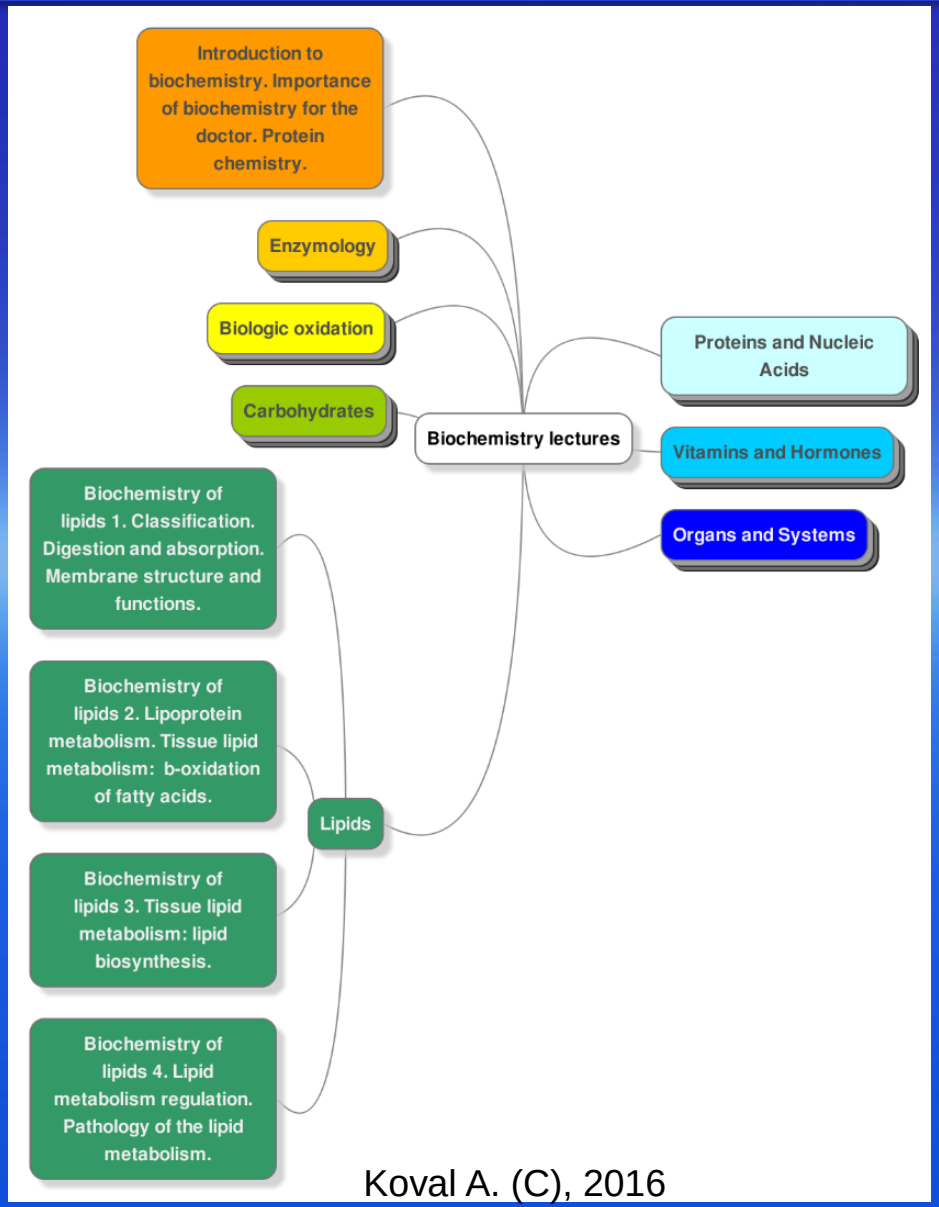
Biochemistry of Lipids

2

Tissue Lipid Metabolism:
β-oxidation of Fatty Acids

Lecturer Alexander N. Koval

The structure of the lecture course



Biochemistry of Lipids-2

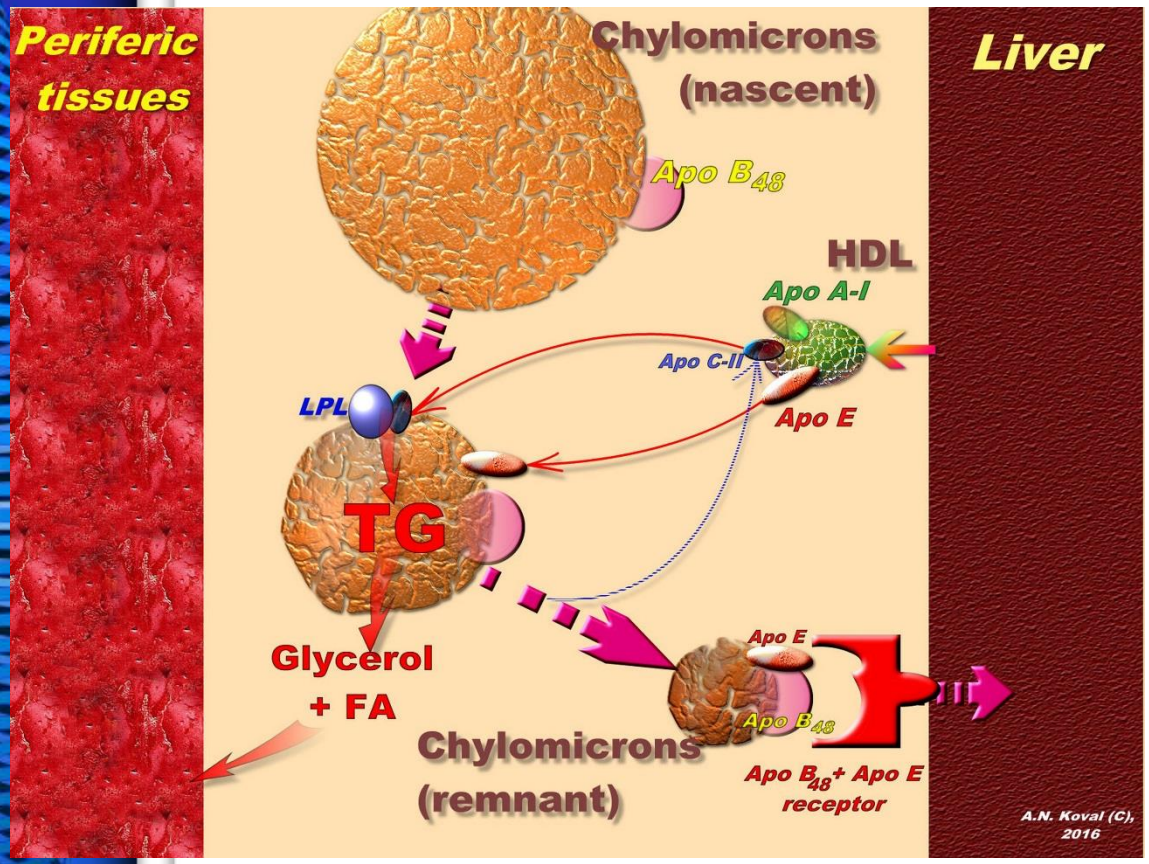
Tissue Lipid Metabolism:

1. β-oxidation of fatty acids
2. Ketone bodies metabolism
3. Acetyl-CoA metabolism

Contents

1. Transportation and absorption of free fatty acids (FFA) in blood.
2. The mechanism of fat mobilization (role of hormones, cAMP and Ca^{2+}).
3. Oxidation of triglycerids (TG) in tissue, oxidation of glycerol, its energy balance.
4. Stages of β-oxidation of saturated fatty acids.
   - ☞ The mechanism of activation and transport of fatty acids through mitochondrial membrane. Role of carnitine.
   - ☞ Features of β-oxidations of unsaturated fatty acids and fatty acids with an odd number of atoms.
   - ☞ The energy balance of oxidation of C_{16}, C_{15}, $C_{18:2}$.
   - ☞ The energy balance of tristearate oxidation.
   - ☞ Physiological role of FFA in stress.
5. Metabolism of Acetyl-CoA (pathways of formation and utilization).
6. Ketone bodies – biosynthesis, utilization, physiological role.

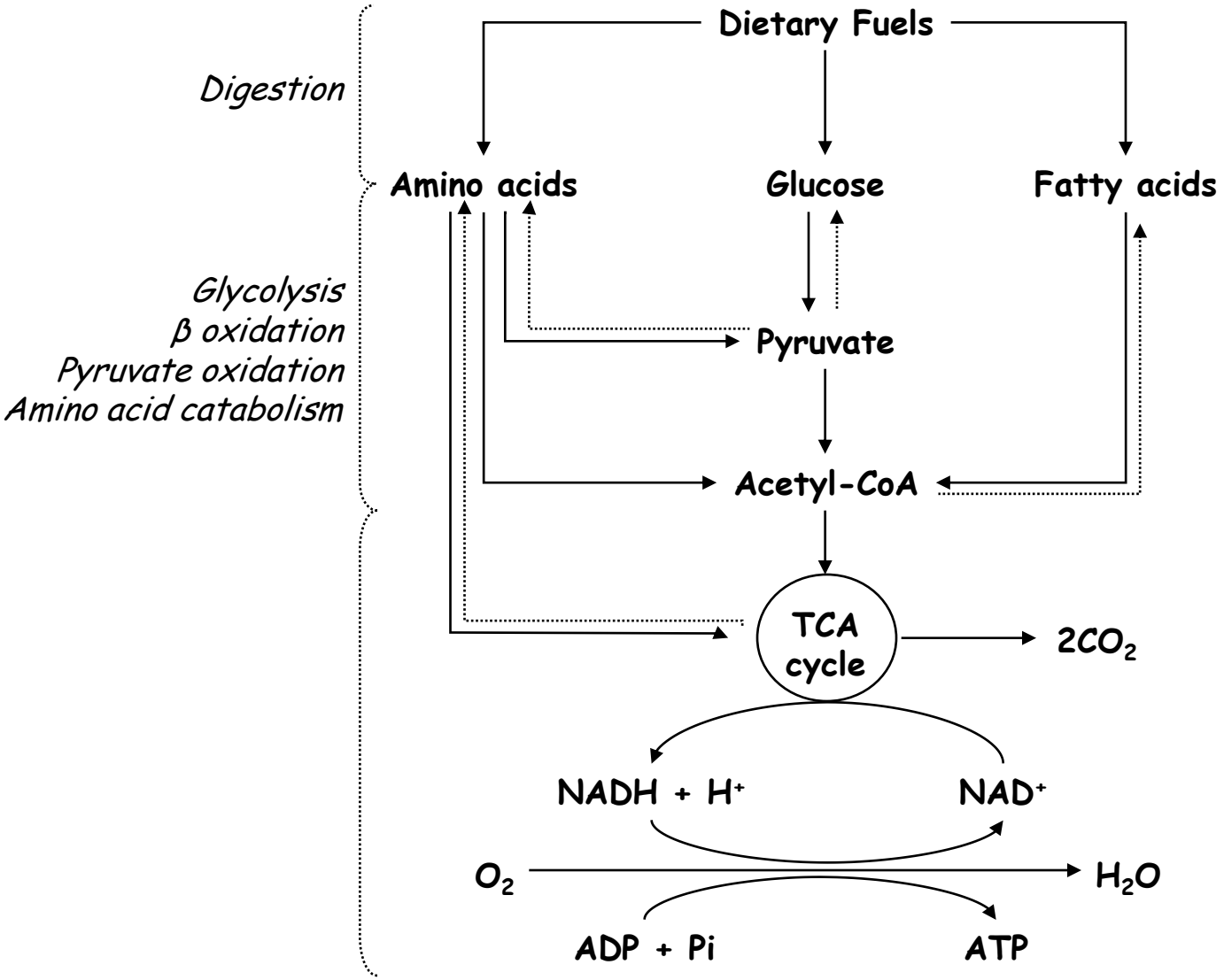
FFA Transportation and Absorption

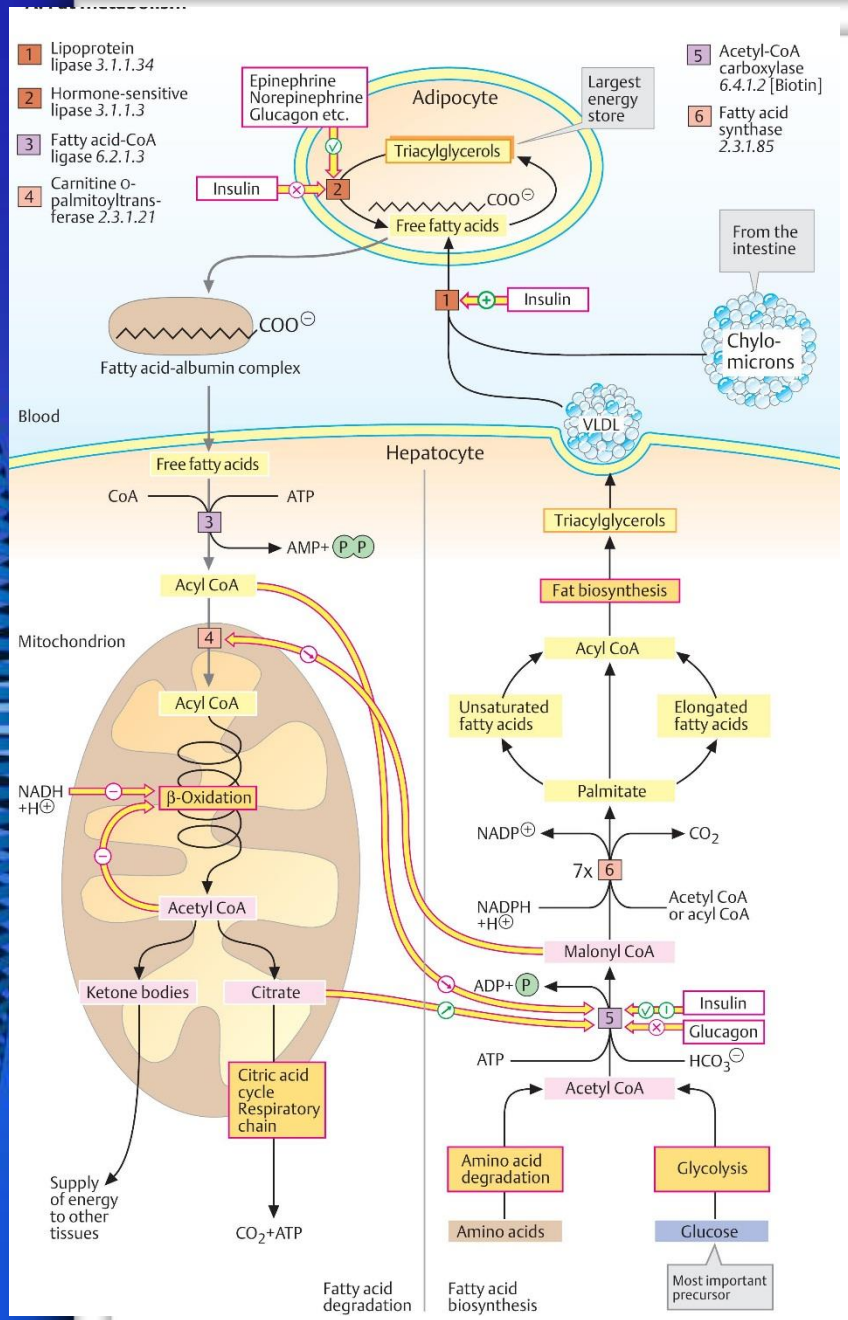


- The triacylglycerol components of VLDLs and chylomicrons are hydrolyzed to **free fatty acids** and **glycerol** in the capillaries of adipose tissue and skeletal muscle by the action of *lipoprotein lipase (LPL)*.

- The free fatty acids are then absorbed by the cells and the glycerol is returned via the blood to the liver (and kidneys).
- The glycerol is then converted to the glycolytic intermediate DHAP.

An overview of tissue metabolism

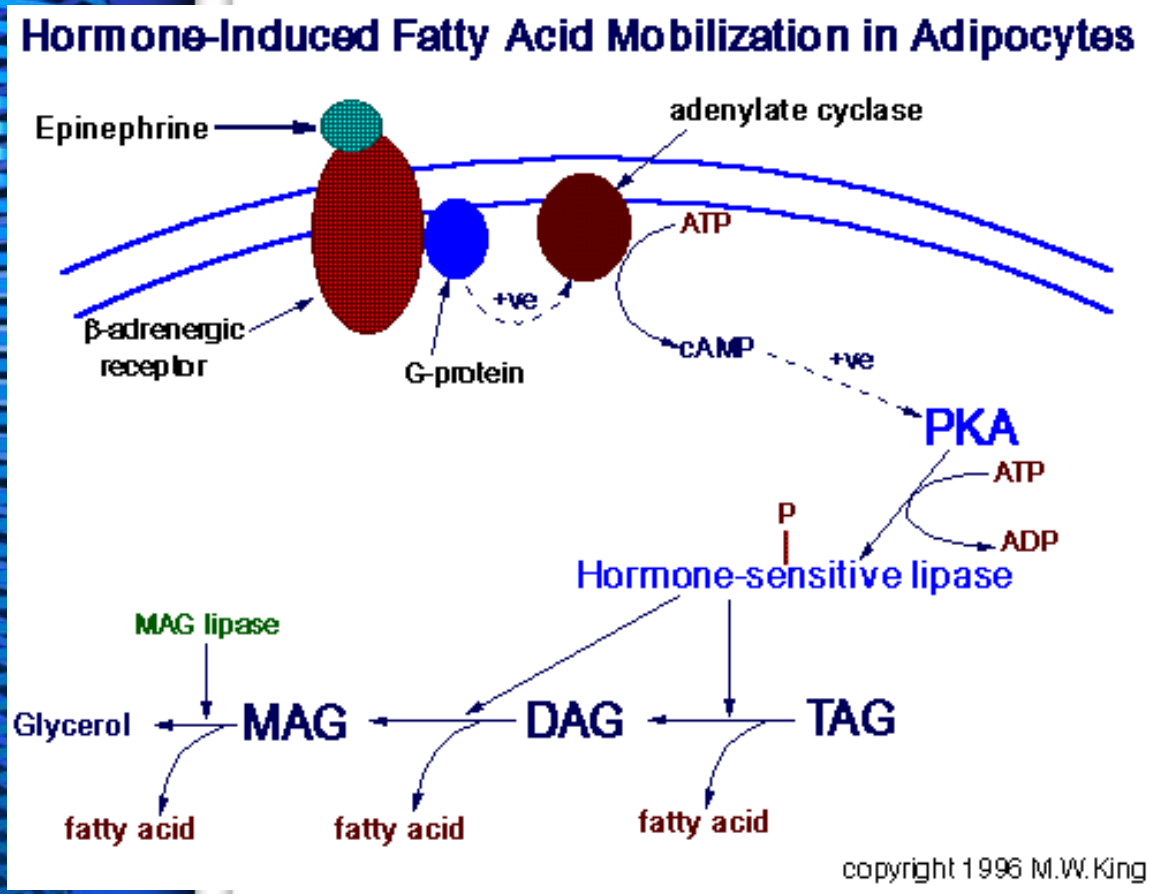




Fat Metabolism

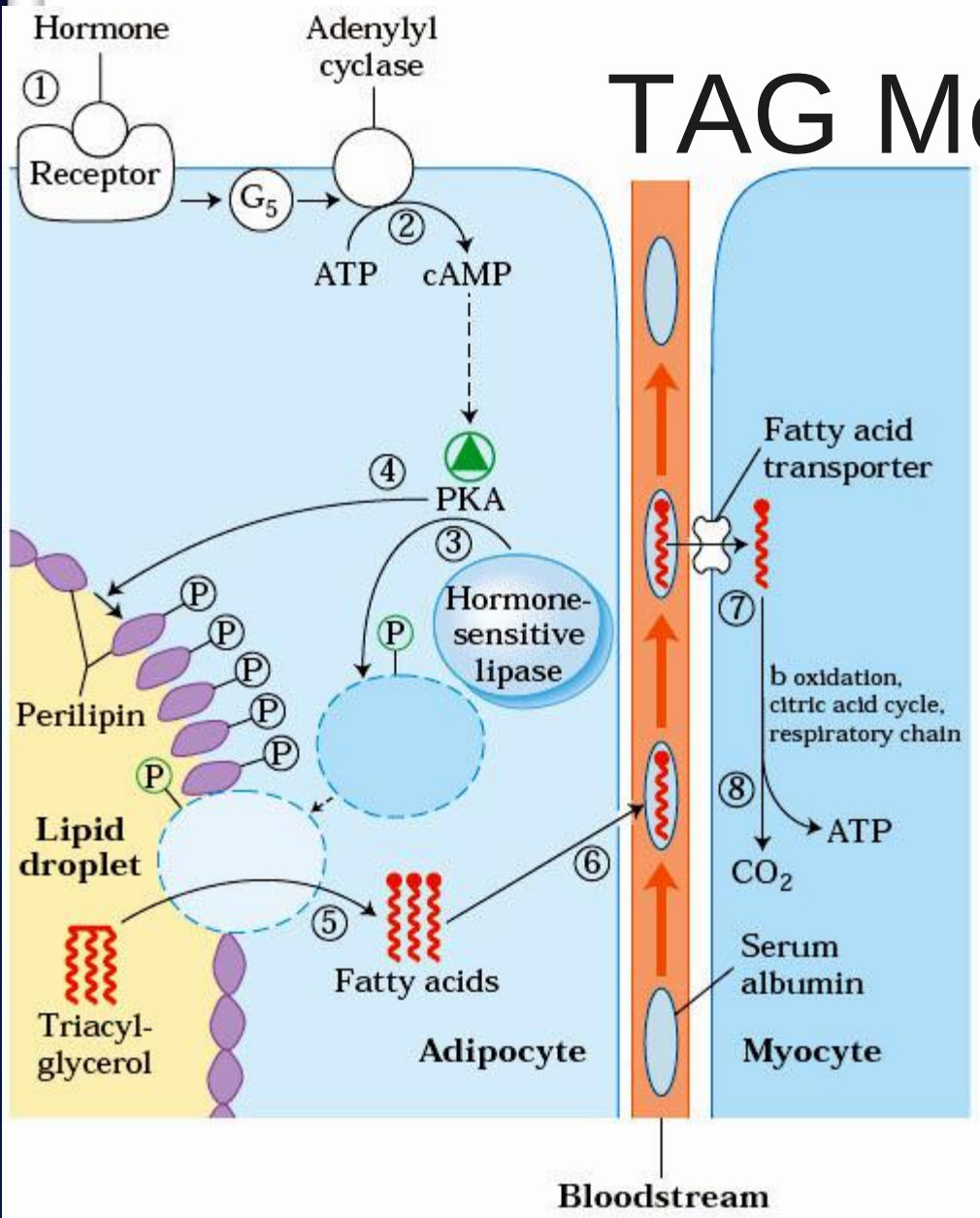
- Fats (triacylglycerols) are the most important energy reserve in the animal organism.
- They are mostly stored in insoluble form in the cells of adipose tissue – the *adipocytes* – where they are constantly being synthesized and broken down again.

Model for the Activation of Hormone-Sensitive Lipase by Epinephrine



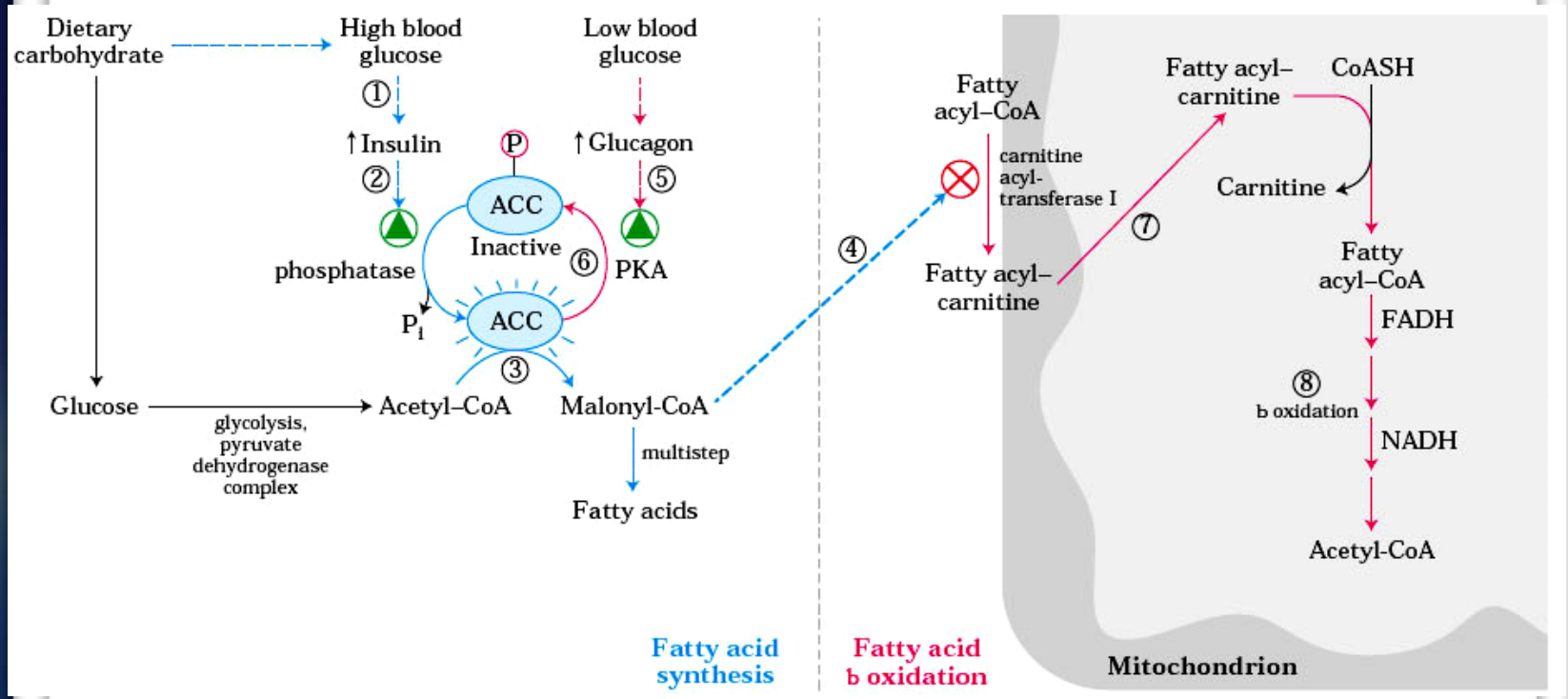
- Epinephrine binds its' receptor and leads to the activation of adenylate cyclase.
- The resultant increase in cAMP activates PKA which then phosphorylates and activates hormone-sensitive lipase.
- Hormone-sensitive lipase hydrolyzes fatty acids from triacylglycerols and diacylglycerols.
- The final fatty acid is released from monoacylglycerols through the action of monoacylglycerol lipase, an enzyme active in the absence of hormonal stimulation.

TAG Mobilization



- Low levels of glucose in the blood trigger the release of glucagon,
- the hormone binds its receptor in the adipocyte membrane and thus
- stimulates adenylyl cyclase, via a G protein, to produce cAMP.
- This activates PKA, which phosphorylates the hormone-sensitive lipase and
- perilipin molecules on the surface of the lipid droplet.
- Phosphorylation of perilipin permits hormonesensitive lipase access to the surface of the lipid droplet, where
- it hydrolyzes triacylglycerols to free fatty acids.
- Fatty acids leave the adipocyte, bind serum albumin in the blood, and are carried in the blood; they are released from the albumin and
- enter a myocyte via a specific fatty acid transporter.
- In the myocyte, fatty acids are oxidized to CO_2, and the energy of oxidation is conserved in ATP, which fuels muscle contraction and other energy requiring metabolism in the myocyte.

Hormonal Regulation of Fatty Acid Metabolism

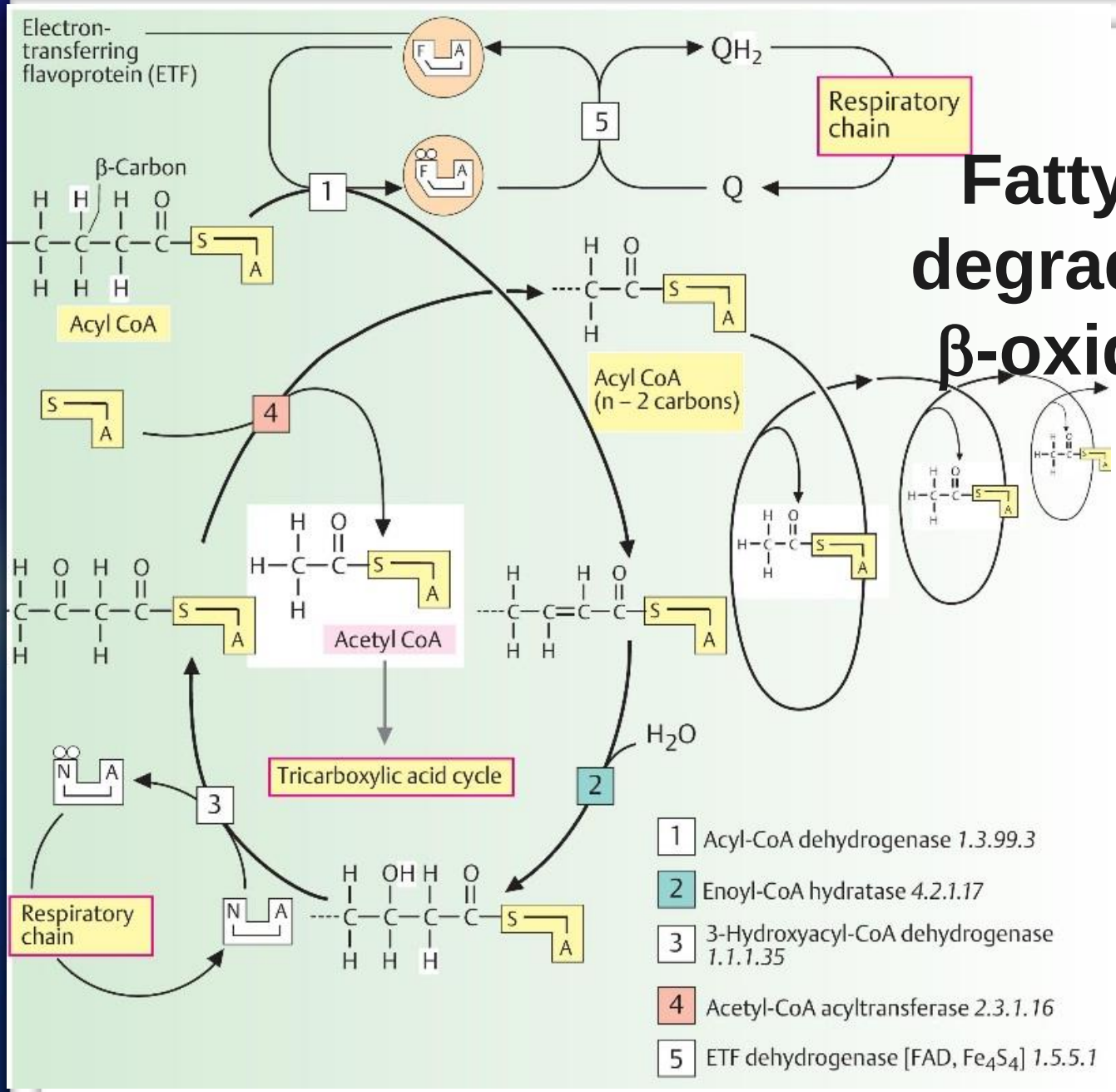


β-Oxidation of Fatty Acids & Ketone Bodies Metabolism

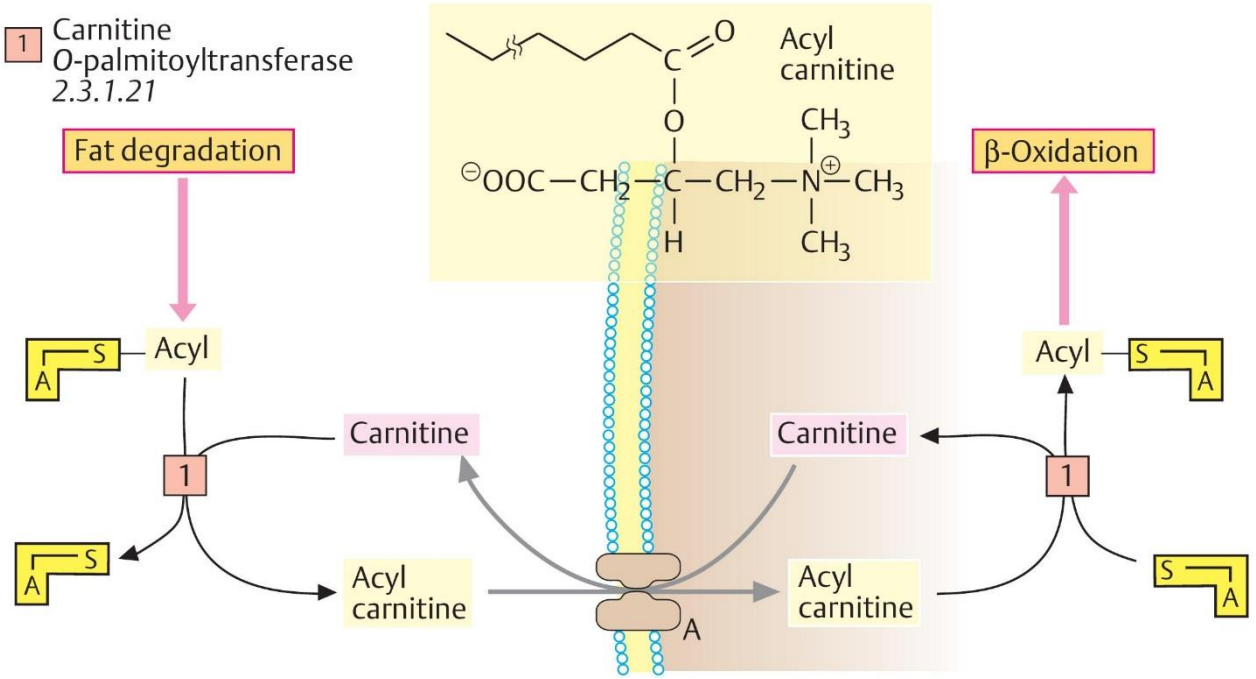
Reactions of Oxidation

- Fatty acids must be activated in the cytoplasm before being oxidized in the mitochondria.
- Activation is catalyzed by fatty **acyl-CoA ligase** (also called **acyl-CoA synthetase** or **thiokinase**).
- The net result of this activation process is the consumption of 2 molar equivalents of ATP.
- **Fatty acid + ATP + CoA -----> Acyl-CoA + PP_i + AMP**

Fatty acid degradation: β-oxidation

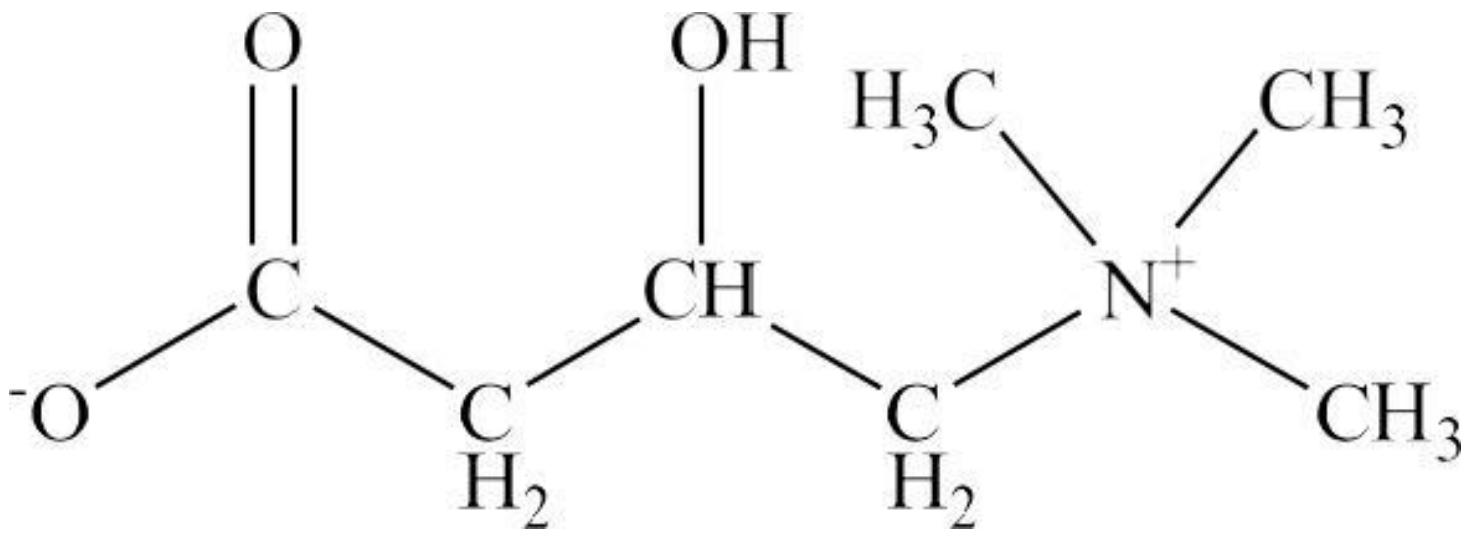


Transport of Fatty Acyl-CoA



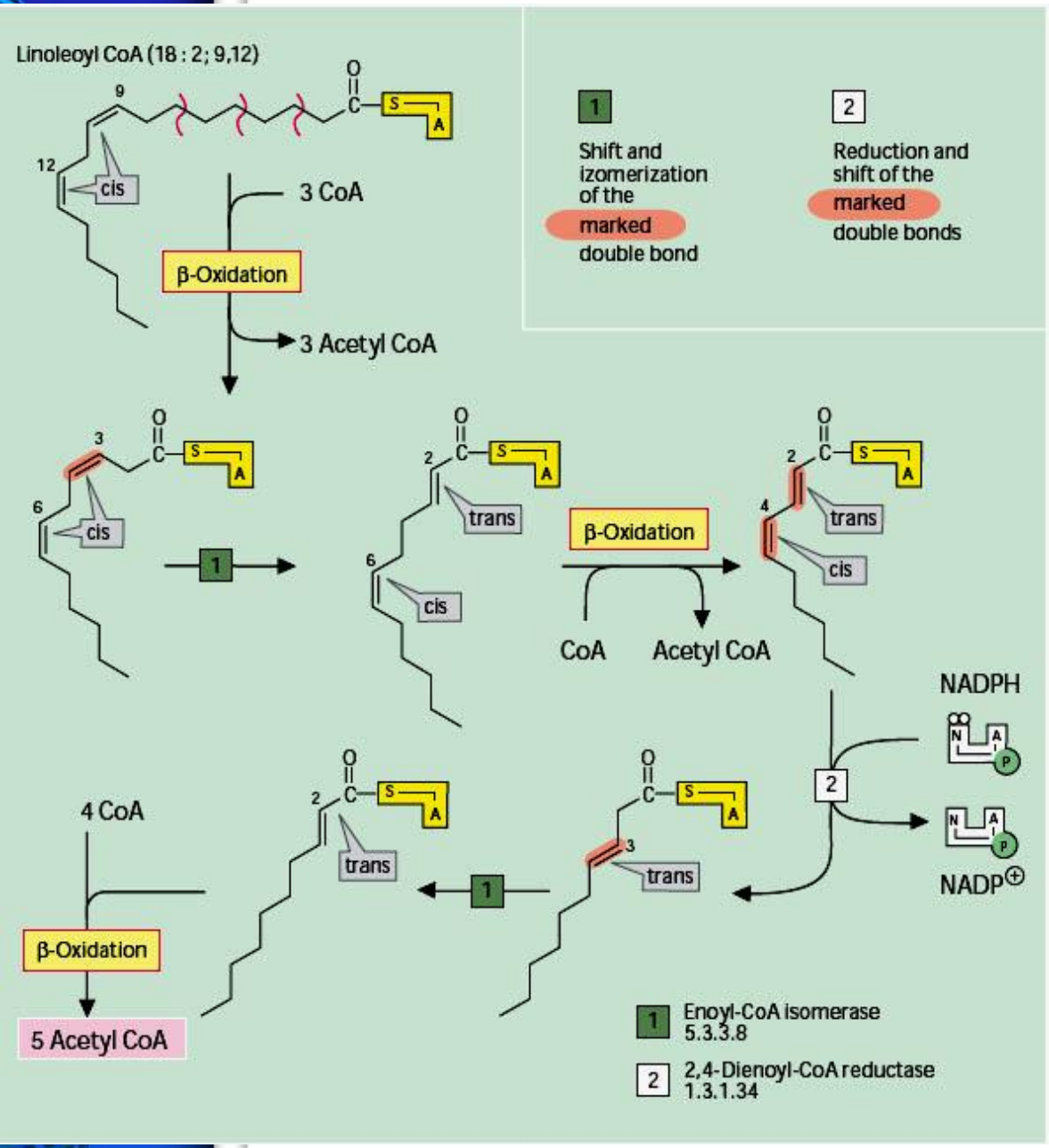
- Oxidation of fatty acids occurs in the mitochondria.
- **Acyl-carnitine** is the transport form of fatty acyl-CoA into the mitochondria
  - enzyme - *carnitine acyltransferase I*,
  - resides in the outer mitochondrial membrane.
- In the mitochondria another enzyme *carnitine acyltransferase II* catalyzes the regeneration of the fatty acyl-CoA molecule.

Carnitine



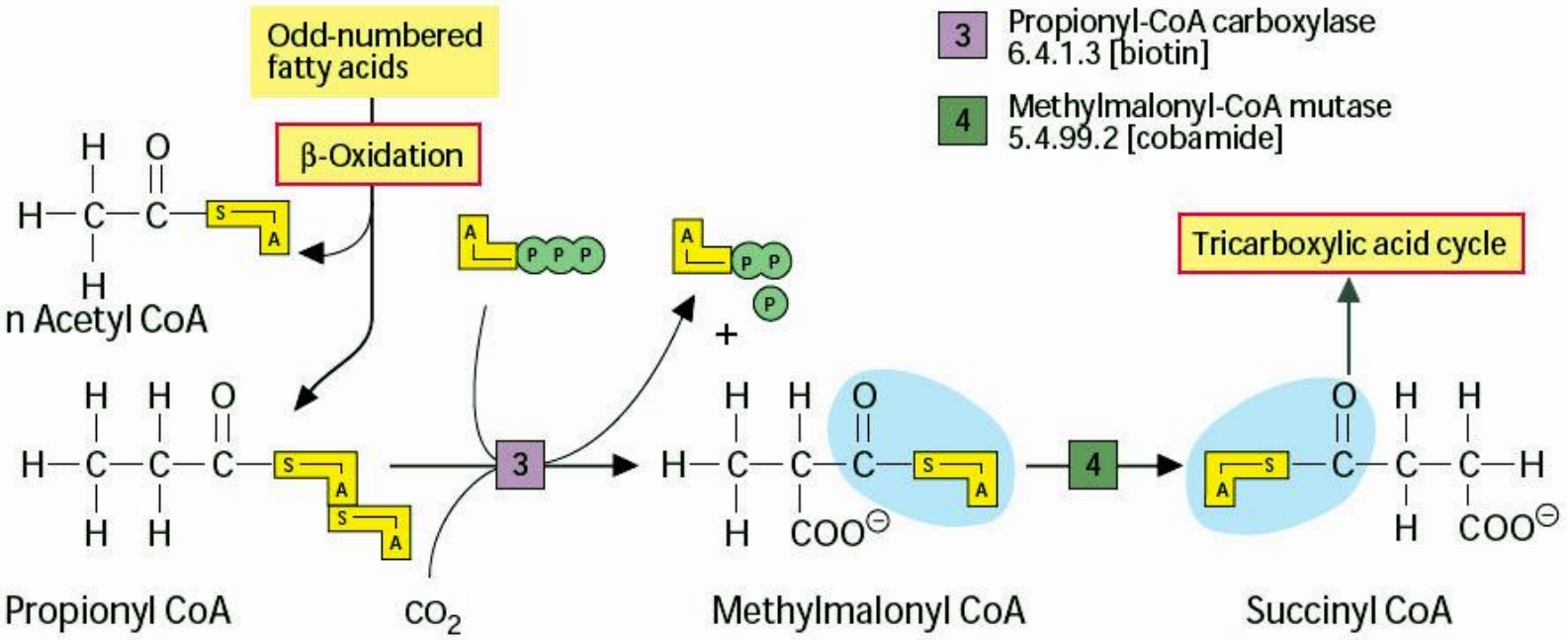
- Activated long-chain fatty acids are transported across the membrane by conjugating them to *carnitine*, a zwitterionic alcohol.
- The acyl group is transferred from the sulfur atom of CoA to the hydroxyl group of carnitine to form *acyl carnitine*.

Degradation of unsaturated fatty acids



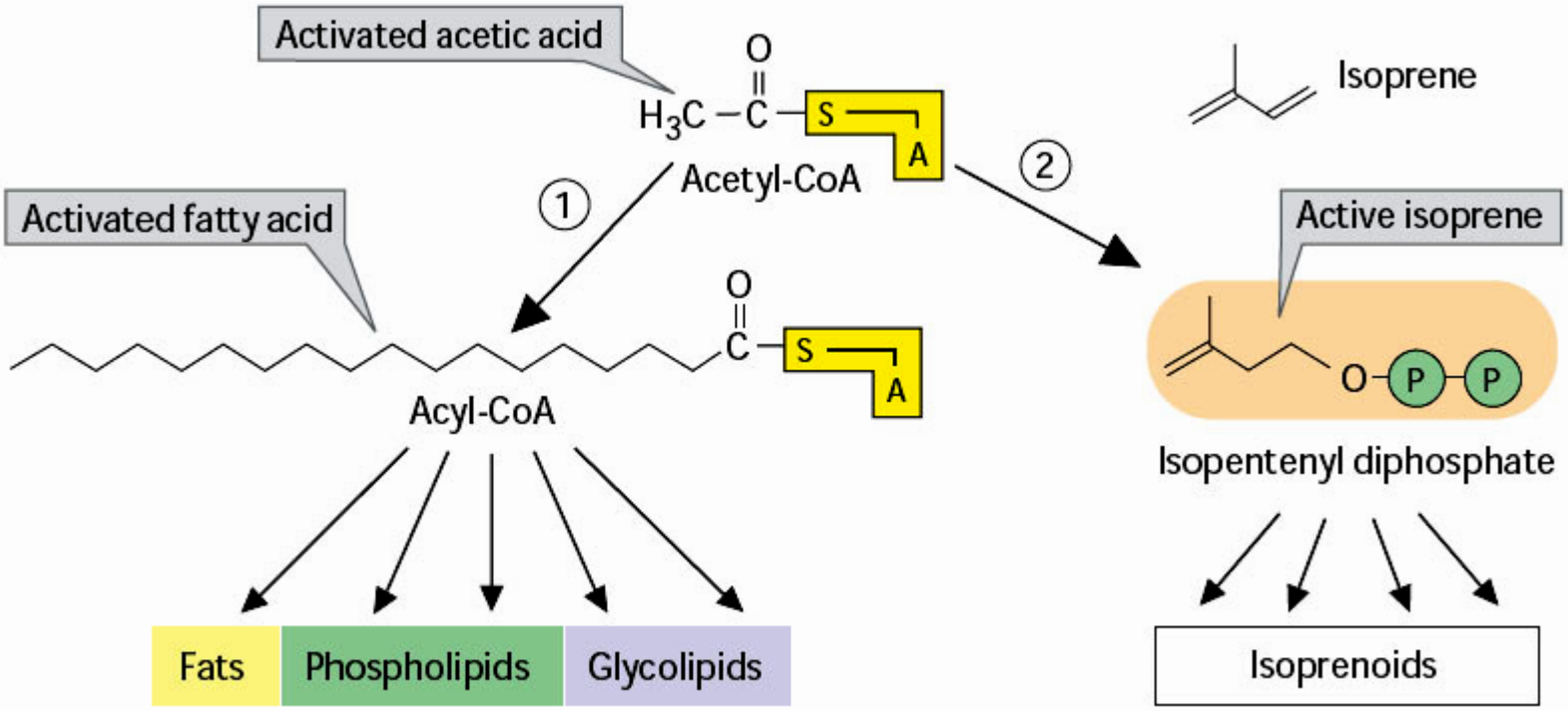
- Unsaturated fatty acids usually contain a *cis* double bond at position 9 or 12 - e. g., linoleic acid (18:2; 9,12).
- Degradation occurs via β-oxidation until the C-9-*cis* double bond is reached.
- Enoyl-CoA is converted by an isomerase from the *cis*-Δ3, *cis*- Δ6 isomer into the *trans*-Δ3,*cis*-Δ6 isomer.
- Degradation continue until a shortened *trans*-Δ2, *cis*-Δ4 derivative occurs in the next cycle.
- This is reduced in an NADPH-dependent way to the *trans*-Δ3 compound.
- After rearrangement by *enoyl-CoA isomerase*, degradation can finally be completed via normal β-oxidation.

Degradation of odd-numbered fatty acids

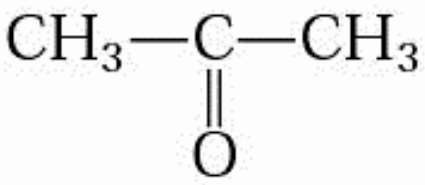


- Fatty acids with an odd number of C atoms are broken down by β−oxidation.
- In the last step, **propionyl CoA** arises instead of acetyl CoA.
- This is first carboxylated by *propionyl CoA carboxylase* into ***(S)*-methylmalonyl CoA**, which – after isomerization into the (*R*) enantiomer (not shown) – is isomerized into **succinyl CoA.**

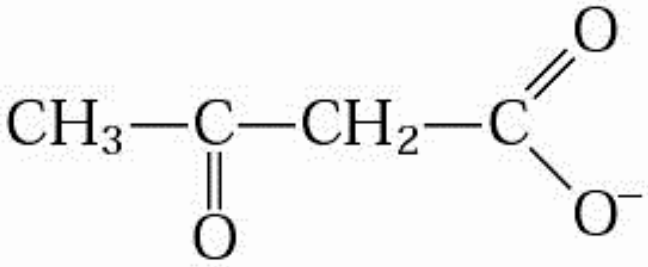
Acetyl-CoA Metabolism



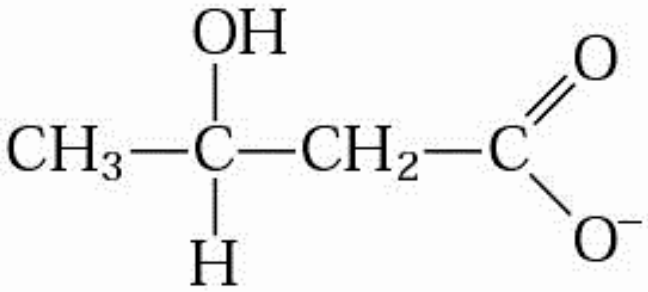
Ketone Bodies



Acetone



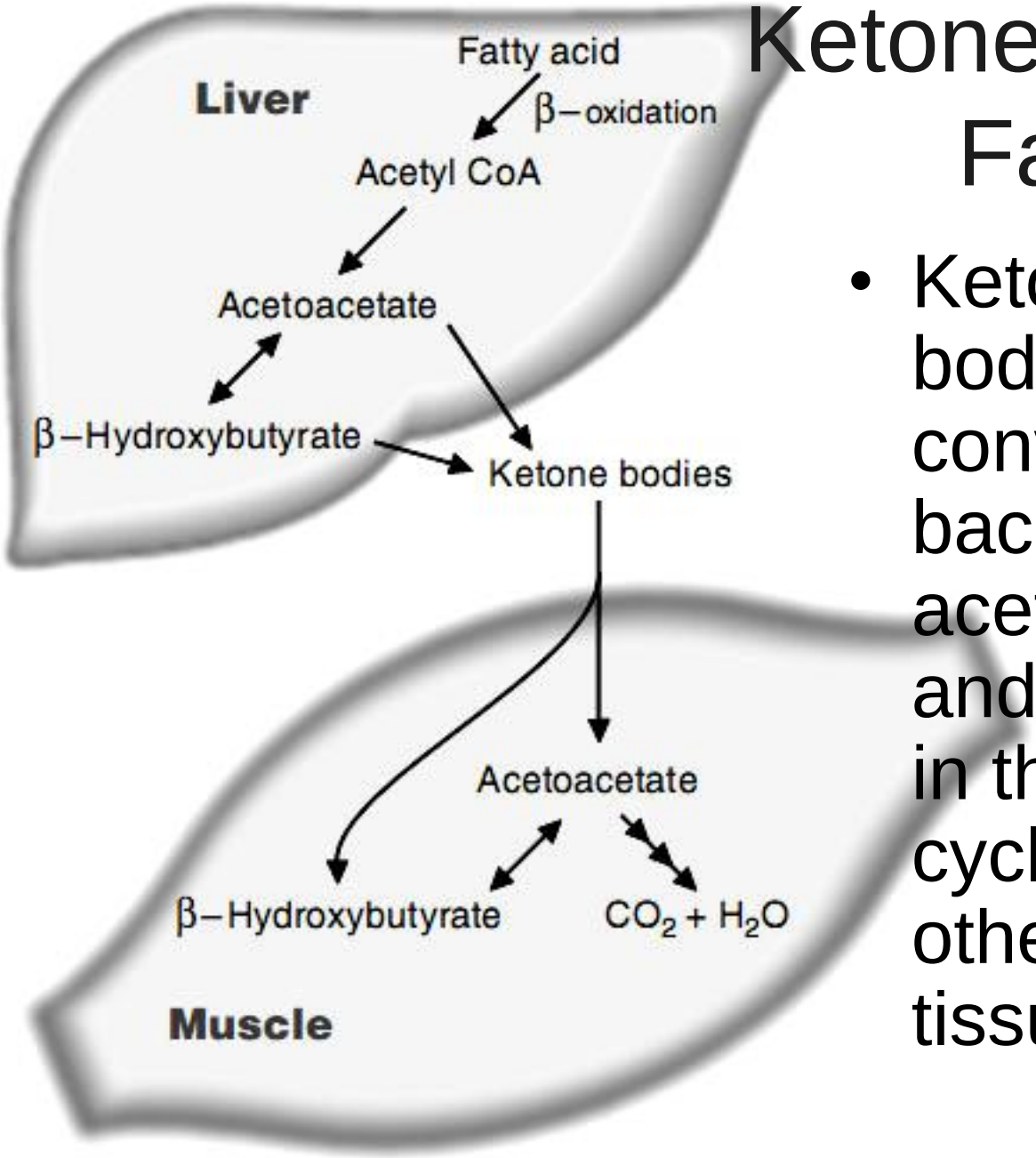
Acetoacetate



D-β-Hydroxybutyrate

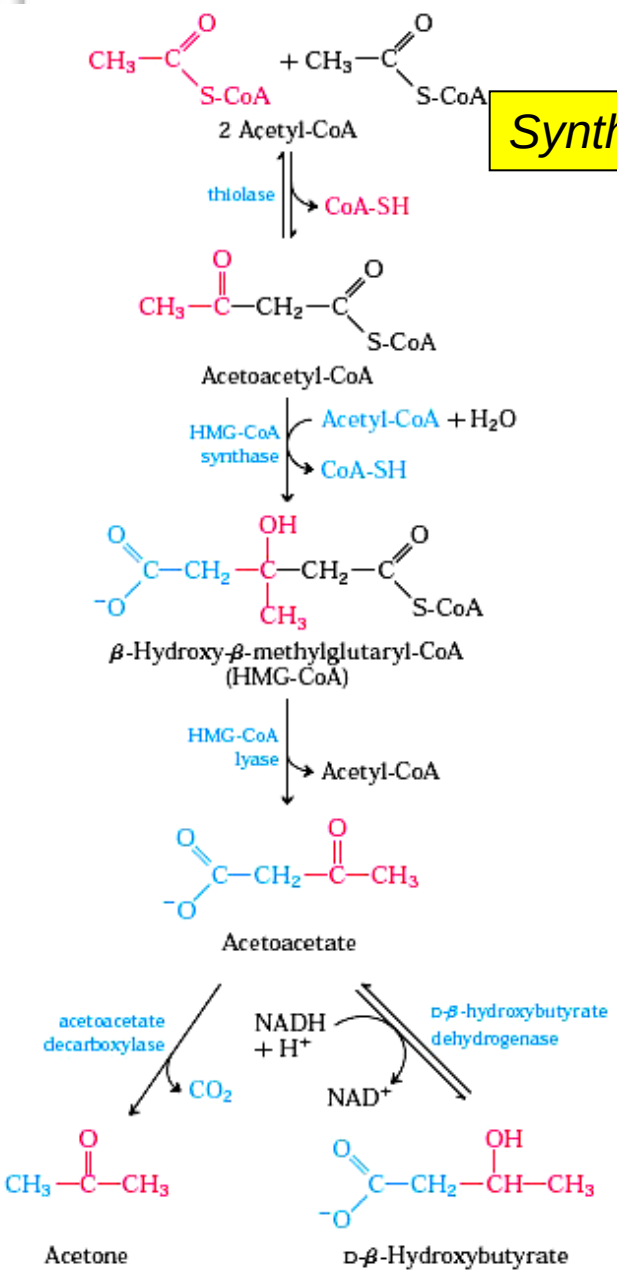
- The ketone bodies are formed in the liver:
  - acetone,
  - acetoacetate,
  - D-β-hydroxybutyrate.
- The latter two – fuel molecules in extrahepatic tissues:
  - oxidation to acetyl-CoA,
  - entry into the TCA.
- Overproduction of ketone bodies (uncontrolled diabetes, severely reduced calorie intake) can lead to **acidosis** or **ketosis**.

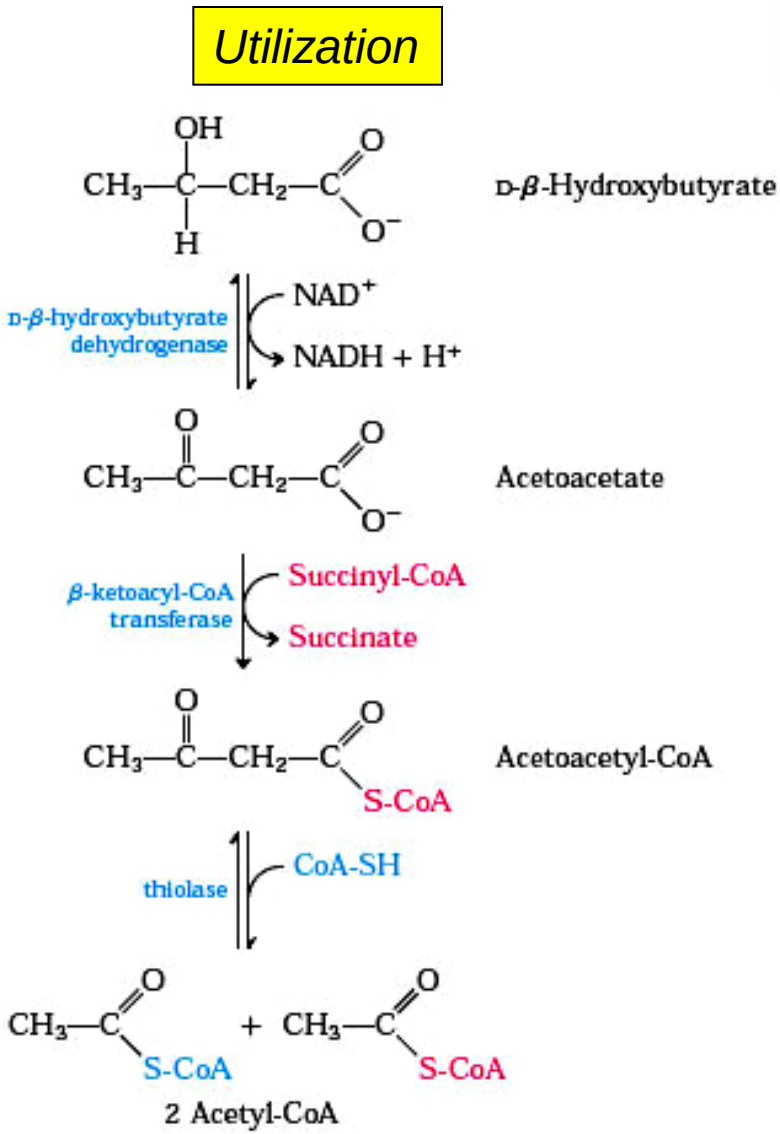
Ketone Bodies Fate



- Ketone bodies are conversed back to acetyl-CoA and oxidized in the TCA cycle in other tissues.

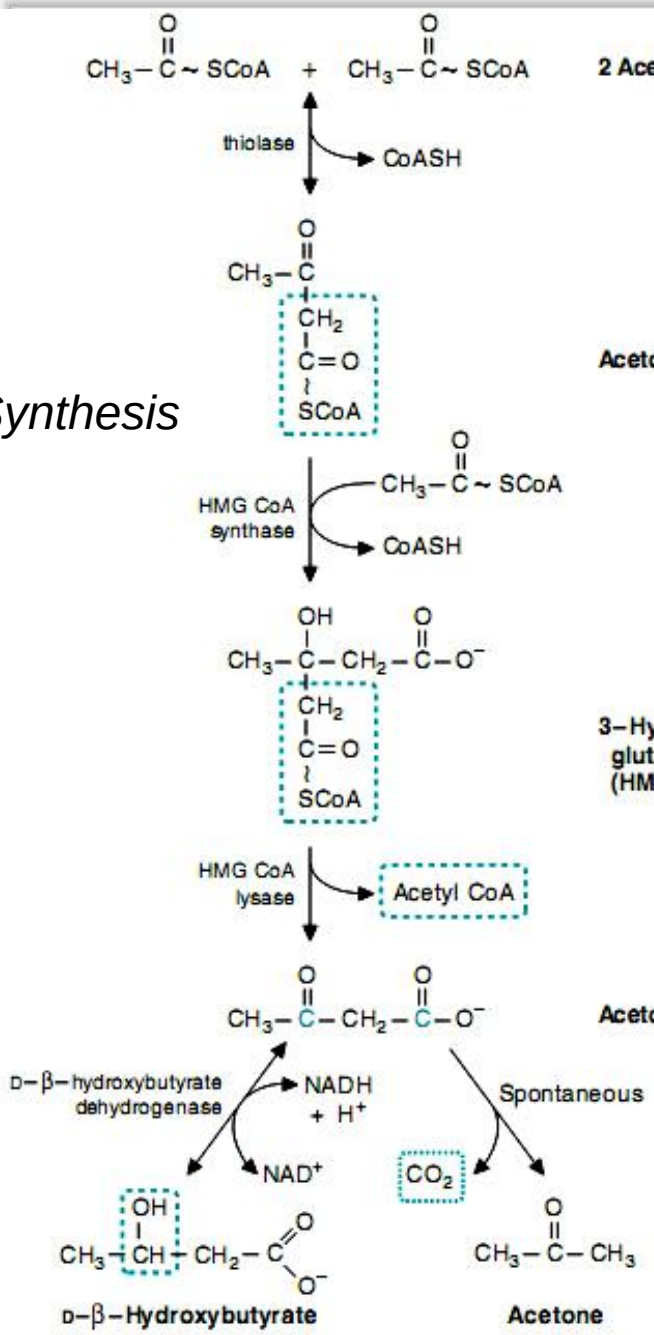
Ketone Bodies Metabolism



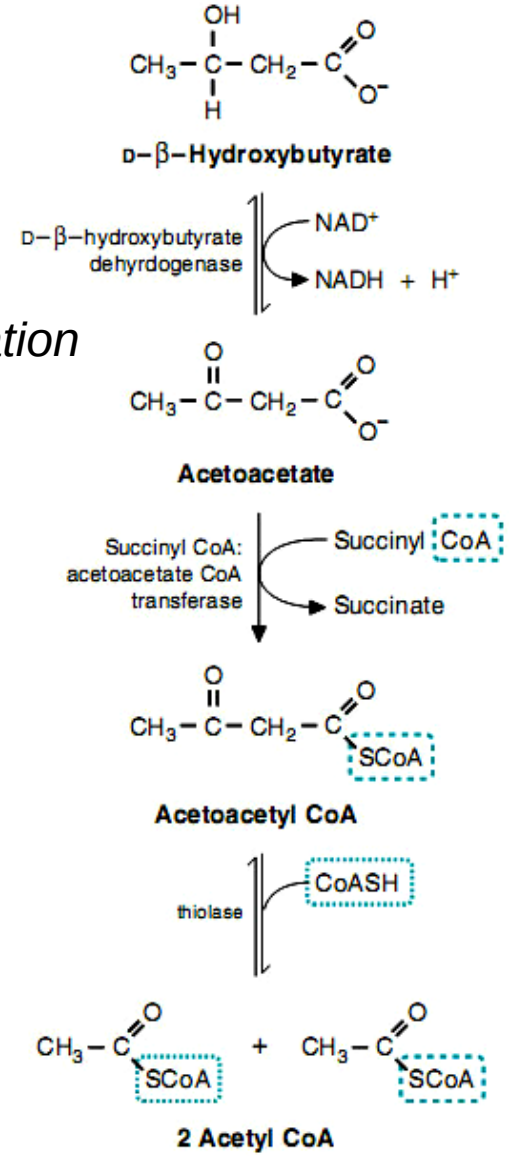


Ketone Bodies Metabolism

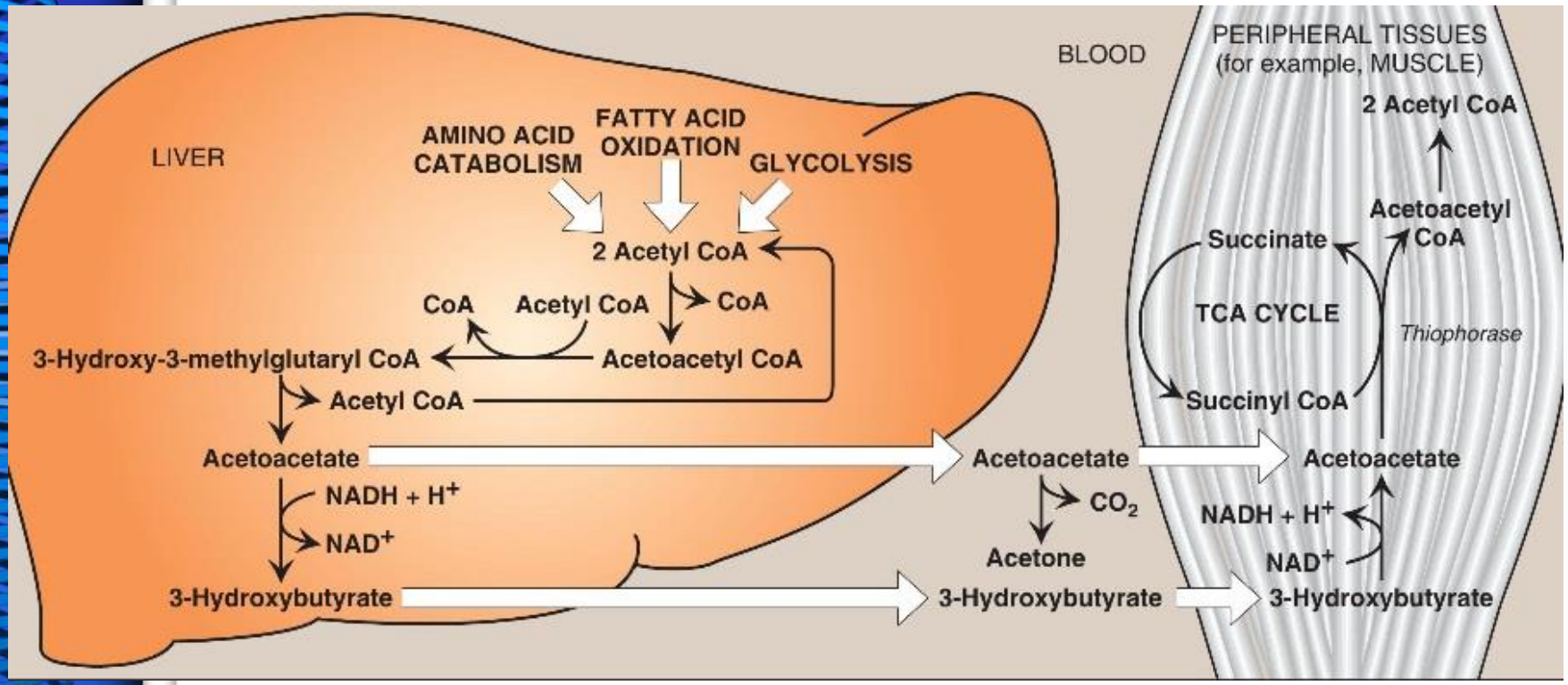
Synthesis



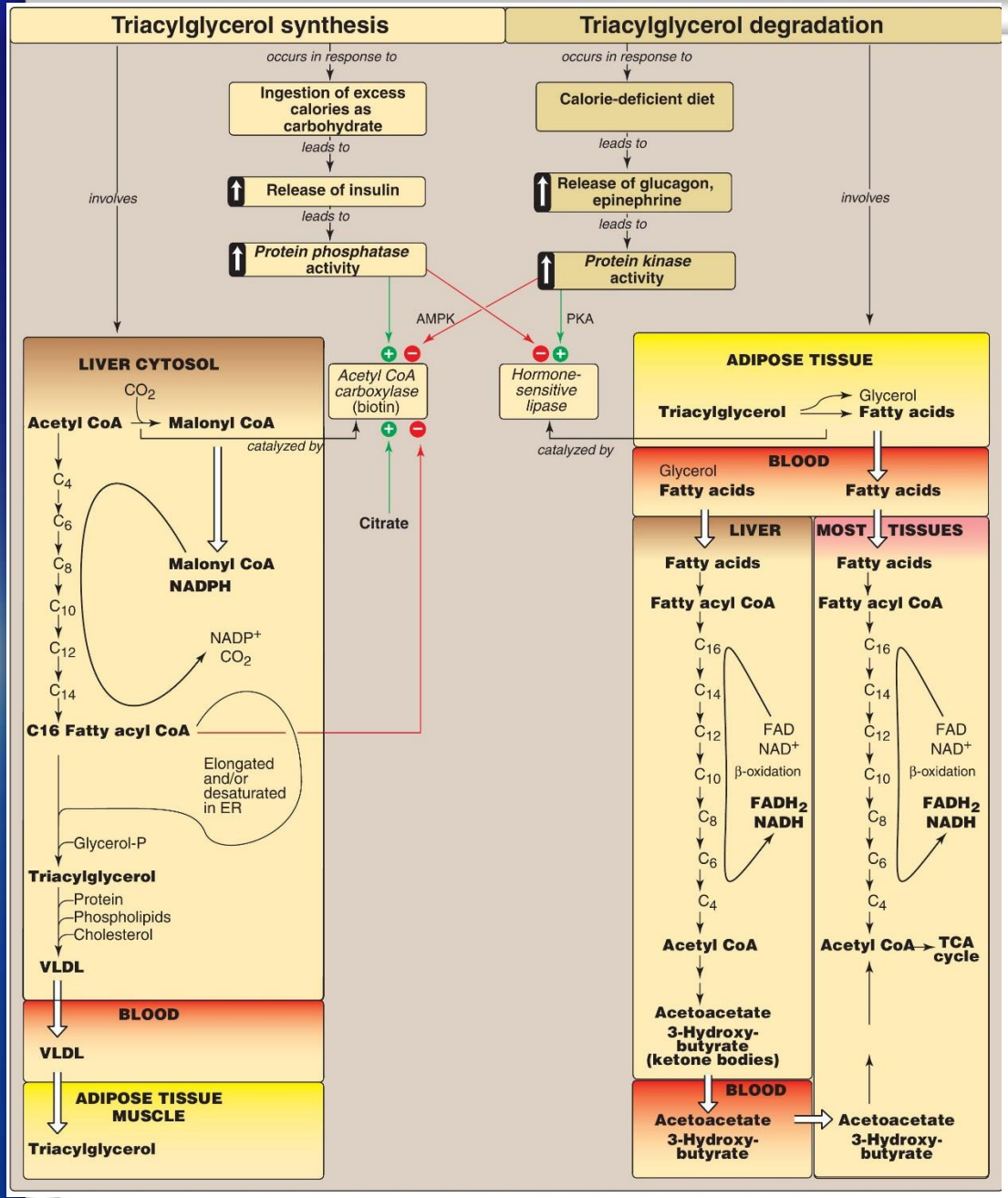
Oxidation



Ketone bodies in the organs: overview



Lippincott, 2011



CONCLUSION: Key concept map for TG biosynthesis and degradation

Lippincott, 2011

Biochemistry of Lipids

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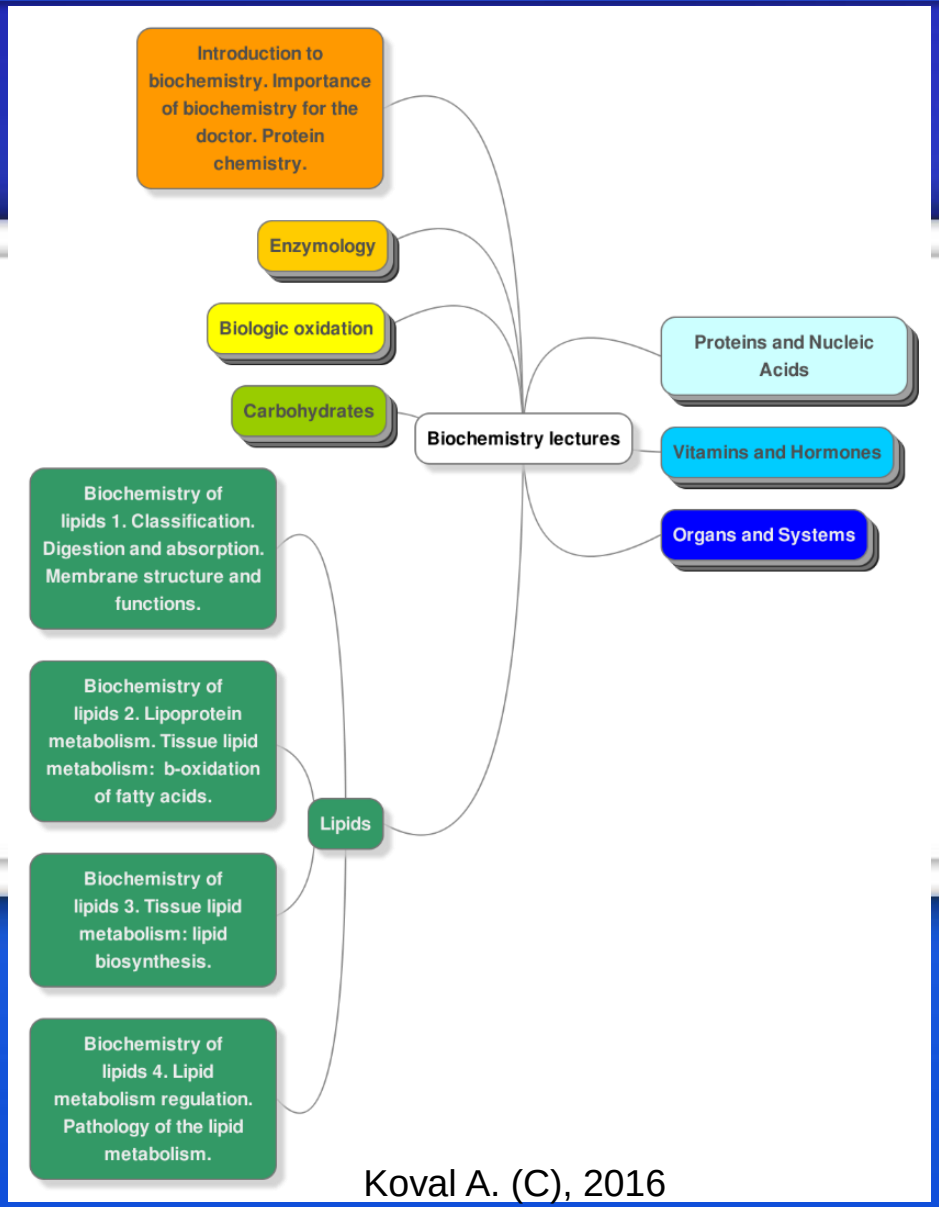
Lipid Biosynthesis

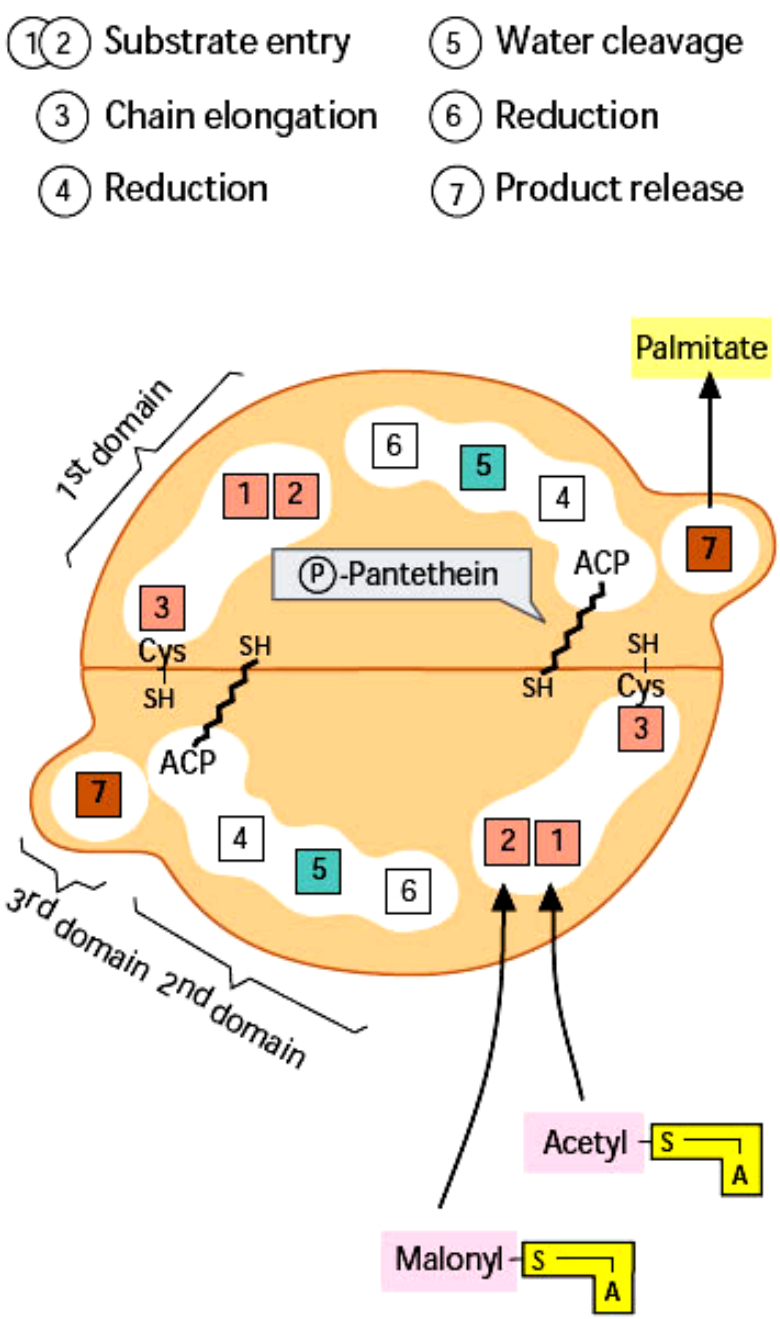
The structure of the lecture course



Contents

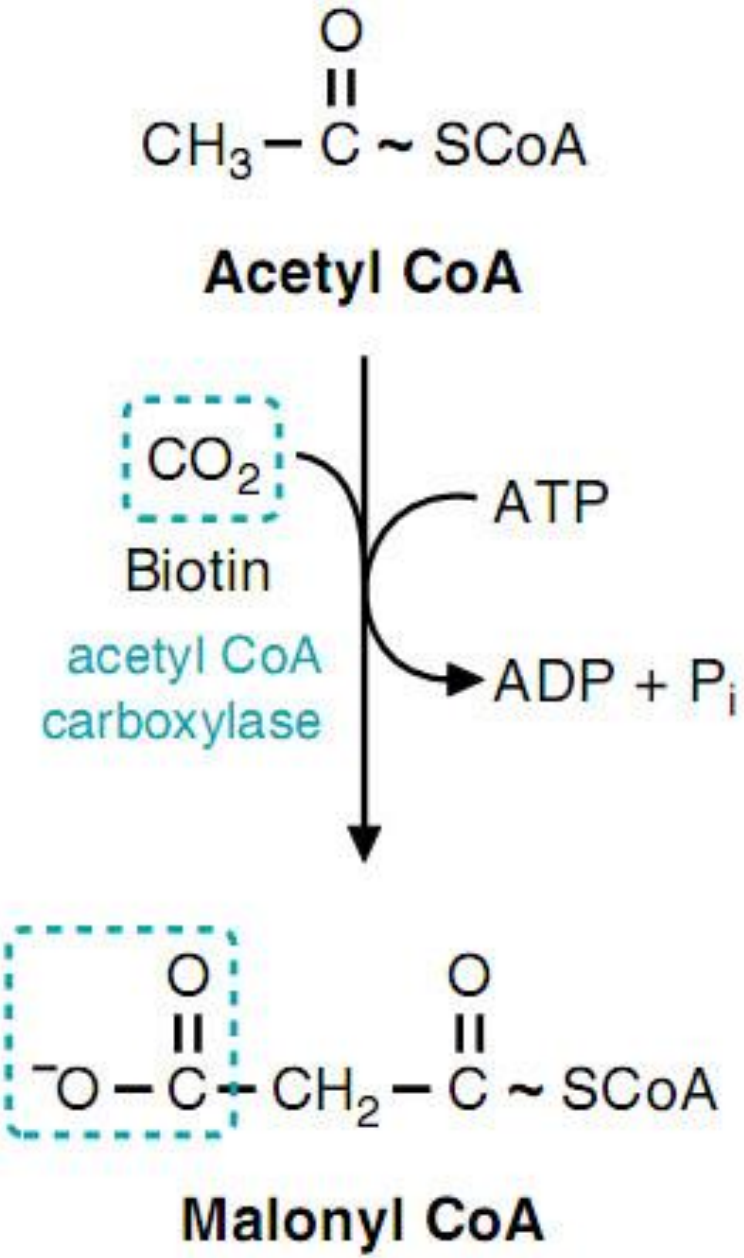
1. Biosynthesis of saturated fatty acids.
   - ☞ Role of acyl carrier protein protein (ACP), pantothen, biotin, NADPH + H^+ and enzymes.
   - ☞ Sources of Acetyl-CoA for biosynthesis of fatty acids (FA).
   - ☞ Regulation of FA biosynthesis.
2. Biosynthesis of triglycerides (TG) and phospholipids.
3. Biosynthesis of cholesterol, its regulation, biological role of cholesterol.
   - ☞ Pool of cholesterol in the cell, its regulation.

Fatty Acid Synthase (Palmitoyl synthase)



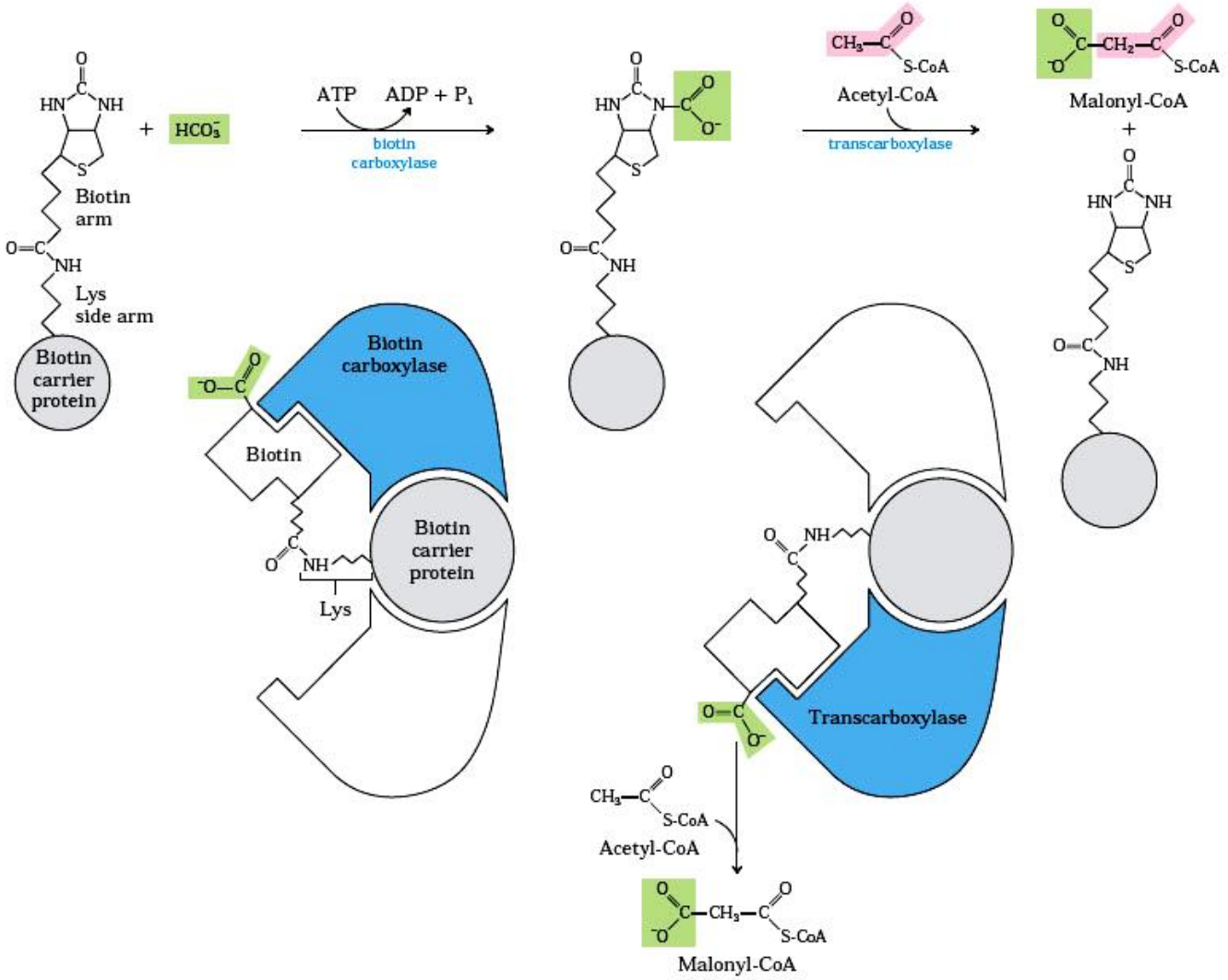
- Multifunctional enzyme.
  - Located in the cytoplasm
  - requires acetyl CoA as a starter molecule.
- The acetyl residue is elongated by one C_2 unit at a time for seven cycles.
- $NADPH+H^+$ is a reducing agent in the process.
- The end product is C_{16} acid, *palmitic acid.*

Acetyl CoA carboxylase

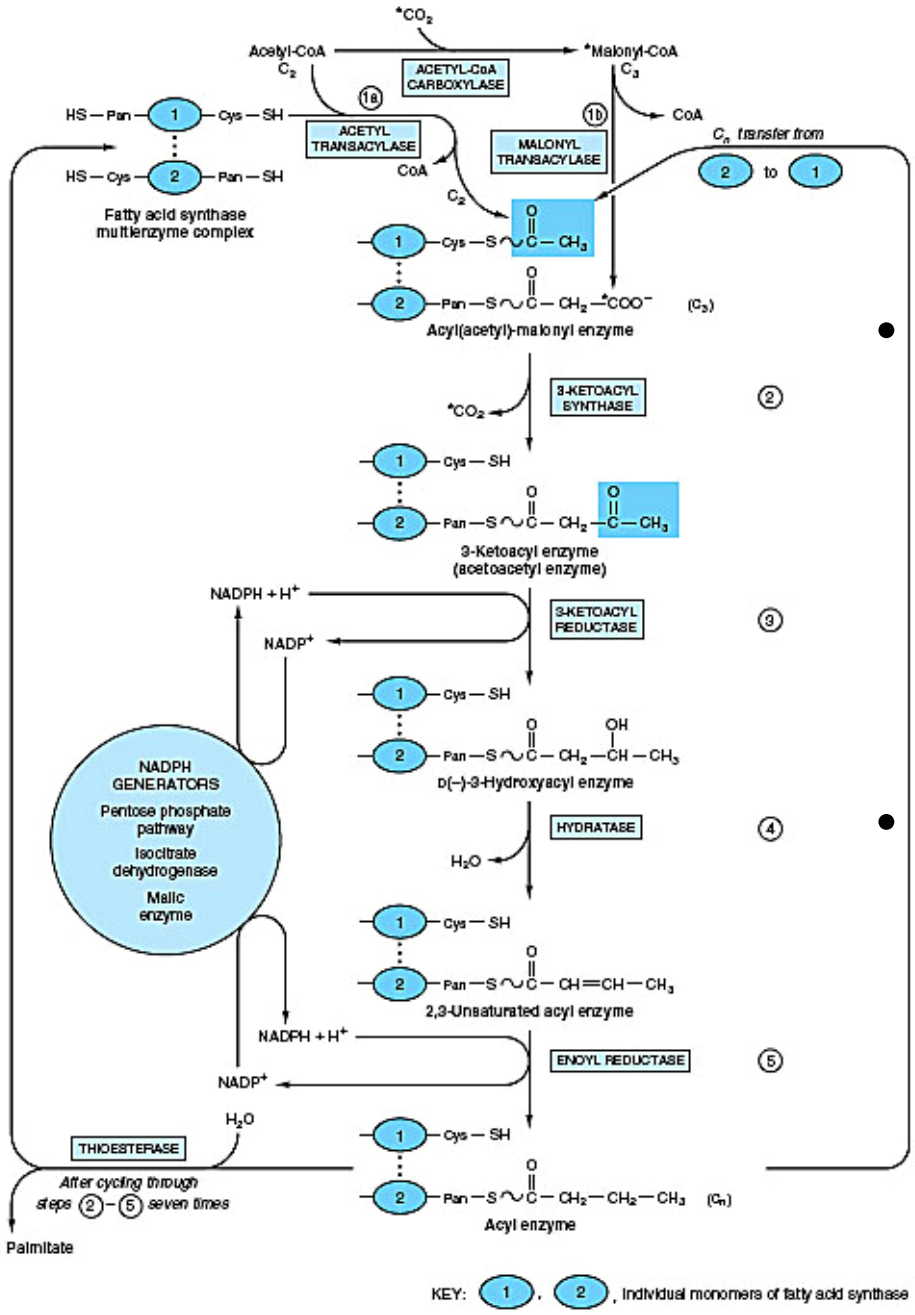


- Covalent binding of CO_2 to acetyl-CoA.
- Coenzyme biotin (vit H).
- Biotin can form bond with avidin (egg protein).

Acetyl-CoA carboxylase mechanism

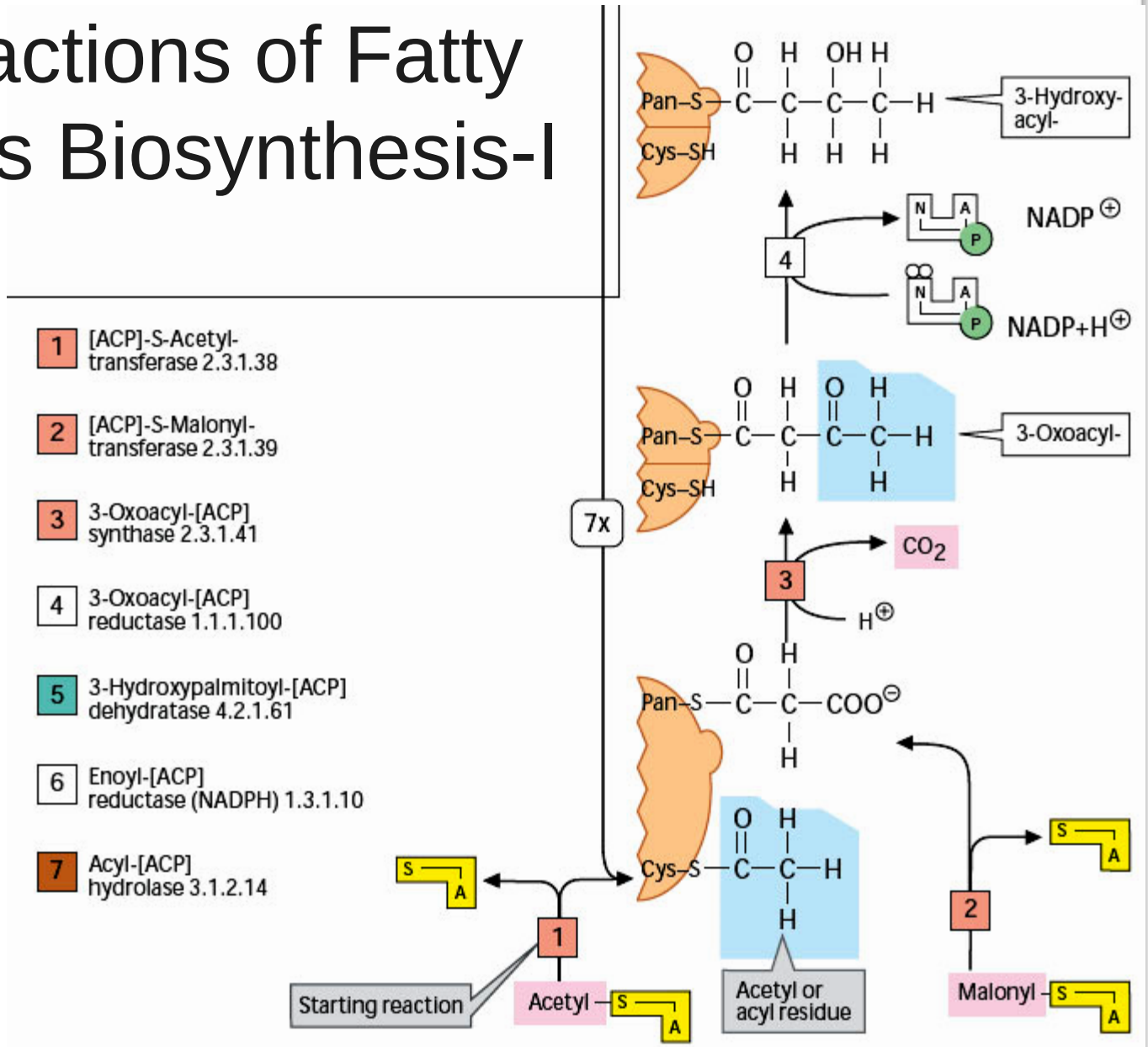


Biosynthesis of long-chain fatty acids



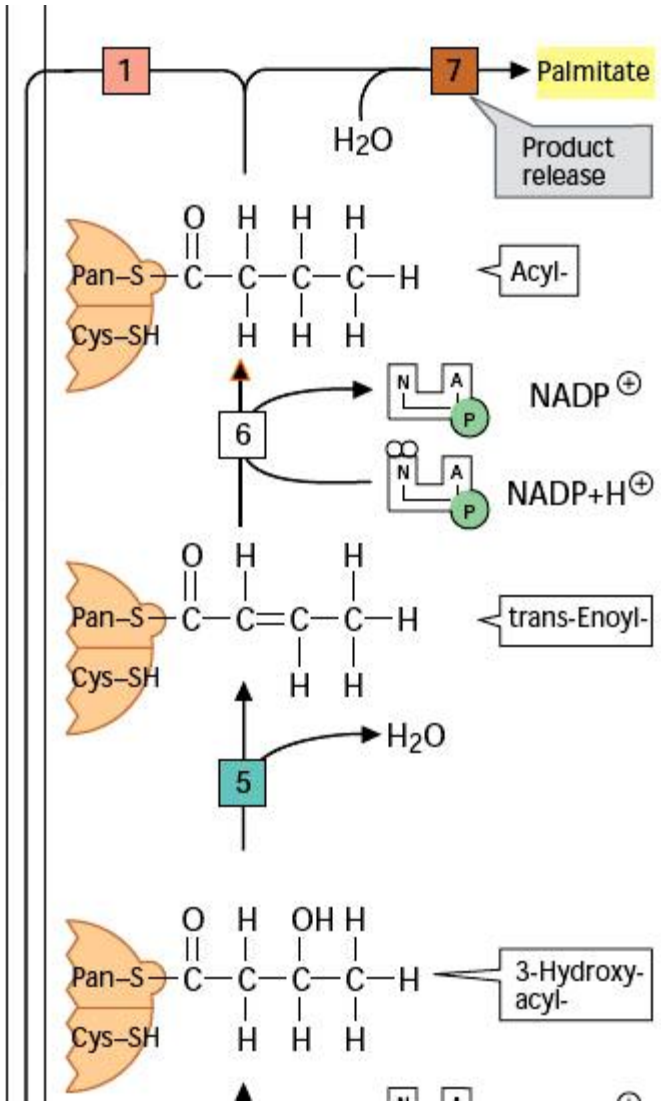
- Malonyl residue causes the acyl chain to grow by two carbon atoms.
  - *Cys*, cysteine residue;
  - *Pan*, 4′-phosphopantetheine
- Initially a C_2 unit derived from acetyl-CoA and subsequently the C_n unit formed in reaction 5.

Reactions of Fatty Acids Biosynthesis-I

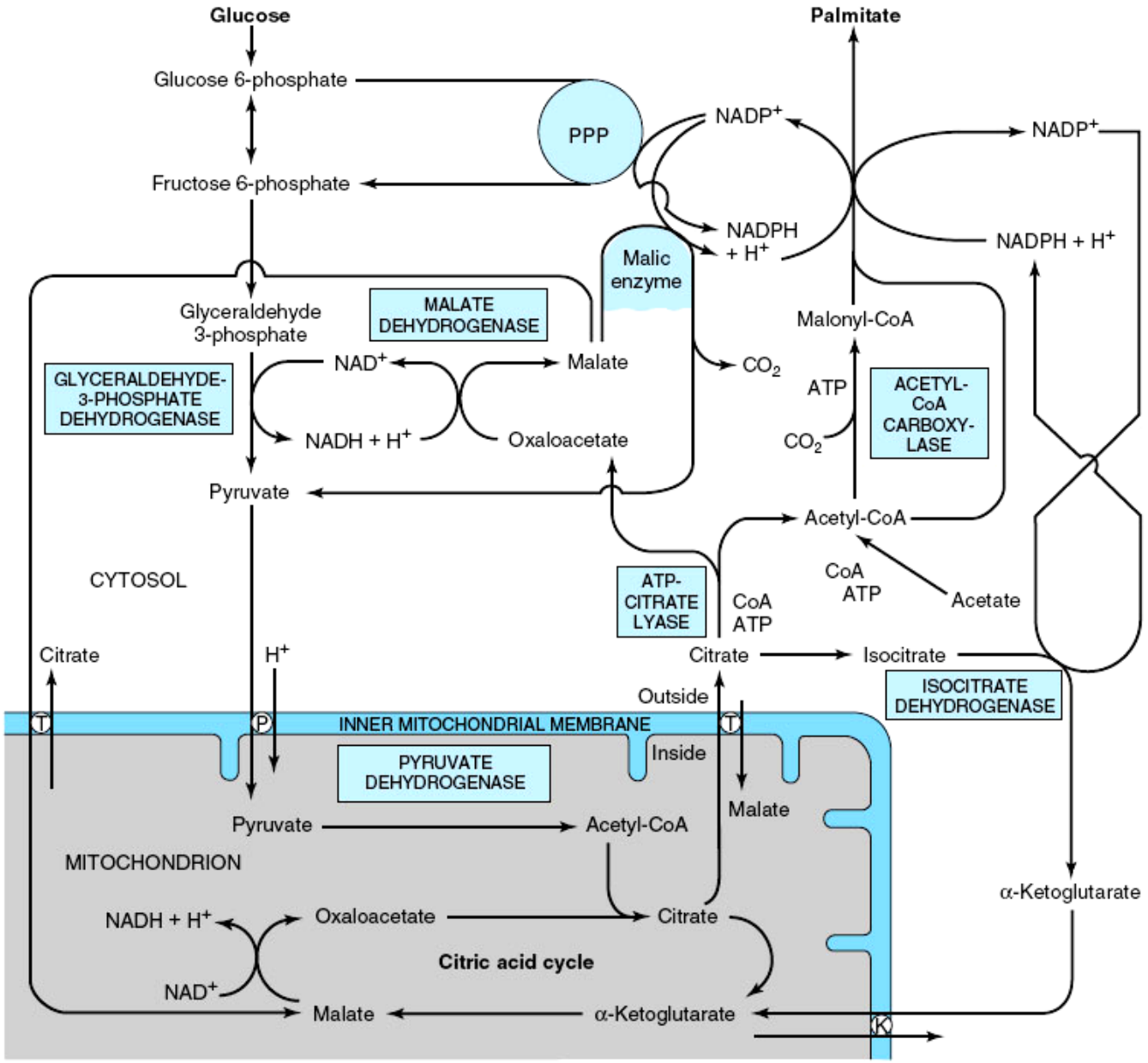


Reactions of Fatty Acids Biosynthesis-II

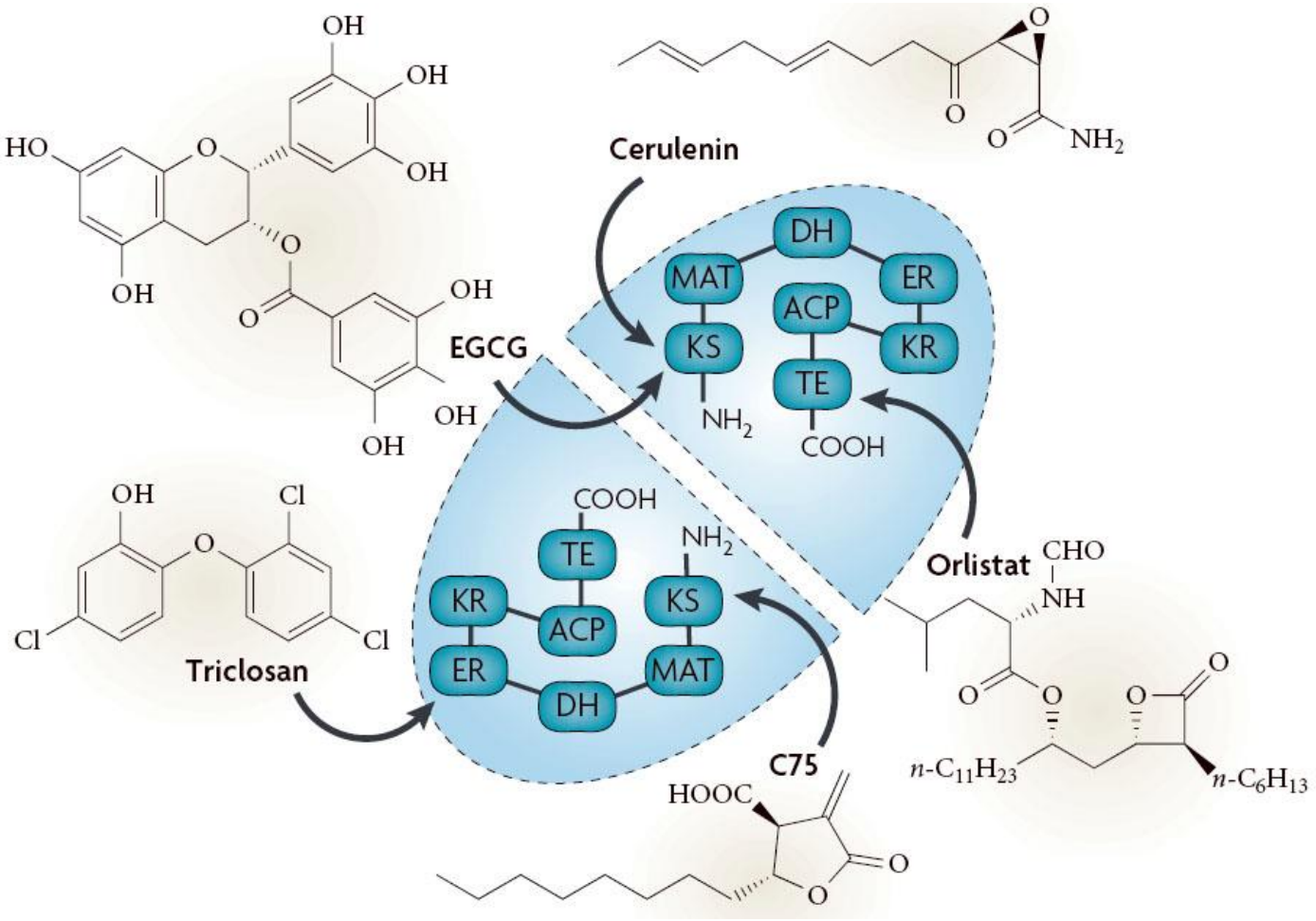
1. [ACP]-S-Acetyl-transferase 2.3.1.38
2. [ACP]-S-Malonyl-transferase 2.3.1.39
3. 3-Oxoacyl-[ACP] synthase 2.3.1.41
4. 3-Oxoacyl-[ACP] reductase 1.1.1.100
5. 3-Hydroxypalmitoyl-[ACP] dehydratase 4.2.1.61
6. Enoyl-[ACP] reductase (NADPH) 1.3.1.10
7. Acyl-[ACP] hydrolase 3.1.2.14

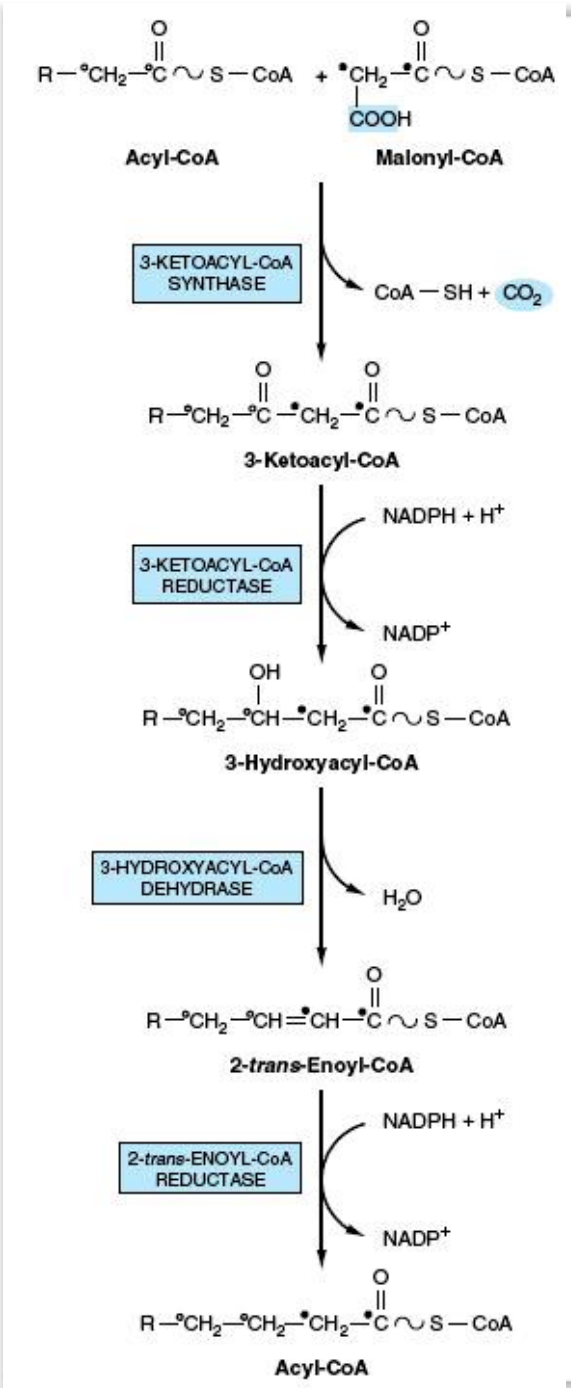


The provision of Acetyl-CoA and NADPH for Lipogenesis



Palmytoyl synthase complex inhibitors

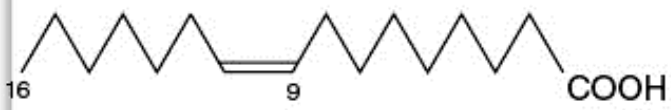




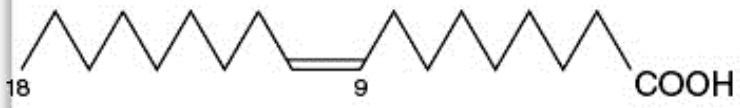
Elongase System

- Microsomal elongase system for fatty acid chain elongation.
- NADH is also used by the reductases, but NADPH is preferred.

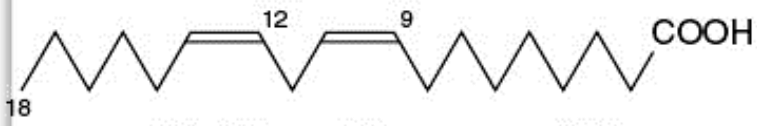
Some Polyunsaturated Fatty Acids



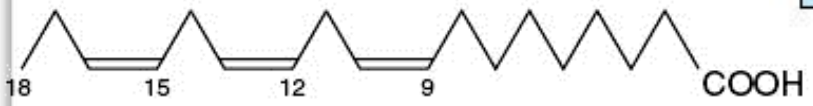
Palmitoleic acid (ω7, 16:1, Δ^9)



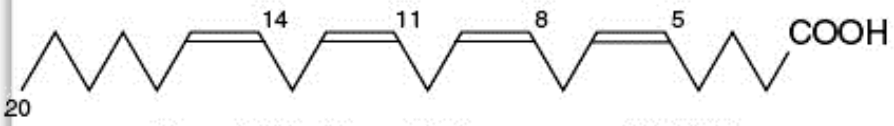
Oleic acid (ω9, 18:1, Δ^9)



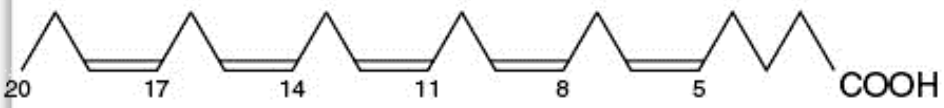
*Linoleic acid (ω6, 18:2, $\Delta^{9,12}$)



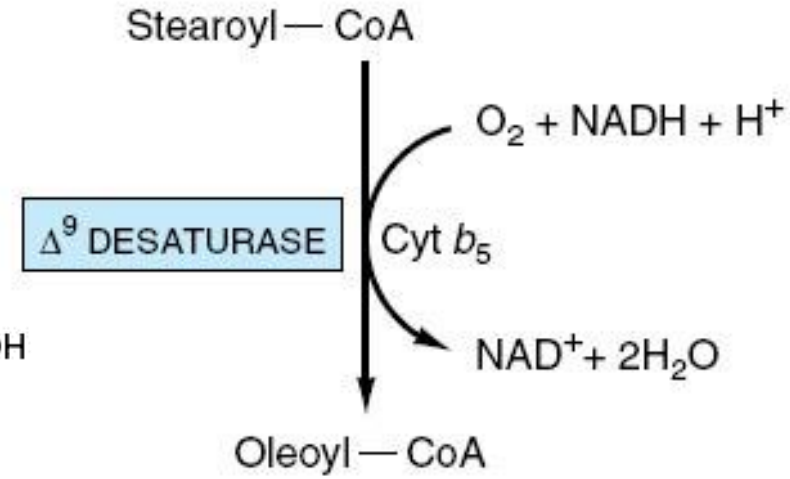
*α-Linolenic acid (ω3, 18:3, $\Delta^{9,12,15}$)



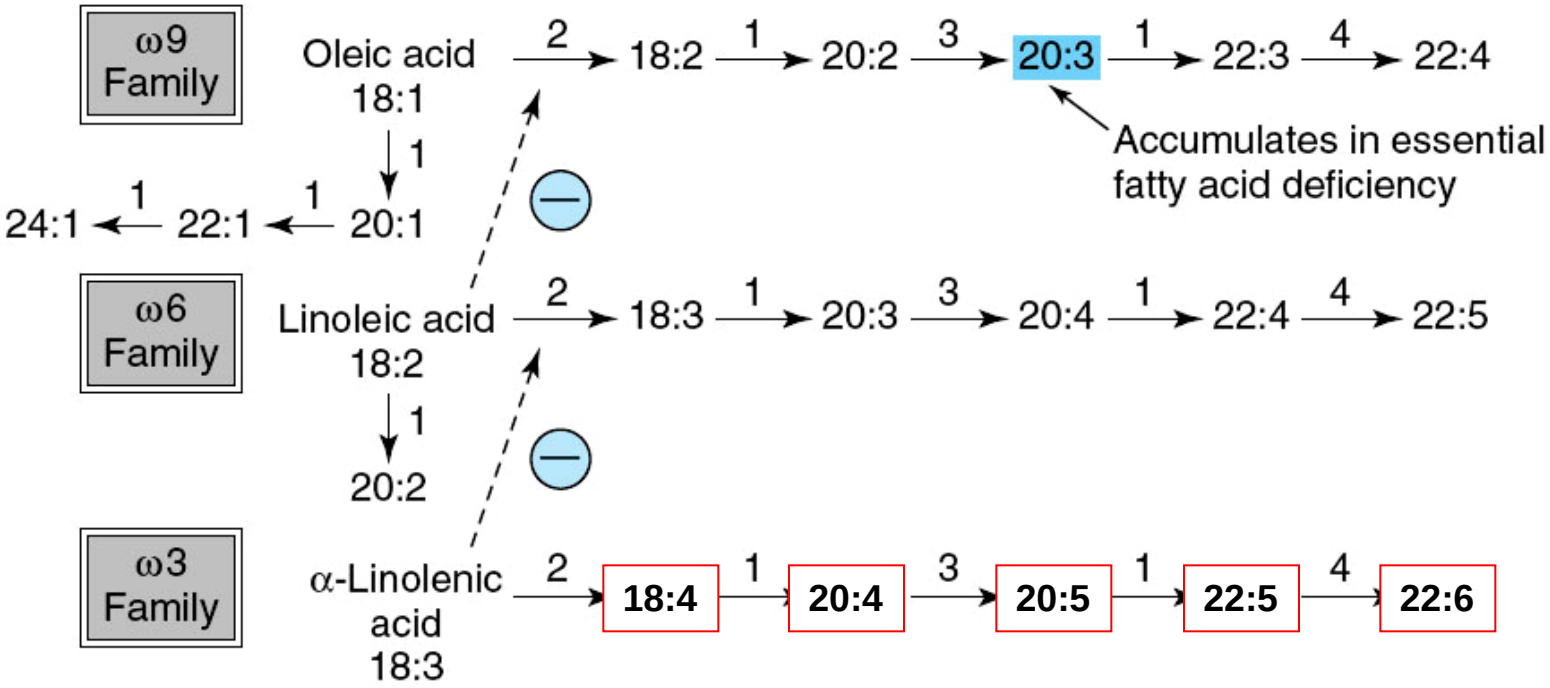
*Arachidonic acid (ω6, 20:4, $\Delta^{5,8,11,14}$)



Eicosapentaenoic acid (ω3, 20:5, $\Delta^{5,8,11,14,17}$)

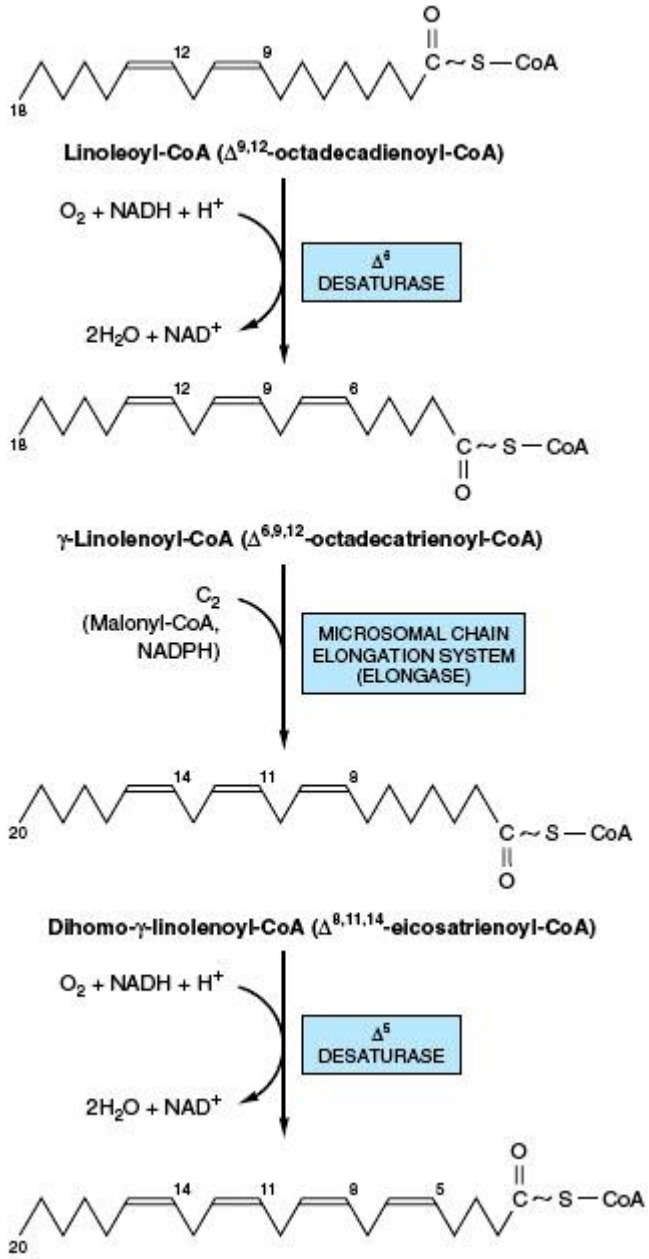


Polyunsaturated Fatty Acids Biosynthesis



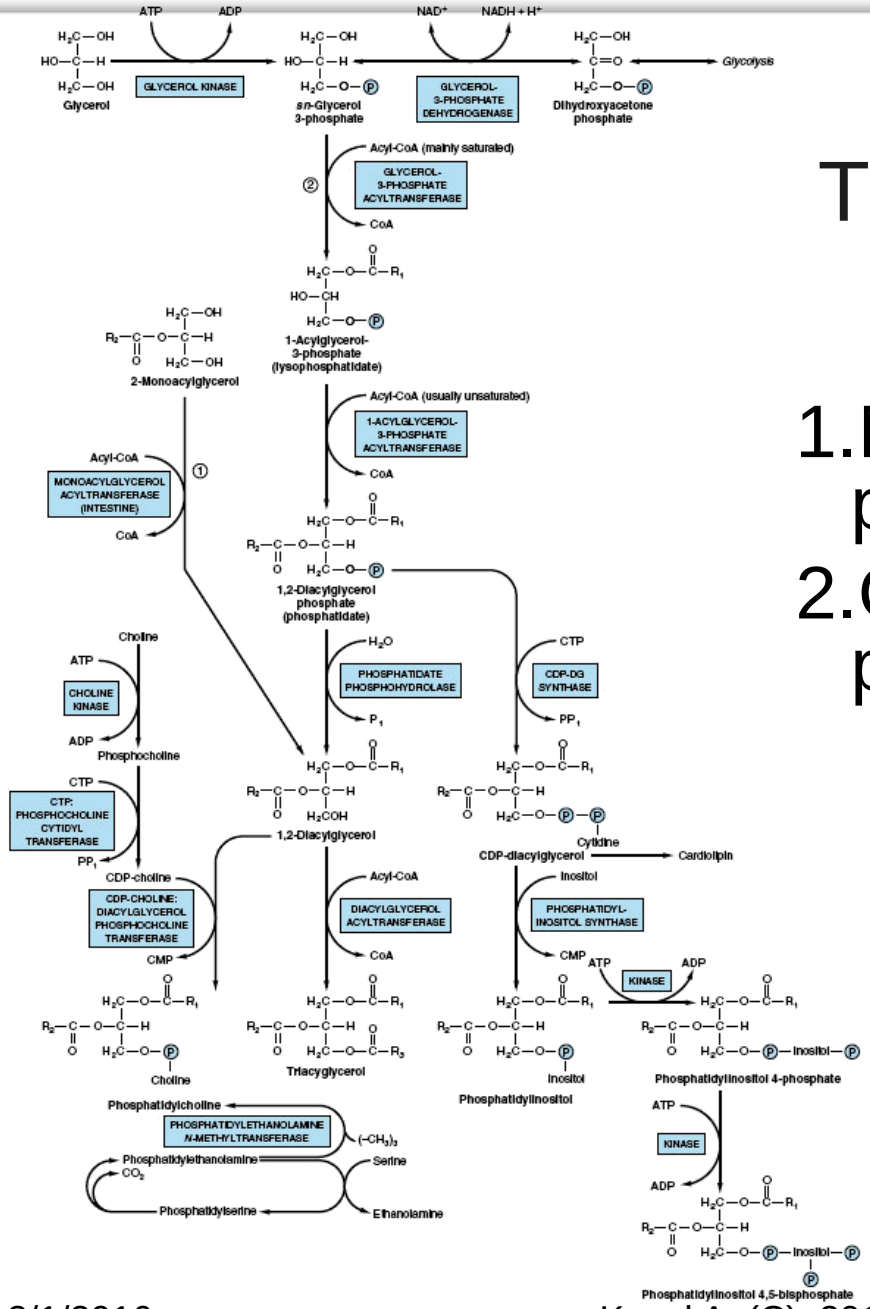
- Biosynthesis of the ω9, ω6, and ω3 families of polyunsaturated fatty acids.
- Each step is catalyzed by the microsomal chain elongation or desaturase system: 1, elongase; 2, Δ6 desaturase; 3, Δ5 desaturase; 4, Δ4 desaturase. (Θ, Inhibition.)

Conversion of Linoleate to Arachidonate



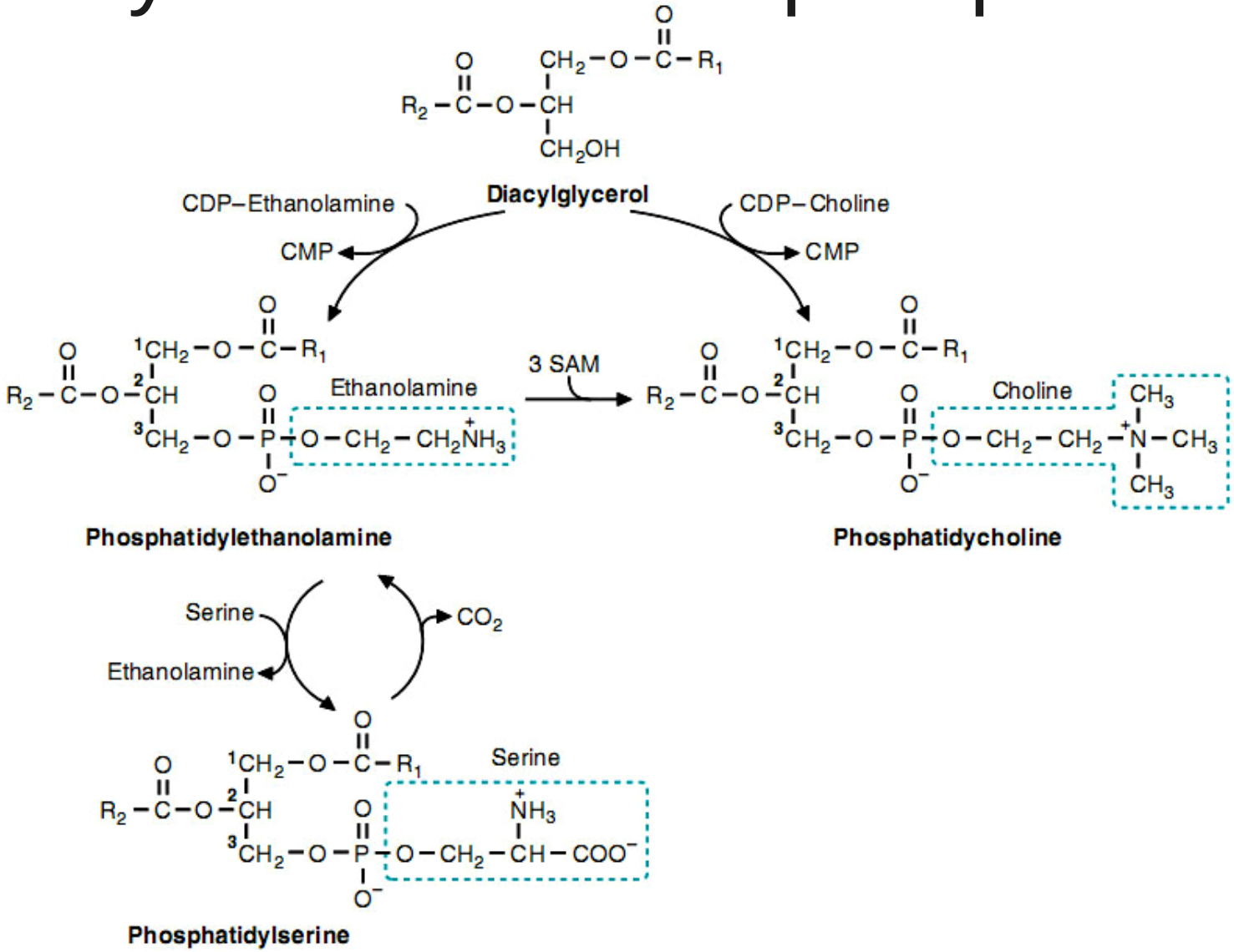
- Cats cannot carry out this conversion owing to absence of Δ6 desaturase and must obtain arachidonate in their diet.

Biosynthesis of Triacylglycerol and Phospholipids

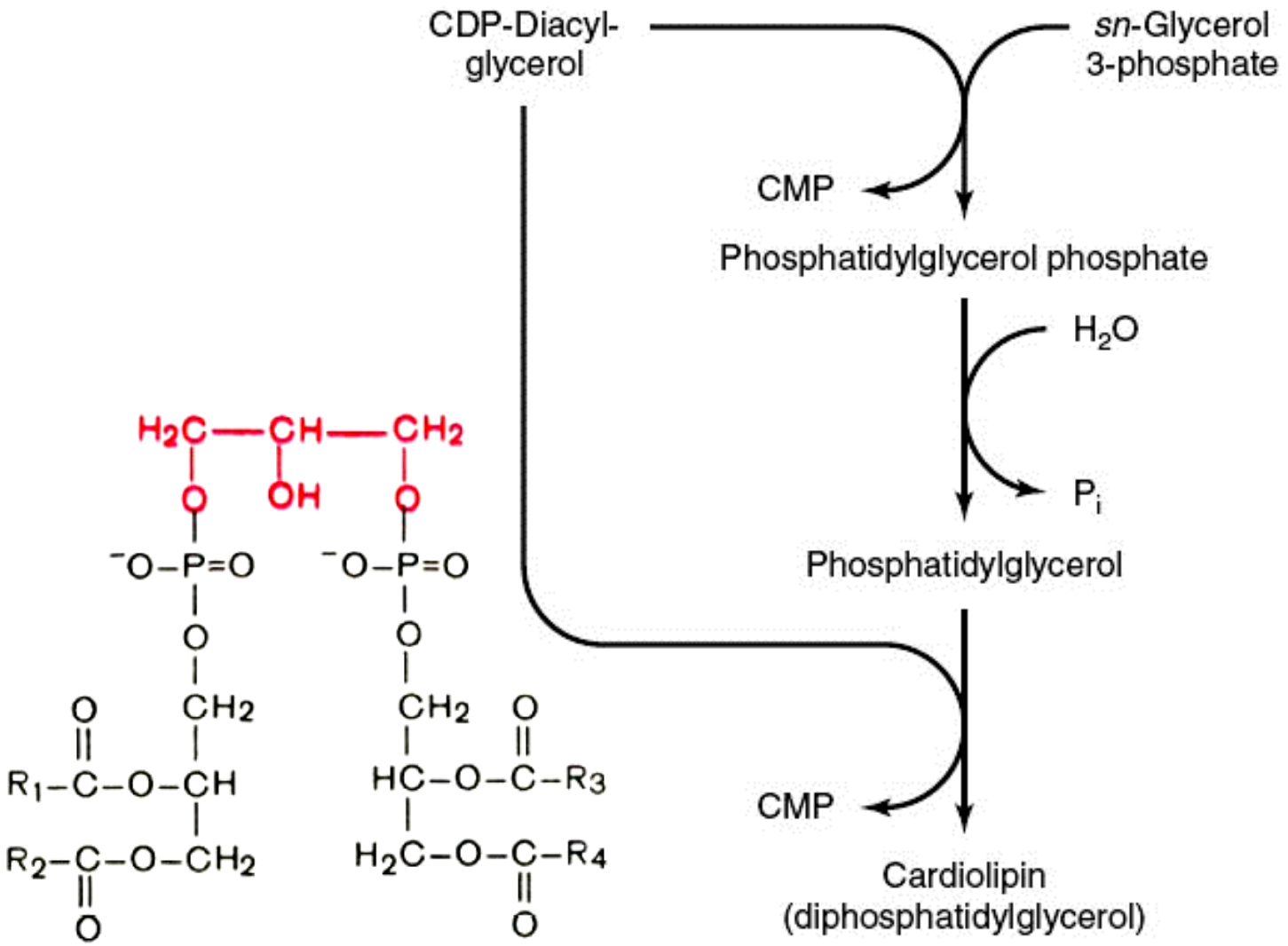


1. Monoacylglycerol pathway;
2. Glycerol phosphate pathway.
   - Phosphatidylethanol-amine may be formed from ethanolamine by a pathway similar to that shown for the formation of phosphatidylcholine from choline.

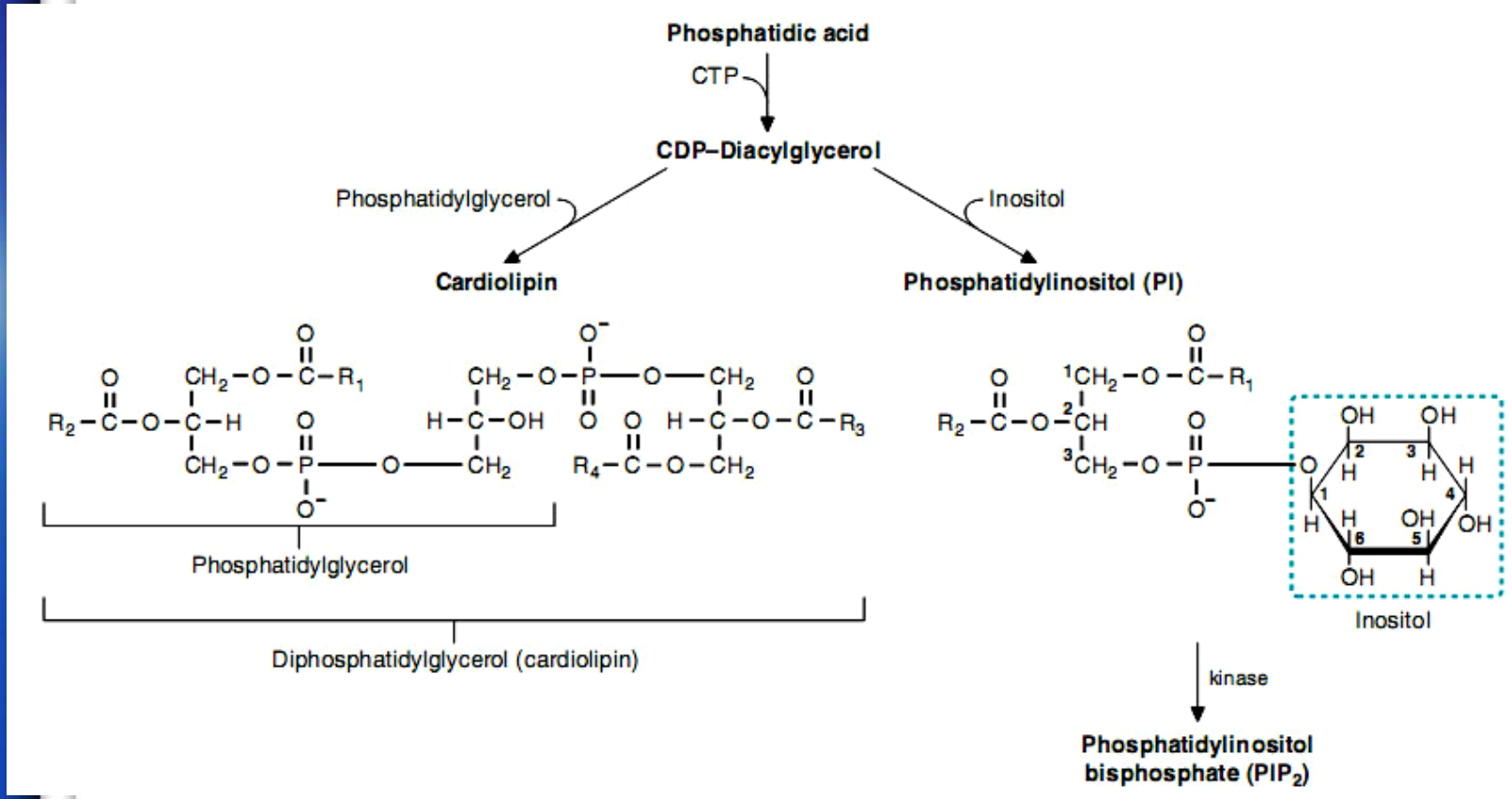
Synthesis of Phospholipids



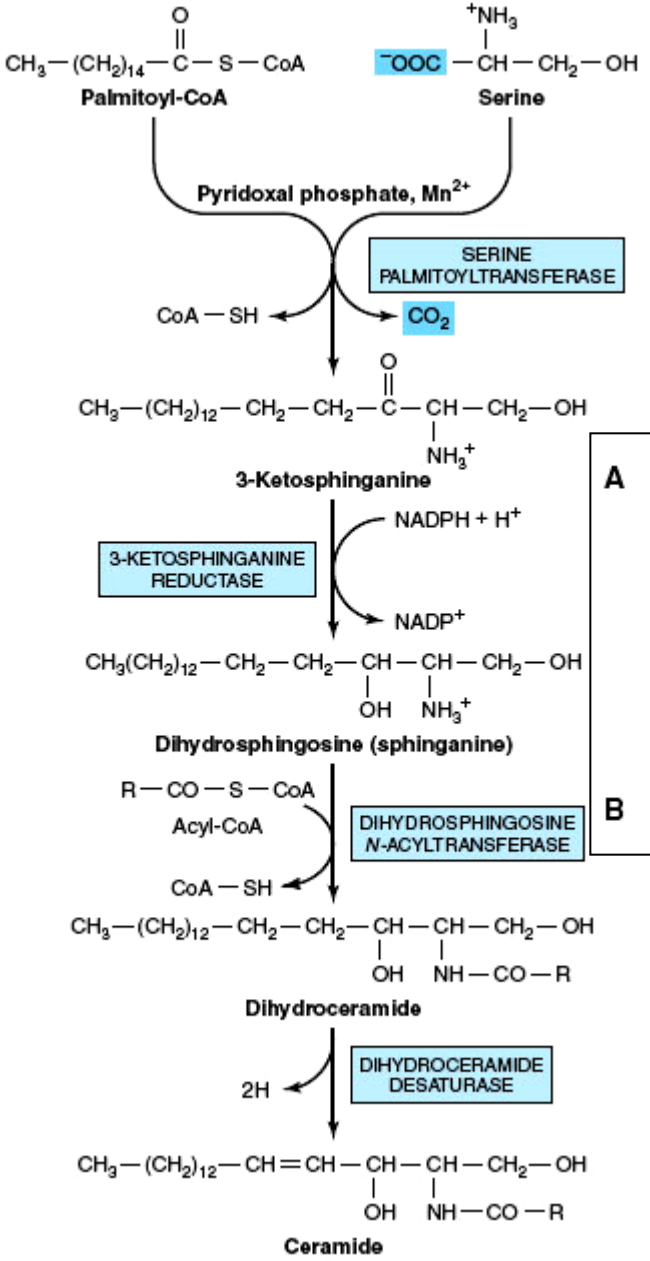
Biosynthesis of cardiolipin

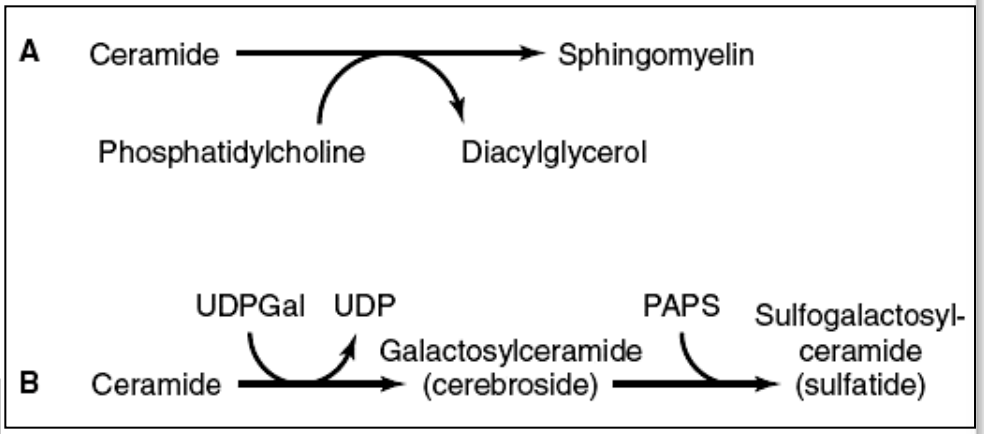


Synthesis of Cardiolipin and Phosphatidylinositol

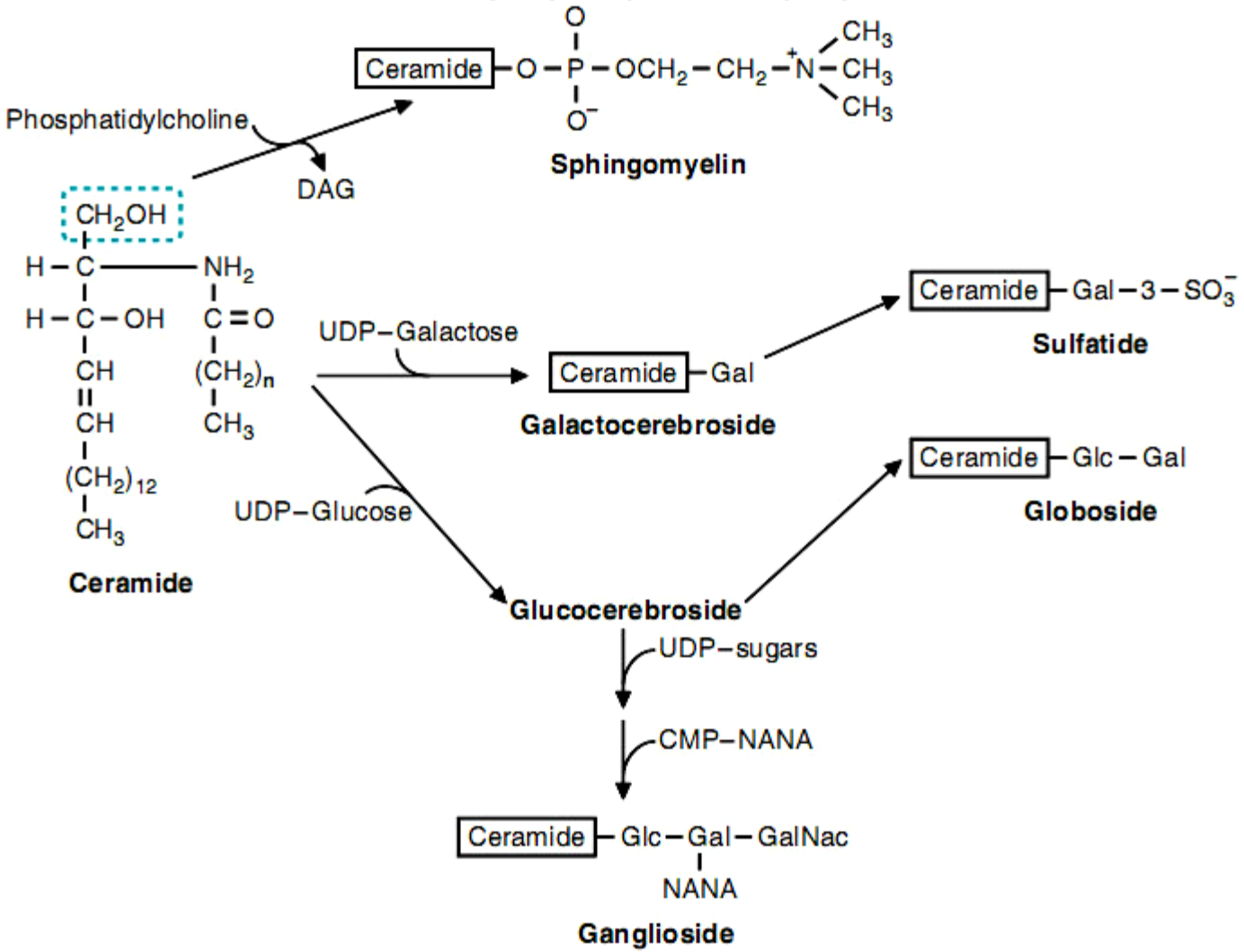


Cerebroside Biosynthesis





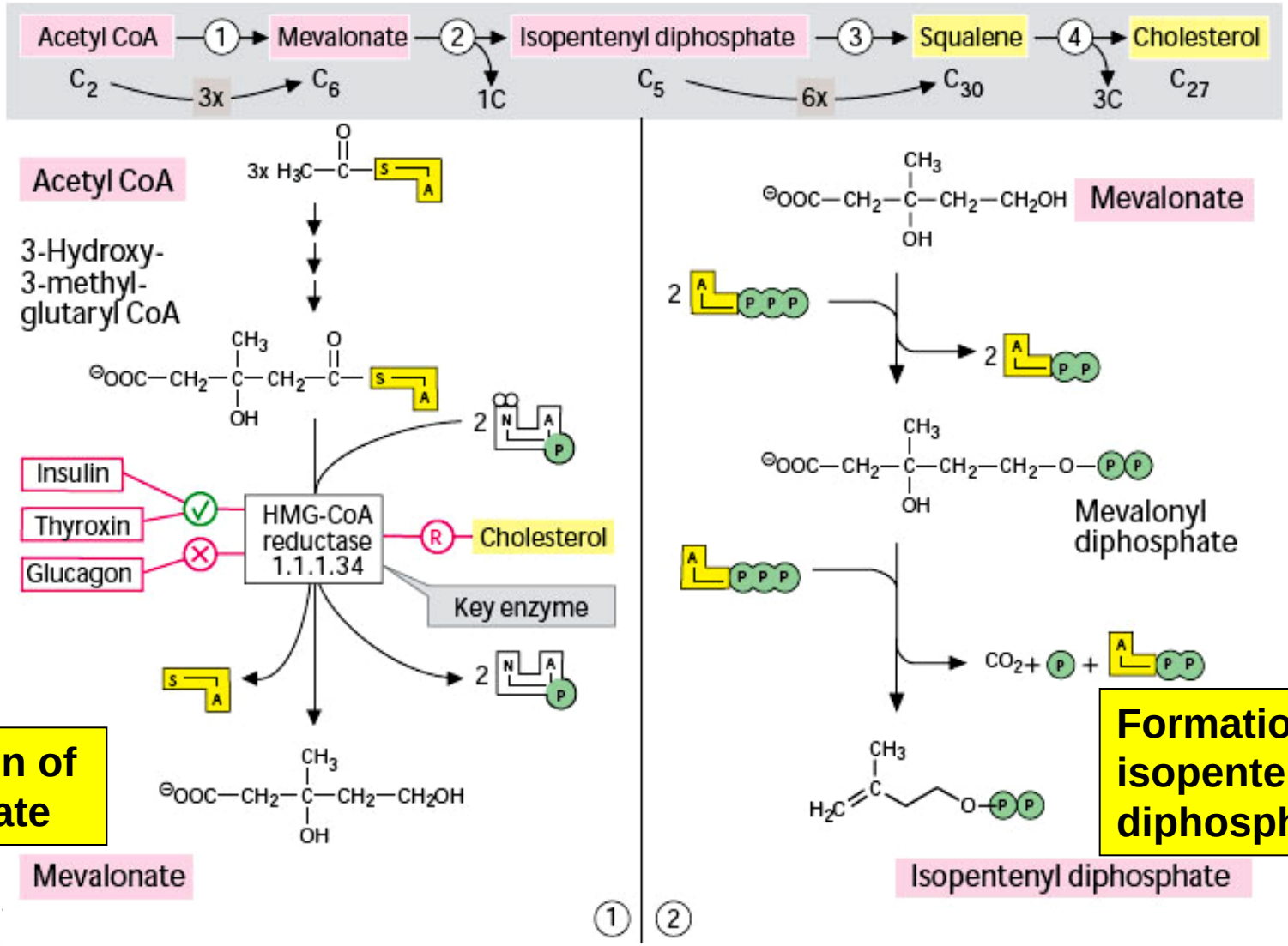
Synthesis of Sphingolipids from Ceramide



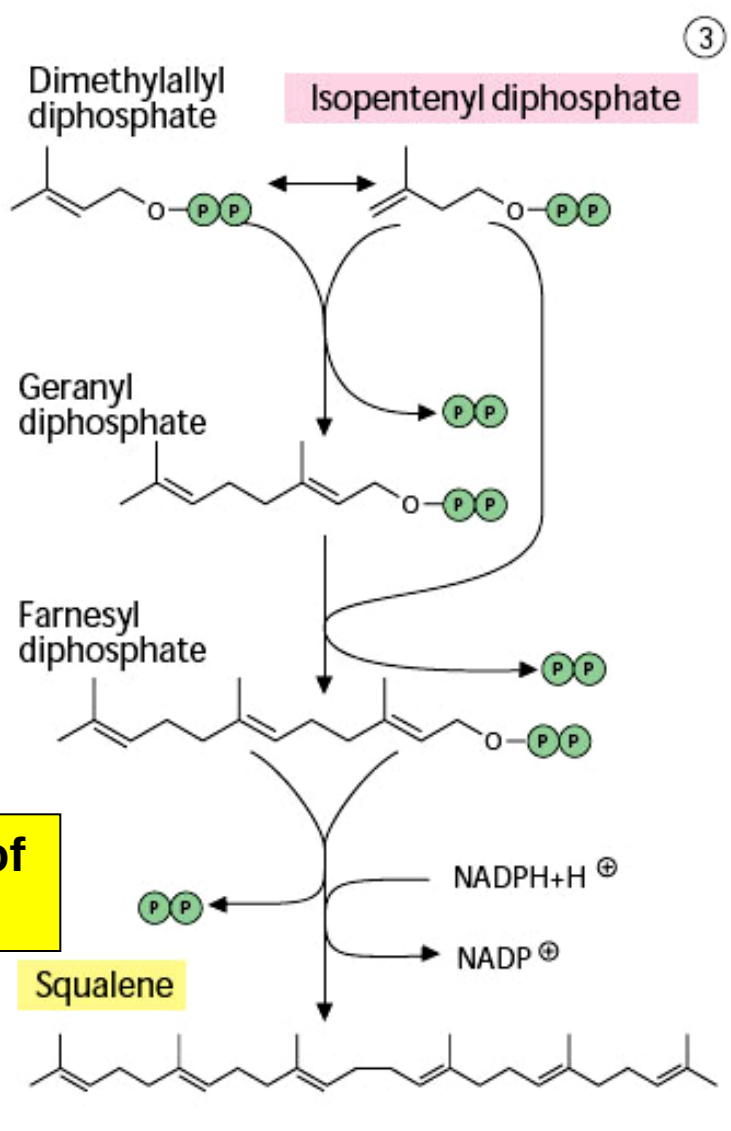
Biosynthesis of Cholesterol

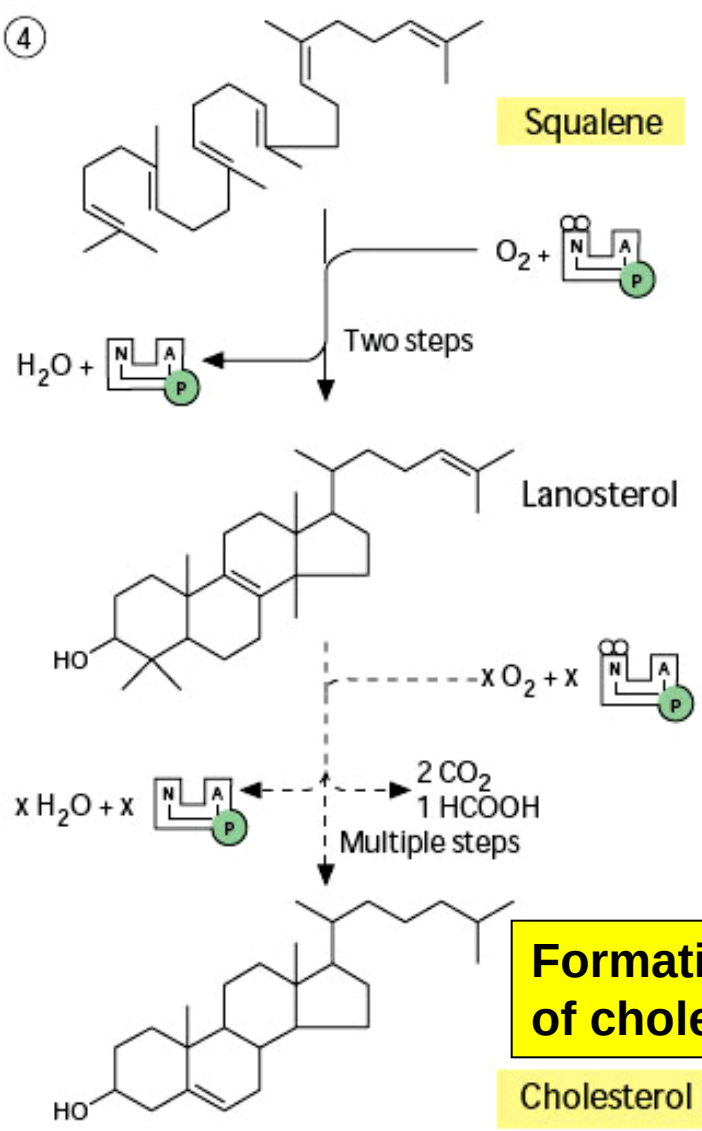
- Cholesterol is a major constituent of the *cell membranes* of animal cells.
  - full daily cholesterol requirement (ca. 1 g) can be synthesized itself$
  - with a mixed diet, only about half of the cholesterol is derived from *endogenous biosynthesis*, which takes place in the intestine and skin, and mainly in the liver (about 50%).
  - The rest is taken up from *food*.
- Most of the cholesterol is incorporated into the lipid layer of plasma membranes, or converted into **bile acids**.
  - A very small amount of cholesterol is used for biosynthesis of the **steroid hormones**.
  - In addition, up to 1 g cholesterol per day is released into the *bile* and thus excreted.

Cholesterol Biosynthesis-I



Cholesterol Biosynthesis-II

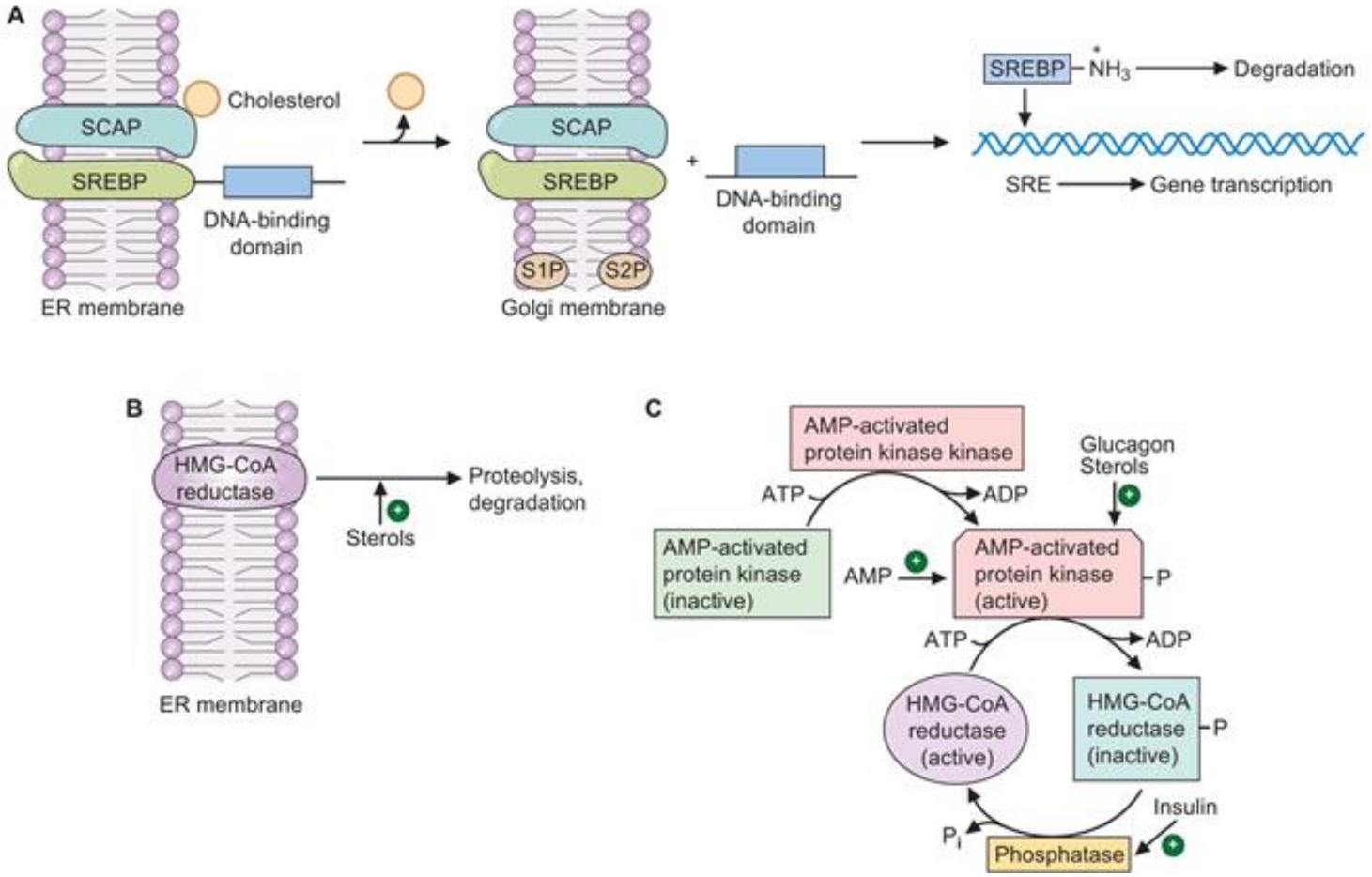




Formation of squalene

Formation of cholesterol

Cholesterol biosynthesis regulation (3 mechanisms)



Conclusion

Biochemistry of Lipids

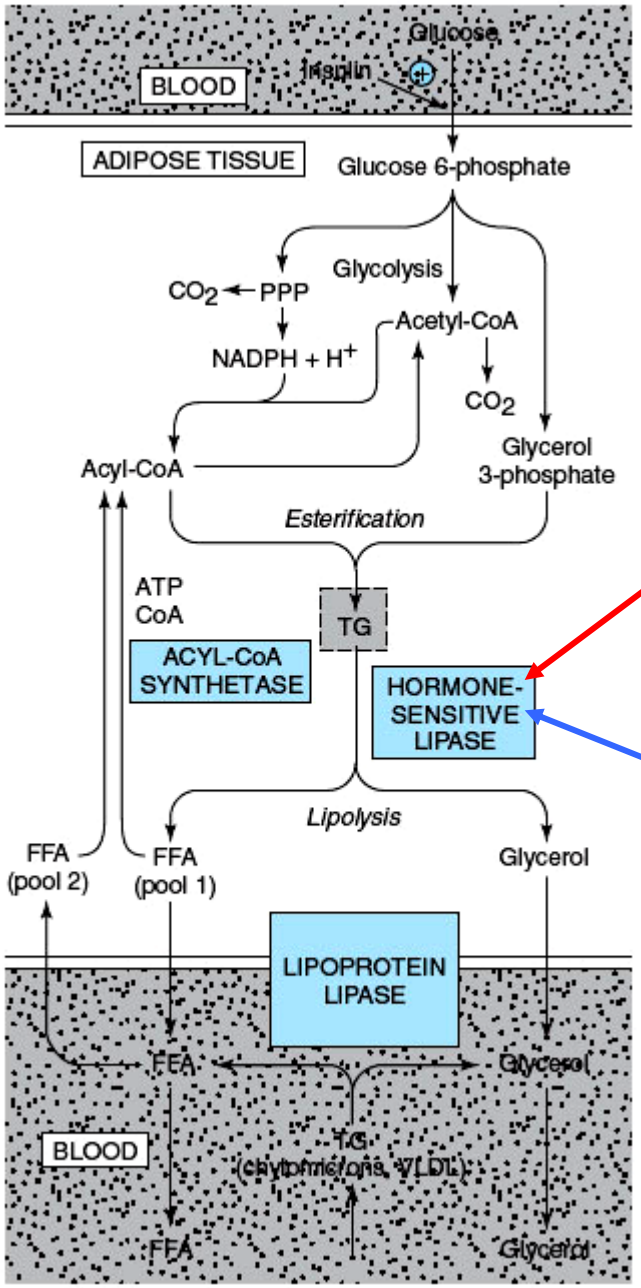
4

Lipid metabolism regulation.
Pathology of the lipid metabolism

Contents

1. Regulation of lipid metabolism.
   - Hormonal regulation of lipolysis and lipogenesis.
   - Integration of lipid and carbohydrate metabolism.
2. Lipid-carbohydrate Randle cycle. Triglycerides – fatty acids cycle.
   - Mechanisms and physiological value.
3. Integration of ketone bodies, FFA and glucose metabolism.
4. Pathology of lipid metabolism.
   - Disorder of lipid digestion and absorption, manifestations.
   - Fat liver – mechanisms of development and prophylaxis.
   - Obesity – types, mechanisms of development and complication.
   - Dislipoproteinemias. Fridrikson's classification, biochemical and clinical and diagnostic characteristic of basic groups.
   - Lipidoses – inheritable disorders of lipid metabolism.
5. Peroxidation of membrane lipids. The mechanism of initiation. Reactions, metabolites. Biological significance in norm and pathology. Antioxidant protection.

Metabolism in Adipose Tissue



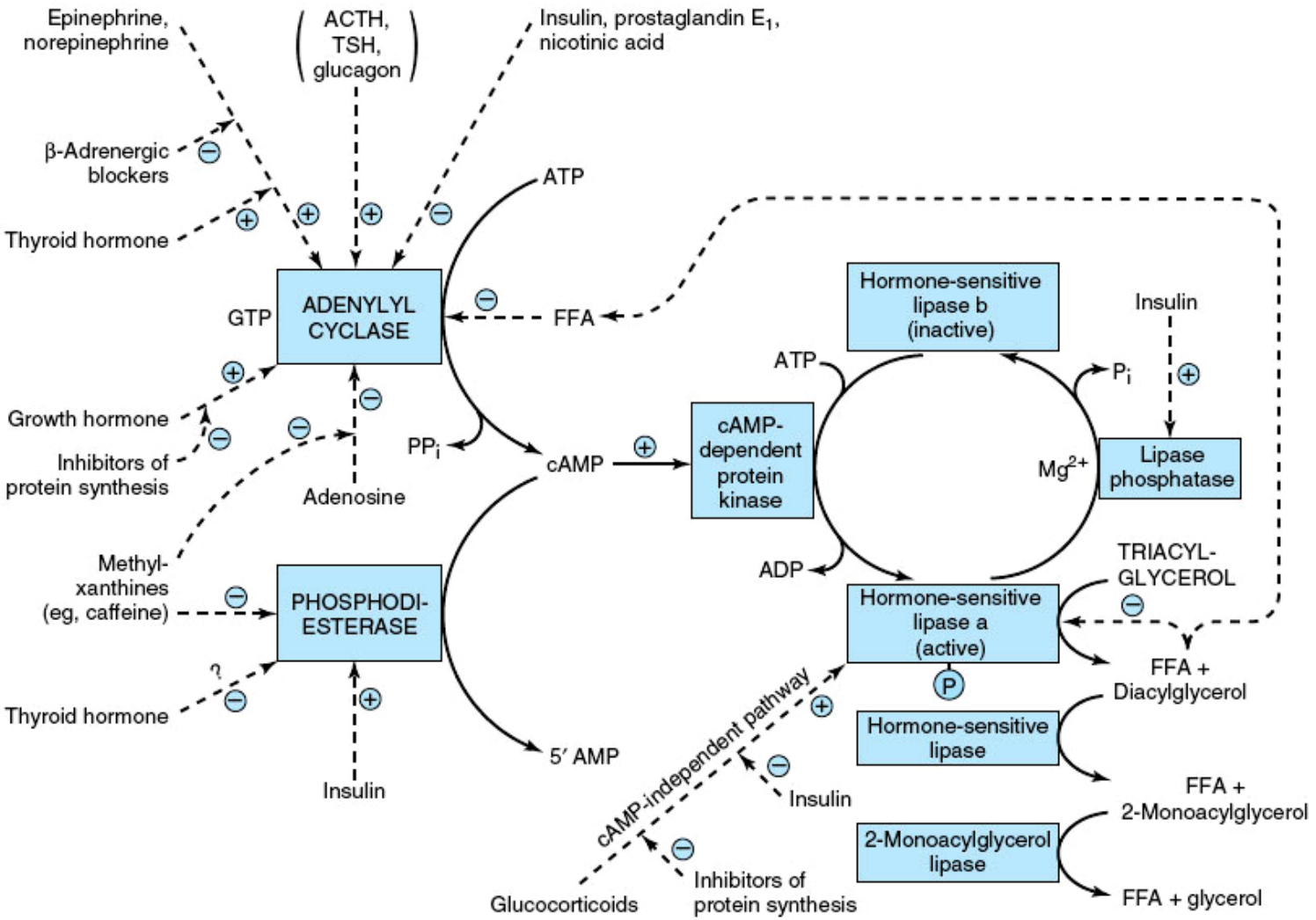
ACTH, TSH, glucagon, epinephrine, norepinephrine, vasopressin

Activators

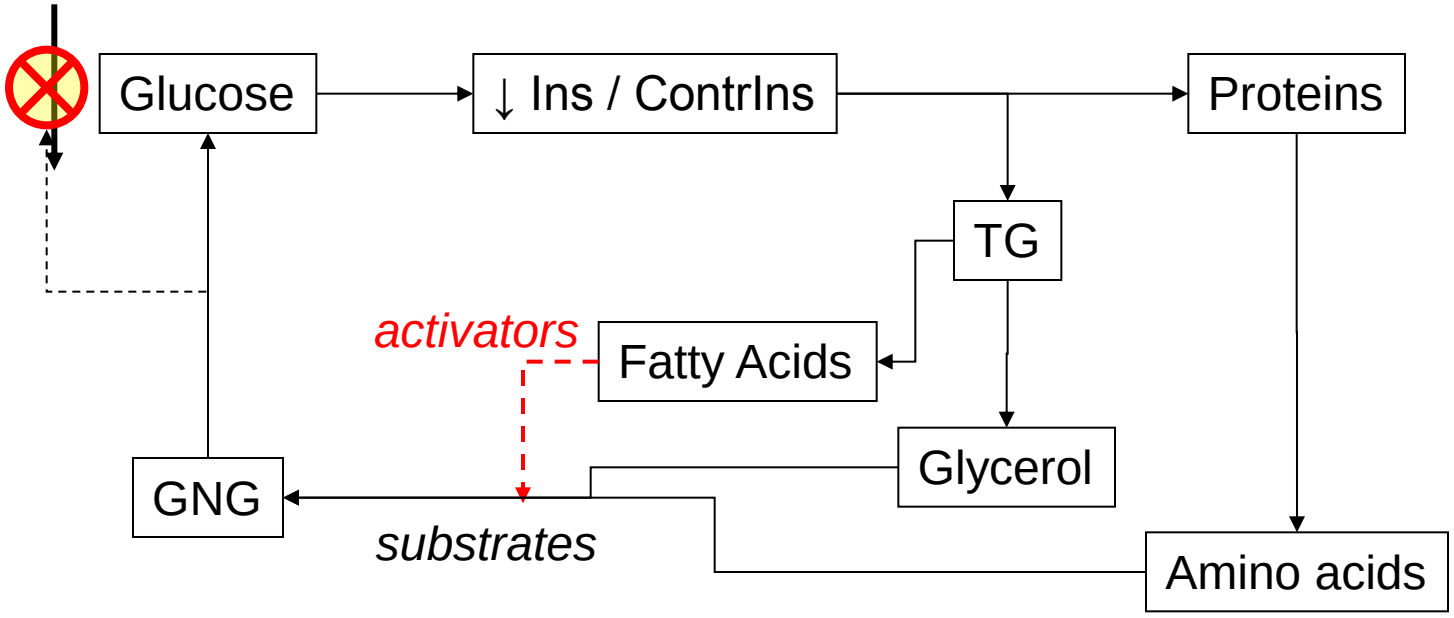
Insulin, prostaglandin E1, nicotinic acid

Inhibitors

Hormonal Regulation of Lipolysis in Adipocytes

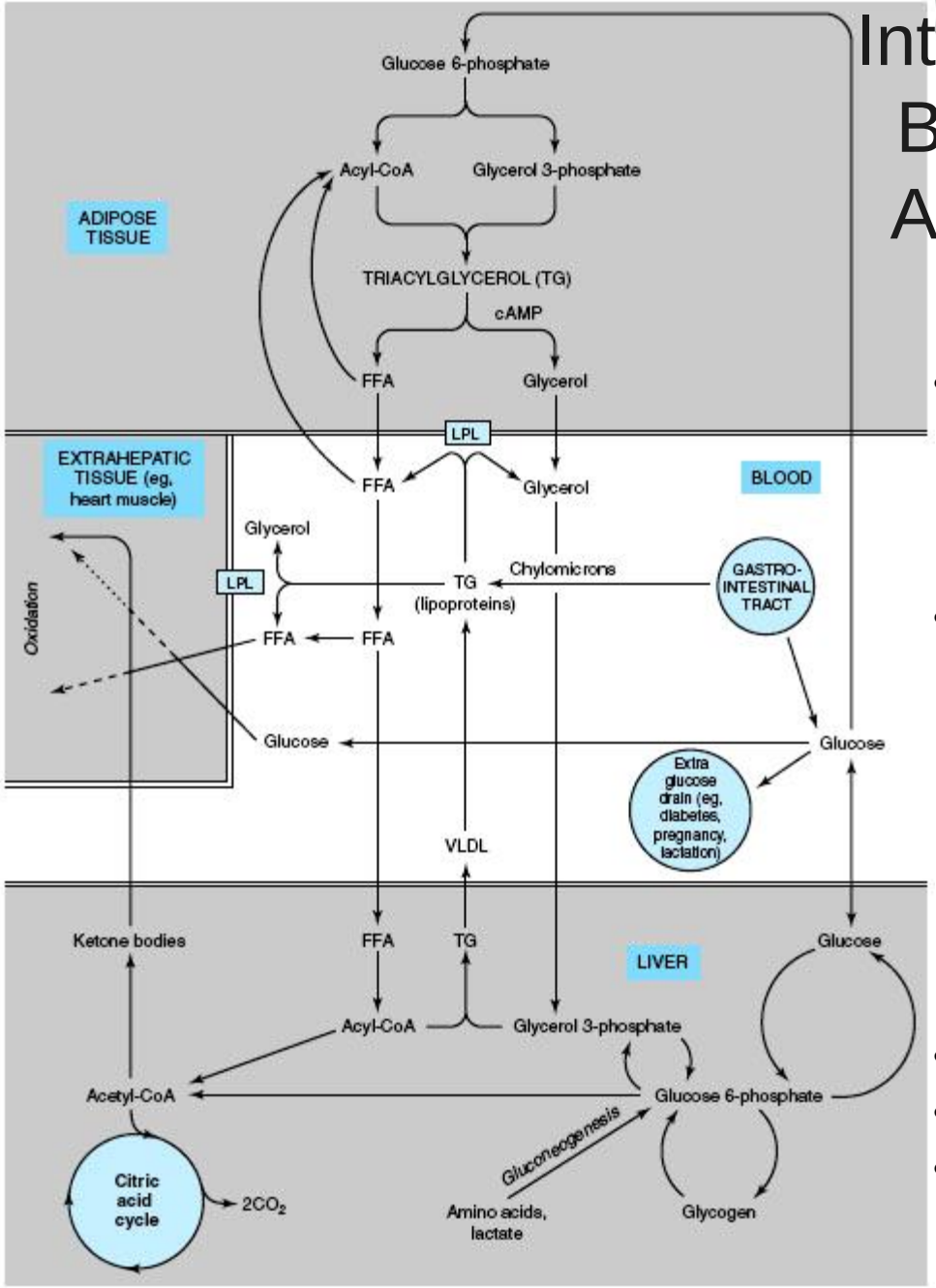


Randle Cycle



- Randle cycle (lipid-carbohydrate cycle) is the mechanism of blood glucose level regulation during starvation.

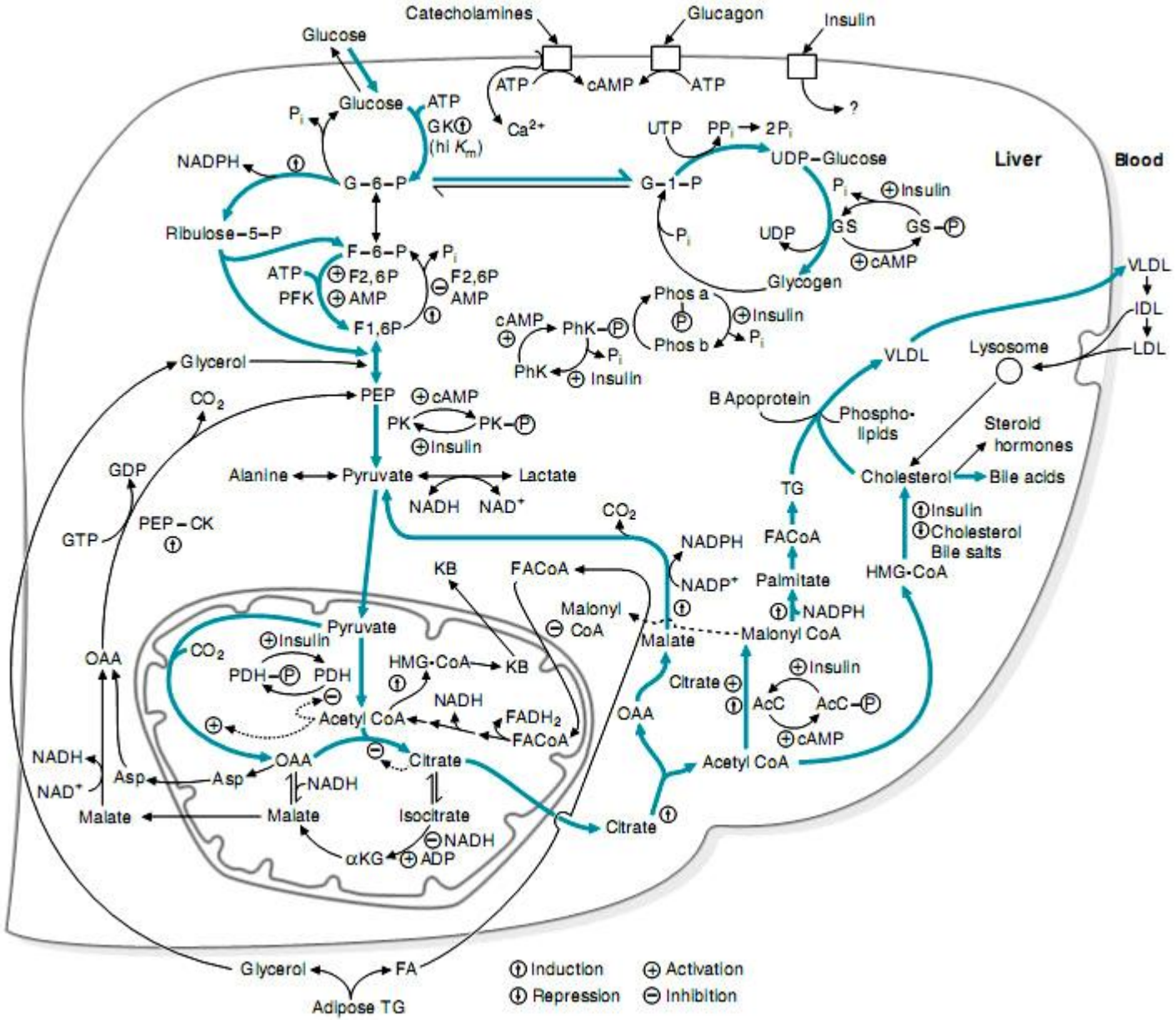
Integration of Ketone Bodies, Free Fatty Acids and Glucose Metabolism



- Metabolic interrelationships between adipose tissue, the liver, and extrahepatic tissues.
- In extrahepatic tissues such as heart, metabolic fuels are oxidized in the following order of preference:
  - ketone bodies,
  - fatty acids,
  - glucose.

- LPL, lipoprotein lipase;
- FFA, free fatty acids;
- VLDL, very low density lipoproteins

Regulation of Carbohydrate and Lipid Metabolism in Liver

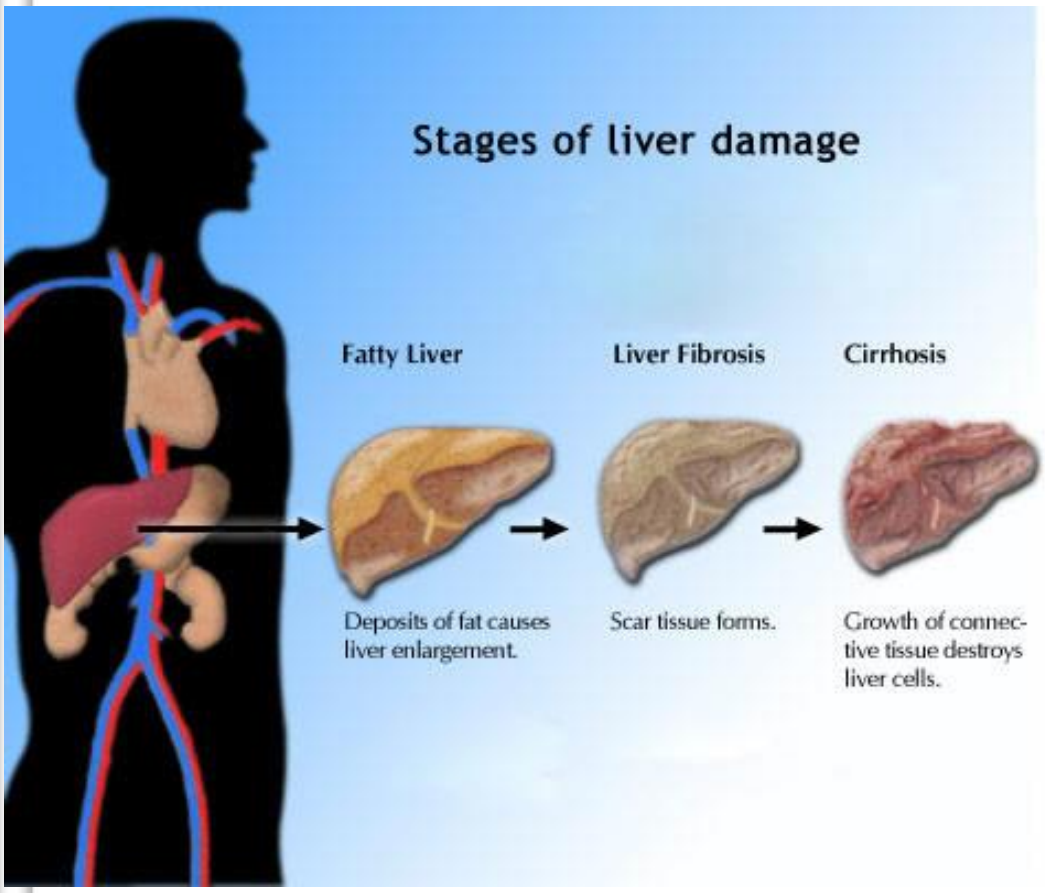


Pathology of Lipid Metabolism

Disorders of Lipid Digestion and Absorption

- There are 3 possible causes:
  - **Hepatic** - abnormalities in bile secretion (obstruction of bile duct).
  - **Pancreatic** - abnormal pancreatic lipase, phospholipase synthesis or secretion, also absense of phospholipase.
  - **Enteric** - inability of enterocytes to absorb fatty acids and monoacylglycerols (colitis, defects in chylomicron synthesis)
- General syndrome – **steatorrhea** (fat in feces).

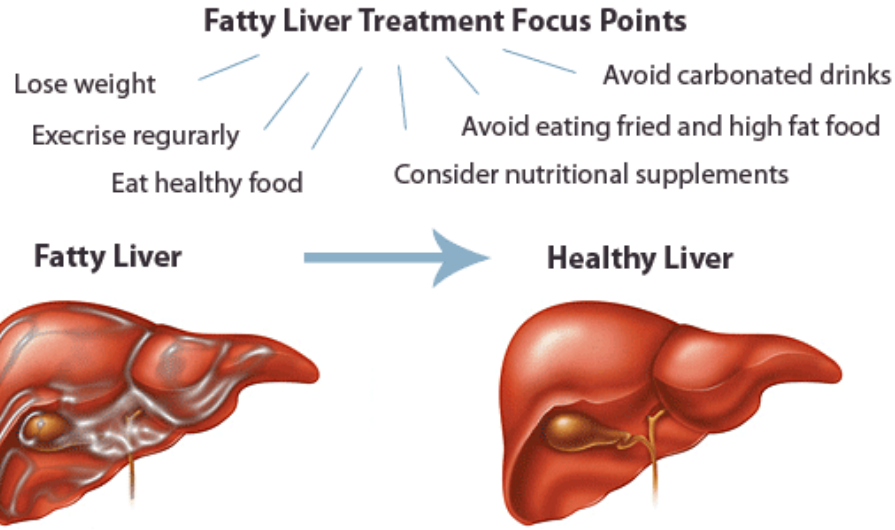
Liver Damaging Factors



- In a subset of individuals hepatic steatosis promotes an inflammatory response in the liver, referred to as steatohepatitis, which can progress to cirrhosis and liver cancer.

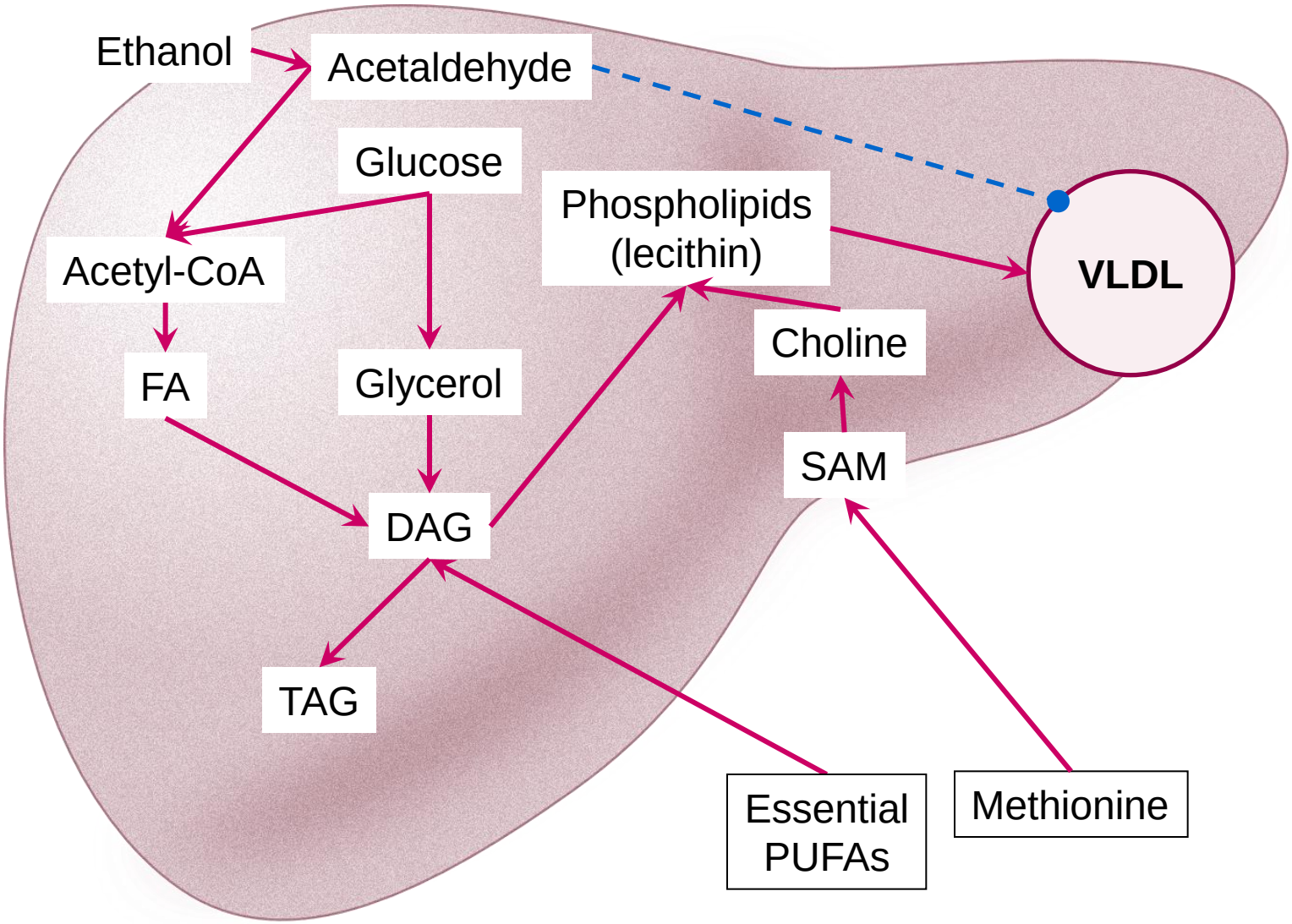
Fatty liver

- Nonalcoholic fatty liver disease (NAFLD) is the most common form of liver disease in Western countries.
- The accumulation of excess triglyceride in the liver, a condition known as **hepatic steatosis** (or **fatty liver**), is associated with adverse metabolic consequences including insulin resistance and dyslipidemia.
- Factors promoting deposition of fat in the liver:
  - obesity,
  - diabetes,
  - insulin resistance,
  - alcohol ingestion.

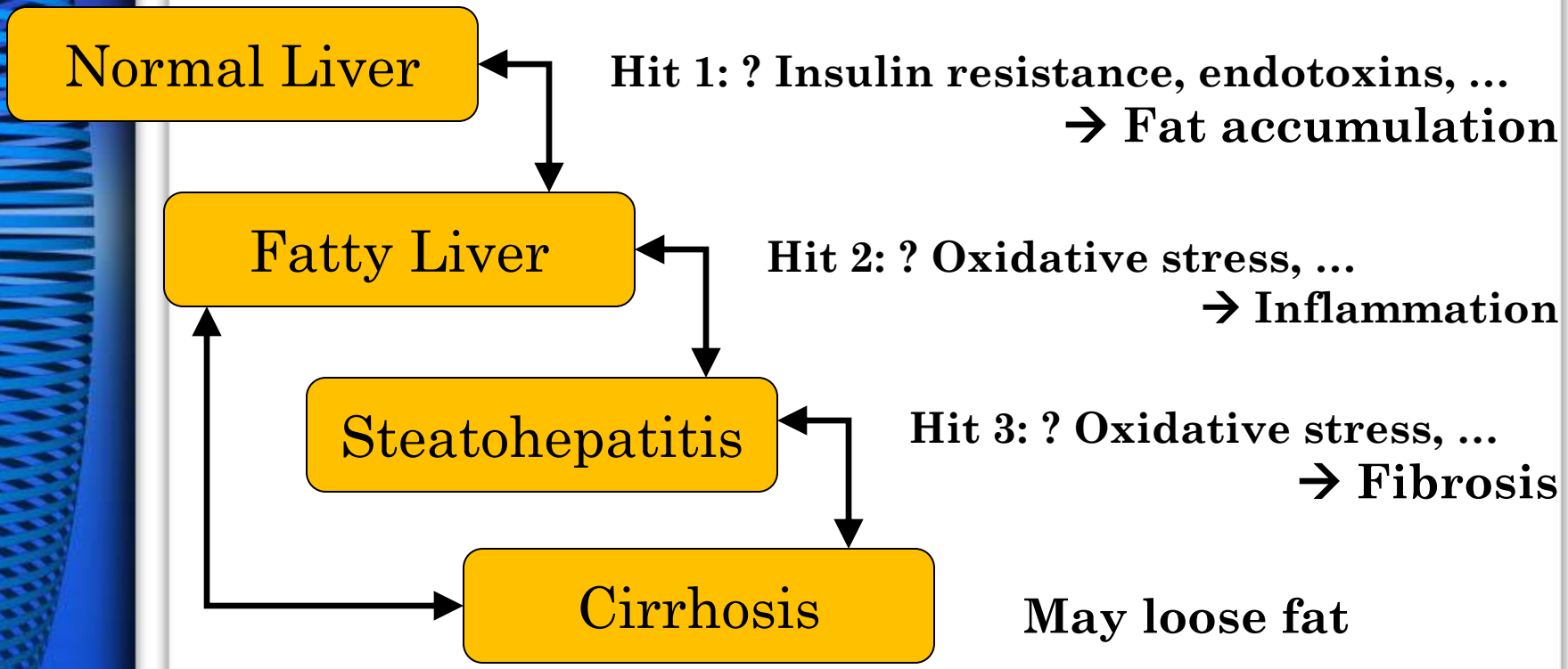


http://www.fatty-liver.com/treatment/

Hepatoprotectors

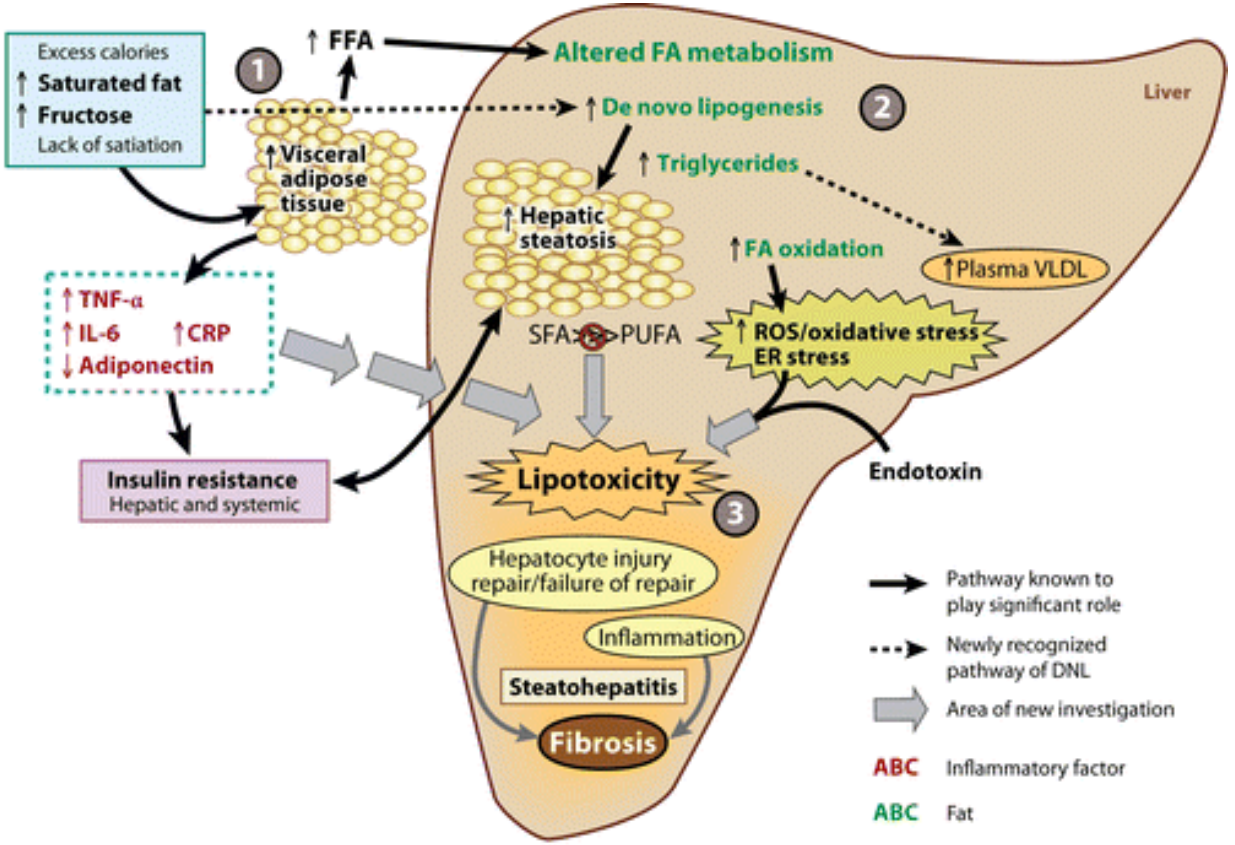


Multiple Hit Theory



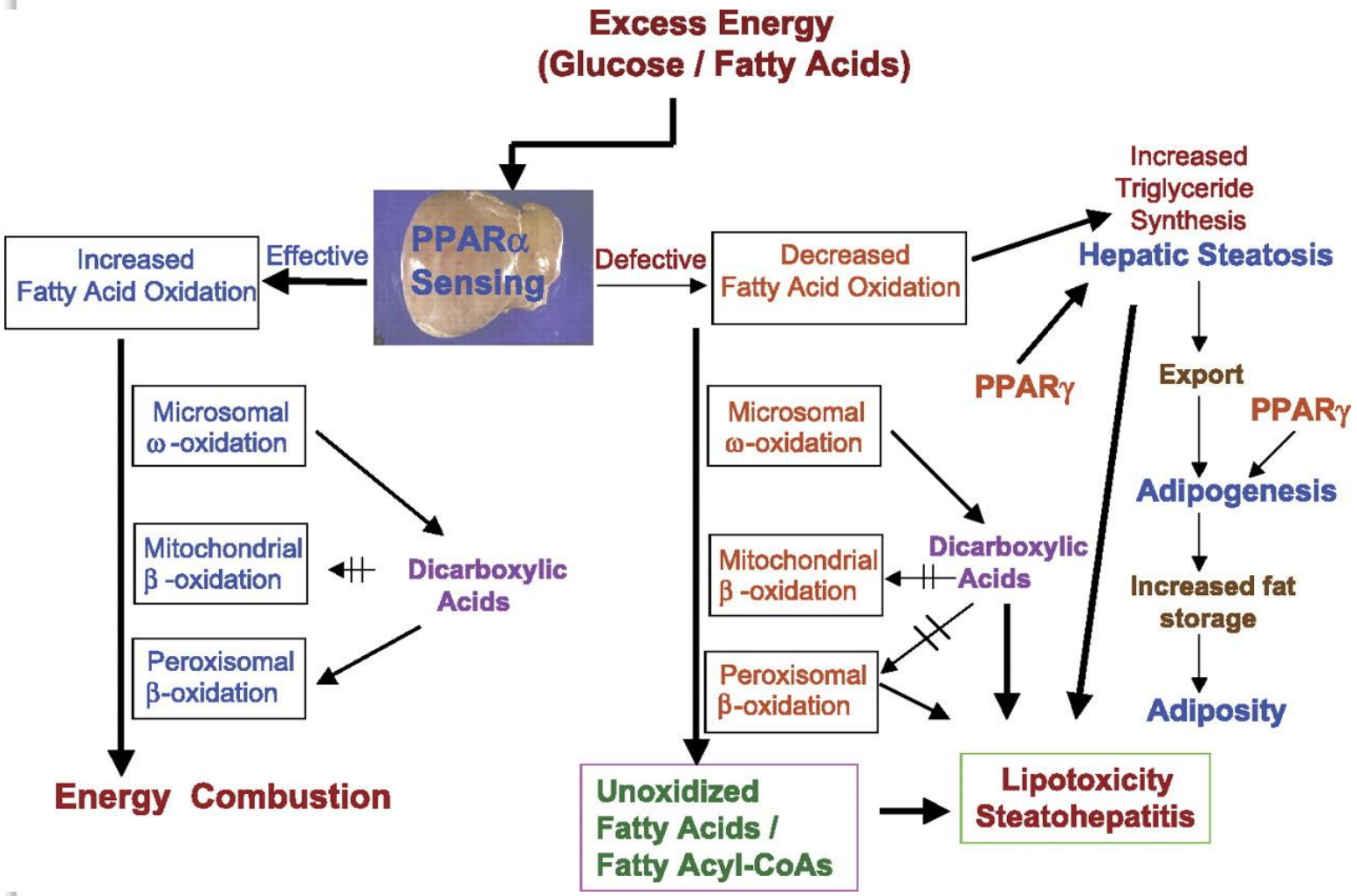
Koval A. (C), 2016

Cytokines in Fatty Liver

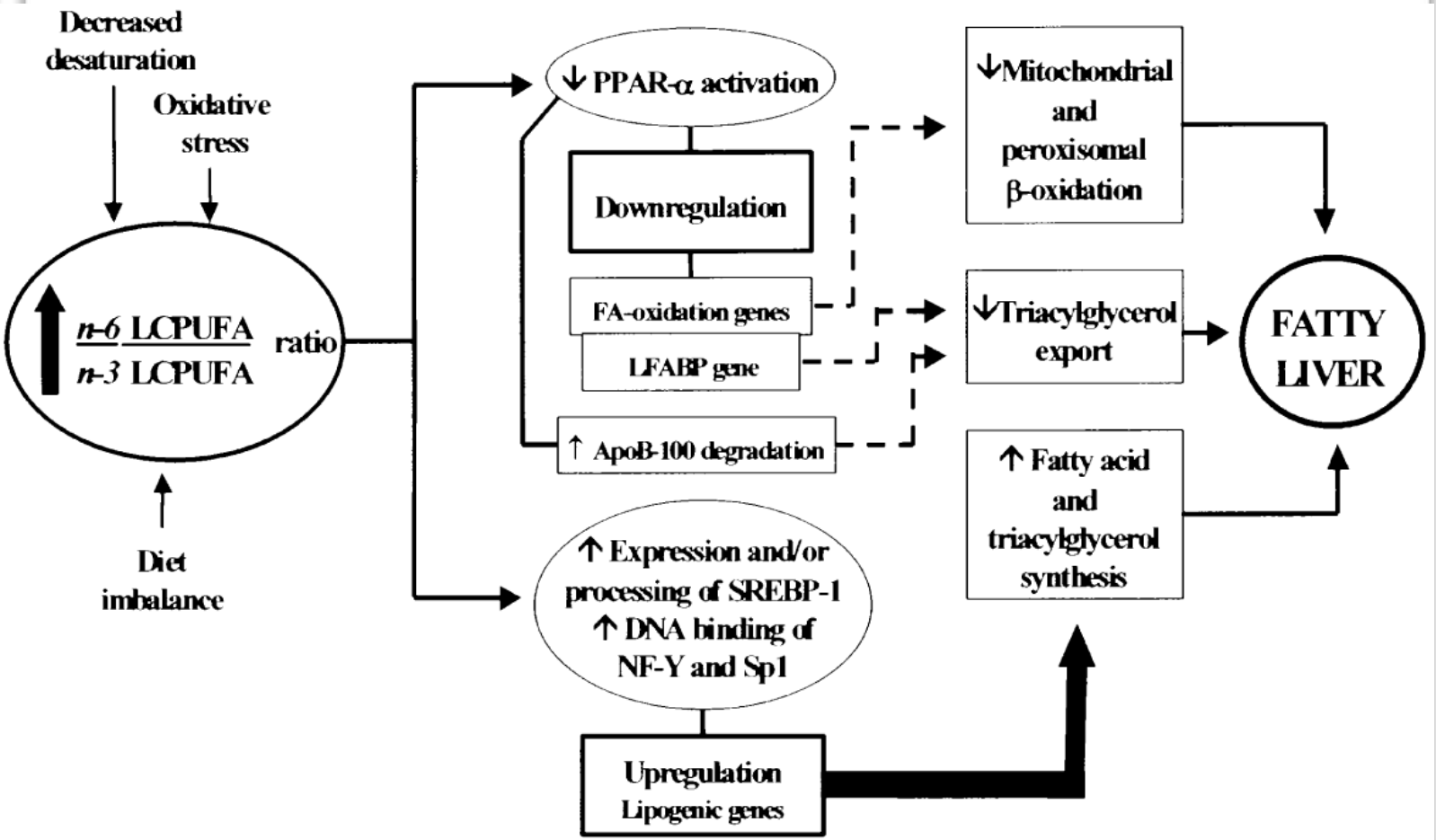


Tiniakos DG, et al. 2010.
Annu. Rev. Pathol. Mech. Dis. 5:145–71

PPARs in Fatty Liver

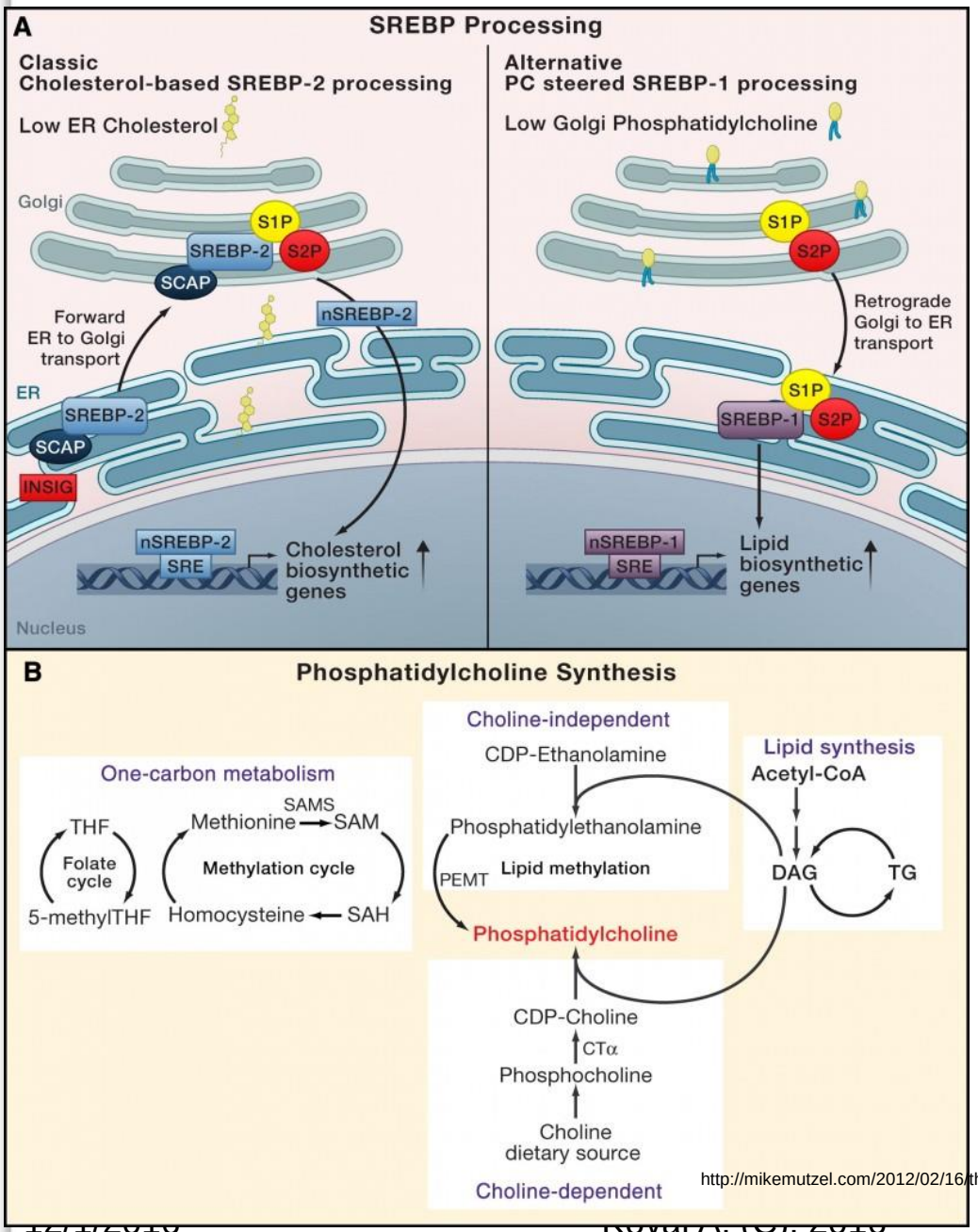


New Data About Fatty Liver



http://www.clinsci.org/cs/106/0635/cs1060635f03.htm

Role of SREBP-4 and ChREBP-1



http://mikemutzel.com/2012/02/16/the-role-of-methyl-donor-deficiency-in-lipid-synthesis-srebp-1/

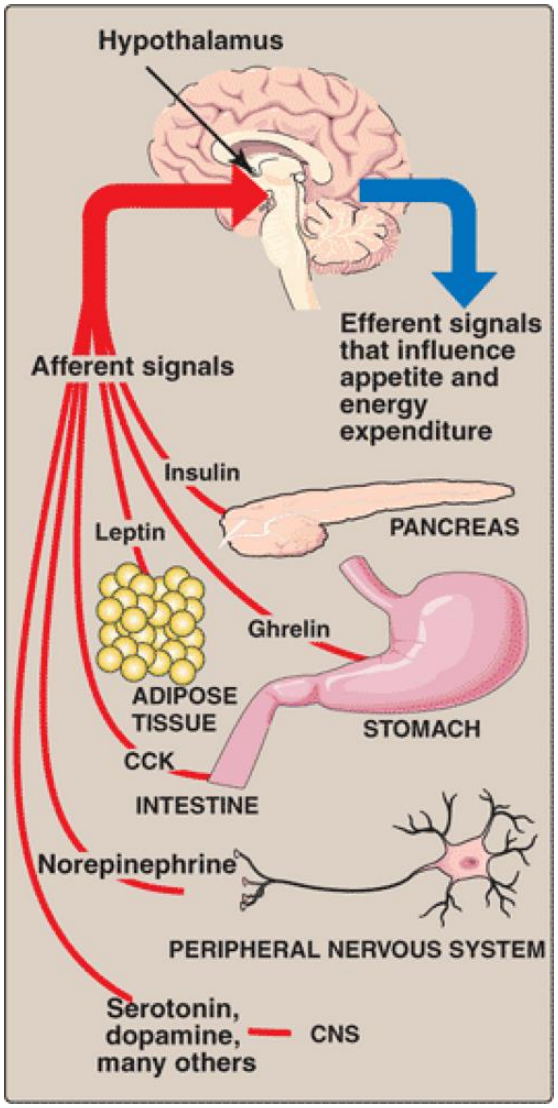
Obesity

- **Obesity** is a disorder of body weight regulatory systems characterized by an accumulation of excess body fat.
  - In primitive societies, in which daily life required a high level of physical activity and food was only available intermittently, a genetic tendency favoring storage of excess calories as fat had a survival value.

Epidemic of Obesity

- Global problem, not limited to the US.
- The prevalence of obesity increases with age.
  - risk of developing associated diseases: insuline resistance, type 2 diabetes, hypertension, gallbladder disease, and cardiovascular disease.
- Explosion of childhood obesity, 3-fold increase over the last two decades.
- There are more obese than undernourished individuals worldwide.

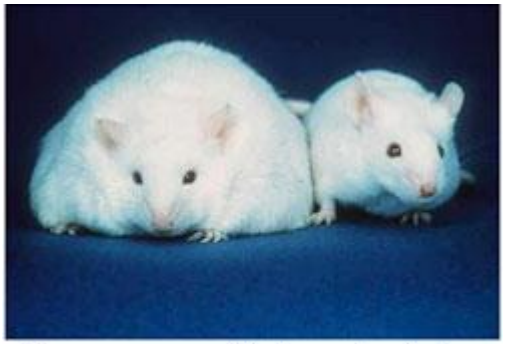
Signaling in Obesity



- Obesity results when energy intake exceeds energy expenditure.
- Mechanism involves a complex interaction of biochemical, neurologic, environmental, and psychologic factors.
  - Afferent neural signals, circulating hormones, and metabolites affects the hypothalamus.
  - release of hypothalamic peptides,
  - activate efferent neural signals.

Body Weight Hormonal Regulation

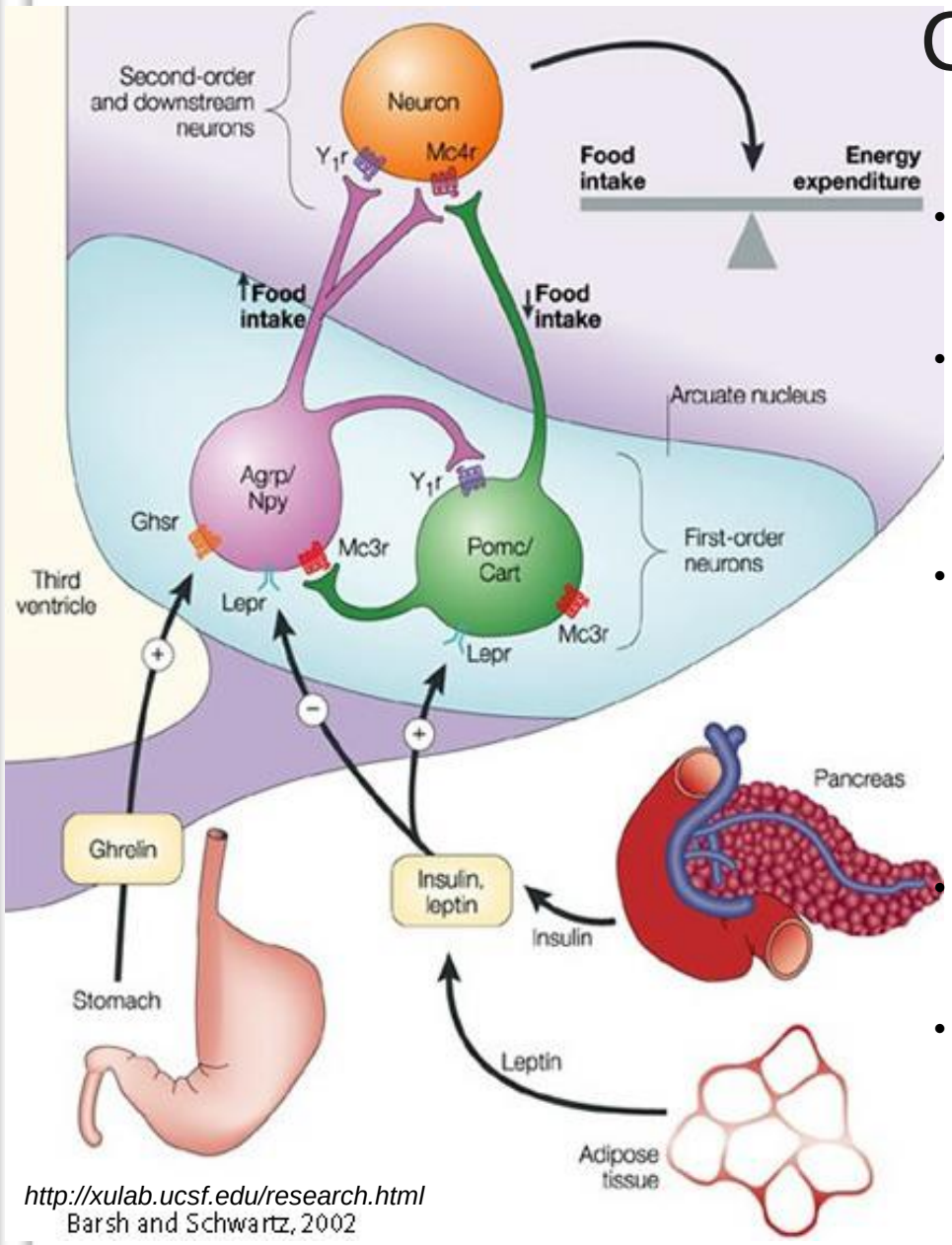
- **Leptin.** Studies of the molecular genetics of mouse obesity have led to the isolation of at least six genes associated with obesity.
  - The most well-known mouse gene, named *ob* (for obesity), leads to severe hereditary obesity in mice.
- **Ghrelin**, a peptide secreted primarily by the stomach, is the only known appetite-stimulating hormone.
  - Injection of ghrelin increases short-term food intake in rodents, and may decrease energy expenditure and fat catabolism.
- Peptides, such as **cholecystokinin**, released from the gut following ingestion of a meal can act as satiety signals to the brain.
- **Insulin** not only influences metabolism, but also promotes decreased energy intake.



knee-deepincortisol.blogspot.com

Obese mouse, unable to produce leptin, and normal mouse

Control of energy homeostasis



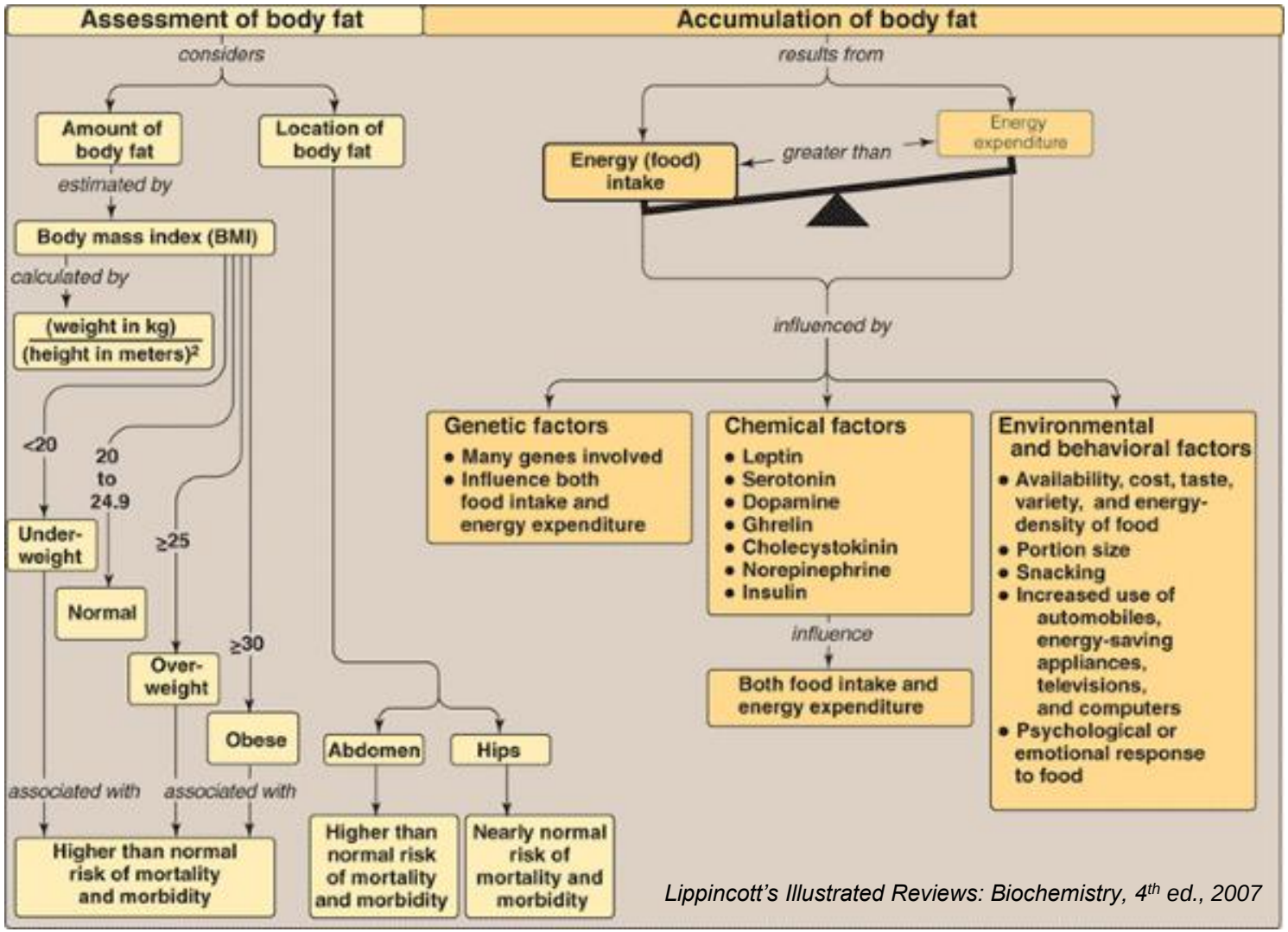
http://xulab.ucsf.edu/research.html
Barsh and Schwartz, 2002

- 2 sets of neurons in the arcuate nucleus – **Agrp/Npy** and **Pomc/Cart**.
- Neuropeptides that stimulate food intake and decrease energy expenditure:
  - **Agrp** (agouti-related protein)
  - **Npy** (neuropeptide Y).
- Neuropeptides that inhibit food intake and increase energy expenditure:
  - **alpha-melanocyte stimulating hormone** (a derivative of proopiomelanocortin, Pomc)
  - **Cart** (cocaine- and amphetamine-regulated transcript).
- **Insulin** and **leptin** inhibit Agrp/Npy neurons and stimulate adjacent Pomc/Cart neurons.
- **Ghrelin** can activate Agrp/Npy neurons, stimulates food intake.
  - **Ghsr**, growth hormone secretagogue receptor;
  - **Lepr**, leptin receptor;
  - **Mc3r/Mc4r**, melanocortin 3/4 receptor;
  - **Y1r**, neuropeptide Y1 receptor.

Obesity Treatment

- Weight reduction: negative energy balance to reduce body weight: by decreasing caloric intake and/or increasing energy expenditure.
- All **diets** that lead to short-term weight loss.
  - Long-term maintenance of weight loss is difficult to achieve.
- Modest reduction in food intake occurs with **pharmacologic treatment**.
- **Surgical procedures** – for severely obese patient when other treatments were non effective.

Key Concept Map For Obesity



Lippincott's Illustrated Reviews: Biochemistry, 4th ed., 2007

Genetic Basis of Familial Hypercholesterolemia

- FH is an inherited disorder comprising four different classes of mutation in the LDL receptor gene.
  - The class 1 defect (the most common) results in a complete loss of receptor synthesis.
  - The class 2 defect results in the synthesis of a receptor protein that is not properly processed in the Golgi apparatus and therefore is not transported to the plasma membrane.
  - The class 3 defect results in an LDL receptor that is incapable of binding LDLs.
  - The class 4 defect results in receptors that bind LDLs but do not cluster in coated pits and are, therefore, not internalized.

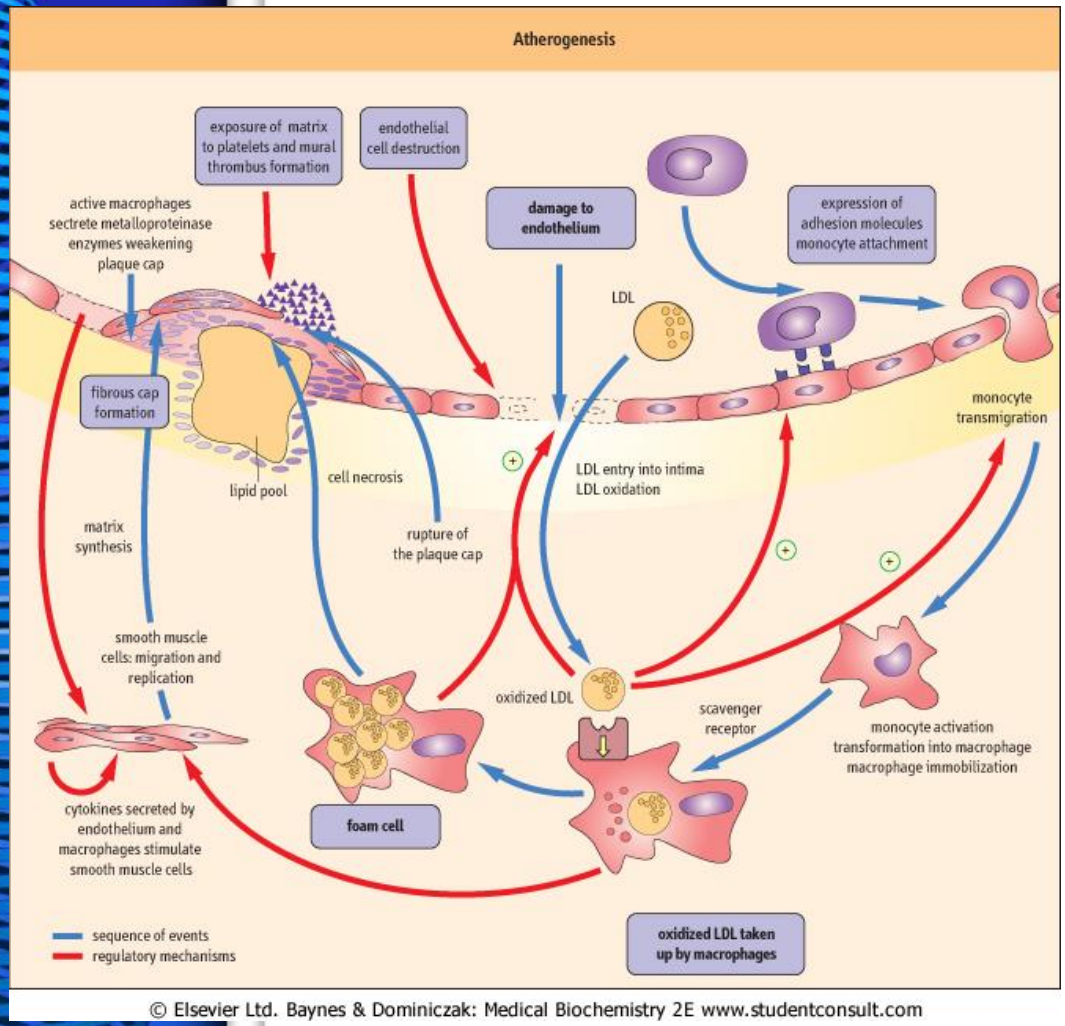
Hyperlipoproteinemias

Disorder	Defect	Comments
Type I (familial LPL deficiency, familial hyperchylomicronemia)	(a) deficiency of LPL; (b) production of abnormal LPL; (c) apoC-II deficiency	slow chylomicron clearance, reduced LDL and HDL levels; treated by low fat/complex carbohydrate diet; no increased risk of coronary artery disease
Type II (familial hypercholesterolemia, FH)	4 classes of LDL receptor defect	reduced LDL clearance leads to hypercholesterolemia, resulting in atherosclerosis and coronary artery disease
Type III (familial dysbetalipoproteinemia, remnant removal disease, broad beta disease, apolipoprotein E deficiency)	hepatic remnant clearance impaired due to apoE abnormality; patients only express the $apoE_2$ isoform that interacts poorly with the apoE receptor	causes xanthomas, hypercholesterolemia and atherosclerosis in peripheral and coronary arteries due to elevated levels of chylomicrons and VLDLs

Phenotypic classification of dyslipidemia (by Fredrickson)

Dyslipidemia type (Fredrickson)	Increased electrophoretic fraction (lipoproteins)	Increased cholesterol	Increased triglyceride
I	chylomicrons	yes	yes
IIa	beta (LDL)	yes	no
IIb	pre-beta & beta (VLDL & LDL)	yes	yes
III	'broad beta' band (IDL)	yes	yes
IV	pre-beta (VLDL)	no	yes
V	pre-beta (VLDL) plus chylomicrons	yes	yes

Atherogenesis: Process & Stages



Atherogenesis is driven by signals mediated by cytokines and growth factors generated by all the major types of cells participating in the process: endothelial cells, macrophages, T lymphocytes and vascular smooth muscle cells (VSMC).

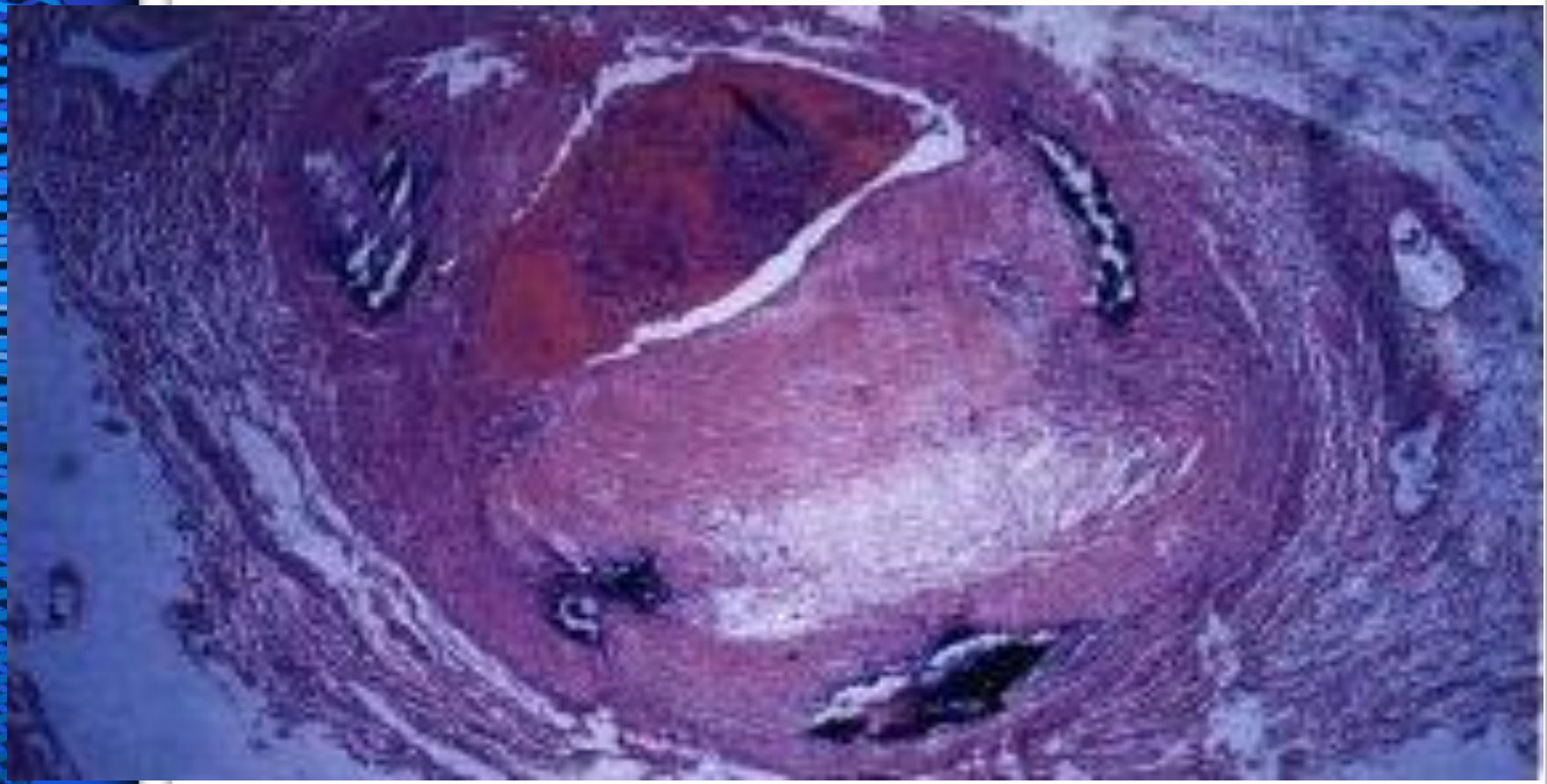
Multiple activation paths:

- the expression of MCP-1 and VCAM-1 may be stimulated by signals generated macrophages as well as by the oxidized LDL.
- VSMC may be stimulated by the dysfunctional endothelial cells, by macrophages, and by T lymphocytes (also the autocrine activation).
- Note that a hormone, angiotensin II also participates in these processes.

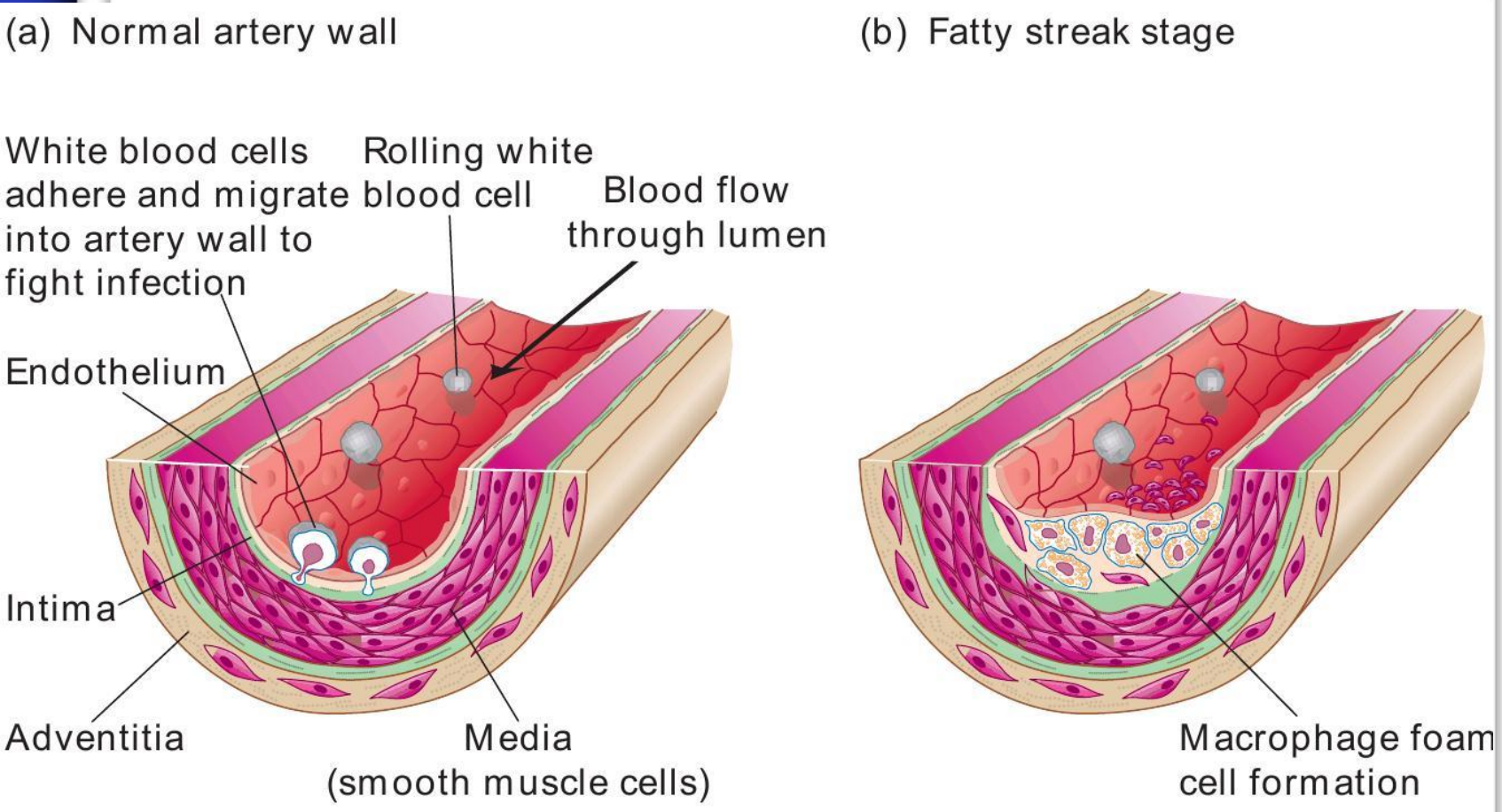
MCP-1: monocyte chemoattractant protein 1, VCAM-1: vascular cell adhesion molecule 1, ICAM-1: intracellular cell adhesion molecule 1, TNFβ: tumor necrosis factor beta, TNFα: tumor necrosis factor alpha, IFNγ: interferon gamma, NO: nitric oxide, PDGF: platelet-derived growth factor, bFGF: basic fibroblast growth factor, IGF-1: insulin-like growth factor 1, EGF: epidermal growth factor, TGFβ: transforming growth factor beta, IL-1: interleukin 1.

Artery in Healthy Man

Plaque Formation: Artery Blocked

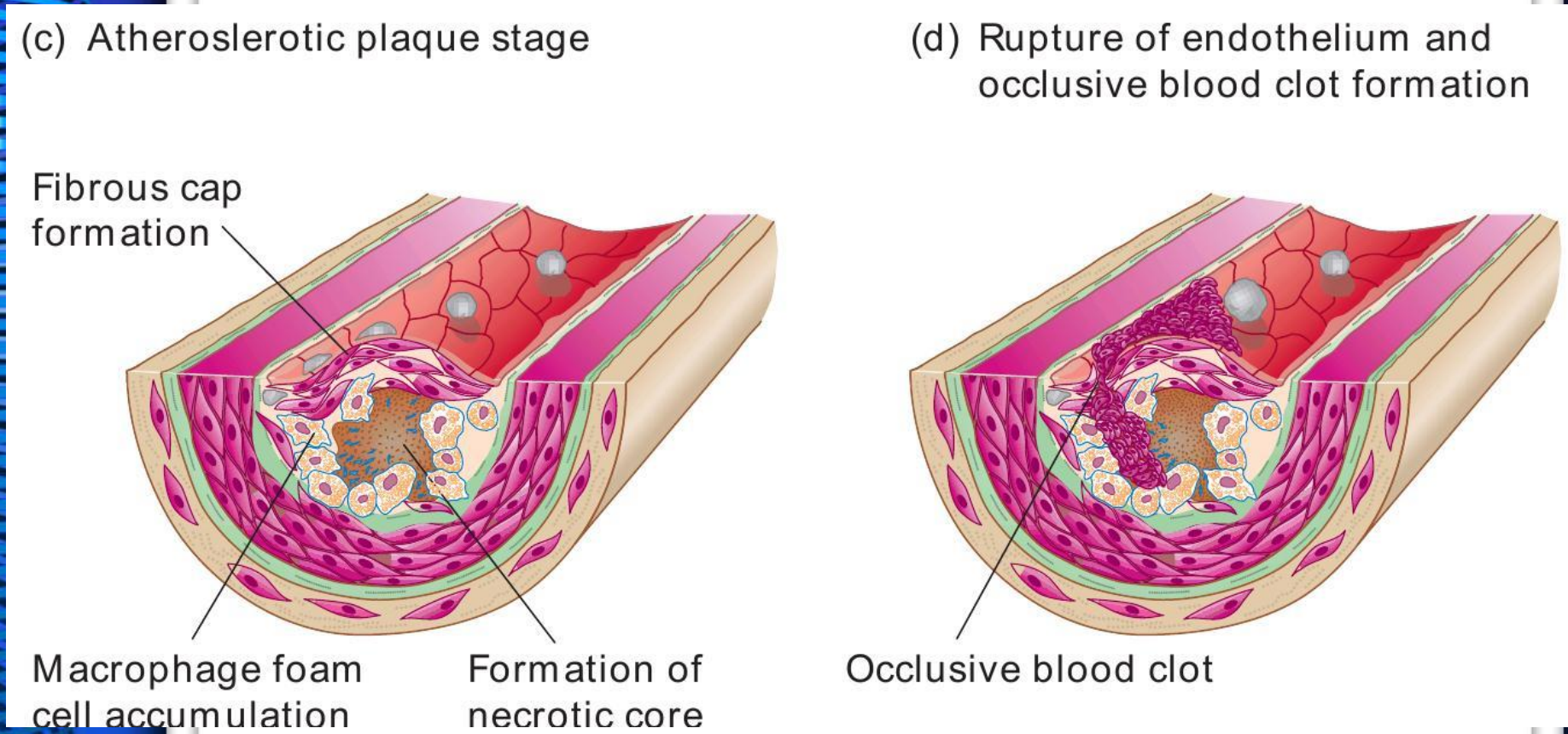


Normal Artery and Fatty Streak Stage



Molecular Cell Biology Lodish 5Th Ed

Plaque Stage and Rupture of Endothelium With Blood Clot Formation



Molecular Cell Biology Lodish 5Th Ed

Lipid Peroxidation Is Source Of Free Radicals

- Peroxidation **(auto-oxidation)** of lipids is responsible for deterioration of foods **(rancidity);** for damage to tissues in vivo, where it may be a cause of **cancer**, **inflammatory diseases, atherosclerosis, and aging.**
- The deleterious effects are considered to be caused by **free radicals** (ROO•, RO•, OH•) produced during peroxide formation from fatty acids containing methylene-interrupted double bonds, ie, those found in the naturally occurring polyunsaturated fatty acids.

Lipid Peroxidation Is a Chain Reaction: Initiation

- Lipid peroxidation is a chain reaction providing a continuous supply of free radicals that initiate further peroxidation. The whole process can be depicted as follows:
- **(1)** Initiation:

$$ROOH + Metal^{(n)+} \rightarrow ROO^{\bullet} + Metal^{(n-1)+} + H^{+}$$

$$X^{\bullet} + RH \rightarrow R^{\bullet} + XH$$

Lipid Peroxidation: Propagation and Termination

- Propagation: $R^{\bullet} + O_2 \rightarrow ROO^{\bullet}$

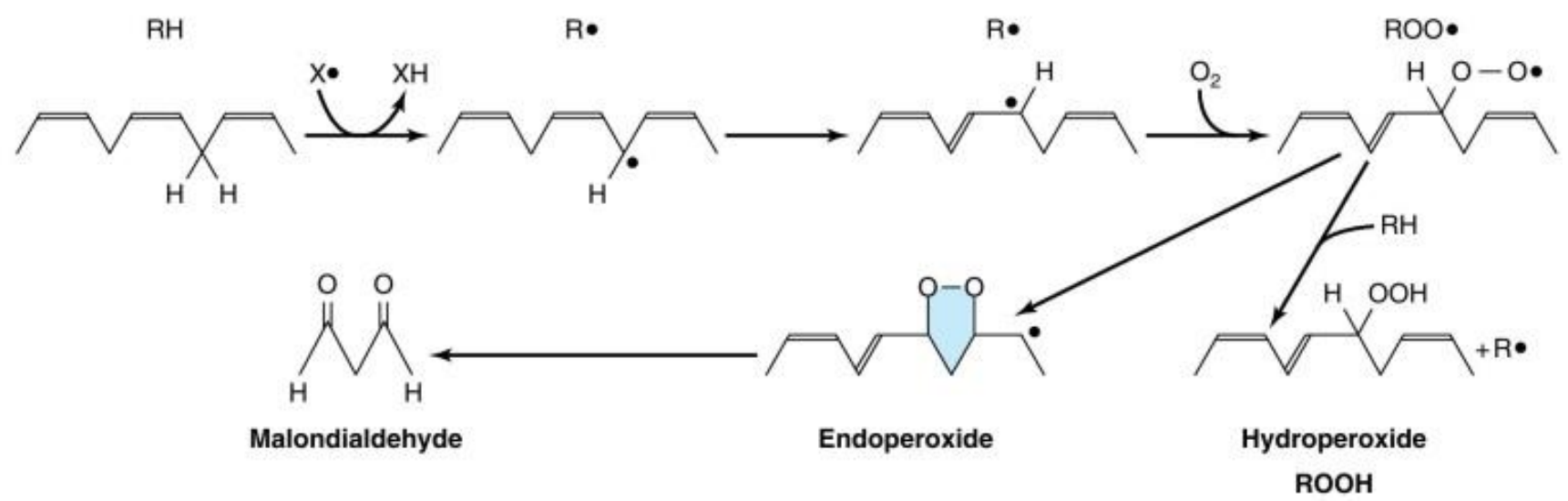
  $ROO^{\bullet} + RH \rightarrow ROOH + R^{\bullet}$, etc

- Termination: $ROO^{\bullet} + ROO^{\bullet} \rightarrow ROOR + O_2$

  $ROO^{\bullet} + R^{\bullet} \rightarrow ROOR$

  $R^{\bullet} + R^{\bullet} \rightarrow RR$

Lipid Peroxidation



Lipid peroxidation. The reaction is initiated by an existing free radical (X•), by light, or by metal ions. Malondialdehyde is only formed by fatty acids with three or more double bonds and is used as a measure of lipid peroxidation together with ethane from the terminal two carbons of ω3 fatty acids and pentane from the terminal five carbons of ω6 fatty acids.

(from Marry, Grenner et al. "Harpers Illustrated Biochemistry", 2004)

Lipidoses (Lipid Storage Diseases) Examples of Sphigolipidoses

Disease	Enzyme Deficiency	Lipid Accumulating	Clinical Symptoms
Tay-Sachs disease	Hexosaminidase A	Cer—Glc—Gal(NeuAc)÷GalNAc G_{M2} Ganglioside	Mental retardation, blindness, muscular weakness
Fabry disease	α-Galactosidase	Cer—Glc—Gal—÷Gal Globotriaosylceramide	Skin rash, kidney failure (full symptoms only in males; X-linked recessive)
Metachromatic leukodystrophy	Arylsulfatase A	Cer—Gal—÷OSO_3 3-Sulfogalactosylceramide	Mental retardation and psychologic disturbances in adults; demyelination
Krabbe disease	β-Galactosidase	Cer—÷Gal Galactosylceramide	Mental retardation; myelin almost absent
Gaucher disease	β-Glucosidase	Cer—÷Glc Glucosylceramide	Enlarged liver and spleen, erosion of long bones, mental retardation in infants
Niemann-Pick disease	Sphingomyelinase	Cer—÷P—choline Sphingomyelin	Enlarged liver and spleen, mental retardation; fatal in early life
Farber disease	Ceramidase	Acyl—÷Sphingosine Ceramide	Hoarseness, dermatitis, skeletal deformation, mental retardation; fatal in early life

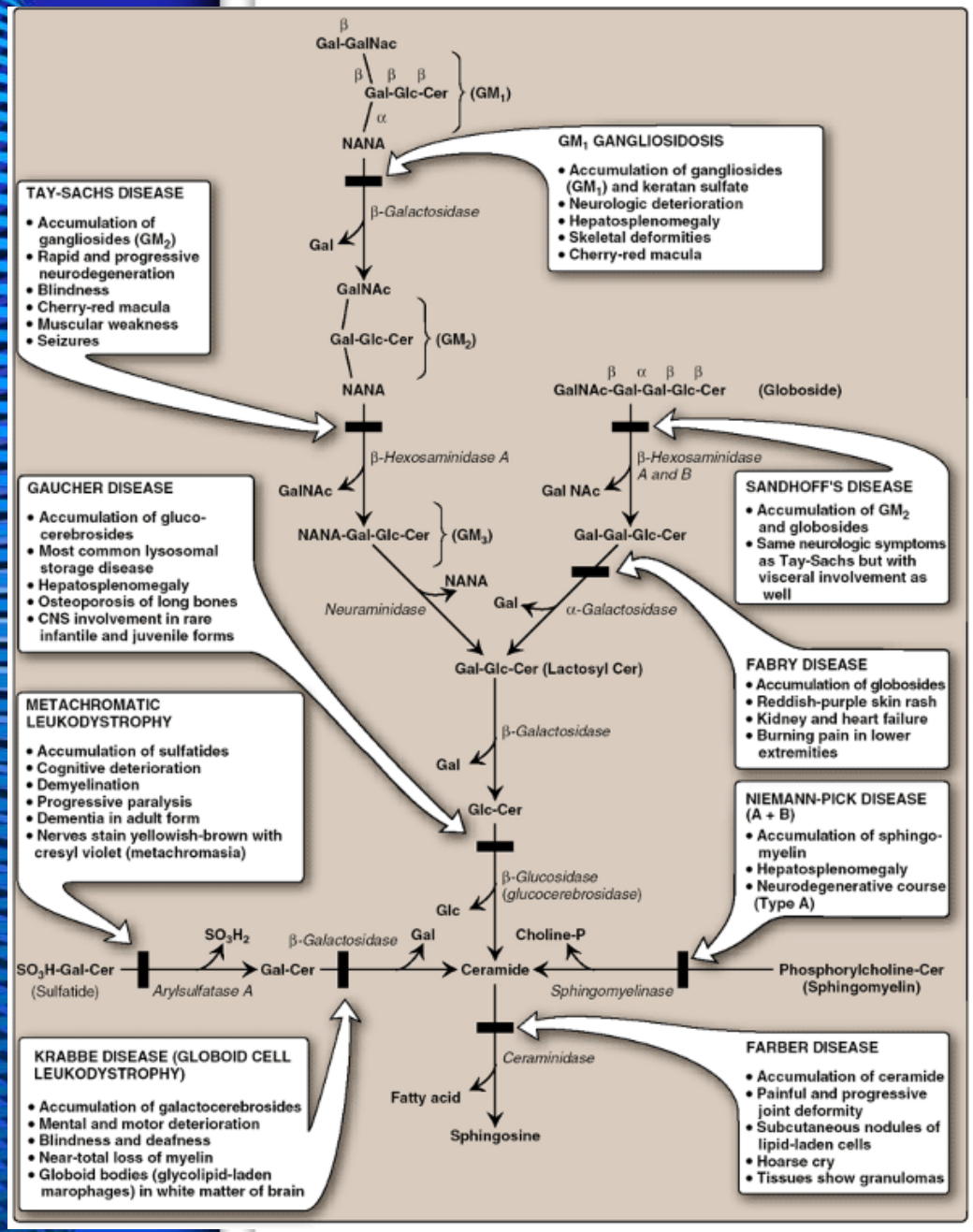
Abbreviations: Cer, ceramide; Gal, galactose; Glc, glucose; NeuAc, *N*-acetylneuraminic acid; ÷, site of deficient enzyme reaction.

Harper's Illustrated Biochemistry, 30th Ed. (2015)

Lipidoses: Symptoms

Disease	Mental retardation	Liver damage	Myelin defects	Specialized symptoms	Fatal
Farber's				Damage to joints, granulomas	X
Niemann-Pick	X	X			X
Gaucher's	X	X		Bone damage	Frequently
Krabbe's	X		X	Globoid bodies in brain	
Fabry's				Rash, kidney failure	
Metachromatic leukodystrophy	X		X	Paralysis, dementia	
Tay-Sachs	X			Blindness, seizures	X
Sandhoff's	X			Same as Tay-Sachs; progresses more rapidly	X
Generalized gangliosidosis	X	X		Bone damage	X

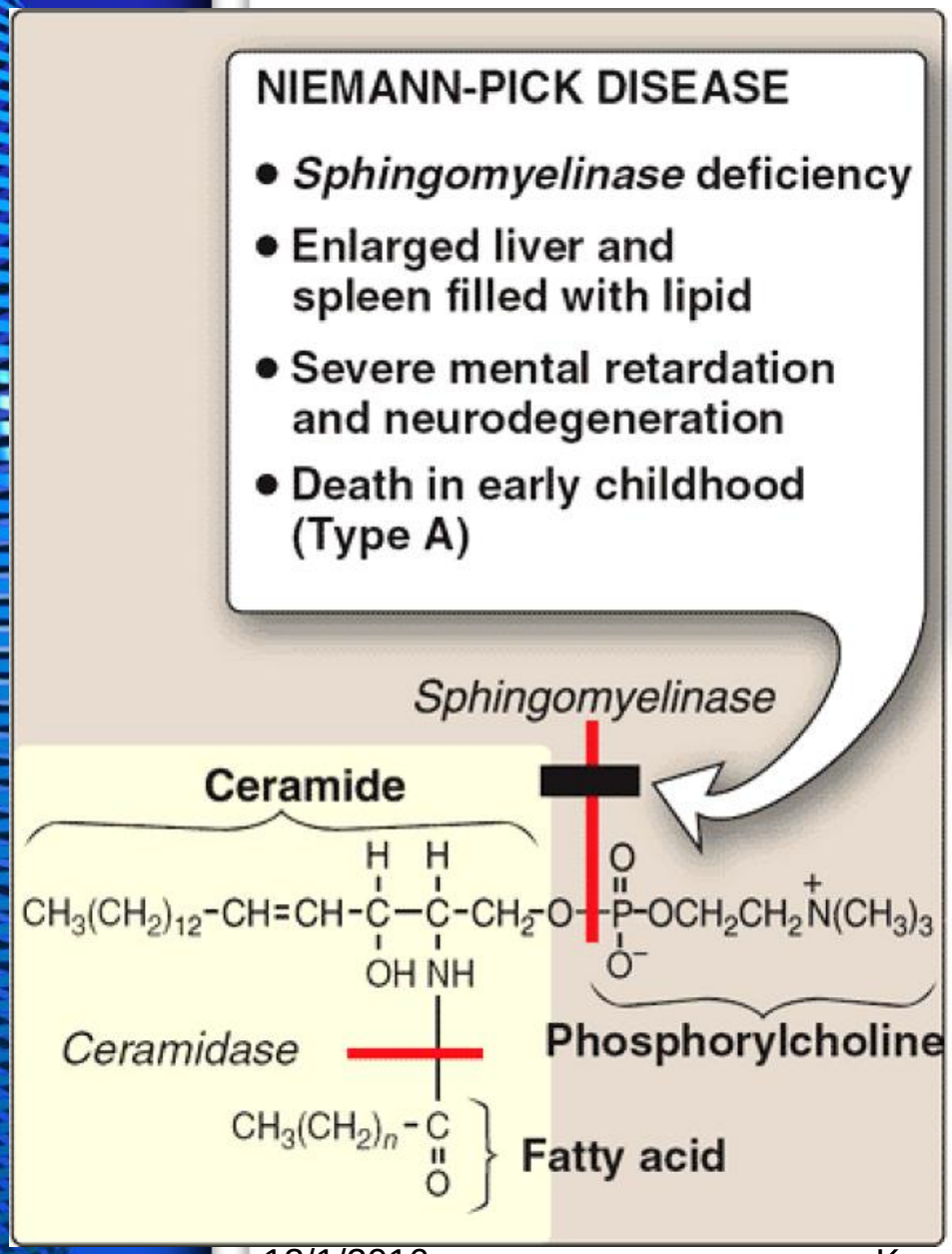
From Robert Horton et al. - Principles of Biochemistry (5th ed.) - 2012



Lipidoses: Sphingolipidoses & Gangliosidoses

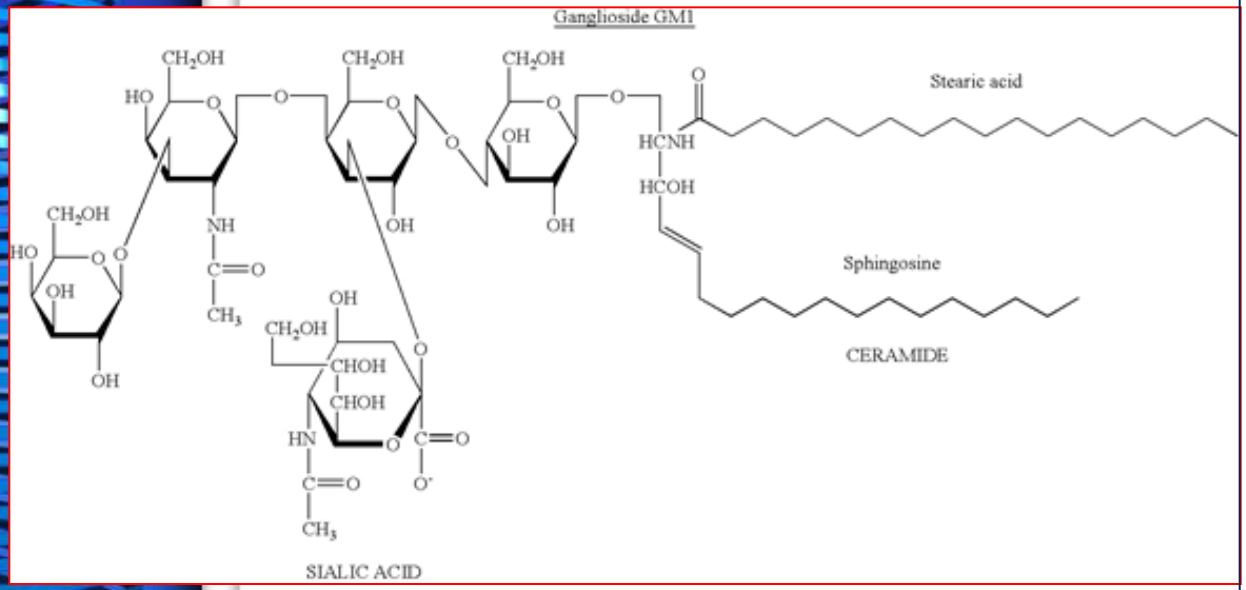
- Degradation of sphingolipids showing the enzymes affected in related genetic diseases, the sphingolipidoses.
- All of the diseases are autosomal recessive except Fabry disease, which is X-linked, and all can be fatal in early life.
- Cer = ceramide.

Niemann-Pick Disease



- Niemann-Pick disease (Types A and B) is an autosomal recessive disease caused by the inability to degrade sphingomyelin.
- Type A:
  - The deficient enzyme is sphingomyelinase - a type of phospholipase C. In the severe infantile form (Type A - less than 1% normal activity), the liver and spleen are the primary sites of lipid deposits and are, therefore, tremendously enlarged.
  - The lipid consists primarily of the sphingomyelin that cannot be degraded.
  - Infants with this disease experience rapid and progressive neurodegeneration as a result of deposition of sphingomyelin in the central nervous system, and they die in early childhood.
- Type B:
  - A less severe variant (Type B - 5% or more) causes little to no damage to neural tissue, but lungs, spleen, liver, and bone marrow are affected, resulting in a chronic form of the disease, with a life expectancy into adulthood.
- Niemann-Pick disease occurs with greater frequency in the Ashkenazi Jewish population.

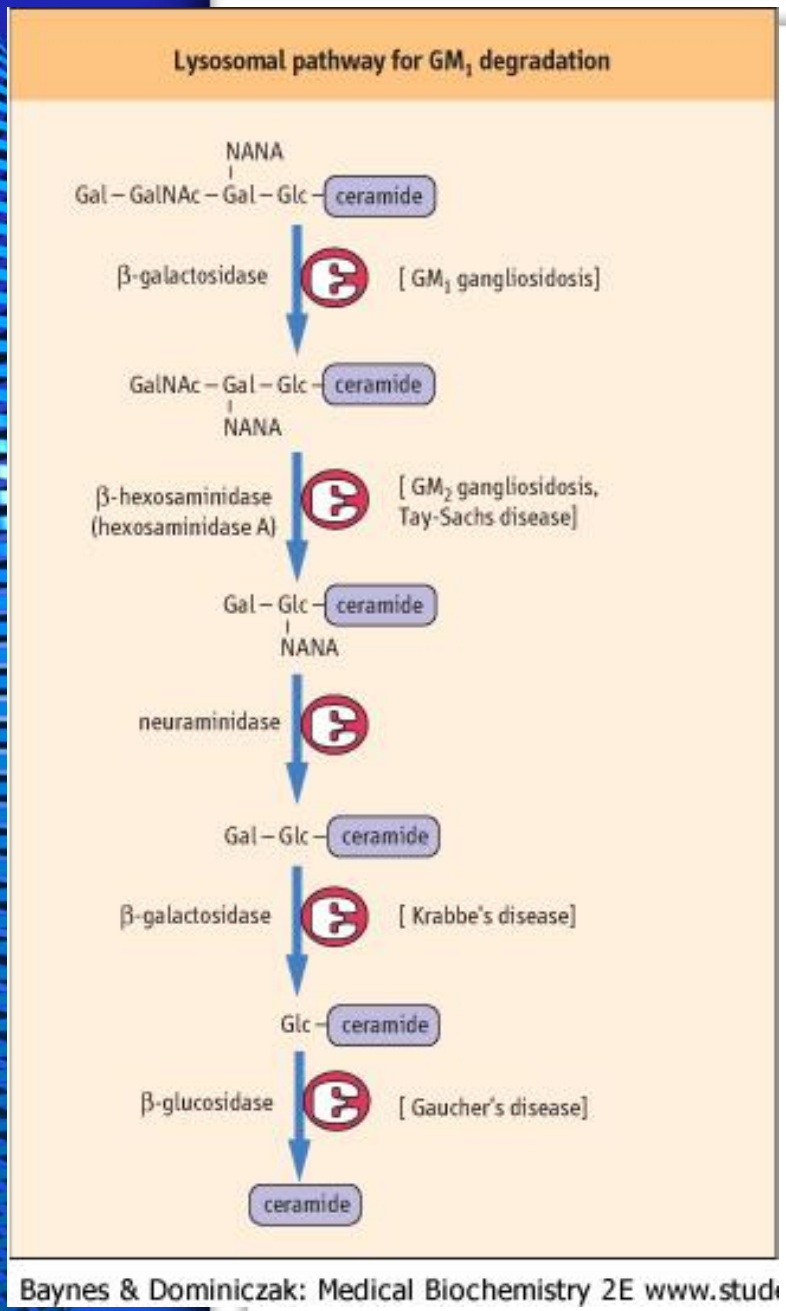
Structure of GM1 Ganglioside



Gangliosides: These are the most complex glycosphingolipids, and are found primarily in the ganglion cells of the central nervous system, particularly at the nerve endings. They are derivatives of ceramide oligosaccharides, and contain one or more molecules of NANA.

The notation for these compounds is G (for ganglioside) plus a subscript M, D, T, or Q to indicate whether there is one (mono), two, three, or four (quatro) molecules of NANA in the ganglioside, respectively. Additional numbers and letters in the subscript designate the sequence of the carbohydrate attached to the ceramide.

Gangliosides are of medical interest because several lipid storage disorders involve the accumulation of NANA-containing glycosphingolipids in cells.



Lysosomal pathway for turnover of ganglioside GM1 in human cells

Various enzymes may be missing in specific lipid storage diseases.

- Gal, galactose;
- GalNAc, N-acetylgalactosamine;
- Glc, glucose;
- NANA, n-acetyl neuraminic acid.

Next time…

- …we'll start the new topic "Protein and Nucleic Acid Biochemistry" and discuss:
  - protein digestion in gastro-intestinal tract
  - amino acid absorption in the intestine.


Thank you
for your attention!