate heat
excreted in feces
convert to brain and nerve tissue
C. Ophardt, c. 2003

Lipids as a energy reserve

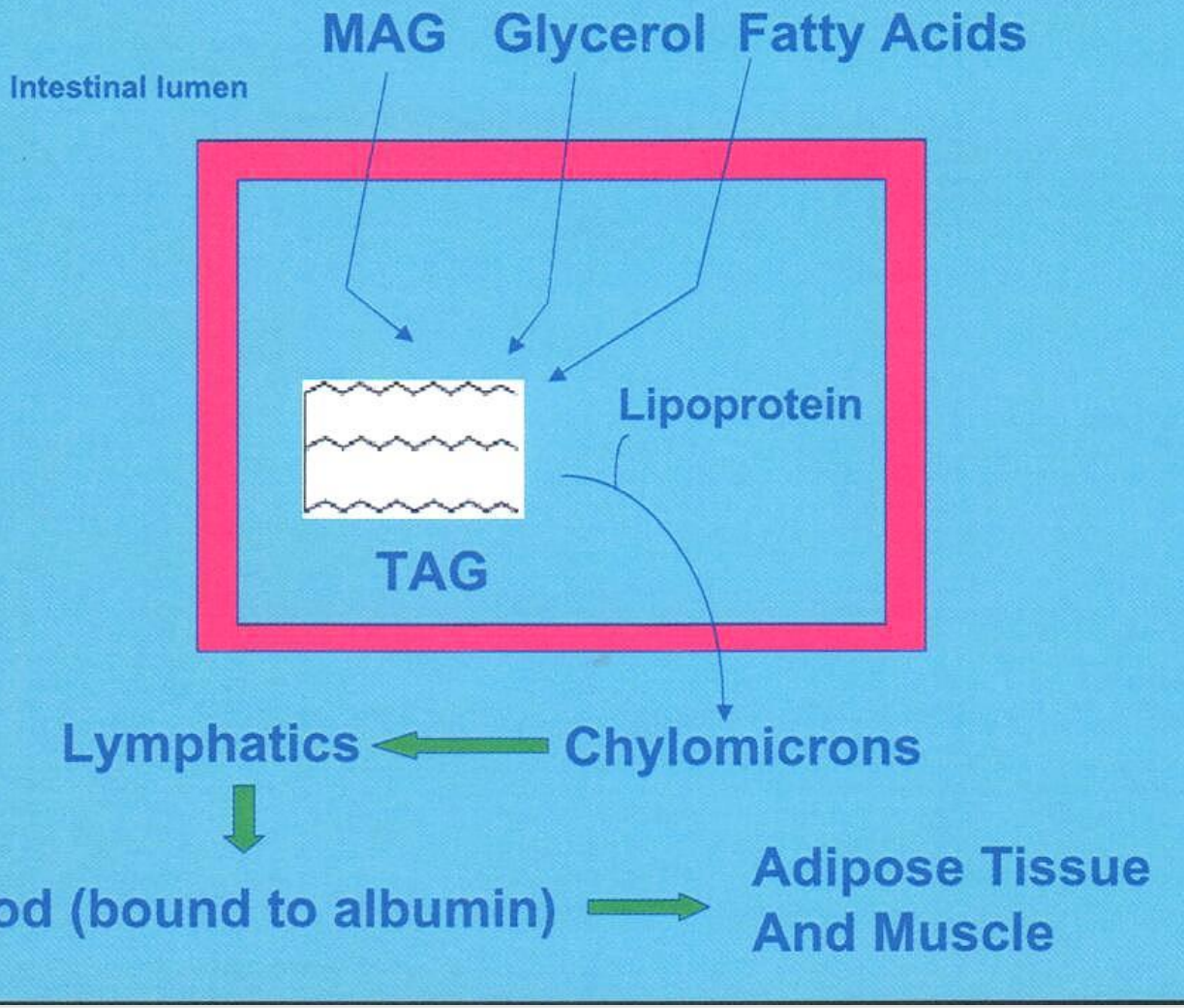
- Most of body energy is formed by oxidation of sugars and lipids.
- Sugars: quick source of energy
- Lipids: energy reserve
- Energy reserve of lipids is much higher compared to glycogen reserve

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


Fatty acids and monoglycerides
Lumen of intestine
Emulsion
Micelles
Absorptive epithelial cell
Golgi
Capillary
Lacteal
Fatty acids and mono-glycerides (resulting from fat digestion) leave micelles and enter epithelial cell
Fatty acids link to form triglycerides
Fatty globules combine with proteins to form chylomicrons (inside Golgi apparatus)
Chylomicrons are extruded from the epithelial cell and enter a lacteal (lymph capillary)
Lymph in the lacteal transports chylomicrons away from intestine

Epithelial Cell (Intestinal Wall)



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

Subcutaneous adipocyte tissue (SCAT) and visceral adipocyte tissue (VAT)

- When compared to SCAT, VAT is more vascular, cellular and innervated. It contains a greater number of immune cells and large adipocytes when compared to that of SCAT. There are also more androgen and glucocorticoid receptors in VAT than in SCAT. Adipocytes in VAT are not only more metabolically active but also are more sensitive to lipolysis than adipocytes in SCAT. VAT also generates higher amounts of free fatty acids, has an enhanced uptake of glucose and a higher sensitivity to adrenergic stimulation, while SCAT is more involved in absorbing circulating free fatty acids and triglycerides (TGs).
- Overall, VAT accumulation increases the risk of metabolic disorders, such as T2D, hypertension, hyperlipidemia and atherosclerosis

Prog Cardiovasc Dis. 2018 May - Jun;61(1):3-9

Due to fructose-induced inflammation (increased infiltration of adipose tissue by macrophages) there is also an increase in 11B-hydroxysteroid dehydrogenase-1. This leads to an increase in intracellular cortisol in subcutaneous adipocyte tissue (essentially making them insulin resistant) causing less fatty acids to enter the subcutaneous adipocyte while more are expelled for storage into visceral depots and in and around organs, such as the liver, skeletal muscle, heart, and pancreas, further disrupting metabolic processes and impairing organ function.

Prog Cardiovasc Dis. 2018 May - Jun;61(1):3-9

TOFI

- Thus, overconsumption of added sugars promotes "thin on the outside, fat on the inside" (TOFI).
- The term TOFI is used to describe lean individuals with an increased fat deposition within their abdomen (visceral adiposity).
- Subjects with TOFI have a body mass index < 25 kg/m^2 with an increase in risk factors associated with the metabolic syndrome. This phenotype is a subtype of "metabolically-obese but normal-weight".
- The prevalence of TOFI is uncertain but it is estimated that 14% of men and 12% of women have TOFI.
- TOFI can be diagnosed by MRI or CT scan which can help in differentiating fat (bright white) and other tissues (dark).

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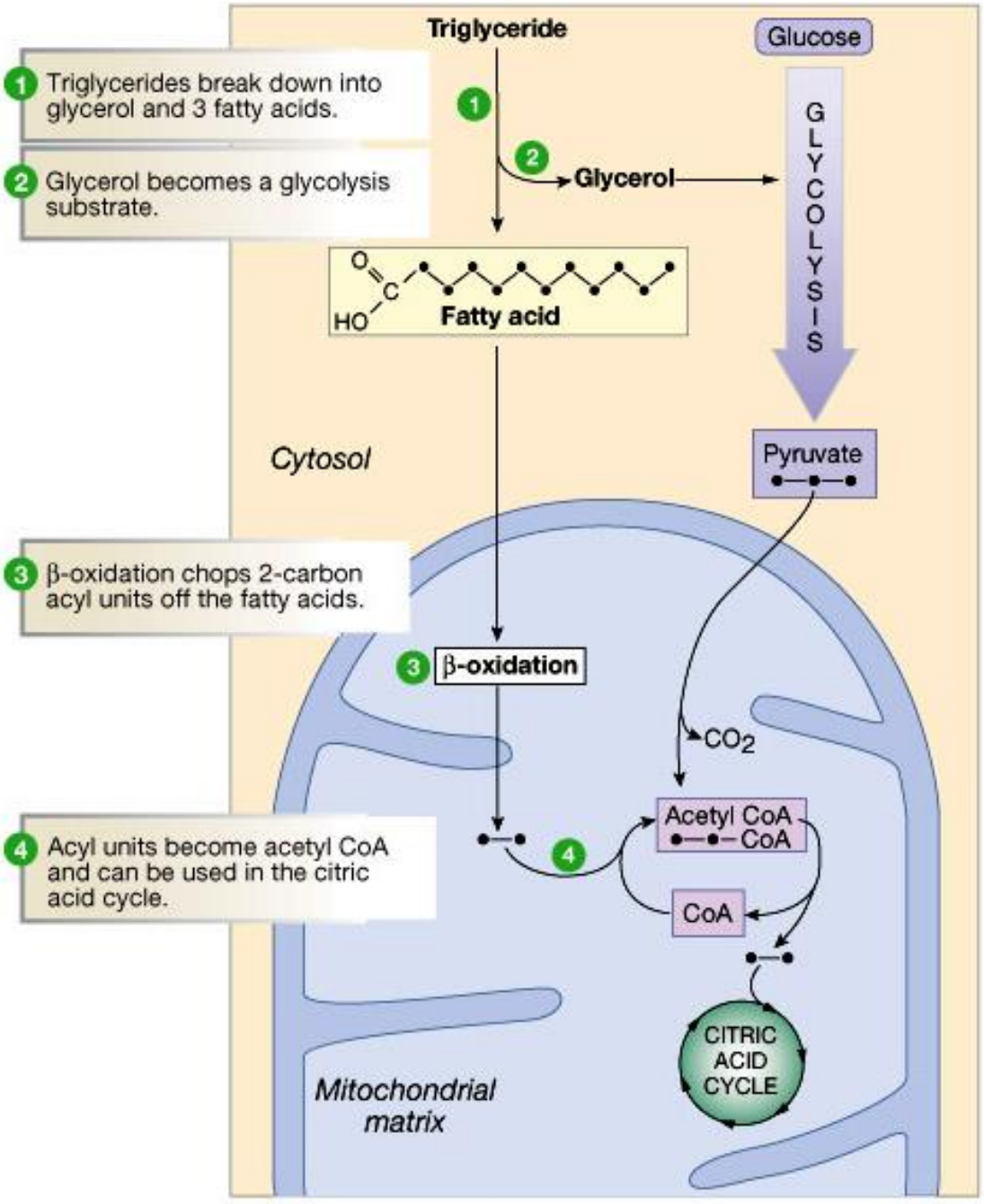
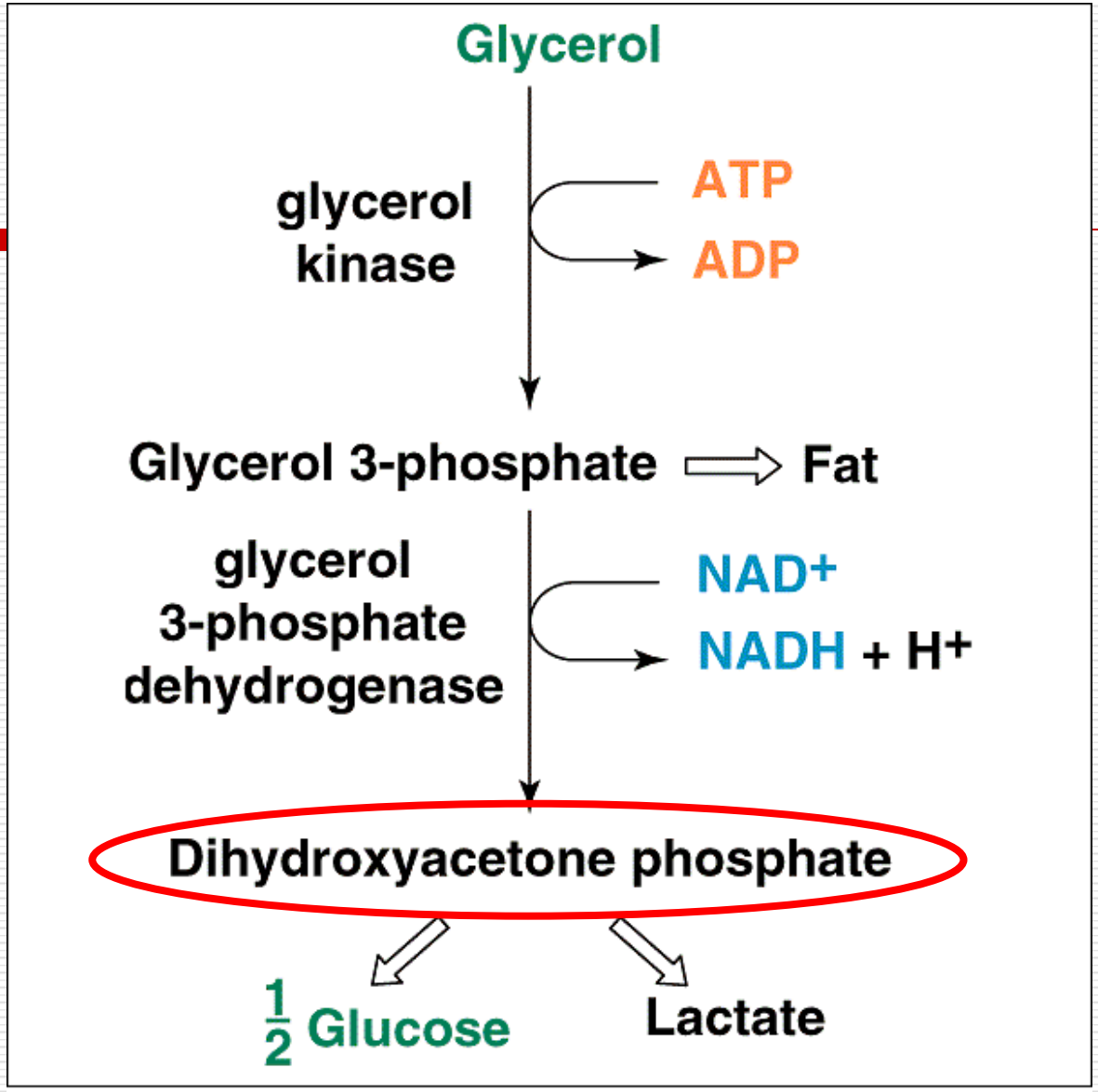
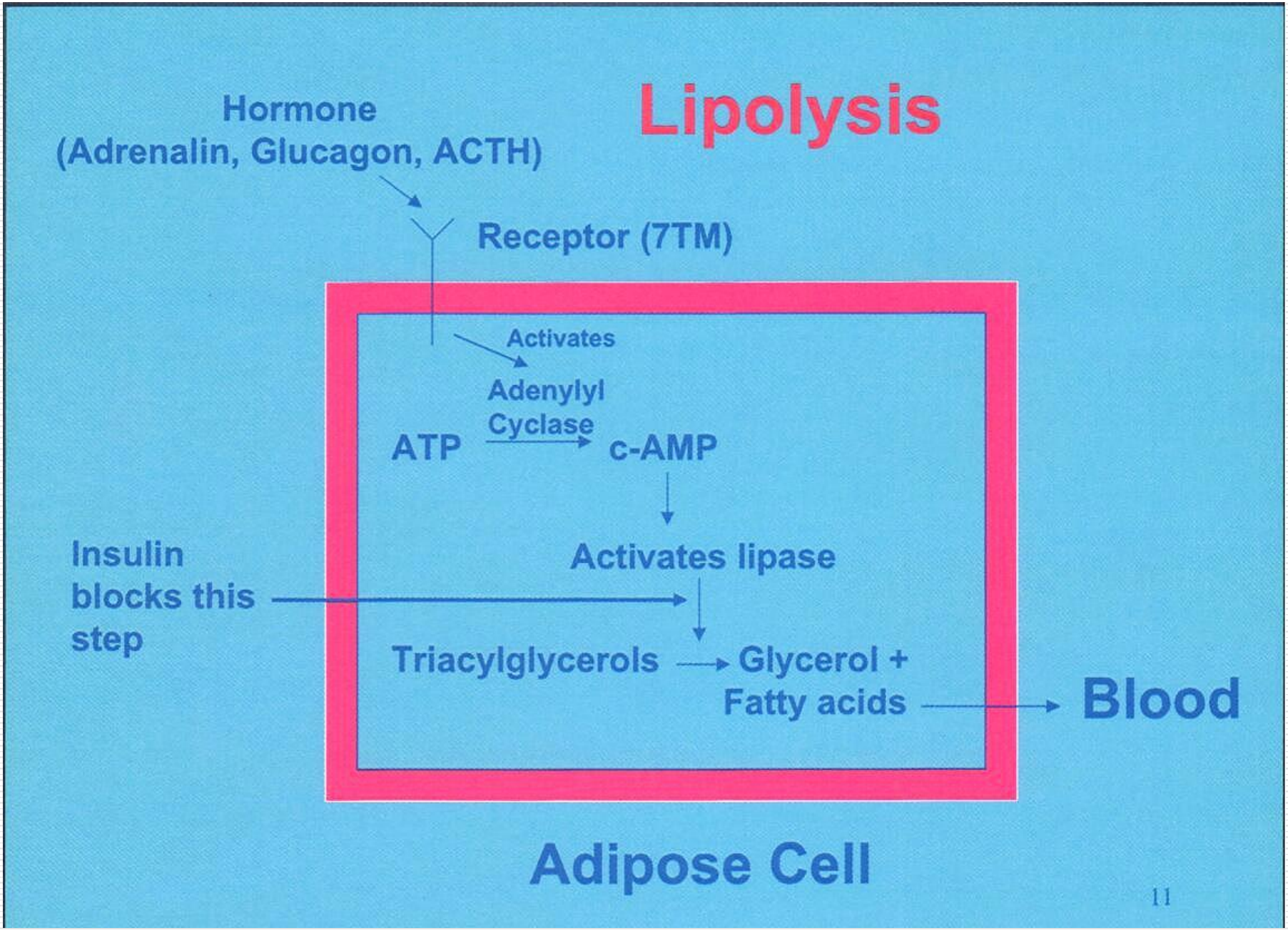
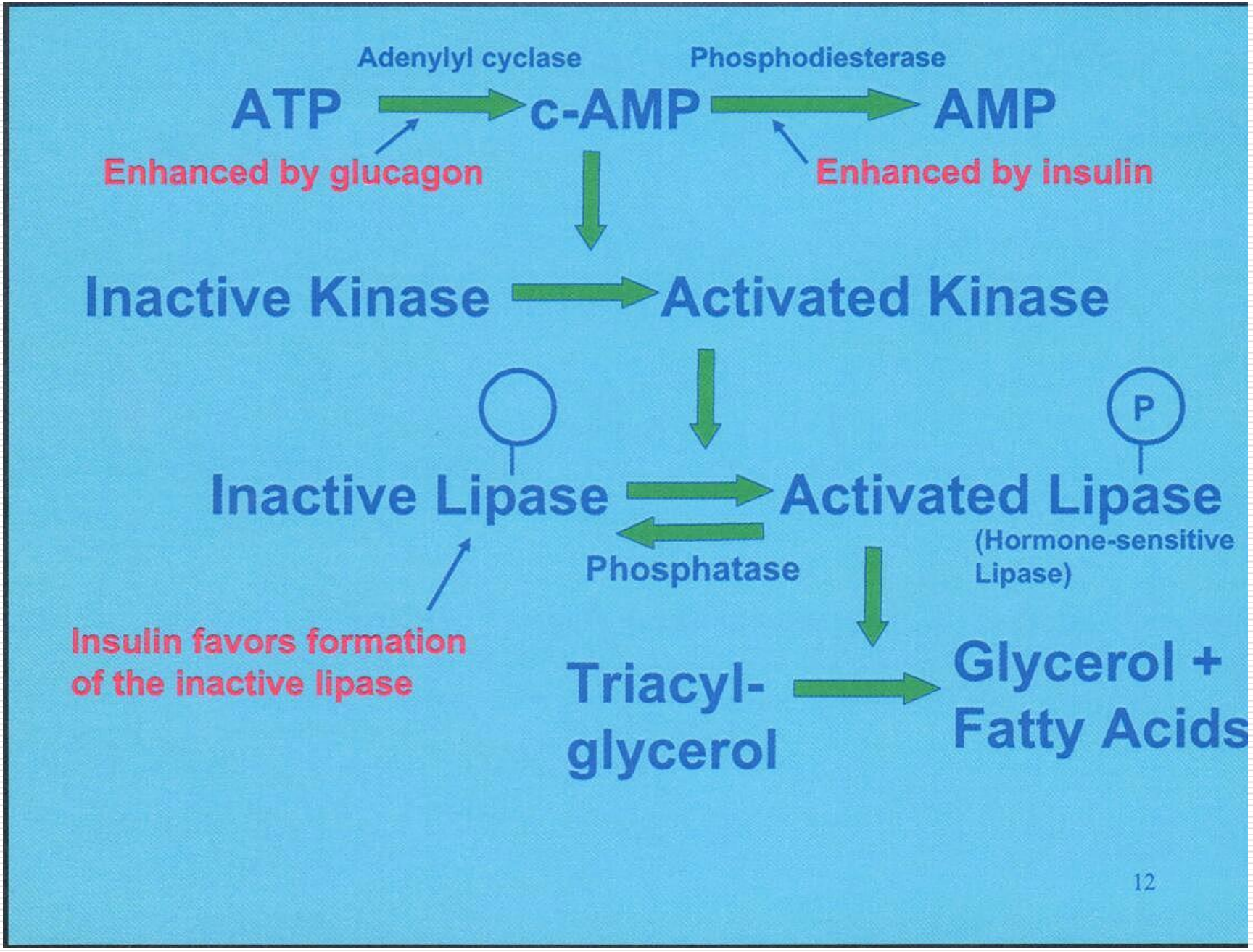
Lipolysis


Triglyceride
Glucose
1 Triglycerides break down into glycerol and 3 fatty acids.
2 Glycerol becomes a glycolysis substrate.
1
2
Glycerol
GLYCOLYSIS
HO
Fatty acid
Cytosol
Pyruvate
3 β-oxidation chops 2-carbon acyl units off the fatty acids.
3 β-oxidation
CO2
Acetyl CoA
CoA
4 Acyl units become acetyl CoA and can be used in the citric acid cycle.
4
CoA
CITRIC ACID CYCLE
Mitochondrial matrix

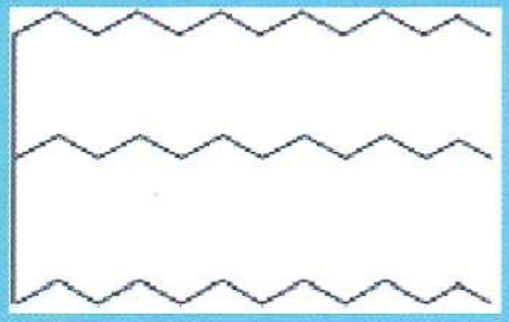


Devlin, T. M. (editor): Textbook of Biochemistry with Clinical Correlations, 4th ed. Wiley-Liss, Inc., New York, 1997. ISBN 0-471-15451-2


Lipolysis
Hormone
(Adrenalin, Glucagon, ACTH)
Receptor (7TM)
Activates
Adenylyl
Cyclase
ATP
c-AMP
Activates lipase
Insulin
blocks this
step
Triacylglycerols
Glycerol +
Fatty acids
Blood
Adipose Cell


Adenylyl cyclase
Phosphodiesterase
ATP
c-AMP
AMP
Enhanced by glucagon
Enhanced by insulin
Inactive Kinase
Activated Kinase
P
Inactive Lipase
Activated Lipase
(Hormone-sensitive Lipase)
Phosphatase
Insulin favors formation of the inactive lipase
Triacyl-glycerol
Glycerol + Fatty Acids

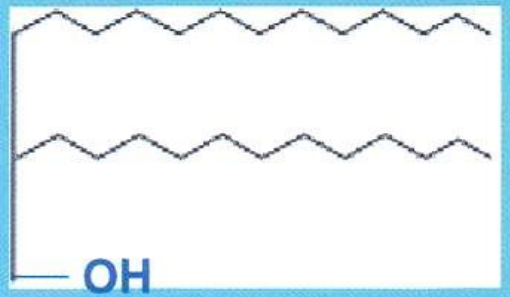
Acylglycerol Lipases



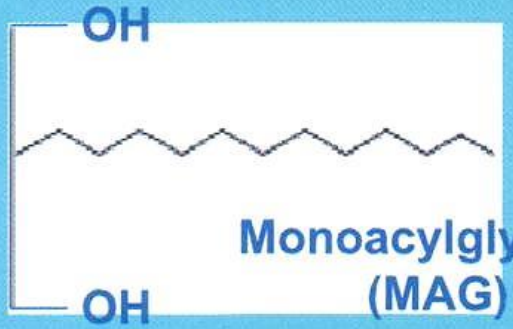
Triacylglycerol (TAG)

Triacylglycerol Lipase

Diacylglycerol (DAG)

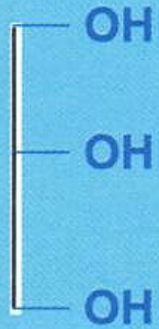


Diacylglycerol Lipase



Monoacylglycerol (MAG)

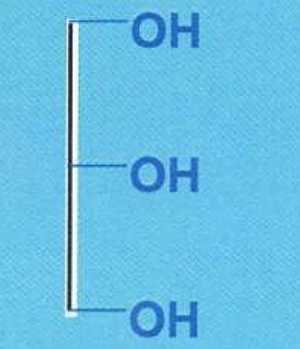
Monoacylglycerol Lipase



Glycerol

Fate of Glycerol

In Liver:



Glycerol

Dihydroxyacetone Phosphate

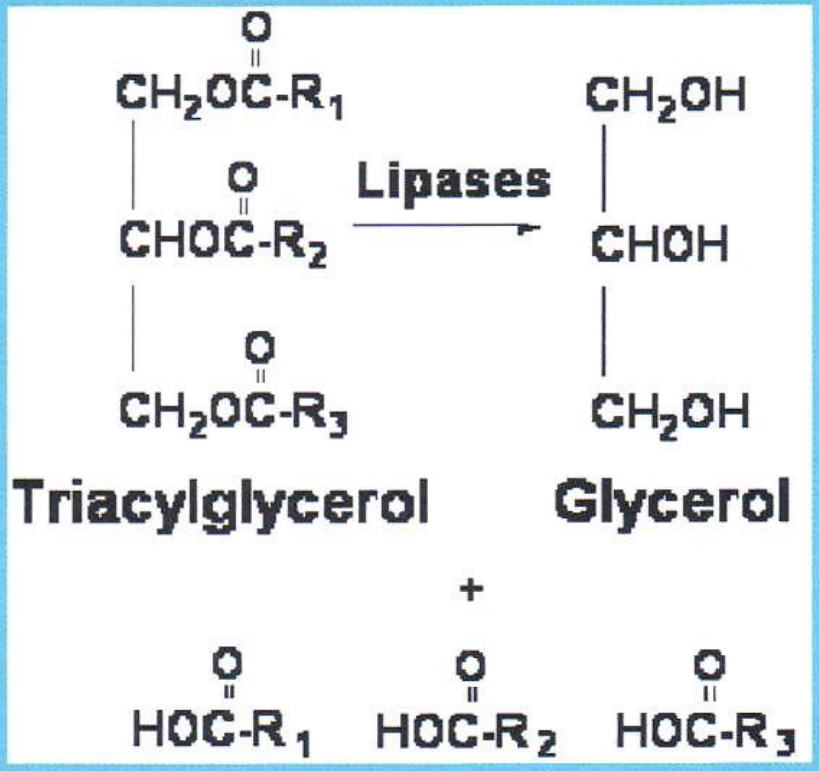
Glycolysis

Pyruvate

Gluconeogenesis

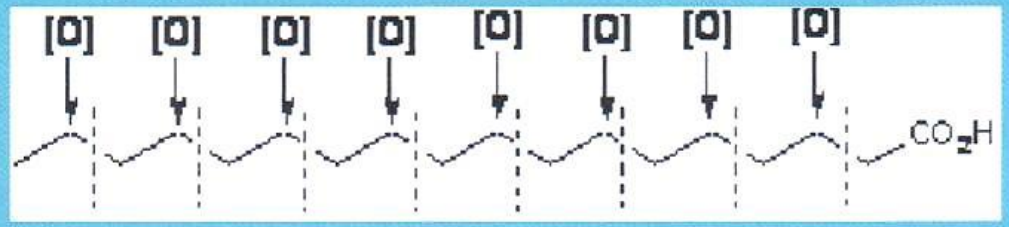
Glucose

Release of Fatty Acids from Triacylglycerols



Beta Oxidation

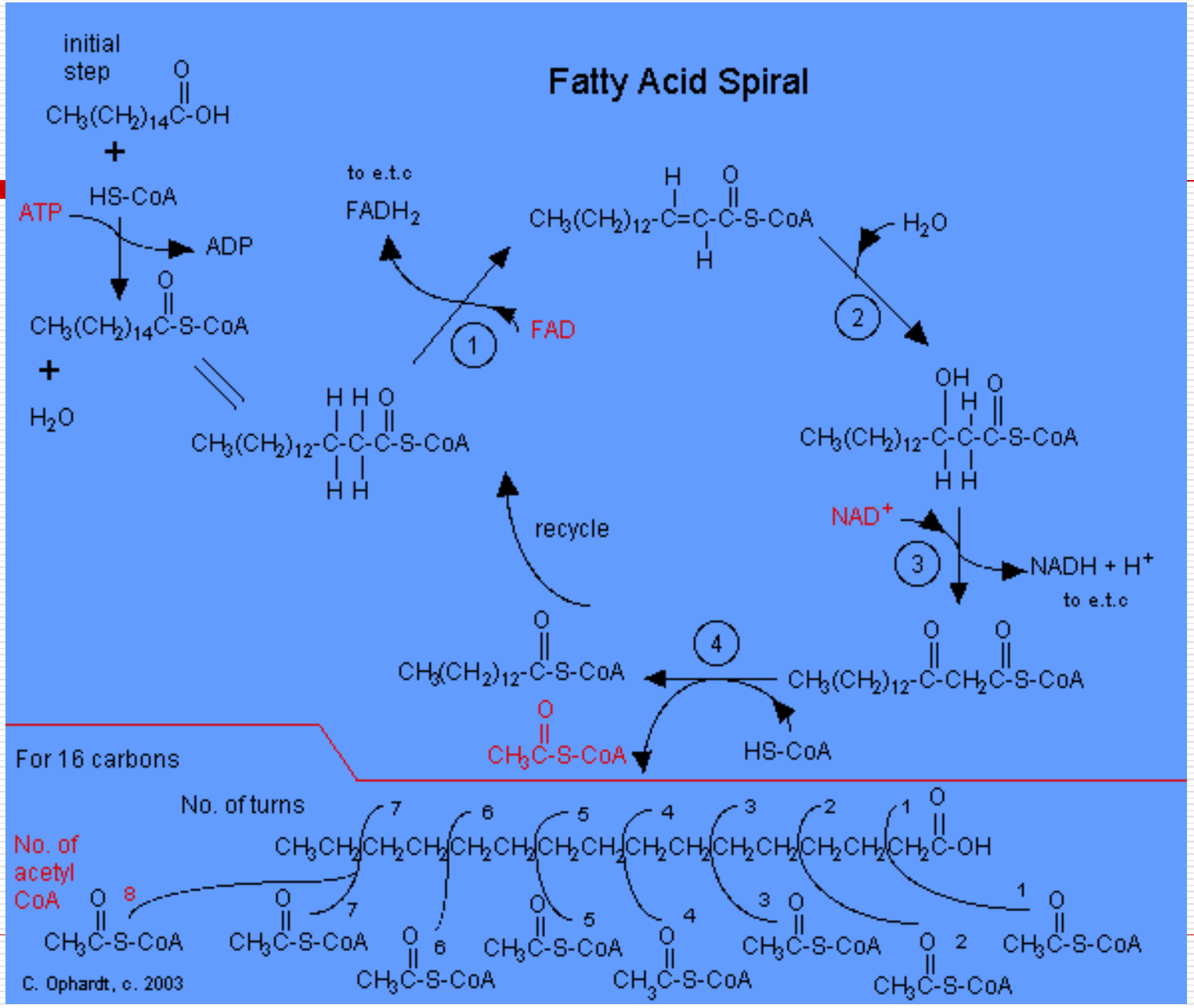
- Cleavage of fatty acids to acetate in tissues
- Occurs in mitochondria

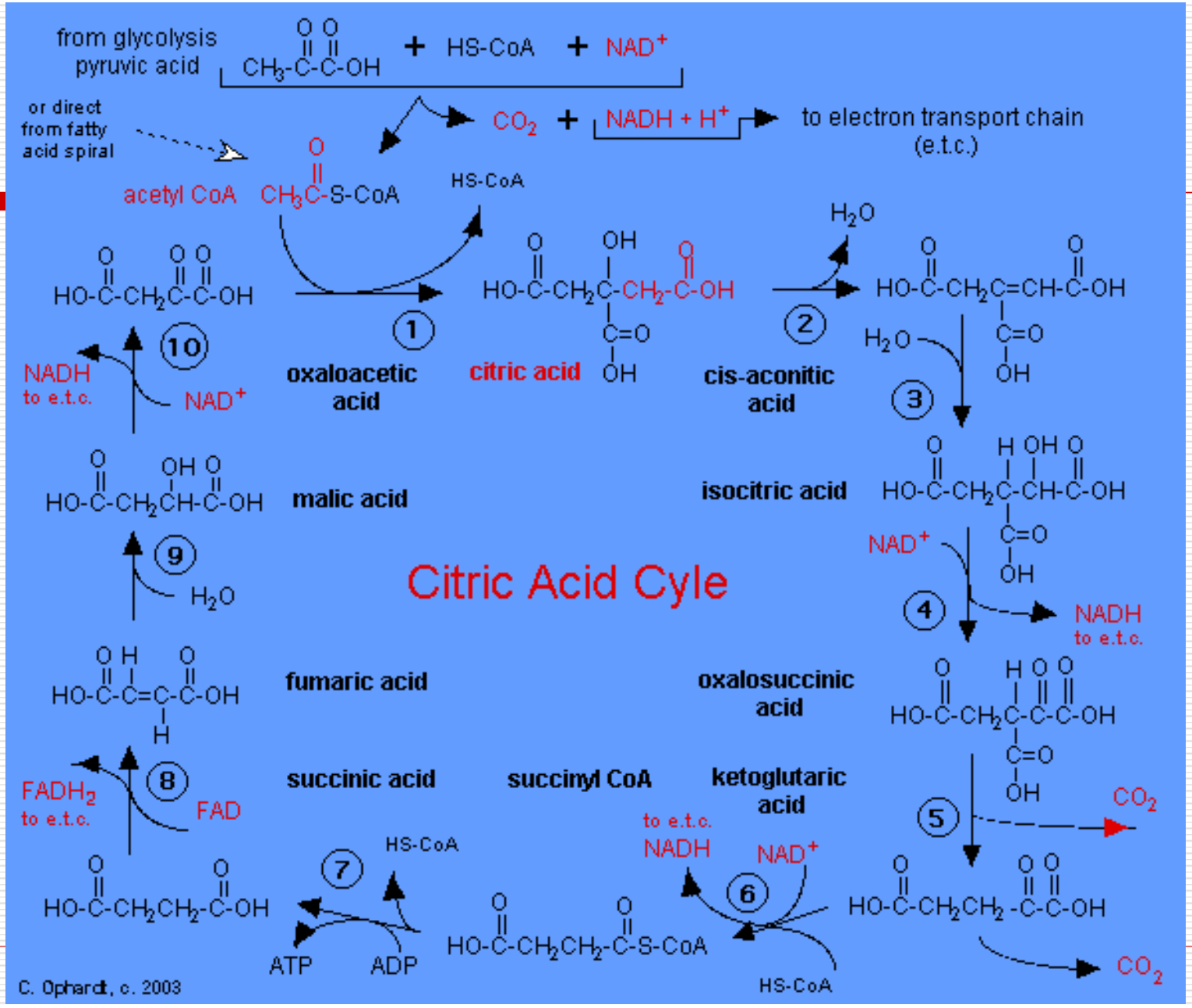


9 $CH_3COSCoA$

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)

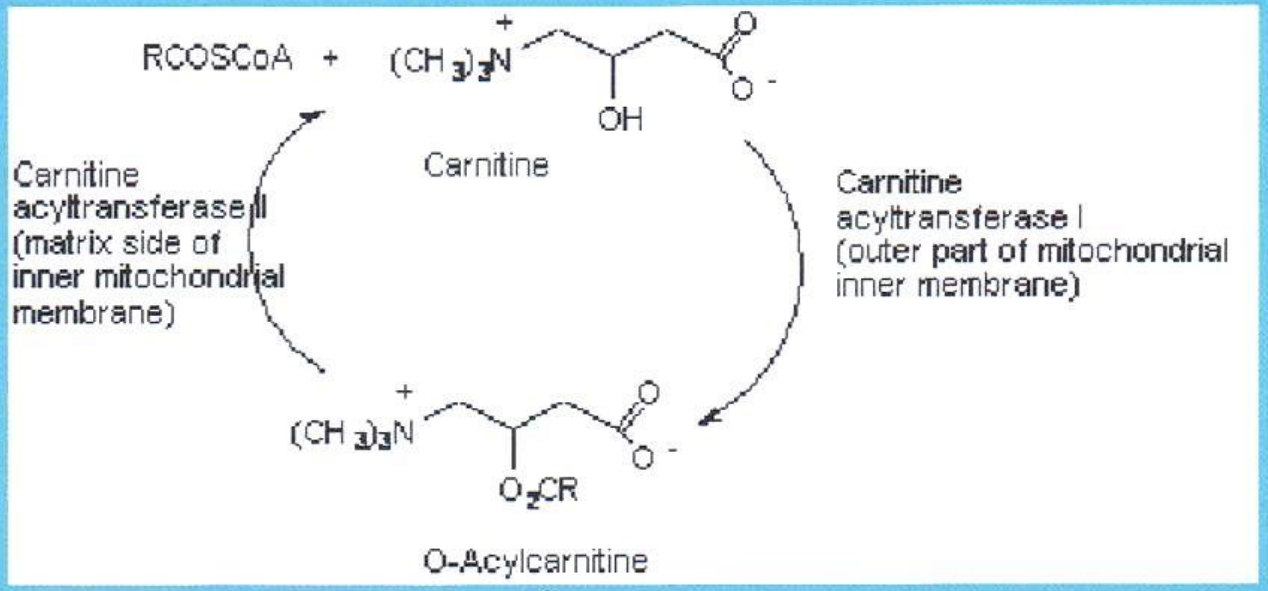

Fatty Acid Spiral
initial step
$CH_3(CH_2)_{14}C$-OH
+
ATP
HS-CoA
ADP
$CH_3(CH_2)_{14}C$-S-CoA
+
H_2O
to e.t.c
$FADH_2$
FAD
1
$CH_3(CH_2)_{12}$-C=C-C-S-CoA
H
H_2O
2
$CH_3(CH_2)_{12}$-C-C-C-S-CoA
OH
NAD+
3
NADH + H^+
to e.t.c
recycle
4
$CH_3(CH_2)_{12}$-C-S-CoA
$CH_3(CH_2)_{12}$-C-CH_2C-S-CoA
CH_3C-S-CoA
HS-CoA
For 16 carbons
No. of turns
No. of acetyl CoA
$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2C$-OH
CH_3C-S-CoA
C. Ophardt, c. 2003


from glycolysis
pyruvic acid
HS-CoA
NAD+
or direct
from fatty
acid spiral
CO2
NADH + H+
to electron transport chain
(e.t.c.)
acetyl CoA
HS-CoA
oxaloacetic
acid
citric acid
cis-aconitic
acid
H2O
NADH
to e.t.c.
NAD+
malic acid
isocitric acid
Citric Acid Cyle
H2O
fumaric acid
oxalosuccinic
acid
NADH
to e.t.c.
FADH2
to e.t.c.
FAD
succinic acid
succinyl CoA
ketoglutaric
acid
CO2
HS-CoA
ATP
ADP
to e.t.c.
NADH
NAD+
HS-CoA
CO2
C. Ophardt, c. 2003

Acetyl CoA

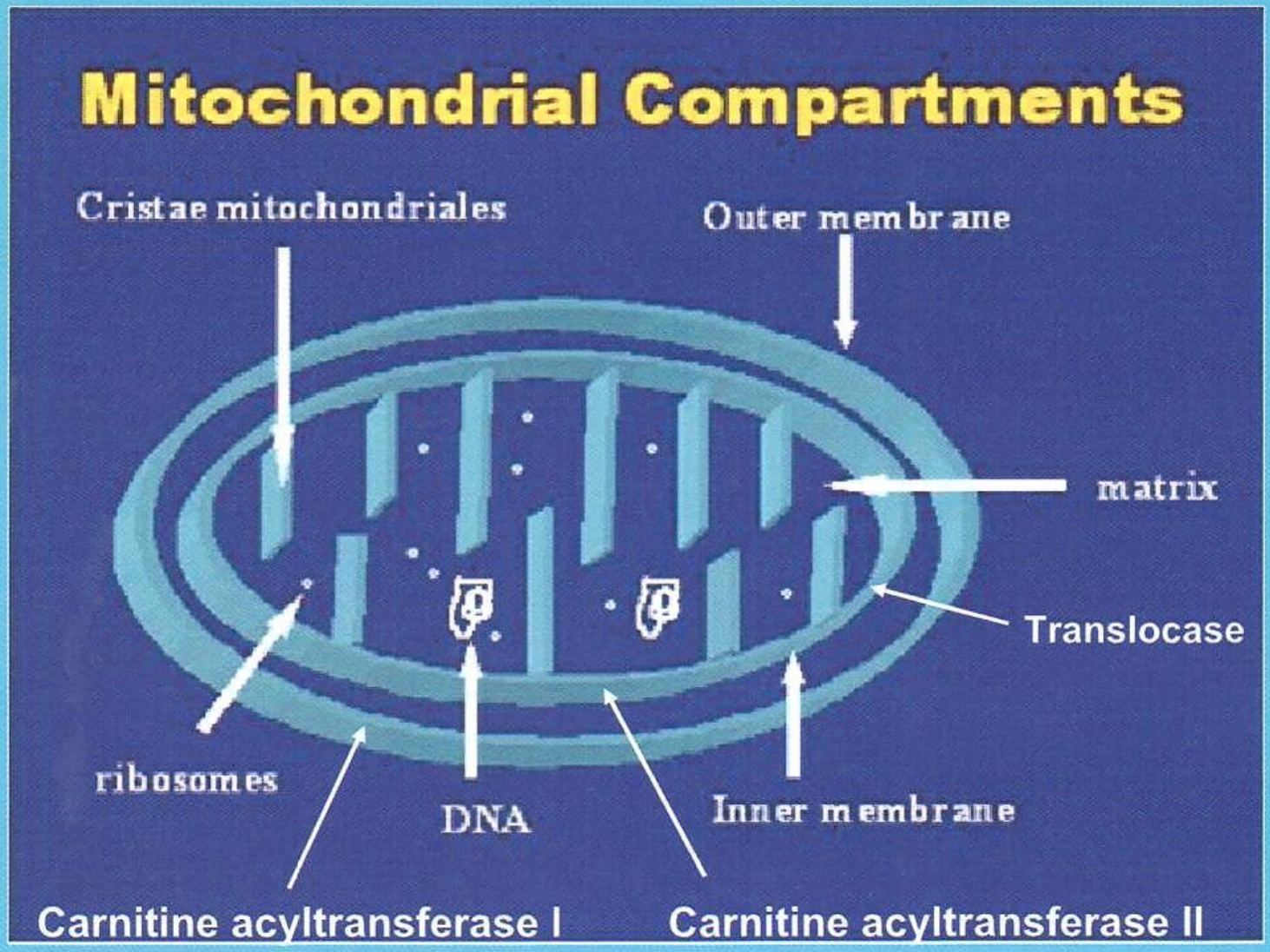
- Under aerobic conditions the end product of glycolysis is pyruvic acid. The next step is the formation of **acetyl coenzyme A**(acetyl CoA) - this step is technically not a part of the citric acid cycle, but is shown on the diagram on the top left.
- Acetyl CoA, whether from glycolysis or the fatty 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



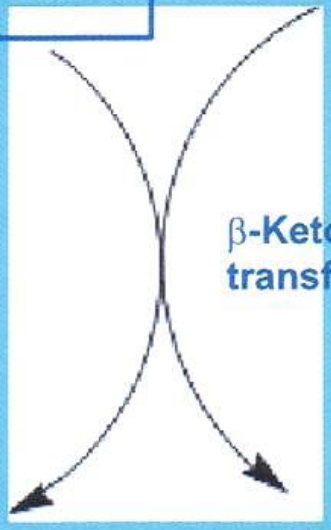
Source: http://cellbio.utmb.edu/cellbio/mitochondria_1.htm

Ketone Bodies As Energy Sources

In liver

β-Hydroxybutyrate ⟷ Acetoacetate

Succinyl CoA



β-Ketoacyl CoA transferase

Not found in liver

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

Thiolase

2 Acetyl CoA ⟷ Acetoacetyl CoA

Succinate

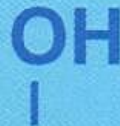
Combines with oxaloacetate

TCA Cycle

Metabolic Acidosis in Untreated Diabetes Mellitus

$CH_3COCH_2CO_2H$ $pK_a = 3.6$

Acetoacetic Acid

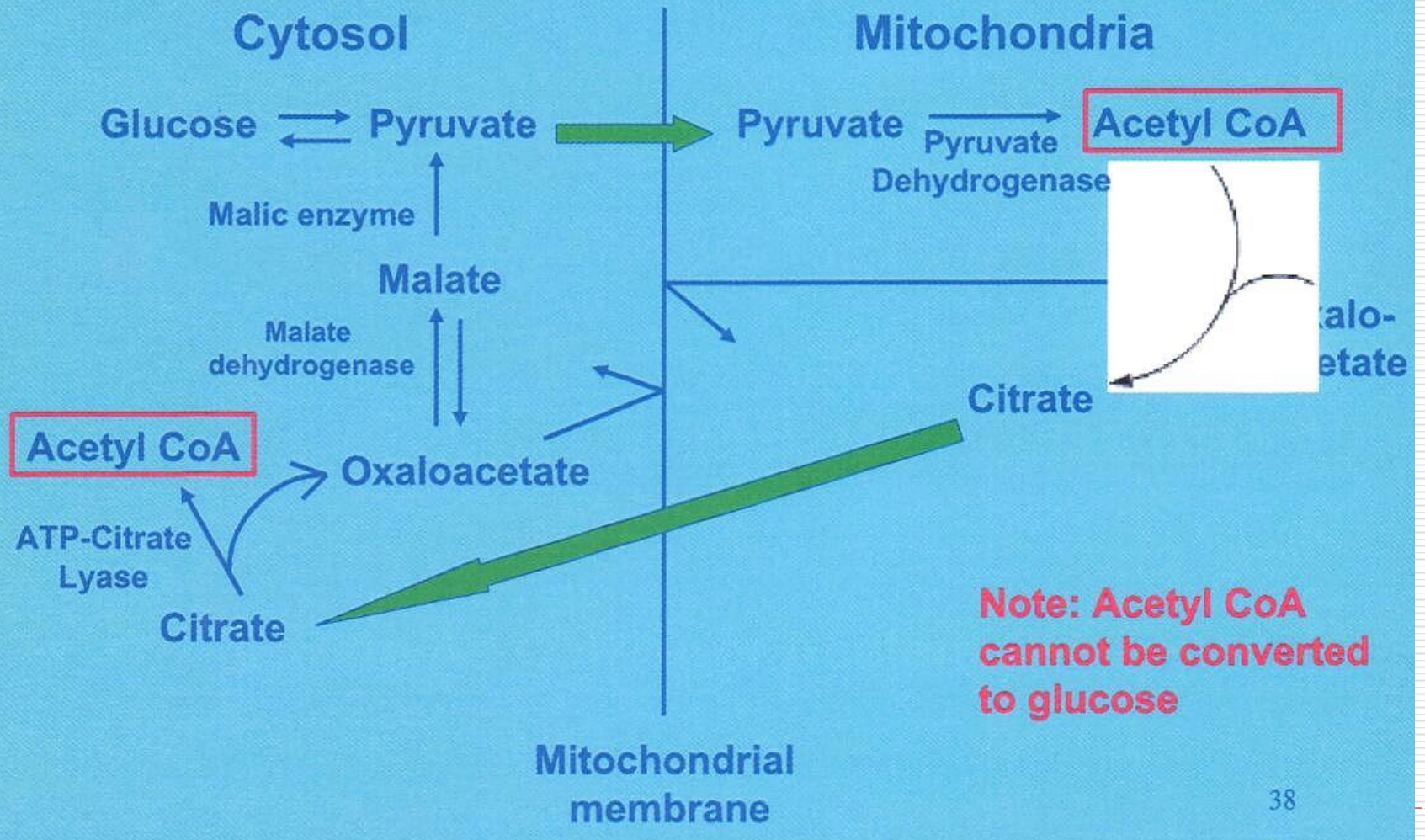


$CH_3CHCH_2CO_2H$ $pK_a = 4.7$

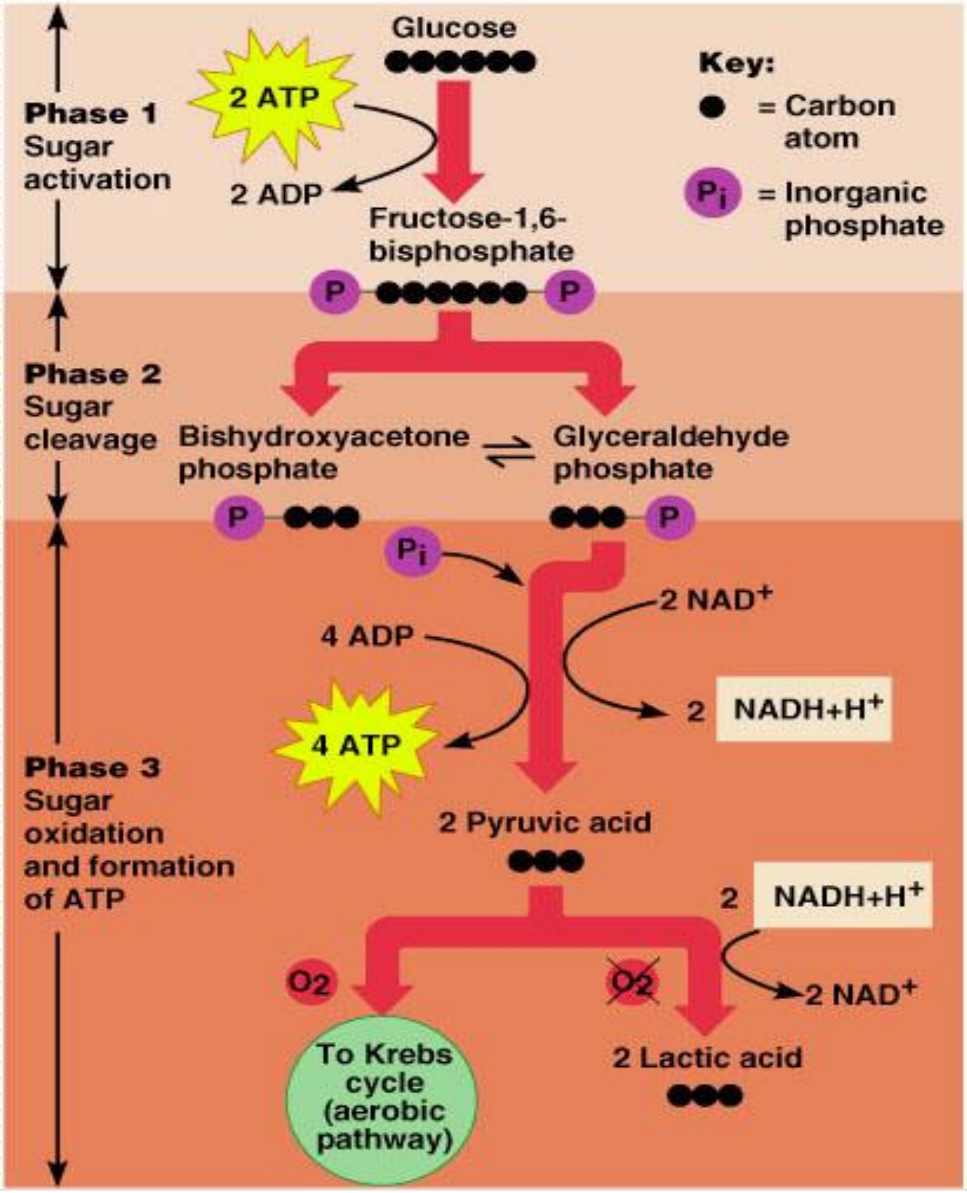
β-Hydroxybutyric acid

↑ Concentration of acetoacetic acid can result in metabolic acidosis (pH 7.1) ⟶ ↓ affinity of Hb for O_2.

Citrate As Carrier of Acetate Groups



Glycolysis



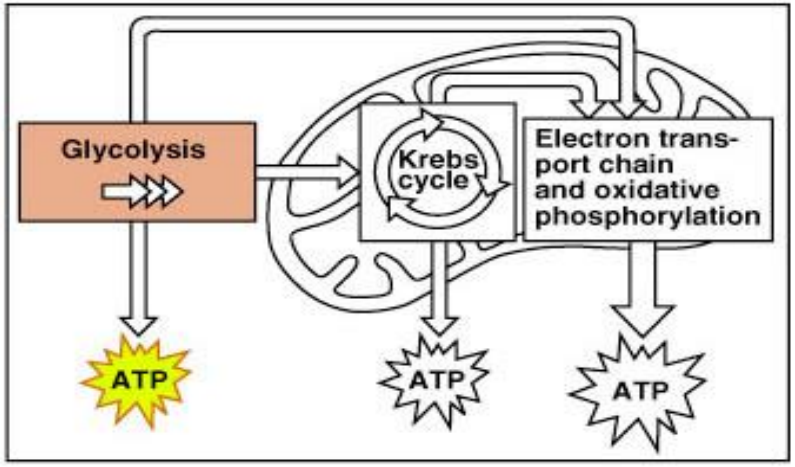
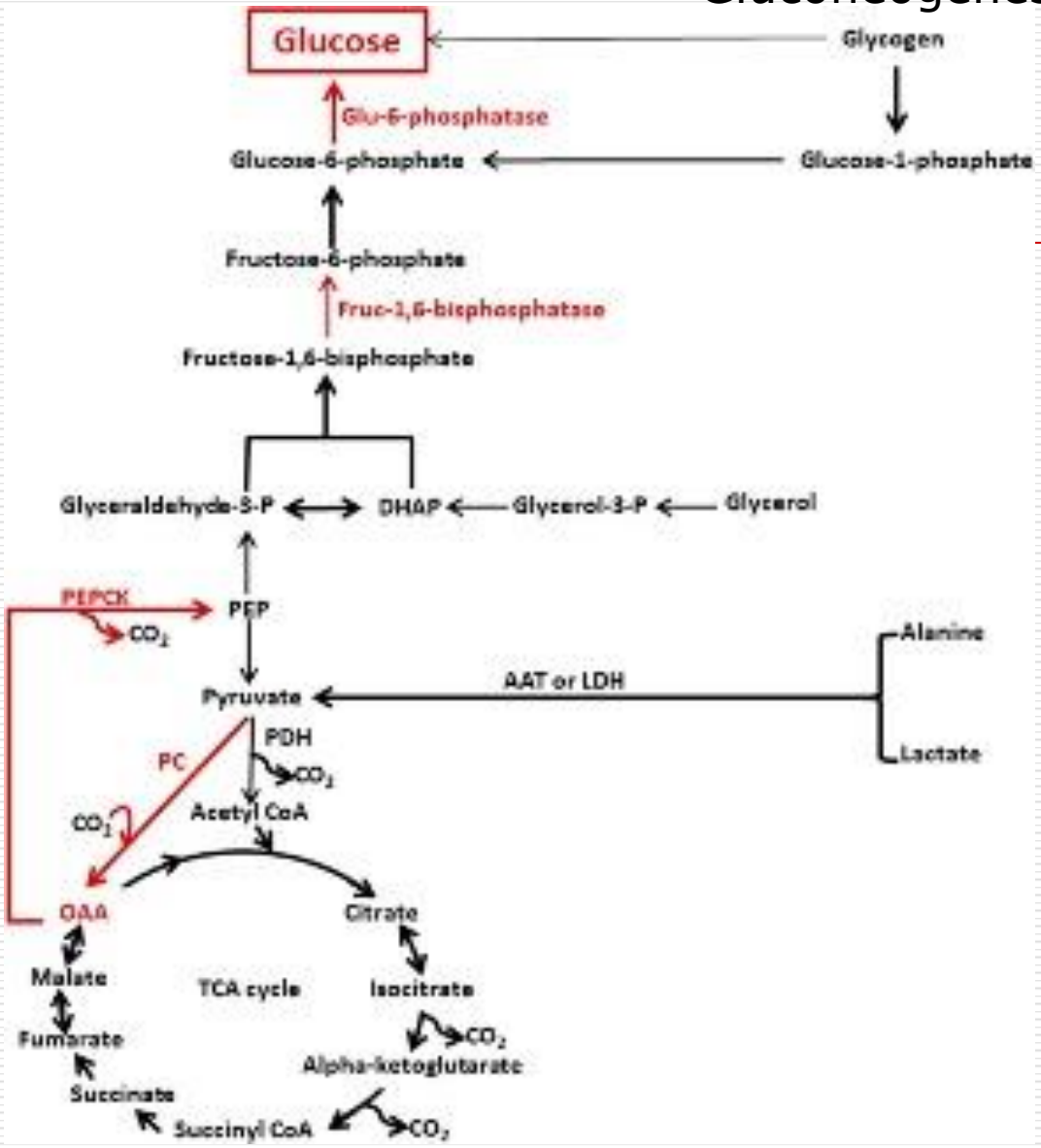


Figure 24.6

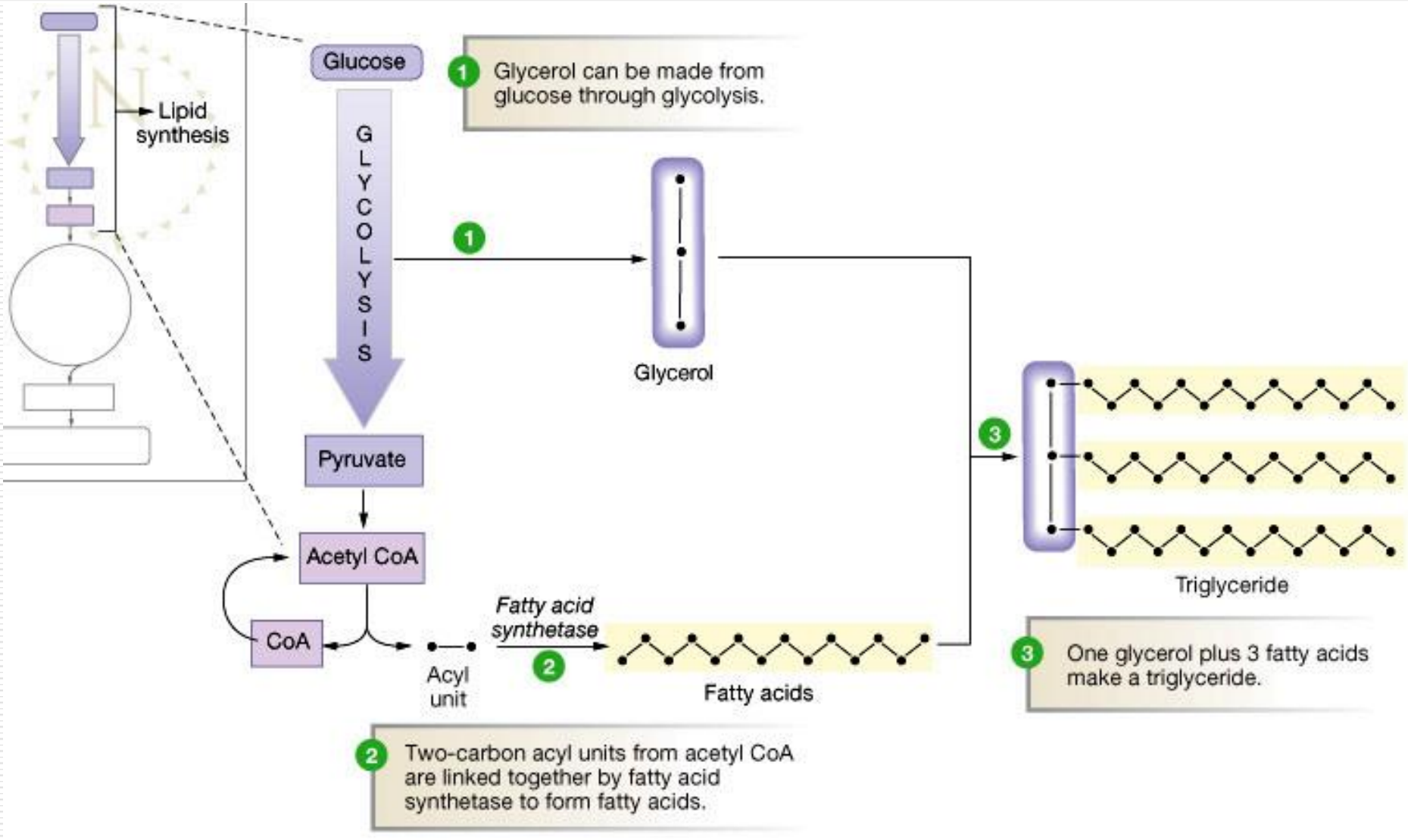
Gluconeogenesis



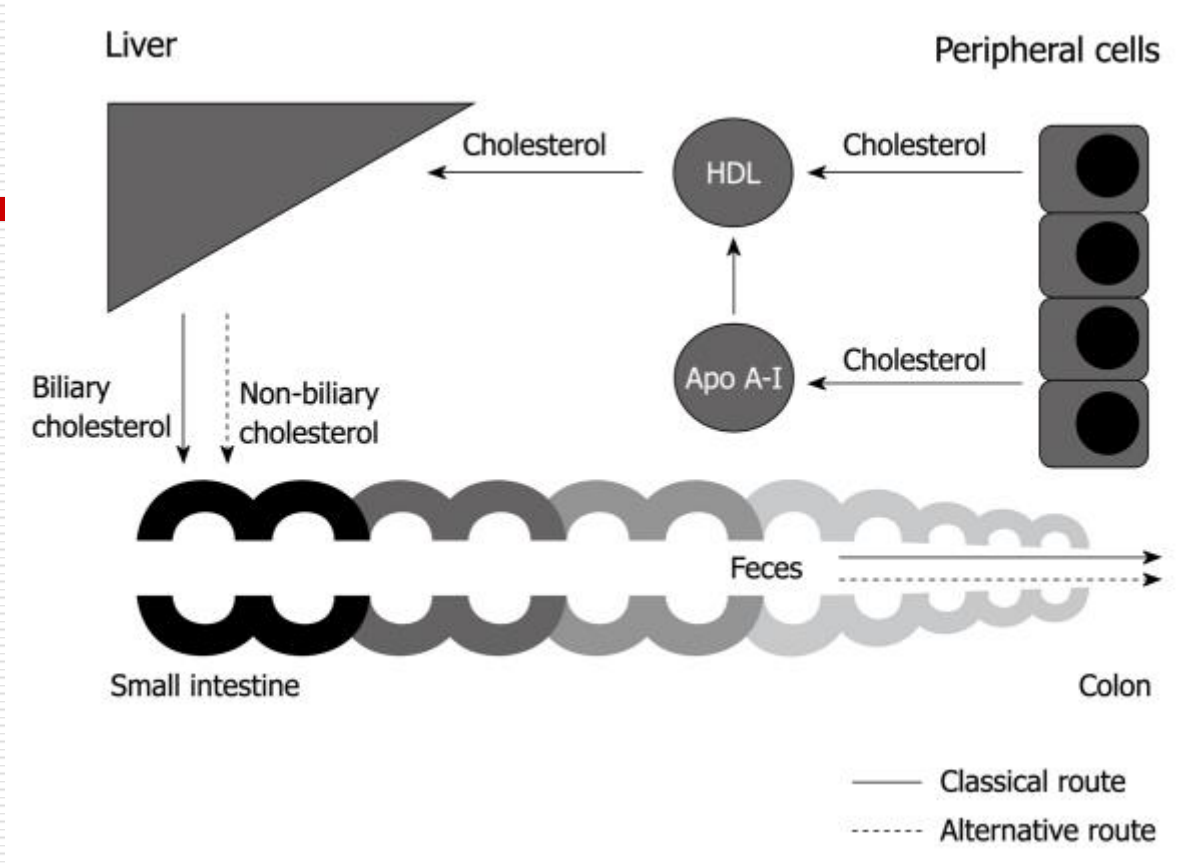
Major enzymes and substrates involved in the regulation of gluconeogenesis. Red arrows and text represent the major enzymes and pathways involved in the regulation of gluconeogenesis. Direct glucose release from glycogen via the debranching enzyme accounts for <10% of the total glucose made via gluconeogenesis.

AAT, alanine aminotransferase;
fruc-1,6-bisphosphatase, fructose-1,6-bisphosphatase;
glu-6-phosphatase, glucose-6-phosphatase;
glyceraldehyde-3-P, glyceraldehyde-3-phosphate;
glycerol-3-P, glycerol-3-phosphate;
LDH, lactate dehydrogenase;
OAA, oxaloacetate;
PC, pyruvate carboxylase;
PDH, pyruvate dehydrogenase
phosphoenolpyruvate carboxykinase (PEPCK)

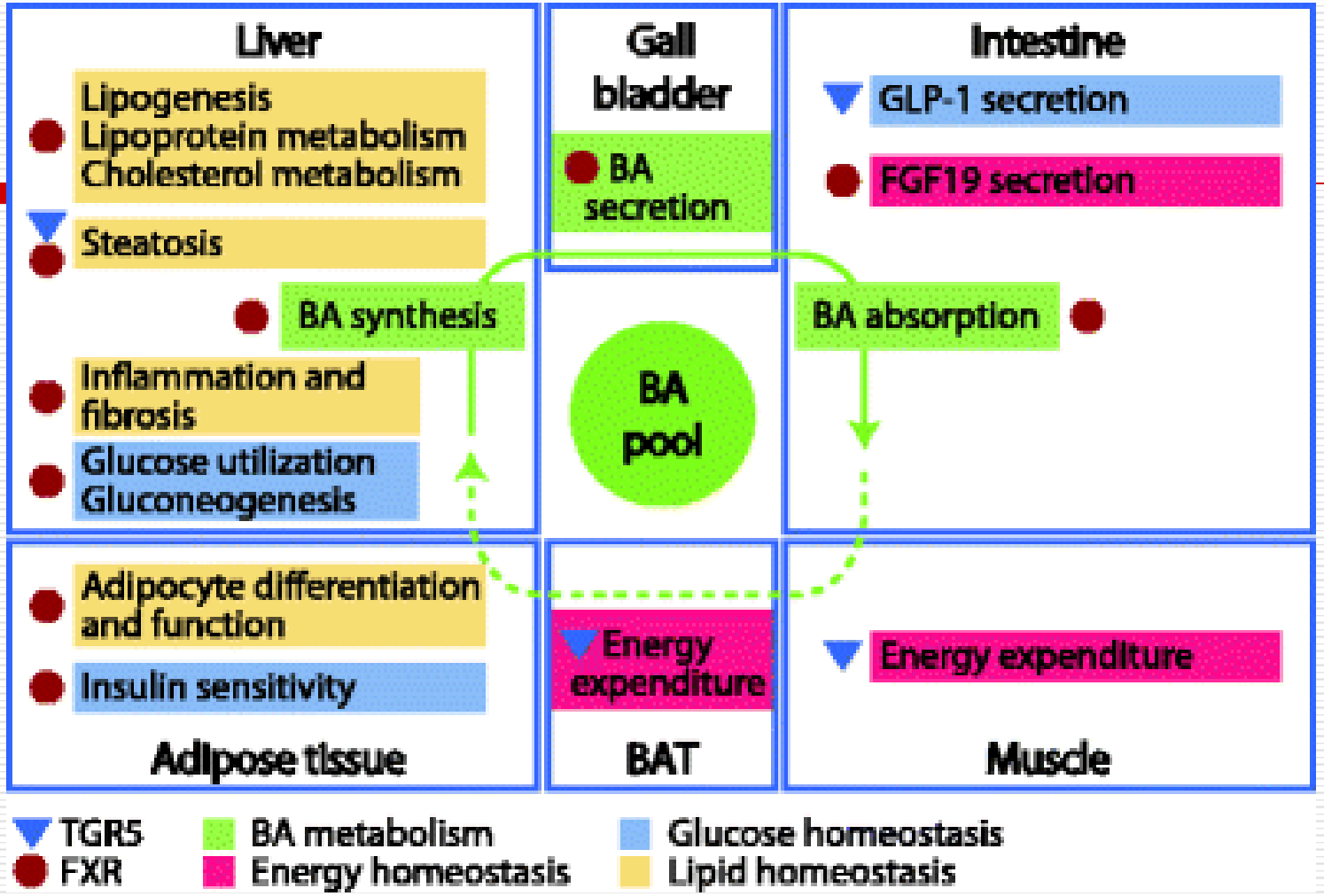
Lipids Synthesis



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

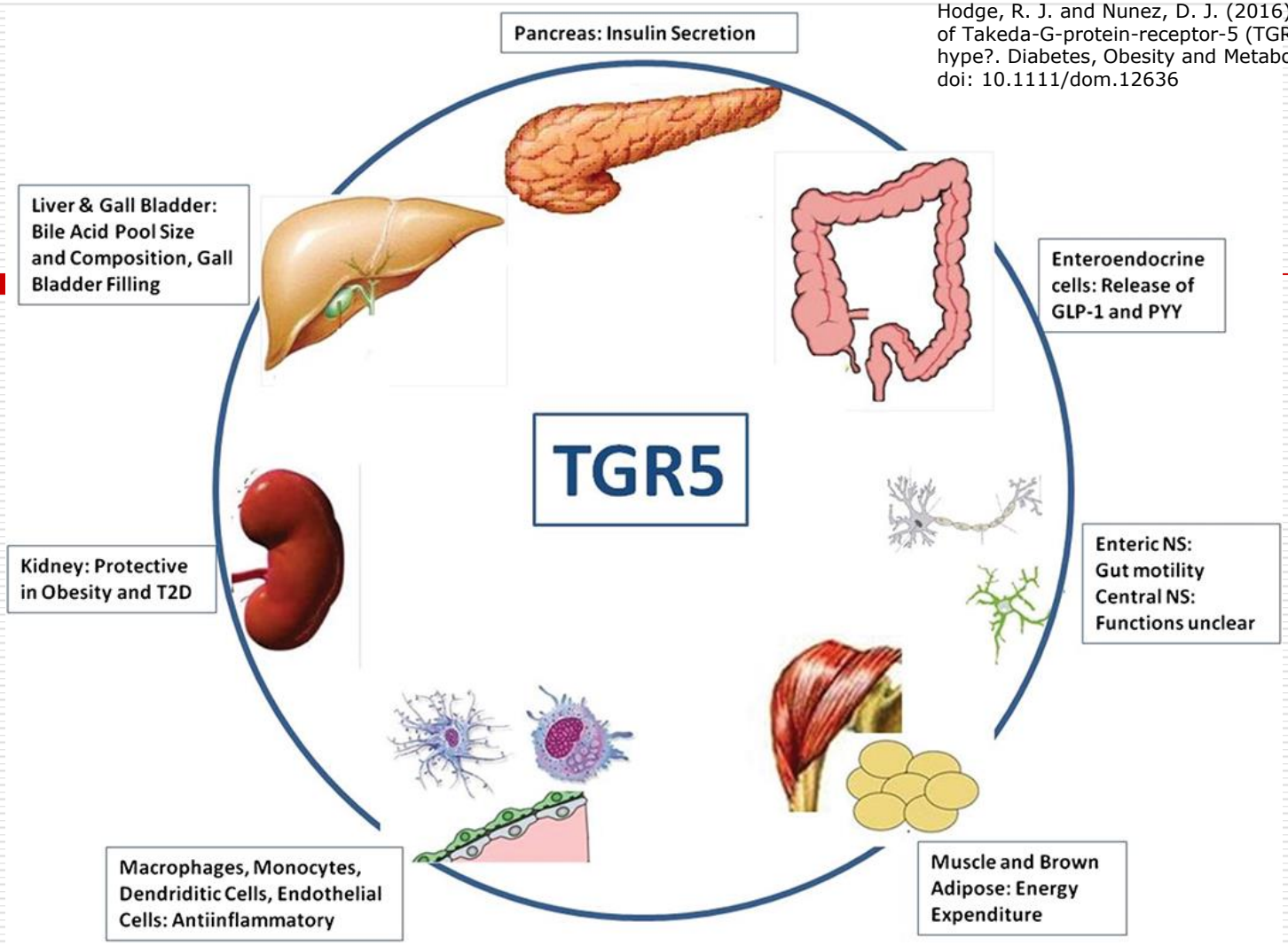


Cholesterol – the ways of excretion.
Biliary and non-biliary cholesterol.



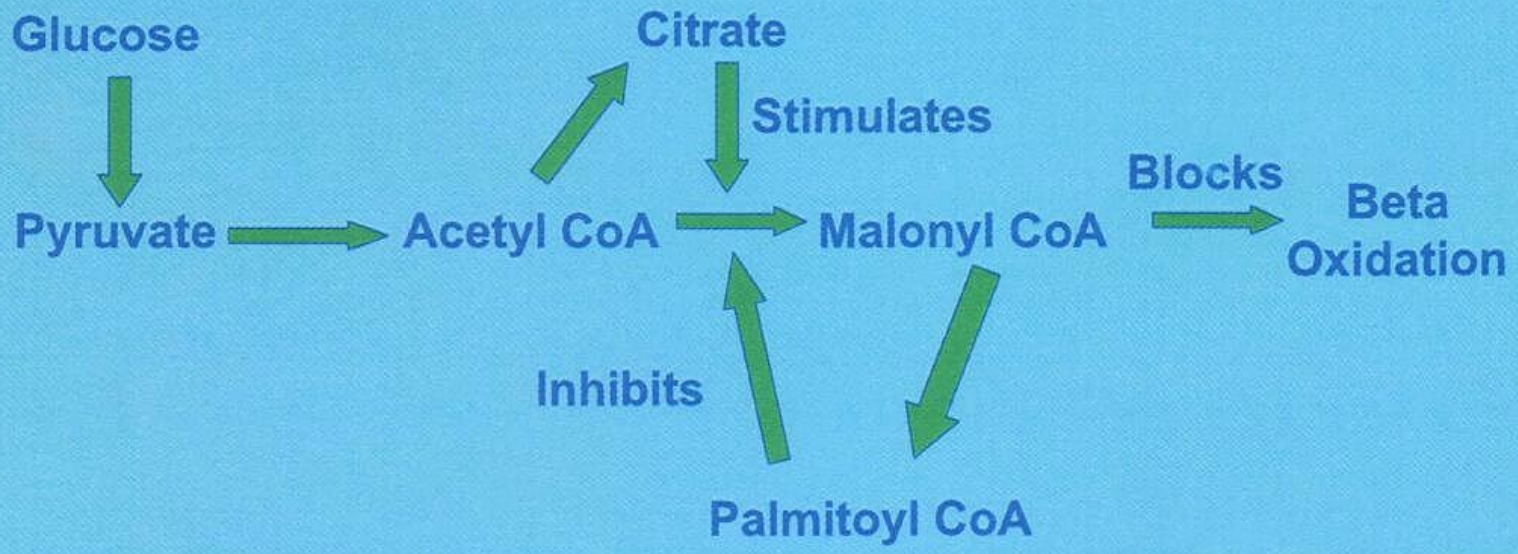
Functions of bile acids (BA) in regulation of BA, energy, glucose and lipid metabolism via farnesoid X receptor (FXR) and TGR5-mediated signaling pathways. BAT—brown adipose tissue; FGF—fibroblast growth factor; GLP-1—glucagon-like peptide 1

Hodge, R. J. and Nunez, D. J. (2016), Therapeutic potential of Takeda-G-protein-receptor-5 (TGR5) agonists. Hope or hype?. Diabetes, Obesity and Metabolism. doi: 10.1111/dom.12636



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

GM_2 (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

Other Gangliosidoses

Gaucher's disease:

Ceramide - O - Glucose

β-glucosidase

Fabry's disease:

Ceramide - O - Glucose - O - Galactose - O - Galactose

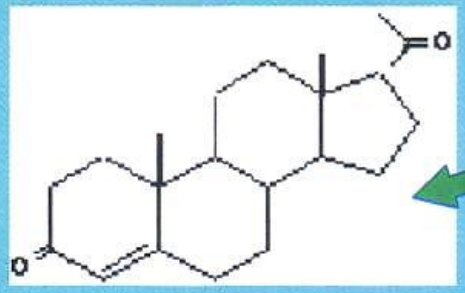
α-galactosidase

Nieman-Pick disease:

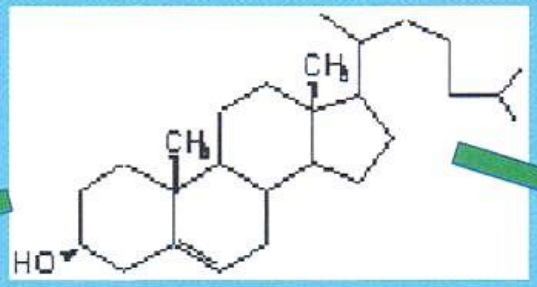
Ceramide - Phosphate - Choline

sphingomyelinase

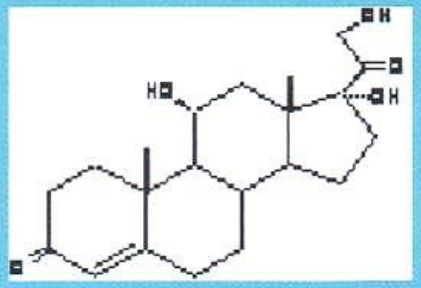
Transformations of Cholesterol: Steroid Hormones



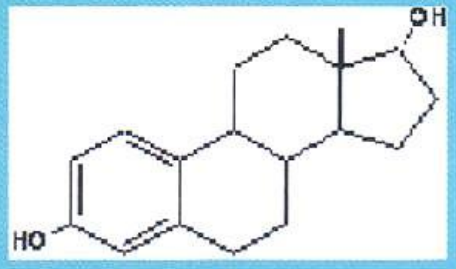
Progesterone



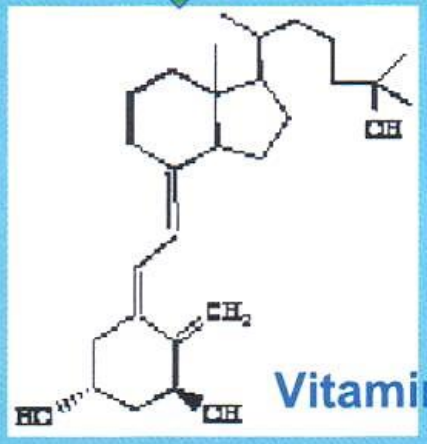
Cholesterol



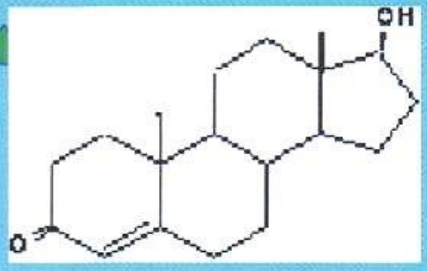
Cortisol



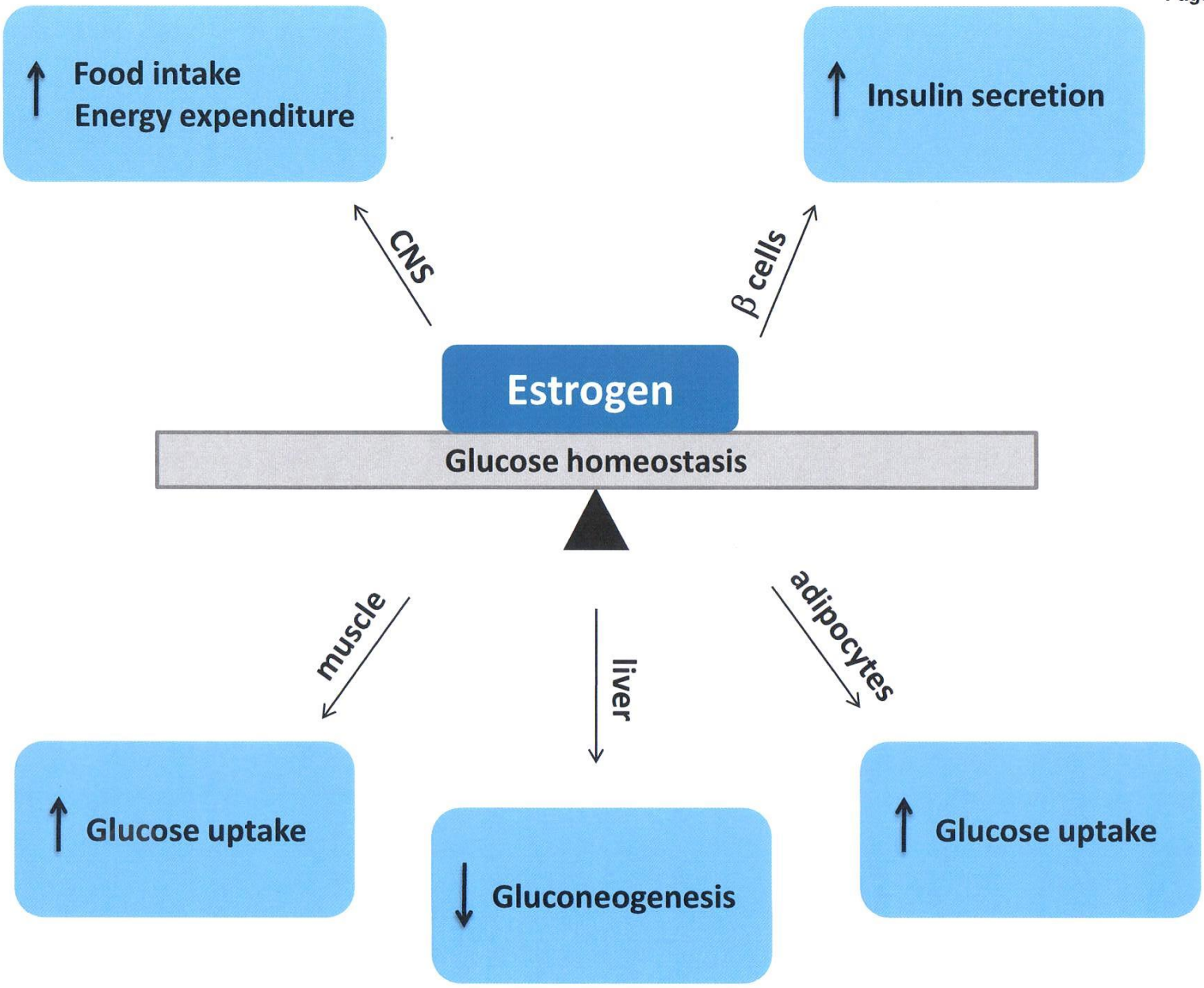
Estradiol



Vitamin D

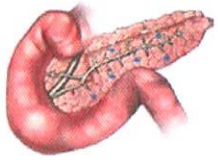


Testosterone


↑ Food intake
Energy expenditure
↑ Insulin secretion
CNS
β cells
Estrogen
Glucose homeostasis
muscle
liver
adipocytes
↑ Glucose uptake
↓ Gluconeogenesis
↑ Glucose uptake

Estrogen deficiency

INSULIN RESISTANCE

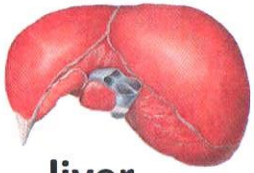


pancreatic β cells

Impaired insulin secretion

muscle

Impaired glucose uptake



liver

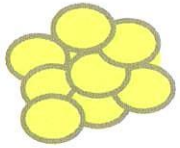
Increased gluconeogenesis

Increased lipogenesis

TG accumulation

Increased VLDL production

Decreased insulin clearance

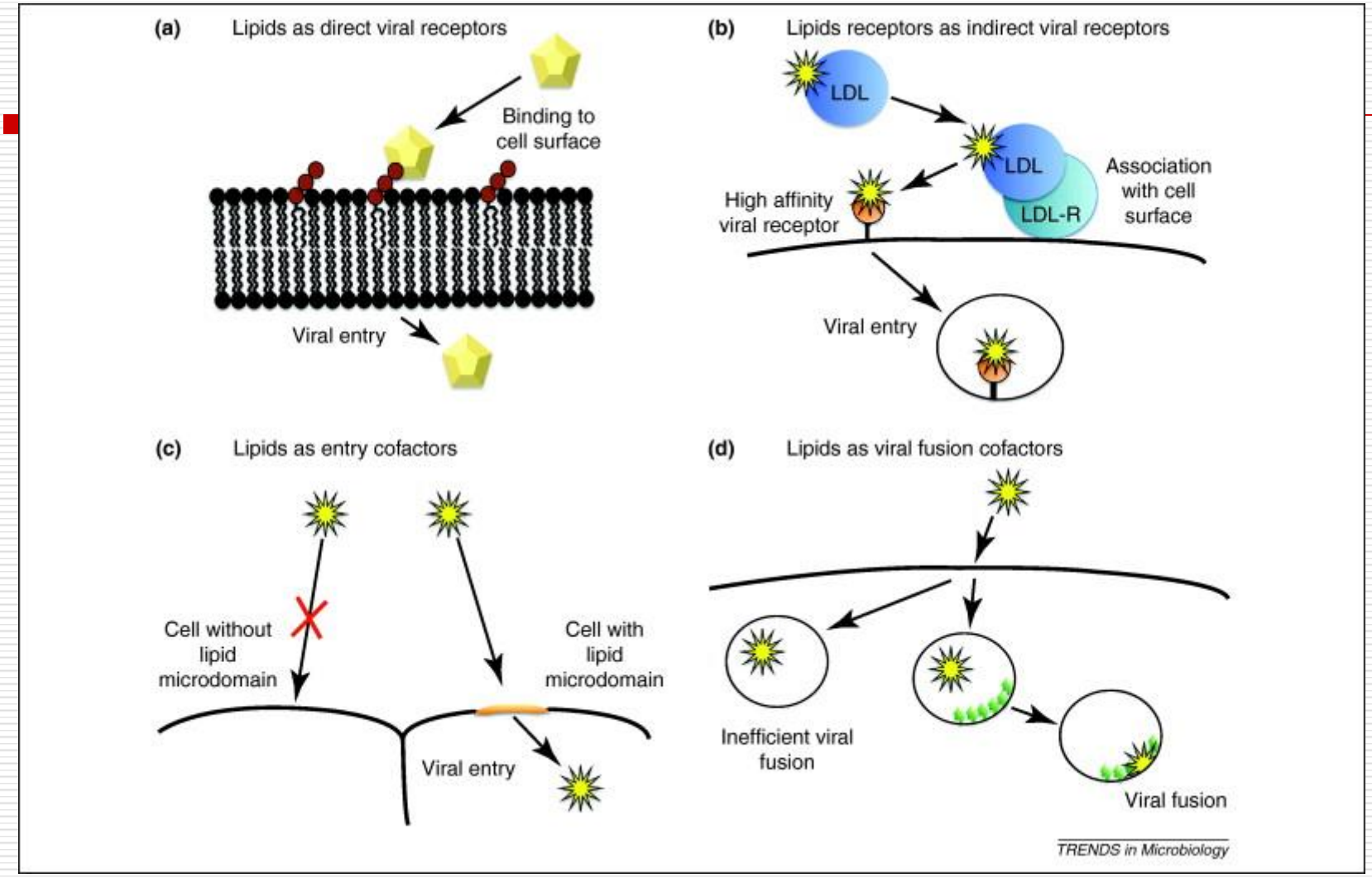


adipose tissue

Increased lipolysis

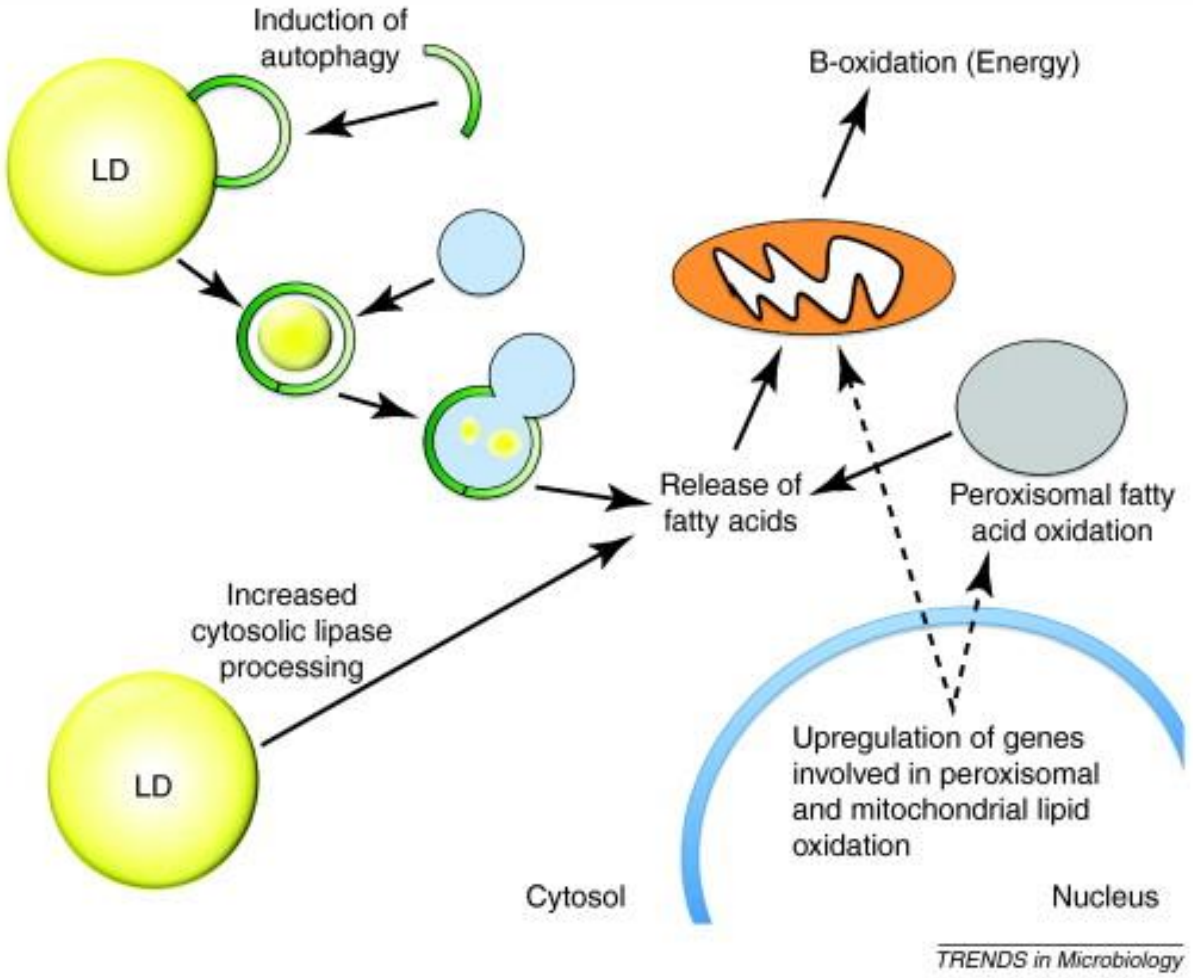
Increased adipocyte size

Inflammation


(a)
Lipids as direct viral receptors
Binding to cell surface
Viral entry
(b)
Lipids receptors as indirect viral receptors
LDL
LDL
LDL-R
Association with cell surface
High affinity viral receptor
Viral entry
(c)
Lipids as entry cofactors
Cell without lipid microdomain
Cell with lipid microdomain
Viral entry
(d)
Lipids as viral fusion cofactors
Inefficient viral fusion
Viral fusion
TRENDS in Microbiology

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.

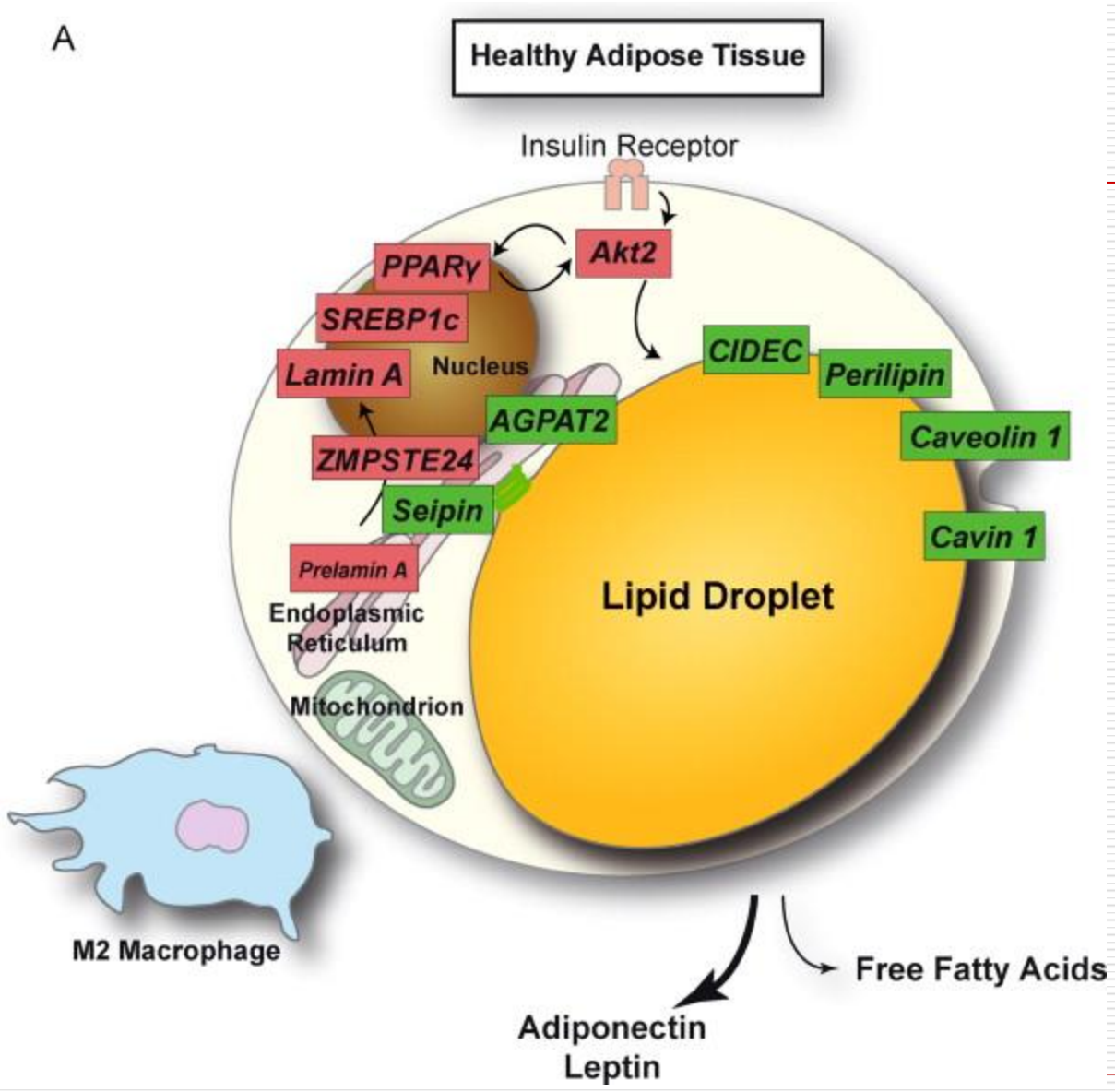

Induction of autophagy
LD
B-oxidation (Energy)
Release of fatty acids
Peroxisomal fatty acid oxidation
Increased cytosolic lipase processing
LD
Upregulation of genes involved in peroxisomal and mitochondrial lipid oxidation
Cytosol
Nucleus
TRENDS in Microbiology

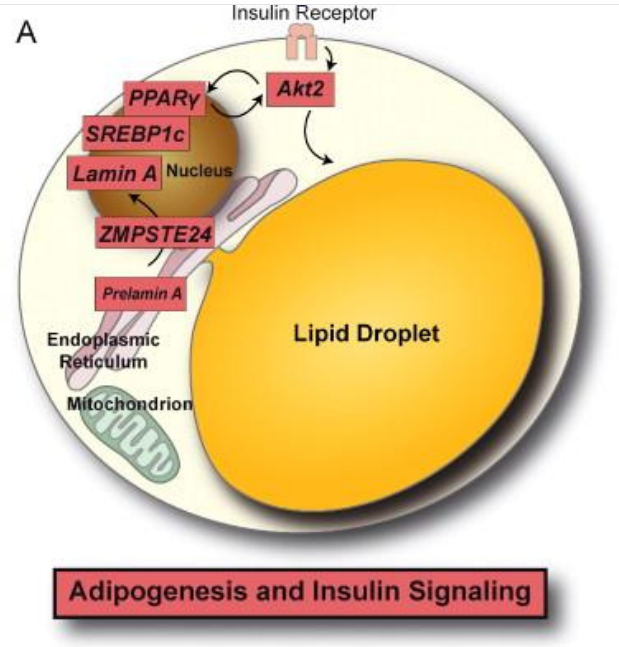
Lipodystrophies

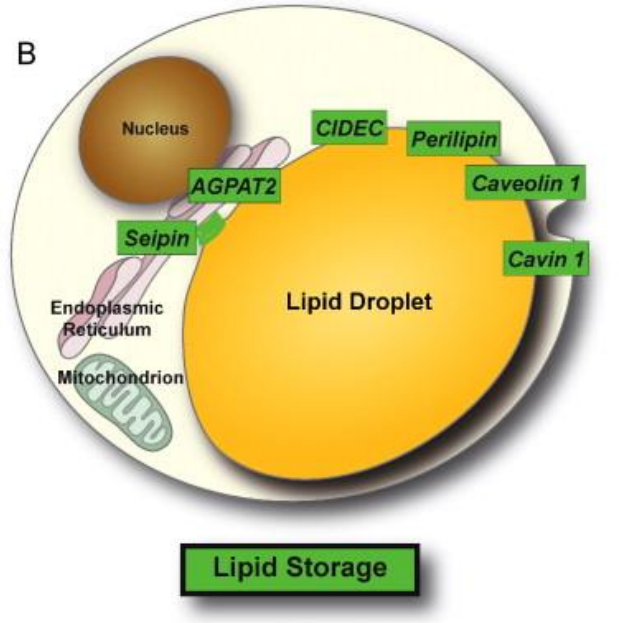
- Heterogenic group of diseases defined as localised or generalised loss of body fat.
- If localised, usually related with fat hypertrophy in other side of the body.
- Usually associated with sever metabolic changes including insulin resistance, dyslipidemia and glucose intolerance.

- Different phenotypes:
- Familiar parcial lipodystrophy, type Dunnigan (FPLD): fat reduction on the lower part of the body, hypetrophy 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
Insulin Receptor
Akt2
PPARγ
SREBP1c
Lamin A
Nucleus
ZMPSTE24
AGPAT2
Seipin
Prelamin A
Endoplasmic Reticulum
Mitochondrion
CIDEC
Perilipin
Caveolin 1
Cavin 1
Lipid Droplet
M2 Macrophage
Free Fatty Acids
Adiponectin
Leptin

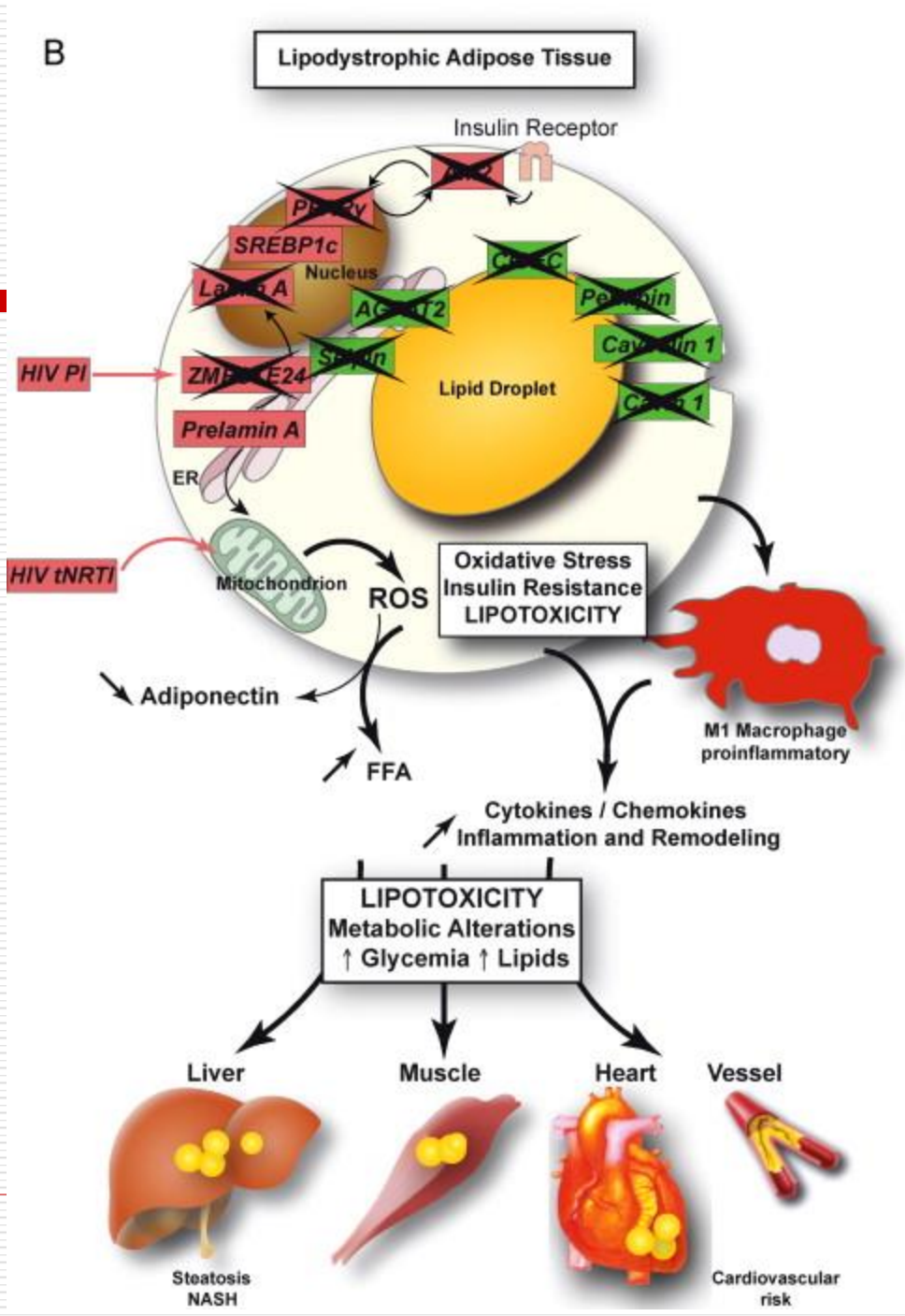




Cellular targets alterated by mutations in lipodystrophies

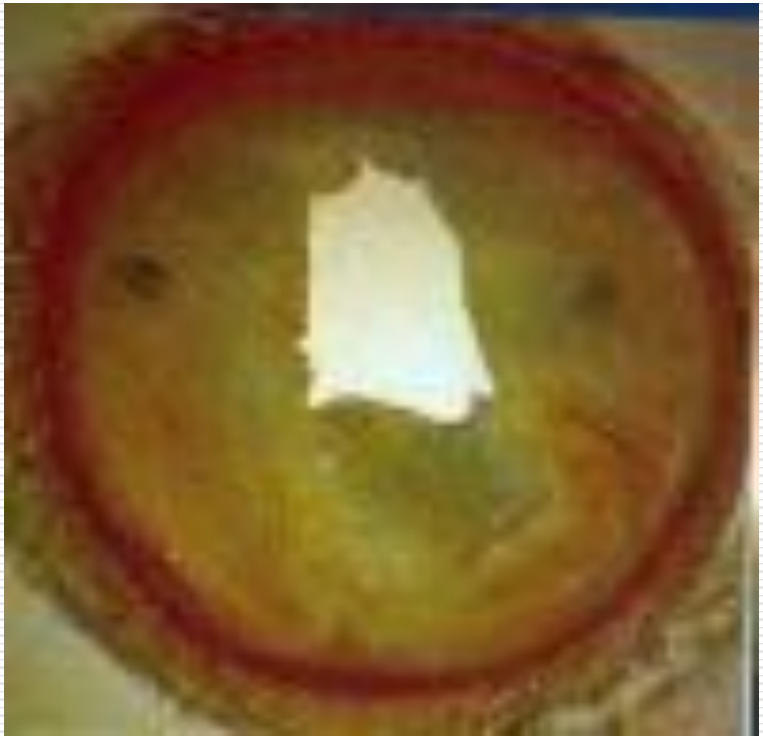
A: proteins taking part in adipogenesis at the level of nuclear DNA and in insulin signal trasnduction pathway

B: proteins of endoplasmatic reticulum and lipid droplets during fat storage


B
Lipodystrophic Adipose Tissue
Insulin Receptor
SREBP1c
Nucleus
Lipid Droplet
Perilipin
Caveolin 1
HIV PI
Prelamin A
ER
HIV tNRTI
Mitochondrion
ROS
Oxidative Stress
Insulin Resistance
LIPOTOXICITY
Adiponectin
FFA
M1 Macrophage
proinflammatory
Cytokines / Chemokines
Inflammation and Remodeling
LIPOTOXICITY
Metabolic Alterations
↑ Glycemia ↑ Lipids
Liver
Muscle
Heart
Vessel
Steatosis
NASH
Cardiovascular
risk

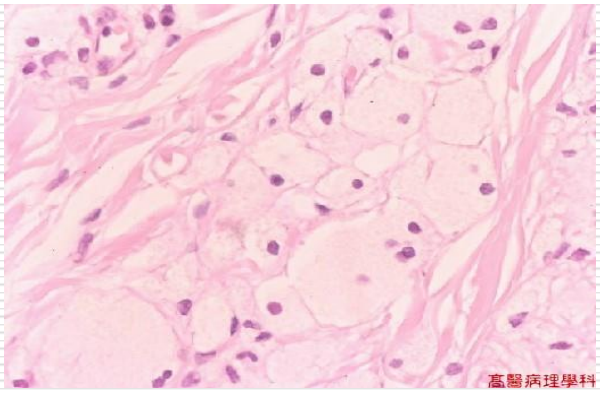
Hyperlipidemia Signs

- Atheroma- plaques in blood vessels



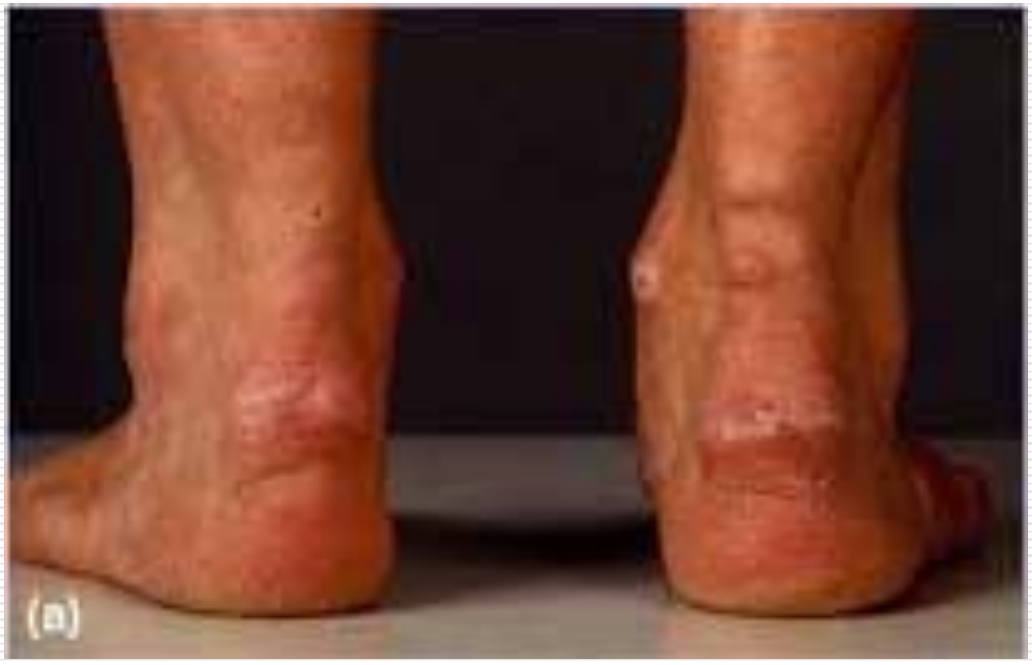
Hyperlipidemia signs

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



Tendenous Xanthoma

Xanthoma deposits in tendon, commonly the Achilles



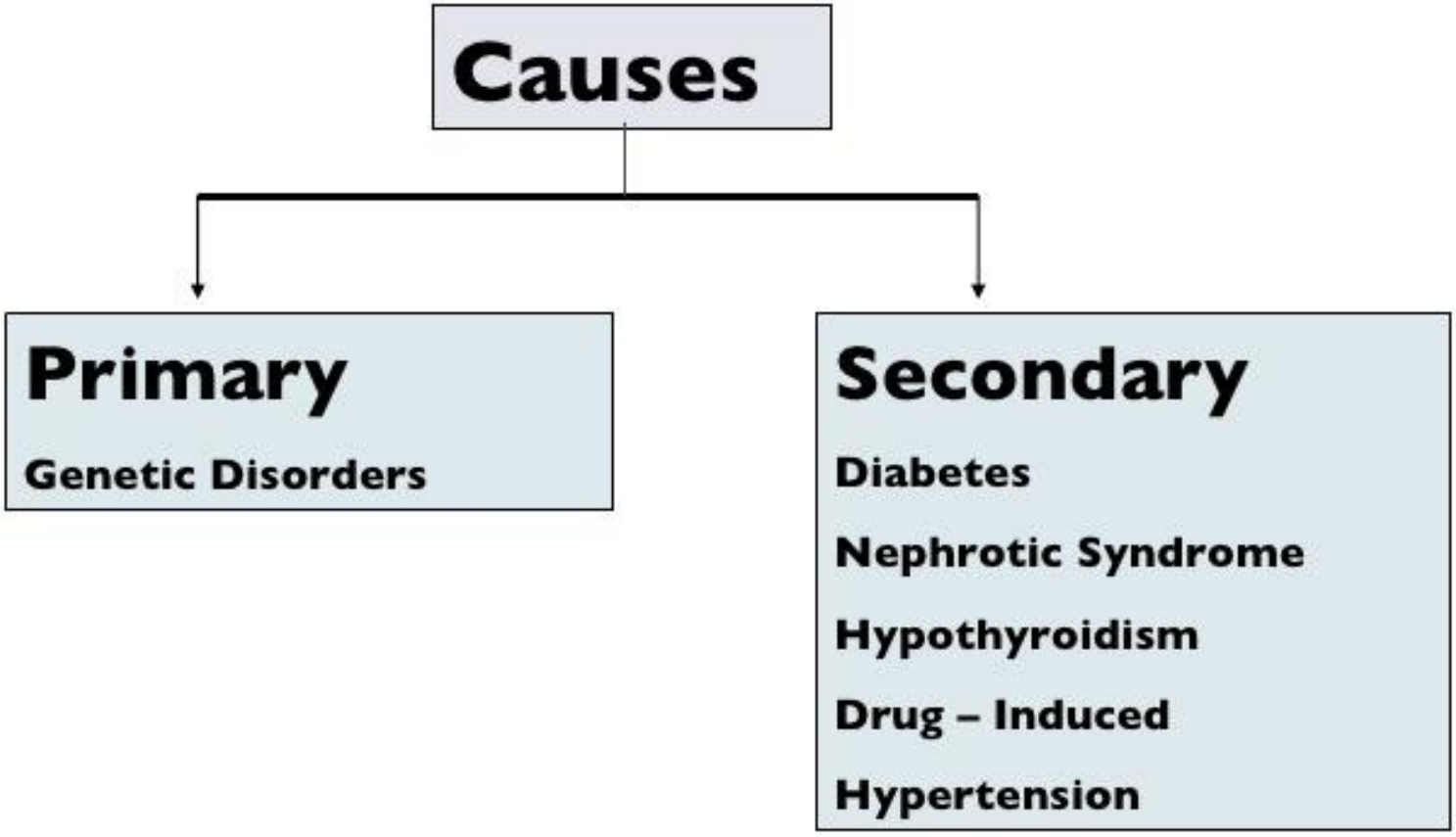
Corneal arcus

- 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



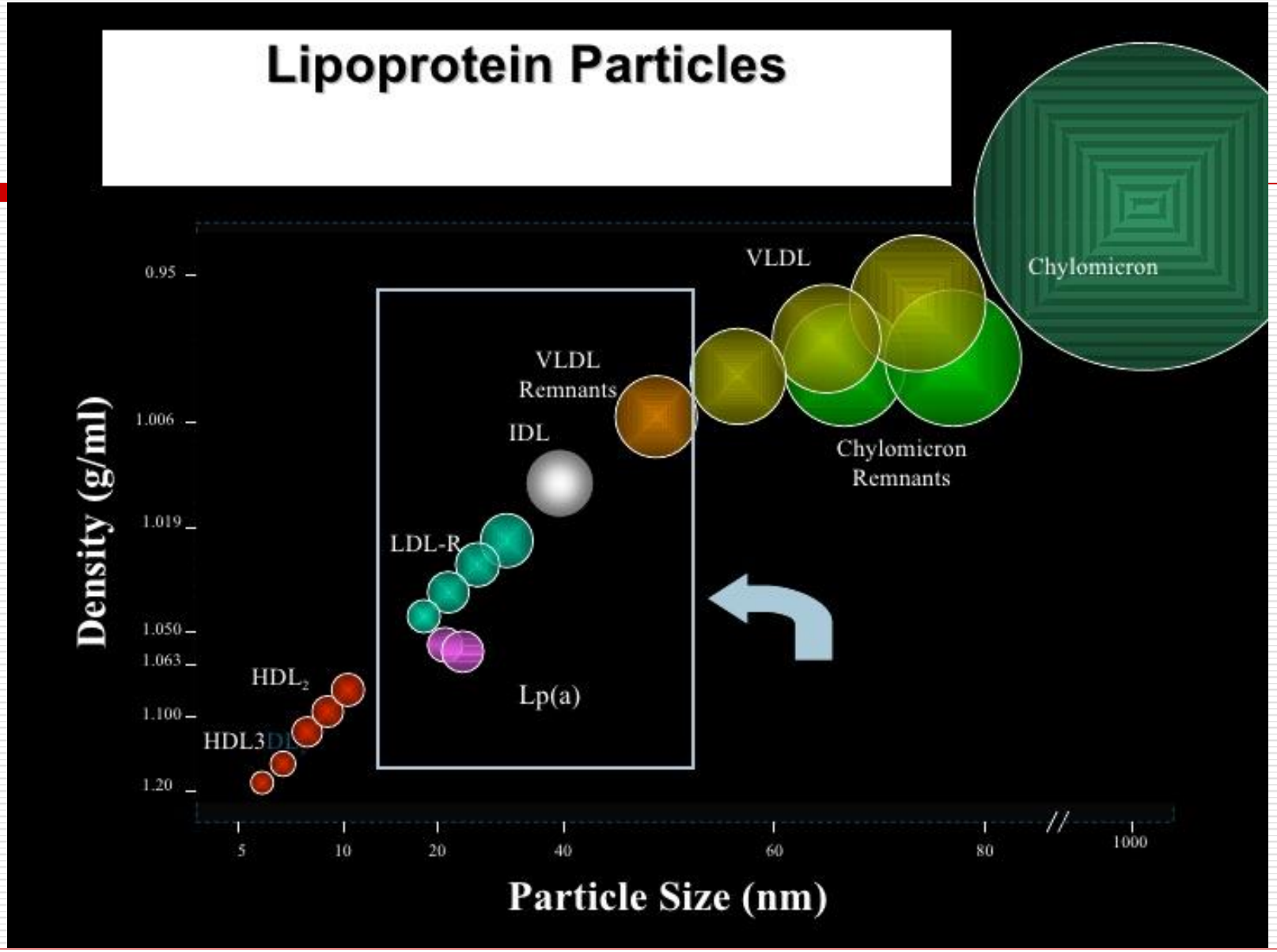
Secondary causes of Dyslipidemia

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

Practical Therapeutics, AFP, 1998


Lipoprotein Particles
VLDL
Chylomicron
VLDL
Remnants
IDL
Chylomicron
Remnants
LDL-R
Lp(a)
HDL2
HDL3
0.95
1.006
1.019
1.050
1.063
1.100
1.20
Density (g/ml)
5
10
20
40
60
80
1000
Particle Size (nm)

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 undetecable 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 AI_{Milano})
- Tangier's Disease
- CETP defects result in increased HDL

Thank you for your attention