LIPIDS

TAG, PL and SL metabolism

Marek Vecka

BIOSYNTHESIS OF TAG

TWO BIOSYNTHETIC PATHWAYS IN MAMMALS

liver, adipose tissue

- use mainly **phosphatidate pathway** (“Kennedy pathway“)

intestine

- **monoacylglycerol pathway**

mammary glands

- use **phosphatidate pathway**

BIOSYNTHESIS OF TAG

I. PHOSPHATIDATE PATHWAY

= Kennedy pathway

1. synthesis of *sn*-glycerol-3-phosphate

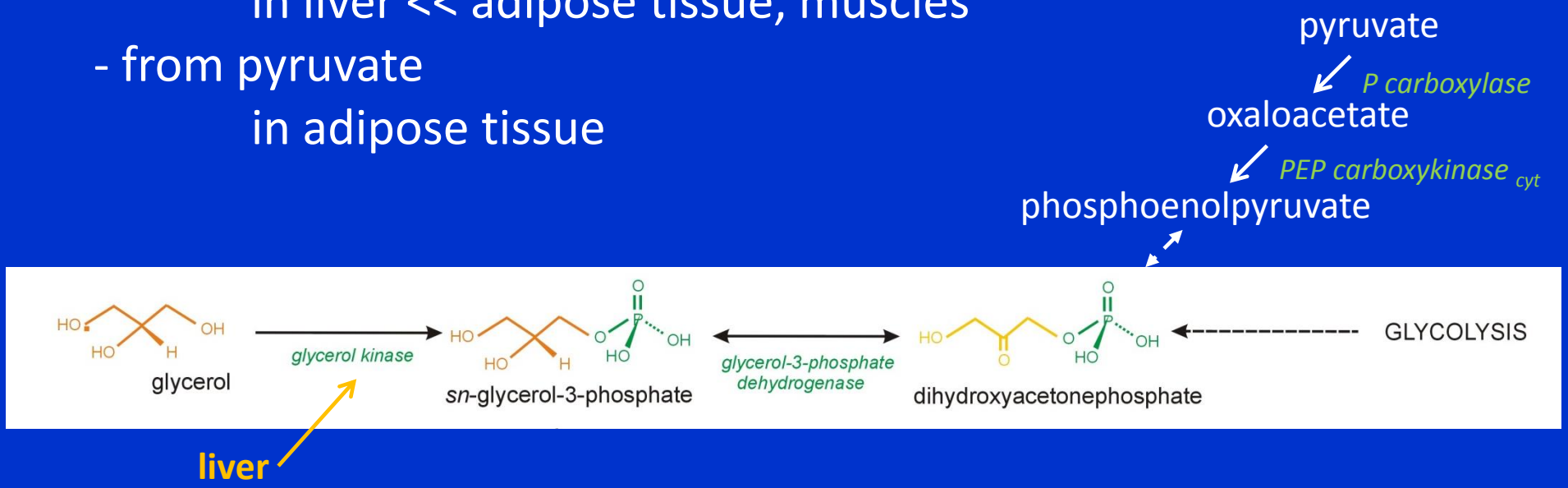
2. synthesis of phosphatidic acid (PA)
   - PA can be utilized for PL synthesis
3. synthesis of TAG

BIOSYNTHESIS OF TAG

I. PHOSPHATIDATE PATHWAY

1. Synthesis of *sn*-glycerol-3-phosphate

- from glycerol
  in liver
- from glycolytic product dihydroxyacetonephosphate
  in liver << adipose tissue, muscles
- from pyruvate
  in adipose tissue

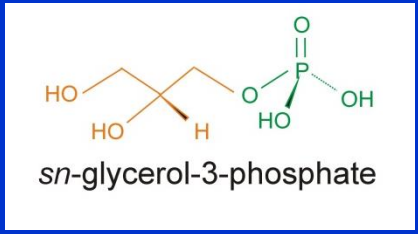


BIOSYNTHESIS OF TAG

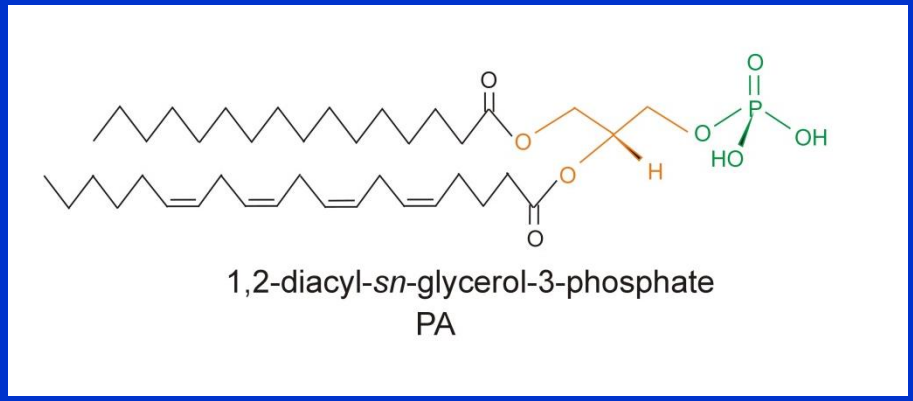
I. PHOSPHATIDATE PATHWAY

2. Synthesis of phosphatidic acid

- addition of fatty acyls to the positions *sn*-1 and *sn*-2



sn-glycerol-3-phosphate



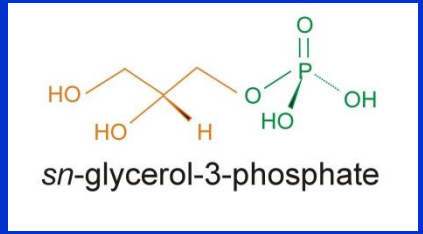
1,2-diacyl-*sn*-glycerol-3-phosphate
PA

BIOSYNTHESIS OF TAG

I. PHOSPHATIDATE PATHWAY

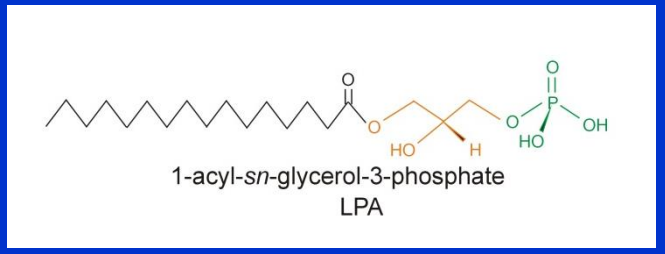
2. Synthesis of phosphatidic acid

- in the endoplasmic reticulum
- many acyltransferases known
  use Acyl CoA



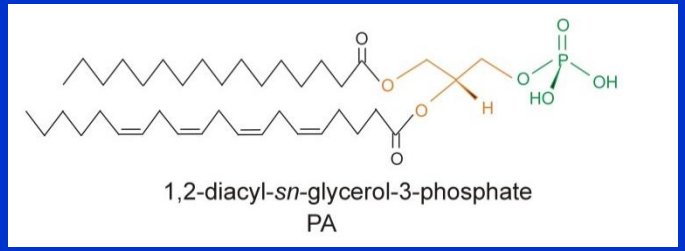
sn-glycerol-3-phosphate

G3P acyltransferase



1-acyl-*sn*-glycerol-3-phosphate
LPA

LPA acyltransferase



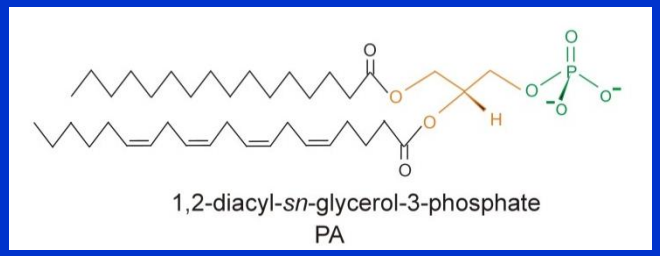
1,2-diacyl-*sn*-glycerol-3-phosphate
PA

BIOSYNTHESIS OF TAG

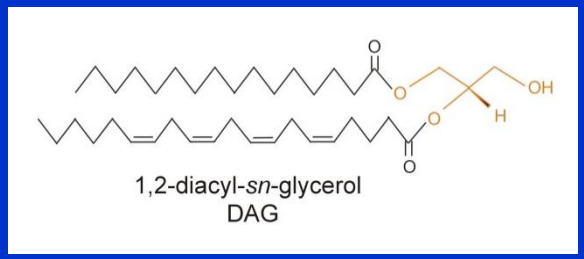
I. PHOSPHATIDATE PATHWAY

3. Synthesis of TAG

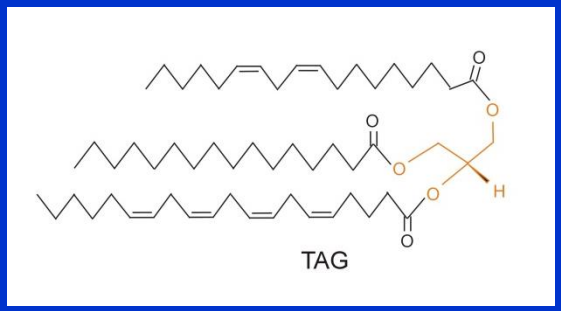
- conversion of PA into TAG



PA phosphatase



DAG acyltransferase



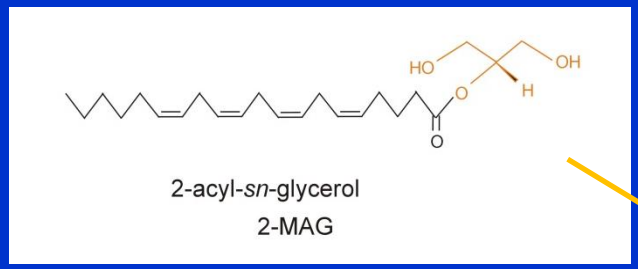
- in endoplasmic reticulum

BIOSYNTHESIS OF TAG

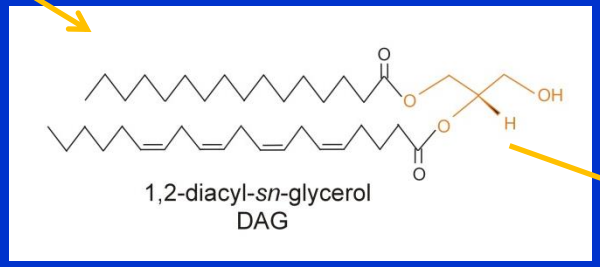
II. MONOACYLGLYCEROL PATHWAY

Occurence

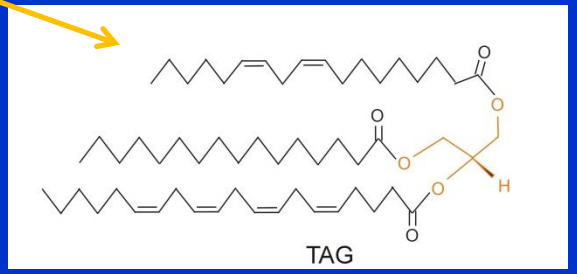
- enterocytes utilize 2-MAG taken from intestinal lumen
- formation of 2,3-DAG is also possible



MAG acyltransferase



DAG acyltransferase

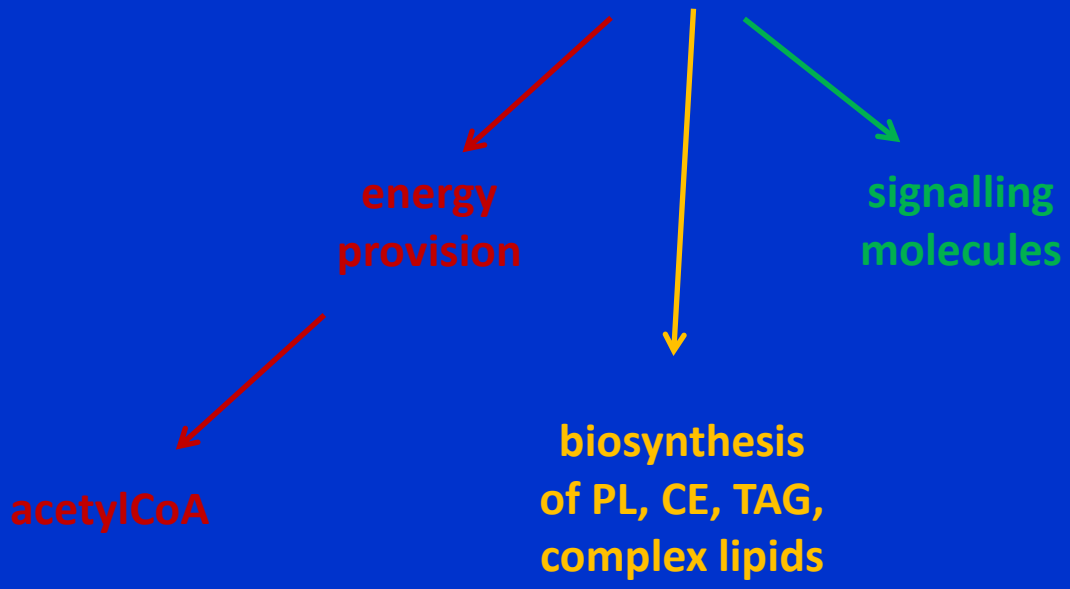


DEGRADATION OF TAG

Metabolic fate of intracellular TAG

overview

- stored TAG are hydrolyzed into fatty acids + glycerol



DEGRADATION OF TAG

Metabolic fate of intracellular TAG

1. Fatty acids as E source

- conversion into activated FA CoA → **tricarboxylic cycle**
- conversion into activated FA CoA → **ketogenesis**

2. Fatty acids as part of lipid biosynthesis

- used for resynthesis of TAG, synthesis of PL (+ VLDL in liver)
- synthesis of sphingolipids (sphinganine + acyl moiety)

3. Signalling molecules derived from fatty acids

- oxylipins (eicosanoids/docosanoids) after liberation of FA from PL molecule and consequent metabolization

DEGRADATION OF TAG

FA as source of energy

1. Liberation of FA from storage molecule = TAG

- called fat mobilization
- enzymatically by lipases

2. Transport FA into the cytoplasma of target cell

- FA are released into the circulation (albumin bound NEFA)
- transport through the cell membrane

3. FA oxidation to acetyl CoA

a) activation of FA into acylCoA

b) degradation of FA chain by β- (α-, ω-) oxidation

DEGRADATION OF TAG

FA as source of energy

1. Liberation of FA from storage molecule = TAG

a) higher energy demand

TAG is the richest source of E (up to 38 kJ/g)

- carbon atoms in highly reduced state
- no H_2O needed for storage (x glycogen)

- during prandial phase
- long term demand = fasting/starvation
- actual consumption of energy = physical exercise

b) part of stress response

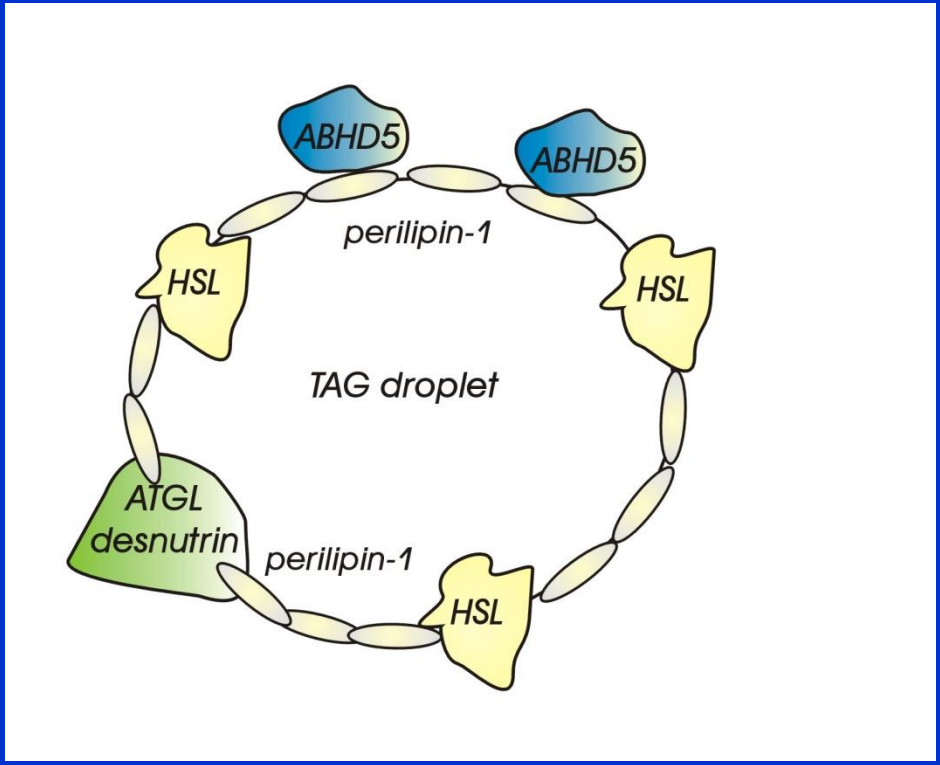
- covers high energy demand + formation of signalling molecules

DEGRADATION OF TAG

FA as source of energy

1. **Liberation of FA from storage molecule = TAG**

   TAG are stored as lipid droplets (adipocytes….)

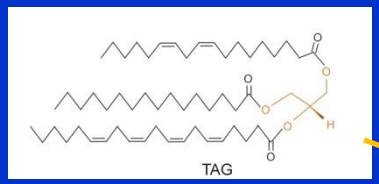


DEGRADATION OF TAG

FA as source of energy

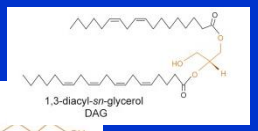
1. Liberation of FA from storage molecule = TAG

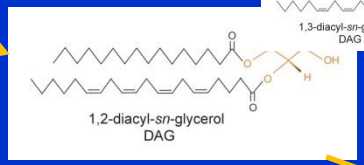
3 FA are consequently cleaved from TAG molecule



TAG

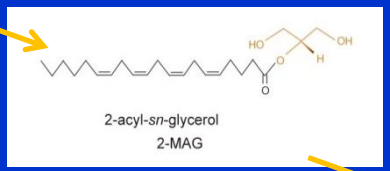
TAG lipase =
desnutrin





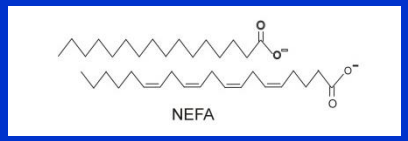
DAG

HSL = hormon
sensitive lipase

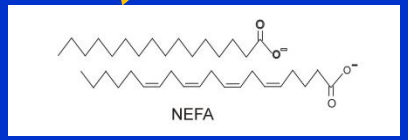


2-MAG

MAG lipase

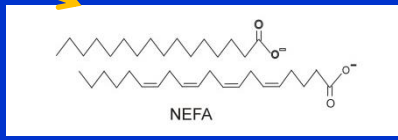


1st NEFA



2nd NEFA

glycerol



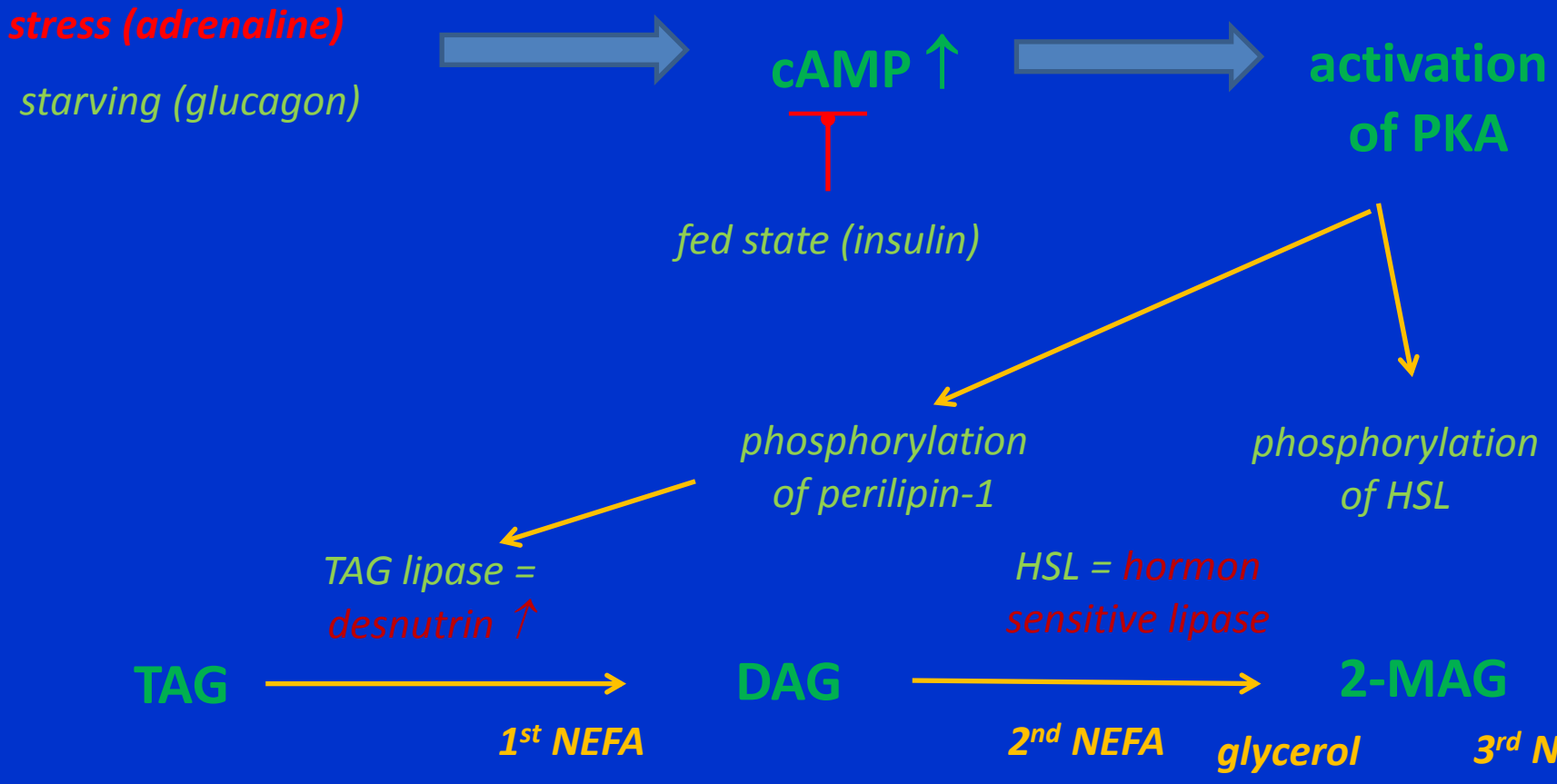
3rd NEFA

DEGRADATION OF TAG

FA as source of energy

1. Liberation of FA from storage molecule = TAG

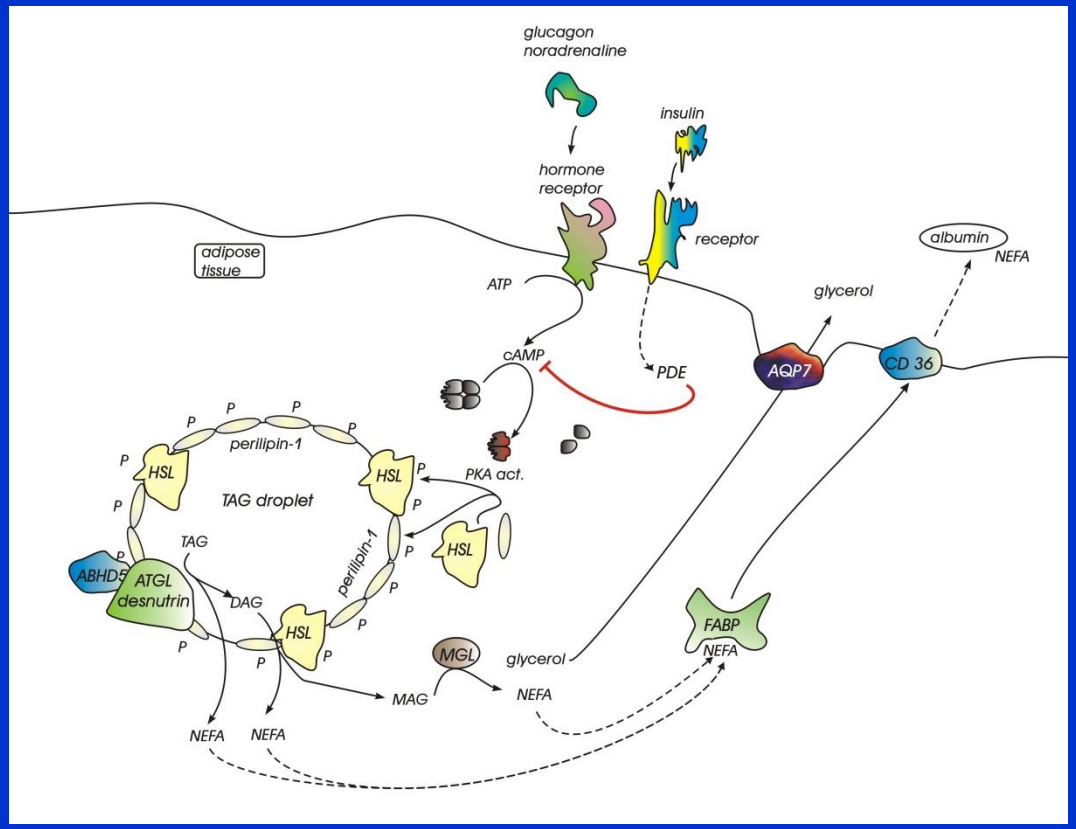
hormonal control of the process



DEGRADATION OF TAG

FA as source of energy

1. **Liberation of FA from storage molecule = TAG**
   hormonal control of the process



DEGRADATION OF TAG

FA as source of energy

2. Transport of FA to the target cell

extracellular – the circulation

NEFA are bound to albumin

adipose tissue → blood → skeletal muscles, heart, liver

passing through plasma membrane of target cell

passive diffusion

facilitated diffusion – transporting molecules (FATP, CD36)

intracellular – cytoplasmatic

binding proteins (FABPs)

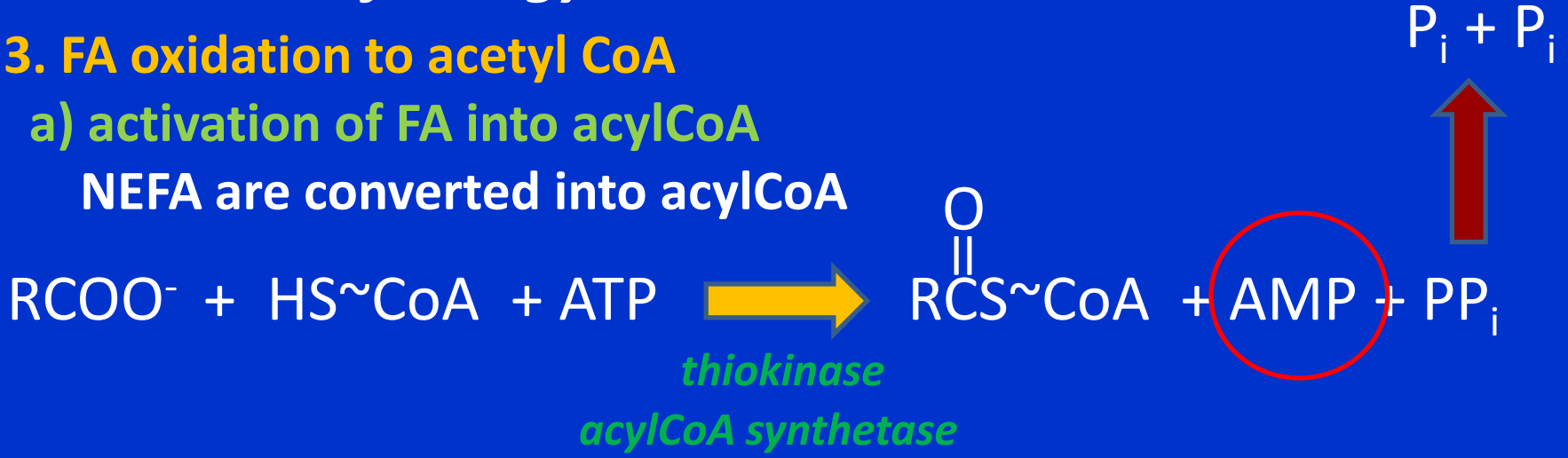
DEGRADATION OF TAG

FA as source of energy

3. FA oxidation to acetyl CoA

a) activation of FA into acylCoA

NEFA are converted into acylCoA



FA are activated in various cell compartments:

- VLCFA in peroxisome membranes
- LCFA in outer mitochondrial membranes/ ER
- MCFA, SCFA in mitochondrial matrix

DEGRADATION OF TAG

FA as source of energy

3. FA oxidation to acetyl CoA

b) degradation of FA CoA chain by β- (α-, ω-) oxidation

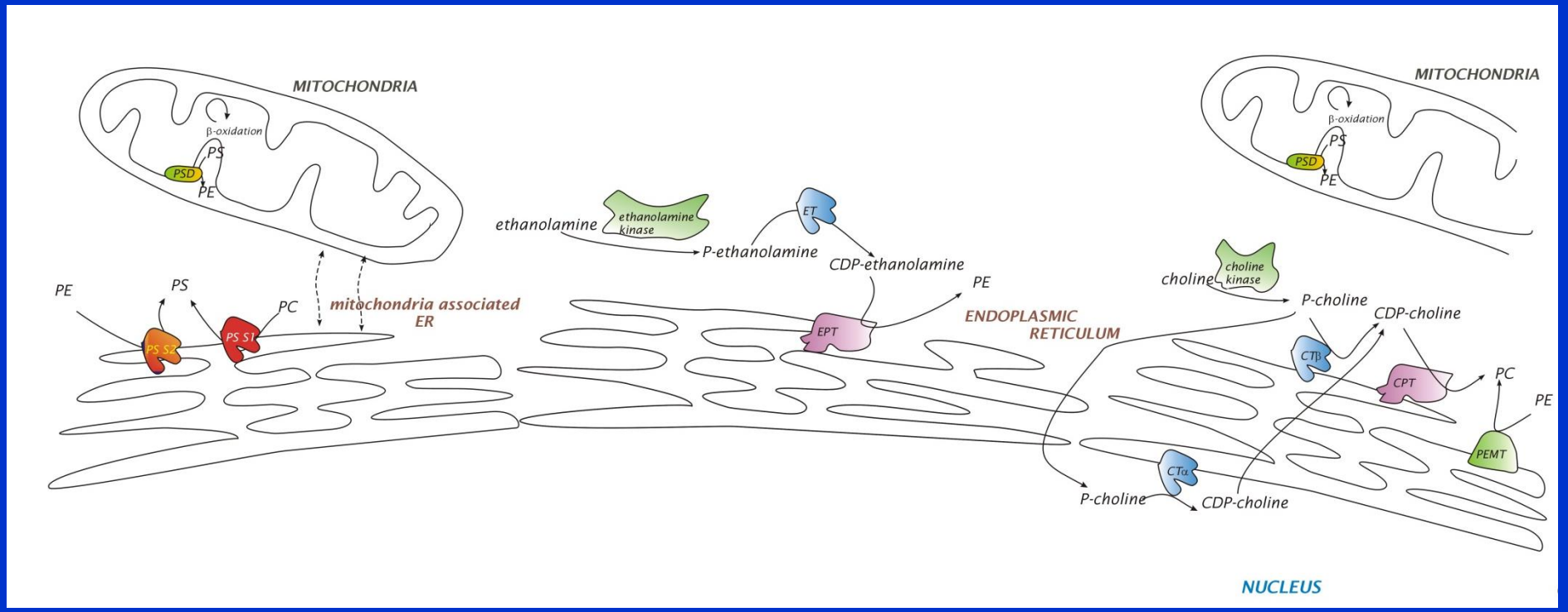
see lecture on FA biosynthesis and degradation

BIOSYNTHESIS OF PHOSPHOLIPIDS

compartmentalization

Occurence

- in all nucleated cells (x not in mature ery)



BIOSYNTHESIS OF PHOSPHOLIPIDS

Phosphatidate biosynthesis

1. Synthesis of PA

- analogous to TAG biosynthesis

(G3P $\rightarrow$ LPA $\rightarrow$ PA)

2. Modification of PA with hydrophilic part

- further activation needed:

a) PC, PE: activated alcohol part

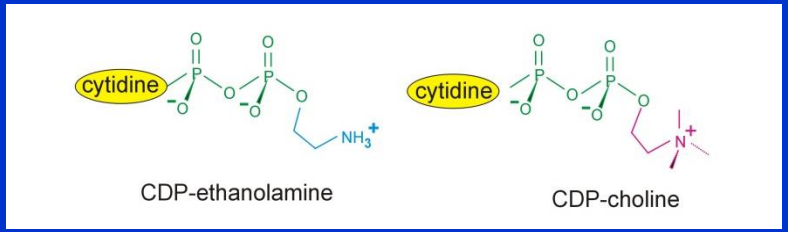
b) PI, DPG, PG: activated DAG part

BIOSYNTHESIS OF PHOSPHOLIPIDS

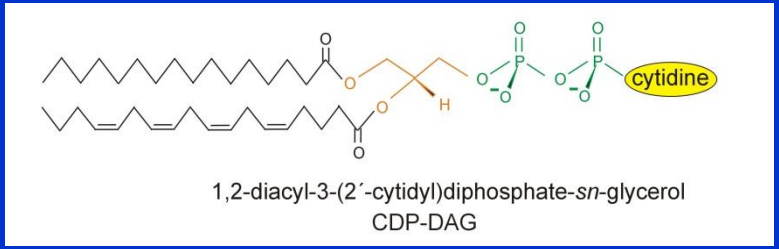
activated intermediates

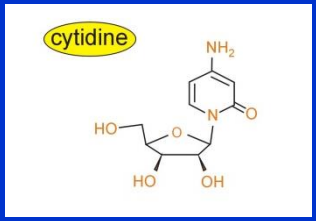
Cytidine nucleotides

a) for PE, PC synthesis:



b) for PG, DPG, PI synthesis:





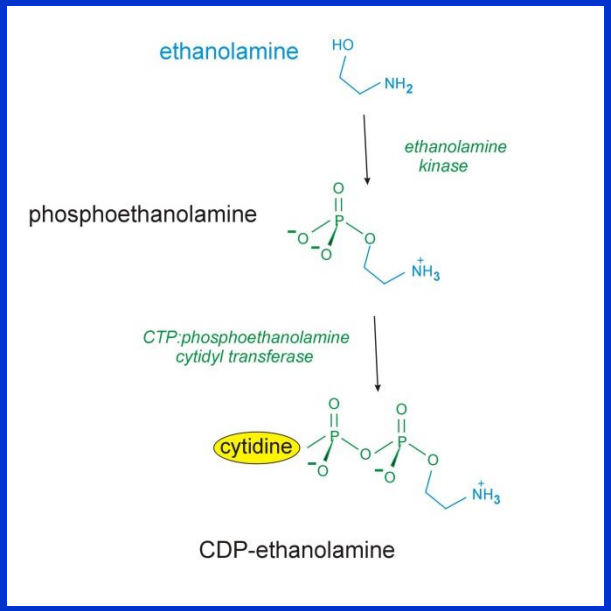
BIOSYNTHESIS OF PHOSPHOLIPIDS

a) PE and PC biosynthesis

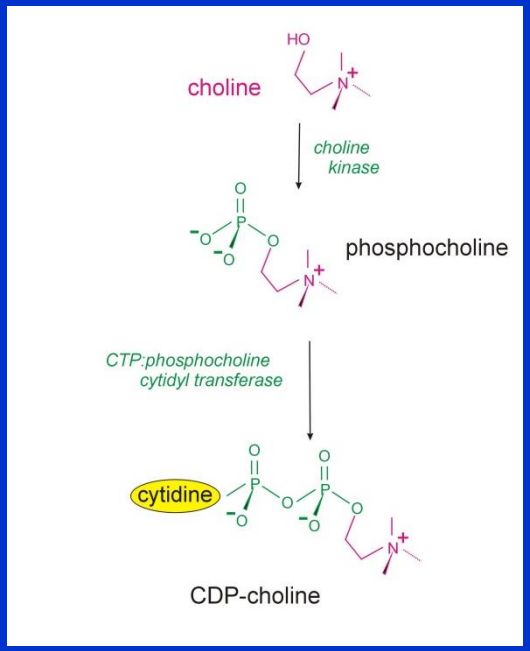
activation of bases

- dietary sources or membrane PL

ethanolamine



choline

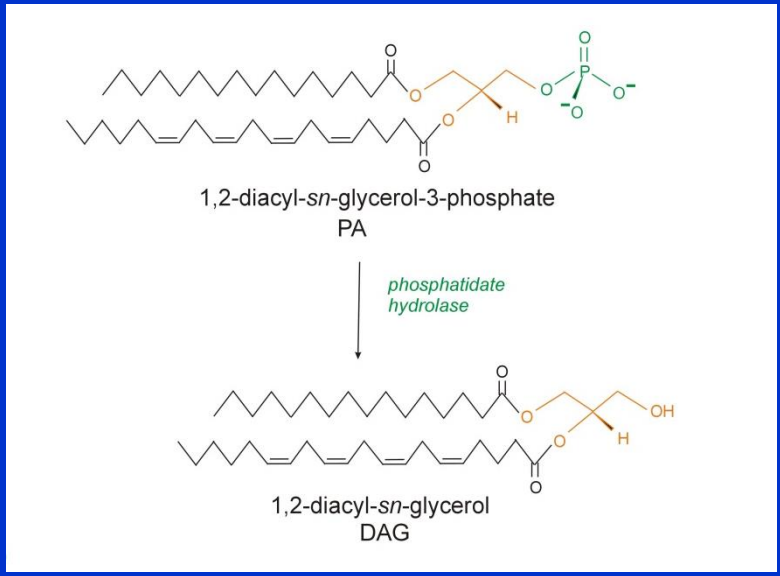


BIOSYNTHESIS OF PHOSPHOLIPIDS

a) PE and PC biosynthesis

Synthesis of DAG

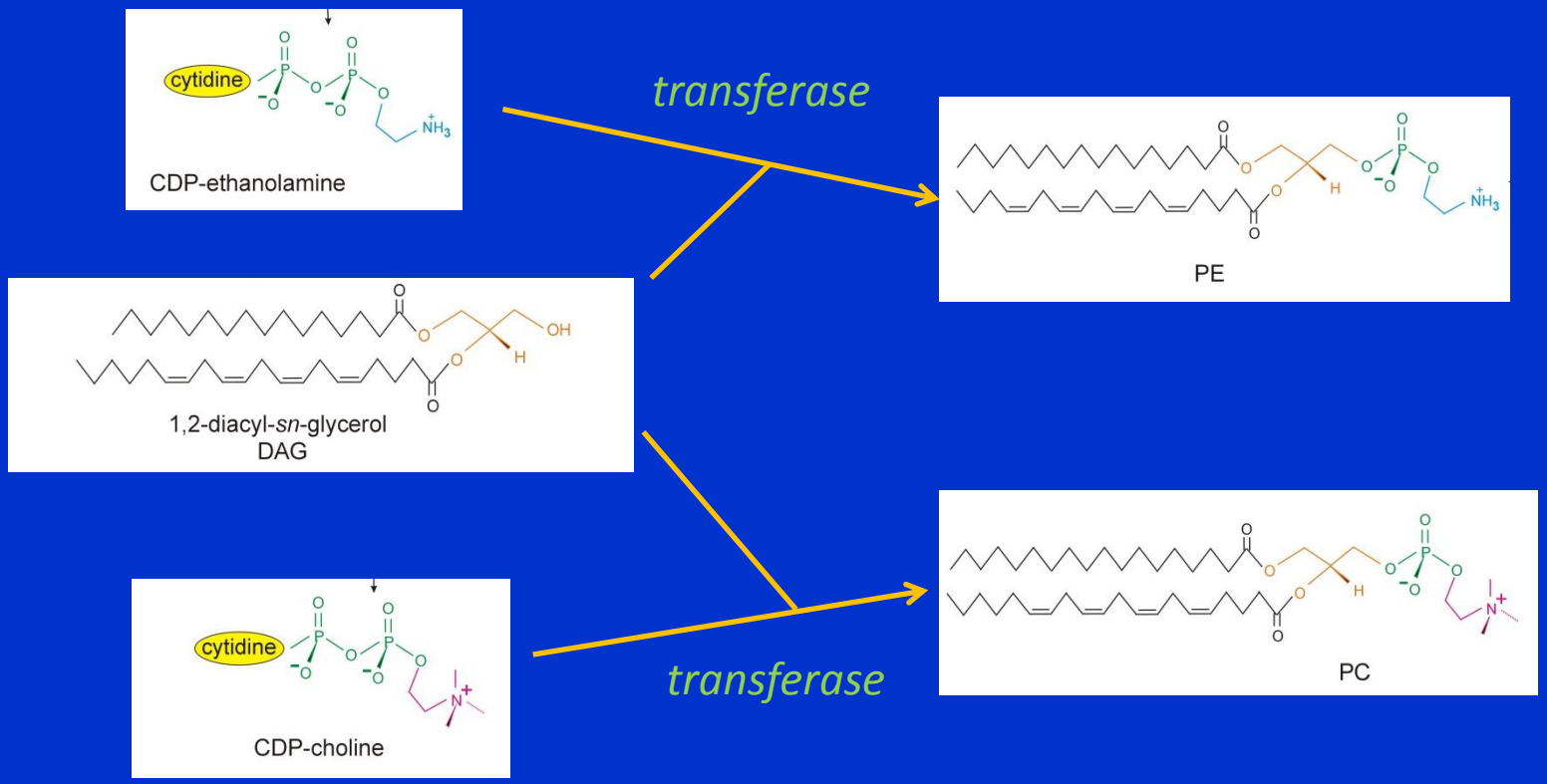
- by hydrolysis of PA



BIOSYNTHESIS OF PHOSPHOLIPIDS

a) PE and PC biosynthesis

Conjugation of activated bases with DAG

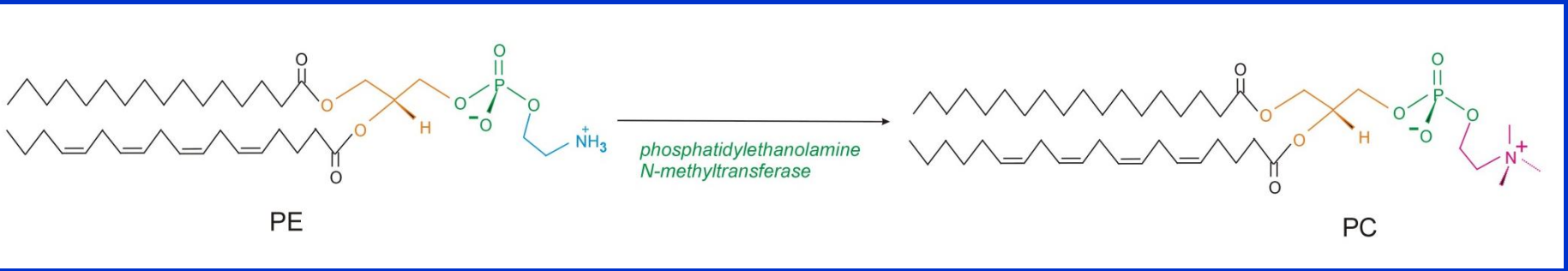


BIOSYNTHESIS OF PHOSPHOLIPIDS

a) PE and PC biosynthesis

Alternative PC biosynthetic pathway

- during starvation/low choline in diet
- transfer of three methyl groups (donor: SAdeMet)
- in liver

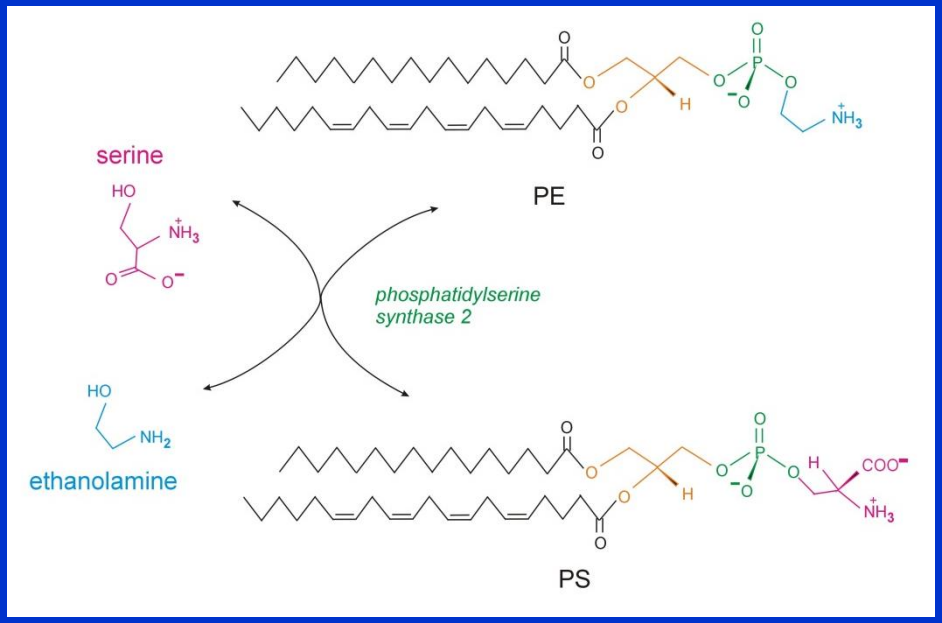


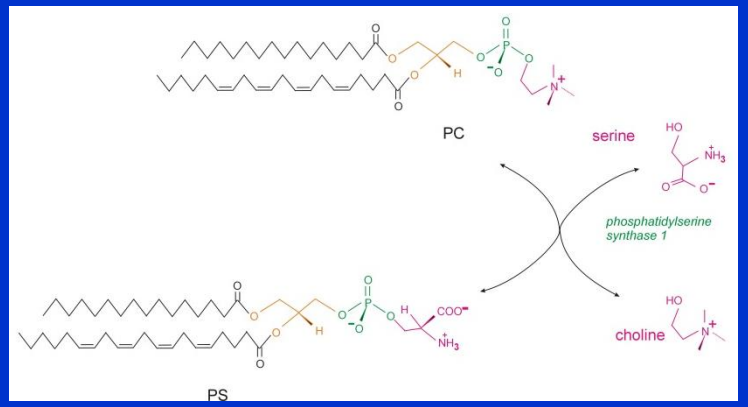
BIOSYNTHESIS OF PHOSPHOLIPIDS

PS biosynthesis

Exchange reaction

- reversibly from PE or PC
- in endoplasmic reticulum



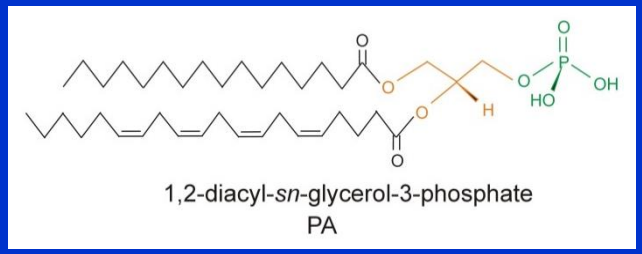


BIOSYNTHESIS OF PHOSPHOLIPIDS

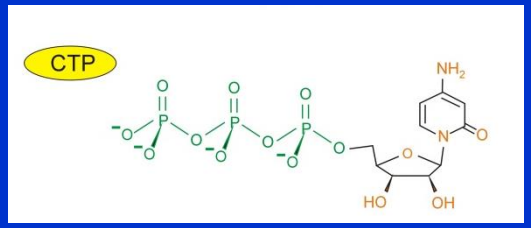
b) PI, PG and DPG biosynthesis

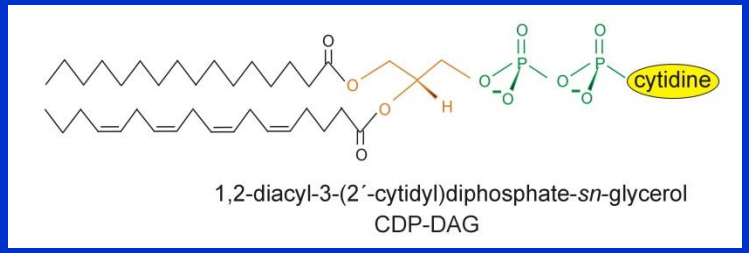
Activated DAG needed

- rapid turnover



CDP-DAG synthase

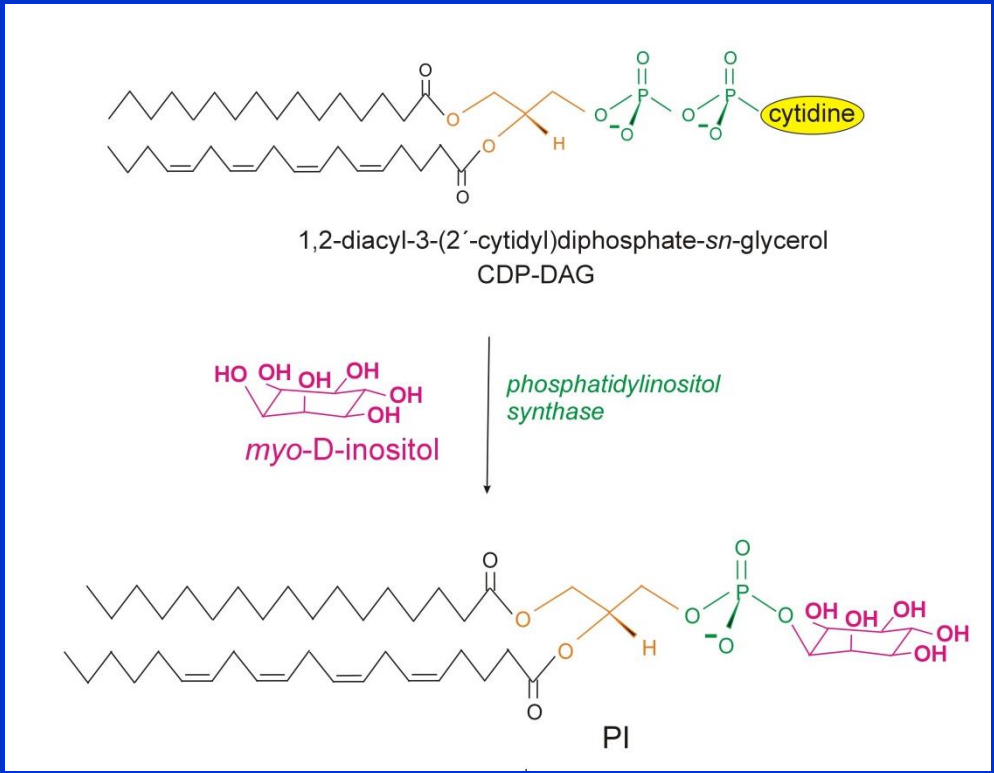




BIOSYNTHESIS OF PHOSPHOLIPIDS

b) PI, PG and DPG biosynthesis

PI biosynthesis

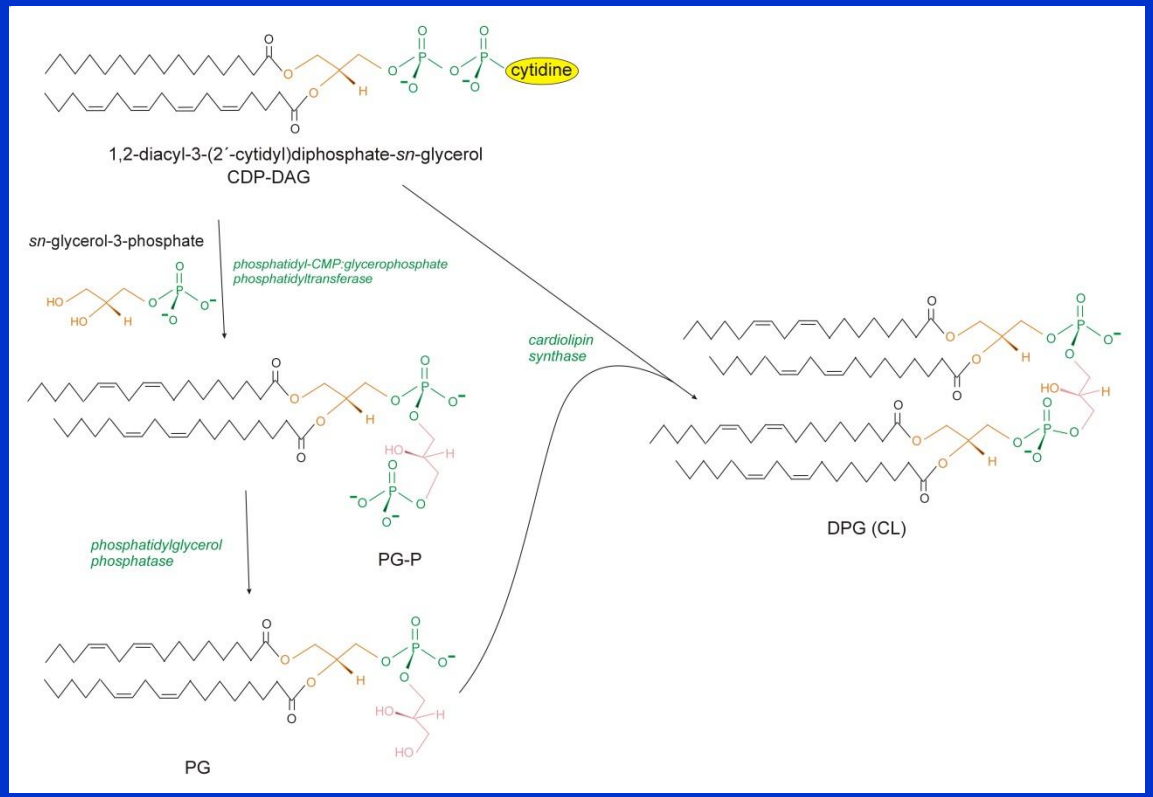


BIOSYNTHESIS OF PHOSPHOLIPIDS

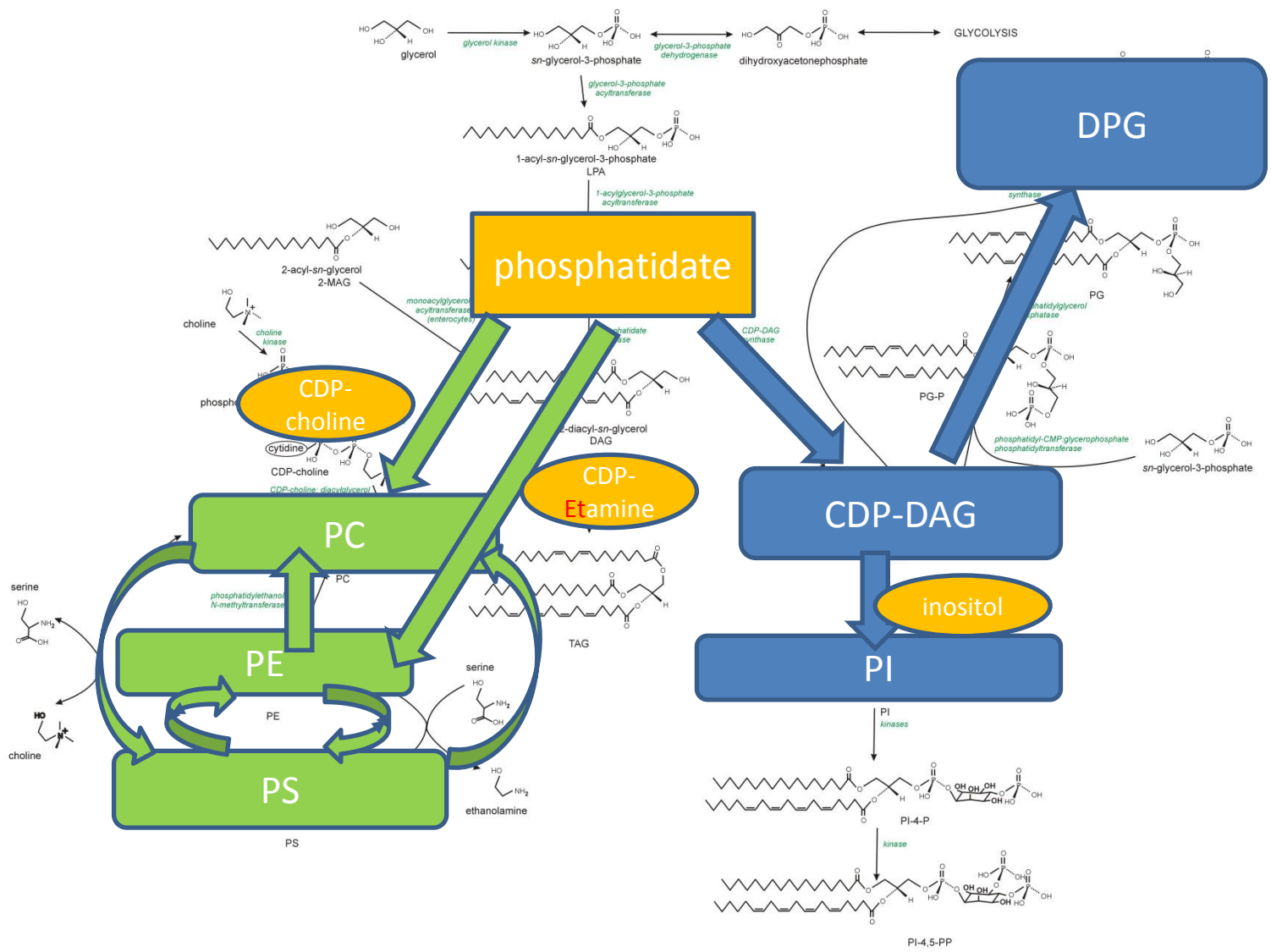
b) PI, PG and DPG biosynthesis

PG and DPG (CL) biosynthesis

- DPG is synthesised only in mitochondrion



BIOSYNTHESIS OF PHOSPHOLIPIDS

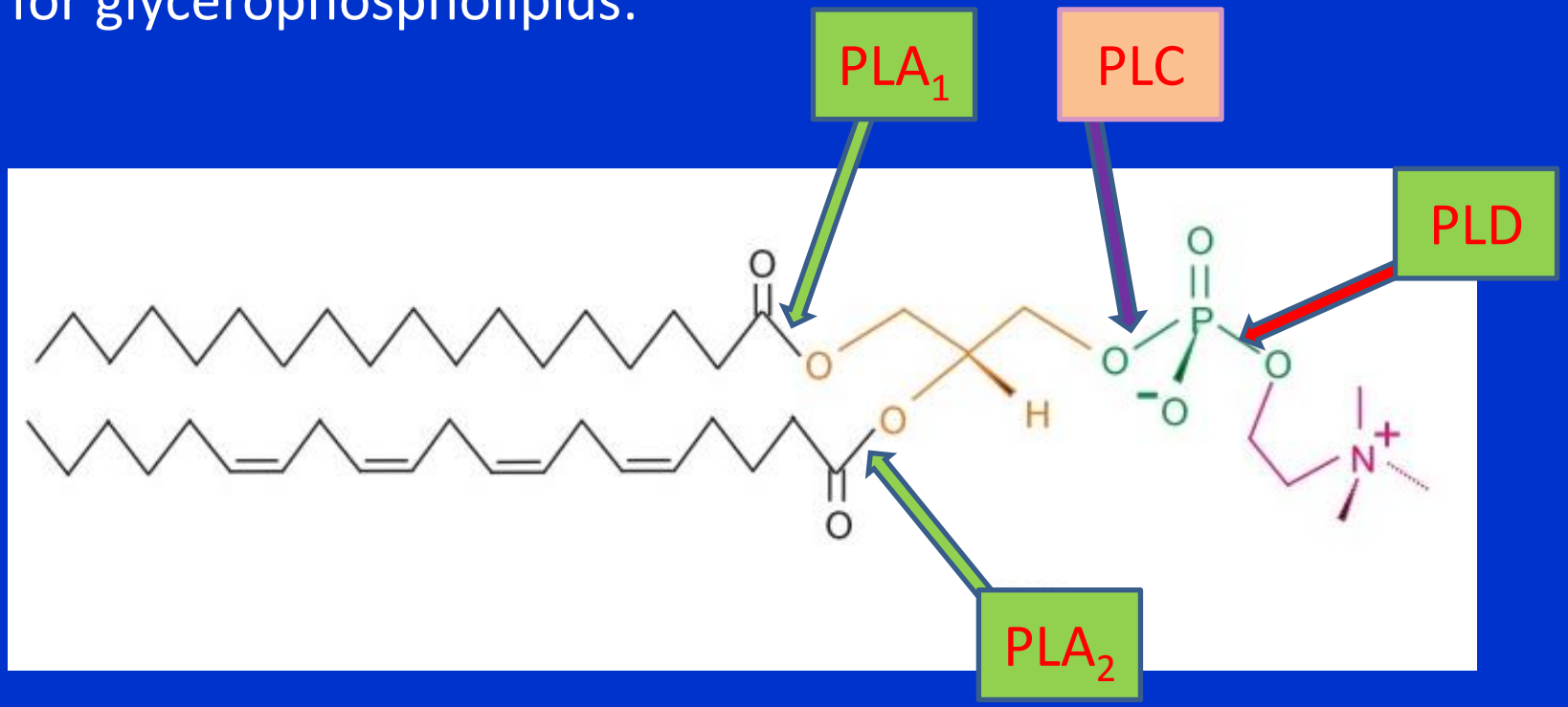


DEGRADATION OF PHOSPHOLIPIDS

phospholipases

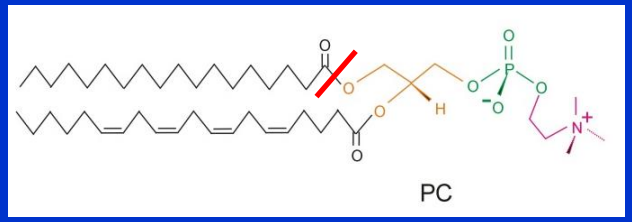
Site specific cleavage of PL

- for glycerophospholipids:



DEGRADATION OF PHOSPHOLIPIDS

phospholipases

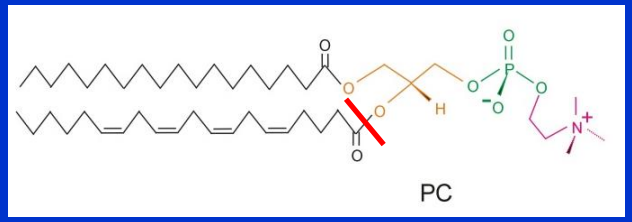


Phosholipases A_1 (PLA_1)

- wide tissue distribution
- physiological functions largely unknown
- some of them are PS, PA specific

DEGRADATION OF PHOSPHOLIPIDS

phospholipases



Phosholipases A_2 (PLA_2)

- wide tissue distribution including pancreatic juice
- liberates PUFA from *sn*-2 position of PL

↓

important part of eicosanoid biosynthesis

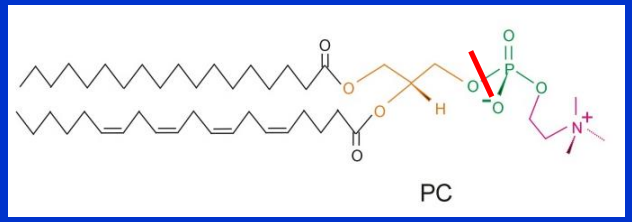
- part of defense against bacteria, viruses (attack of membranes)
- can hydrolyze oxidized PUFAs in PL
- **inhibited by glucocorticoids**
- PLA_2 in snake venom – generated lysoPL are effective detergents

↓

erythrocyte lysis

DEGRADATION OF PHOSPHOLIPIDS

phospholipases

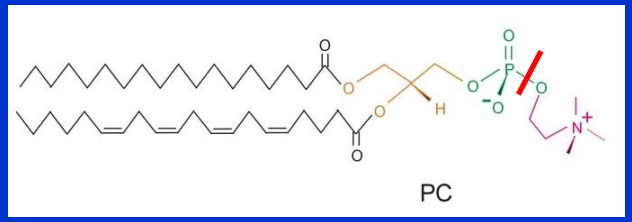


Phosholipases C (PLC)

- wide tissue distribution
- production of second messengers (e.g. PI-4,5PP → DAG + IP_3)
- high number of PI specific isozymes
  divided into classes β, δ, ε, γ, η, ζ
- **activated by hormones**

DEGRADATION OF PHOSPHOLIPIDS

phospholipases



Phosholipases D (PLD)

- wide tissue distribution
- physiological functions largely unknown (PA + base)
- need phosphoinositides as a cofactor for activity

BIOSYNTHESIS OF SPHINGOLIPIDS

overview

1. Synthesis of sphinganine

- from serine and palmitoylCoA

2. Acylation

- forming of amide bond (→ ceramides)

3. Addition of hydrophilic moiety

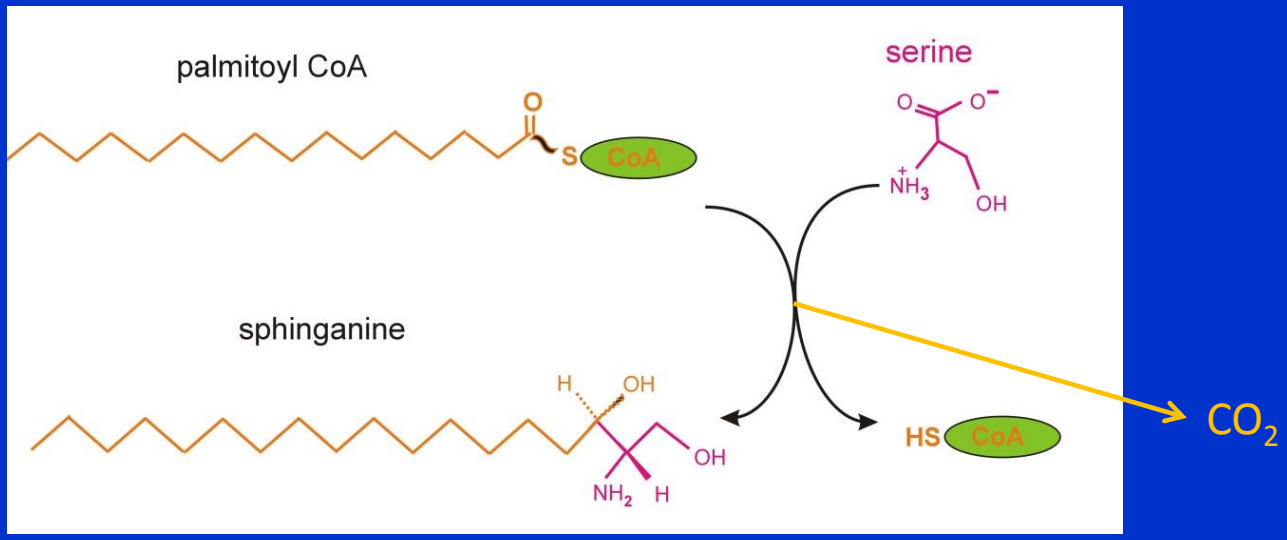
- various groups (→ various sphingolipid classes)

BIOSYNTHESIS OF SPHINGOLIPIDS

sphinganine biosynthesis

Condenzation of palmitoyl CoA and serine

- NADPH + H^+ needed

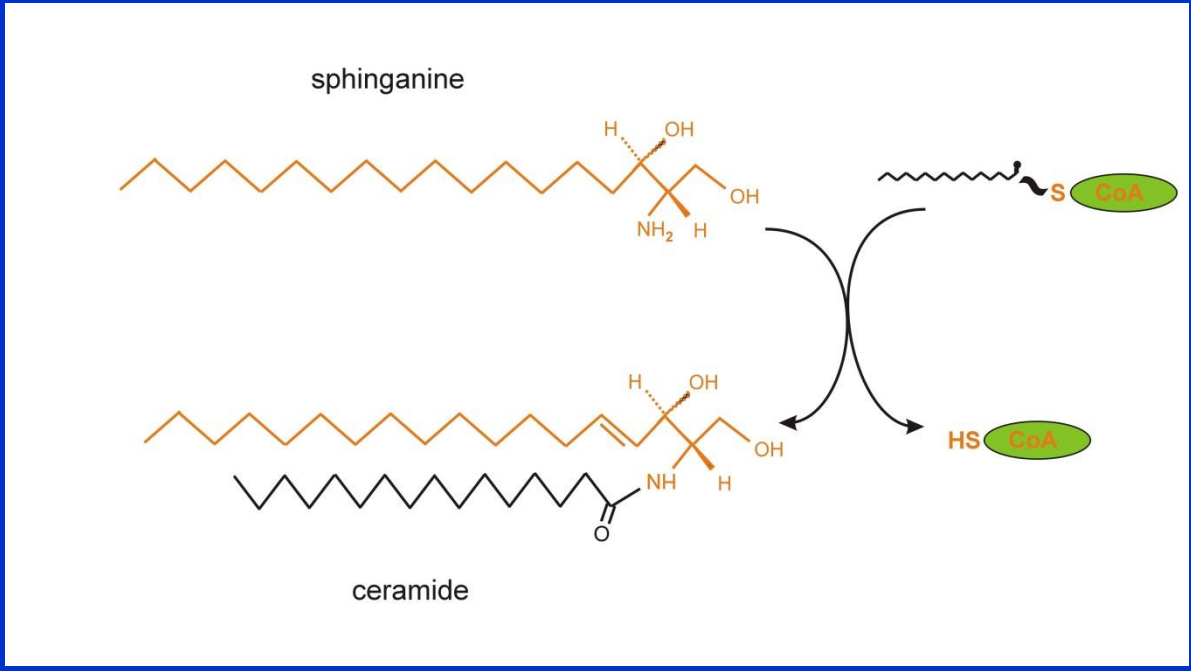


BIOSYNTHESIS OF SPHINGOLIPIDS

ceramide biosynthesis

Acyl transfer to sphinganine backbone

- *de novo* or products of sphingolipid catabolism



BIOSYNTHESIS OF SPHINGOLIPIDS

further metabolization of ceramides

Hydrophilic part addition

1. + phosphocholine → **sphingomyelines**

2. + saccharide moiety

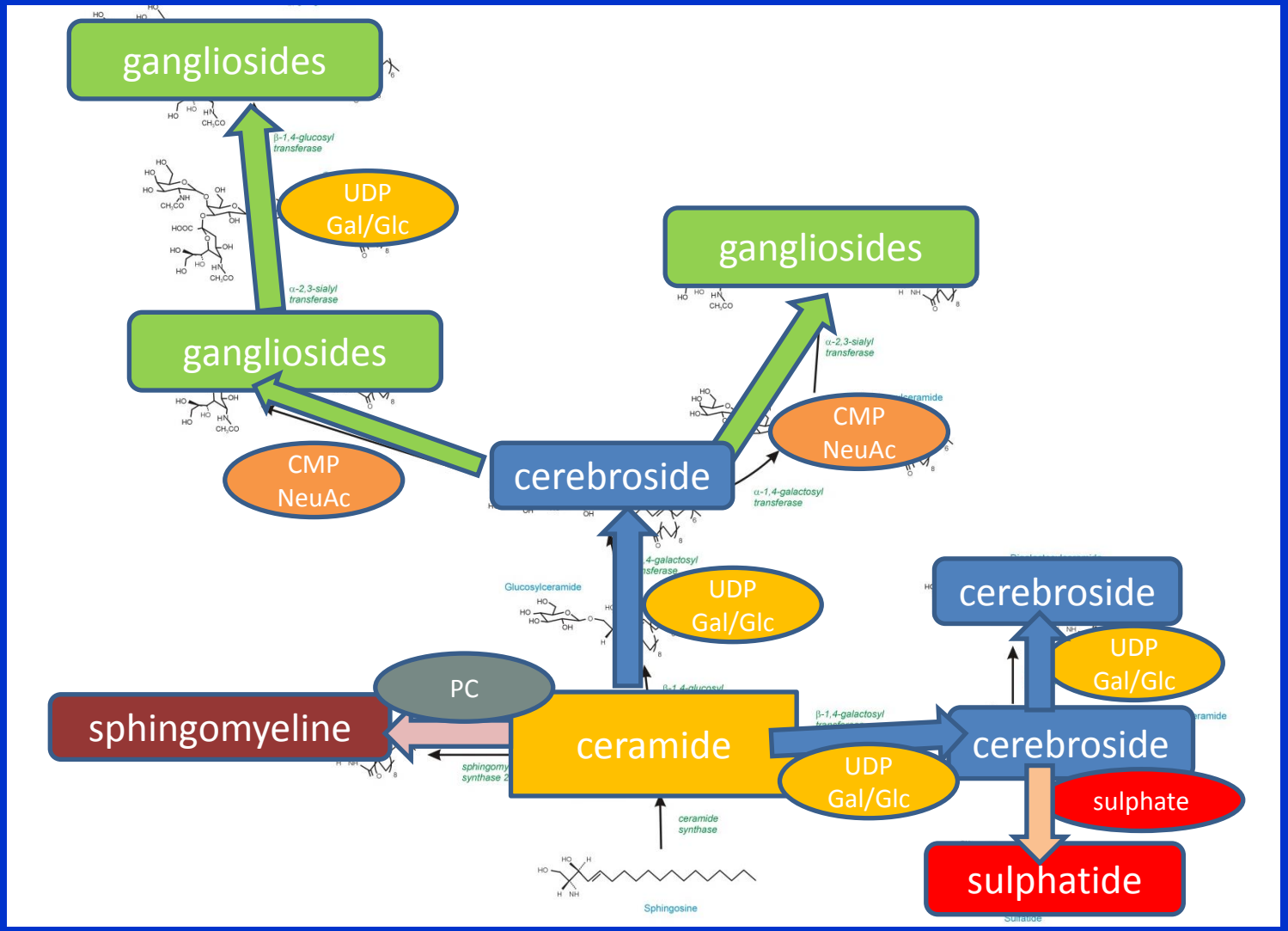
+ UDP-activated saccharide units → **glycosphingolipids**

- monosaccharide → *cerebrosides*
- di-, tri- saccharide → *oligoglycosylceramides*

further modification with CMP-activated sialic acids → **gangliosides**

BIOSYNTHESIS OF SPHINGOLIPIDS

overview



DEGRADATION OF SPHINGOLIPIDS

Hydrolytic degradation

- lysosomal hydrolases with saposins (special coactivators)

→ sialic acids + sugars + long-chain bases + fatty acids

deficit in enzymes → accumulation of intermediates

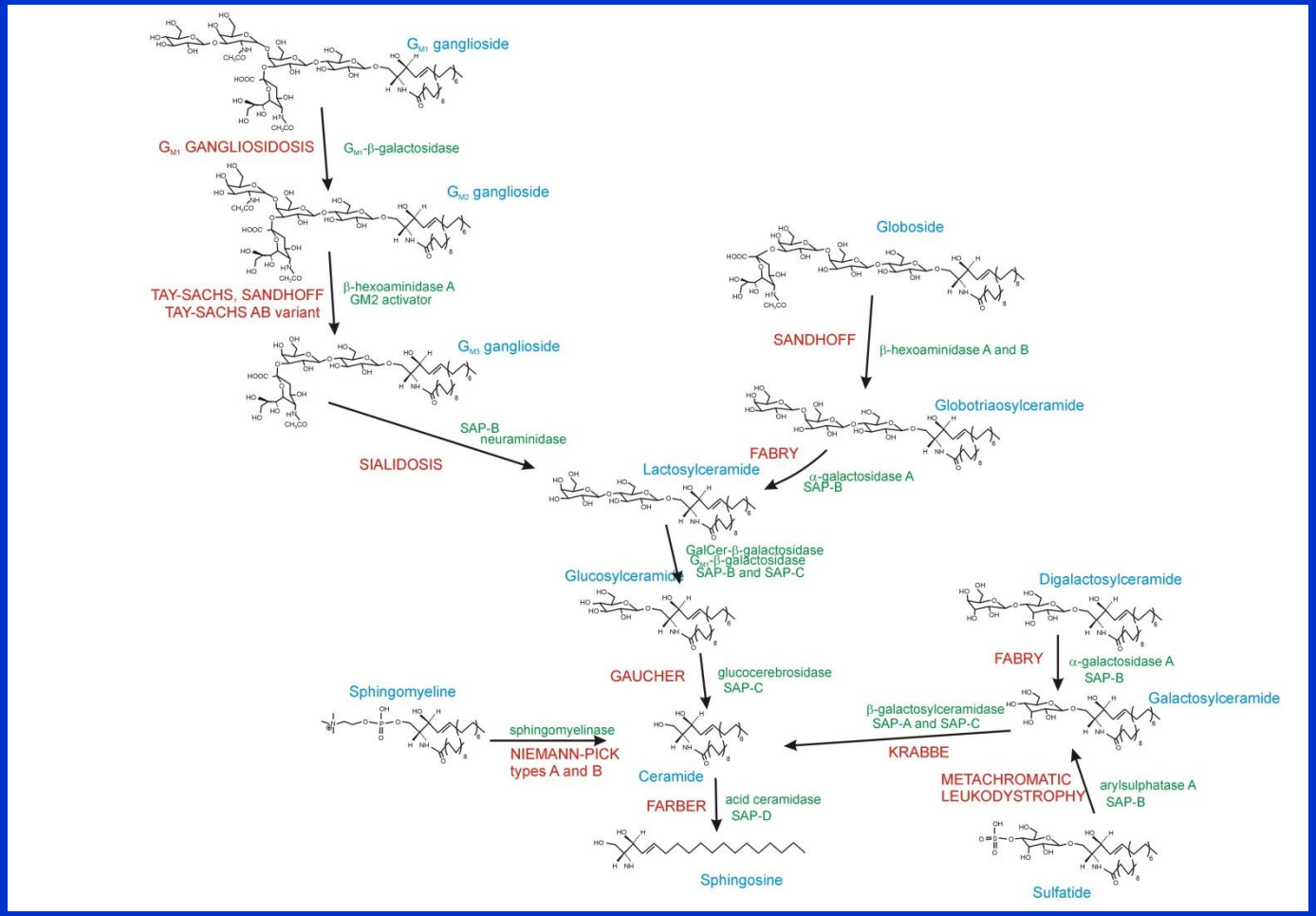
→ **metabolic diseases (lysosomal sphingolipidoses)**

- neurological symptoms
- enlargement of liver

DEGRADATION OF SPHINGOLIPIDS

Hydrolytic degradation

- lysosomal hydrolases with saposins (special coactivators)



Further reading

Textbooks, monographs

Biochemistry of Lipids, Lipoproteins and Membranes (5th Ed); Vance DE, Vance Je (Eds.), Elsevier, Amsterodam (The Netherlands) 2008

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Web sources

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http://themedicalbiochemistrypage.org - the Medical Biochemistry Page