

LIPID METABOLISM

DIGESTIVE MECHANISM FOR LIPIDS

The average lipid intake is about 80g/day, of which more than 90% is triacylglycerol (TAG); the remainder consists of cholesterol, cholesteryl esters, phospholipids, free fatty acids

1. In the stomach:

- acid-stable **lingual lipase** (originates at the back of the tongue) that acts on TAG molecules particularly on those containing FA of short and medium-chain length (<12C such as those in milk fat);
- they are also degraded by **gastric lipase** (secreted by the gastric mucosa);
- both enzymes are acid stable (optimum pH 4-6); they have an important part in the digestion of neonates and of individuals with pancreatic insufficiency (cystic fibrosis, a lethal autosomal recessive genetic disorder = mutations to the gene for a protein CFTR that acts as Cl channel on epithelium; it determines the decreased Cl secretion and increased Na and H₂O reabsorption, thus a thickened secretion that is not able to reach the intestine, resulting in pancreatic insufficiency)

DIGESTIVE MECHANISM FOR LIPIDS

2. In the intestine:

Emulsification of dietary lipids in duodenum increases the surface area of hydrophobic lipid droplets so that the digestive enzymes can act effectively – bile salts and mechanical mixing due to peristalsis

The lipids are degraded by the pancreatic enzymes

1. TAG degradation:

- **pancreatic lipase** preferentially removes the FA at C₁ and C₃ thus the **2-monoacyl glycerol** and **fatty acids** are formed
- **Colipase** is secreted by the pancreas as the zymogen, procolipase, which is activated in the intestine by the trypsin; it determines a conformational change in the lipase that exposes its active site

2. Cholesterol exists mostly in free form and 10-15% as cholesteryl esters, which are hydrolysed by **cholesteryl ester hydrolase (cholesterol esterase)** stimulated by the presence of bile salts; the result is **cholesterol** and **FA**

3. Phospholipids degradation:

- **Phospholipase A₂**, activated by trypsin and in the presence of bile salts, removes FA from C₂ leaving a **lysophospholipid**;
- the remaining FA at C₁ can be removed by **lysophospholipase**
- The **glycerylphosphoryl** base may be further degraded or absorbed or excreted in the feces.

DIGESTIVE MECHANISM FOR LIPIDS

Hormonal control of digestion:

- **Cholecystokinin (CCK) = pancreozymin**
 - Secreted by cells in the jejunum and lower duodenum mucosa, when lipids and partially digested proteins enter these regions of intestine
 - Action:
 - the gall bladder contracts and releases the bile, containing bile salts, phospholipids and free cholesterol
 - the exocrine cells of the pancreas produce digestive enzymes
 - the gastric motility decreases
- **Secretin**
 - Produced by other intestinal cells when the low pH of the chyme enters the intestine
 - Determines the pancreas and liver to produce a watery solution of bicarbonate, helping to neutralize the pH, to the optimum pH for the pancreatic enzymes

ABSORPTION BY INTESTINAL MUCOSA CELLS

- Free FA, free cholesterol, 2-monoacylglycerol are primary products of the digestion in the jejunum
- They form mixed **micelles**: clusters of amphipathic lipids that are oriented with
 - the hydrophobic groups on the inside and
 - their hydrophilic groups on the outside, making them soluble in the aqueous environment of the intestinal lumen.
- The brush border membrane of the enterocytes is separated from the liquid content of the lumen by a water layer; the hydrophilic surface of the micelles facilitate the transport of the hydrophobic lipids through the unstirred water layer to the brush border membrane where they are absorbed.
- Cholesterol is poorly absorbed
- Short and medium-chain length FA do not require the presence of micelles for absorption

RESYNTHESIS OF TAG AND CHOLESTERYL ESTERS

The mixture of lipids migrates to the endoplasmic reticulum:

fatty acyl-CoA synthetase

- Long chain FA + CoA-SH + ATP \longrightarrow fatty acyl-CoA + AMP + PPi

Acyl-CoA:monoacylglycerol acyl transferase

Acyl-CoA:diacylglycerol acyl transferase

- 2-monoacylglycerol + fatty acyl-CoA \longrightarrow TAG + 2 CoA-SH

acyl-CoA:cholesterol acyltransferase

- Cholesterol + fatty acyl-CoA \longrightarrow Cholesteryl ester + CoA-SH

- Lysophospholipids are re-acylated to form phospholipids by **acyltransferases**

- Short and medium-chain length FA are released into the portal circulation and carried by serum albumin to the liver

SECRETION OF THE LIPIDS FROM ENTEROCYTES

- The newly synthesized TAG and cholesteryl esters are hydrophobic; they aggregate as particles of lipid droplet surrounded by a thin layer of phospholipids, unesterified cholesterol and apolipoprotein B-48.
- These particles, **chylomicrons**, are released from the enterocytes to the lymphatic vessels (forming the chyle) transported to the thoracic duct, to the left subclavian vein where they enter into the blood.

USE OF DIETARY LIPIDS BY THE TISSUES

TAG in the chylomicrons are degraded to **free FA** and **glycerol** by **lipoproteinlipase** (synthesized by the adipocytes and muscle cells):

- **Fatty acids**

- may directly enter muscle cells or adipocytes or
- may be transported in the blood in association with the albumins and taken up by the cells
- in most cells they are oxidized to produce energy.
- in the adipocytes they can be re-esterified to TAG and stored

- **Glycerol**

- in the liver the glycerol-3-P is formed
- it may enter
 - Glycolysis (anaerobic, aerobic),
 - Gluconeogenesis
 - Resynthesis of TAG
 - Synthesis of phospholipids

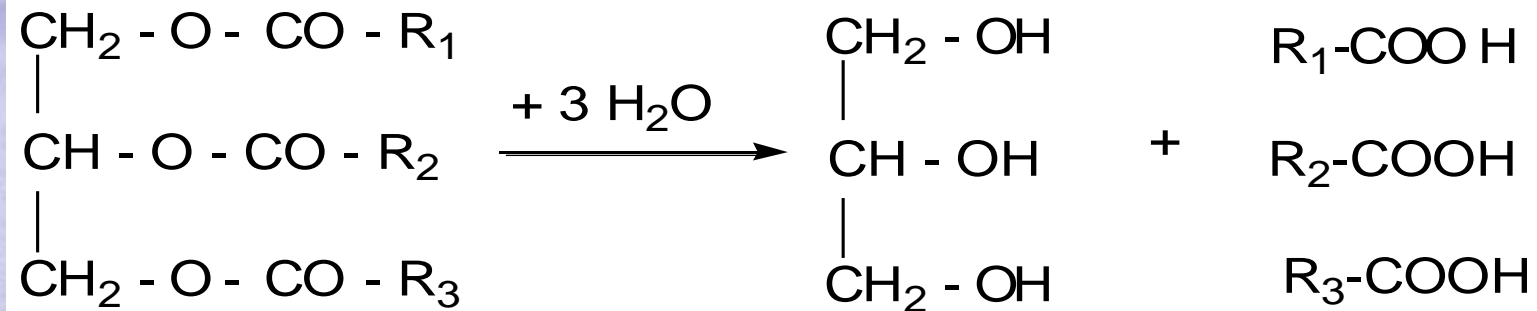
- Remnants of chylomicrons (CE, PL, ApoLP, fat soluble vitamins, some TAG) are endocytosed by liver cells and hydrolysed to component parts

RELEASE OF FATTY ACIDS FROM TAG

- In the adipose tissue the TAGs are stored in the adipocytes as “depot fat” used when the body needs them for fuel generating 9kcal/g fat.
- In the liver, little TAGs are stored
- Most are associated with CE, C, PL, apo B-100 forming **VLDL** that are secreted into the blood and transport the endogenous lipids to the peripheral tissues

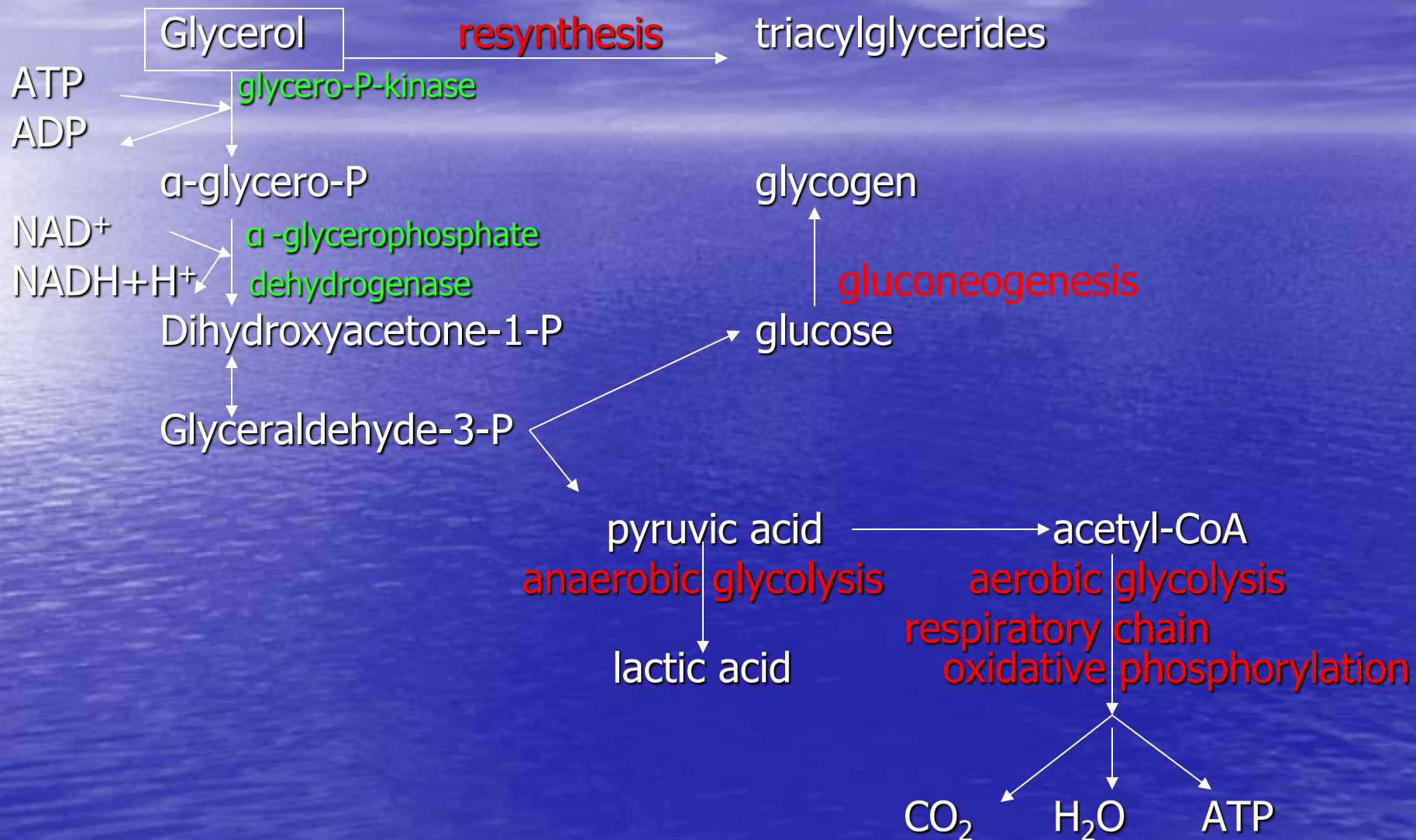
TRIACYLGLYCERIDES CATABOLISM - LIPOLYSIS

- In the tissues TAG lipase catalyses the hydrolysis of TAG to glycerol and fatty acids



- The control is hormonal:
 - epinephrine and glucagon bind to the membrane receptor and activate adenylyl cyclase; the 3'5'cAMP is produced in the adipocyte. An enzyme 3'5'cAMP-dependent protein kinase phosphorylates the hormone-sensitive lipase (HSL)
 - In the presence of high concentration of insulin and glucose HSL is dephosphorylated, becoming inactive
- Glycerol cannot be metabolized in the adipocytes and is transported to the liver where it can be phosphorylated
- FA move through the membrane of adipocyte to the blood, transported to the tissues, transformed in fatty acyl-CoA, oxidized for energy.

OXIDATION OF GLYCEROL



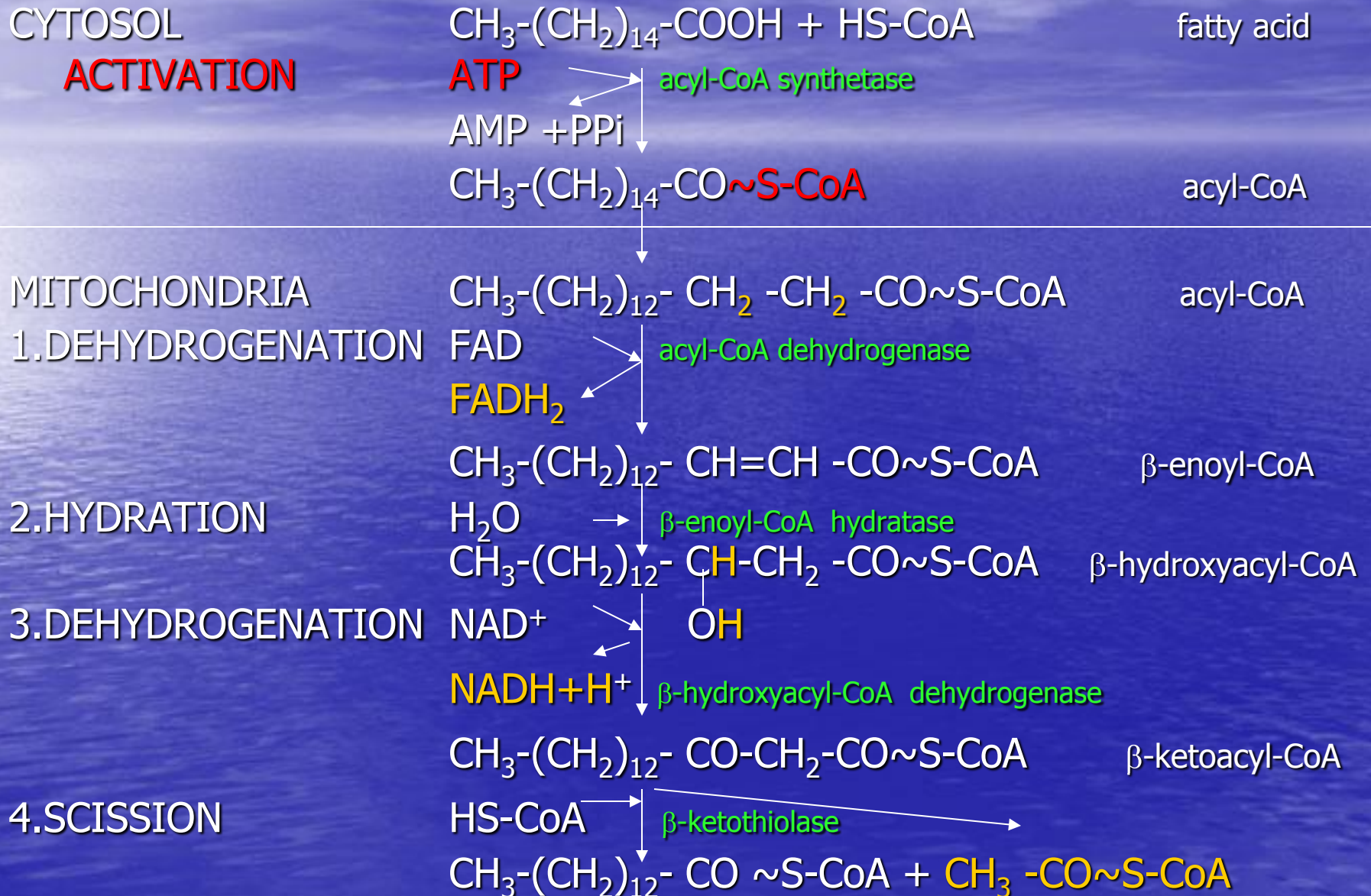
THE FATTY ACIDS CATABOLISM

- The fatty acids are activated forming a thioester bond with CoA by **acyl-CoA synthetase** action and an ATP; **acyl-CoA** results
- The activated FA are transported from the cytosol across the outer mitochondrial membrane into the intermembrane space
- **Carnitine** (dipeptide) transports the FA across the inner mitochondrial membrane into the matrix
- (carnitine – exogeneous source, meat or synthesized in liver and kidney from lysine and methionine)

Inside the matrix **β -oxidation** = energy producing process, with 4 reactions:

1. The single bond between α and β carbon of acyl-CoA is oxidized to a trans double bond \rightarrow β -enoyl-CoA
(**acyl-CoA dehydrogenase**, FAD dependent)
2. A molecule H_2O is added to the double bond \rightarrow β -hydroxyacyl-CoA (**β -enoyl-CoA hydratase**)
3. β -hydroxyacyl-CoA is oxidized to β -ketoacyl-CoA
(**β -hydroxyacyl-CoA dehydrogenase**, NAD^+ dependent)
4. Cleavage of β -ketoacyl-CoA (**β -ketothiolase = acetylCoA acetyltransferase**) in the presence of a molecule of CoA producing acetyl-CoA and an acyl-CoA that is 2 carbons shorter than the original FA molecule

FATTY ACID BETA-OXYDATION.



The shortened FA chain repeats the four steps of the β -oxidation until the FA is completely oxidized to acetyl-CoA (Knoop-Lynen spira)

There are $nC/2$ cycles. Each cycle produces:

1 $FADH_2$,

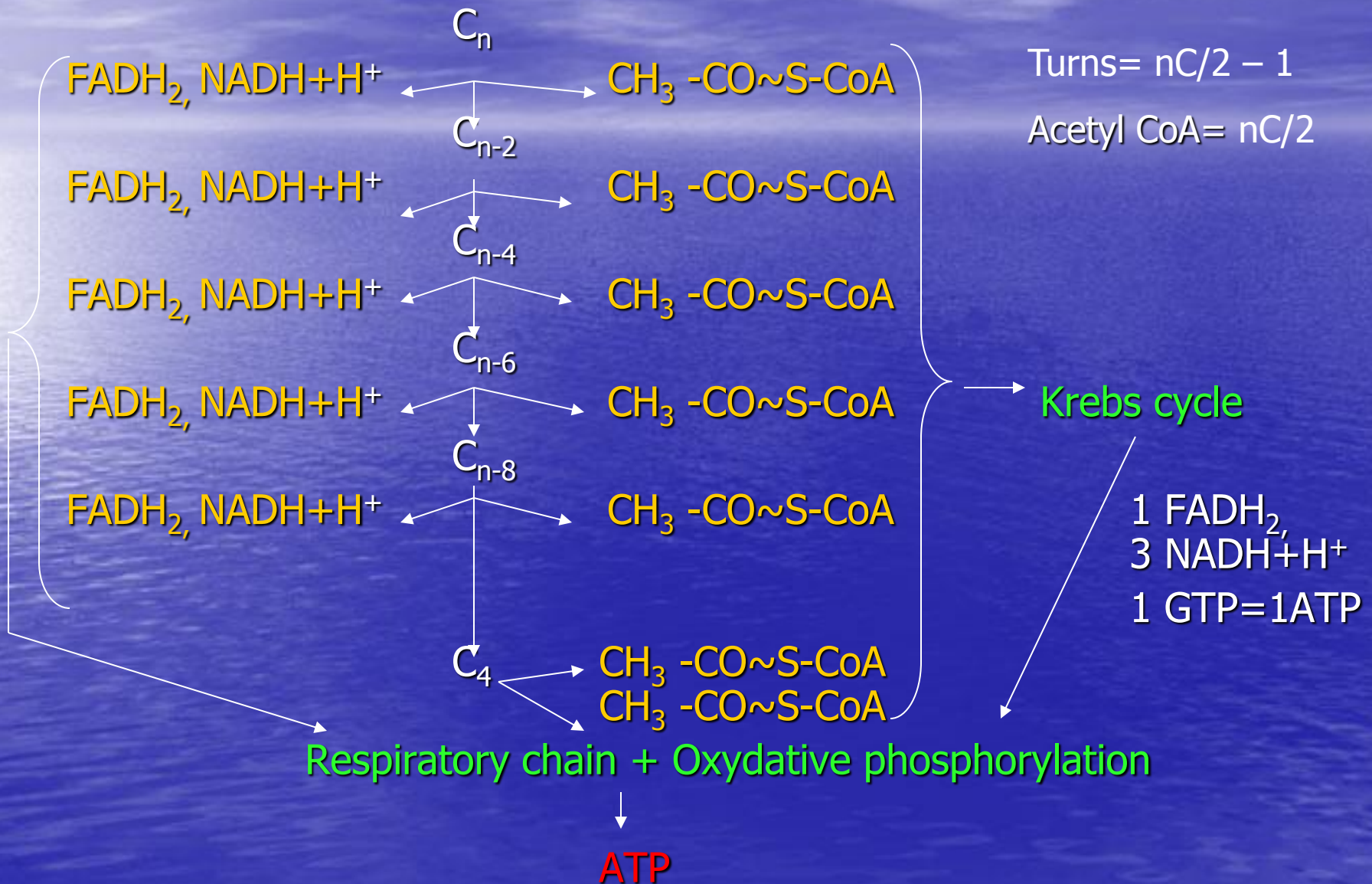
1 $NADH+H^+$,

1 acetyl-CoA.

The last cycle produces 2 acetyl-CoA.

They enter in the Krebs cycle, respiratory chain and oxidative phosphorylation generating ATP (e.g. 129 ATP/palmitic acid)

KNOOP-LYNEN SPIRA

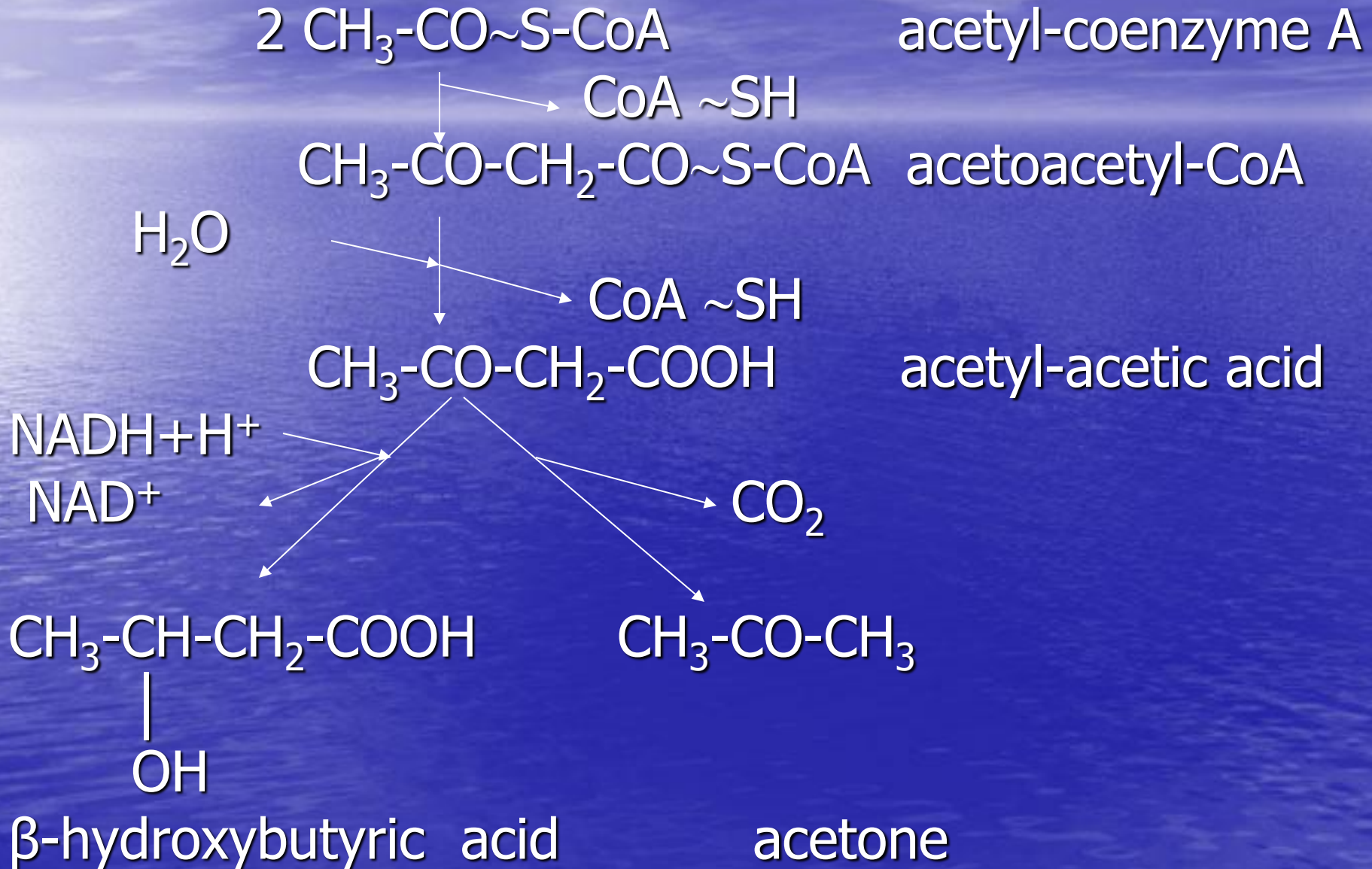


KETONE BODIES PRODUCTION - KETOGENESIS

- During fasting or starvation fat is mobilized from adipose tissue and metabolized for energy; in diabetes, the glucose is not available for glucolysis due to the shortage of insulin that prevents the glucose entry in the cell; thus, acetyl-CoA is used preferentially over glucose as an energy source.
- Acetyl-CoA is in higher amount than oxaloacetate and besides joining the TCA cycle, the excess forms aceto-acetyl-CoA → acetoacetic acid that is spontaneously decarboxylated to acetone and β -hydroxybutyric acid.
- **Acetoacetic acid, β -hydroxybutyric acid and acetone** are called **ketone bodies**.
- Acetoacetate and β -hydroxybutyrate were considered nonfunctional byproducts; they are energy sources of heart and in starvation or diabetes of the brain

In healthy states, acetyl-CoA not used for energy is used to synthesize fatty acids – storage forms of energy

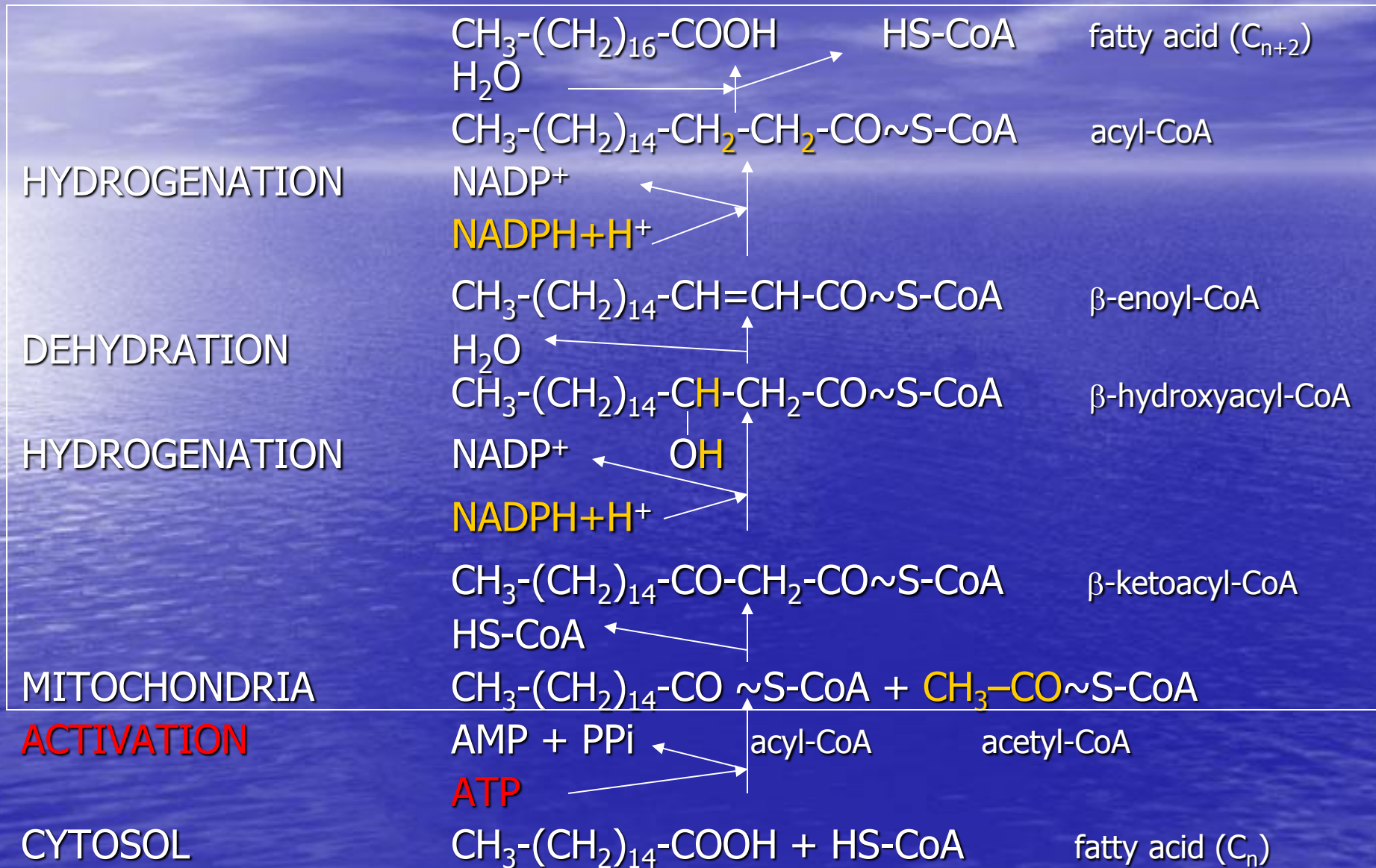
KETOGENESIS



FATTY ACID SYNTHESIS

1. In the cytosol of the liver cells – **malonyl-CoA pathway**
 - 2 preliminary steps:
 - Acetyl-CoA is produced in the mitochondria both from β -oxidation and from pyruvate (in glycolysis, **pyruvate dehydrogenase**); it does not cross the mitochondrial membrane; it reacts with oxaloacetate to form citrate (**citrate synthetase**) that is transported from the mitochondria into the cytosol; the citrate crosses the outer mitochondrial membrane and reacts with CoA and ATP forming acetyl-CoA, oxaloacetate, ADP, H_3PO_4 .
 - CO_2 as bicarbonate ion (HCO_3^-) is added to acetyl-CoA to form malonyl-CoA (**acetyl-CoA carboxylase**, ATP, Mn^{2+})
 - Successive addition of 2 carbon units to malonyl-CoA
2. In the mitochondria - **β -elongation**

FATTY ACID SYNTHESIS (ELONGATION)



CHOLESTEROL SYNTHESIS

In the cytosol

All the 27 C derived from acetyl-CoA

- Acetyl-CoA is complexed with acetoacetyl-CoA forming 3-hydroxy-3-methylglutaryl CoA (**HMG-CoA**) (C_6)
- HMG-CoA is converted to **mevalonate** (**HMG-CoA reductase**)
- Mevalonate is converted in **isopentenyl pyrophosphate** (C_5) in 3 reactions that use ATP
- Isomerisation to **dimethylallyl pyrophosphate**
- 2 molecules condense in **geranyl pyrophosphate** (C_{10})
- Condensation with dimethylallyl pyrophosphate forming **farnesyl pyrophosphate** (C_{15})
- 2 molecule condense in **squalene** (C_{30})
- Squalene is oxidized forming **epoxide**
- Epoxide cyclizes to form **lanosterol**
- 3 C are removed forming **cholesterol** (C_{27})

REGULATION OF CHOLESTEROL SYNTHESIS

- HMG CoA reductase is the rate-limiting enzyme is controlled by:
 - Sterol levels low increase synthesis of a complex SREBP-SCAP (sterol regulatory element-binding protein – SREBP cleavage activating protein) that intensifies the synthesis of HMGCoA reductase and cholesterol
 - Sterol levels high the reductase degradation is accelerated
 - Sterol-independent phosphorylation/dephosphorylation; the phosphorylated enzyme is inactive the dephosphorylated form is active
 - Hormonal regulation: insulin increase favors up-regulation of the gene-regulation for HMG-CoA reductase; glucagon has opposite effect.
 - Inhibition of drugs: Statins are structural analogs of HMG-CoA reductase and determine the reversible, competitive inhibition

CHOLESTEROL DEGRADATION

- Cholesterol can not be metabolized in humans
- The sterol nucleus is converted to bile acids and bile salts excreted in the feces