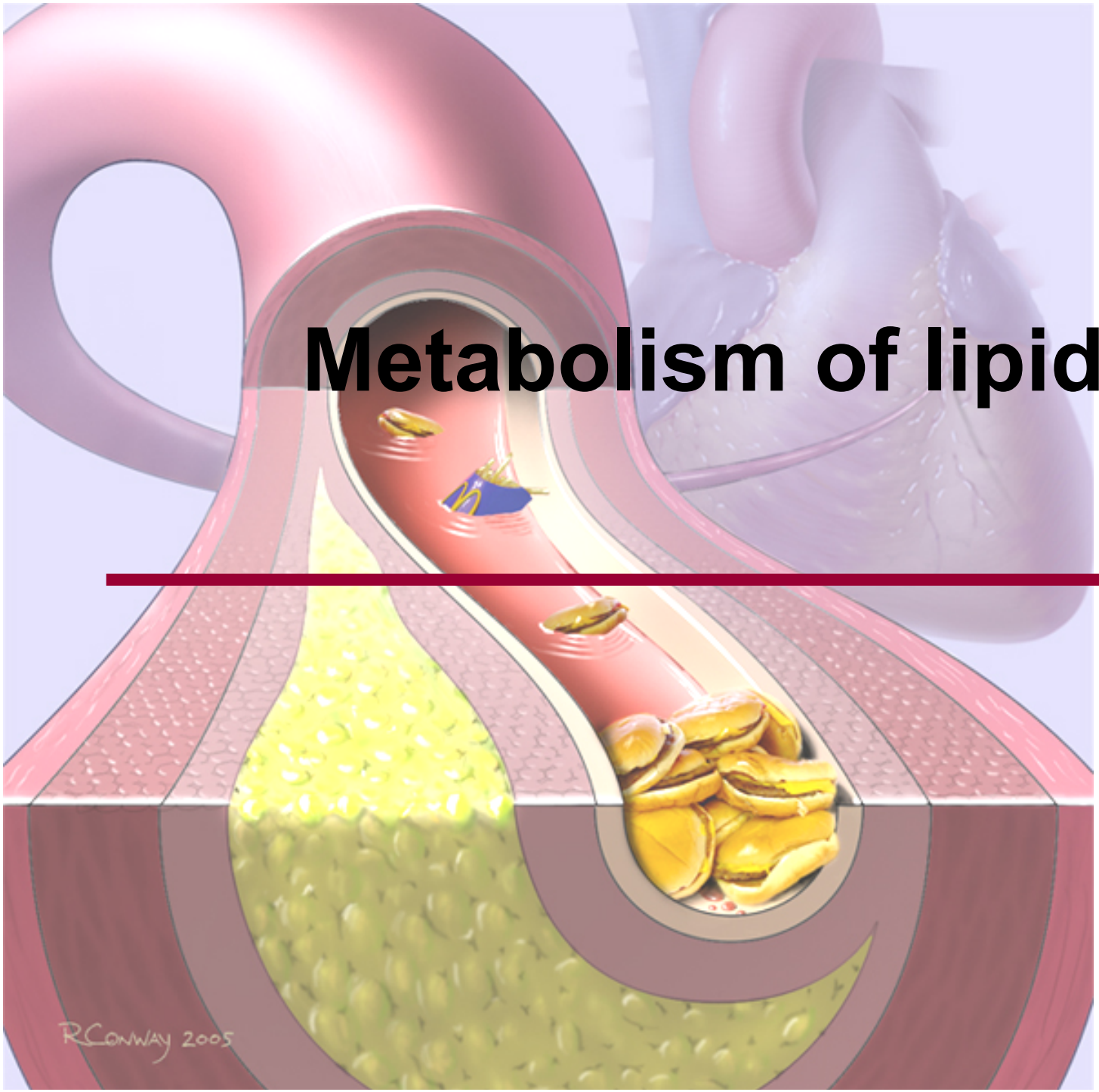
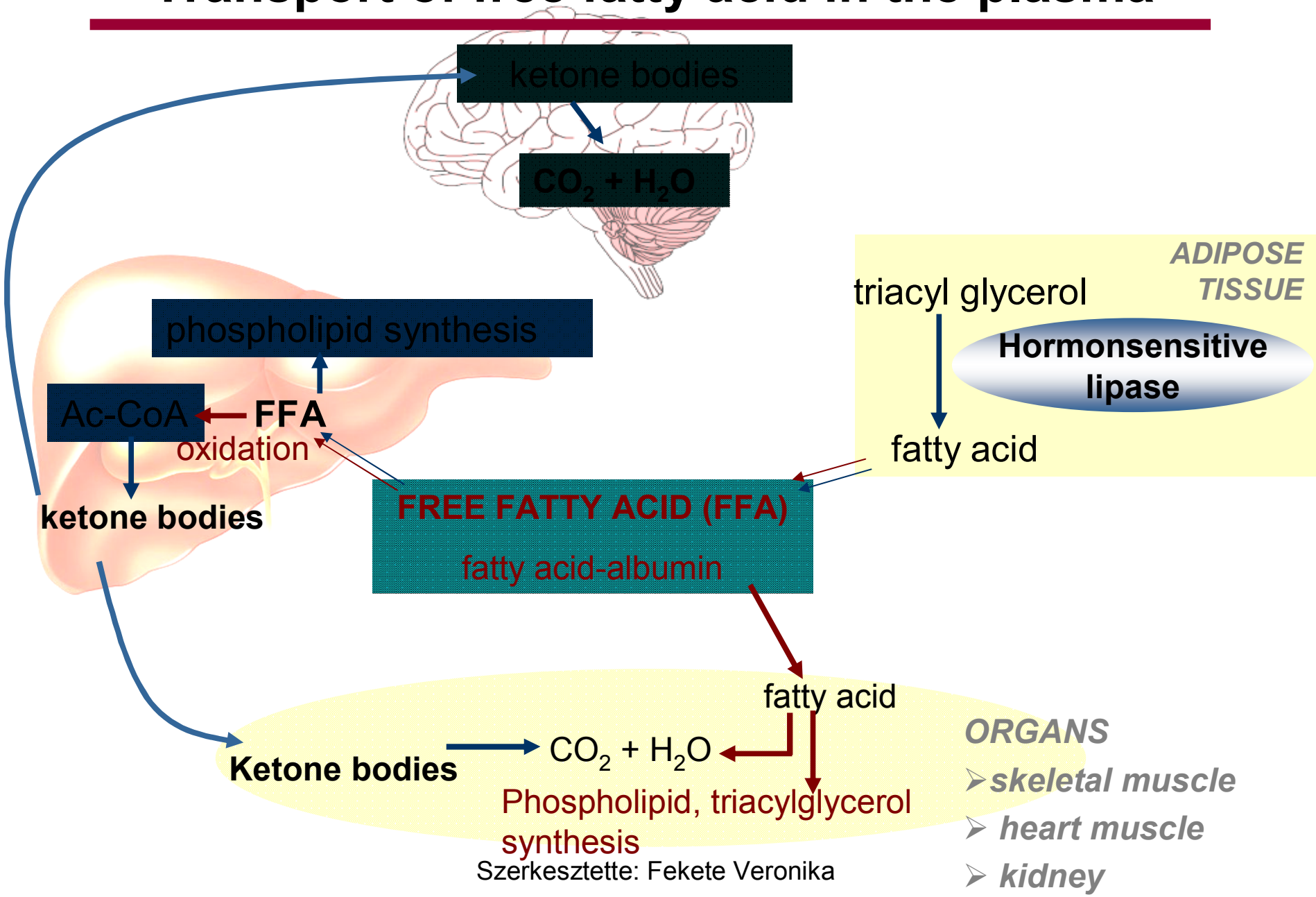
Metabolism of lipids



Transport of free fatty acid in the plasma



Szerkesztette: Fekete Veronika

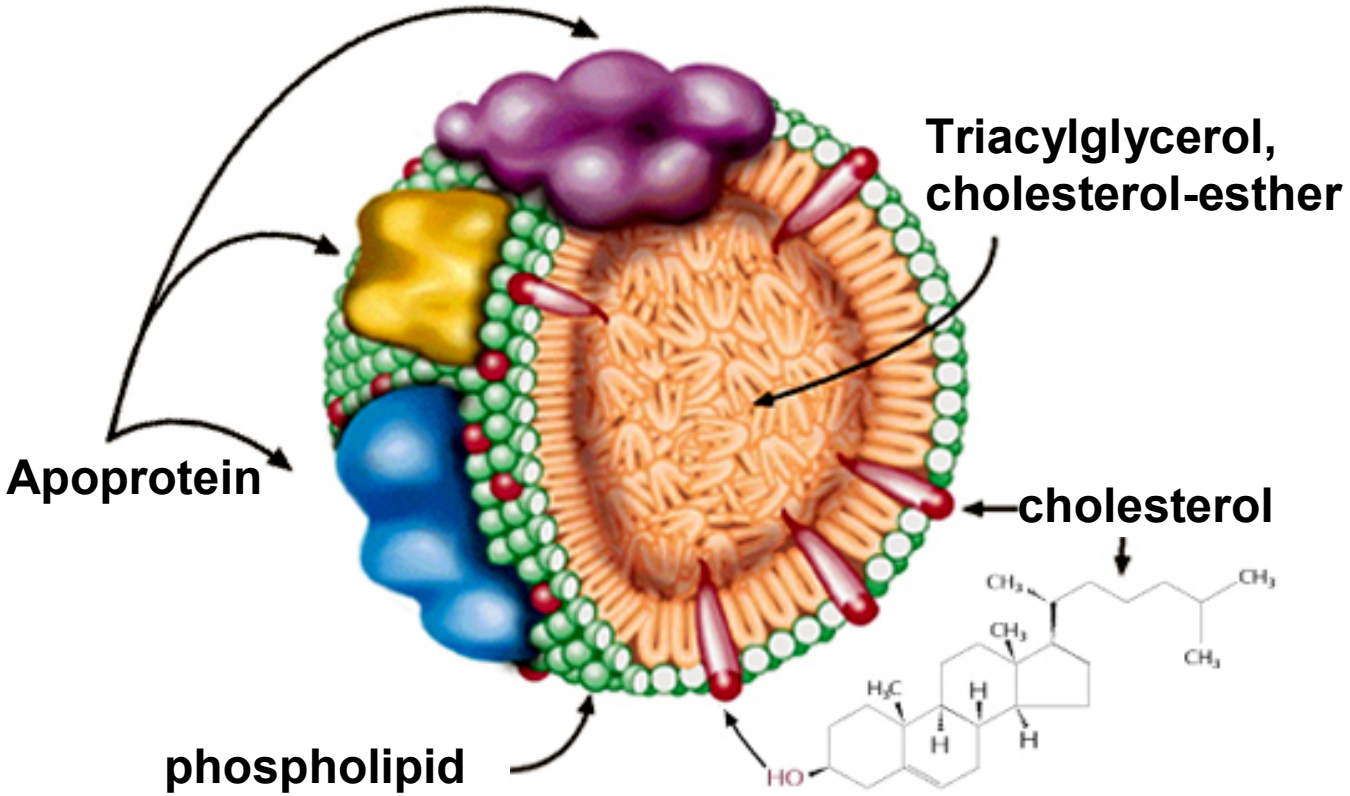
Composition of lipoproteins

- **Surface**:
  - apoproteins
  - phospholipids
  - cholesterol

  } polar

- **Core components**:
  - triacylglycerols
  - cholesterol-esthers

  } apolar



Szerkesztette: Fekete Veronika

Characteristics of lipoproteins

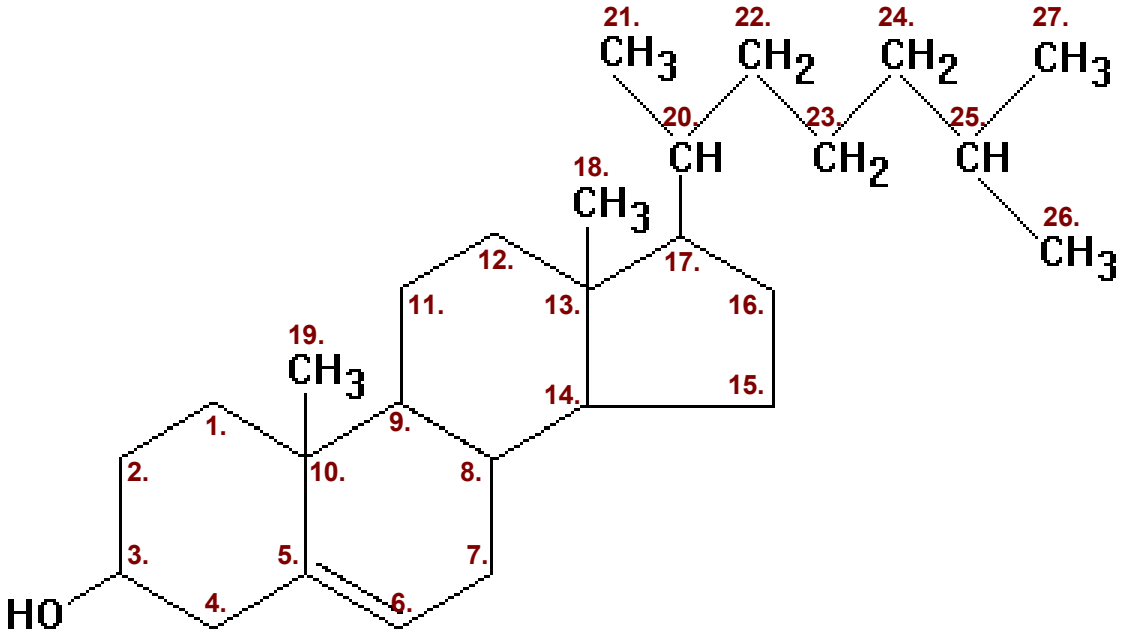
Lipoprotein	Density	Protein content (%)	Lipid content (%)	important lipid	Apoprotein
Chylo-mikron (CM)	↓	1-2	98-99	Triacylglycerol	B-48, C-II, C-III, E
VLDL		7-10	90-93	Triacylglycerol	B-100, C-I, C-II, C-III, E
IDL		15-20	80-85	Triacylglycerol cholesterol-esther	B-100, E
LDL		20-25	75-80	cholesterol-esther	B-100
HDL		40-55	50-55	phospholipid, cholesterol-esther	A-I, A-II, C-I, C-II, C-III, E

Structure of cholesterol

Basic structure: sterol ring (ciklopentanoperhydrofenantren)

Hydrofobic, non-water soluble

70 % of it exits in cholesterol-esther form

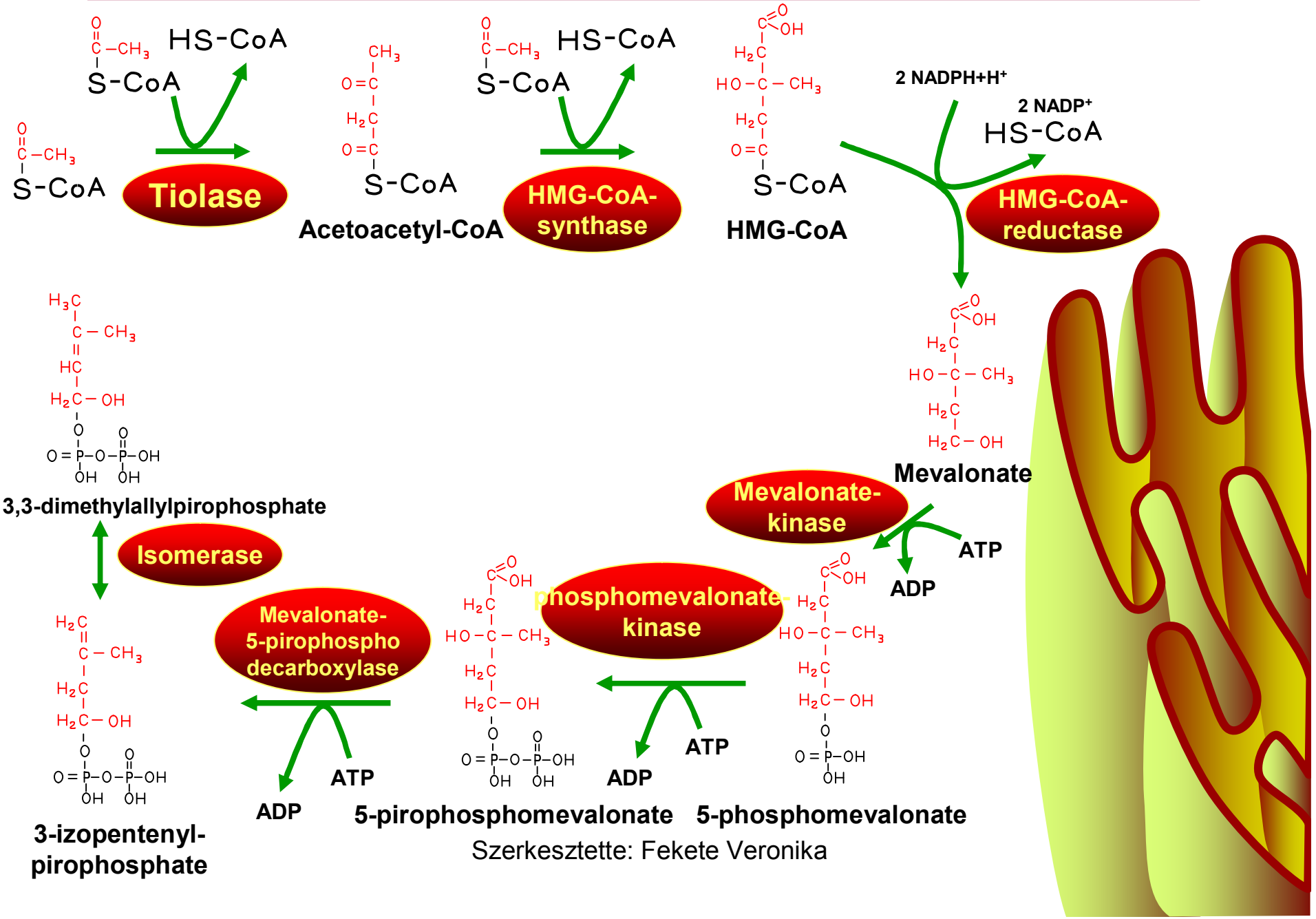


Szerkesztette: Fekete Veronika

Role of cholesterol

- it can be found in all cell types
- origin:
  - exogen: (food intake)
  - endogen: intracellular de novo synthesis
- role:
  - regulation of membrane fuidity
  - precursor for steroid hormon synthesis
  - precursor for bile acid synthesis
  - precursor for vitamin D_3

Synthesis of cholesterol I.



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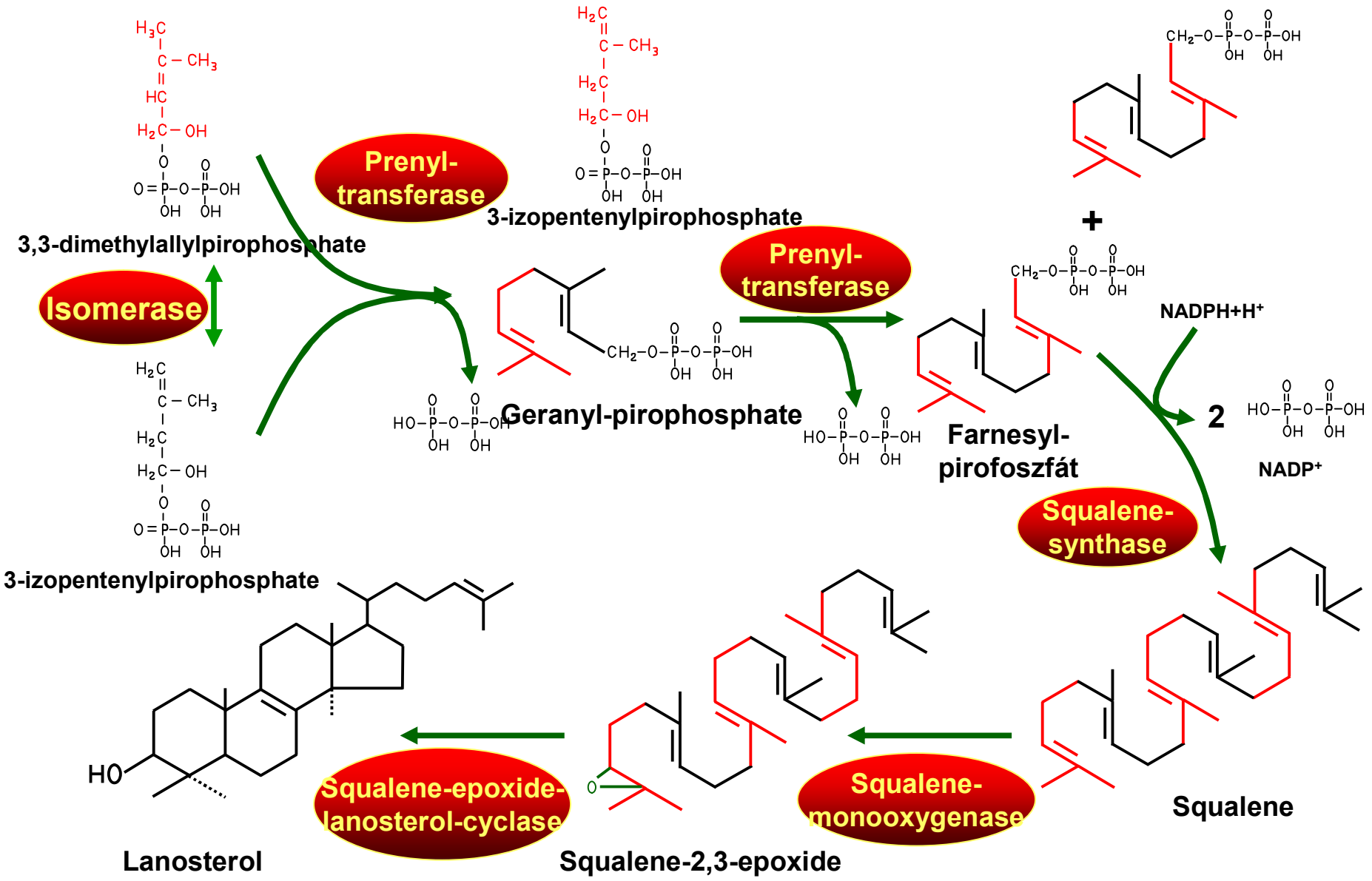
Synthesis of cholesterol II.



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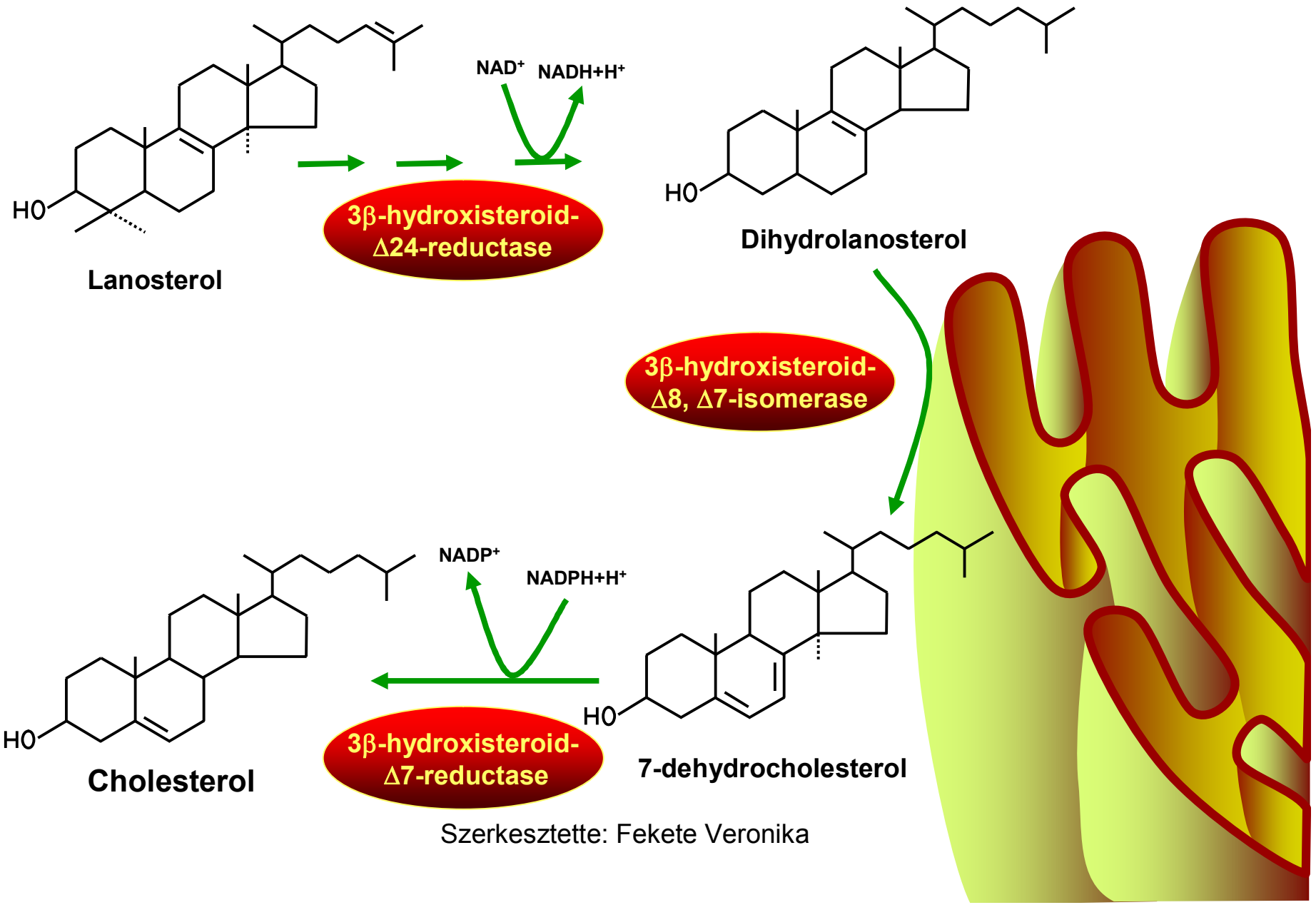
Synthesis of cholesterol III.



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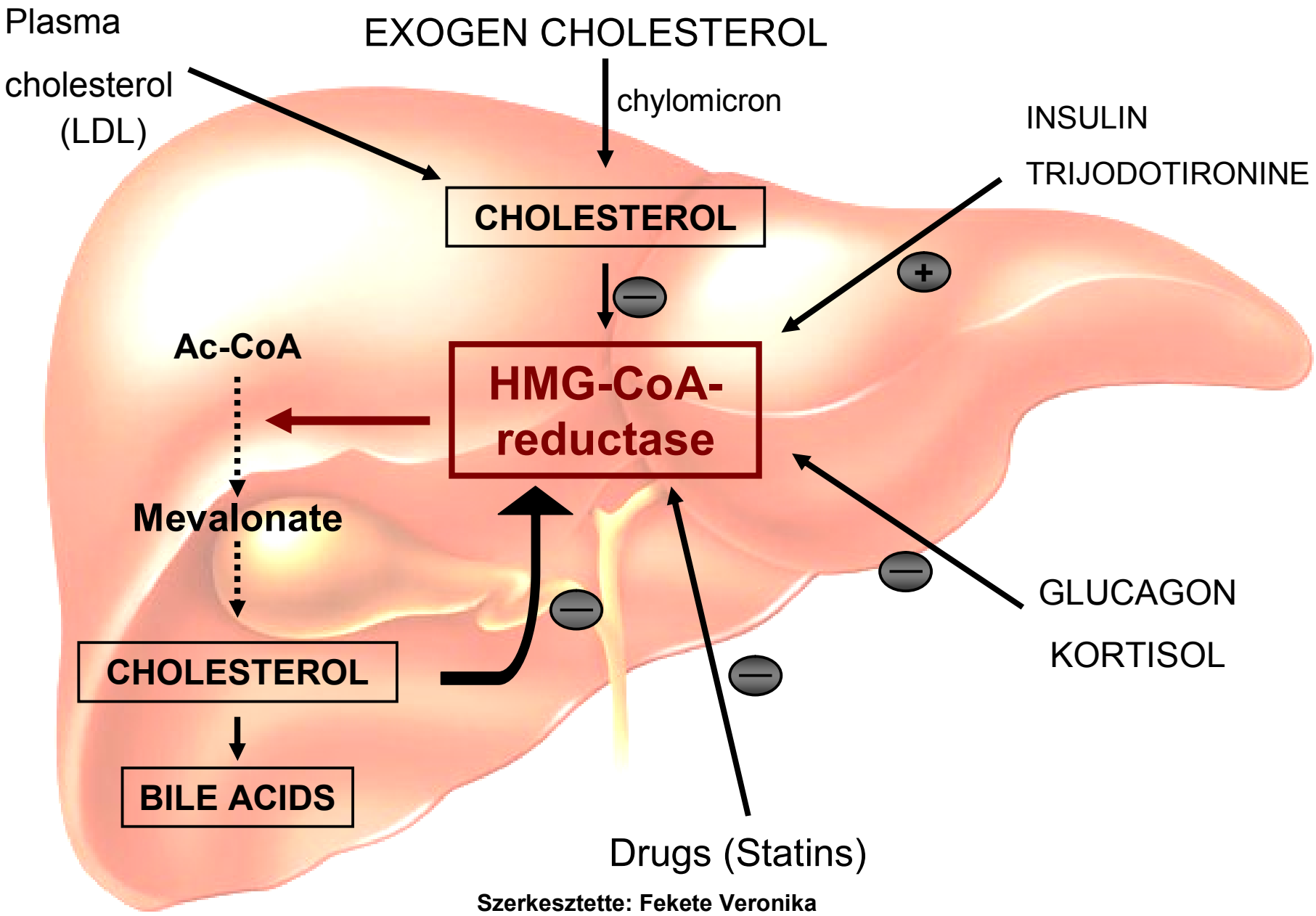
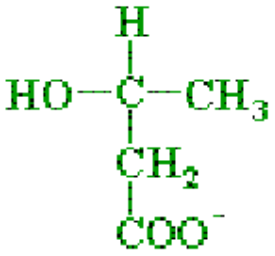
Regulation of cholesterol synthesis



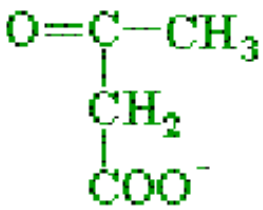
Szerkesztette: Fekete Veronika

Introduction

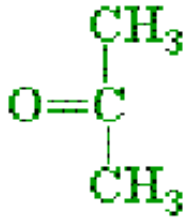
Ketone bodies:



β-hydroxi-butyrate



acetoacetate



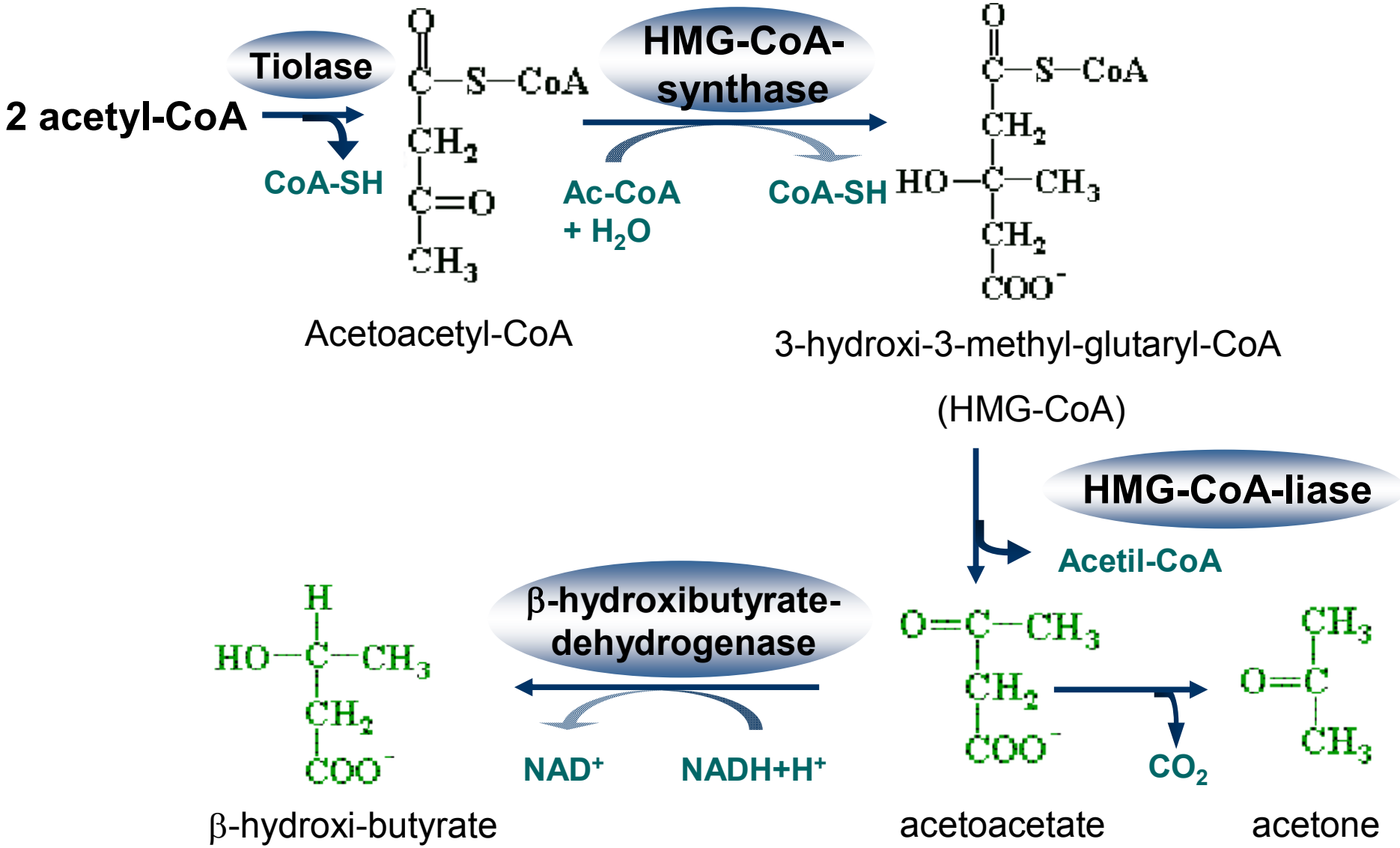
acetone

- concentration in blood stream < 0,2 mM

Characteristics:

- formation from Acetyl-CoA
- water soluble molecules
- produced mainly by liver, less by
- alternative energy sources for peripherial tissues

Synthesis of ketone bodies



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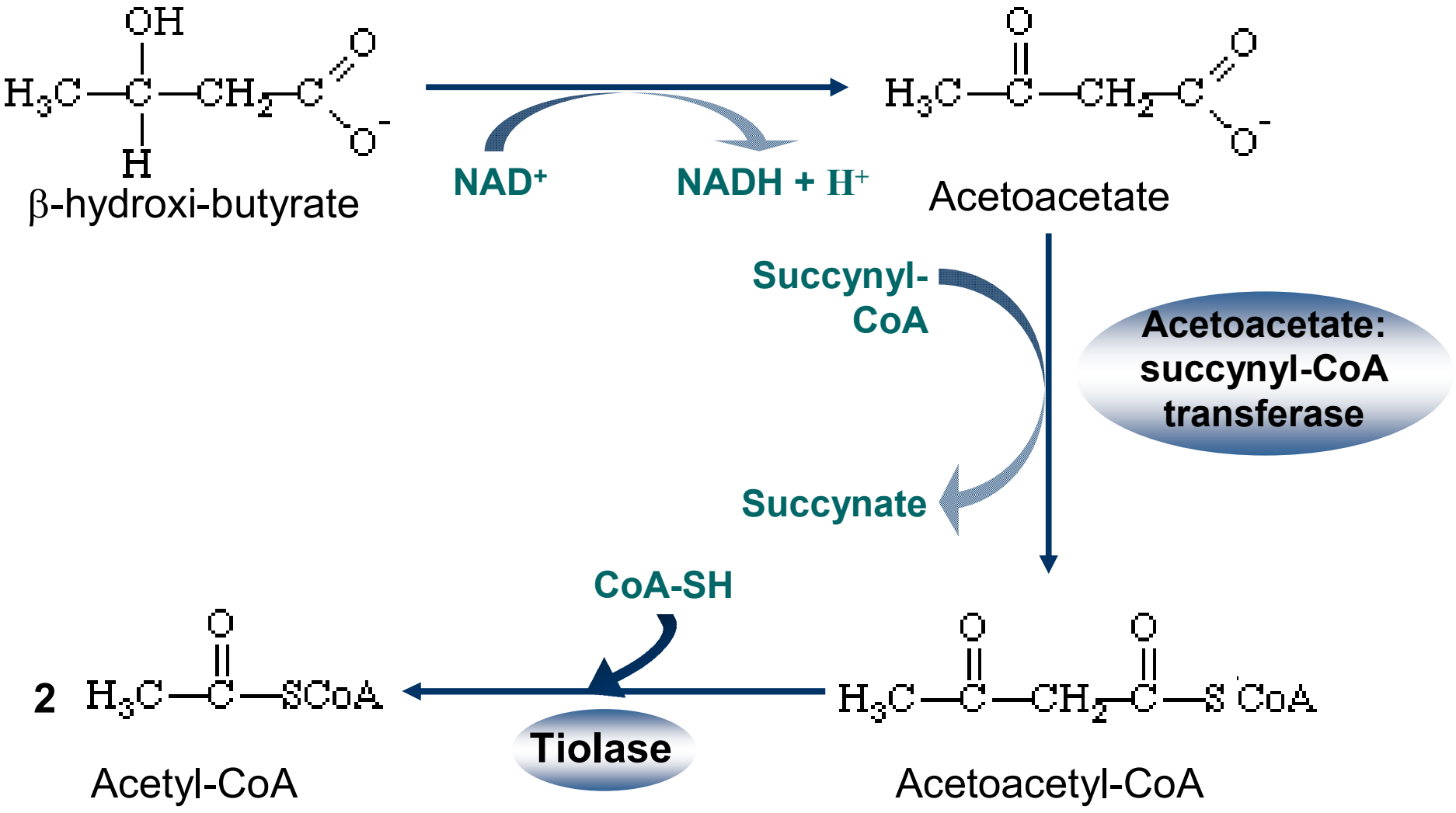
Utilisation of ketone bodies

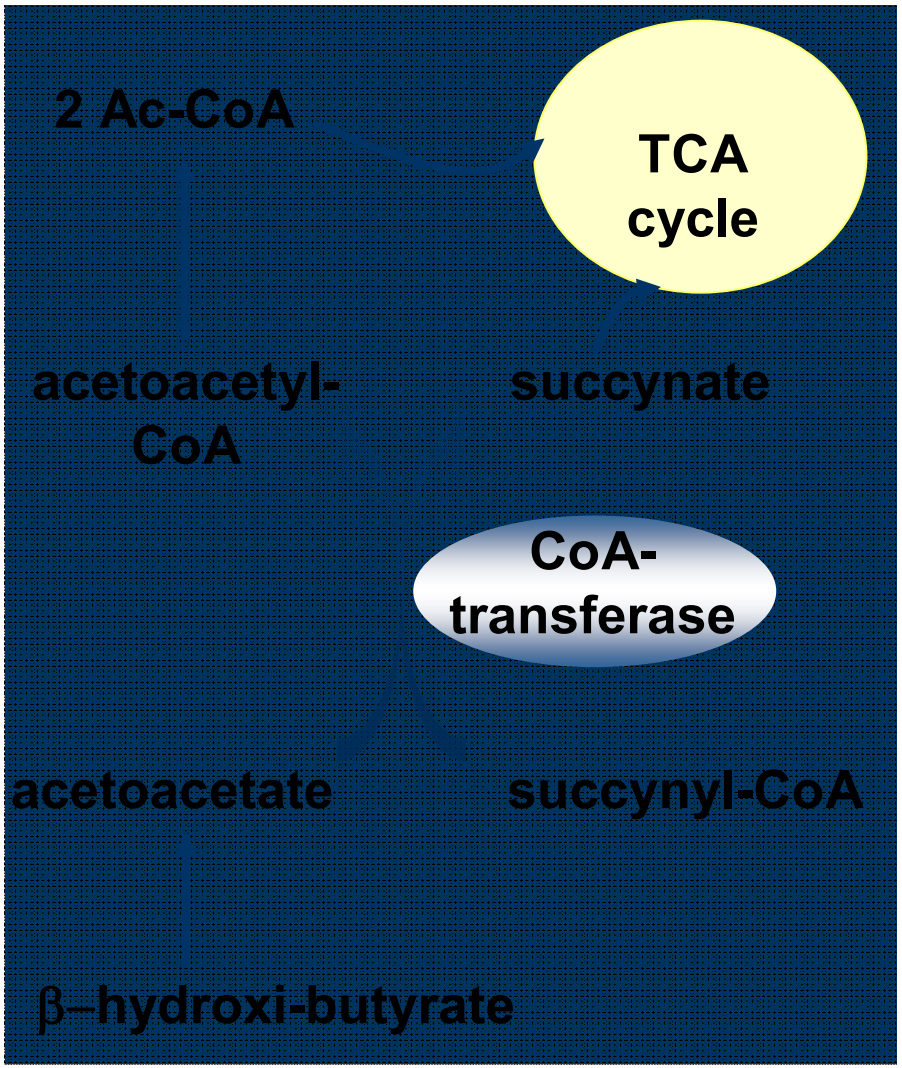


Szerkesztette: Fekete Veronika

Utilisation of ketone bodies

Peripheral tissues:

- heart muscle
- skeletal muscle
- kidney
- brain



acetoacetate ⟹

β–hydroxi-butyrate ⟹

Szerkesztette: Fekete Veronika

Utilisation of fatty acids

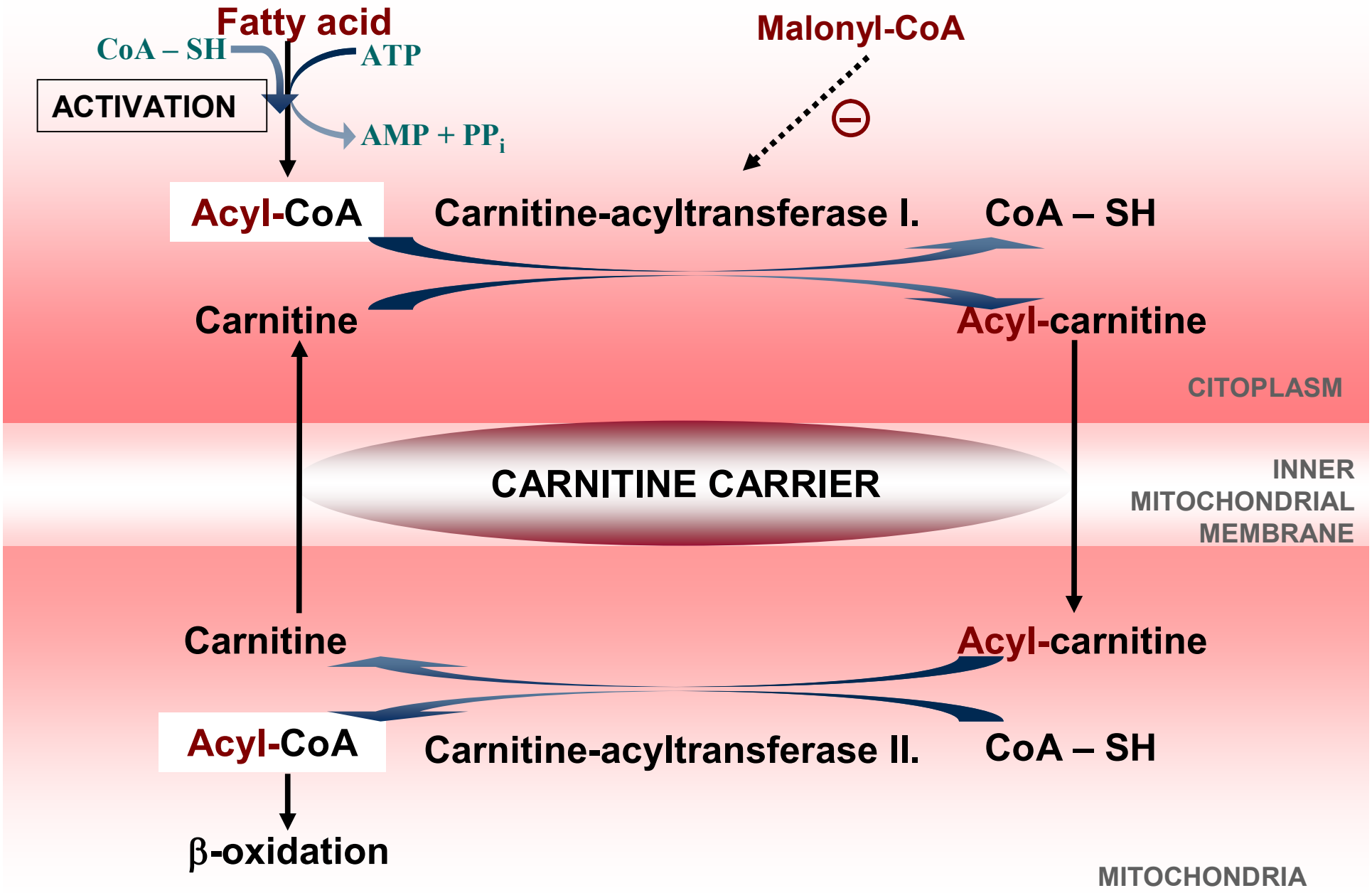
Tissues are not supported by fatty acids:

- nervous tissue
- red blood cell
- adrenal medulla

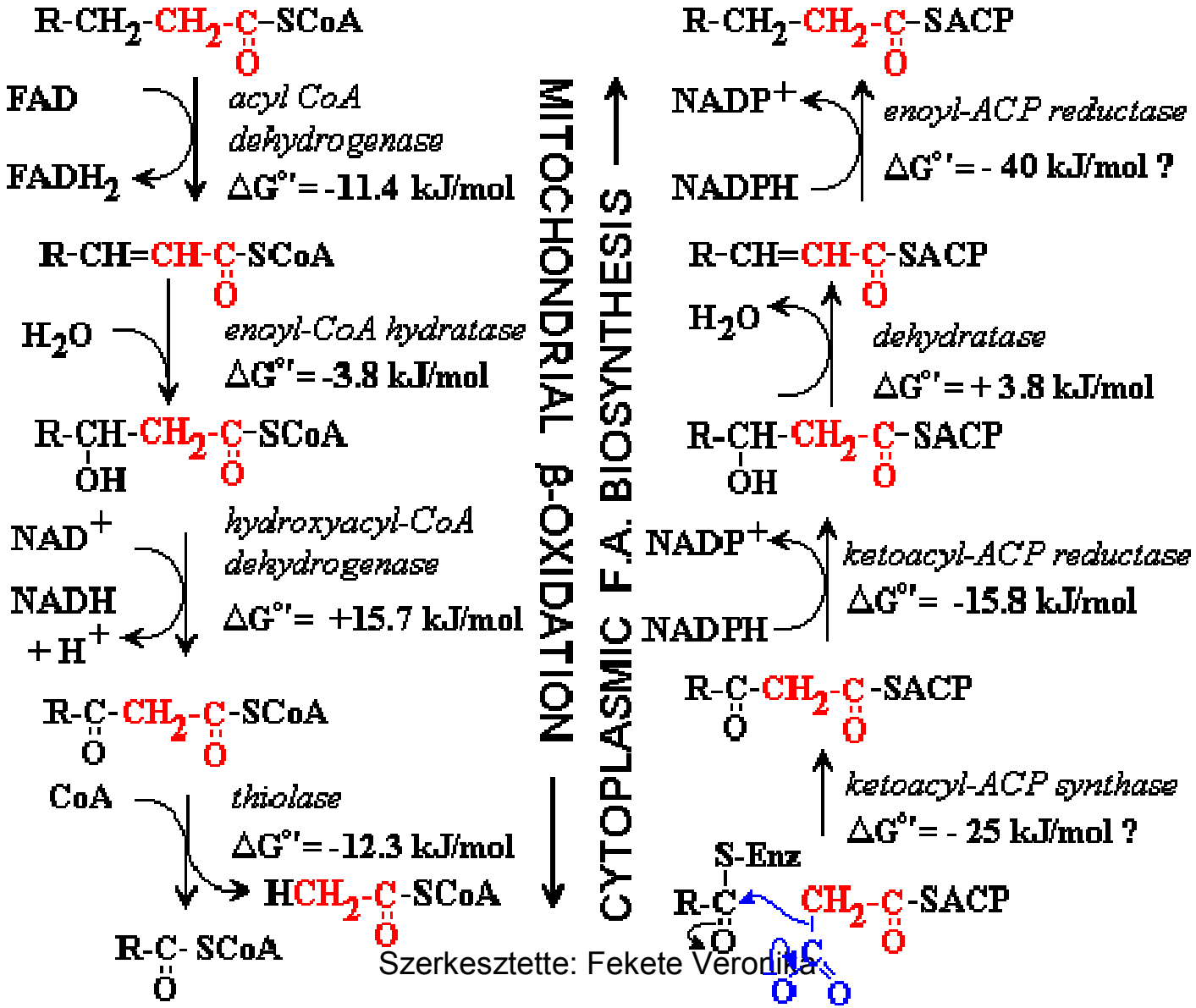
Fatty acids are predominant energy supply for heart and skeletal muscle

Utilisation of fatty acids by tissues mainly depends on actual need

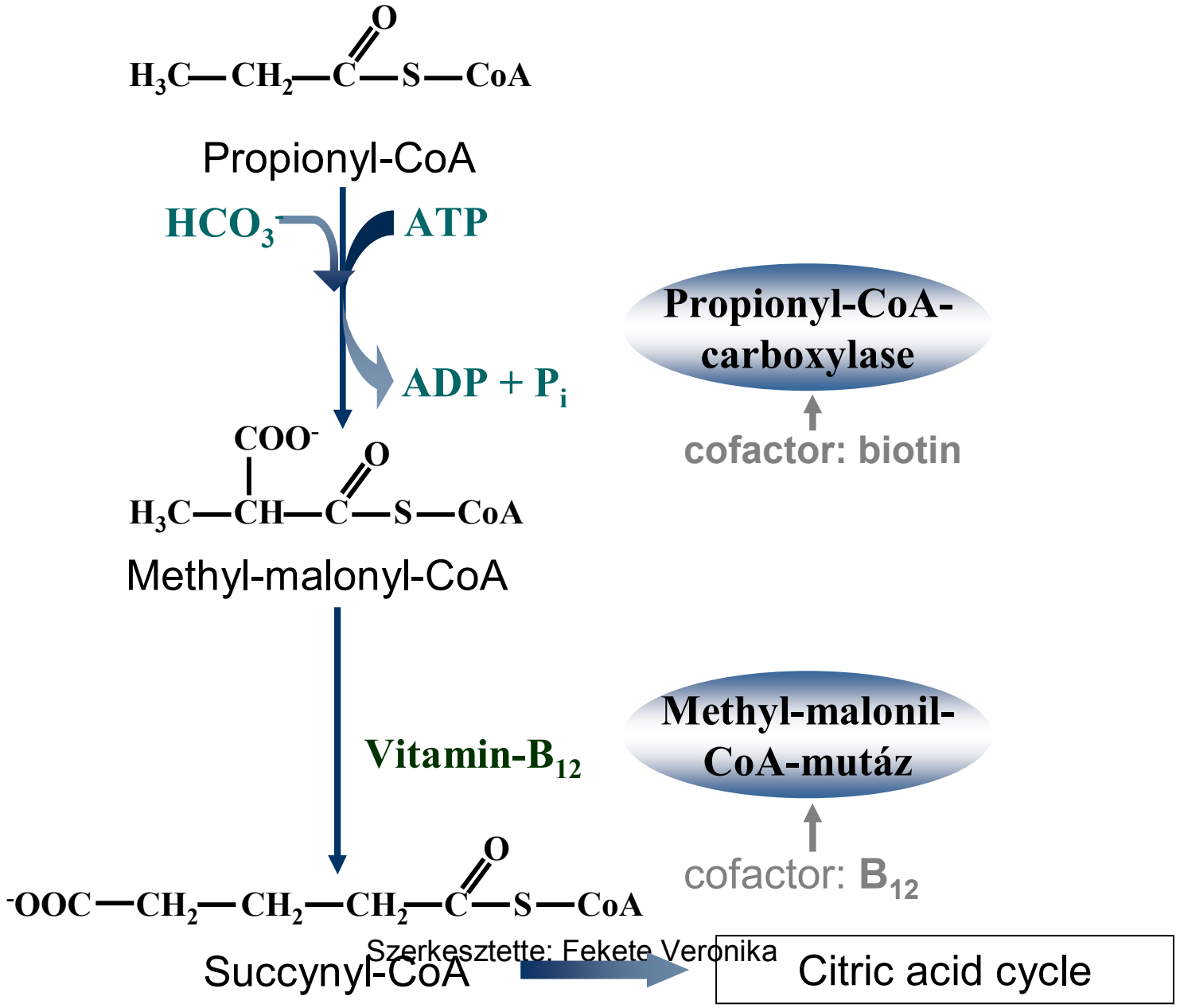
Transport of fatty acids to mitochondria



Oxidation of Even numbered fatty acids – β-oxidation

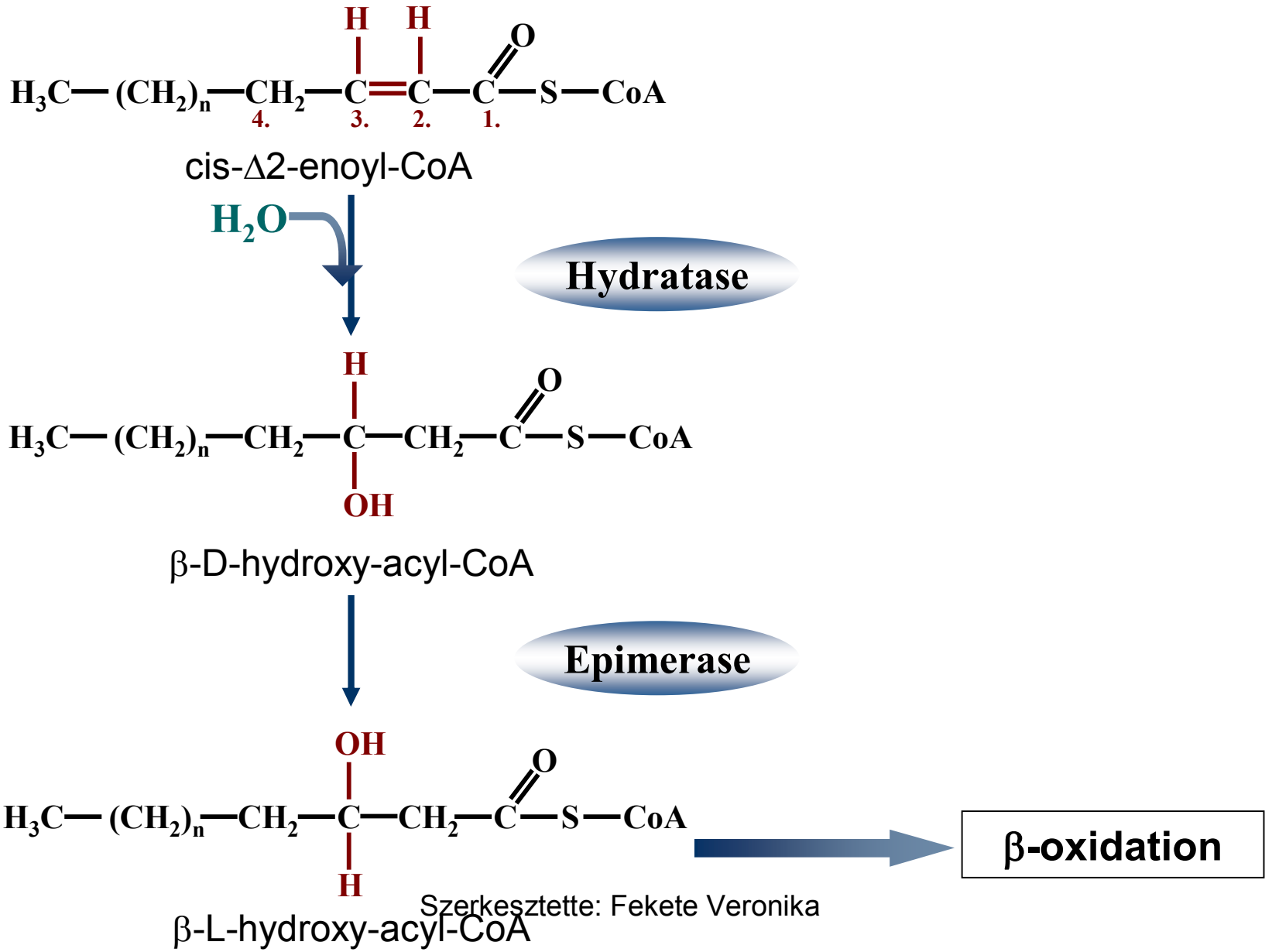


Metabolism of propionyl-CoA



Szerkesztette: Fekete Veronika

Oxidation of fatty acids with „cis” conformation I.



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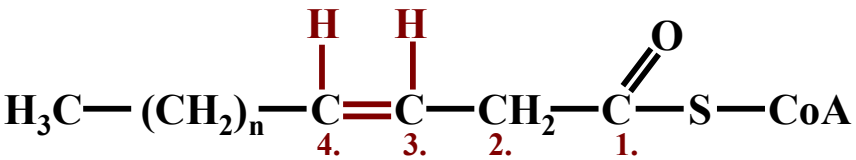
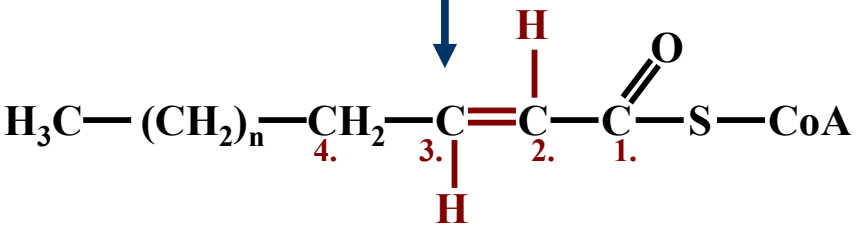
Oxidation of fatty acids with „cis” conformation II.



cis-Δ3-enoyl-CoA

Izomerase



trans-Δ2-enoyl-CoA

β-oxidation

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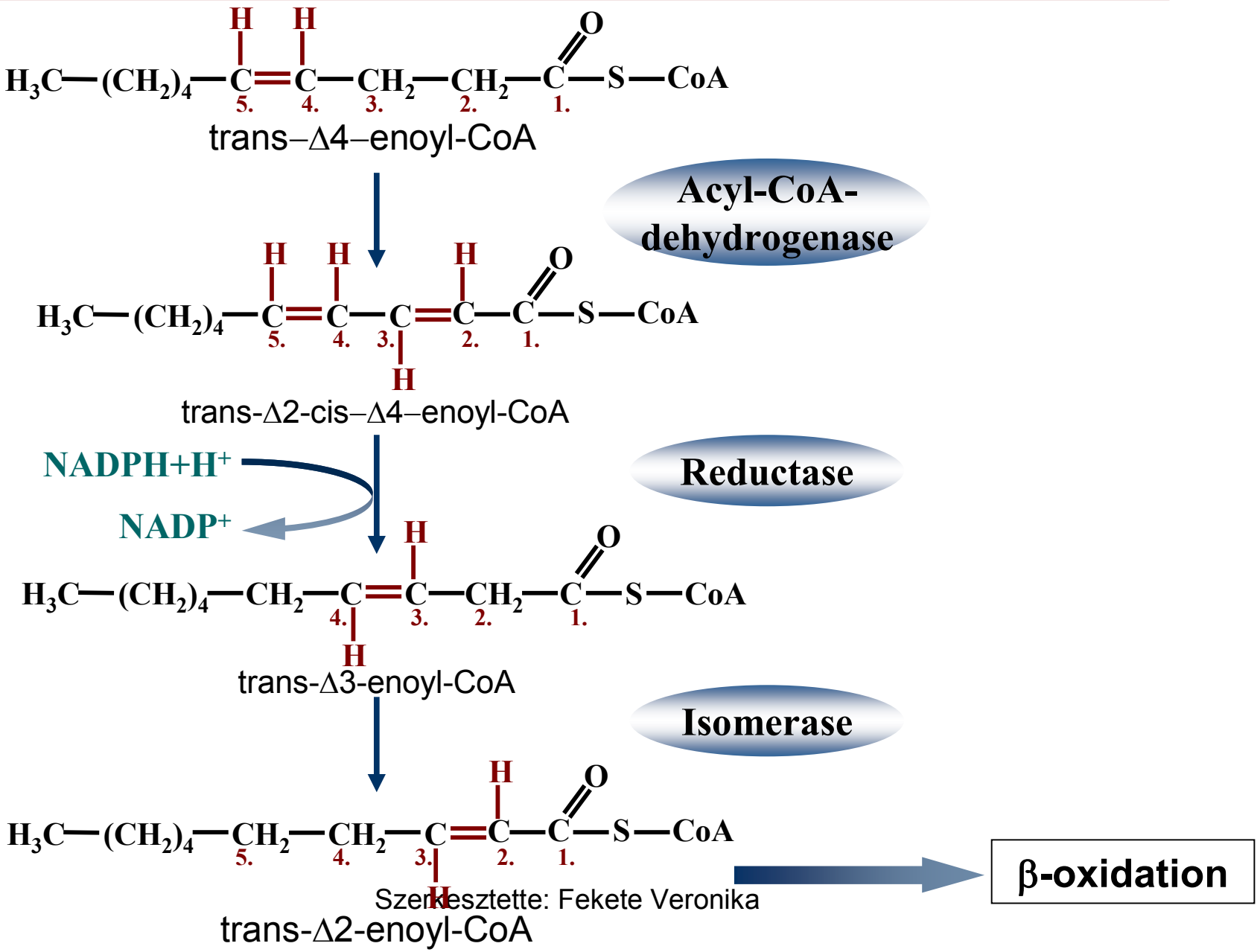
Additional steps of oxidation of linolic acid (18:2Δ9,12)



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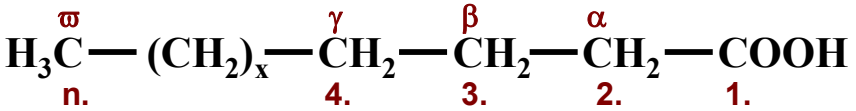
Saturated fatty acids

- carbon chain and terminal carboxyl group
- the carbon chain does not contain any double bonds
- flexible, linear structure

- **General structure:**



  - short chain: n=2 – 5
  - middle chain: n=6 – 11
  - long chain: n=12 – 26

Unsaturated fatty acids

Fatty acid	Number of carbons	Number of double bonds	Position of double bonds
Palmitic acid	16	0	
Palmitoleic acid	16	1	Δ9 ϖ-7
Stearic acid	18	0	
Oleic acid	18	1	Δ9 ϖ-9
Linoic acid*	18	2	Δ9,12 ϖ-6
Linolenic acid*	18	3	Δ9,12,15 ϖ-3
Arachidonic acid	20	4	Δ5,8,11,14 ϖ-6

*: essential fatty acids

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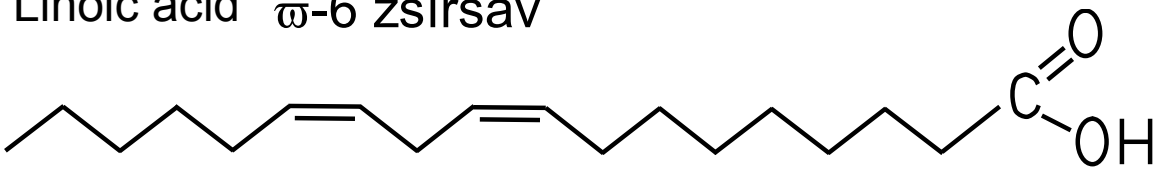
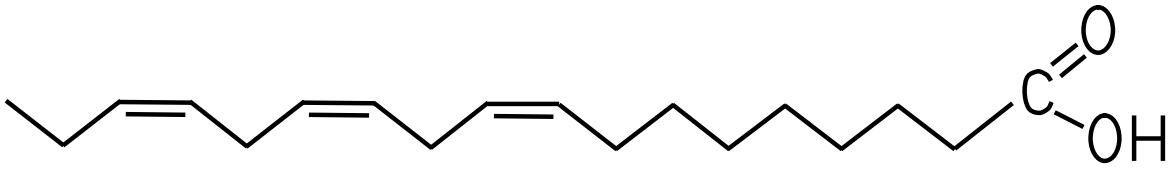
Essential fatty acids

Linoic acid ϖ-6 zsírsav



Linolenic acid ϖ-3 zsírsav



Role:

- synthesis of eikozanoids
- synthesis of poli-unsaturated fatty acids taking part in formation of biological membranes

Occurence:

- linoic acid: plant oils
- linolenic acid: sea fish

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Origin of components required for fatty acid synthesis

Acetyl-CoA:

- from carbohydrate metabolism (reaction catalysed by pyruvate-dehydrogenase enzyme complex)

NADPH:

- direct oxidation of glucose
- reaction catalysed by malic enzyme in cytoplasm
- reaction catalysed by az isocitrate-dehydrogenase

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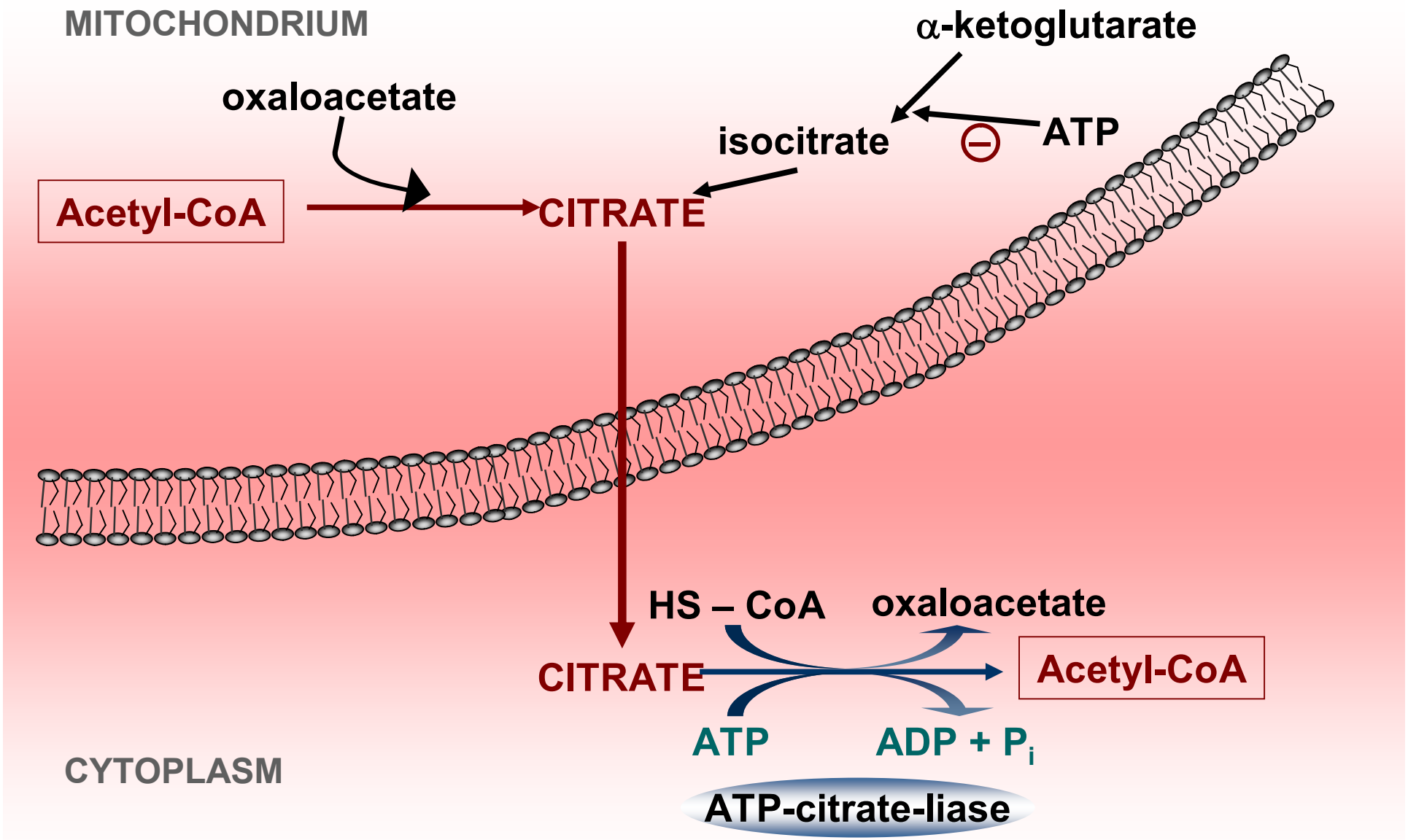
Transport of acetyl-CoA to the cytoplasm



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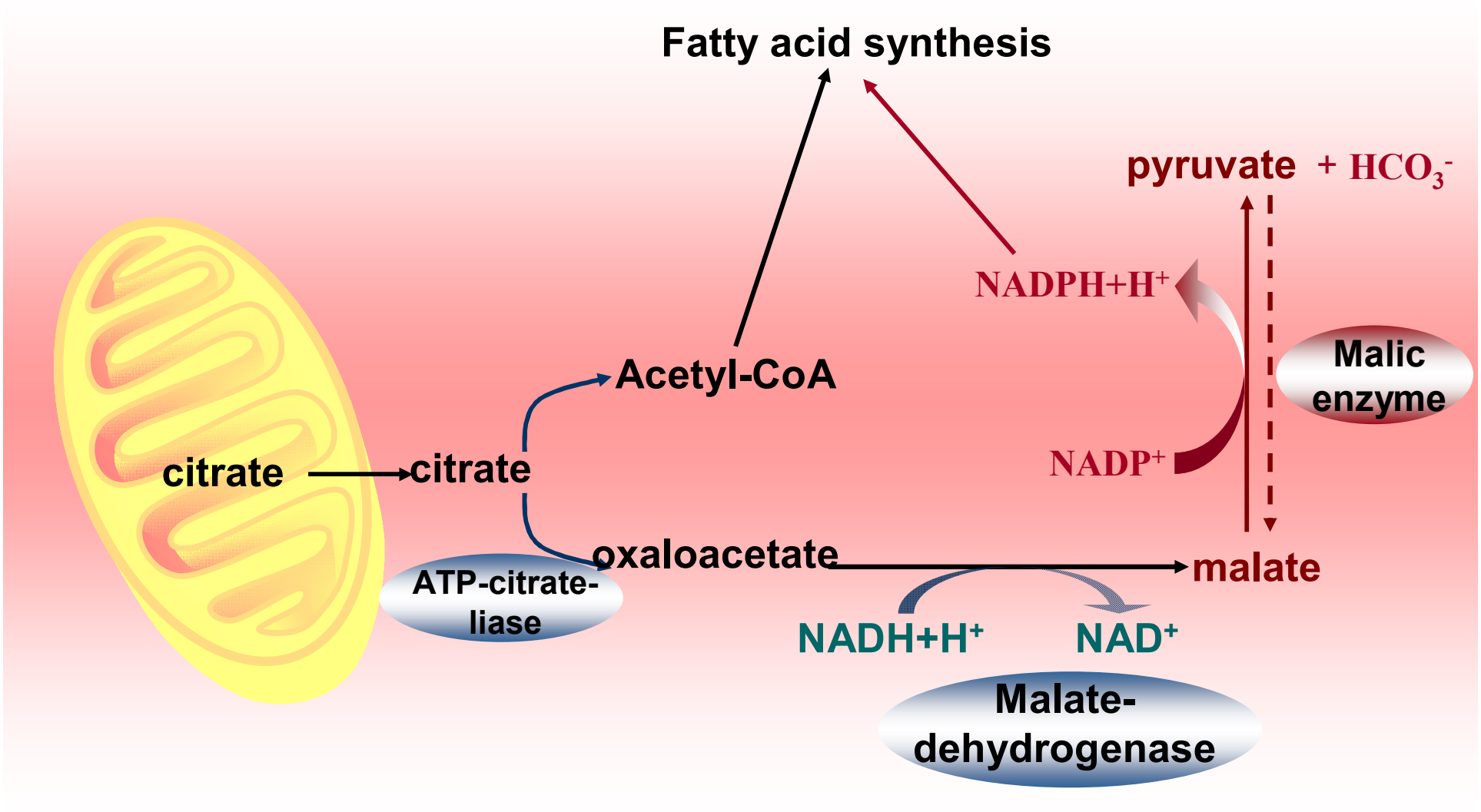
Source of NADPH

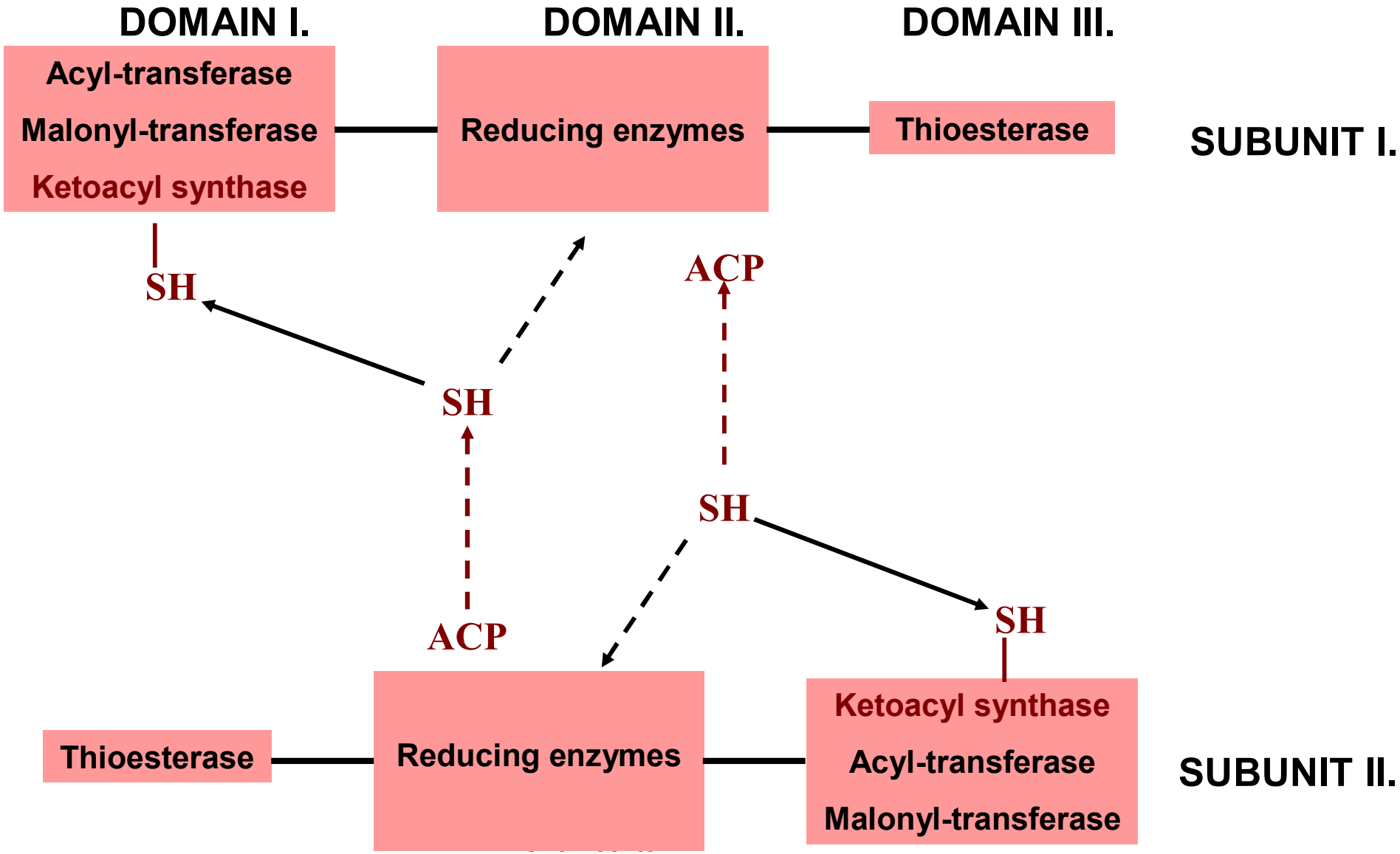


Szerkesztette: Fekete Veronika

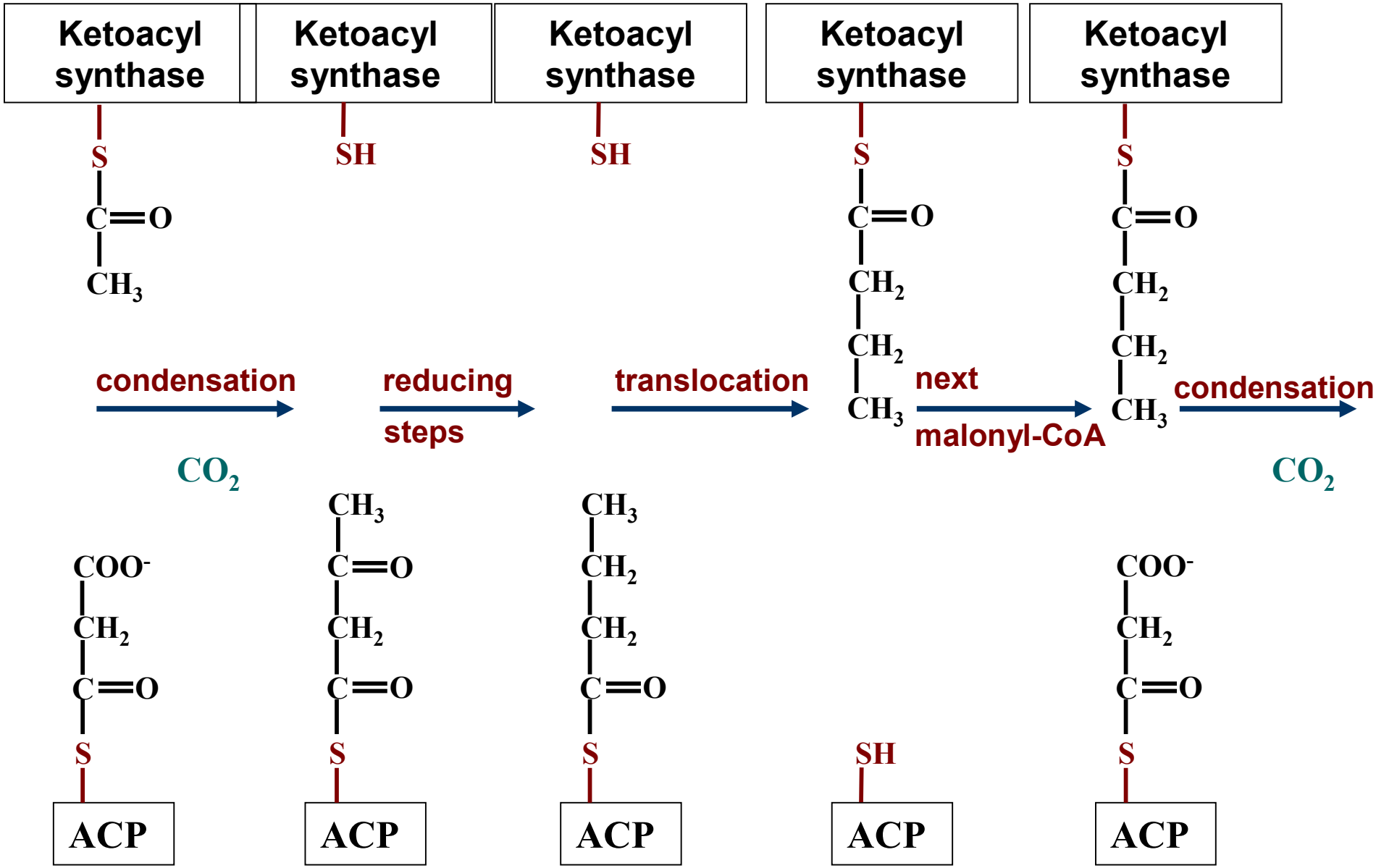
de novo synthesis of fatty acids

- all fatty acids synthesised from palmitic acid
- Catalytic anzyme: fatty acid synthase
  - 2 subunit – 7 different protein with biological activity
  - 2 –SH-groups for binding of acyl- and acetyl groups in each subunits
  - ACP (acyl carrier protein): binding of 4'-foszfopantetheine
  - Enzymes:
    - acyl-transferase
    - malonyl-CoA-ACP-transzacylase (malonyl-transferase)
    - β-ketoacyl-ACP-synthase (kondenzáló enzim)
    - enzymes redukáló enzimek
    - tioészteráz

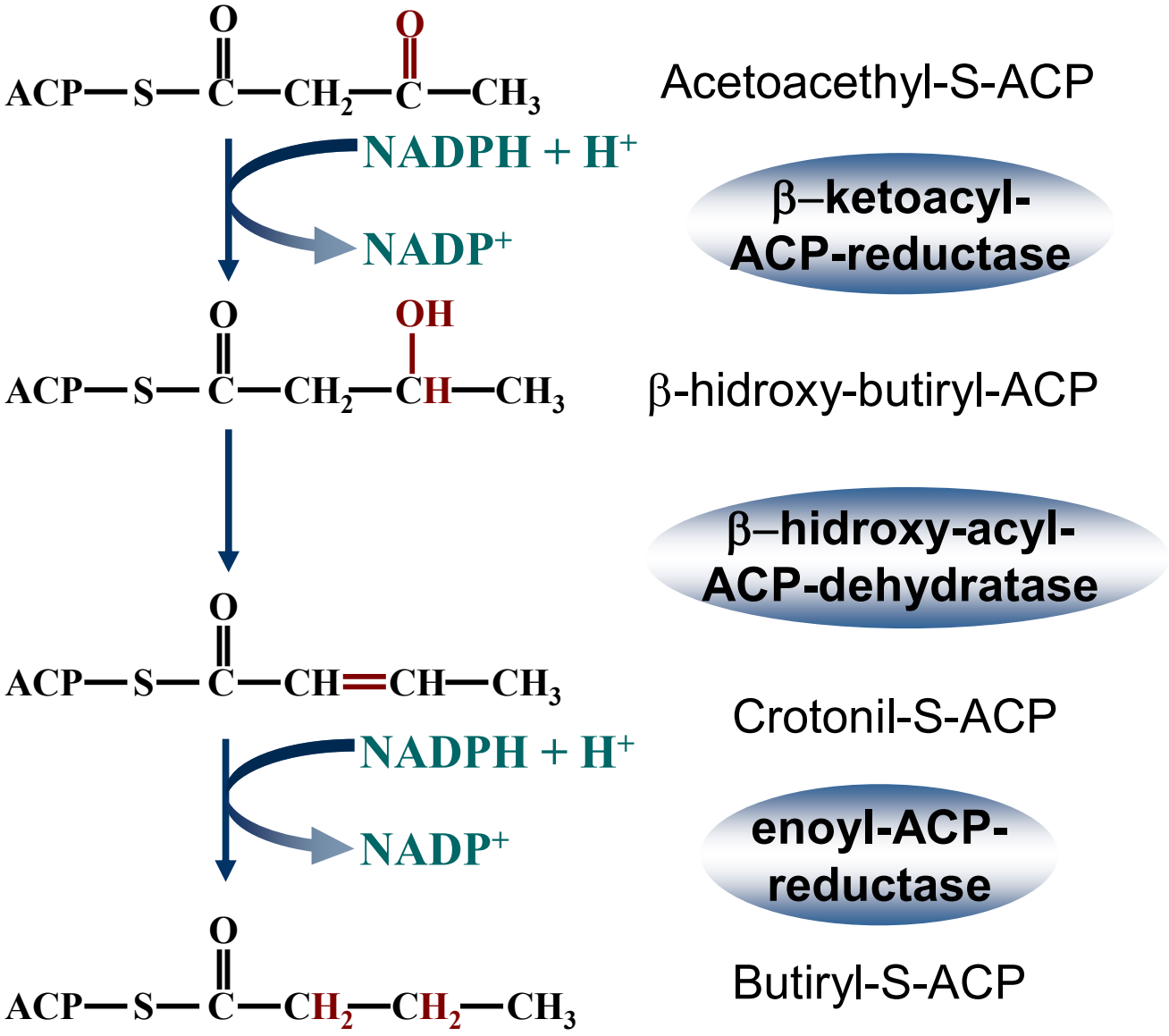
Model of fatty acid synthase



Synthesis of fatty acid



Reducing steps in fatty acid synthesis



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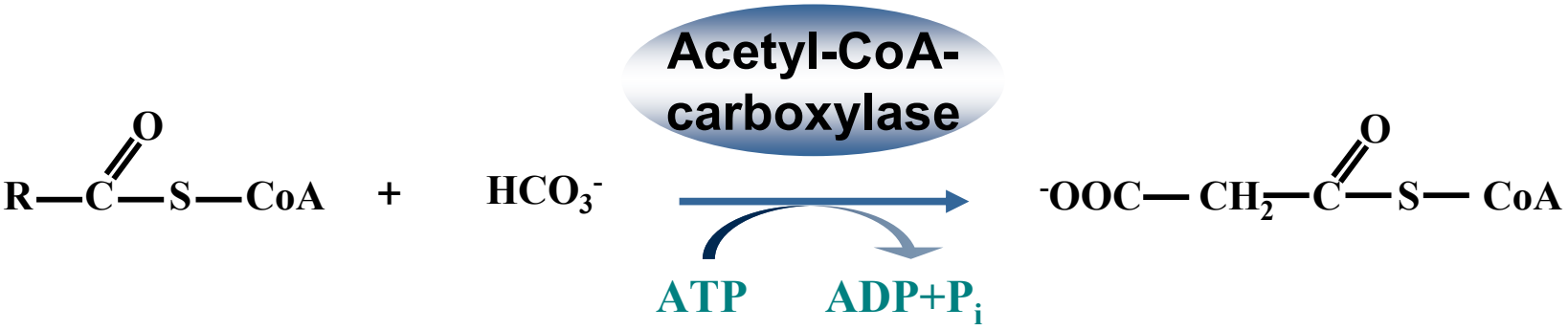
Regulation of fatty acid synthesis



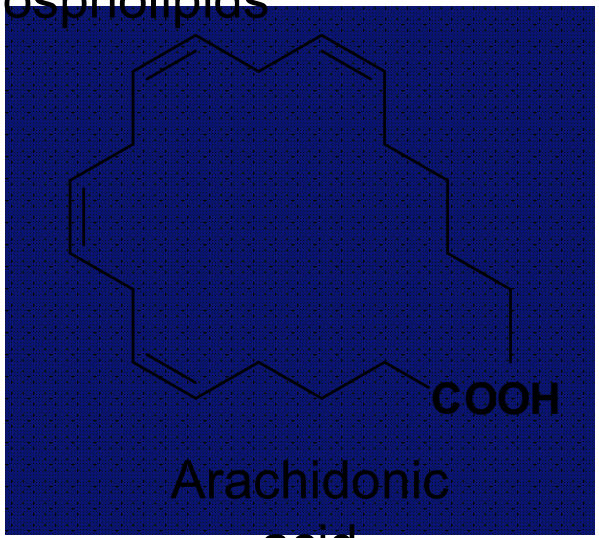
Main step of fatty acid synthesis: **acetyl-CoA-carboxylase**

- Cofactor: biotin – binding of CO_2 with usage of ATP
- Regulation:
  - ➢ allosteric activator: citrate – it helps in formation of active polimer
  - ➢ allosteric inhibitor: malonyl-CoA, palmitoyl-CoA – they inhibit the formation of active polimer
  - ➢ transcription of the enzyme adapts to the fed-state of the body

Szerkesztette: Fekete Veronika

Characterisation of arachidonic acid

- synthesis precursors are linoleic and linolenic acids
- 2-acyl position of a glicerophospholipids is saturated by arachidonic acid
- free arachidonic acid concentration of cytosol is very limited
- Committed step of eicosanoid biosynthesis is deliberation of arachidonic acod from phospholipids



Arachidonic acid

Szerkesztette: Fekete Veronika

Deliberation of arachidonic acid from phospholipids

1. **Phospholipase A_2 (PLA_2)**

   a) high molecular weight PLA_2

   - Specific for arachidonic acid
   - Increase in the intracellular Ca^{2+} concentration support its translocation to the plasma membrane

   b) low molecular weight PLA_2

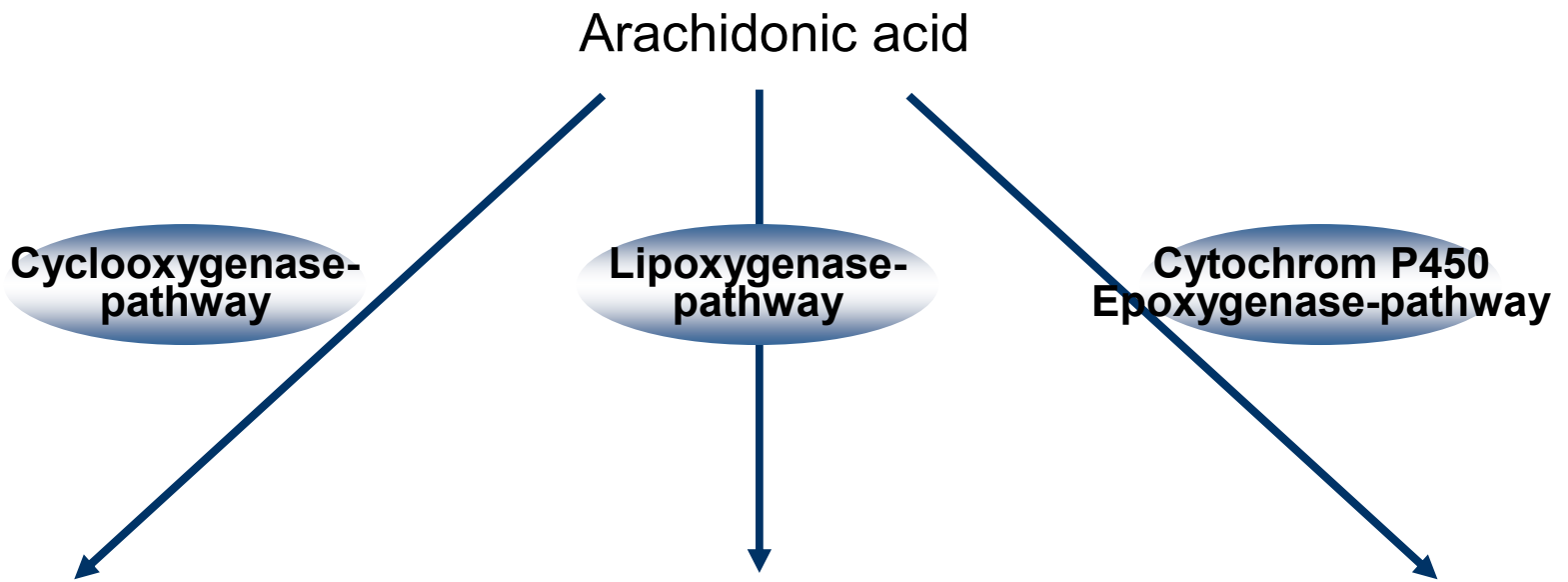
   - Not specific for arachidonic acid
   - Glucocorticoids inhibit it

2. **Phospholipase C (PLC) and DAG-lipase**

   - Arachidonic acid deliberated from diacyl glycerol by DAG lipase which originated from TG by a PLC
   - platelets

Szerkesztette: Fekete Veronika

Oxidation of arachidonic acid in the cells



- Prostaglandins (PG)
- Thromboxanes (Tx)

- Hydroperoxieicosa-tetraenoic acids (HPETE)
- Hydroxyeicosatetraenoic acids (HETE)
- Leukotrienes (LT)

- Epoxieicosa-tetraenoic acids (EET)
- Lipoxins

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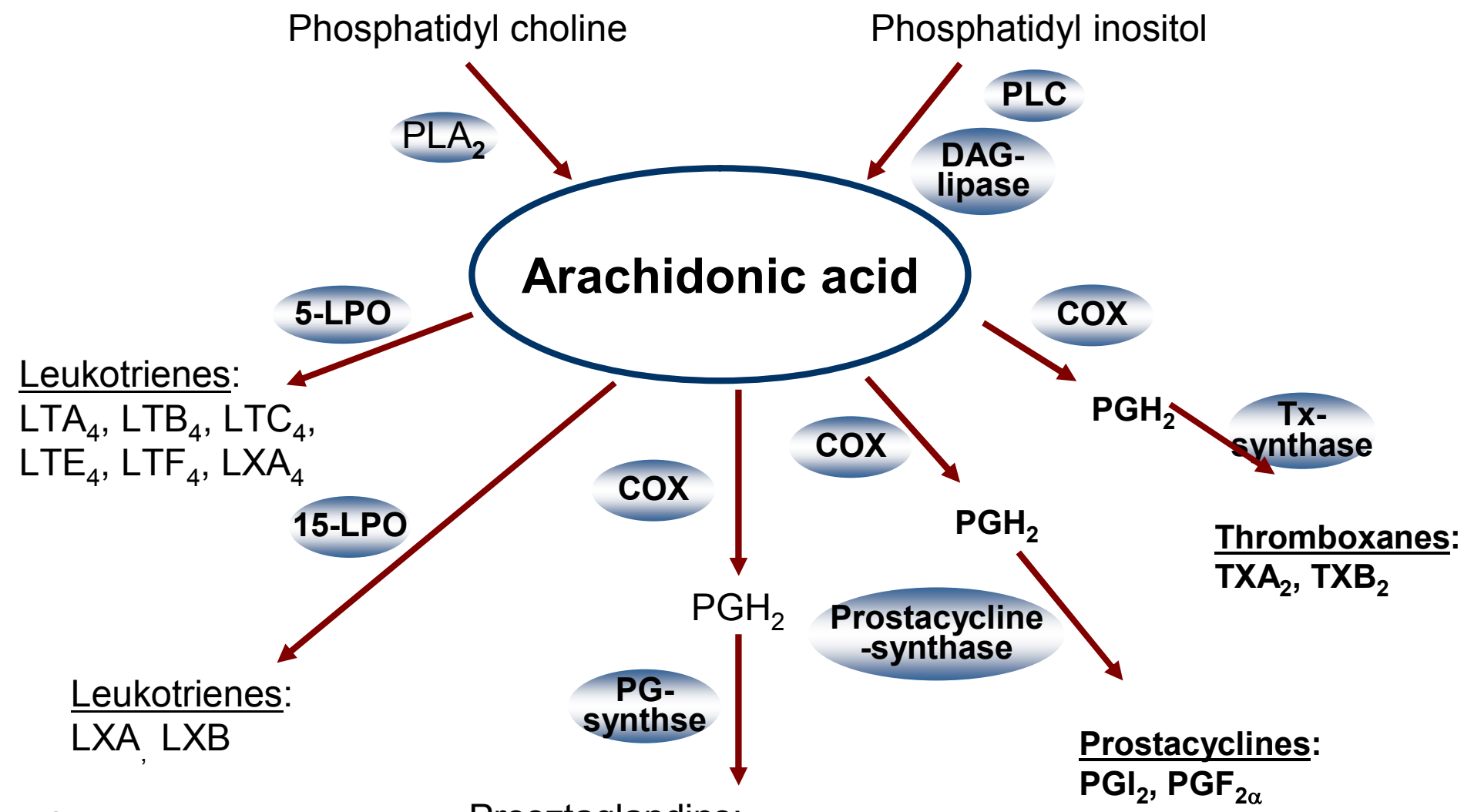
Oxidation of arachidonic acid



DAG: diacyl-glycerol

COX: cyclooxygenase

Tx: thromboxane

LPO: lipoxygenase

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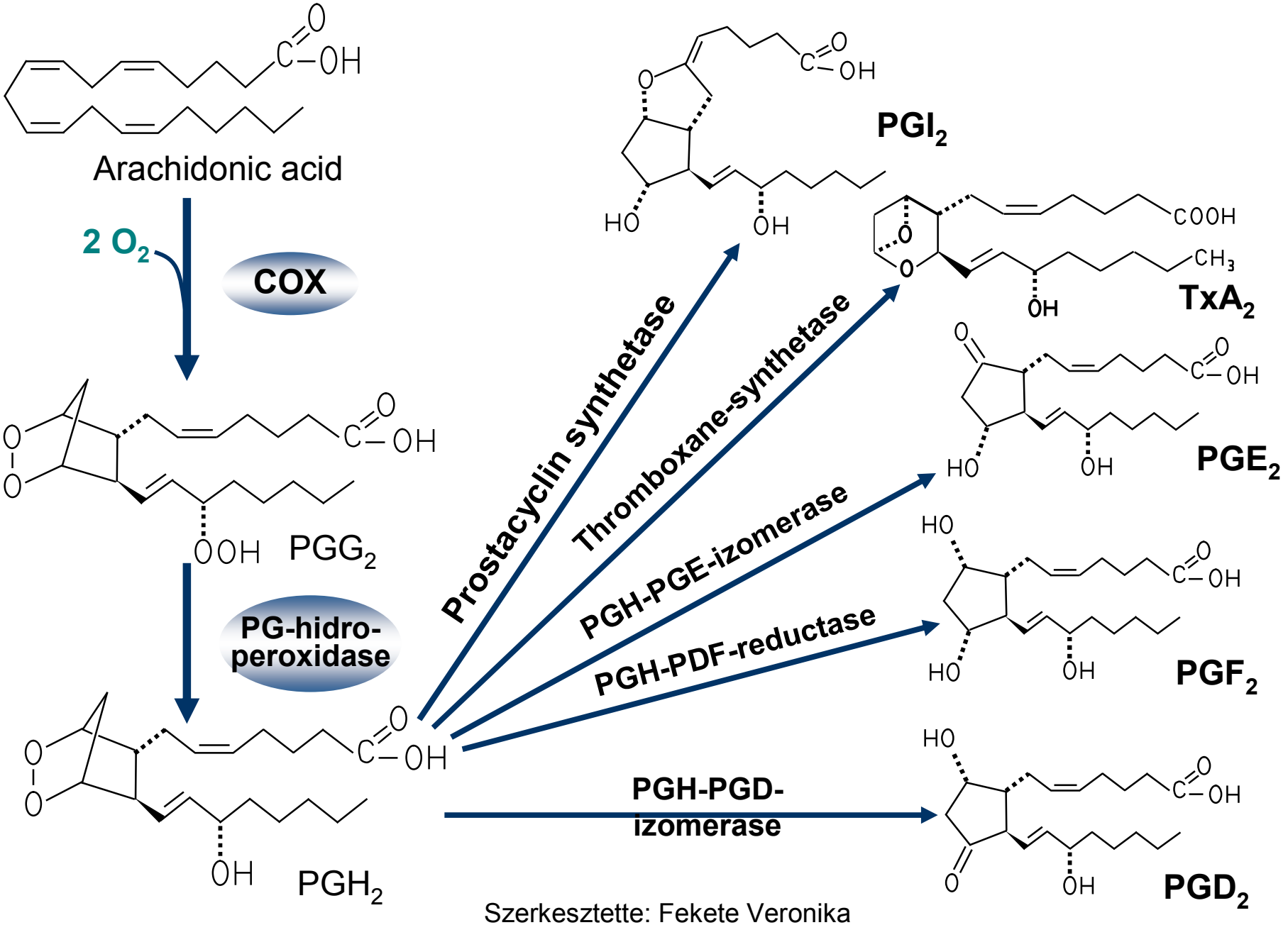
The cyclooxygenase-pathway



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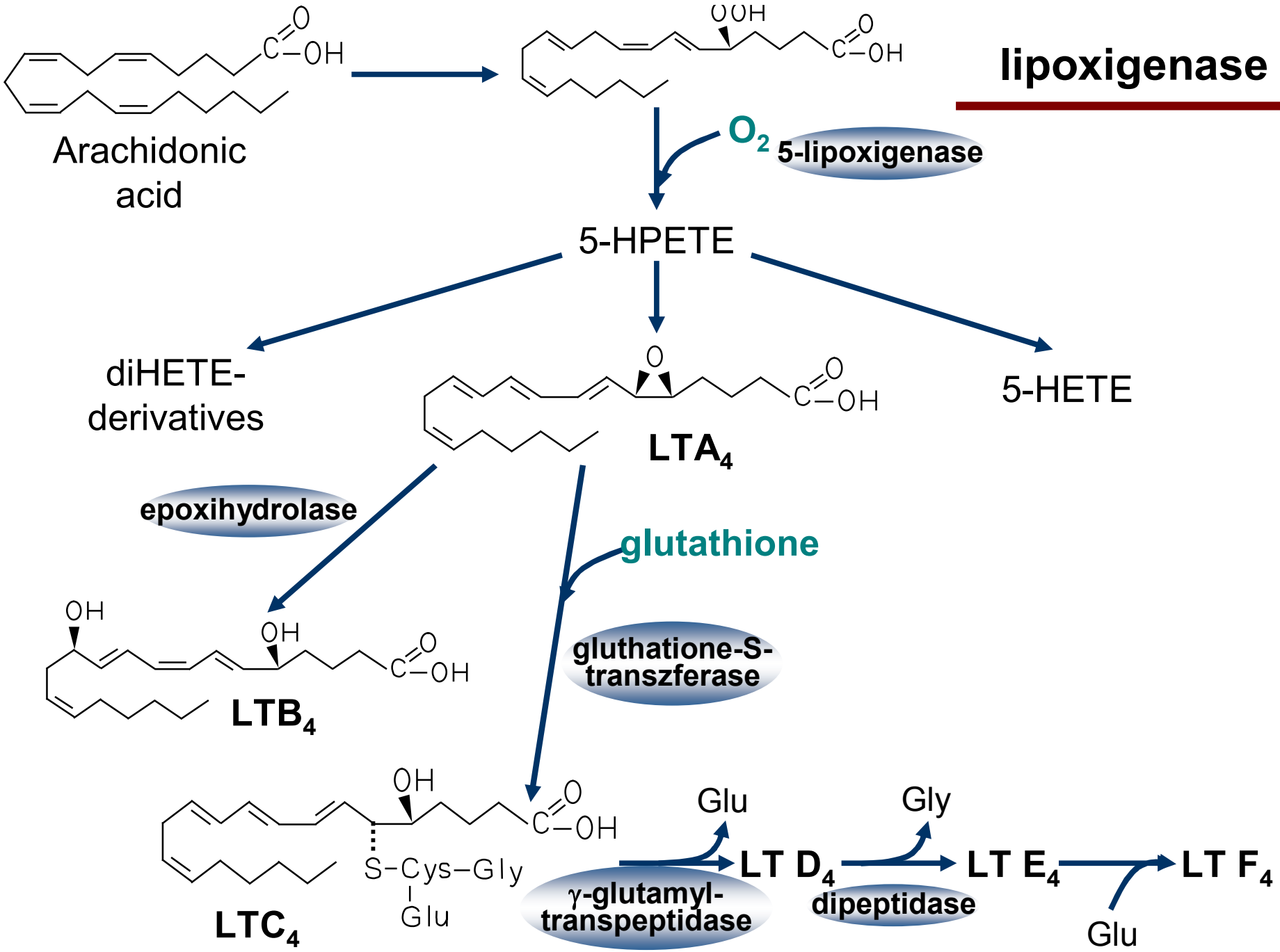

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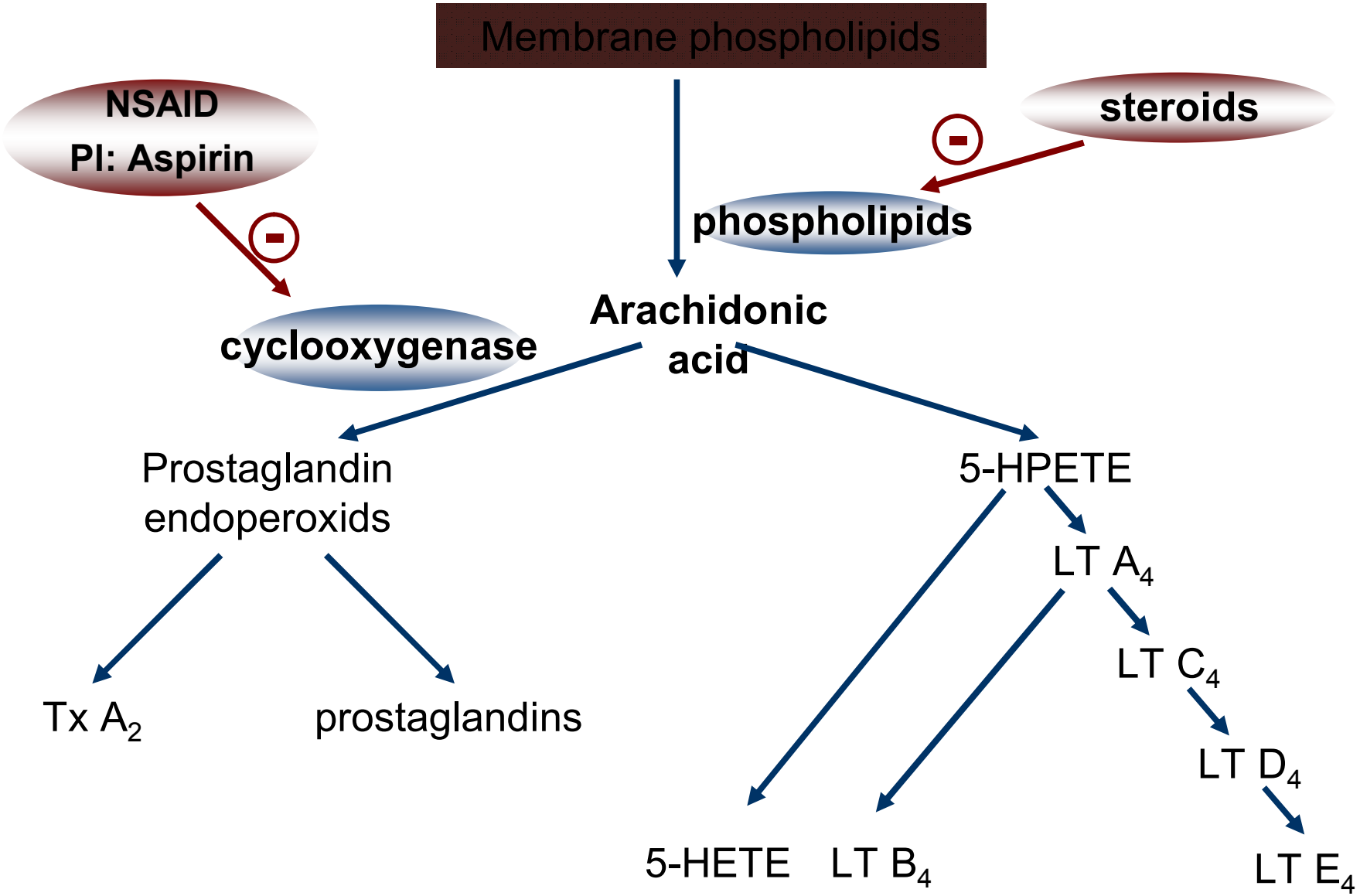
Action of anti-inflammatory drugs



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