AL-FARABI KAZAKH NATIONAL UNIVERSITY
FACULTY OF BIOLOGY AND BIOTECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY

Lecture 6

Biosynthesis of Fatty Acids & Eicosanoids. Lipid Transport & Storage

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Lecture Plan

1. Fatty Acid Biosynthesis
2. Acetyl-CoA and Malonyl-CoA
3. Fatty Acid Synthase
4. Steps of Fatty Acid Synthesis
5. Regulation of Lipogenesis
6. Essential and Unsaturated Fatty Acids
7. Eicosanoids and Their Biosynthesis
8. Lipid Transport
9. Lipid Storage and Mobilization
10. Integration and Student Tasks

CONTENTS

Learning objectives

By theend of the lecture, students should beable to:

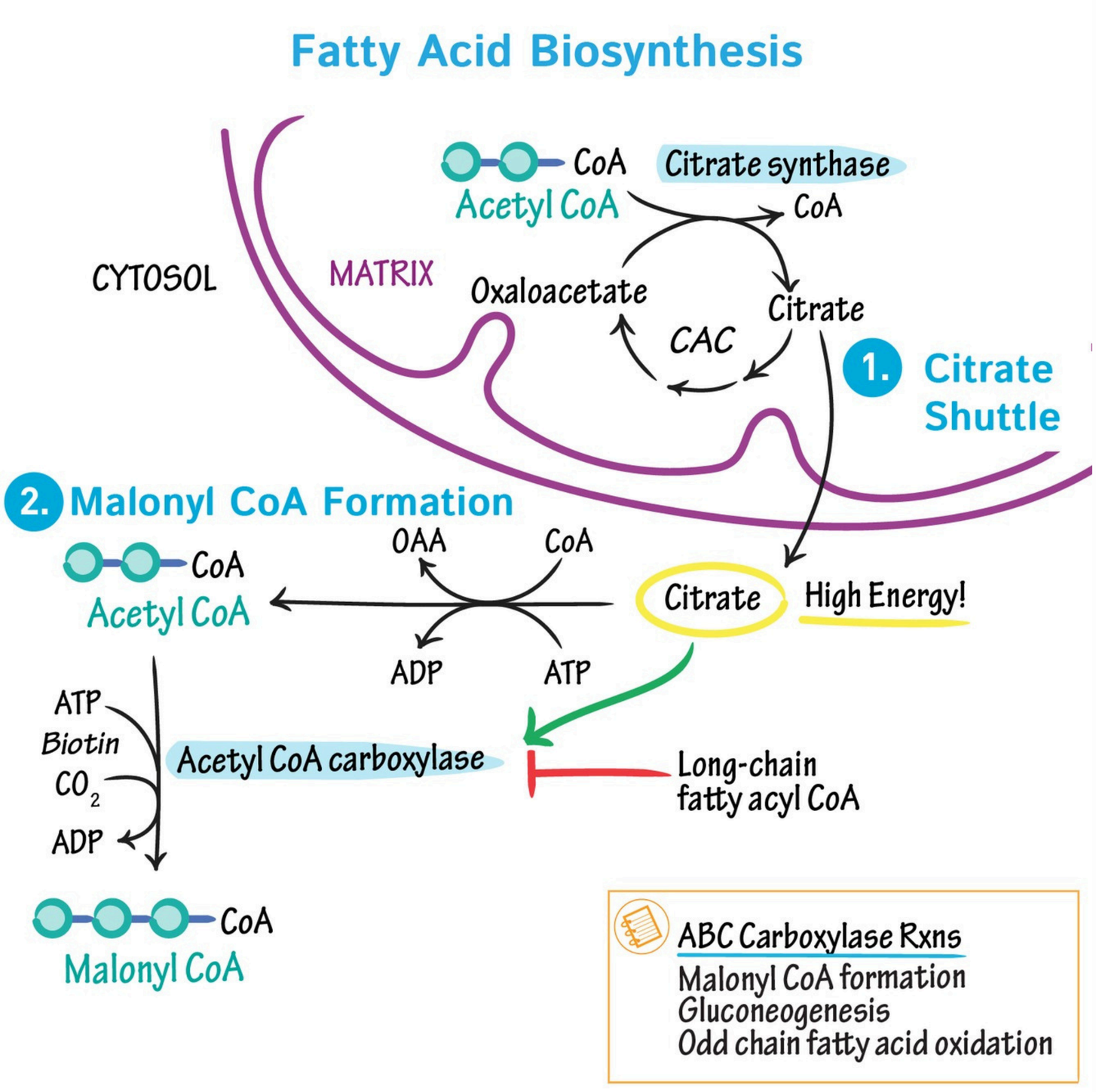
- Explain how fatty acids are synthesized from acetyl-CoA.
- Describe the role of acetyl-CoA carboxylase and malonyl-CoA.
- Explain the function of the fatty acid synthase complex.
- Identify the main steps and energy requirements of fatty acid synthesis.
- Describe how fatty acid synthesis is regulated.
- Distinguish between essential and non-essential fatty acids.
- Explain the formation and functions of eicosanoids.
- Describe the major lipoproteins involved in lipid transport.
- Explain how triacylglycerols are stored and mobilized.

What is fatty acid biosynthesis ?

Fatty acid biosynthesis, or lipogenesis,isananabolicpathway that produces fatty acids from acetyl-CoA.

It is especially active when energy and carbohydrate availability are high. Excess carbohydrate can be converted into acetyl-CoA and subsequently used for fatty acid synthesis.

In humans, de novo fatty acid synthesis occurs mainly in the cytosol, particularly in the liver and adipose tissue.



Fatty acid synthesis is favored when the body has more energy and nutrients than it currently needs.

After a carbohydrate-rich meal, insulin levels increase and glucose is readily available. Excess carbohydrate can be converted into acetyl-CoA and used for lipogenesis.

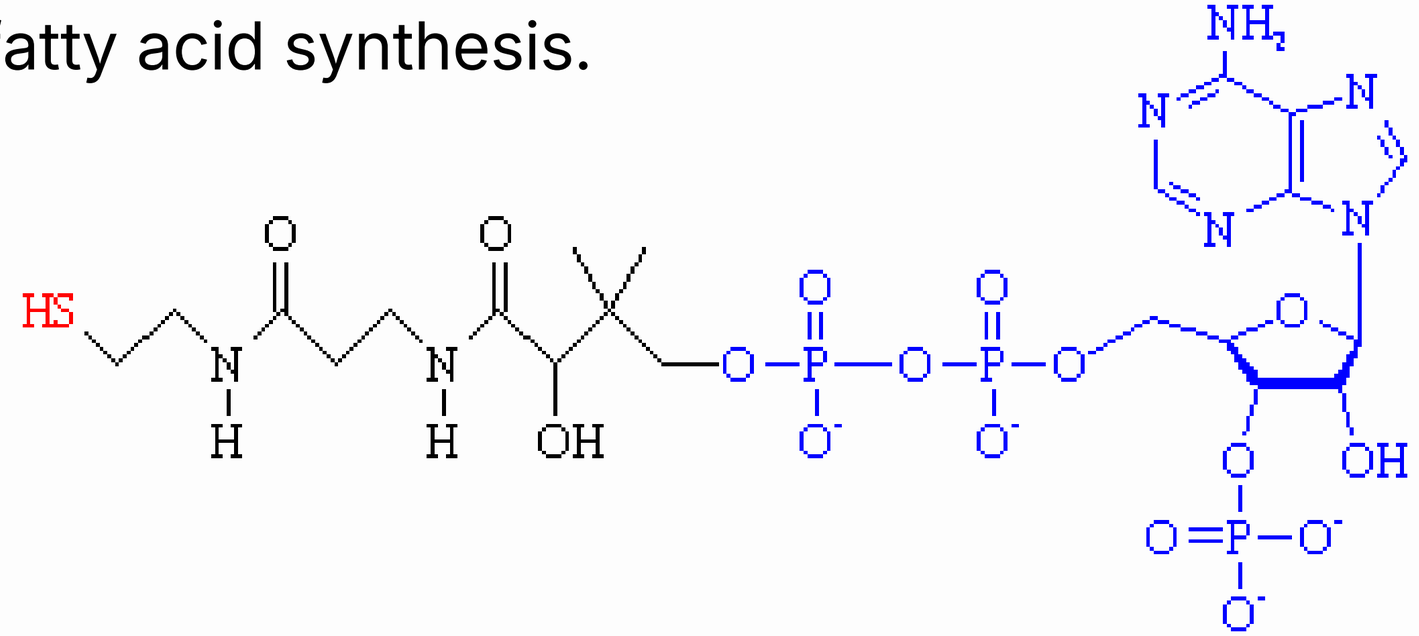
During fasting, however, fatty acid synthesis decreases and fatty acid oxidation becomes more important.

Fed state → synthesis and storage

Fasting state → mobilization and oxidation

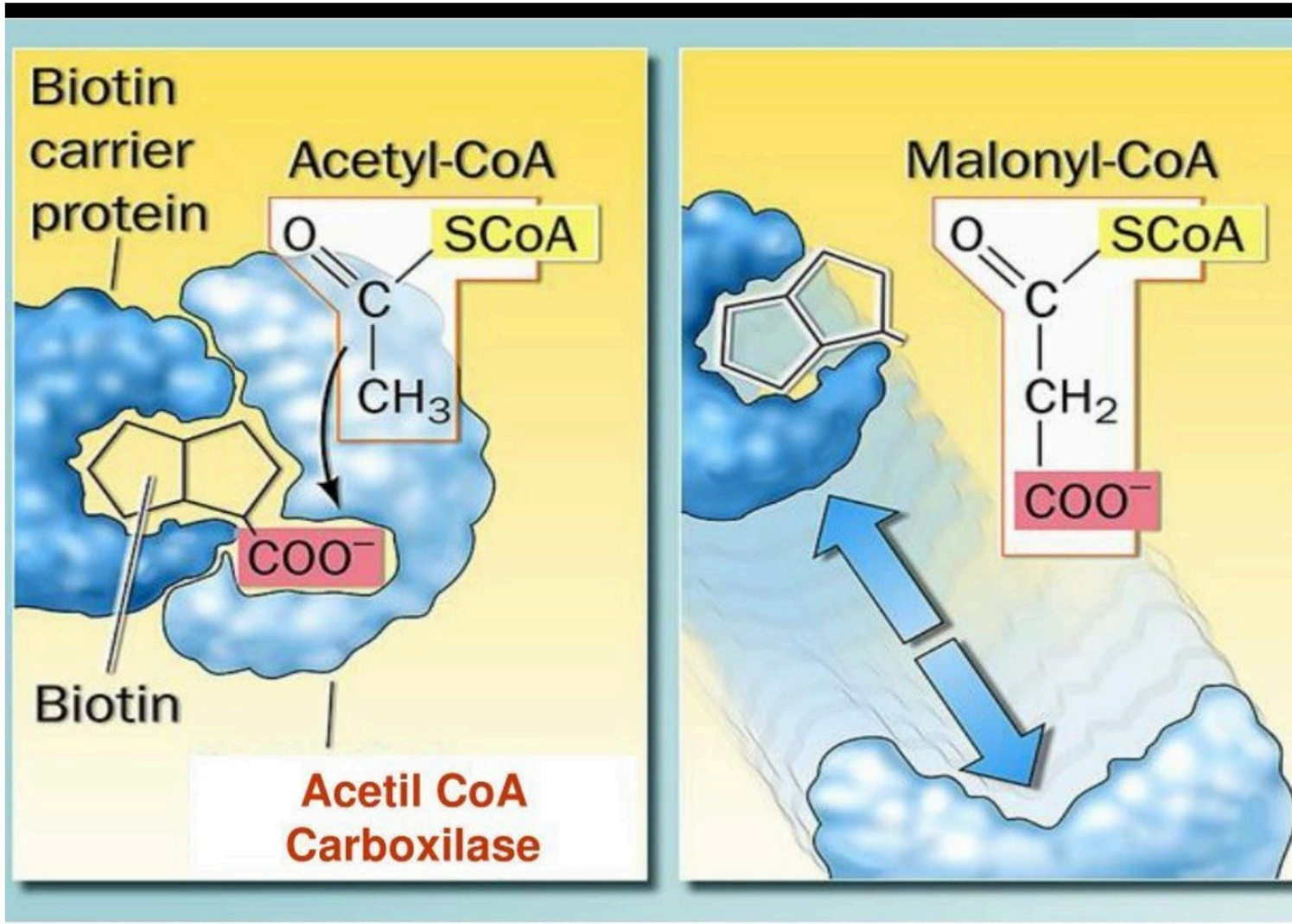
The main carbon source for fatty acid synthesis is acetyl-CoA. Acetyl-CoA is produced mainly from glucose-derived pyruvate in mitochondria. Because acetyl-CoA itself cannot directly cross the inner mitochondrial membrane, its carbon is transported to the cytosol mainly through citrate.

In the cytosol, citrate is converted back into acetyl-CoA, providing the substrate for fatty acid synthesis.



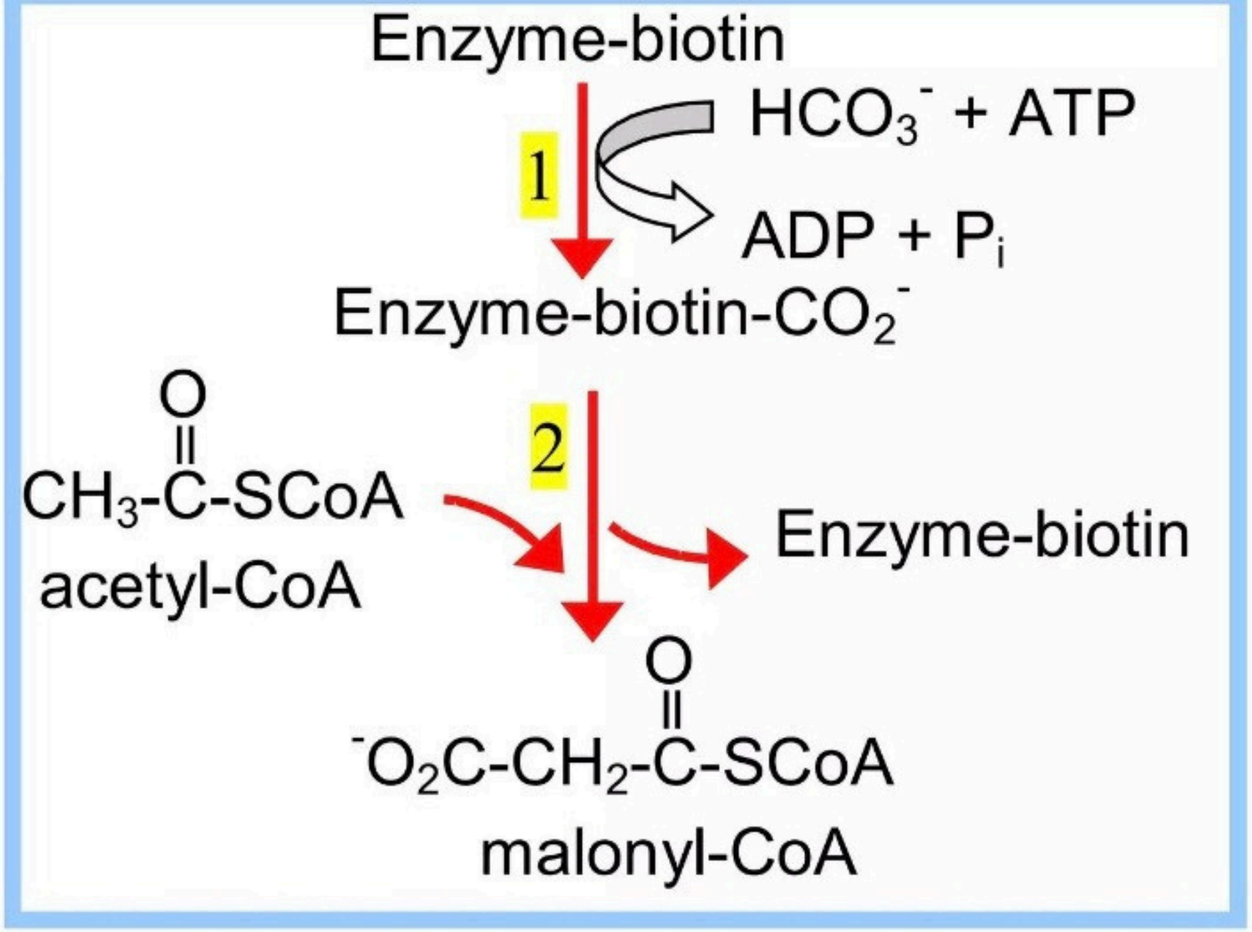
Formation of malonyl-CoA

The first committed and major regulatory step of fatty acid synthesis is the conversion of acetyl-CoA into malonyl-CoA.
The reaction is catalyzed by: Acetyl-CoA carboxylase (ACC)
ACC requires ATP, bicarbonate and biotin.
Acetyl-CoA → Malonyl-CoA
Malonyl-CoA provides the two-carbon units that are added during fatty acid chain elongation.



$HCO_3^- + ATP + acetil\text{-}CoA \rightarrow ADP + P_i + malonil\text{-}CoA$

Acetyl-CoA Carboxylase catalyzes the **2-step** reaction by which acetyl-CoA is carboxylated to form **malonyl-CoA**

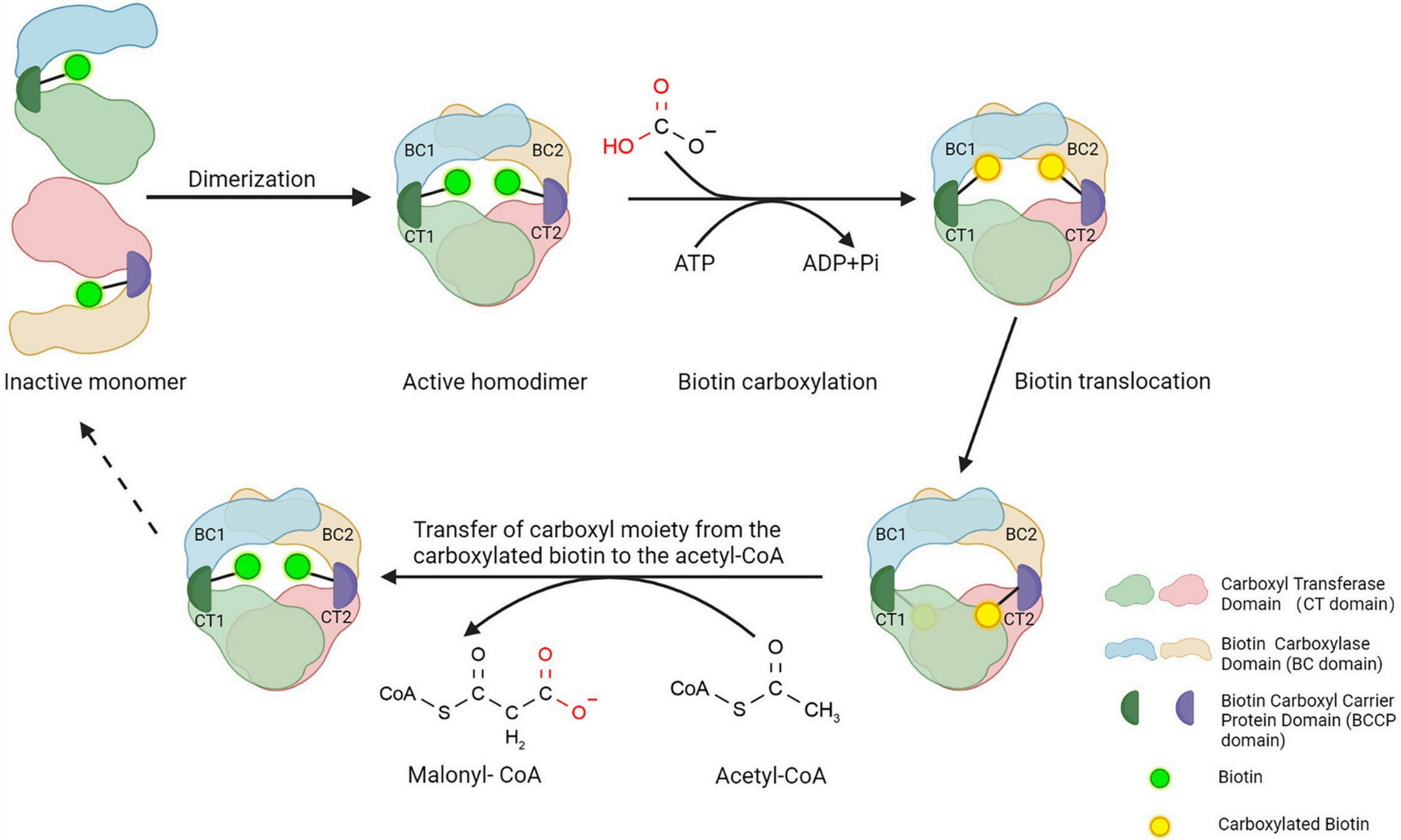


As with other carboxylation reactions, the enzyme prosthetic group is **biotin**

ATP-dependent carboxylation of the biotin, carried out at one active site 1 , is followed by transfer of the carboxyl group to acetyl-CoA at a second active site 2 .

The key regulatory enzyme

Acetyl-CoA carboxylase(ACC) is the majorregulatory enzyme of fatty acid synthesis.
Its activity increases when the cell has sufficient energy and nutrients, particularly in the fed state.
Insulin promotes ACC activity, favoring fatty acid synthesis.
When energy availability is low, ACC activity decreases and fatty acid synthesis is inhibited.
Key point:
ACC controls the entry of acetyl-CoA into fatty acid synthesis.


Dimerization
BC1
BC2
CT1
CT2
HO
O
C
O⁻
ATP
ADP+Pi
Inactive monomer
Active homodimer
Biotin carboxylation
Biotin translocation
Transfer of carboxyl moiety from the carboxylated biotin to the acetyl-CoA
CoA
S
H2
CH3
Malonyl- CoA
Acetyl-CoA
Carboxyl Transferase Domain (CT domain)
Biotin Carboxylase Domain (BC domain)
Biotin Carboxyl Carrier Protein Domain (BCCP domain)
Biotin
Carboxylated Biotin

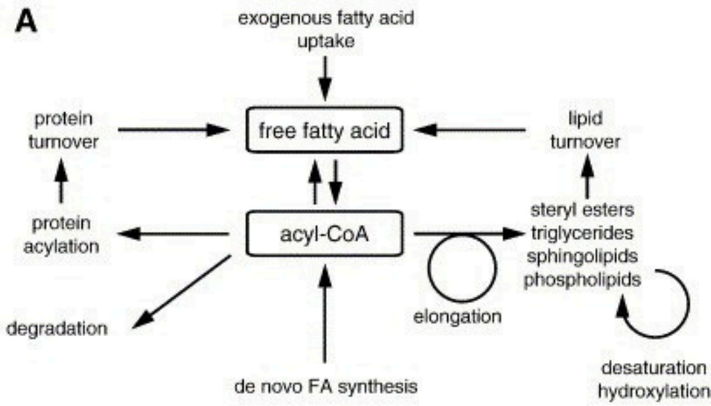
Fatty acid synthesis

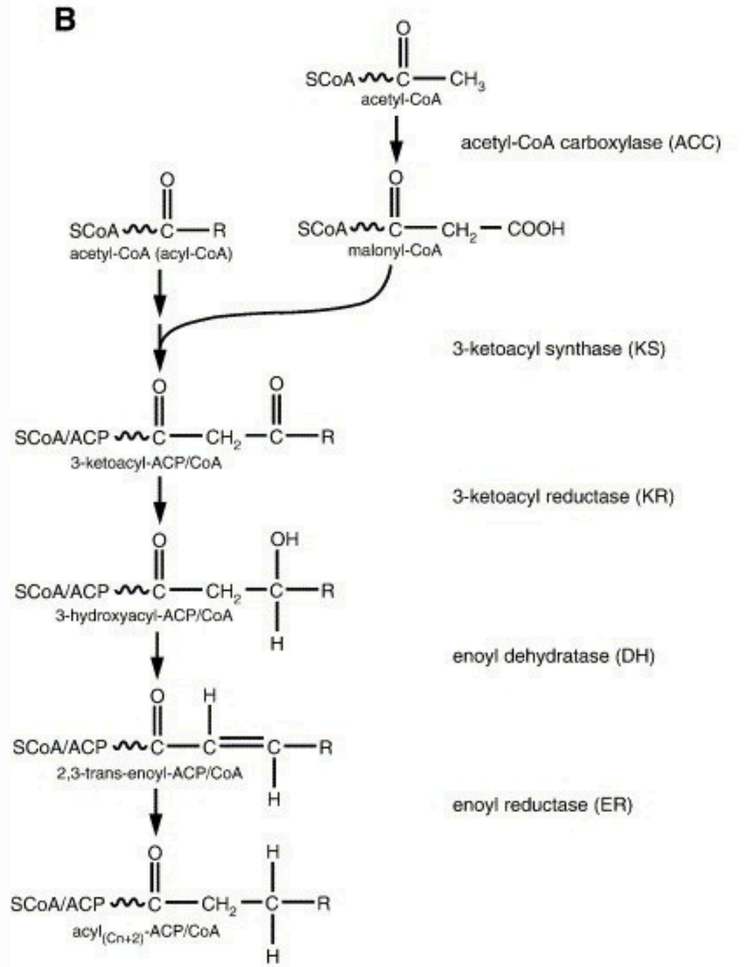
The next stages of fatty acid synthesis are carried out by the fatty acid synthase (FAS) complex.

FAS is a multifunctional enzyme complex that uses acetyl-CoA and malonyl-CoA to build a growing fatty acid chain.

The pathway repeatedly adds two-carbon units to the growing chain.

In most tissues, the main end product of the FAS pathway is the 16-carbon saturated fatty acid palmitate (16:0).





Component/substrate	Role in fatty acid synthesis
Acetyl-CoA	Provides the initial 2-carbon unit
Malonyl-CoA	Provides 2-carbon units for chain elongation
ACP	Carries the growing fatty acid chain
NADPH	Provides reducing power
Fatty acid synthase	Catalyzes the repeated reactions of fatty acid synthesis
Palmitate (16:0)	Main final product of the FAS complex

Each cycle of fatty acid synthesis includes four major reactions:

1. Condensation
2. Reduction
3. Dehydration
4. Reduction

These reactions extend the fatty acid chain by two carbon atoms during each cycle.

NADPH provides the reducing power required for the reduction steps.

The cycle is repeated until the 16-carbon palmitate chain is formed.

The synthesis of palmitate requires:

- **8 acetyl-CoA equivalents**
- **7 ATP**
- **14 NADPH**

The final product is:

Palmitate (16:0)

The high requirement for NADPH demonstrates that fatty acid synthesis is a

reductive anabolic process.

A major source of NADPH for lipogenesis is the

Pentose Phosphate Pathway

Fatty acid synthesis and **β**-oxidation are not simply the same pathway running in opposite directions.

Feature	**Fatty acid synthesis**	**beta-Oxidation**
Function	Builds fatty acids	Breaks down fatty acids
Main location	Cytosol	Mitochondrial matrix
Redox cofactor	NADPH	NAD+ and FAD
Carrier	ACP	CoA
Two-carbon unit	Malonyl-CoA	Acetyl-CoA
Metabolic state	Fed	Fasting/ energy demand

Nutritional regulation of lipogenesis

The nutritional state strongly influences fatty acid synthesis.

Fed state

High glucose and insulin levels promote fatty acid synthesis and storage.

Fasting state

Low insulin and increased glucagon signaling reduce lipogenesis and favor fatty acid mobilization and oxidation.

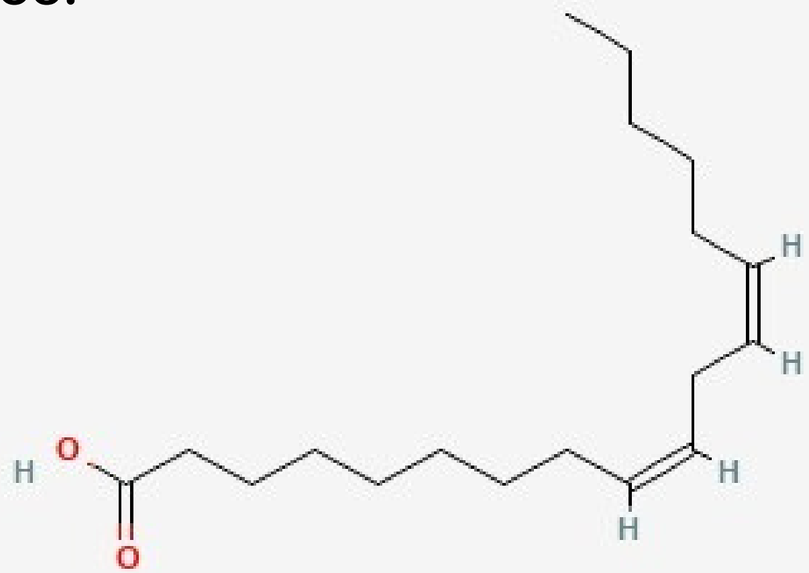
This allows metabolism to switch between energy storage and energy utilization according to the body's needs

Fed State		Fasting State
Food	Fuel Source	Stored Glycogen/Fat
⬆	Insulin	⬇
⬆	Blood Glucose	⬇
⬇	Ketones	⬆
⬇	Metabolic Rate	⬆
Anabolic	Metabolic State	Catabolic
⬆ Protein Synthesis		⬆ Autophagy
⬆ Glycogenesis		⬆ Glycogenolysis
⬆ De Novo Lipogenesis		⬆ Lipolysis

Humans cannot synthesize all fatty acids because our enzymes cannot introduce double bonds at certain positions in the carbon chain.
Therefore, some polyunsaturated fatty acids must be obtained from the diet.
The two major essential fatty acids are:

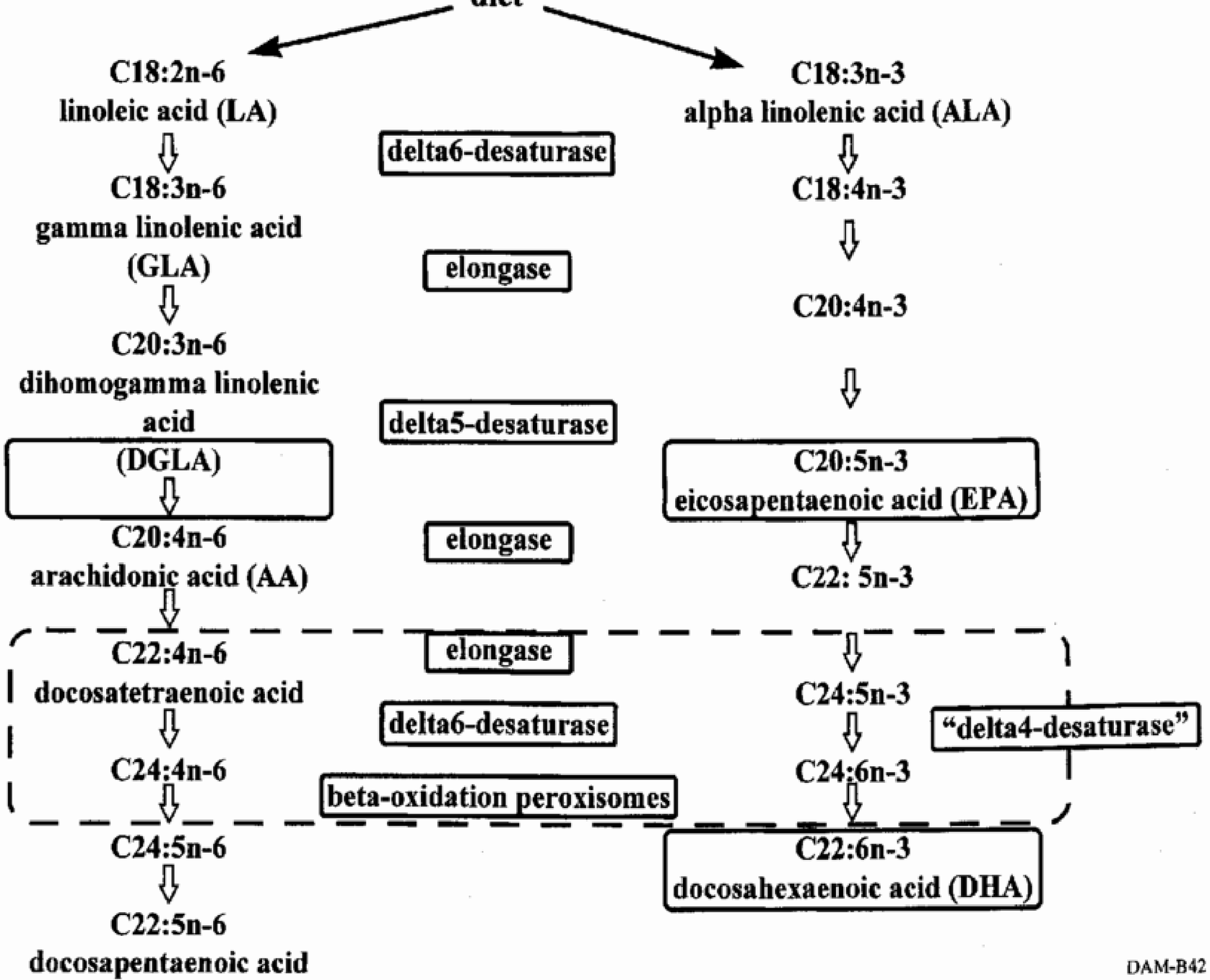
- Linoleic acid (18:2, ω-6)
- α-Linolenic acid (18:3, ω-3)

They serve as precursors for other important polyunsaturated fatty acids and signaling molecules.





Elongation and desaturation of n-6 and n-3 polyunsaturated fatty acids



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What Are Eicosanoids?

Eicosanoids are biologically active lipid mediators derived mainly from 20-carbon polyunsaturated fatty acids.

Important eicosanoids include:

1. **Prostaglandins**
2. **Thromboxanes**
3. **Leukotrienes**
4. **Lipoxins**

Unlike many hormones, eicosanoids are generally produced locally when needed rather than stored in large amounts.

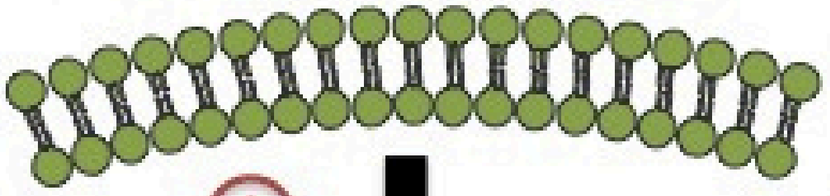
They participate in the regulation of:

- inflammation;
- vascular tone;
- platelet function;
- smooth muscle contraction;
- pain and fever;
- immune responses.

Their effects depend on the specific eicosanoid and the target tissue.

Eicosanoids

signaling molecules
made by oxidation of fatty acids



Arachidonic acid esterified in membrane phospholipid

Inflammatory stimuli (+) → Phospholipase A_2 ⊣ *Corticosteroids (annexin A1)*

Arachidonic acid

Cyt P450 Epoxygenase → **Epoxyeicosatrienoic acids (EETs)**

aspirin NSAIDs ⊣ **COX 1** **COX 2** (*inducible*) → ***Prostanoids***

- **Prostaglandins**
- **Prostacylin (PGI_2)**
- **Thromboxane (TXA_2)**

LOX ⊣ *zileuton* → **HETEs** **Leukotrienes** **Lipoxins**

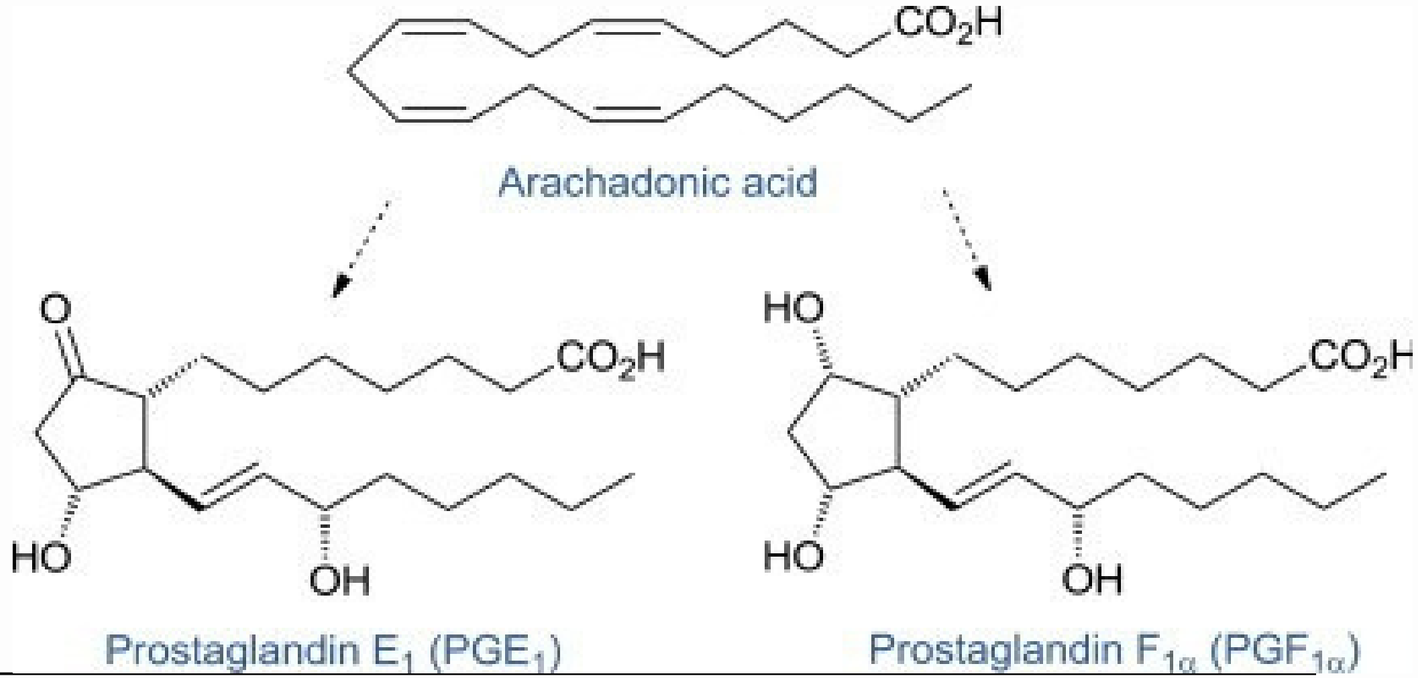
⊣ *montelukast* *zafirlukast*

Arachidonic acid is a 20-carbon ω-6 polyunsaturated fatty acid and an important precursor of eicosanoids.

It is usually present in membrane phospholipids.

When a cell is activated, phospholipase A_2 can release arachidonic acid from membrane phospholipids.

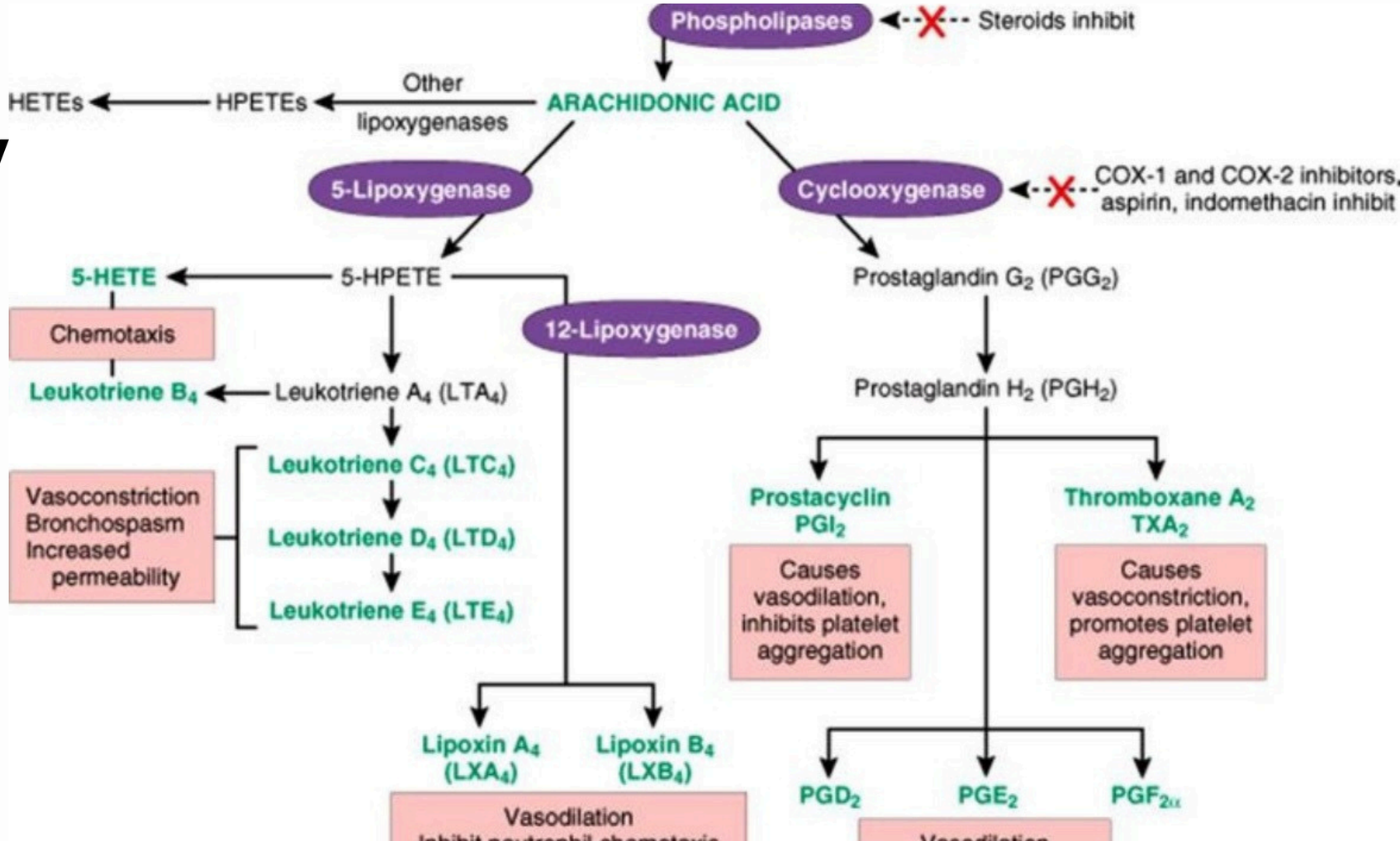
The released arachidonic acid can then enter different enzymatic pathways to produce eicosanoids.



Arachidonic acid can be metabolized through two major pathways. These pathways generate different lipid mediators with different biological effects.

Cyclooxygenase pathway
Produces prostaglandins, prostacyclin and thromboxanes.

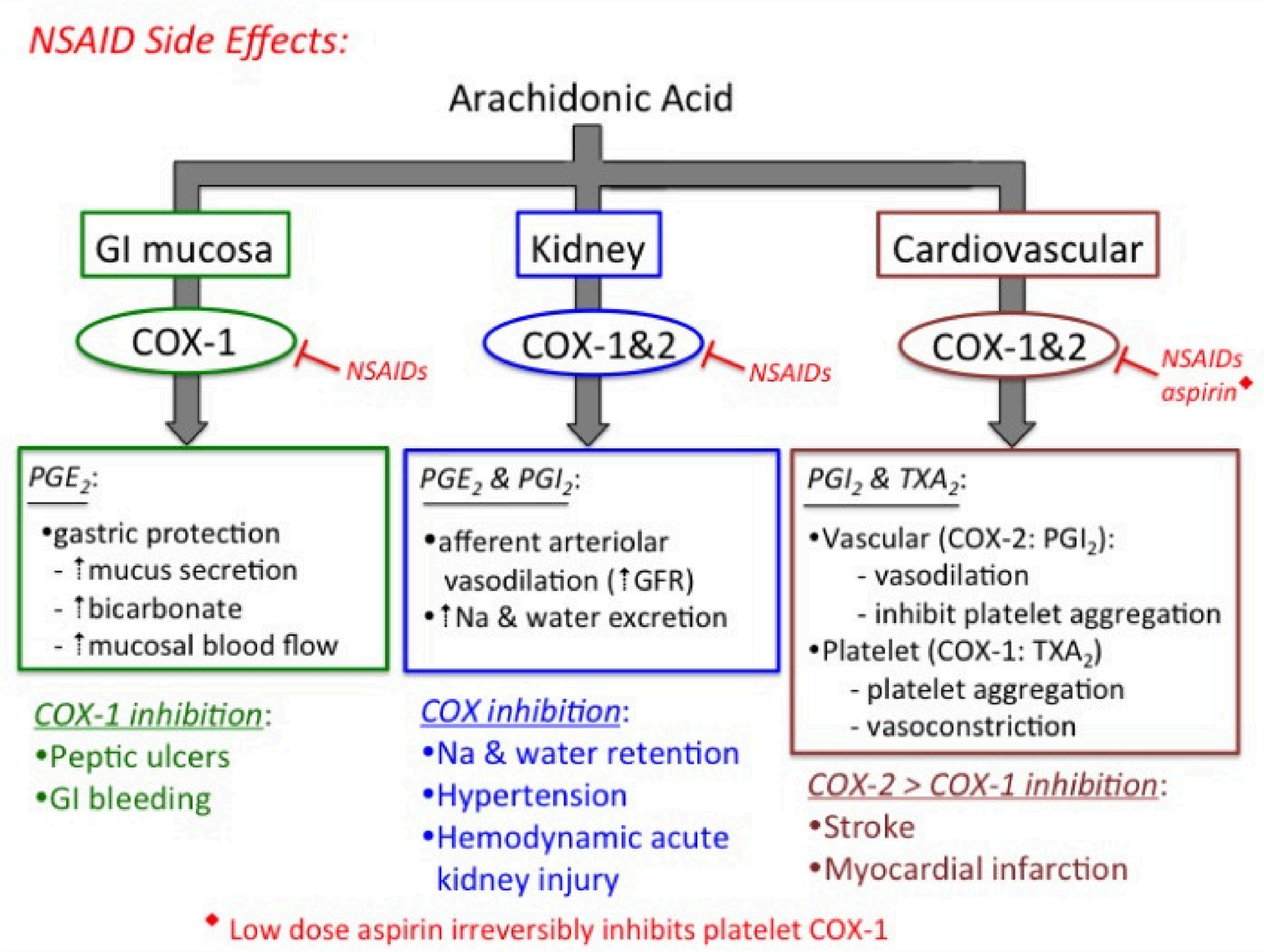
Lipoxygenase pathway
Produces leukotrienes and lipoxins.



The cyclooxygenase (COX) pathway is responsible for the formation of prostaglandins and thromboxanes from arachidonic acid.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen inhibit COX activity.

As a result, prostaglandin synthesis decreases, which contributes to their anti-inflammatory, analgesic and antipyretic effects.



Lipid transport

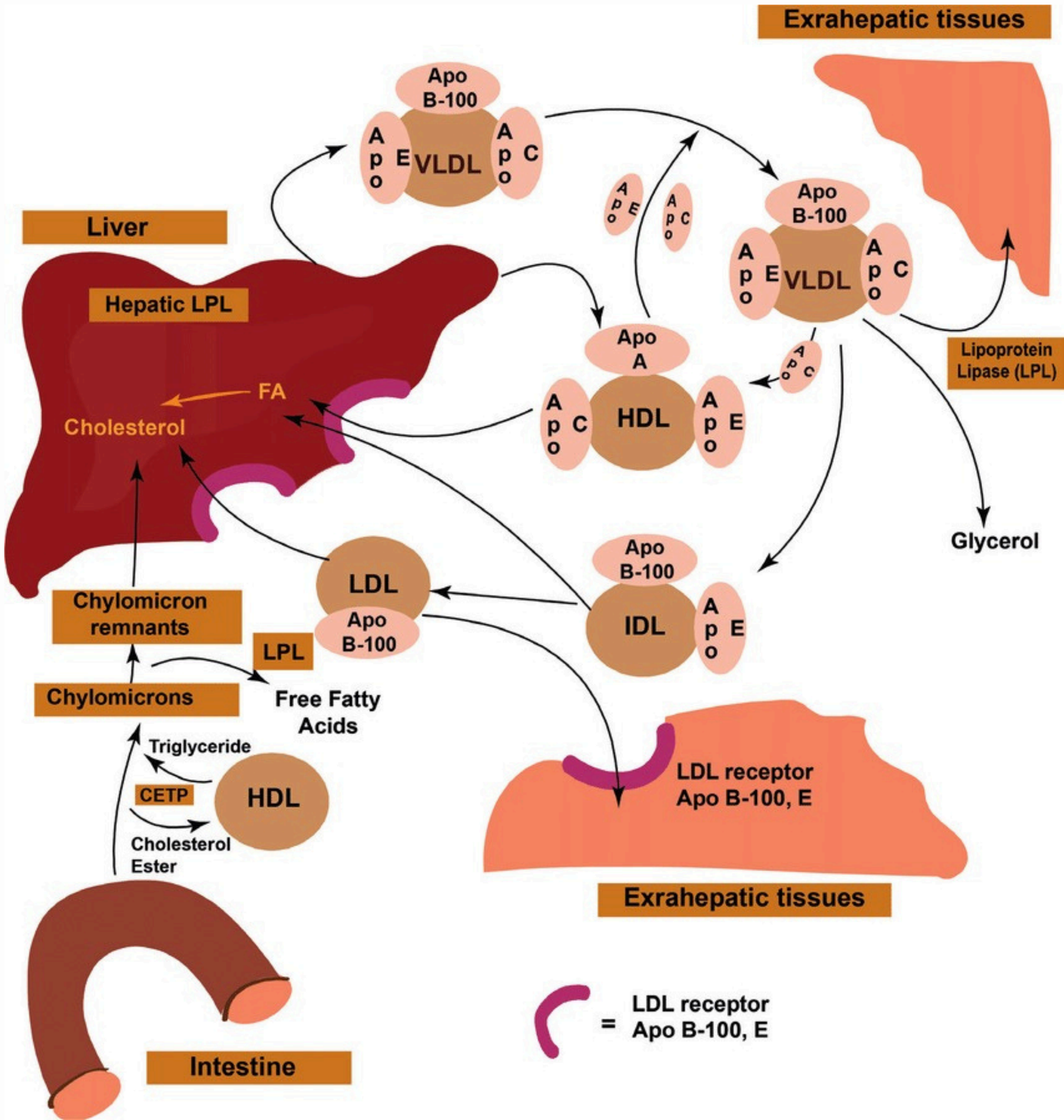
Mostlipids are poorly solubleinwater, while blood plasma is primarily aqueous.
Therefore, lipids must be transported in specialized structures called lipoproteins.
Lipoproteins contain:

- a hydrophobic core containing triacylglycerols and cholesterol esters;
- a surface containing phospholipids, free cholesterol and apolipoproteins.

This structure allows lipids to circulate through the bloodstream.

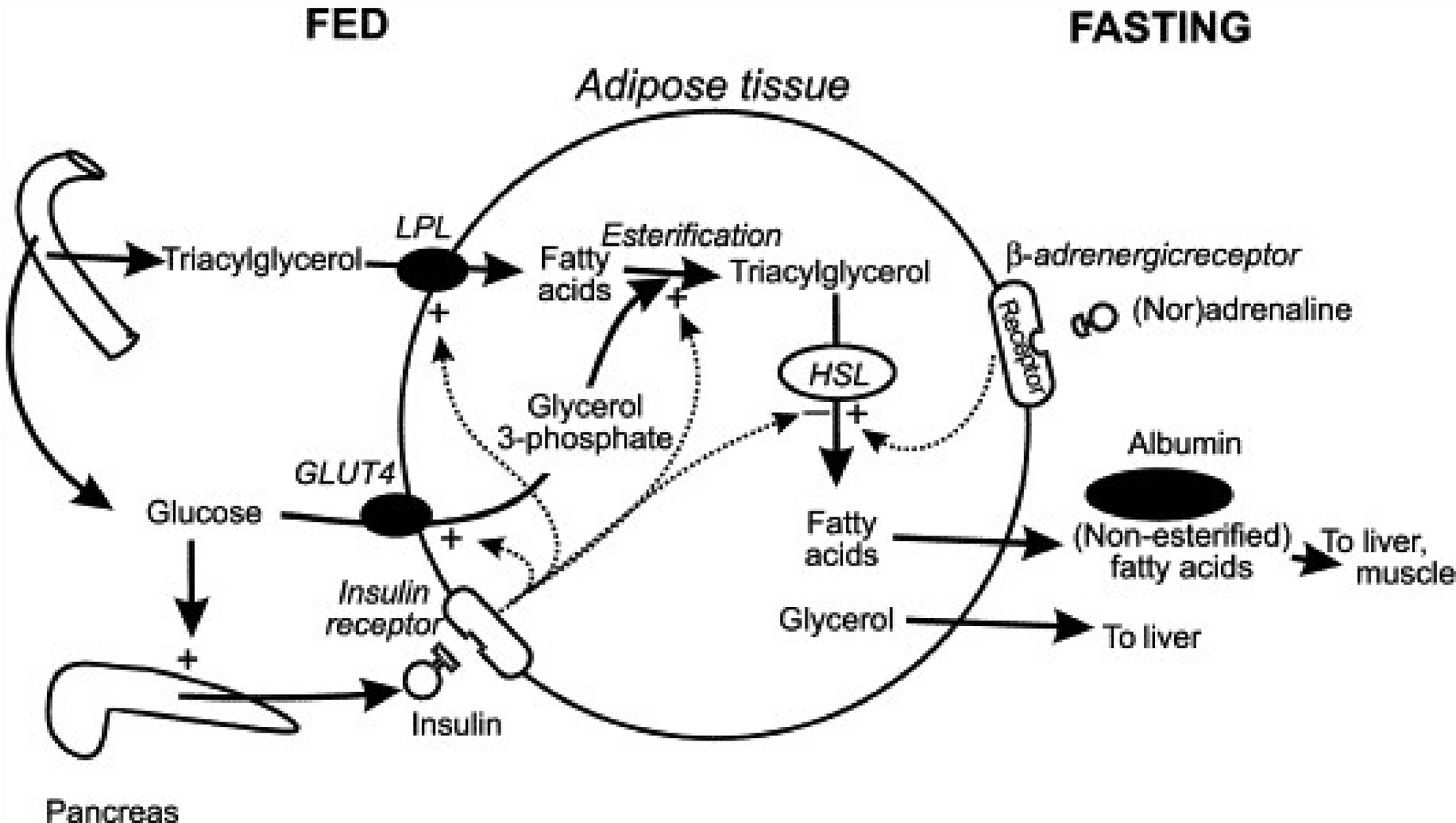
After a meal, dietary triacylglycerols are packaged into chylomicrons in intestinal cells.
Chylomicrons enter the circulation and deliver fatty acids to tissues.
The remaining chylomicron remnants are taken up by the liver.
The liver can then package endogenous triacylglycerols into VLDL, which transports them to peripheral tissues.

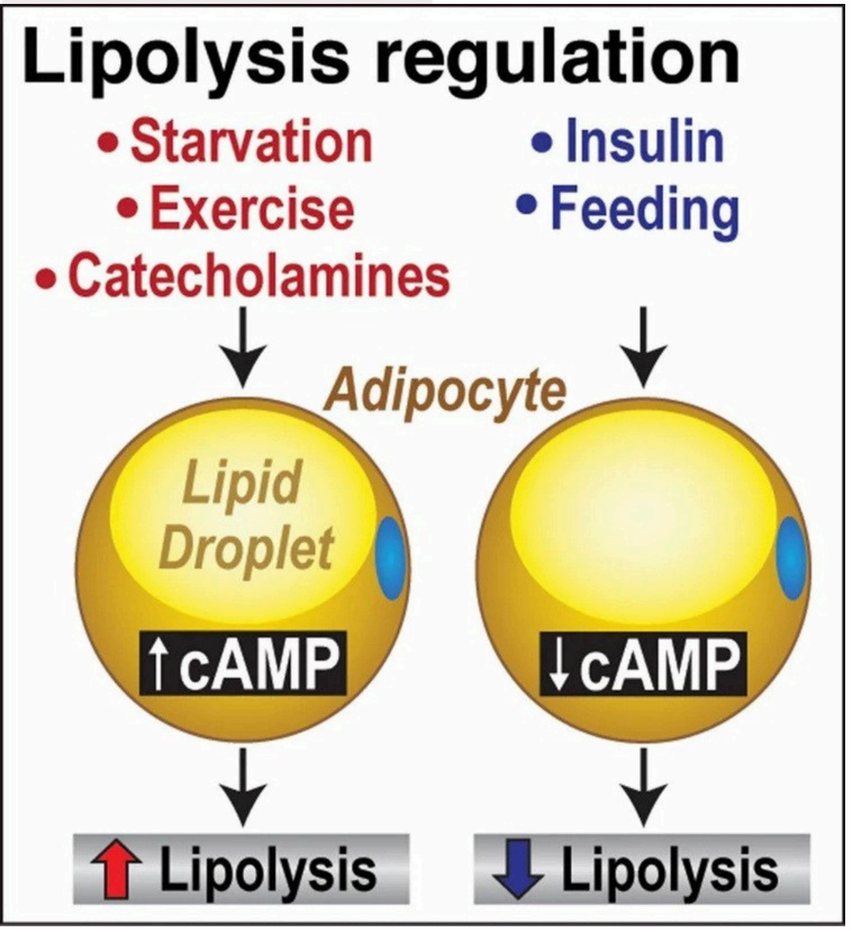
Lipoprotein	Main function
Chylomicrons	Transport dietary TAGs from intestine
VLDL	Transport TAGs from liver
LDL	Deliver cholesterol to peripheral tissues
HDL	Transport cholesterol from tissues toward liver



The major storage form of excess energy is triacylglycerol. Triacylglycerols are stored mainly in adipocytes as lipid droplets. During periods of energy excess, insulin promotes glucose uptake and fatty acid storage.

During fasting, stored triacylglycerols can be mobilized and hydrolyzed to release fatty acids for energy production.





When energy is required, stored triacylglycerols undergo lipolysis.

Lipolysis releases:

- free fatty acids
- glycerol

Free fatty acids enter the blood and are transported to tissues for oxidation.

Glycerol can be transported to the liver and used in carbohydrate metabolism.

Main regulators:

Insulin ↓ lipolysis

Glucagon / epinephrine ↑ lipolysis

Fatty acid synthesis, lipid transport and lipid storage are closely connected.
After a carbohydrate-rich meal, excess glucose can contribute to fatty acid synthesis. Newly synthesized fatty acids can be incorporated into triacylglycerols and stored in adipose tissue.
During fasting, stored triacylglycerols are mobilized and fatty acids are transported to tissues for oxidation.

Metabolism continuously switches between:
Synthesis → Transport → Storage
and
Mobilization → Oxidation → Energy production

Student task

1. Explain why acetyl-CoAmust be transported from mitochondria to the cytosol for fatty acid synthesis.
2. What is the role of acetyl-CoA carboxylase?
3. Why is malonyl-CoA important?
4. What are the four reactions repeated during fatty acid synthesis?
5. Why is NADPH required?
6. Compare fatty acid synthesis with β-oxidation.
7. What are essential fatty acids?
8. How is arachidonic acid released from membrane phospholipids?
9. Compare the COX and LOX pathways.
10. What are the main functions of chylomicrons, VLDL, LDL and HDL?
11. How are triacylglycerols stored and mobilized?
12. How does insulin affect lipid storage?

Conclusion

Fatty acid synthesis occurs mainly in the cytosol. ACC produces malonyl-CoA, and fatty acid synthase uses NADPH to build palmitate.

Insulin promotes synthesis and lipid storage after meals. Fasting shifts metabolism toward fat mobilization and oxidation.

Linoleic acid and alpha-linolenic acid are essential dietary fatty acids. Eicosanoids act locally to regulate inflammation and other responses.

The COX pathway produces prostaglandins and thromboxanes. LOX pathways produce leukotrienes and lipoxins.

Lipoproteins transport lipids in blood. Adipose tissue stores triacylglycerols and releases fatty acids and glycerol during lipolysis.

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