Metabolism of Lipid（2）

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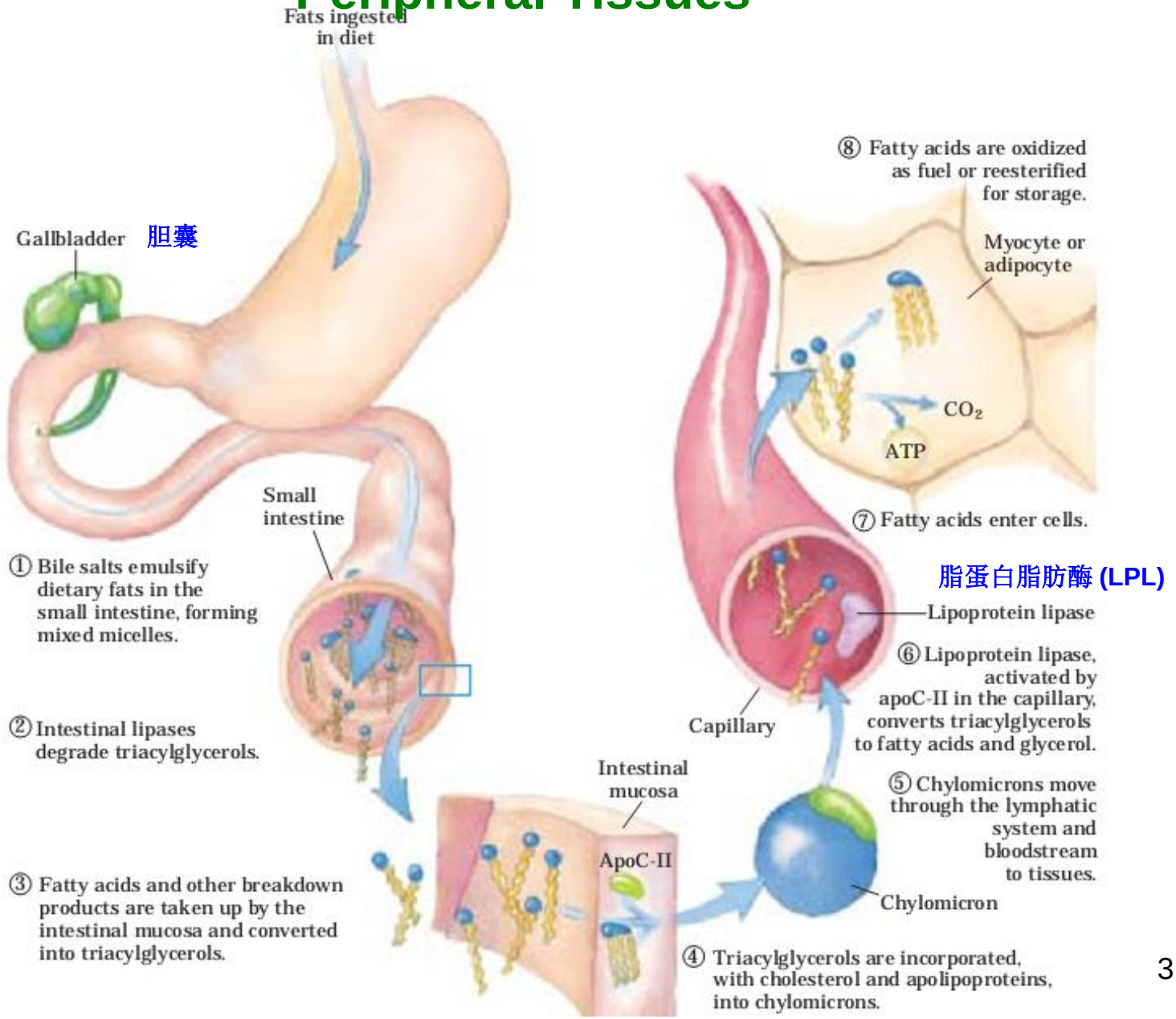
outline

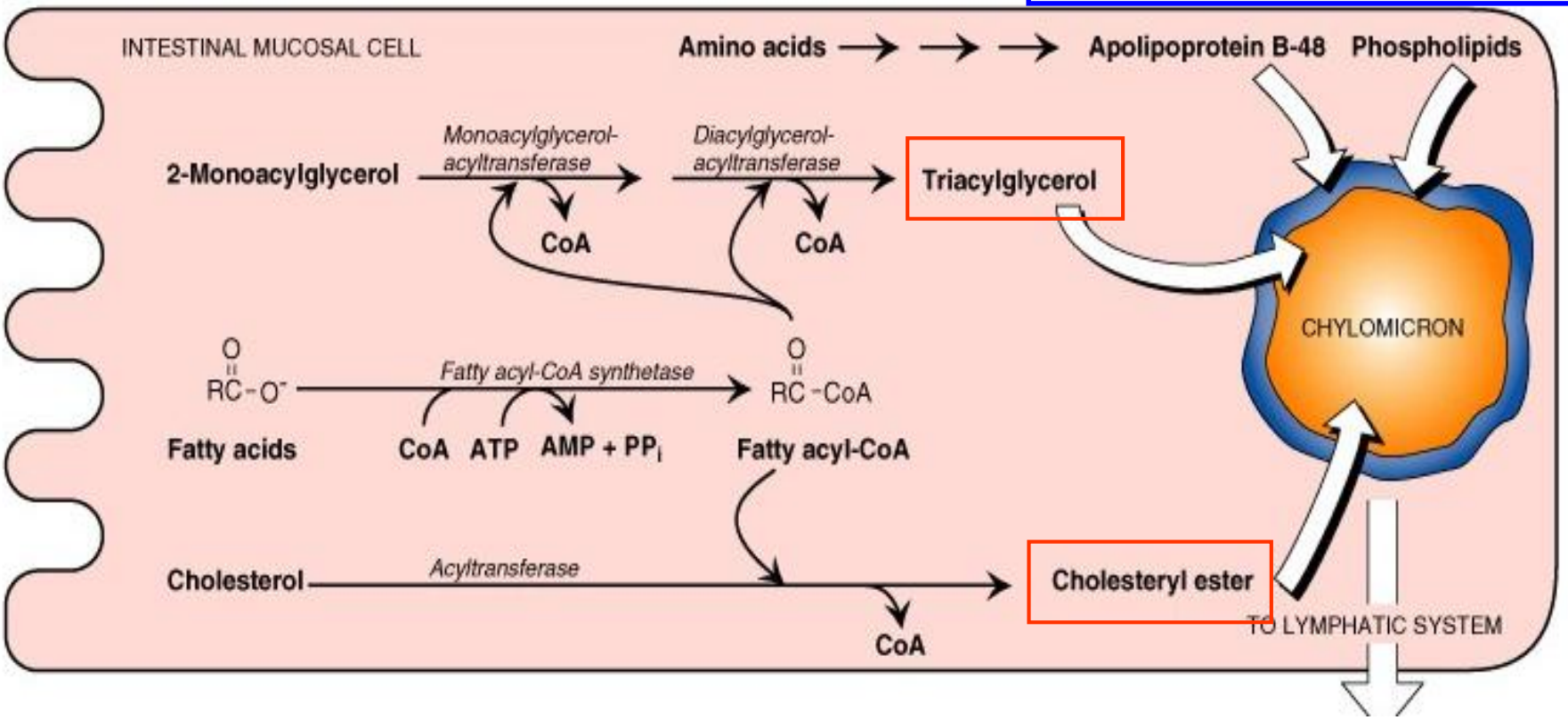
- **Introduction to FA**
- **Mobilization of fats（TG） from dietary intake and adipose tissues**
- **fatty acids oxidation**
- **Ketone bodies（酮体）**
- **FA metabolism regulation and control**

Movement of Dietary Lipid from Small Intestine to Peripheral Tissues



Assembly and Secretion of Chylomicrons from Intestinal Mucosal Cells

Increase the solubility of chylomicrons.



Glycerol and short FAs pass thru intestinal cell via passive diffusion.

To bloodstream & then to tissues.

3. Utilization of FAs as Fuel

Three stages：

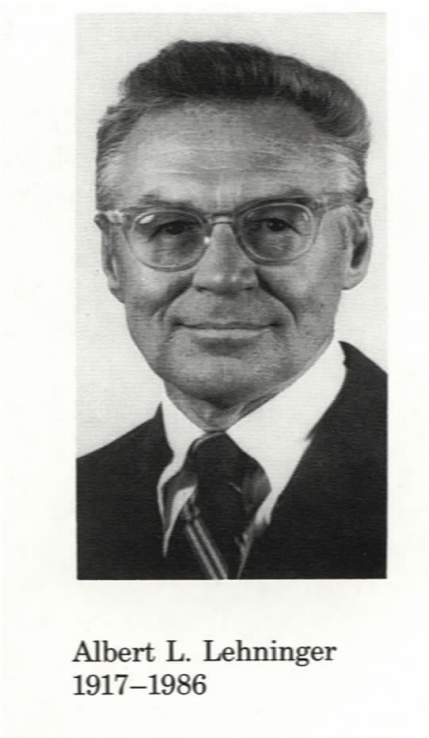
1) TGs → FAs + glycerol in the adipose tissue（脂肪组织）and transported to other tissues.

2) FAs are activated → Mit

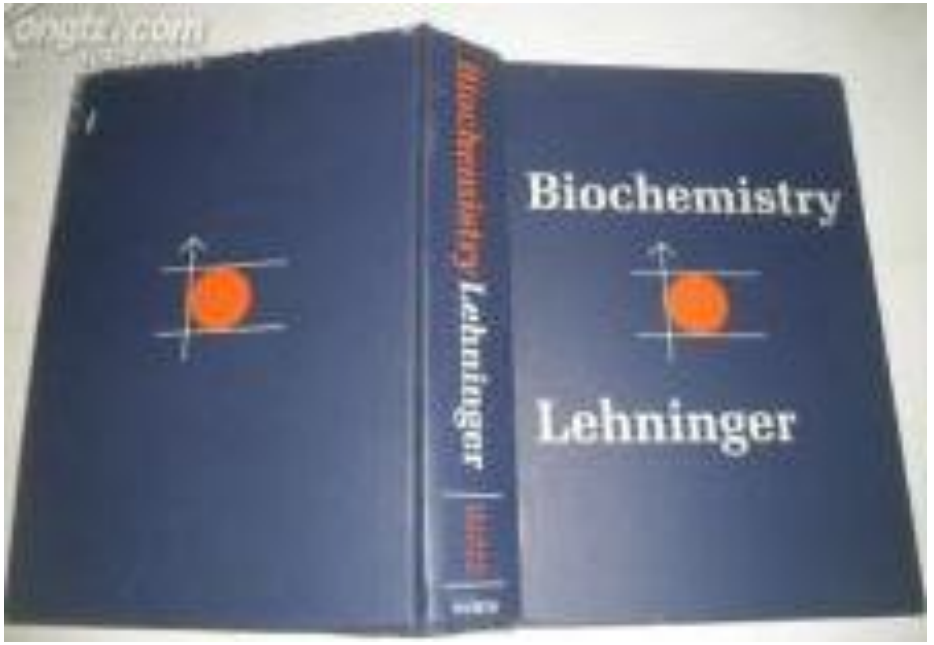
3) FAs → acetyl–CoA →TCA

3.1 β-Oxidation of FAs

- **Franz Knoop's** labeling experiments (1904)
- The process begins with oxidation of the "beta" carbon to the carboxyl carbon --- "**beta-oxidation**"
- Localized in the **mitochondria matrix**. Revealed by Eugene Kennedy and **Albert Lehninger** in 1948.



Albert L. Lehninger
1917–1986

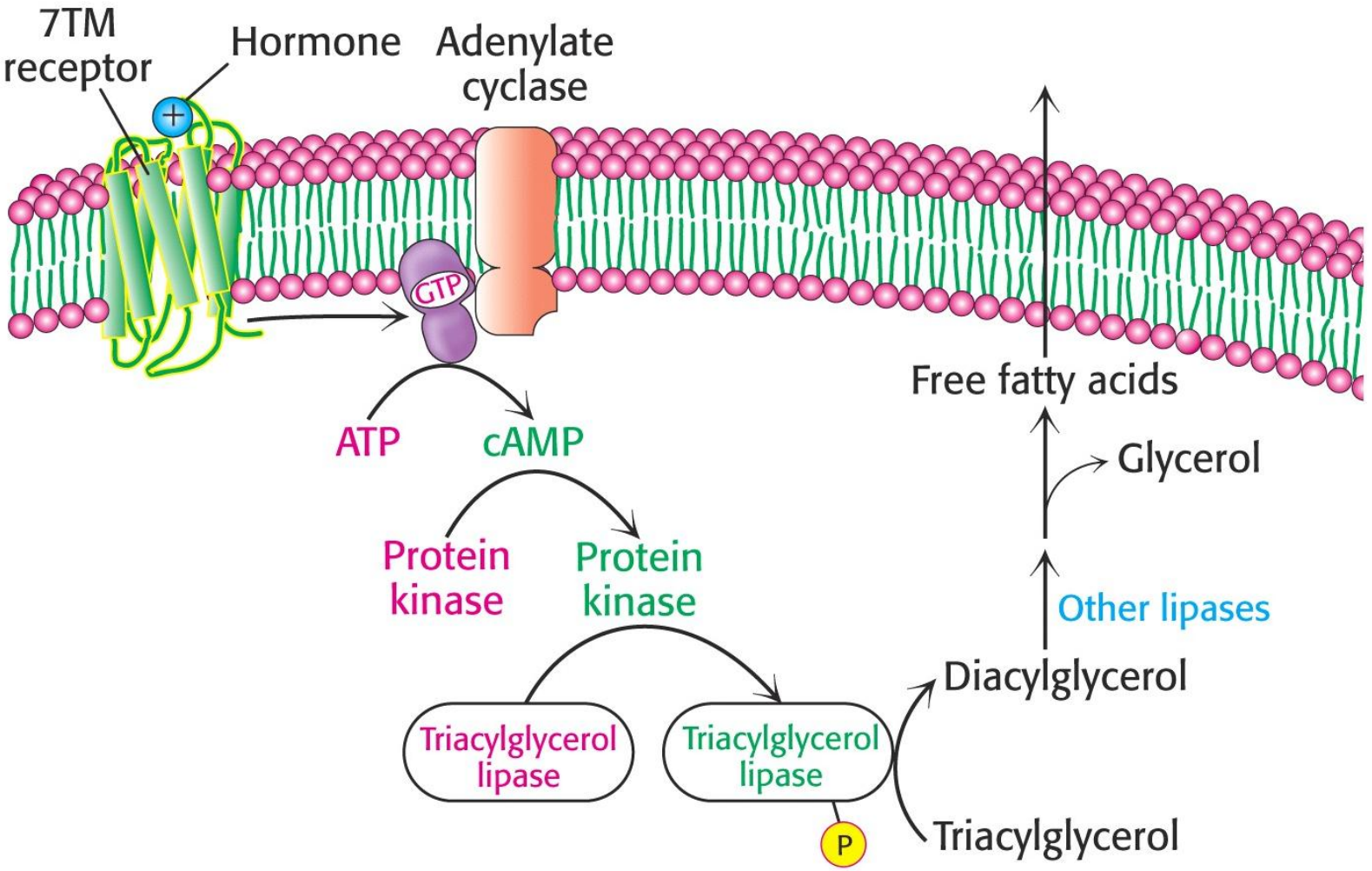


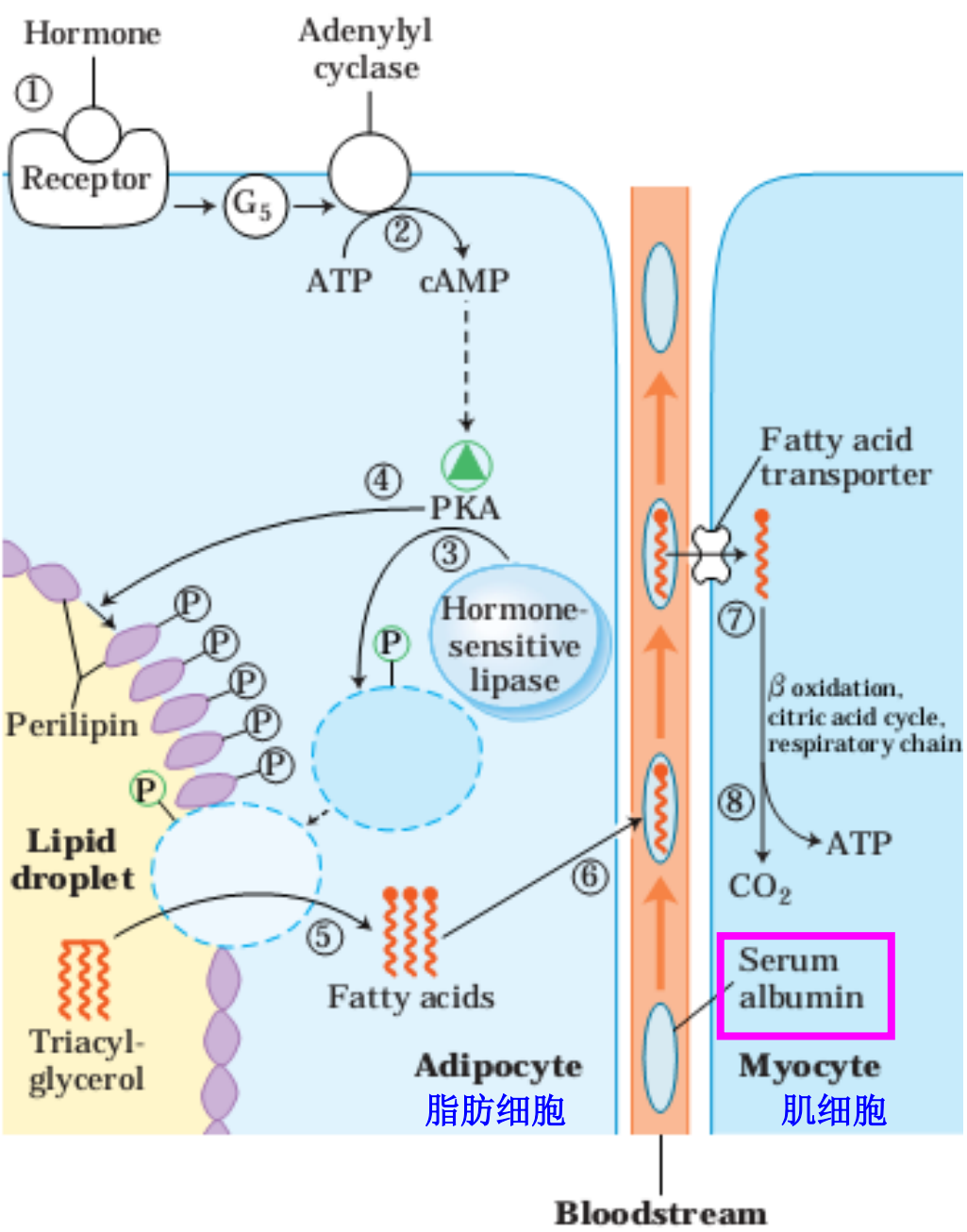
3.1 β-Oxidation of Fatty Acids

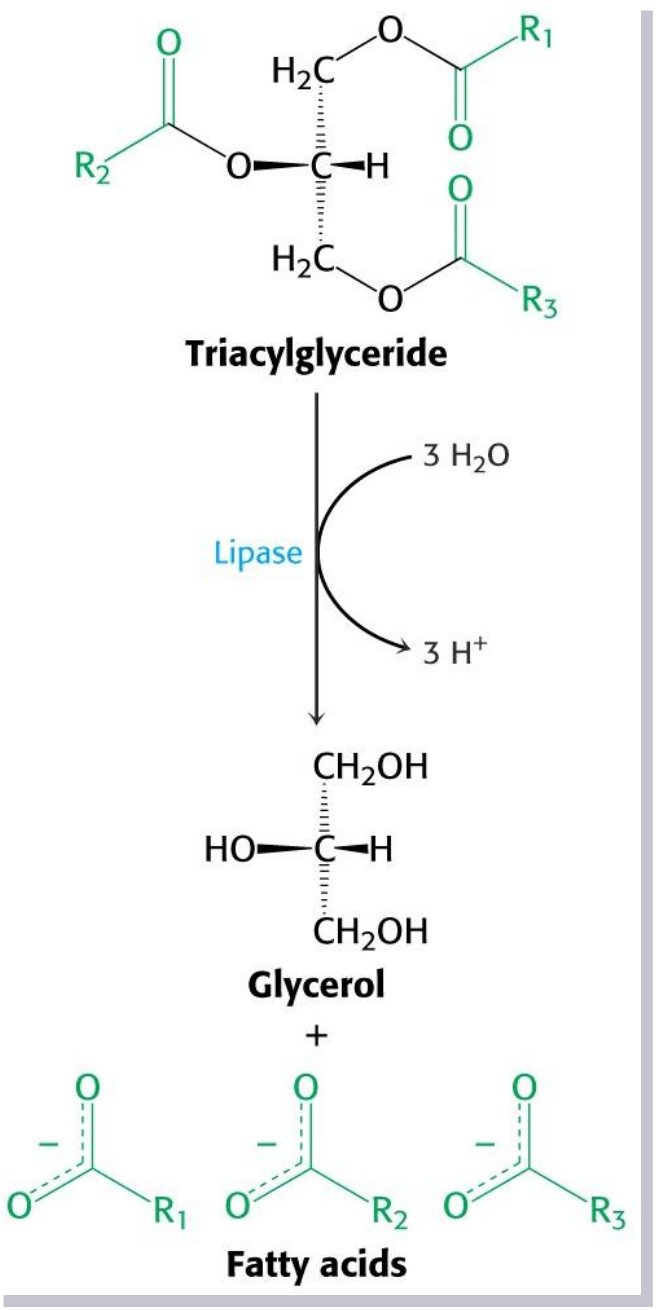
- **Mitochondrial β-oxidation** provides energy
- **A similar pathway occurs in peroxisomes (**过氧化物酶体）
  - The only pathway in yeast, lower eukaryotes
  - In mammals, **peroxisomal** β-oxidation long-chain FAs

3.1.1 Breakdown of TGs

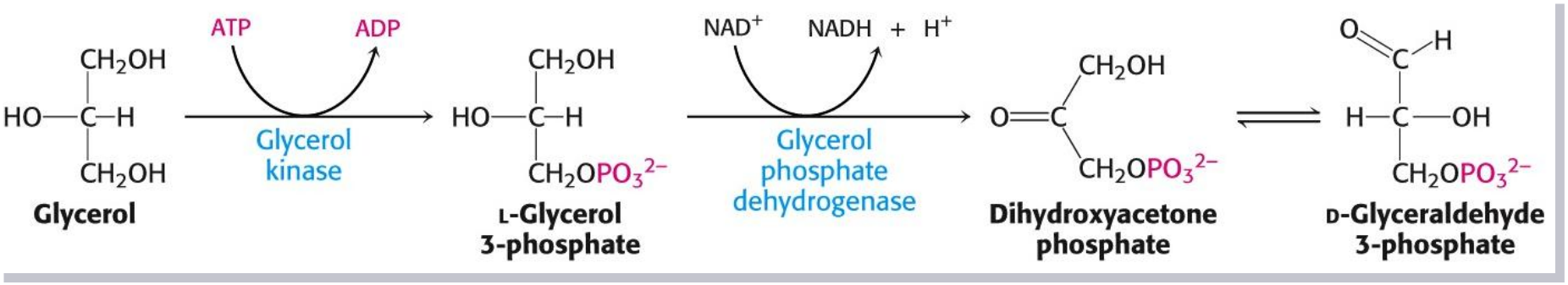
- In the **adipose tissue** (脂肪组织), **lipases are activated by hormone**




Hormone
Adenylyl cyclase
①
Receptor
G_s
②
ATP
cAMP
④
PKA
③
Hormone-sensitive lipase
Perilipin
P
Lipid droplet
⑤
Fatty acids
Triacyl-glycerol
⑥
Fatty acid transporter
⑦
β oxidation, citric acid cycle, respiratory chain
⑧
ATP
CO_2
Serum albumin
Adipocyte
脂肪细胞
Myocyte
肌细胞
Bloodstream

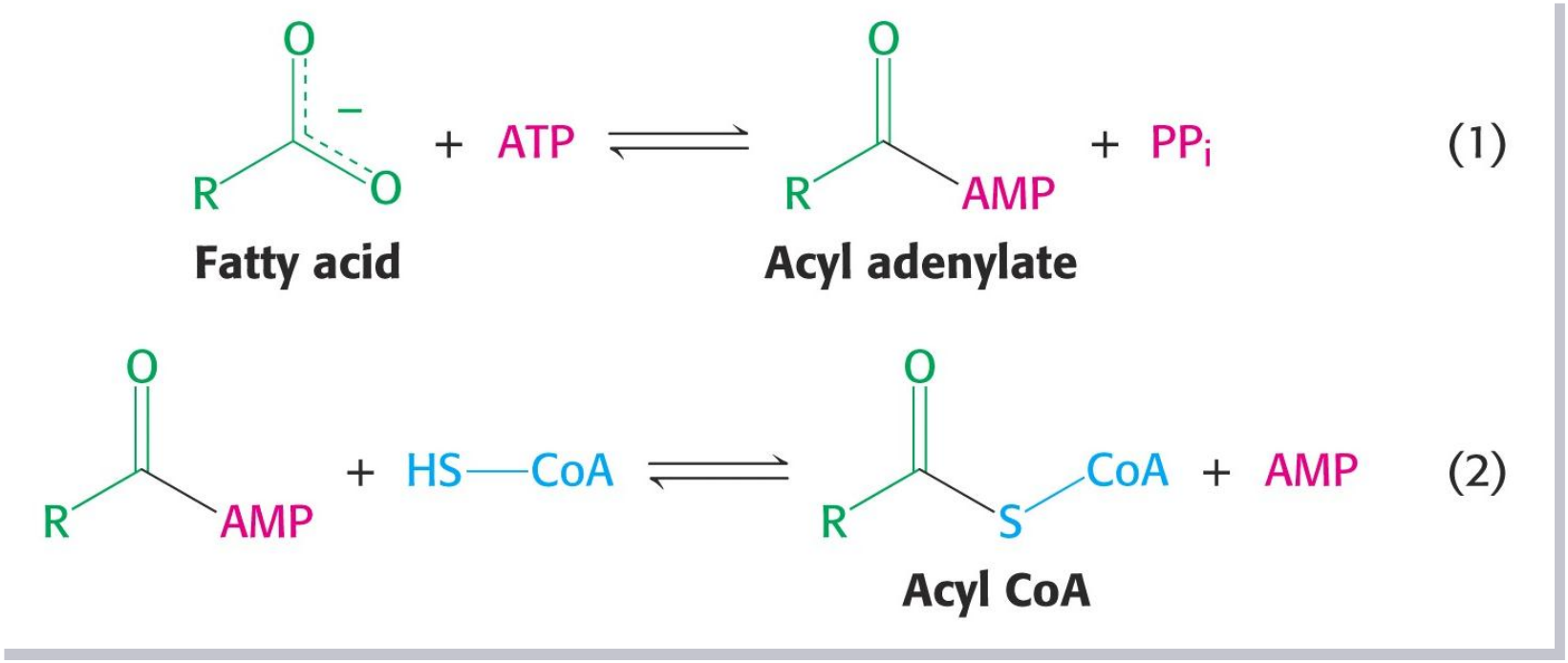

Triacylglyceride
3 H_2O
Lipase
3 H^+
Glycerol
+
Fatty acids

glycerol → liver

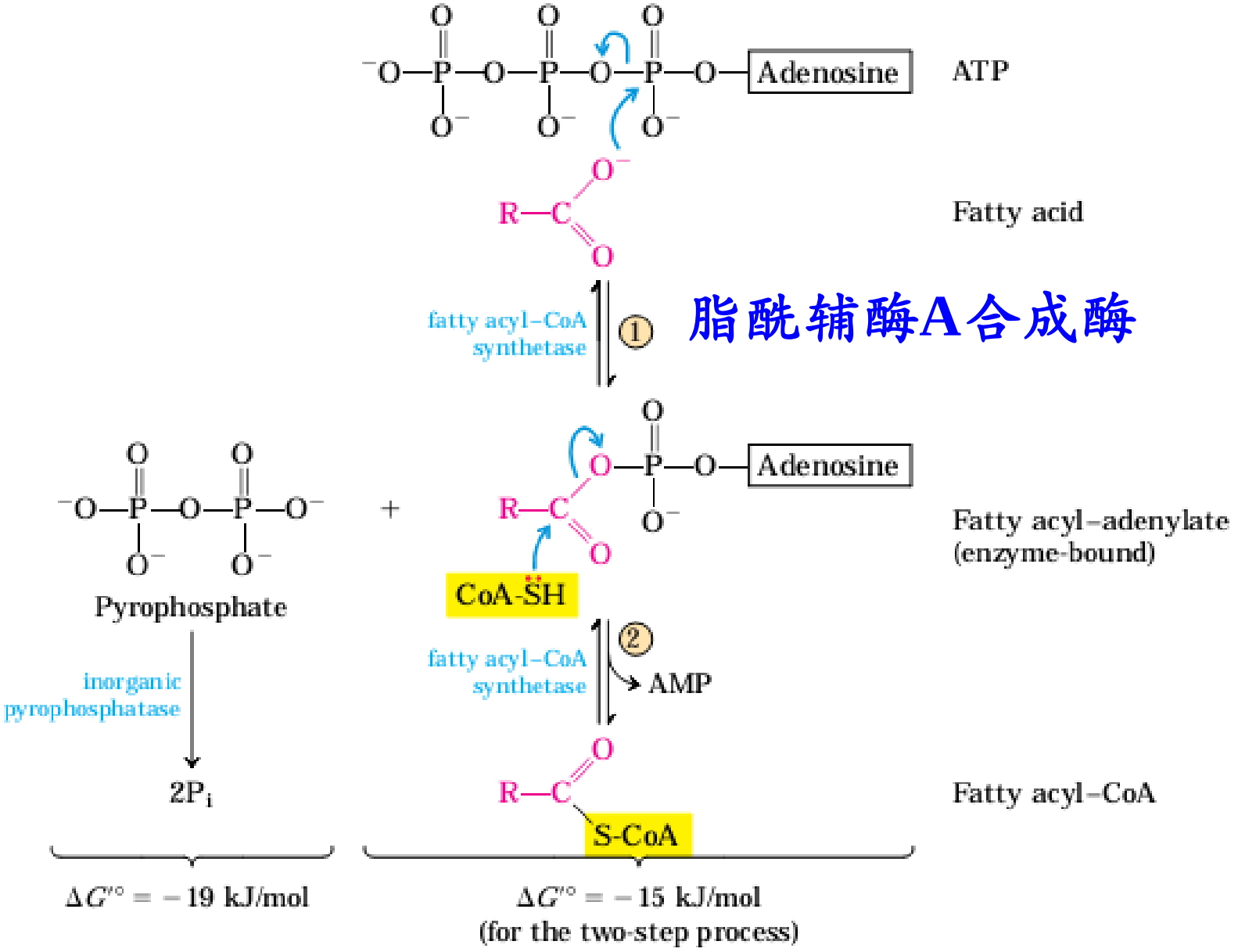


3.1.2 Activation of FAs（活化）

- **Acyl CoA synthetase** - **mitochondrial membrane**

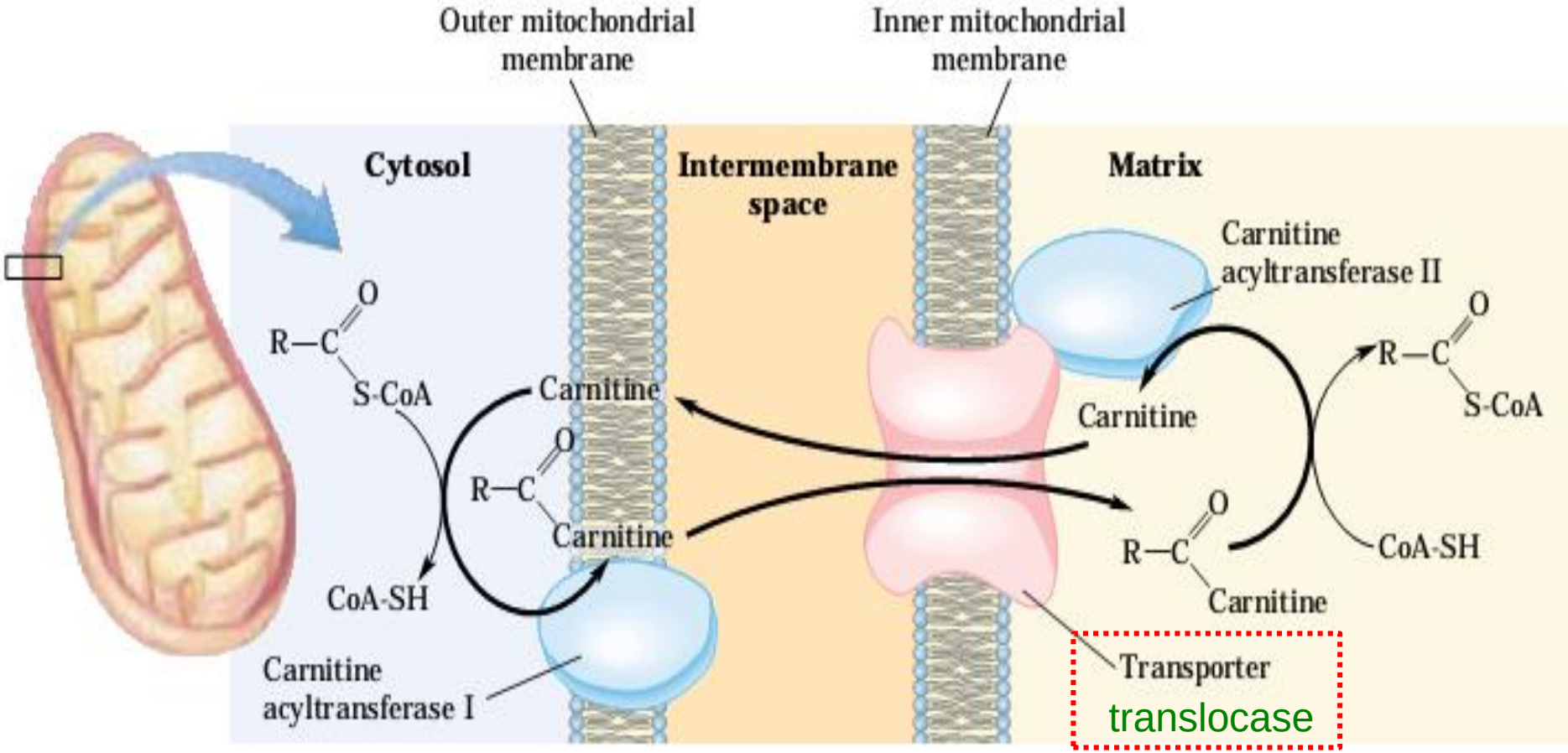


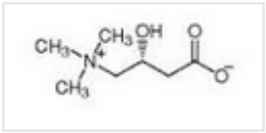
- Consumption of **2 ATP**


Adenosine
ATP
Fatty acid
fatty acyl–CoA synthetase
①
脂酰辅酶A合成酶
Adenosine
Fatty acyl–adenylate (enzyme-bound)
Pyrophosphate
CoA-SH
fatty acyl–CoA synthetase
②
AMP
inorganic pyrophosphatase
2Pi
S-CoA
Fatty acyl–CoA
ΔG'° = −19 kJ/mol
ΔG'° = −15 kJ/mol
(for the two-step process)

3.1.3 Transport into Mitochondrial Matrix

- **Short chain FA**s（**≤C6**）are carried **directly** into the Mit matrix
- **medium and long chain FA**s (**C8~ C20**）





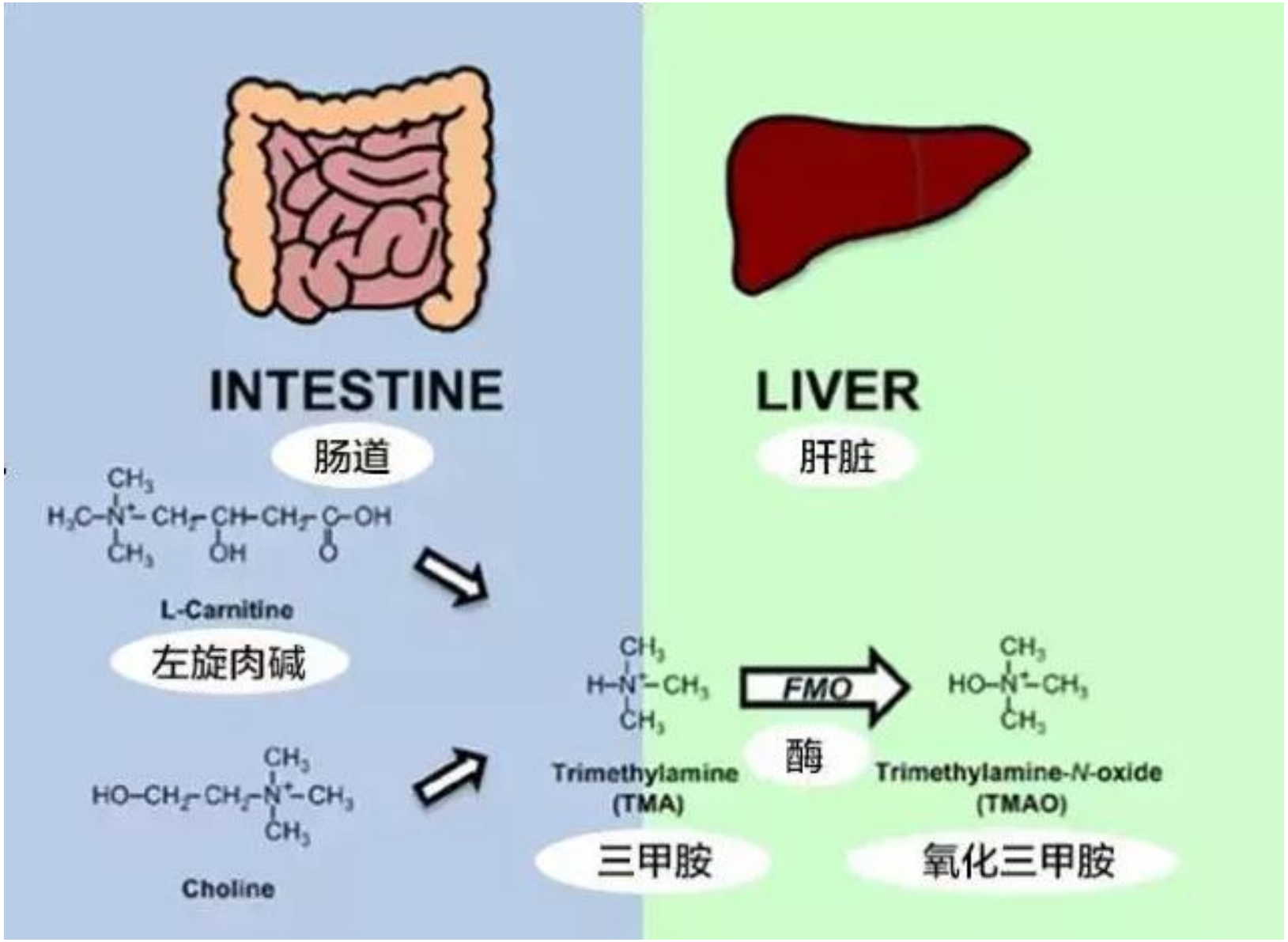
左旋肉碱分子式

左旋肉碱（L-carnitine），Left－肉碱，别称L－肉碱、维生素BT，化学名称左旋肉碱粉末β－羟基γ－三甲铵丁酸，是一种白色晶状体或白色透明细粉，又称L-肉碱或音译卡尼丁。在医学上主要用于慢性肾衰血透病人因肉碱缺乏产生的并发症。左旋肉碱还是一种类维生素营养素，有搬运脂肪的职能。

编辑摘要

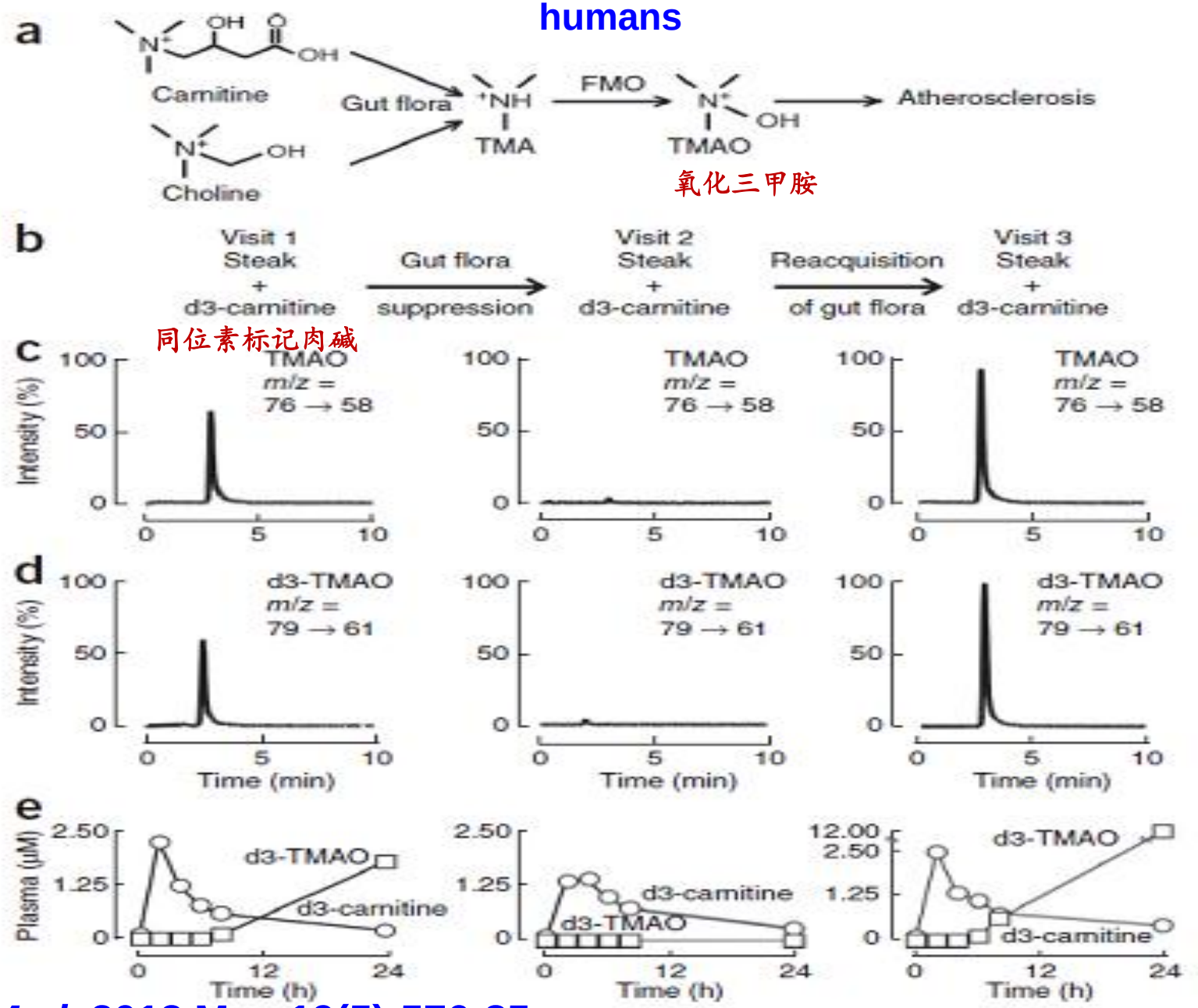
编辑信息模块

中文名：	左旋肉碱	**别名：**	卡尼儿丁
英文名：	L-carnitine	**化学式：**	C7H15NO3
IUPAC名：	(R)-3-羟基-4-三甲基铵基丁酸内盐	**CAS号：**	541-15-1
摩尔质量：	161.199 g/mol	**熔点：**	208-212℃
	2500 g/L (20°C)		

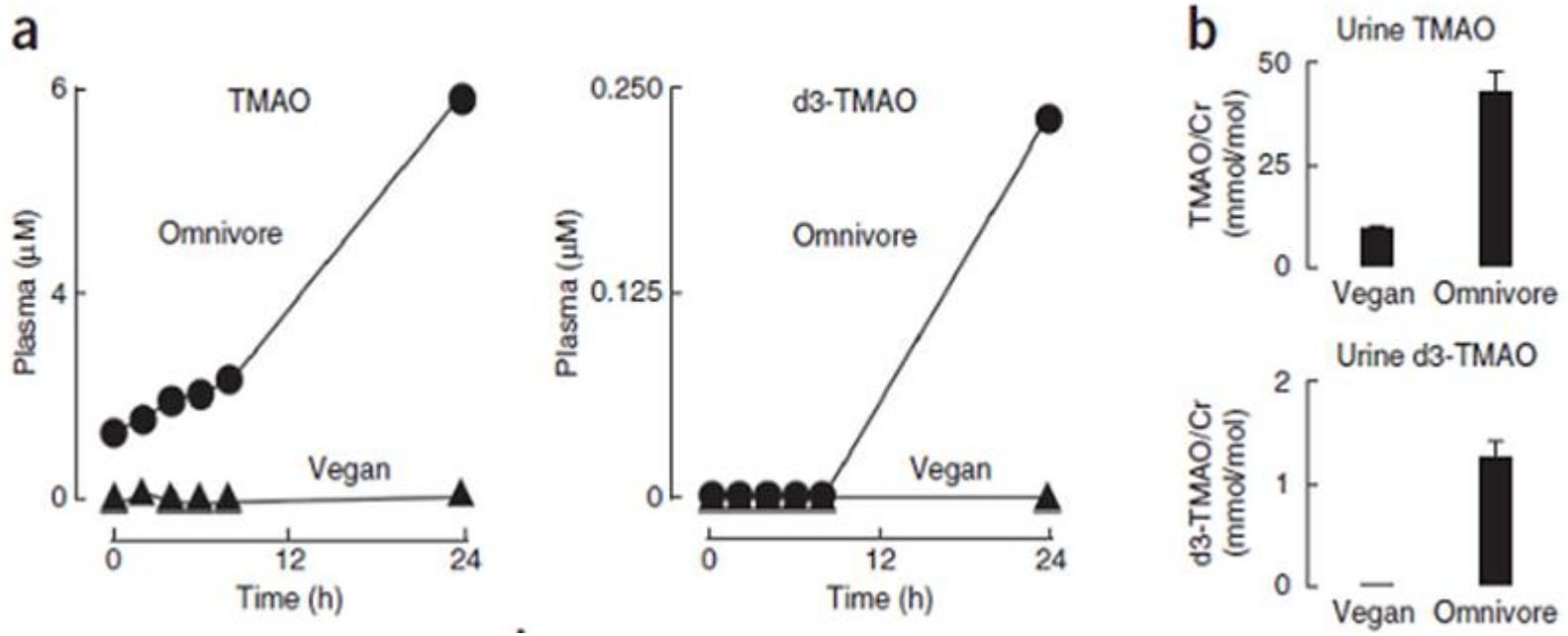


Atherosclerosis, 2013, 231(2):456-461.

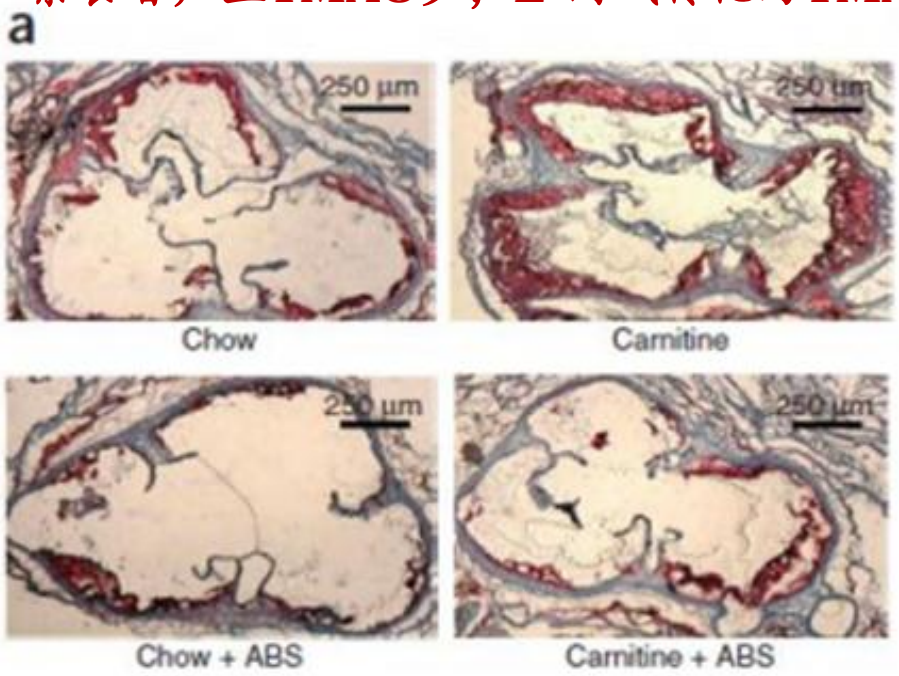
TMAO（氧化三甲胺） production from carnitine is microbiota dependent in humans



Nat Med. 2013 May;19(5):576-85



素食者产生TMAO少，L-肉碱转化为TMAO比杂食者低



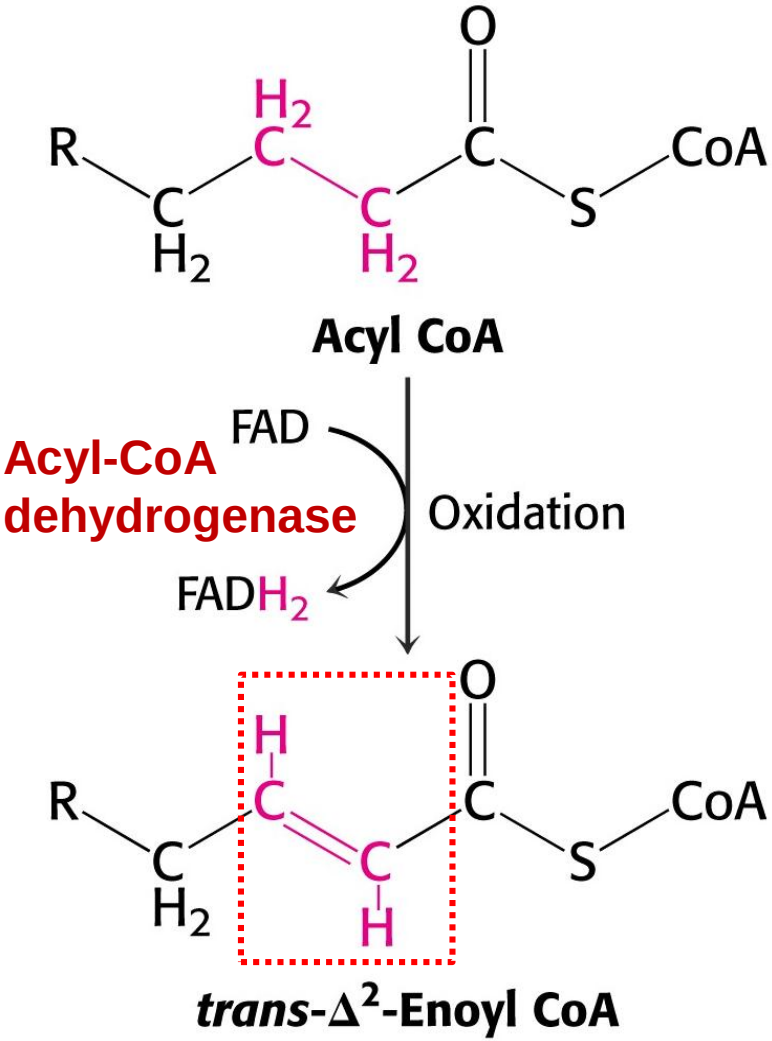
19 week C57BL/6J

ABS：antibiotics

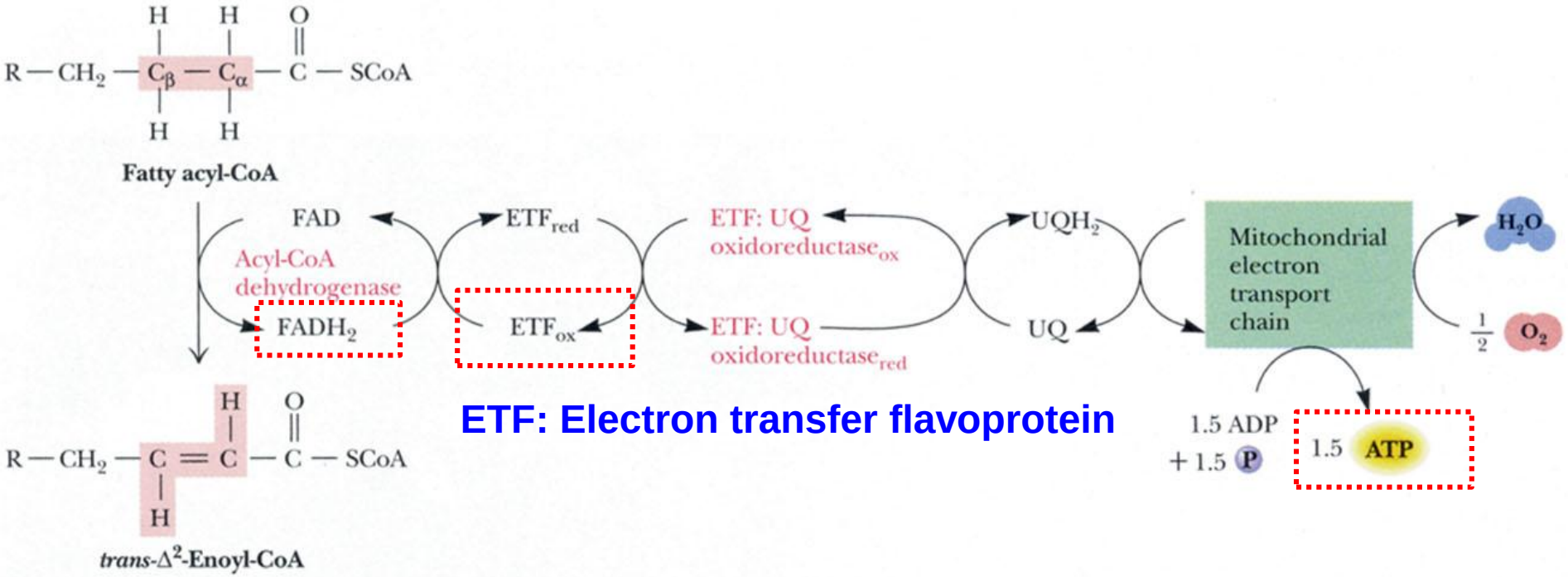
3.1.4 FAs oxidation（β-Oxidation）

1). oxidation to *trans*-Δ^2-Enoly-CoA

（氧化）



反式烯酰CoA



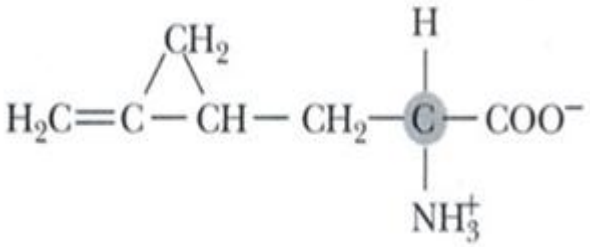
ETF: Electron transfer flavoprotein

acyl-CoA dehydrogenase

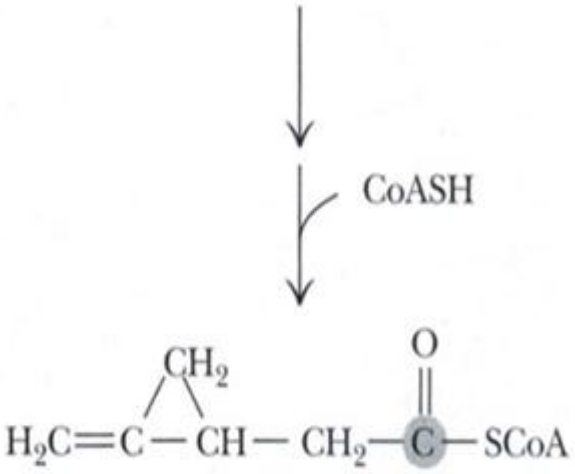
脂酰-CoA脱氢酶

一、阿开木

阿开木也叫西非荔枝果，原产于西非，但是提到阿开木最容易联想到牙买加。如果果实没有完全成熟，吃下去会导致严重呕吐。(生的果实中含有次甘氨酸)只要果实前端自己爆开，就可以安心食用里面的黄色果实。



降糖氨酸A Hypoglycin A

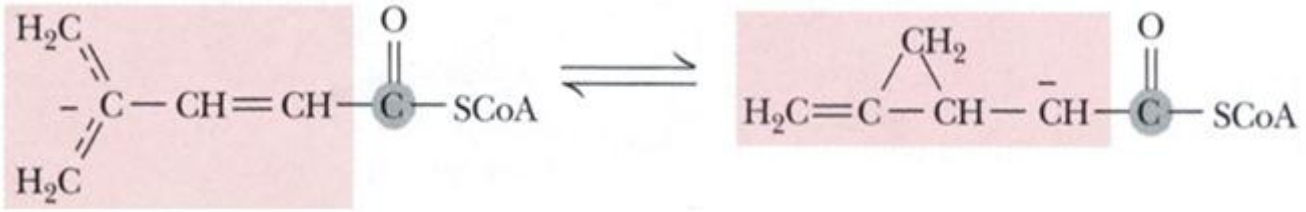


Methylenecyclopropylacetyl-CoA (MCPA-CoA)

akee未成熟果实中的**降糖氨酸A** (hypoglycinA)代谢物MCPA抑制**脂酰-CoA脱氢酶**

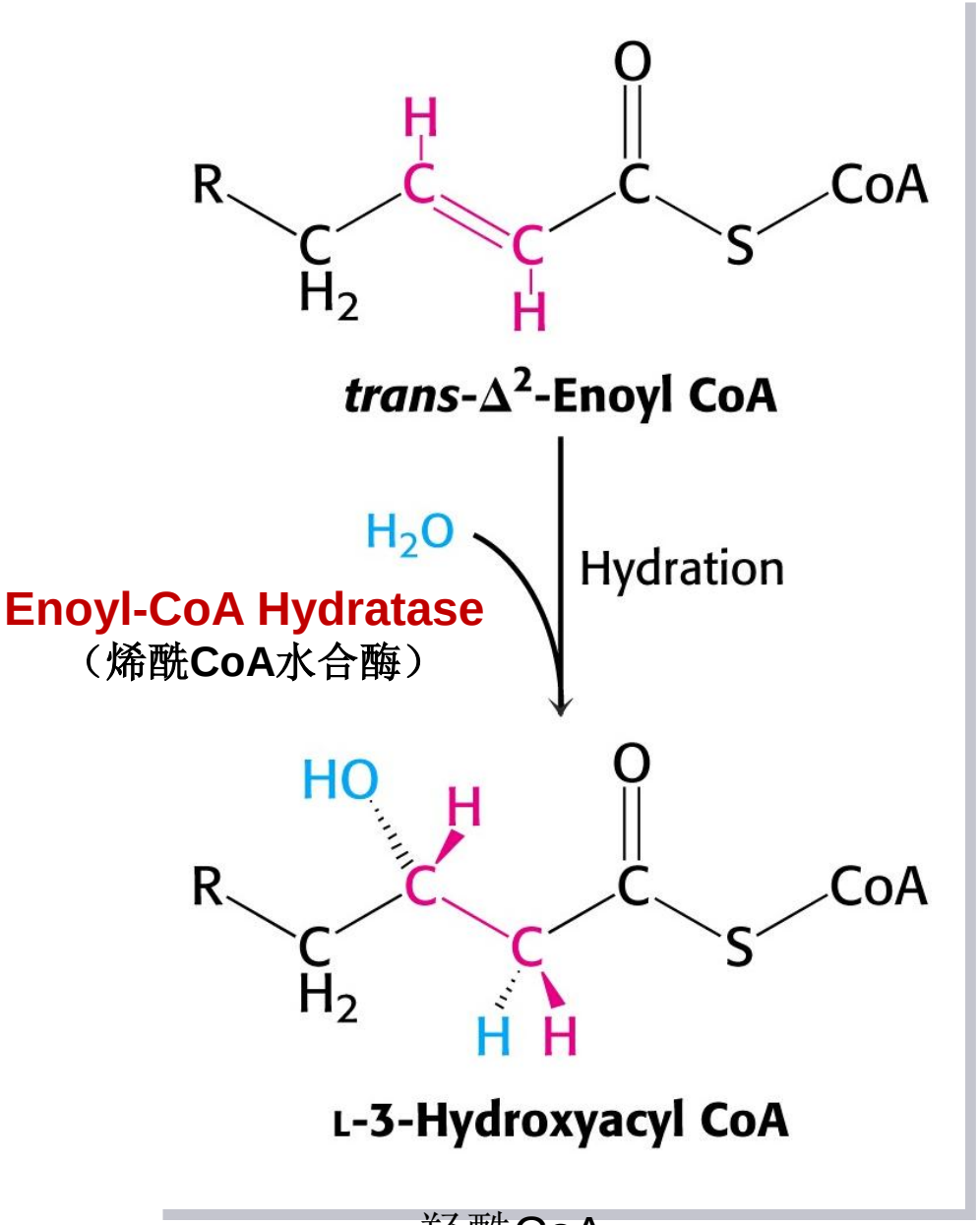
甲叉环丙基乙酰CoA与脱氢酶的FAD反应，抑制酶活

脂酰-CoA脱氢酶



2). Hydration to L–3–Hydroxylacyl CoA

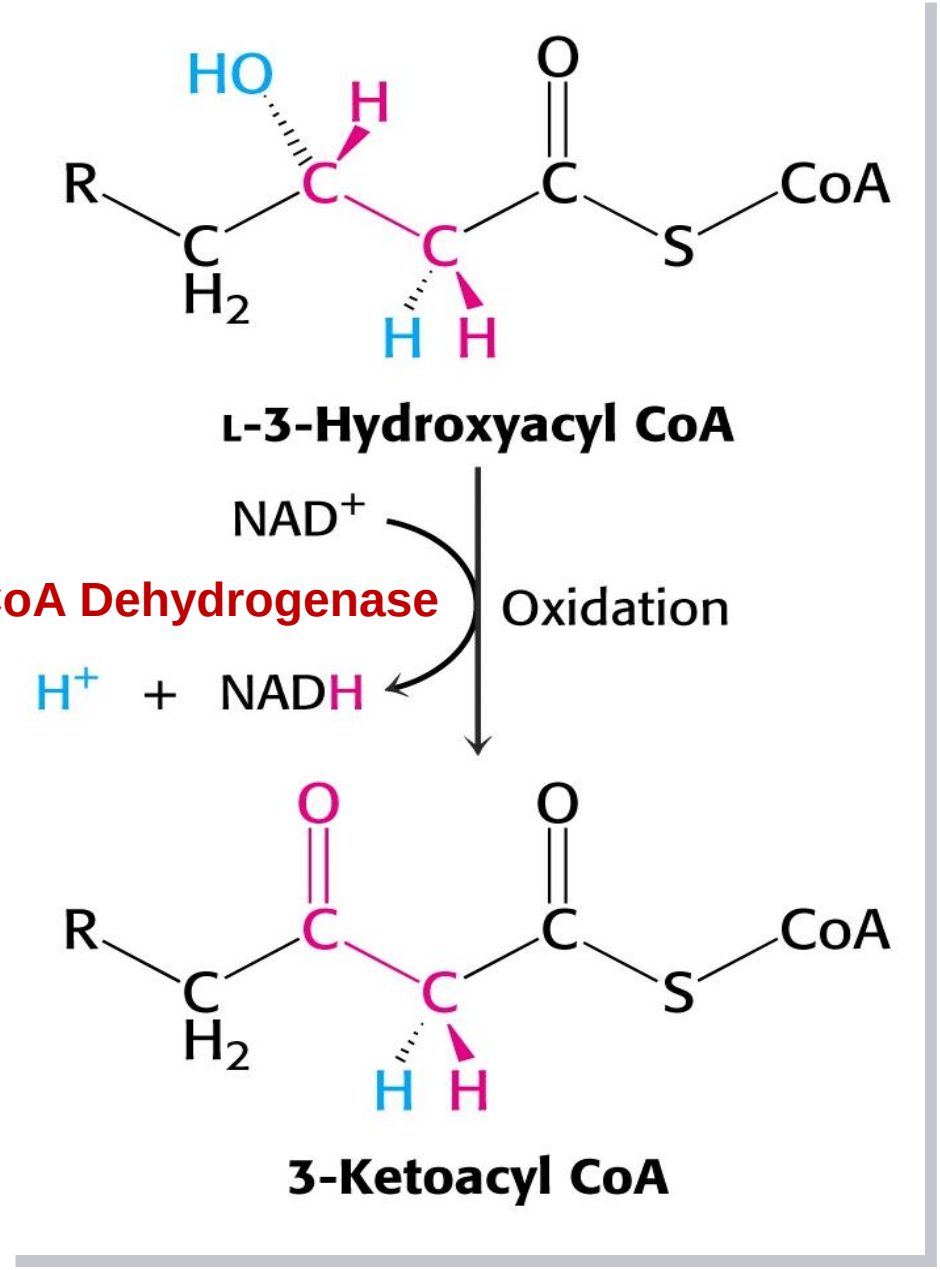
（水合）



羟酰CoA

3). Oxidation to 3-Ketoacyl CoA

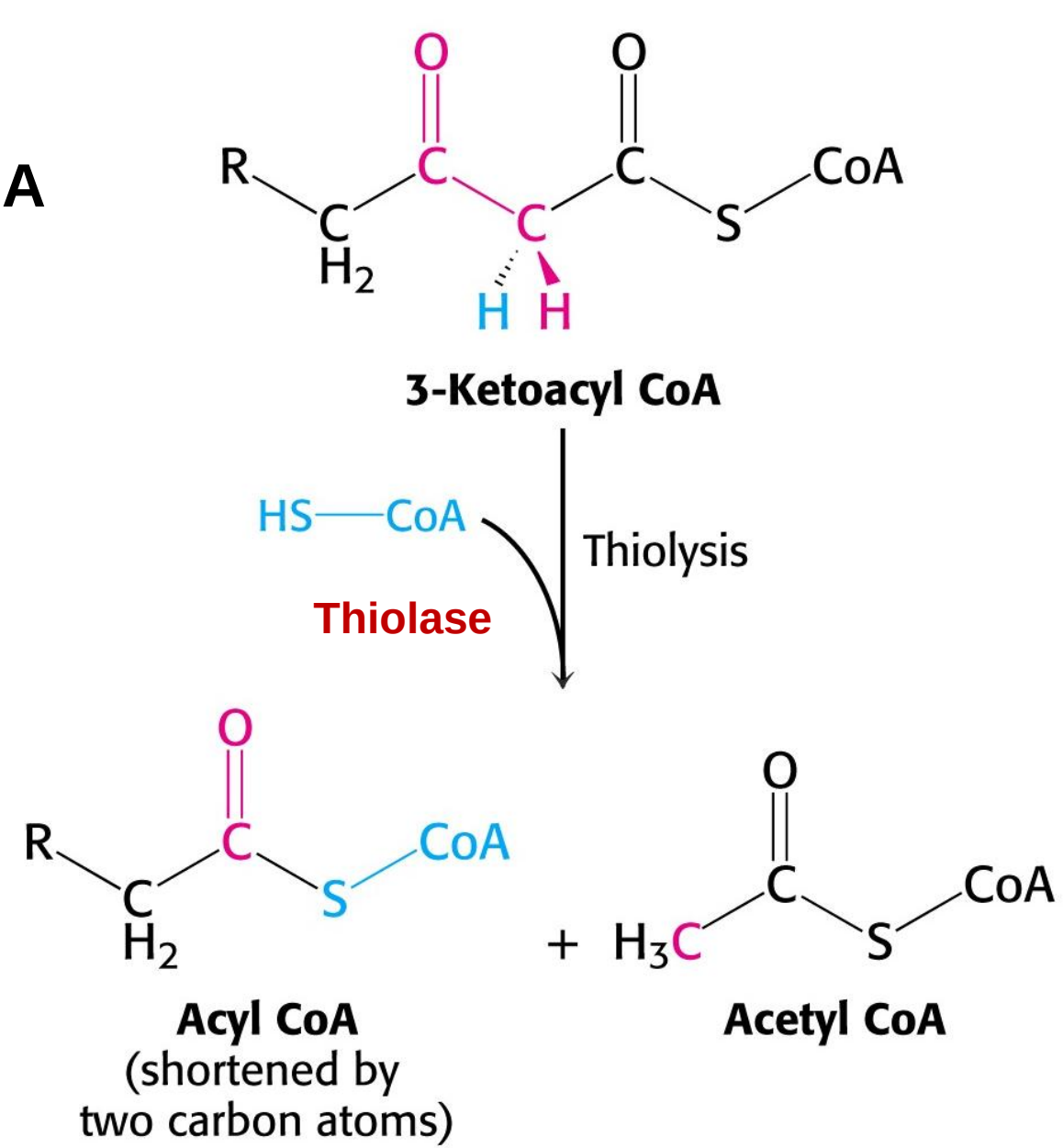
（氧化）



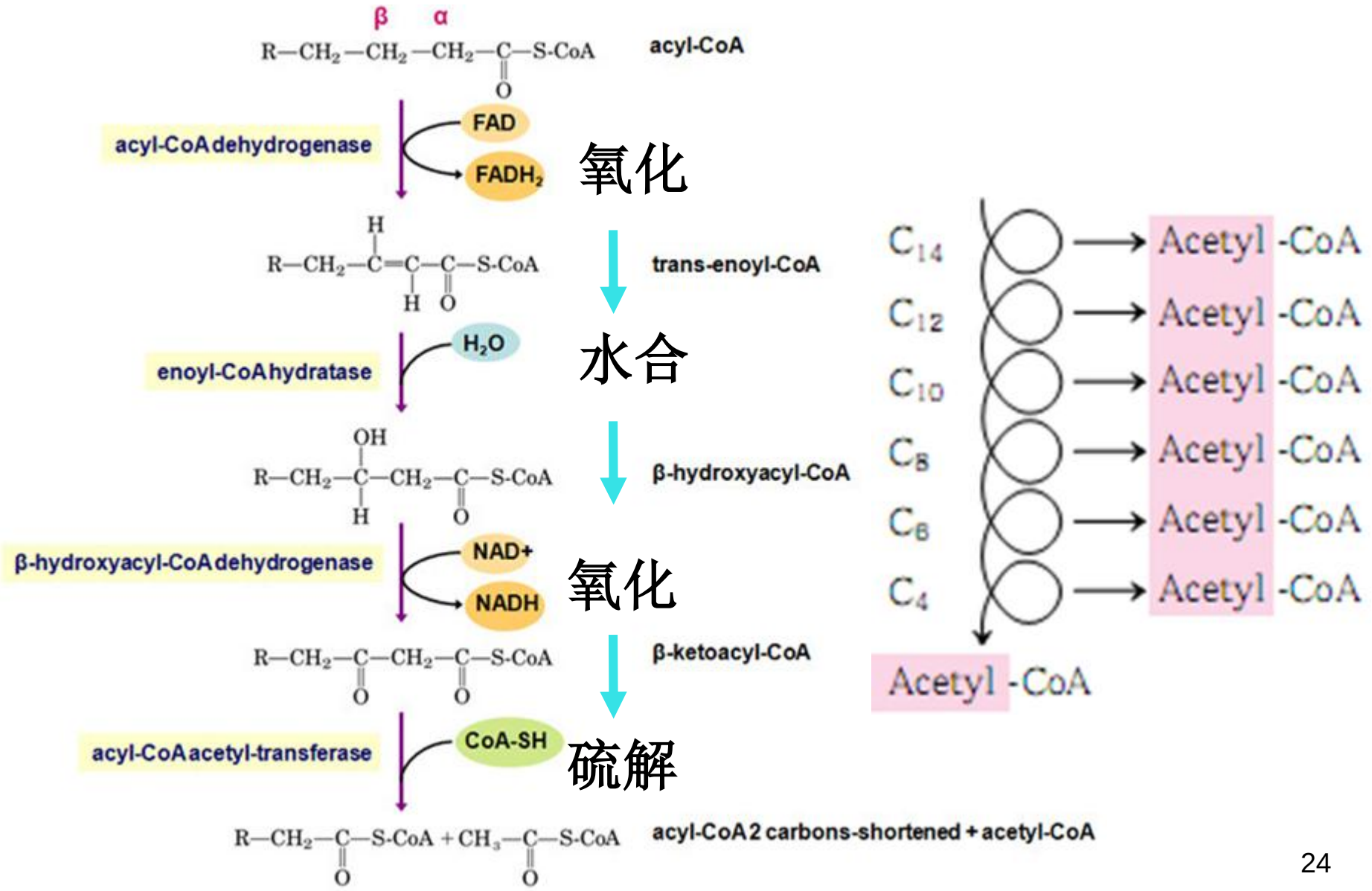
酮酰CoA

4). Thiolysis to produce Acetyl-CoA

（硫解）

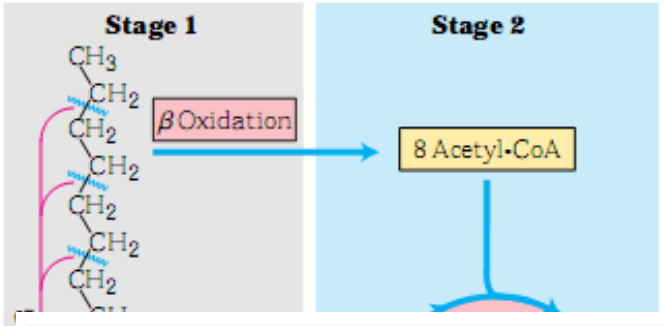


β-Oxidation


β α
R—CH2—CH2—CH2—C—S-CoA
acyl-CoA
acyl-CoA dehydrogenase
FAD
FADH2
氧化
trans-enoyl-CoA
enoyl-CoA hydratase
H2O
水合
β-hydroxyacyl-CoA
β-hydroxyacyl-CoA dehydrogenase
NAD+
NADH
氧化
β-ketoacyl-CoA
acyl-CoA acetyl-transferase
CoA-SH
硫解
acyl-CoA 2 carbons-shortened + acetyl-CoA
C14
C12
C10
C8
C6
C4
Acetyl -CoA

3.1.5 ATP Yield

16C palmitate （棕榈酸） produces 106 ATPs 【Minus the 2 for the activation】



$$\text{Palmitoyl-CoA} + 7\ \text{FAD} + 7\ \text{NAD}^+ \ 7\ \text{CoASH} + \text{H}_2\text{O} \longrightarrow$$

$$8\ \text{Acetyl-CoA} + 7\ \text{FADH}_2 + 7\ \text{NADH} + 7\ \text{H}^+$$

TABLE 17–1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

Enzyme catalyzing the oxidation step	*Number of NADH or $FADH_2$ formed*	*Number of ATP ultimately formed**
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8†
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 NADH	20
Total		108

*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.

†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. XXX).

Migratory birds travel long distances on energy from fatty acid oxidation

(c) Golden plover 金斑鸻

- 70% dry weight body in migratory birds
- ≤30% non-migratory birds

FAs oxidation is an important source of metabolic water for some animals

(a) Gerbil 沙鼠

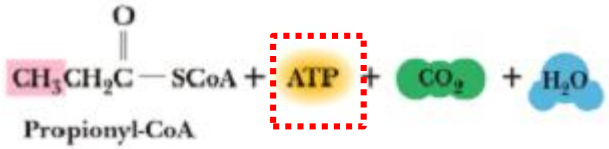
3.2 Odd-Carbon FAs

β-Oxidation yields propionyl-CoA

- **Odd-carbon FAs** - common in plants, marine organisms
- Odd FAs in diets --- **propionyl-CoA**
- Met, Val, Ile →**Propionyl-CoA**

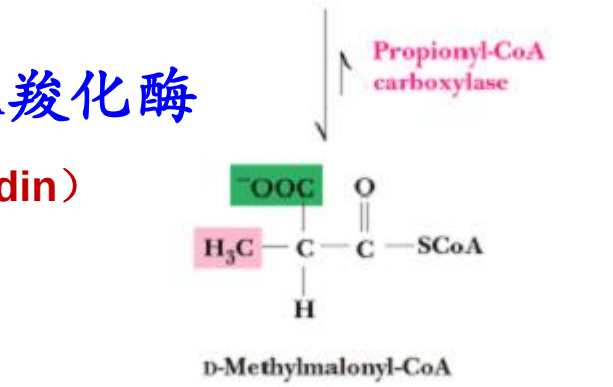
- **3 reactions**： **propionyl-CoA** to succinyl-CoA→TCA

丙酰CoA



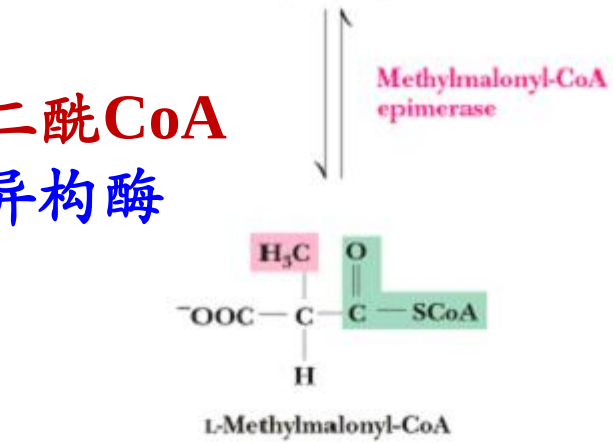
丙酰CoA羧化酶

（Biotin-Avidin）



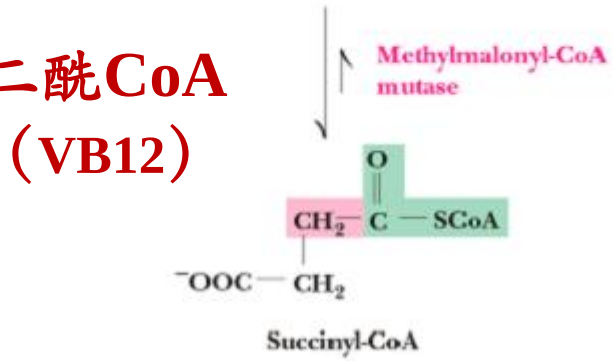
D-甲基丙二酰辅酶A

甲基丙二酰CoA
差向异构酶



L-甲基丙二酰辅酶A

甲基丙二酰CoA
变位酶（VB12）



琥珀酰CoA

3.3 Monounsaturated FAs

- Oleic acid (油酸18：1△^{9}), palmitoleic acid(棕榈油酸16：1△^{9})
- Normal β-oxidation for 3 cycles
- **Enoyl-CoA isomerase（异构酶）** converts Cis-Δ^3 acyl-CoA to trans-Δ^2 acyl-CoA
- β-oxidation continues

油酰CoA

β-Oxidation

顺式十烯酰CoA

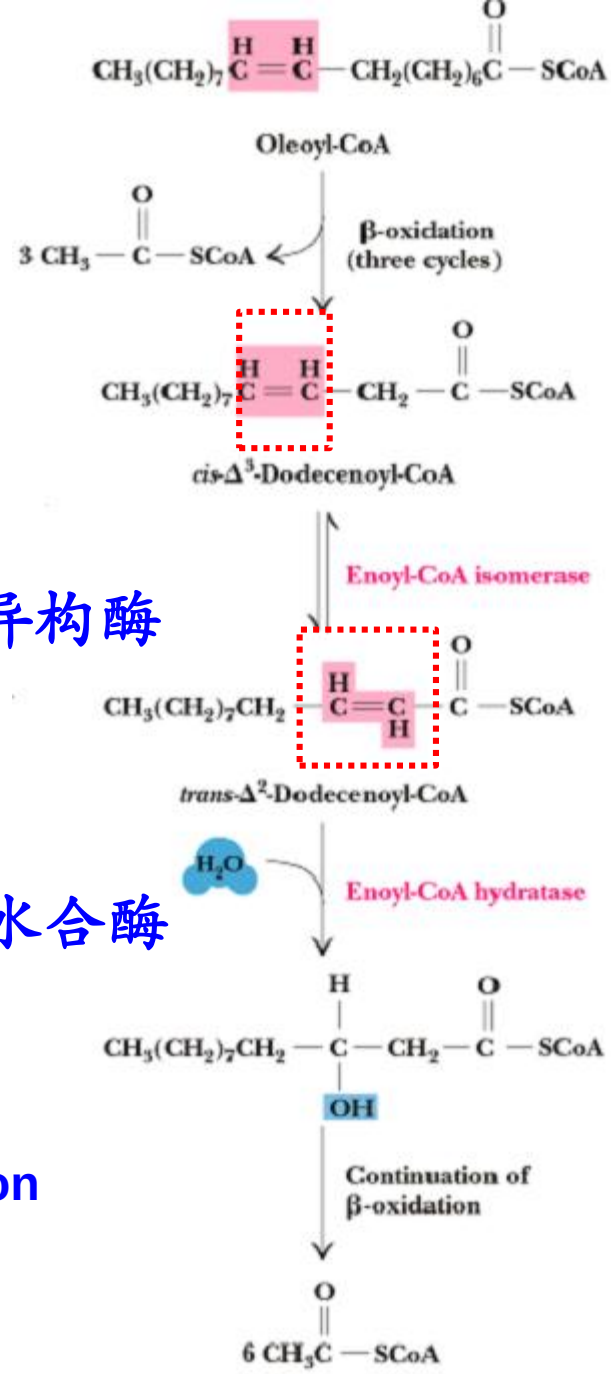
烯酰CoA异构酶

反式十烯酰CoA

烯酰CoA水合酶

羟酰CoA

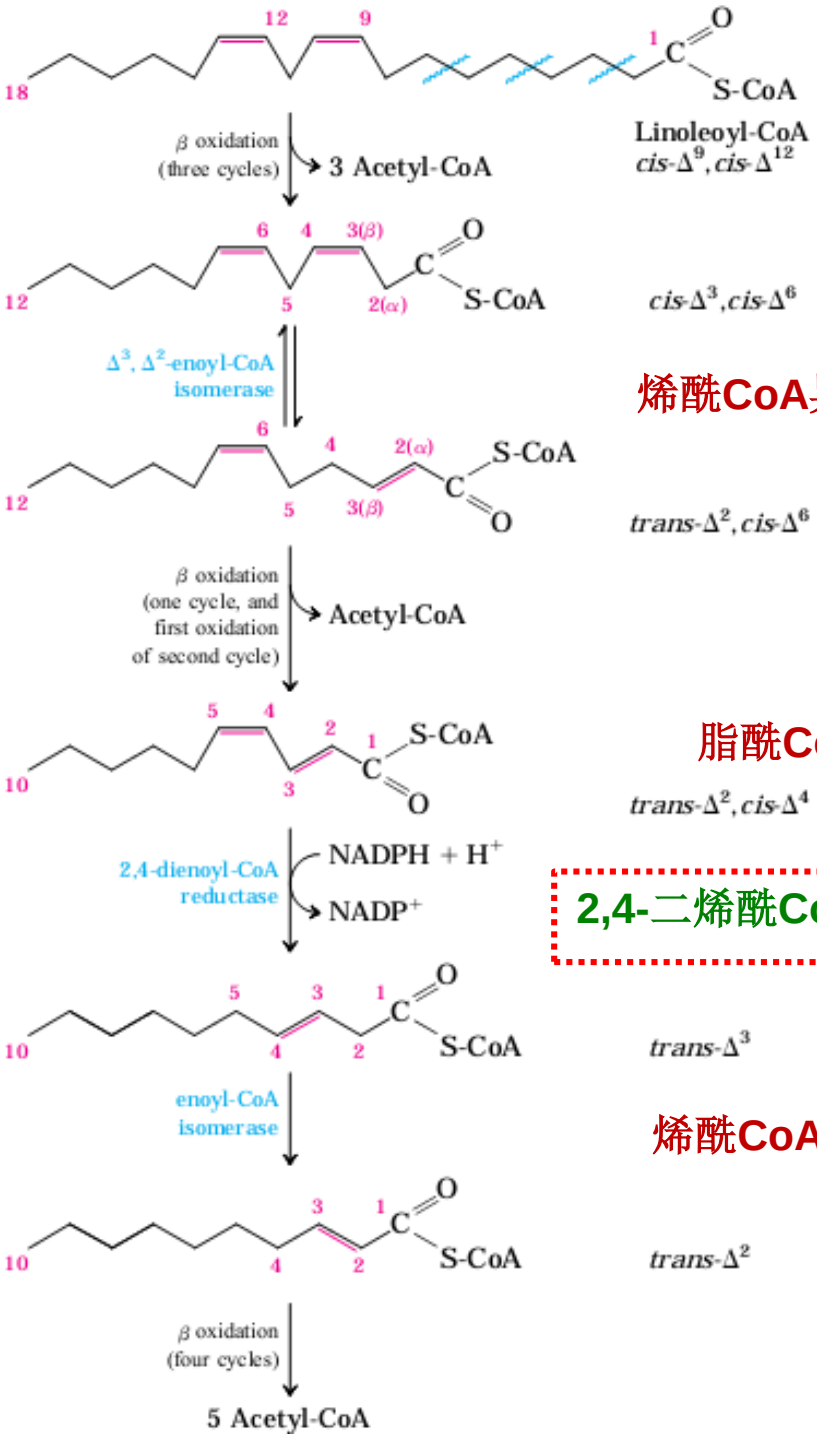
β-Oxidation



3.4 Polyunsaturated FAs

Linoleic (亚油酸）18：2 $\triangle^{9,12}$

- – 3 cycles of β-oxidation
  - – enoyl-CoA isomerase （异构酶）
  - – 1 more round of β-oxidation
  - – trans-Δ^2 , cis-Δ^4 structure is a problem!
- **2,4-Dienoyl-CoA reductase（2,4-二烯酰CoA还原酶）**



亚油酰CoA

↓ β-Oxidation（ 3 rounds）

cis-Δ^3 ,*cis*-Δ^6

烯酰CoA异构酶

↓

trans-Δ^2 , *cis*-Δ^6

↓ β-Oxidation

cis-Δ^4

脂酰CoA脱氢酶

↓

trans-Δ^2 , *cis*-Δ^4

2,4-二烯酰CoA还原酶

↓

trans-Δ^3

烯酰CoA异构酶

↓

trans-Δ^2

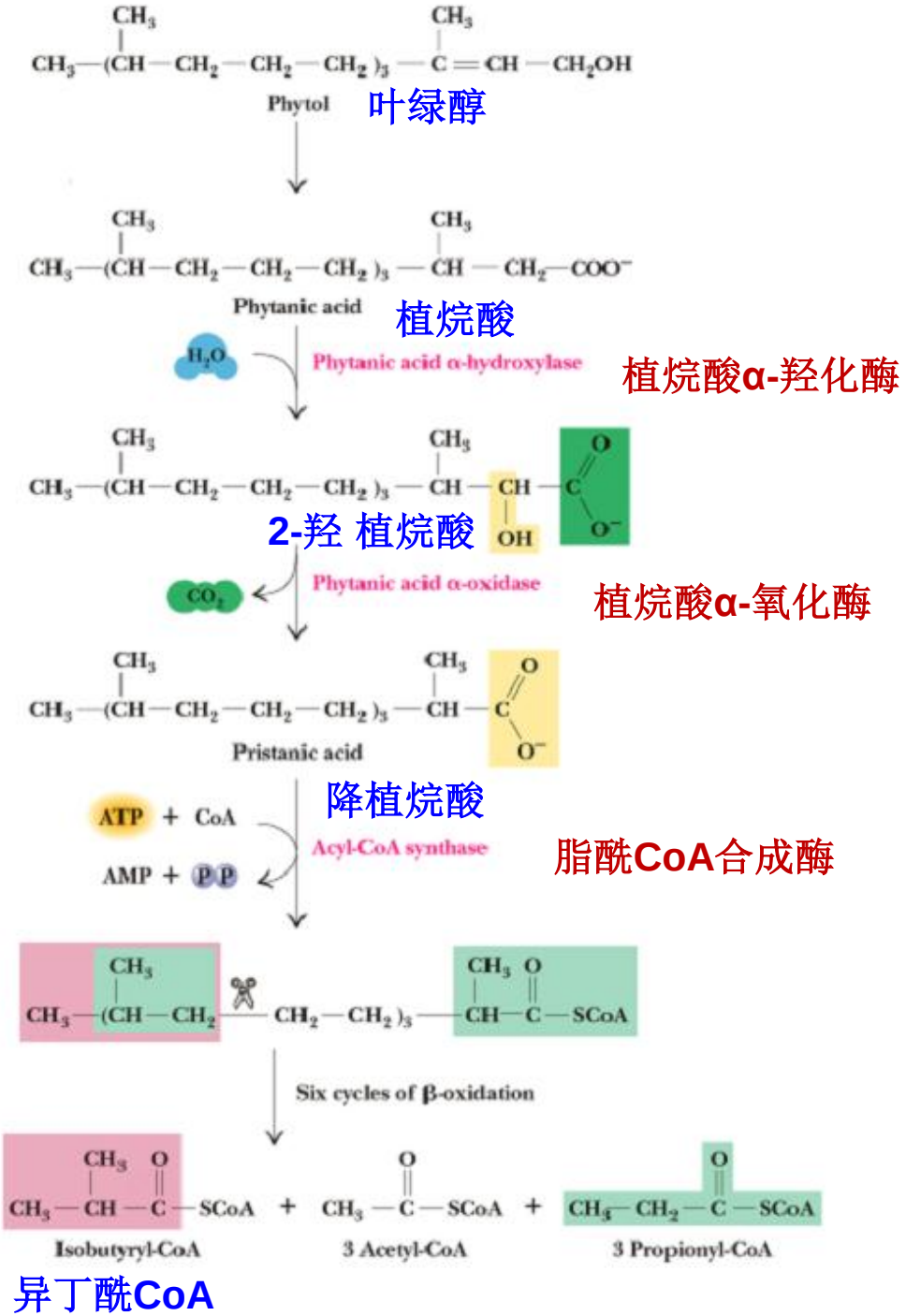
↓ β-Oxidation

3.5 Branched-Chain FAs

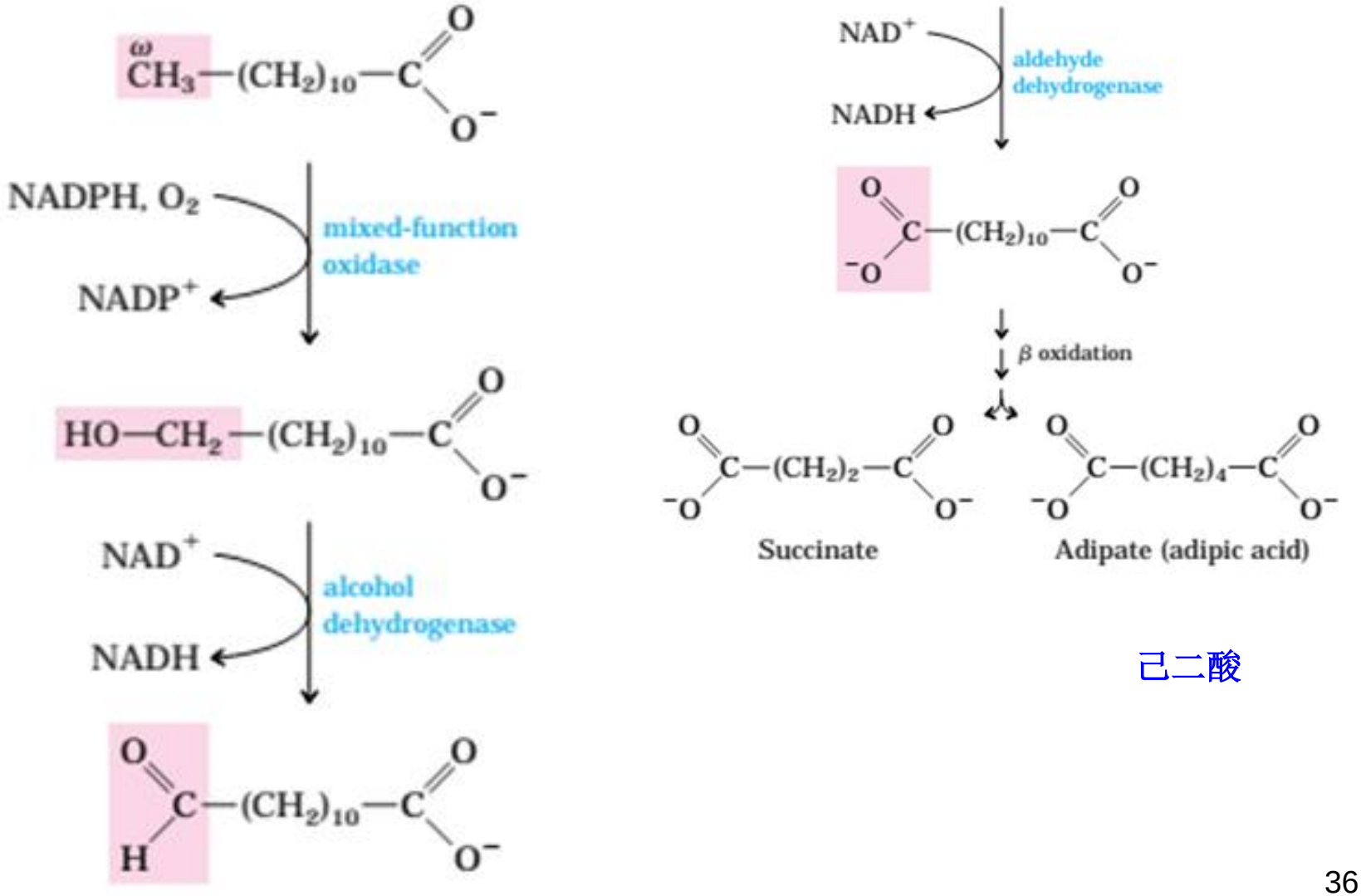
α-oxidation

- **Branched chain FAs with alkyl(烷基)** are not good substrates for β-oxidation
- **α-oxidation** is an alternative
- Ruminants(反刍动物) oxidizes phytol（叶绿醇）→ phytanic acid (植烷酸)

α-oxidation


Phytol
叶绿醇
Phytanic acid
植烷酸
Phytanic acid α-hydroxylase
植烷酸α-羟化酶
2-羟 植烷酸
Phytanic acid α-oxidase
植烷酸α-氧化酶
Pristanic acid
降植烷酸
ATP + CoA
AMP + PP
Acyl-CoA synthase
脂酰CoA合成酶
Six cycles of β-oxidation
Isobutyryl-CoA
3 Acetyl-CoA
3 Propionyl-CoA
异丁酰CoA

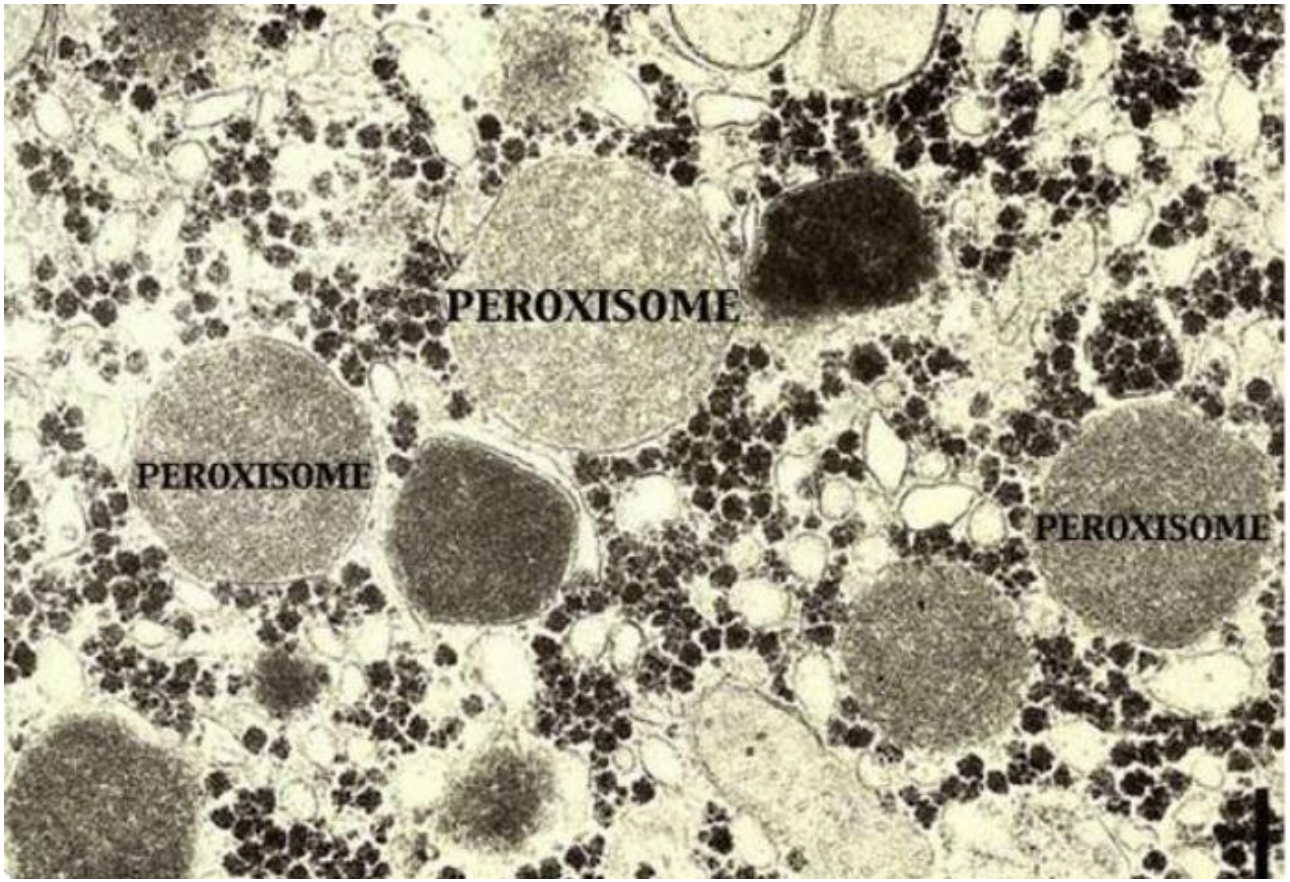
ω-oxidation in the ER（<12 C）



己二酸

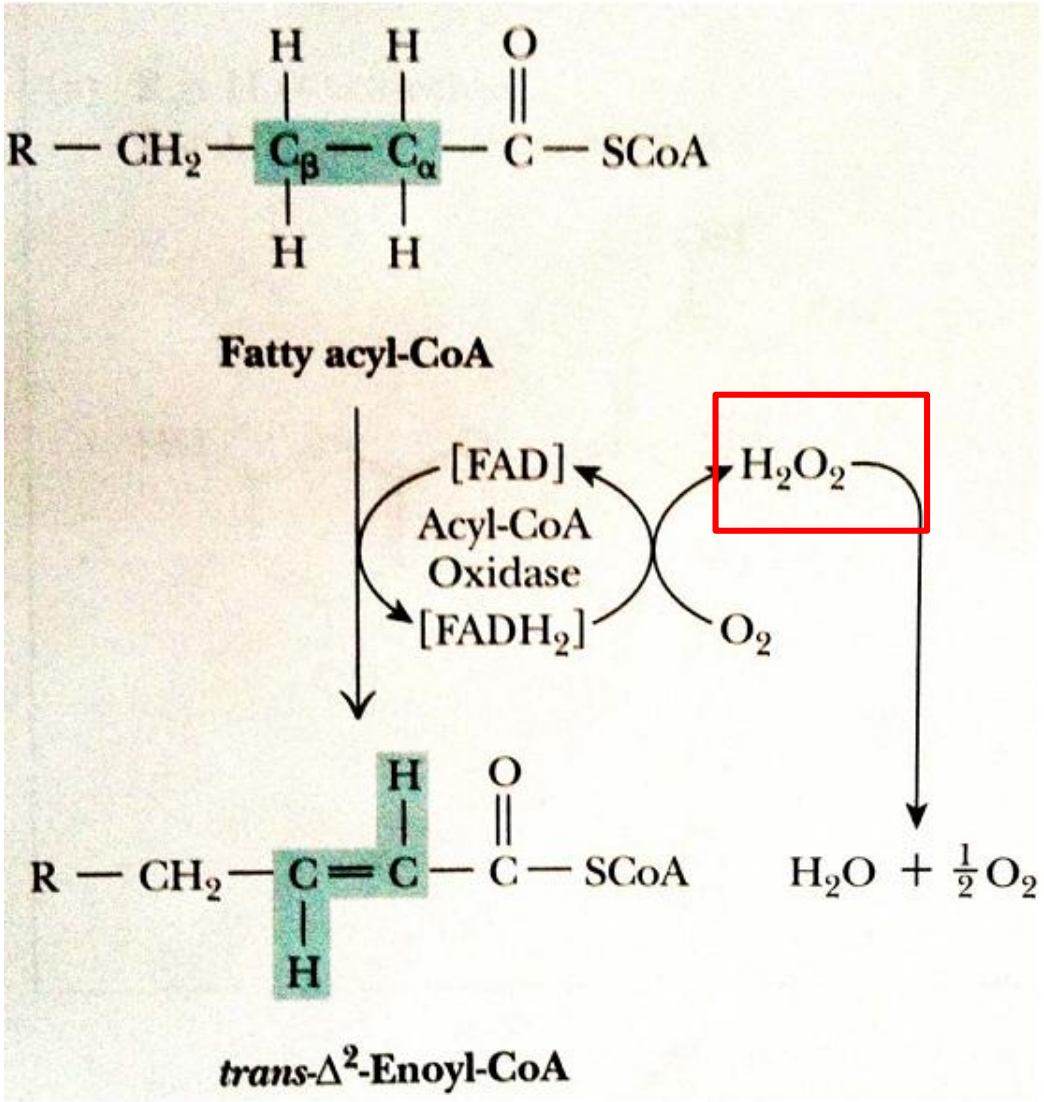
3.6 Peroxisomal β-Oxidation

Peroxisomes - organelles that carry out flavin-dependent oxidations, regenerating oxidized flavins by reaction with O_2 to produce H_2O_2

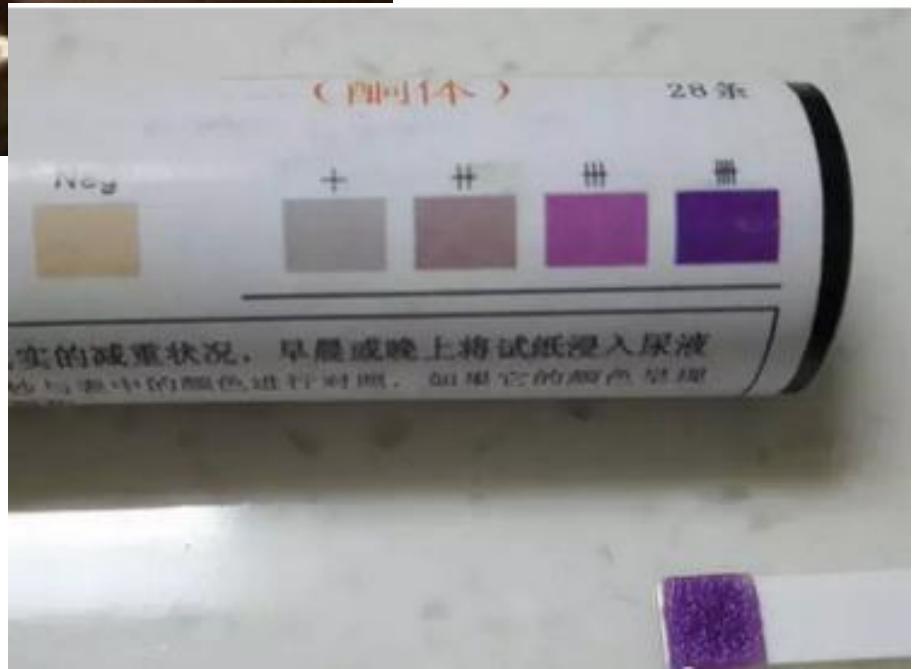


1954 Rhodin

- Similar to mitochondrial β-oxidation, but initial double bond formation is by **acyl-CoA oxidase in peroxisomes**



有没有燃脂呢？



- 乙酰乙酸、丙酮与亚硝基铁氰化钠反应　生成紫红色的复合物。

4. Ketone Bodies

A special source of fuel and energy for certain tissues

◆ **acetone（丙酮）, acetoacetate（乙酰乙酸）, and D-β-hydroxybutyrate（β-羟丁酸）**

◆ **synthesized primarily in liver mitochondria**

◆ Major energy for brain during starvation

◆ Acetoacetate and β-hydroxybutyrate are normal substrates for kidney cortex and heart muscle

◆ **Transport** without serum albumin and other fatty acid-binding proteins!

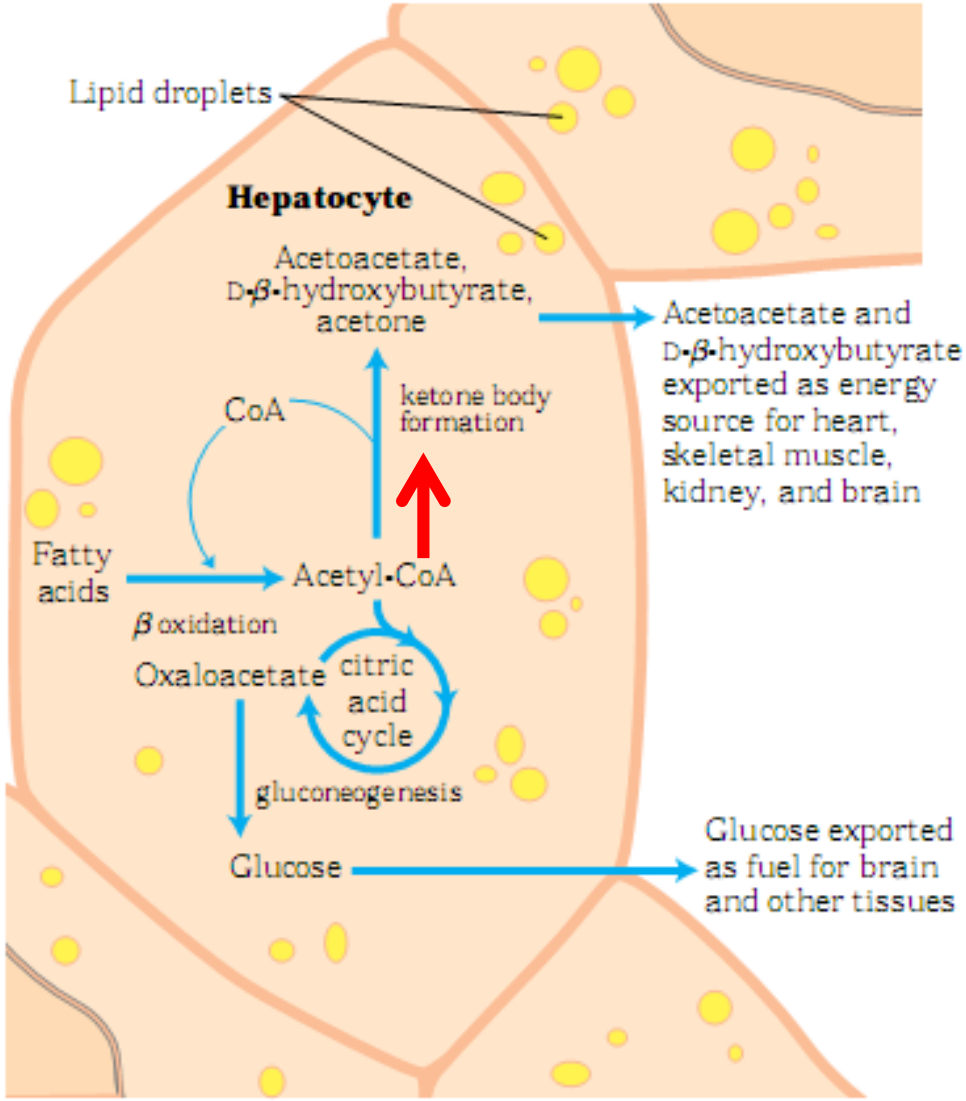
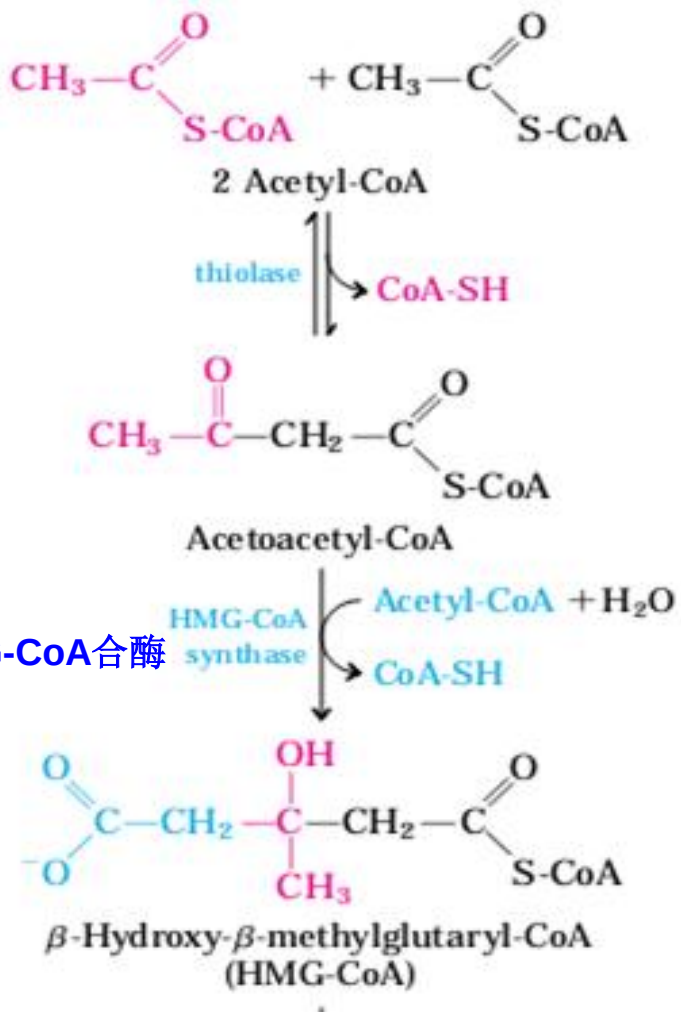
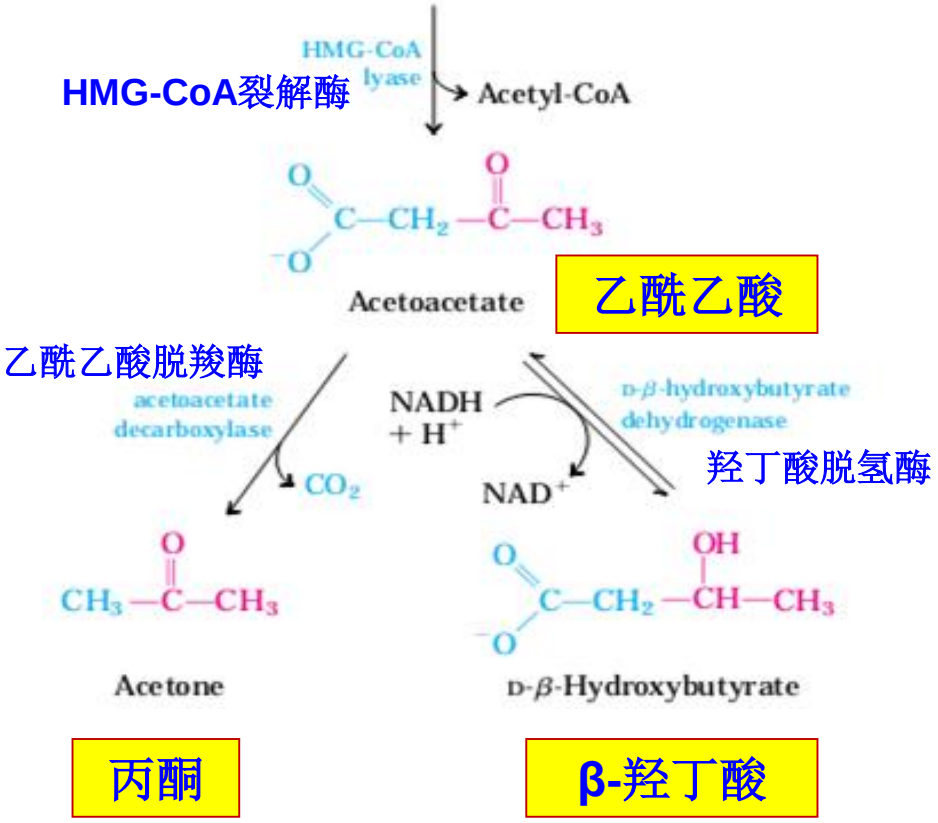


FIGURE 17–20 **Ketone body formation and export from the liver.** Conditions that promote gluconeogenesis (untreated diabetes, severely reduced food intake) slow the citric acid cycle (by drawing off oxaloacetate) and enhance the conversion of acetyl-CoA to acetoacetate. The released coenzyme A allows continued β oxidation of fatty acids.



HMG-CoA合酶



HMG-CoA裂解酶

乙酰乙酸

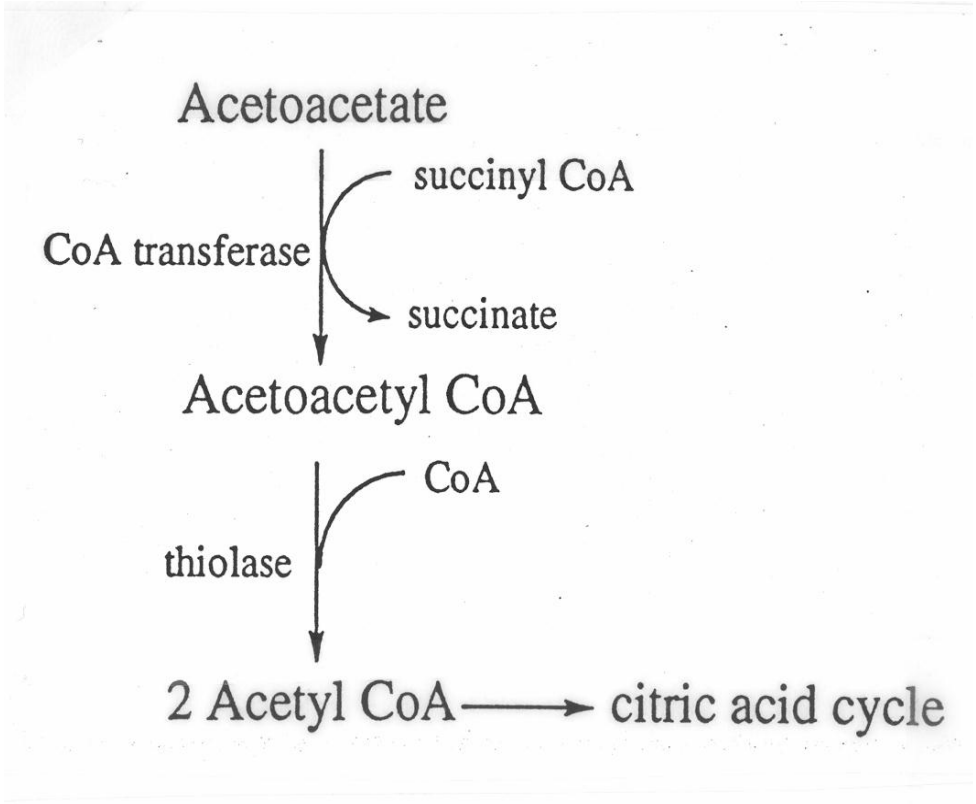
乙酰乙酸脱羧酶

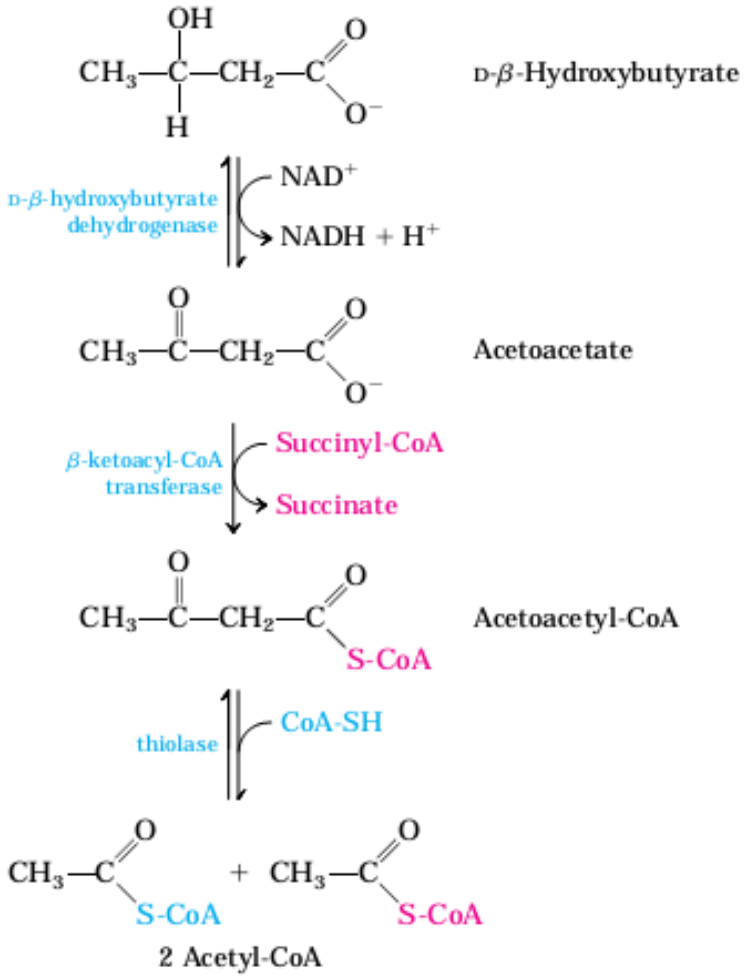
羟丁酸脱氢酶

丙酮

β-羟丁酸

Utilization of Ketone Bodies by the Peripheral Tissues





The liver lacks CoA transferase.

A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice

Ingredient (g/kg diet)	Control	Low-carbohydrate	Ketogenic
Protein, of which	203	316.7	183.7
Casein	*200*	*312*	*181*
L-cystein	*3*	*4.7*	-
D-methionine	-	-	*2.7*
Carbohydrates, of which	630	112	-
Corn starch	*398*	-	-
Maltodextrin	*132*	-	-
Sucrose	*100*	*112*	-
Fat, of which	70	423	631
Soybean oil	*70*	*70*	*70*
Lard	-	*353*	*561*
Choline bitartrate	2.5	2.5	‡
Cellulose (73.5 mg/day)	50	71	85
Tert-butylhydroquinone	0.014	0.085	0.126
Mineral mix	35	60	60
Vitamin mix	10	15	13
Other minerals	-	-	27.5

‡, included in the vitamin mix

	蛋白	碳水	脂肪
正常（control）	18%	65%	17%
LCD（低碳水）	20%	10%	70%
KD（生酮饮食）	10%	1%	89%

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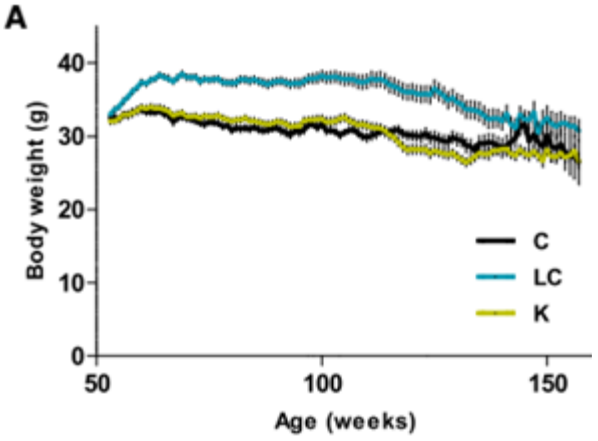
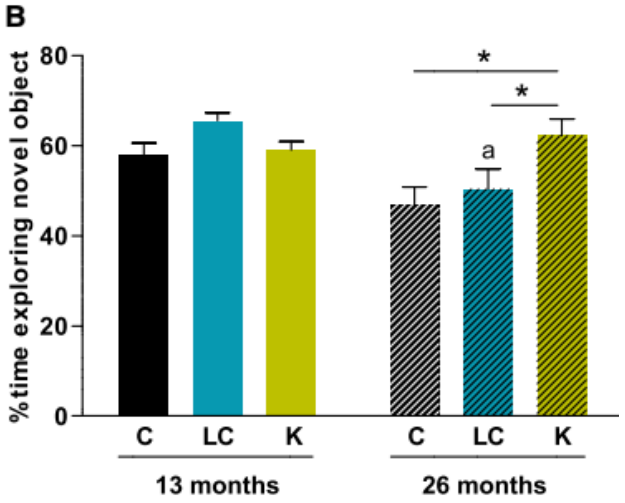
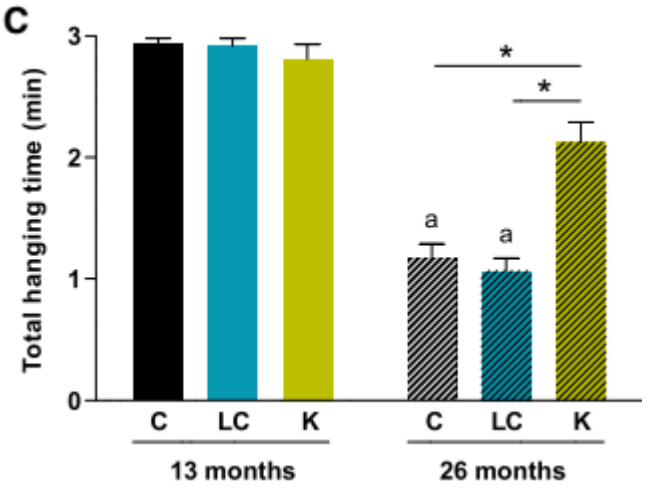
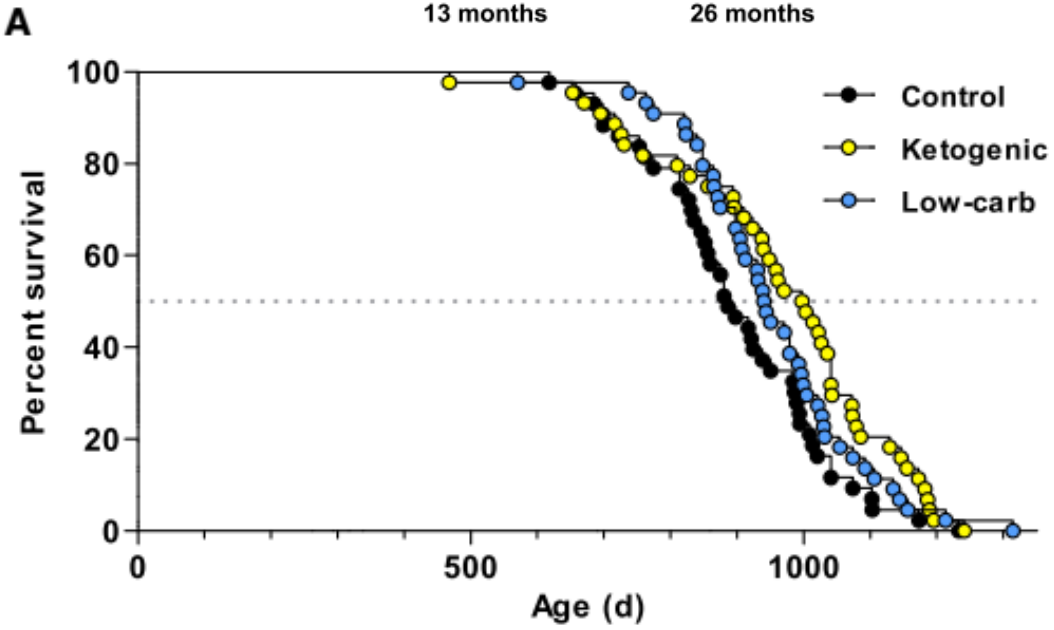

A
Body weight (g)
40
30
20
10
0
50
100
150
Age (weeks)
C
LC
K


B
% time exploring novel object
80
60
40
20
0
C
LC
K
C
LC
K
13 months
26 months
*
*
a

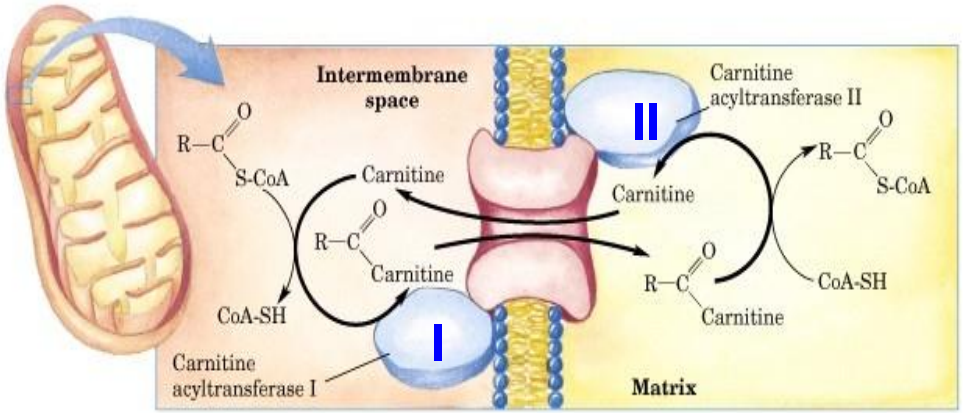

C
Total hanging time (min)
3
2
1
0
C
LC
K
C
LC
K
13 months
26 months
*
*
a
a

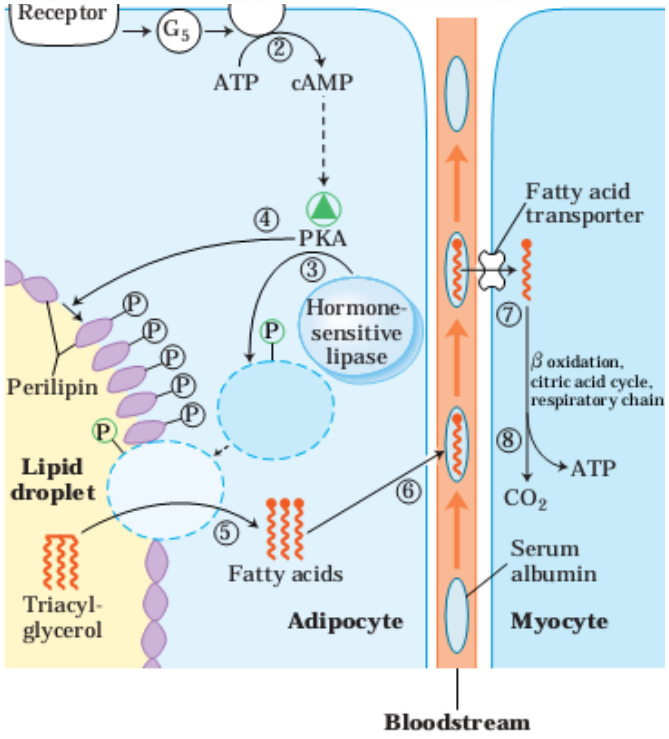

A
Percent survival
100
80
60
40
20
0
0
500
1000
Age (d)
Control
Ketogenic
Low-carb

5. FA metabolism regulation and control

- FA → Mit
- In heart- **inhibit by acety**

  CoA and NADH
- Hormone
- Body metabolism need
- Long term diet change





SUMMARY

■ **four reactions remove acetyl-CoA from fatty acyl–CoA:**

- **dehydrogenation** (FAD-linked acyl-CoA dehydrogenases)
- **hydration** (enoyl-CoA hydratase)
- **dehydrogenation** (NAD-β-hydroxyacyl-CoA dehydrogenase)
- **thiolase**

■ **In the second stage**

- **acetyl-CoA → TCA →oxidative phosphorylation**.

■ **Malonyl-CoA(丙二酰辅酶A) inhibits carnitine acyltransferase I.**

■ **Genetic defects in the medium-chain acyl-CoA dehydrogenase （MCAD） result in serious human disease.**

Questions

- What are ketone bodies? What role do ketone bodies play in metabolism?
- 什么是β-氧化？ 一分子棕榈酸彻底氧化分解可产生多少**ATP**？
- 不饱和脂肪酸和奇数碳原子脂肪酸的氧化和一般脂肪酸的β-氧化有何区别？