(a) Gerbil

(b) Ruby-throated hummingbird

(c) Golden plover

(d) Orca

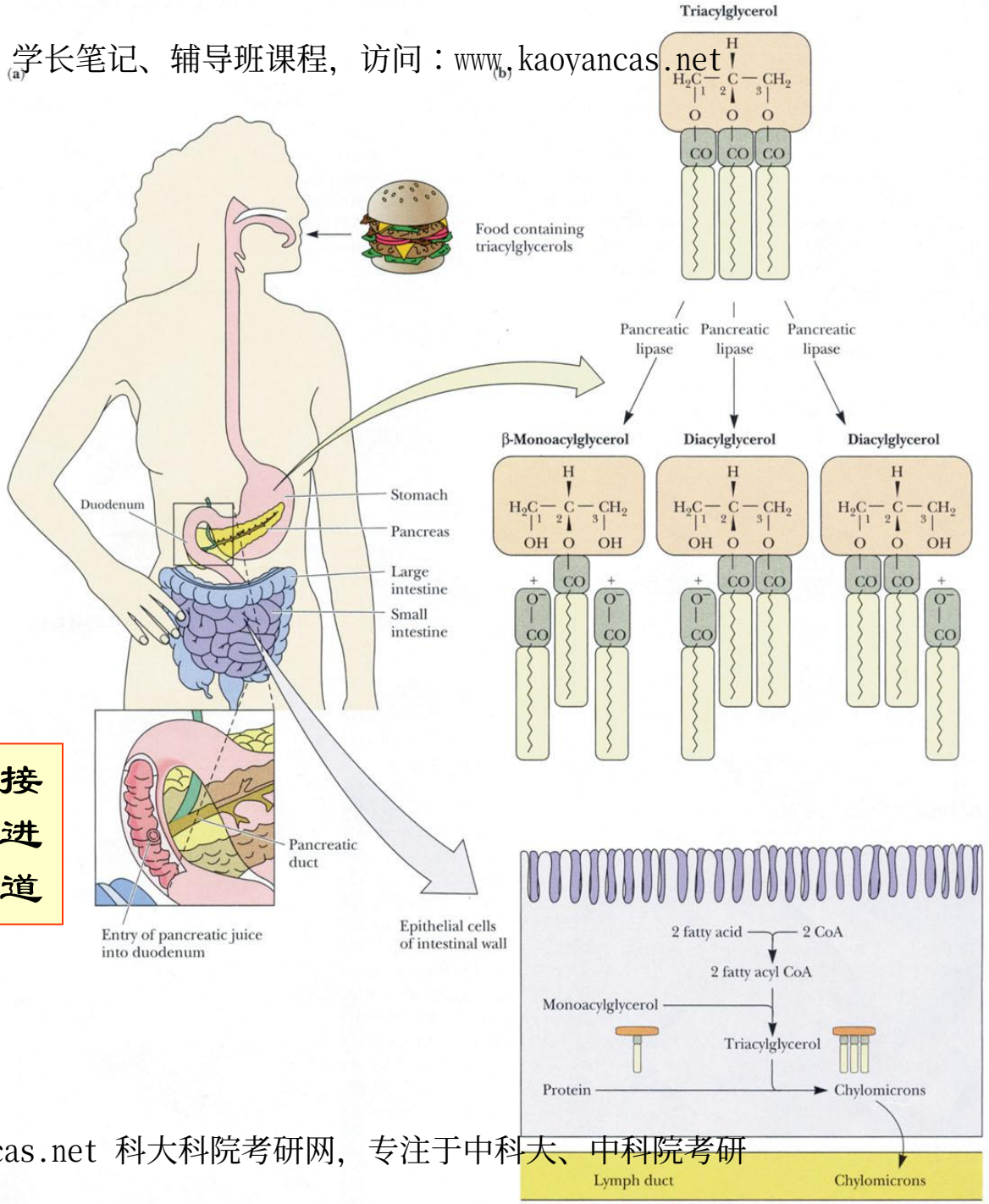
(e) Camels

第28章 脂肪酸的分解代谢

一、脂质的消化、吸收和传送

甘油三酯被胰脏和十二指肠分泌的酯酶分解

胰脏和十二指肠接头处胰脏分泌液进入十二指肠的通道

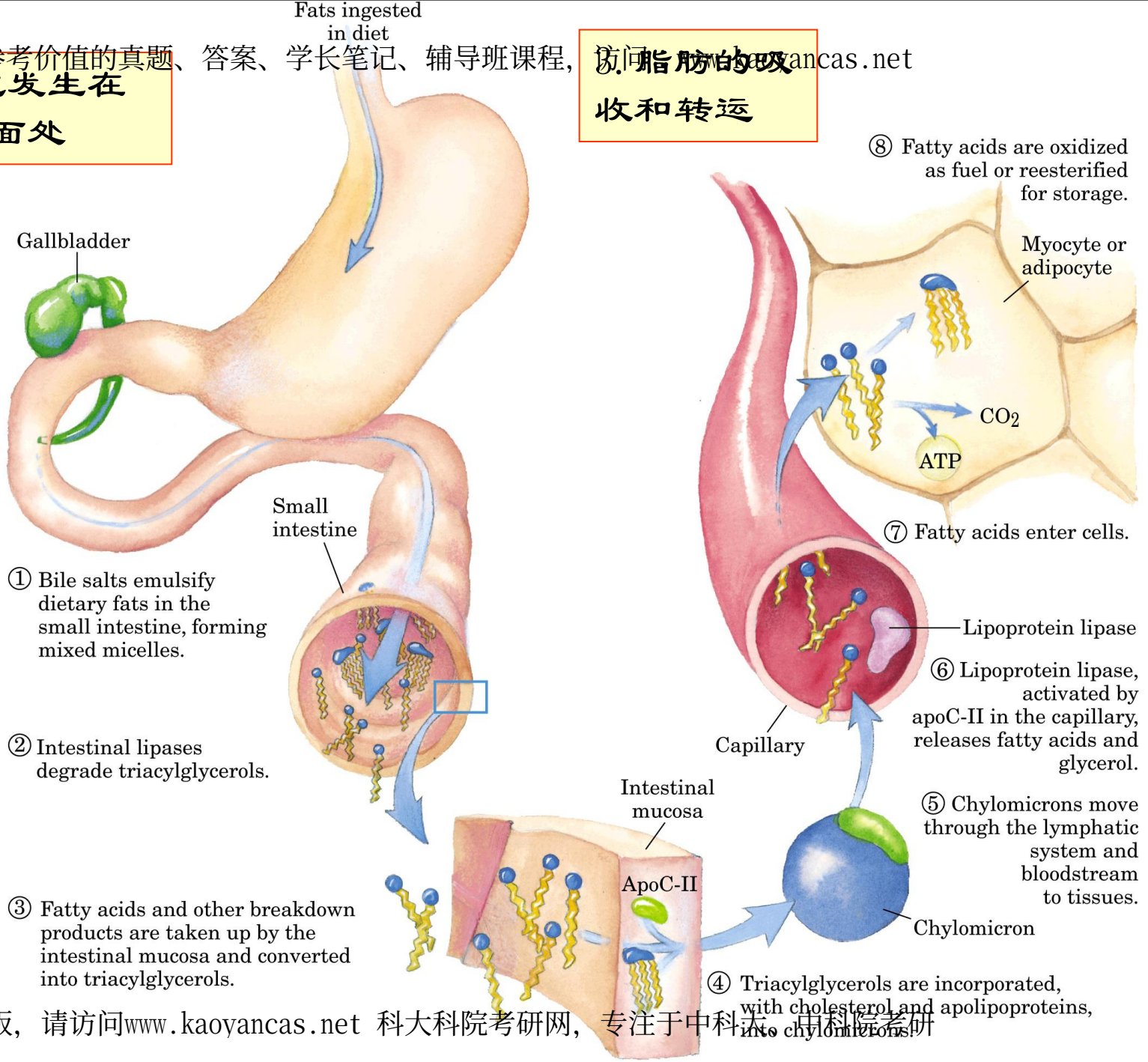


1. 脂肪的消化发生在脂质-水的界面处

2. 胆汁盐促进脂类在小肠中被吸收

在小肠脂肪酸与胆酸盐结合形成微囊，将脂肪酸运输到小肠上皮细胞，在小肠上皮细胞再合成甘油三酯.

3. 脂肪的吸收和转运



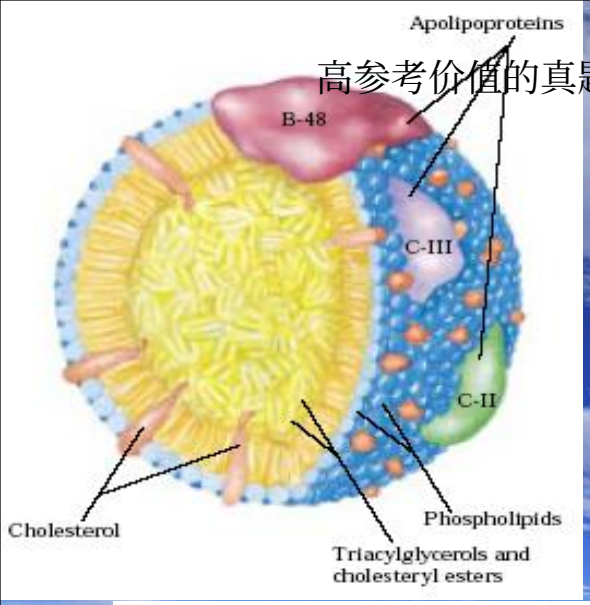
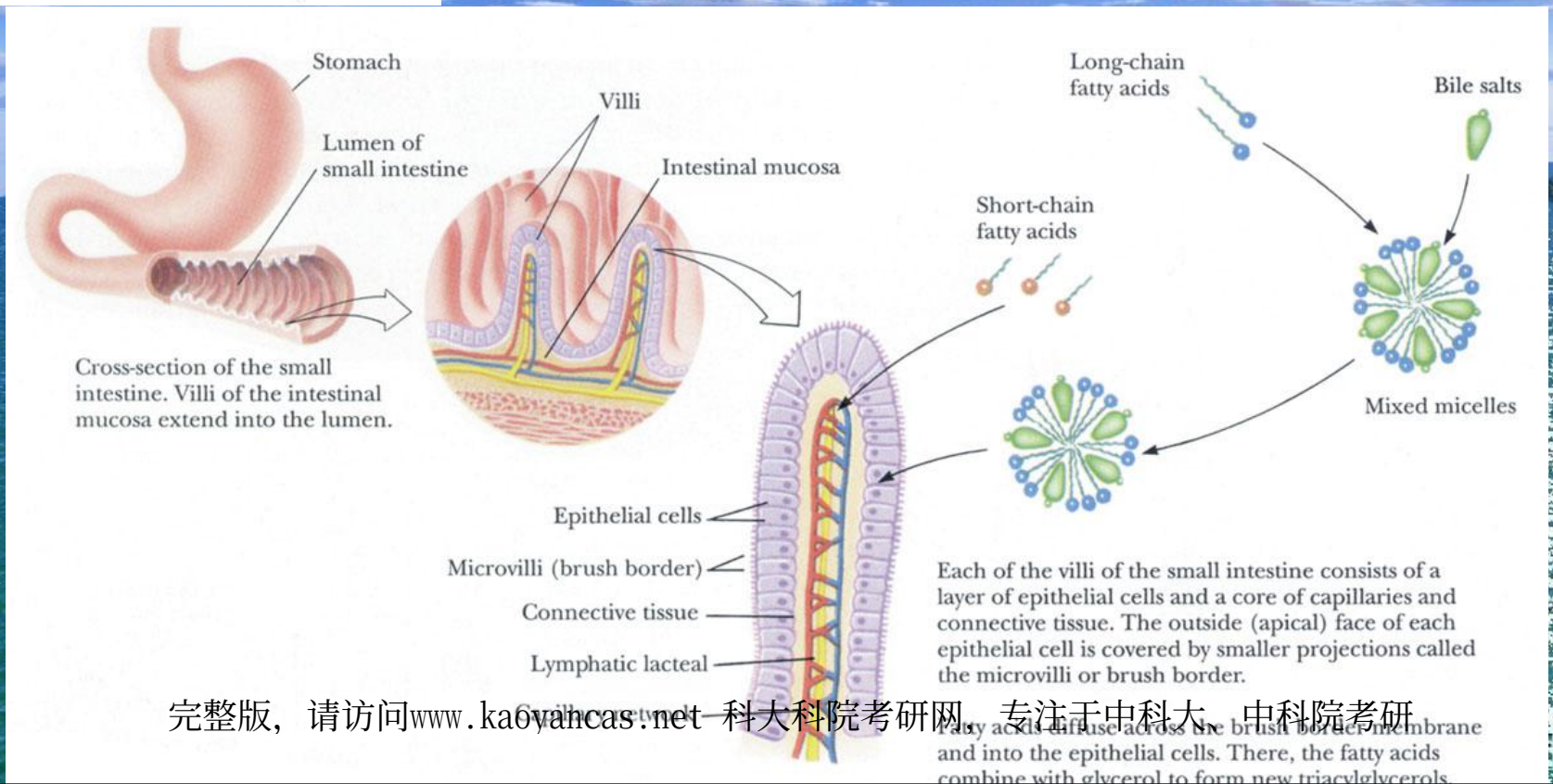
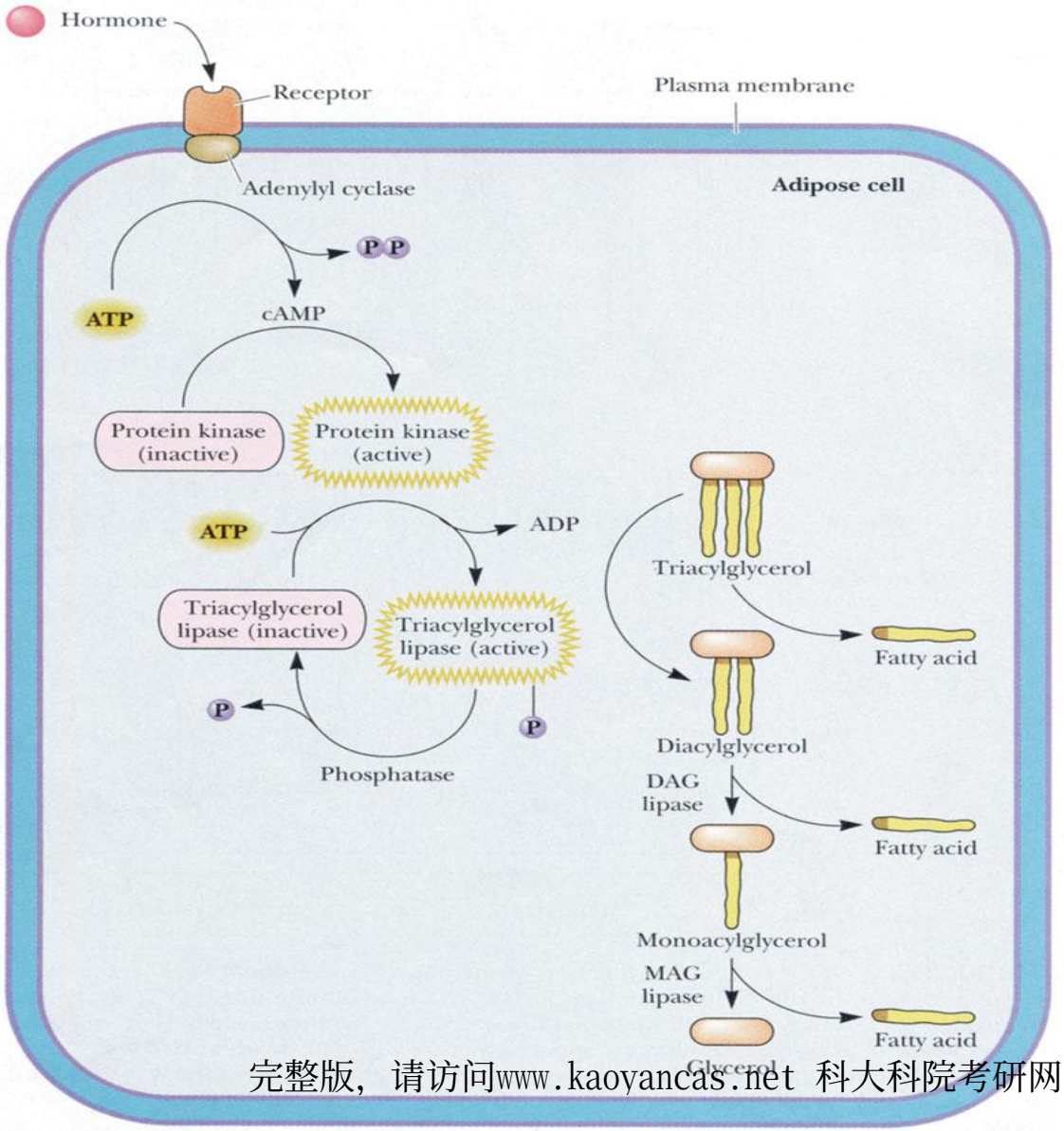
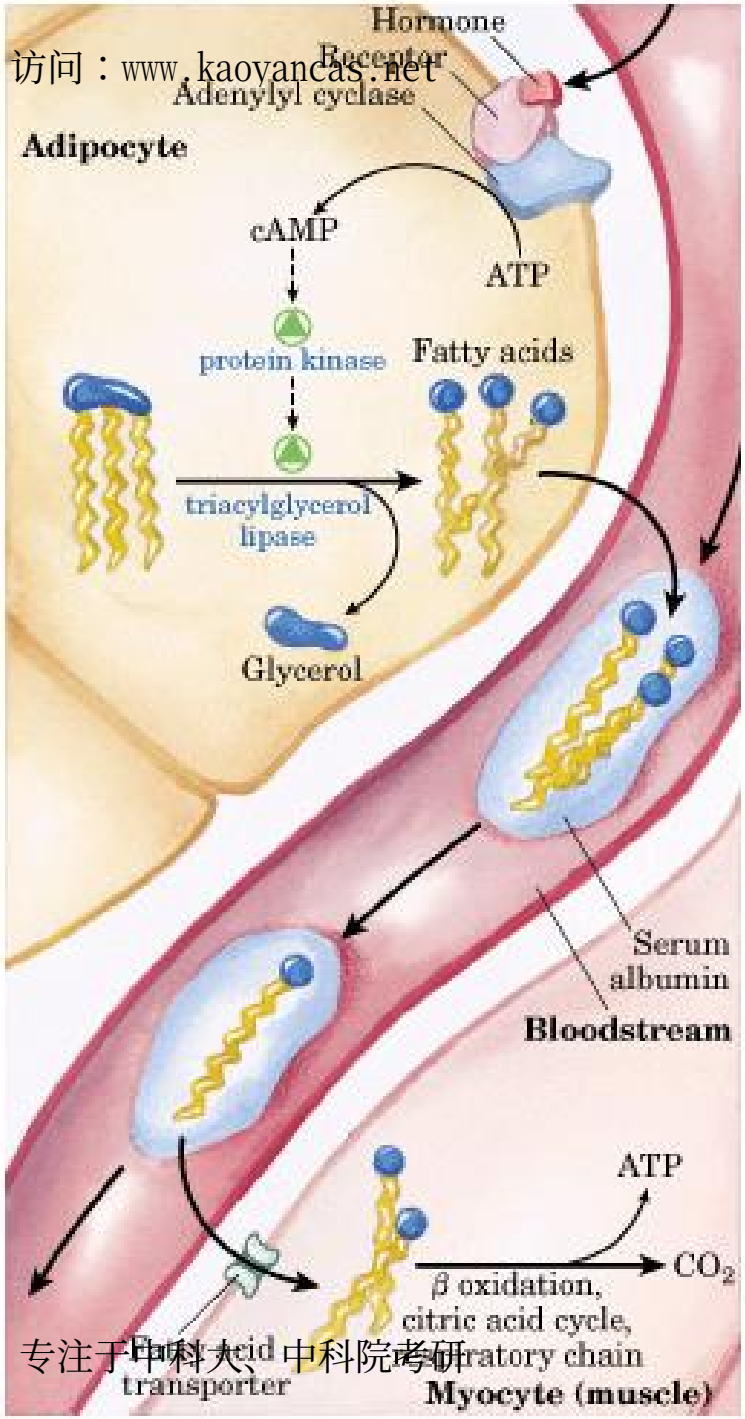


FIGURE 17–2 Molecular structure of a chylomicron. The surface is a layer of phospholipids, with head groups facing the aqueous phase. Triacylglycerols sequestered in the interior (yellow) make up more than 80% of the mass. Several apolipoproteins that protrude from the surface (B-48, C-III, C-II) act as signals in the uptake and metabolism of chylomicron contents. The diameter of chylomicrons ranges from about 100 to 500 nm.



4.脂肪组织释放脂肪酸受激素的调控



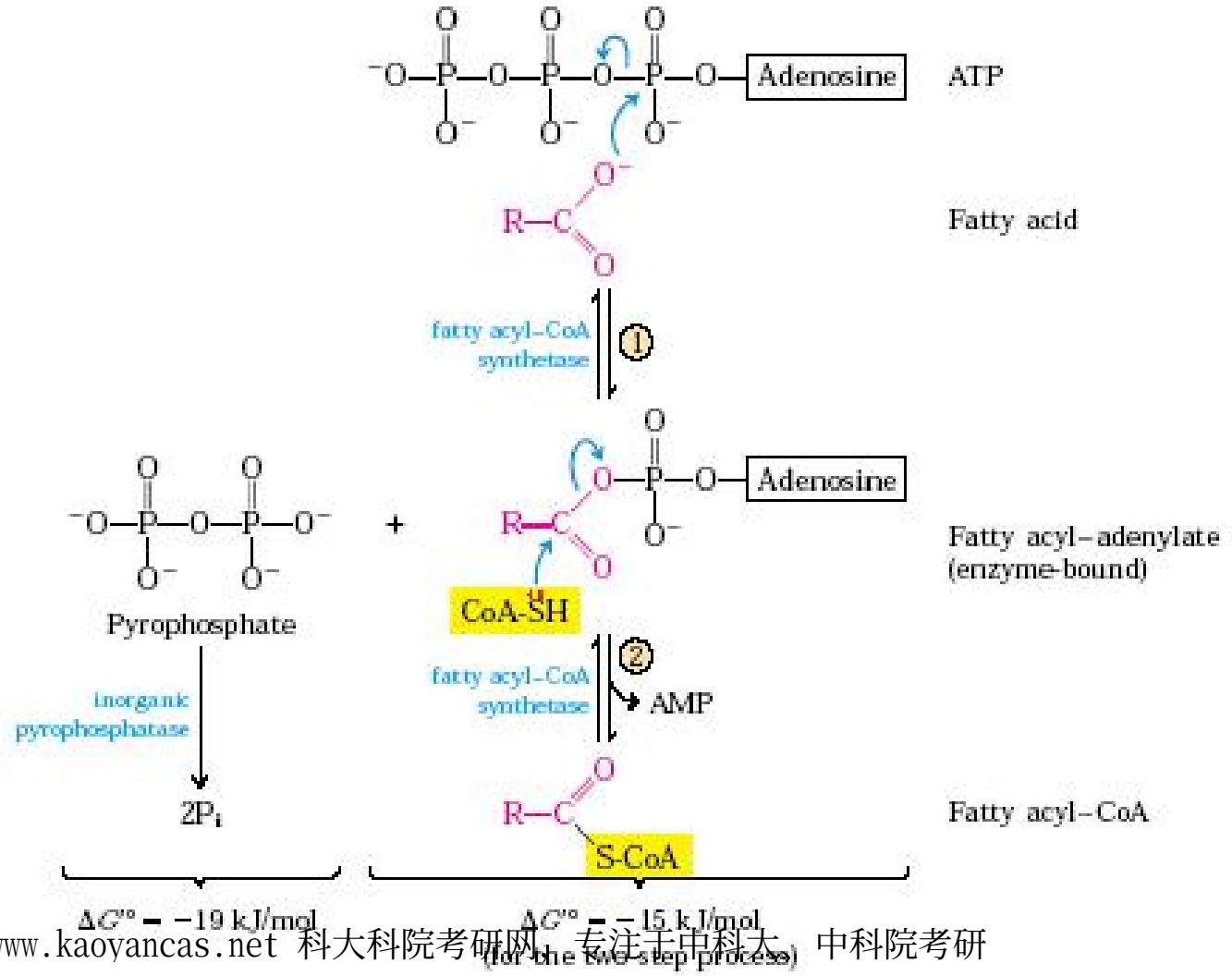


二、脂肪酸的氧化

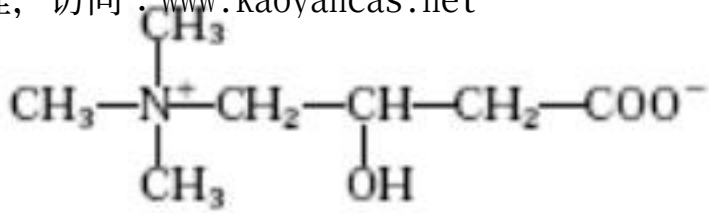
(一) 脂肪酸的活化

MECHANISM FIGURE 17–5

Conversion of a fatty acid to a fatty acyl–CoA. The conversion is catalyzed by fatty acyl–CoA synthetase and inorganic pyrophosphatase. Fatty acid activation by formation of the fatty acyl–CoA derivative occurs in two steps. In step ①, the carboxylate ion displaces the outer two (β and γ) phosphates of ATP to form a fatty acyl–adenylate, the mixed anhydride of a carboxylic acid and a phosphoric acid. The other product is PP_i, an excellent leaving group that is immediately hydrolyzed to two P_i, pulling the reaction in the forward direction. In step ②, the thiol group of coenzyme A carries out nucleophilic attack on the enzyme-bound mixed anhydride, displacing AMP and forming the thioester fatty acyl–CoA. The overall reaction is highly exergonic.



(二)脂肪酸转入线粒体



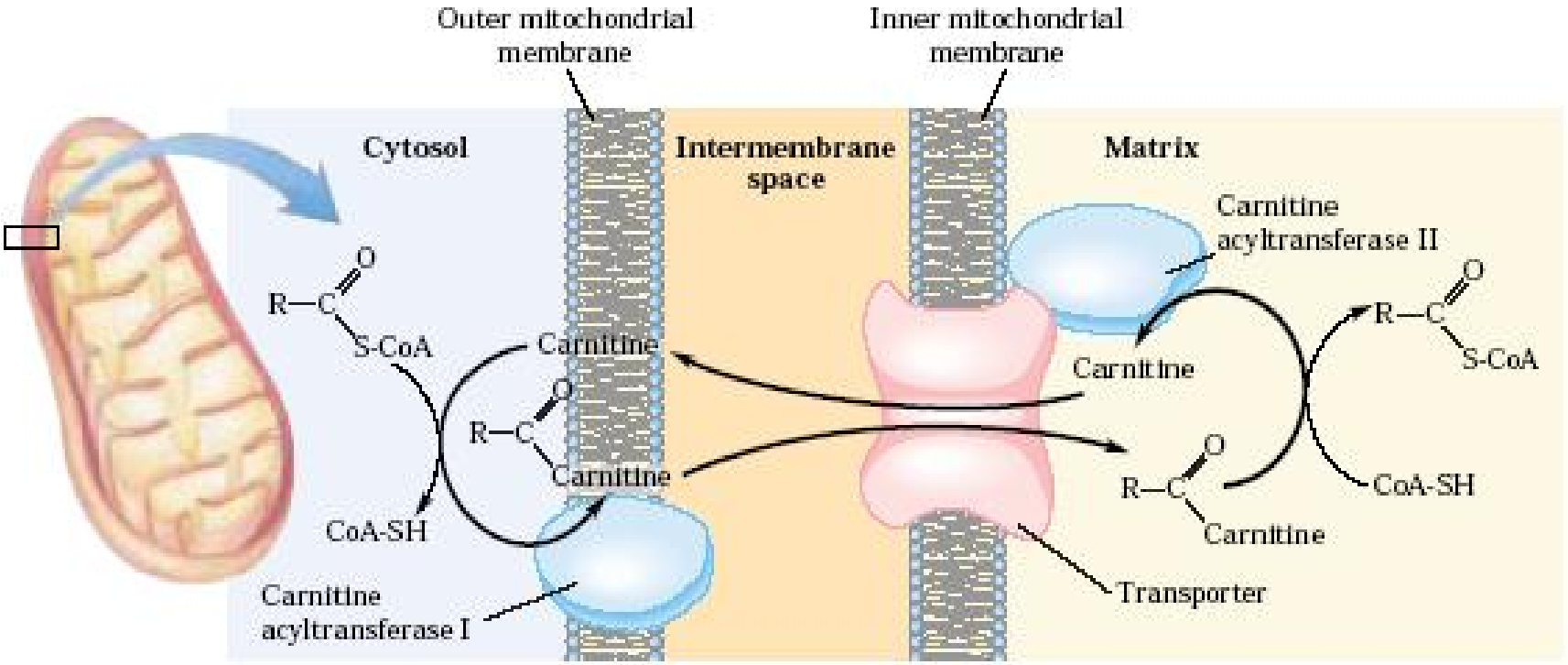
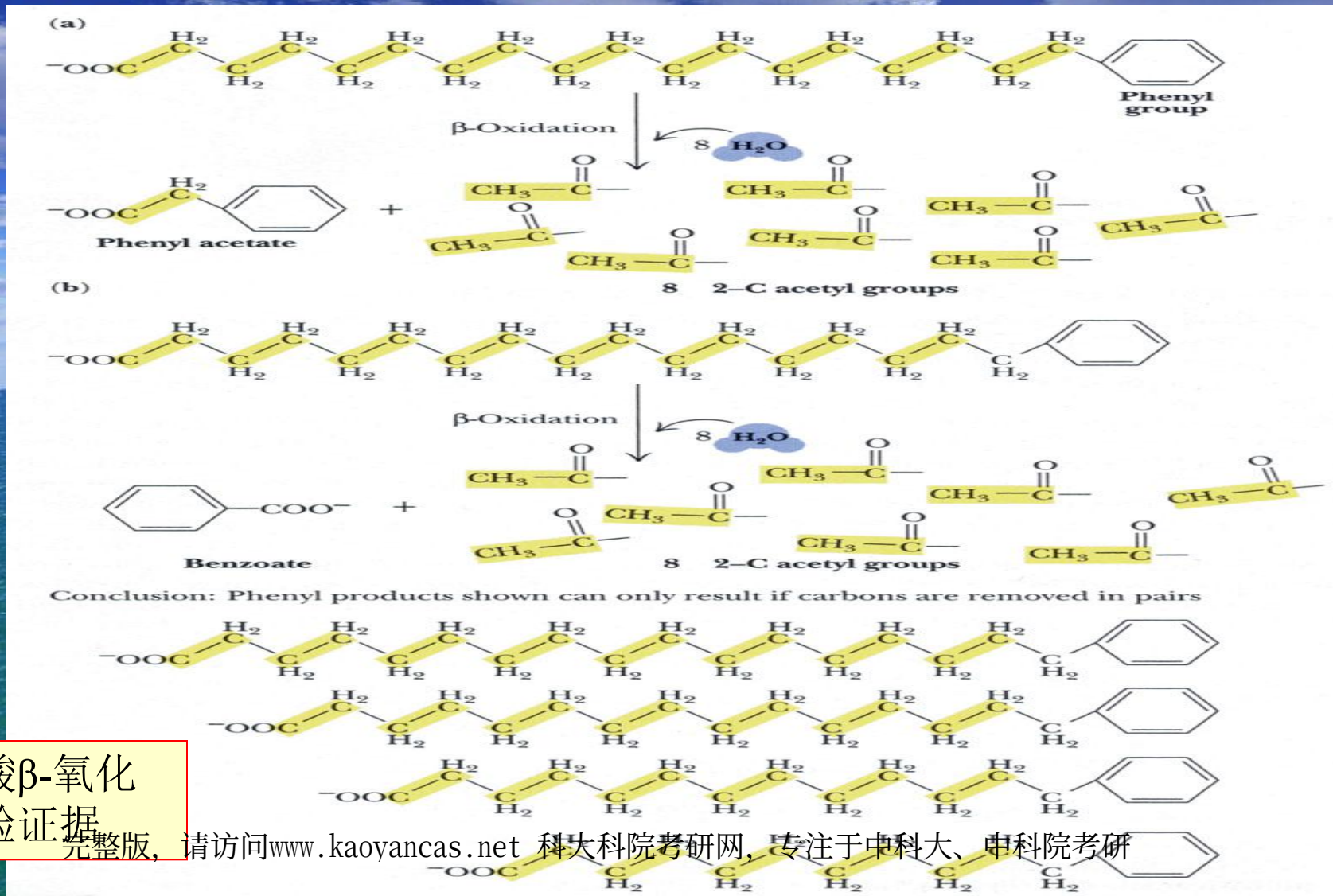


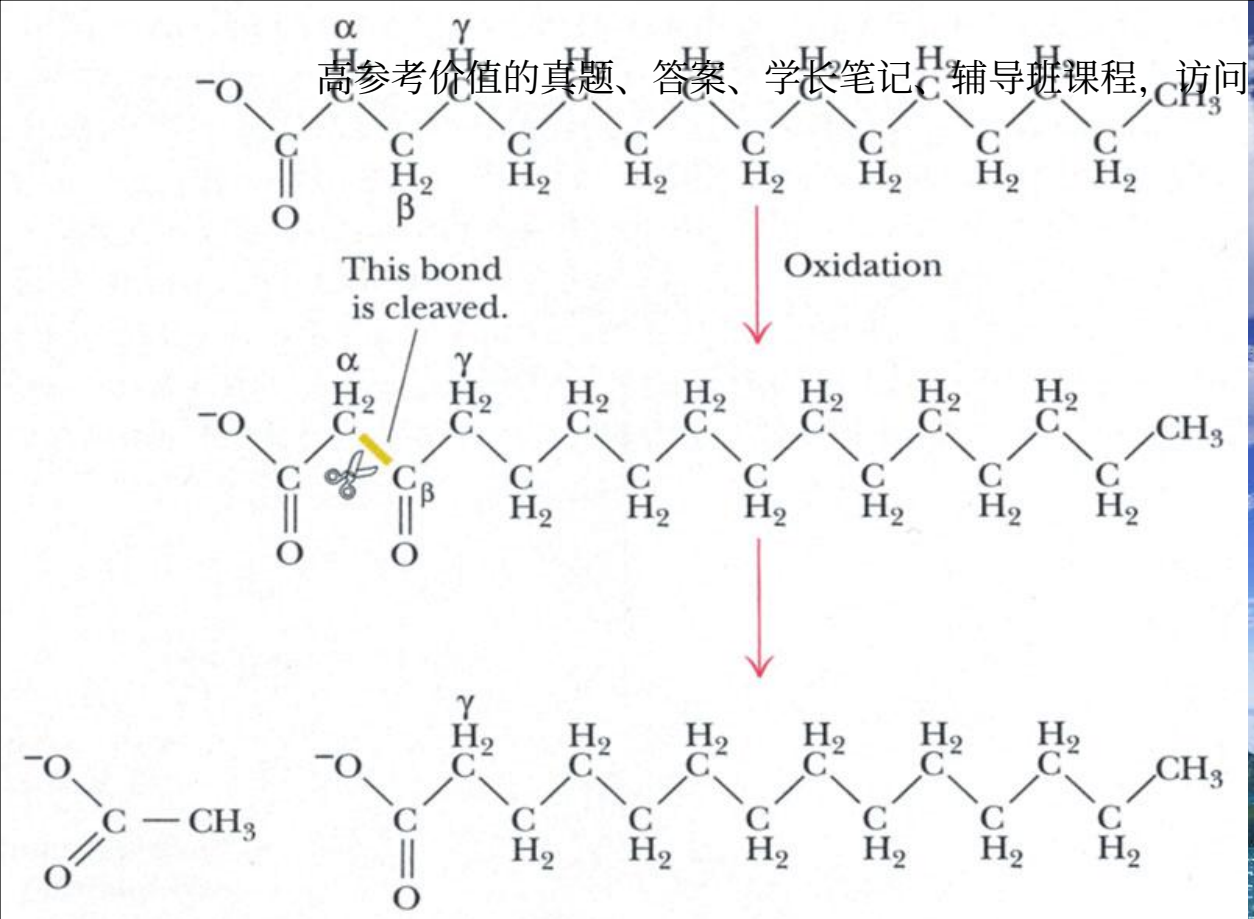
FIGURE 17–6 Fatty acid entry into mitochondria via the acyl-carnitine/carnitine transporter. After fatty acyl–carnitine is formed at the outer membrane or in the intermembrane space, it moves into the matrix by facilitated diffusion through the transporter in the inner membrane. In the matrix, the acyl group is transferred to mitochondrial coenzyme A, freeing carnitine to return to the intermembrane space through the same transporter. Acyltransferase I is inhibited by malonyl-CoA, the first intermediate in fatty acid synthesis (see Fig. 21–1). This inhibition prevents the simultaneous synthesis and degradation of fatty acids.

(三) β-氧化

Franz Knoop's labeling Experiments (1904): fatty acids are degraded by oxidation at the β carbon, i.e., β **oxidation**.



脂肪酸β-氧化的实验证据



Albert L. Lehninger
1917–1986

Enzymes of fatty acid oxidation in animal cells were localized in the mitochondria matrix. Revealed by Eugene Kennedy and Albert Lehninger in 1948.

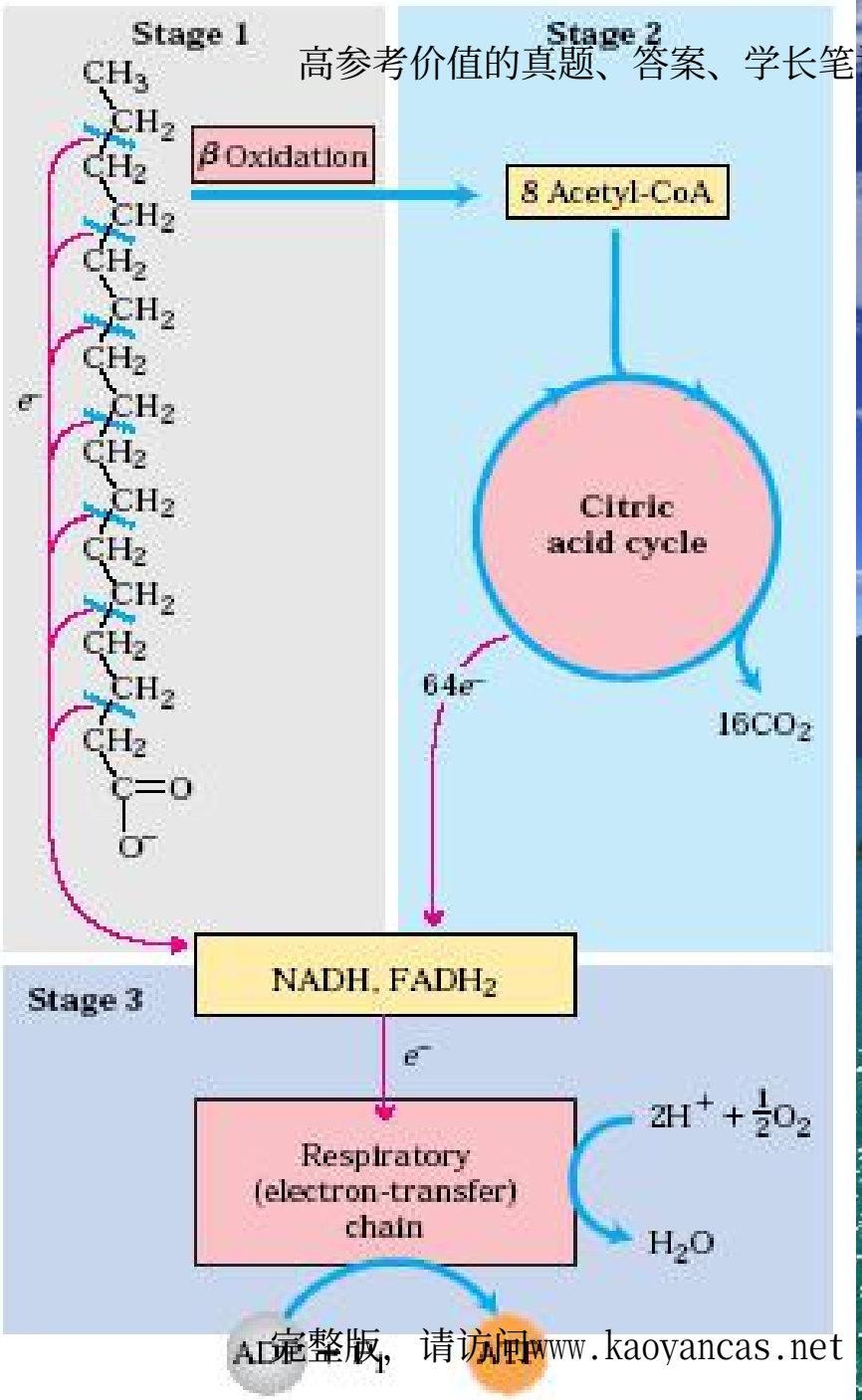
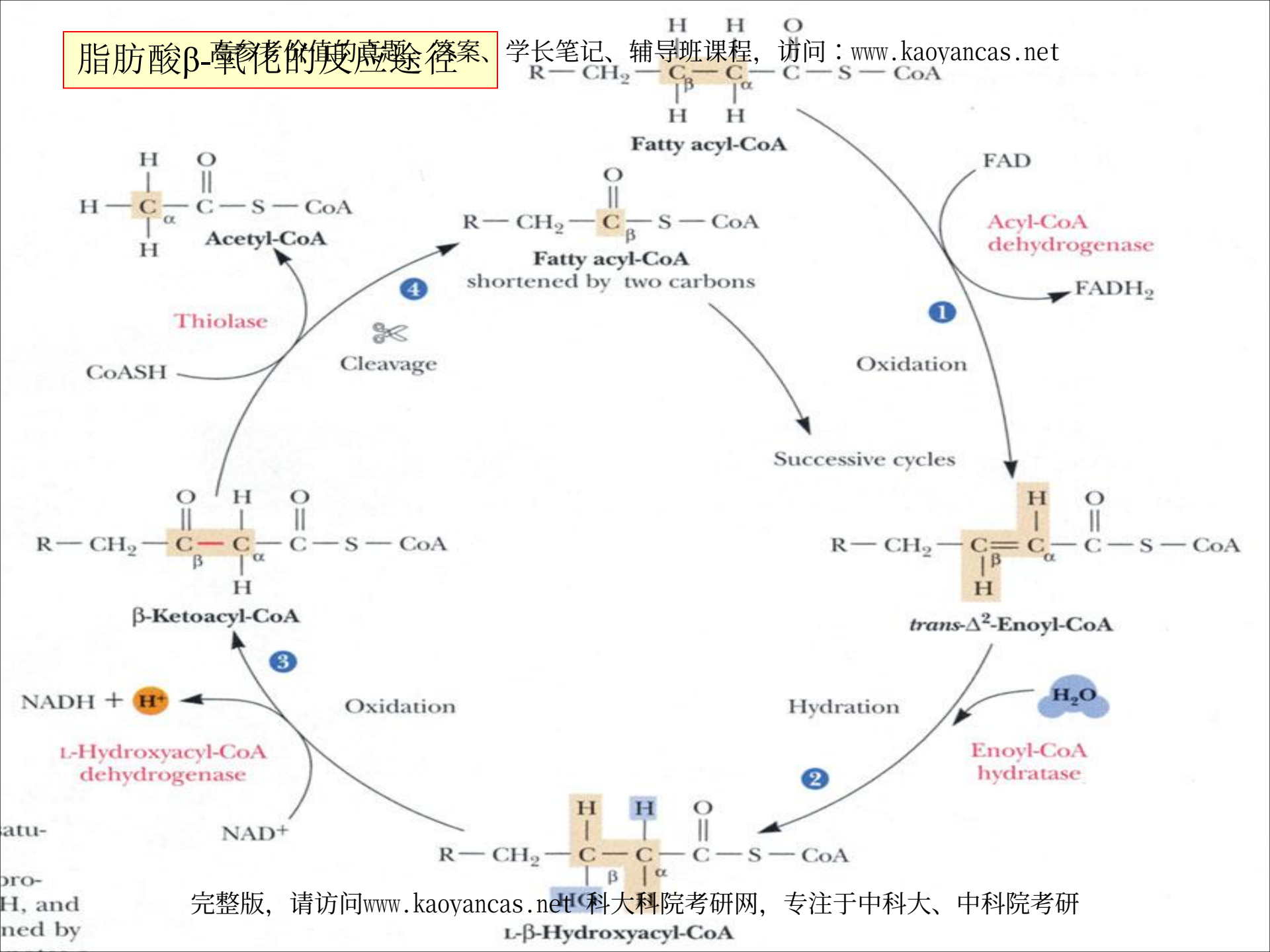
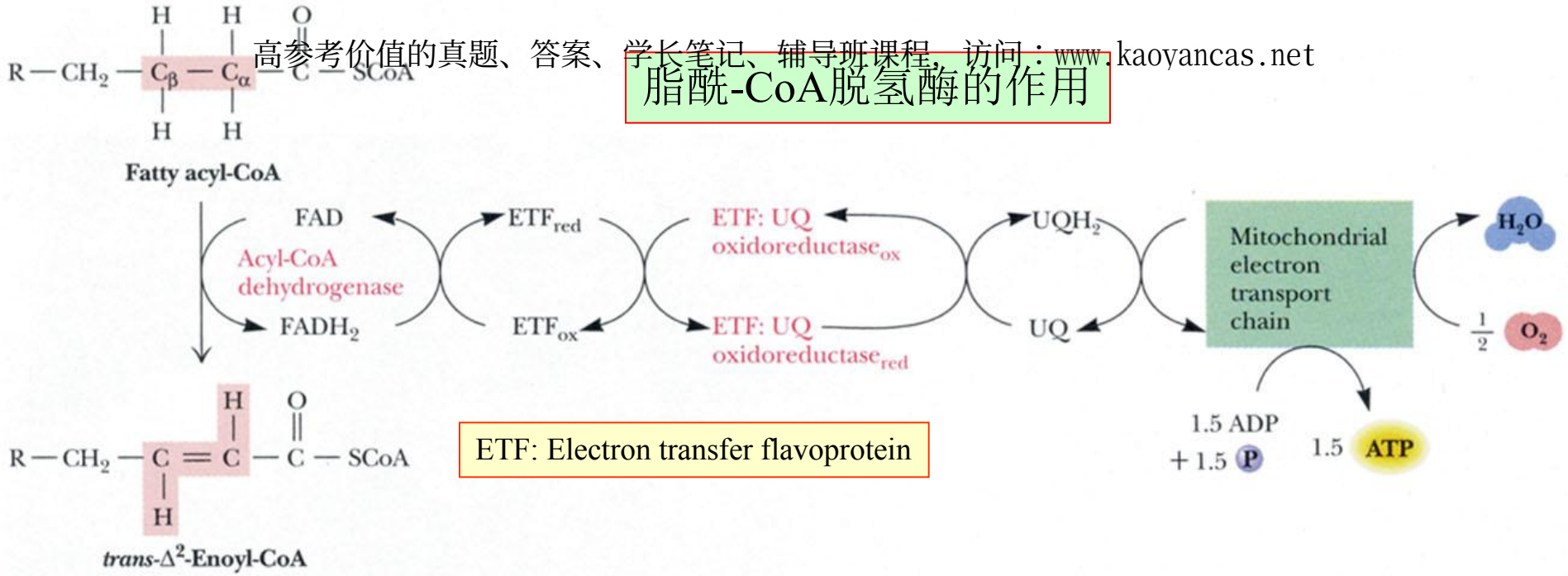


FIGURE 17–7 Stages of fatty acid oxidation. Stage 1: A long-chain fatty acid is oxidized to yield acetyl residues in the form of acetyl-CoA. This process is called β oxidation. Stage 2: The acetyl groups are oxidized to CO_2 via the citric acid cycle. Stage 3: Electrons derived from the oxidations of stages 1 and 2 pass to O_2 via the mitochondrial respiratory chain, providing the energy for ATP synthesis by oxidative phosphorylation.

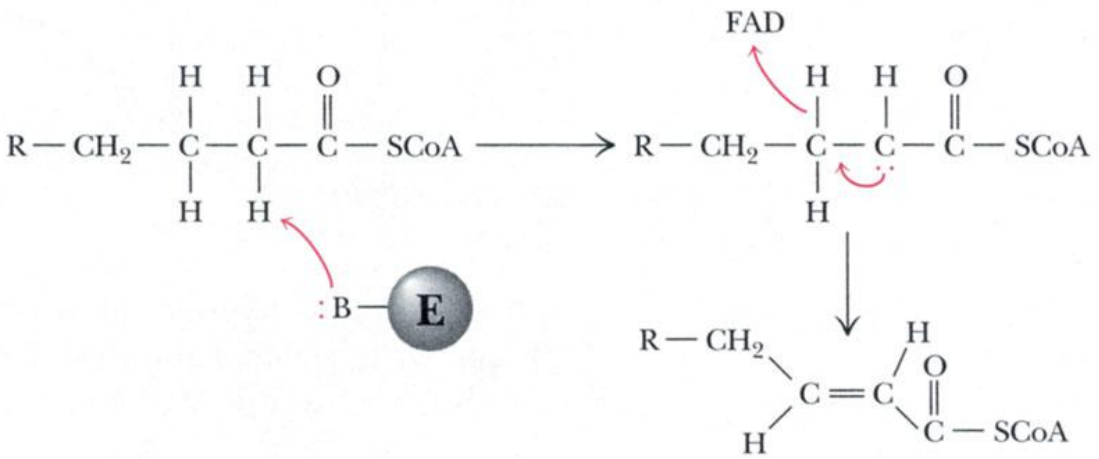
脂肪酸β-氧化的反应途径

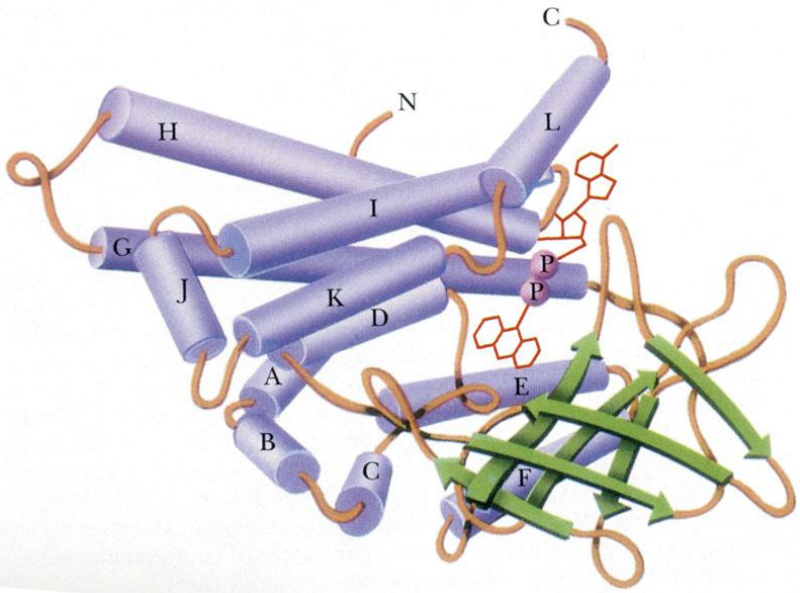


脂酰-CoA脱氢酶的作用



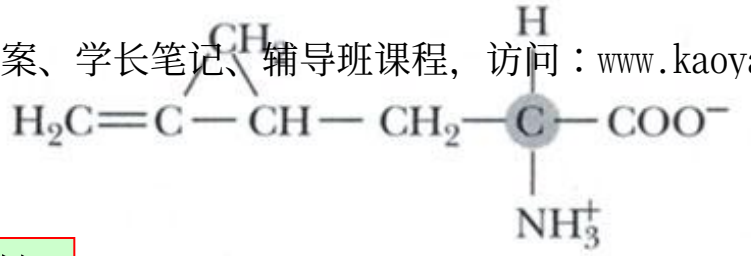
ETF: Electron transfer flavoprotein



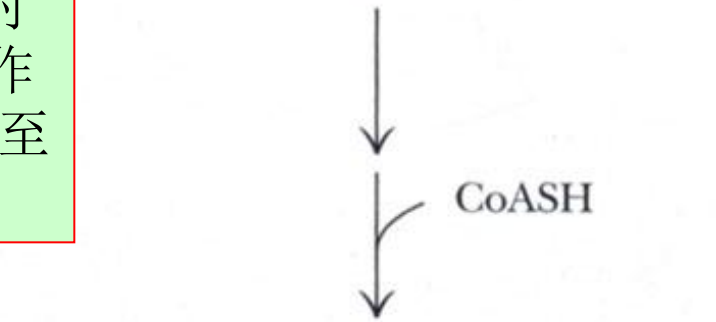


从猪肝脏线粒体分离的脂酰辅酶A脱氢酶中间链的亚基结构

存在于akee未成熟果实中的降糖氨酸A(hypoglycinA)对脂酰辅酶A脱氢酶有抑制作用，可引起呕吐、昏迷甚至死亡。



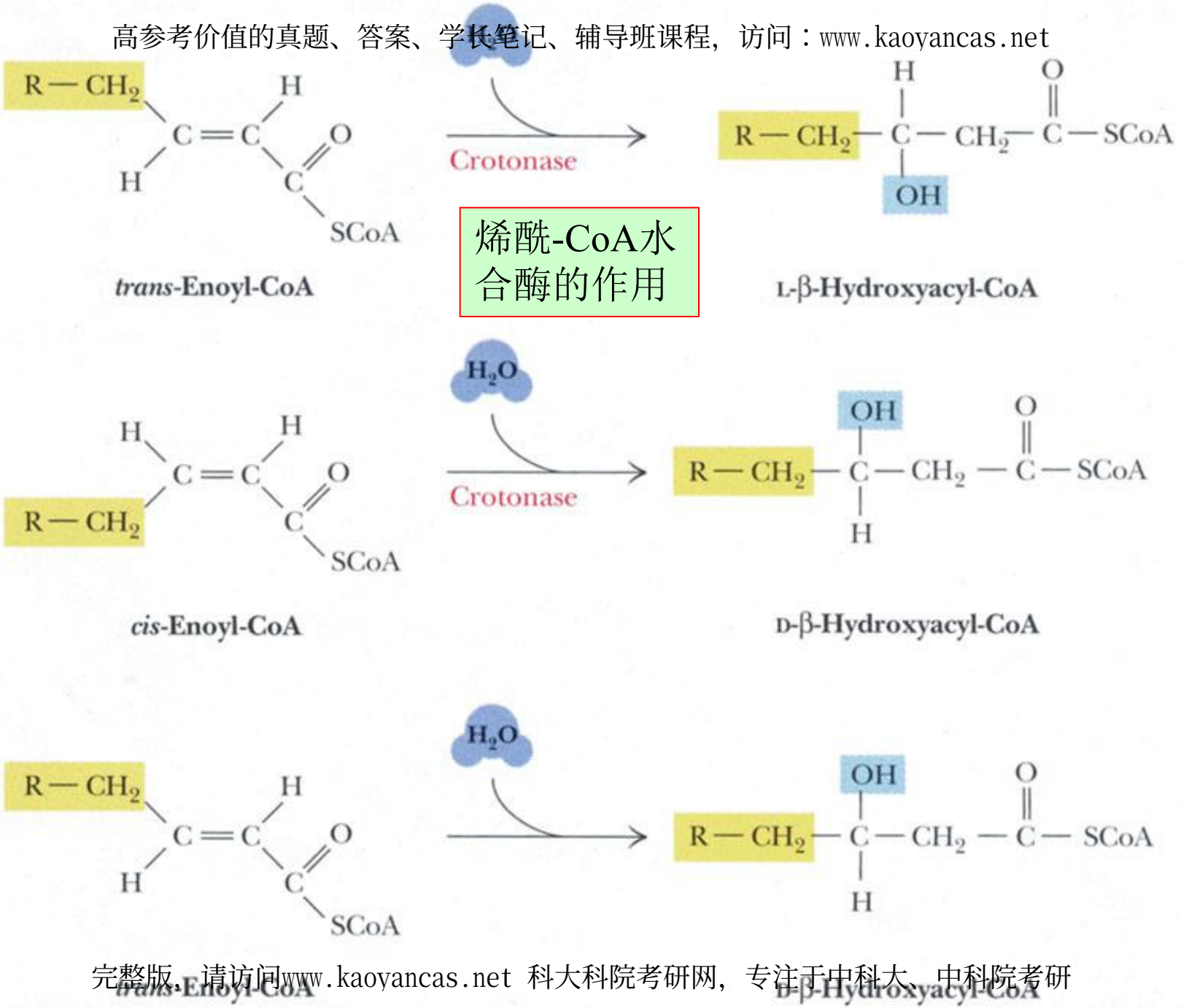
Hypoglycin A

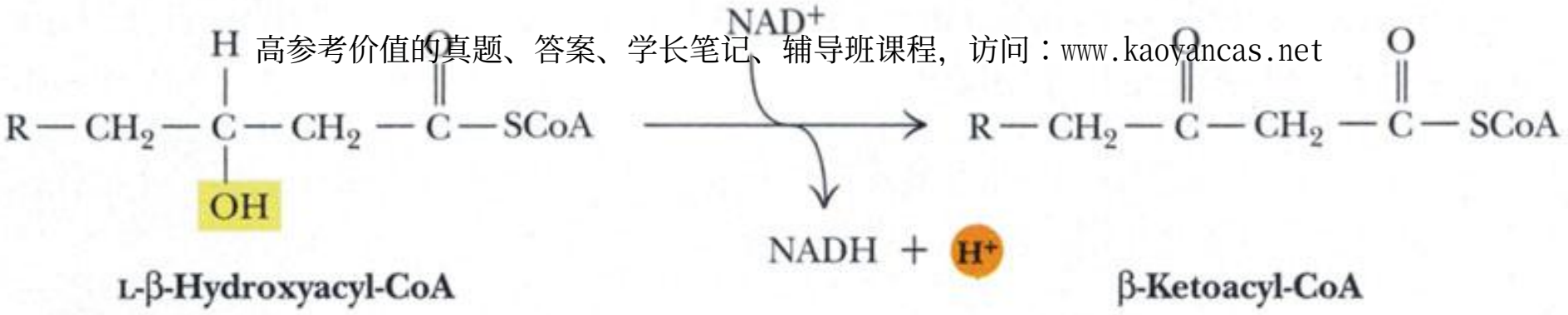


Methylenecyclopropylacetyl-CoA
(MCPA-CoA)

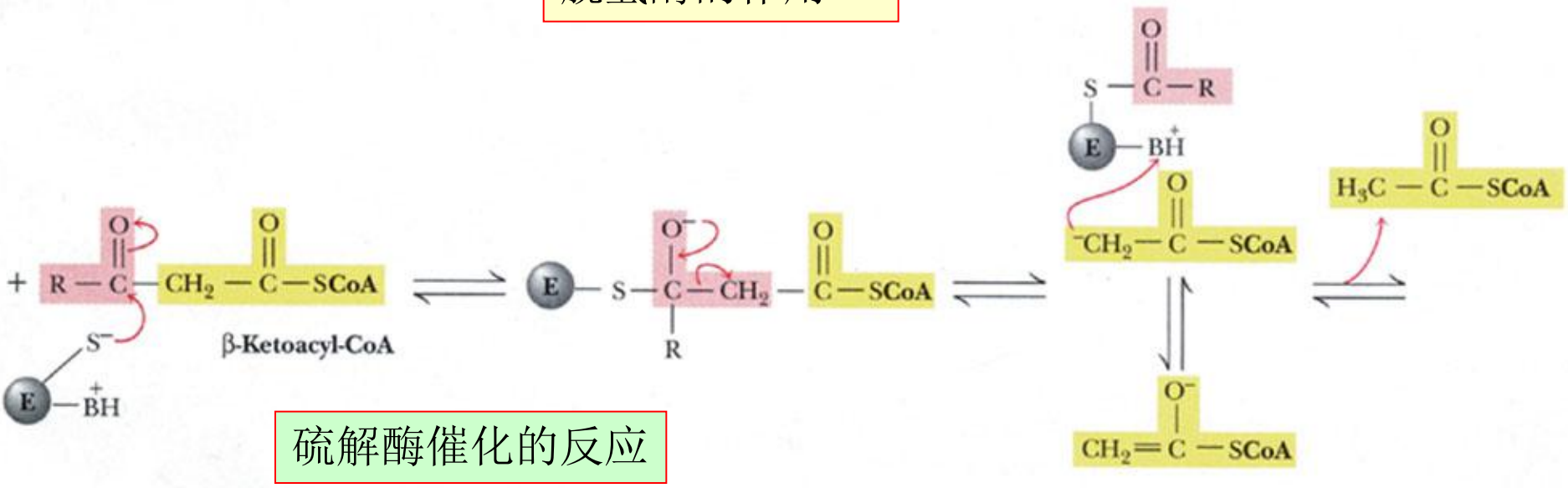
可以与脂酰辅酶A脱氢酶的FAD辅基反应，抑制酶的活性。

Reactive intermediate





L- β-羟酰-CoA
脱氢酶的作用



硫解酶催化的反应

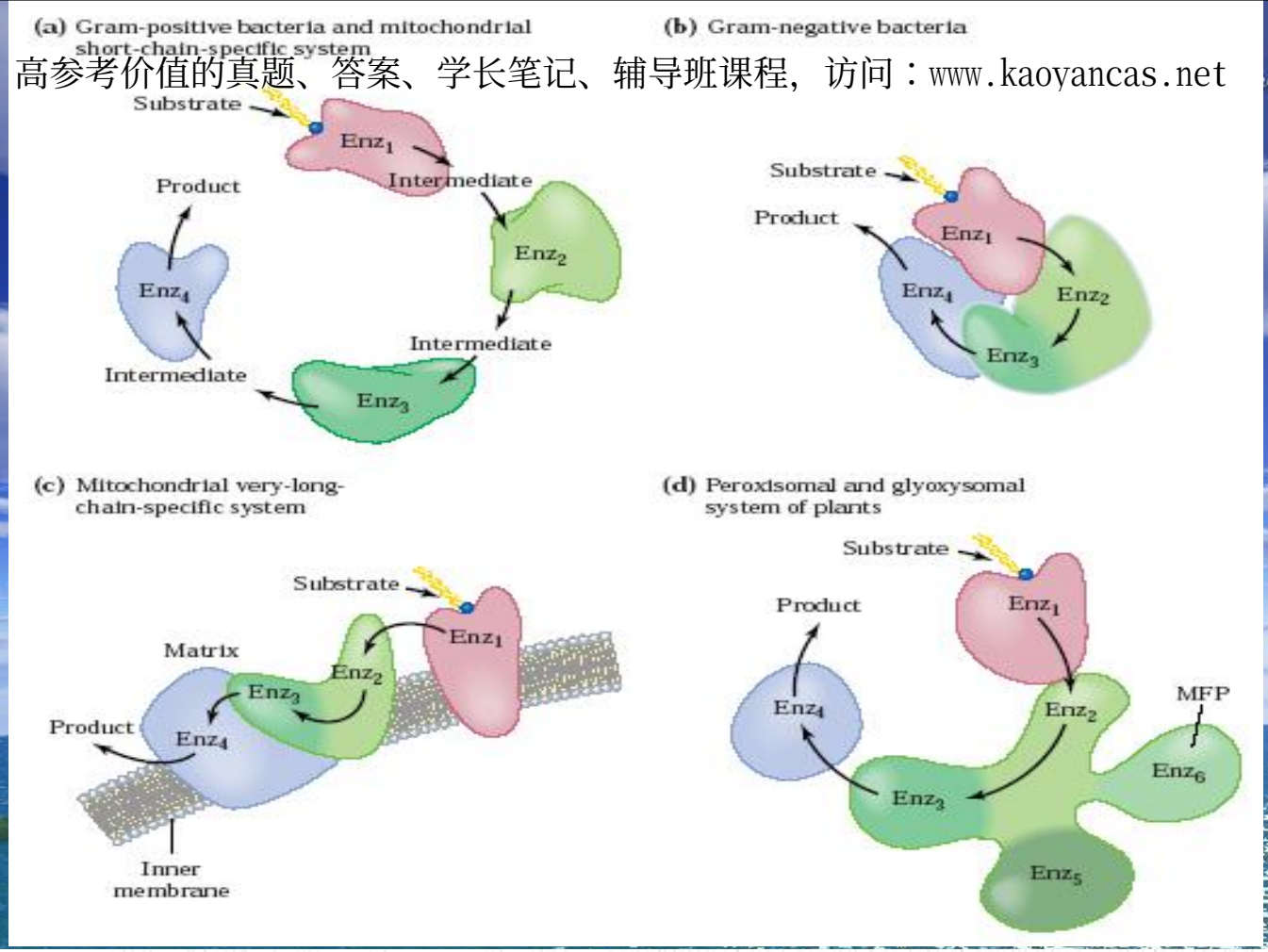


FIGURE 17–15 The enzymes of β oxidation. Shown here are the different subunit structures of the enzymes of β oxidation in gram-positive and gram-negative bacteria, mitochondria, and plant peroxisomes and glyoxysomes. Enz_1 is acyl-CoA dehydrogenase; Enz_2, enoyl-CoA hydratase; Enz_3, L-β-hydroxyacyl-CoA dehydrogenase; Enz_4, thiolase; Enz_5, D-3-hydroxyacyl-CoA epimerase, and Enz_6, Δ^3,Δ^2-enoyl-CoA isomerase. (a) The four enzymes of β oxidation in gram-positive bacteria are separate, soluble proteins. (b) In gram-negative bacteria, the four enzyme activities reside in three polypeptides; enzymes 2 and 3 are parts of a single polypeptide chain. (c) The very-long-chain-specific system of mitochondria is also composed of three polypeptides, one of which includes the activities of enzymes 2 and 3; in this case, the system is bound to the inner mitochondrial membrane. (d) In the peroxisomal and glyoxysomal β-oxidation systems of plants, enzymes 1 and 4 are separate polypeptides, but enzymes 2 and 3, as well as two auxiliary system of mitochondria. (b) In gram-negative bacteria, the four enzyme [illegible] multifunctional protein, MFP.

（四）脂肪酸氧化生成ATP的总结算

脂肪酸β氧化1次生成$FADH_2$和NADH各1个，电子经呼吸链传递给氧，可生成4个ATP。

1个乙酰CoA经柠檬酸循环可生成10个ATP。

以软脂酸为例，16个碳原子，经7次β氧化生成8个乙酰CoA。ATP的生成数为：

$4\times7+10\times8=108$

脂肪酸激活时消耗2个ATP，则：108-2=106

过去的计算是：$5\times7+12\times8-2=129$。

$$\text{Palmitoyl-CoA} + 7\text{CoA} + 7\text{FAD} + 7\text{NAD}^+ + 7\text{H}_2\text{O} \longrightarrow 8\ \text{acetyl-CoA} + 7\text{FADH}_2 + 7\text{NADH} + 7\text{H}^+$$

$$8\ \text{Acetyl-CoA} + 16\text{O}_2 + 80\text{P}_i + 80\text{ADP} \longrightarrow 8\text{CoA} + 80\text{ATP} + 16\text{CO}_2 + 16\text{H}_2\text{O}$$

$$\text{Palmitoyl-CoA} + 23\text{O}_2 + 108\text{P}_i + 108\text{ADP} \longrightarrow \text{CoA} + 108\text{ATP} + 16\text{CO}_2 + 23\text{H}_2\text{O}$$

table 17–1

Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

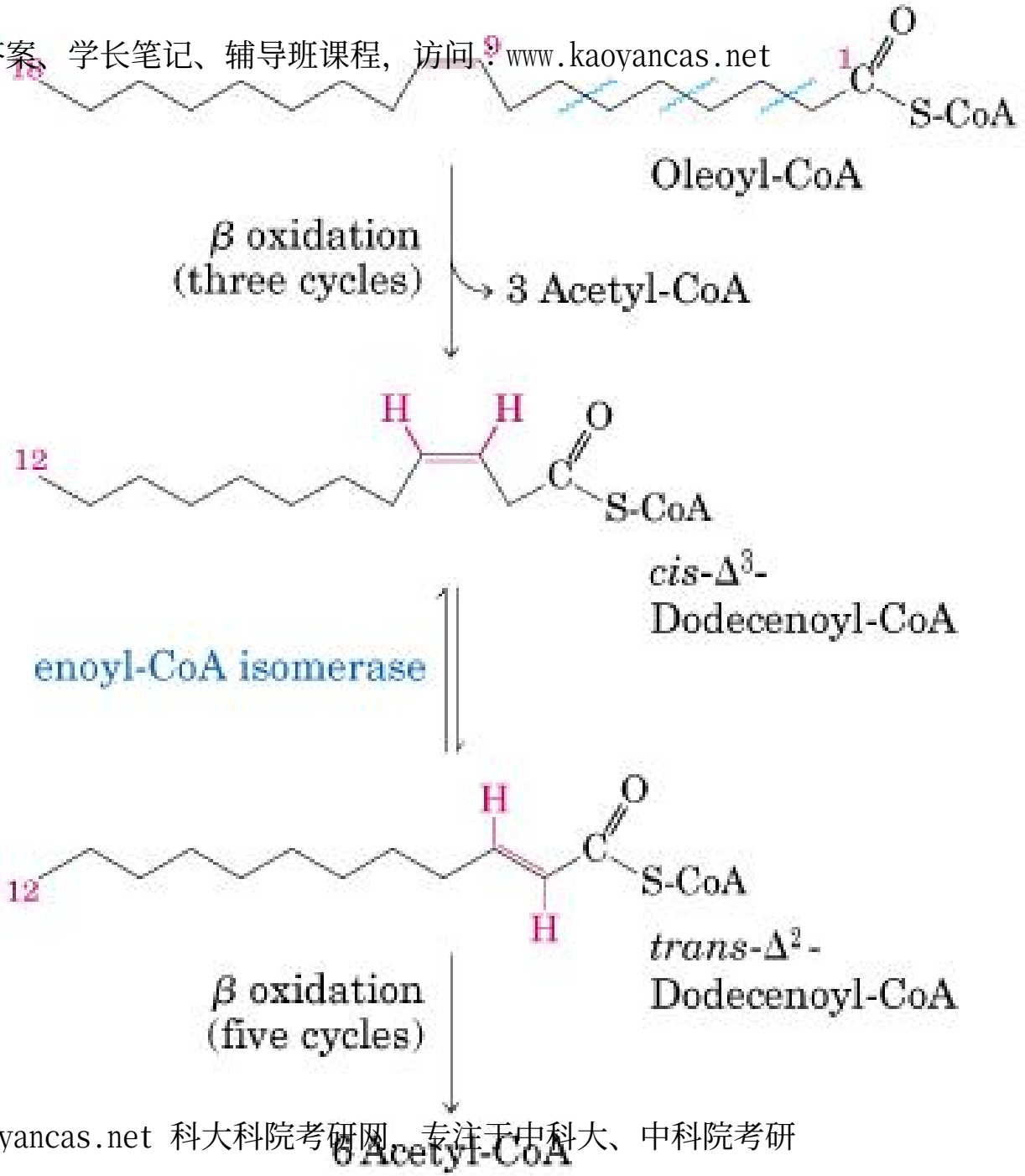
Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed*
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8†
Succinate dehydrogenase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

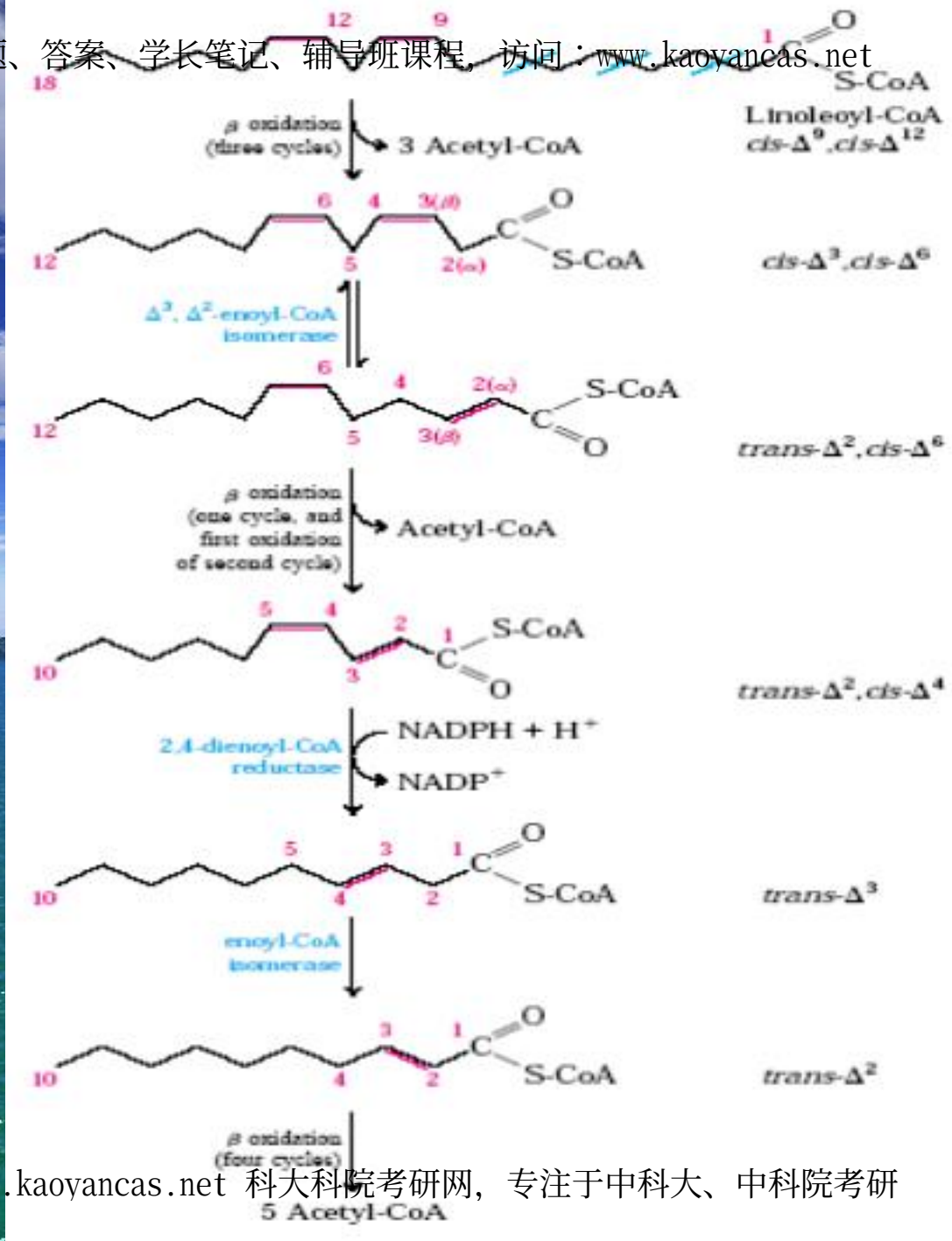
†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 578).

（五）不饱和脂肪酸的氧化

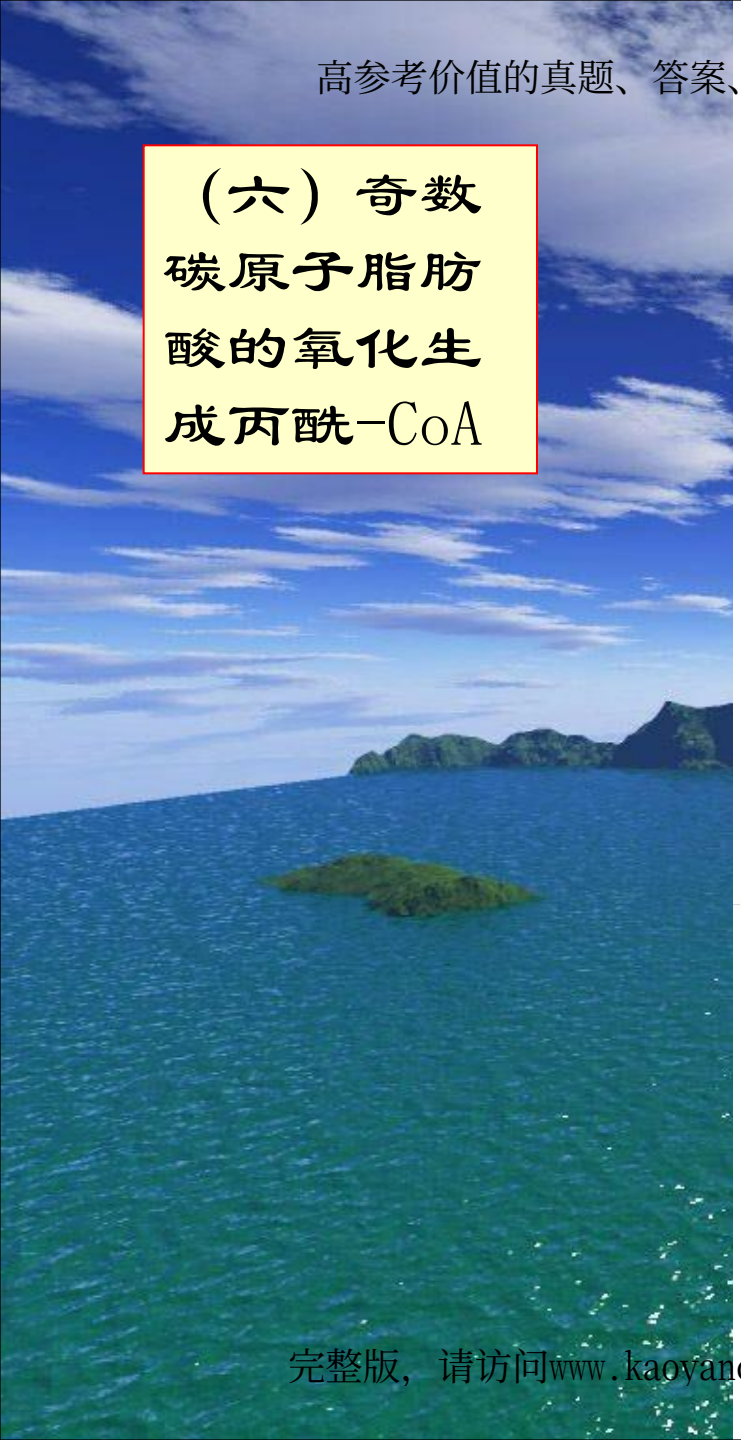
油酰CoA的氧化

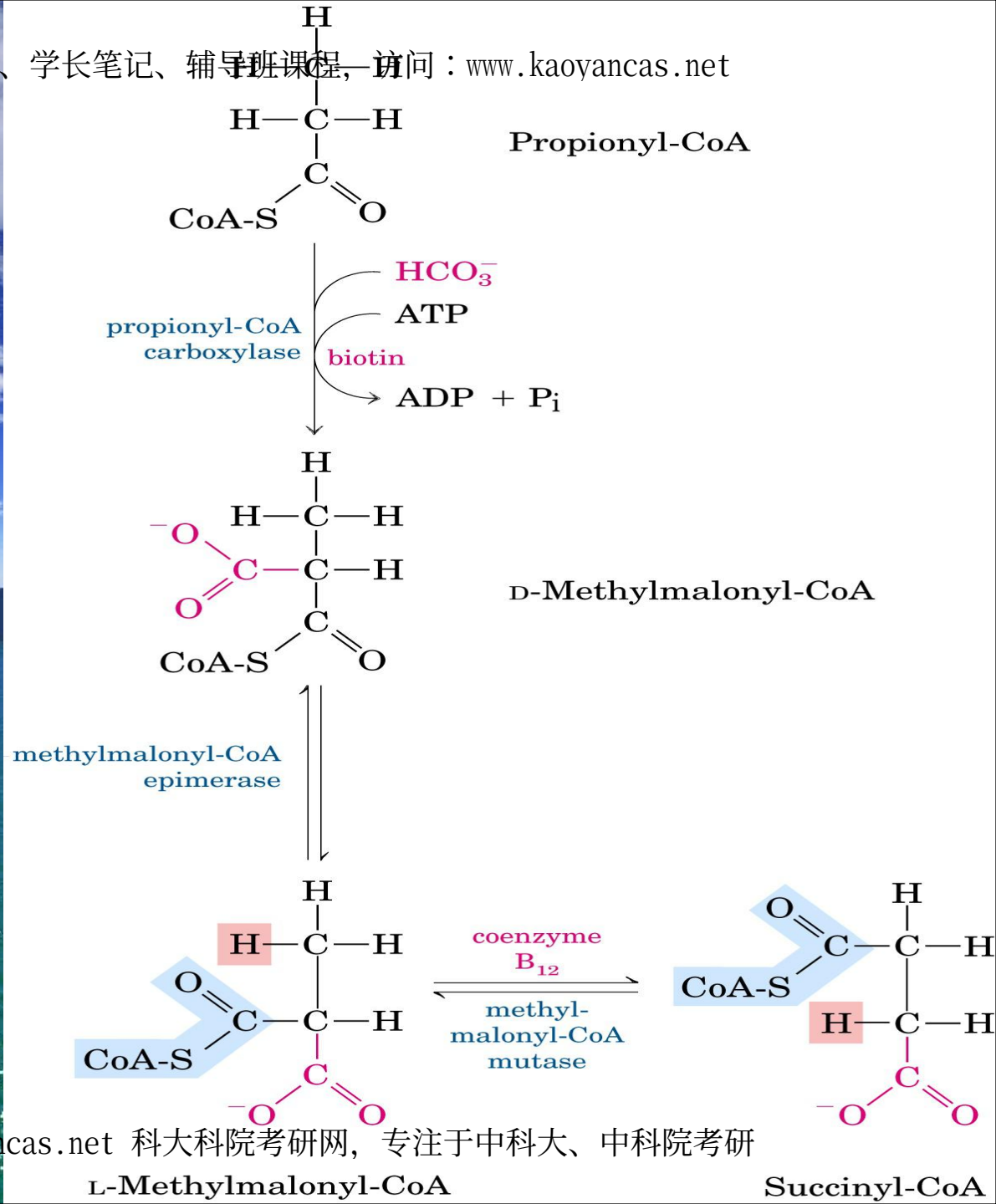


亚油酰CoA的氧化

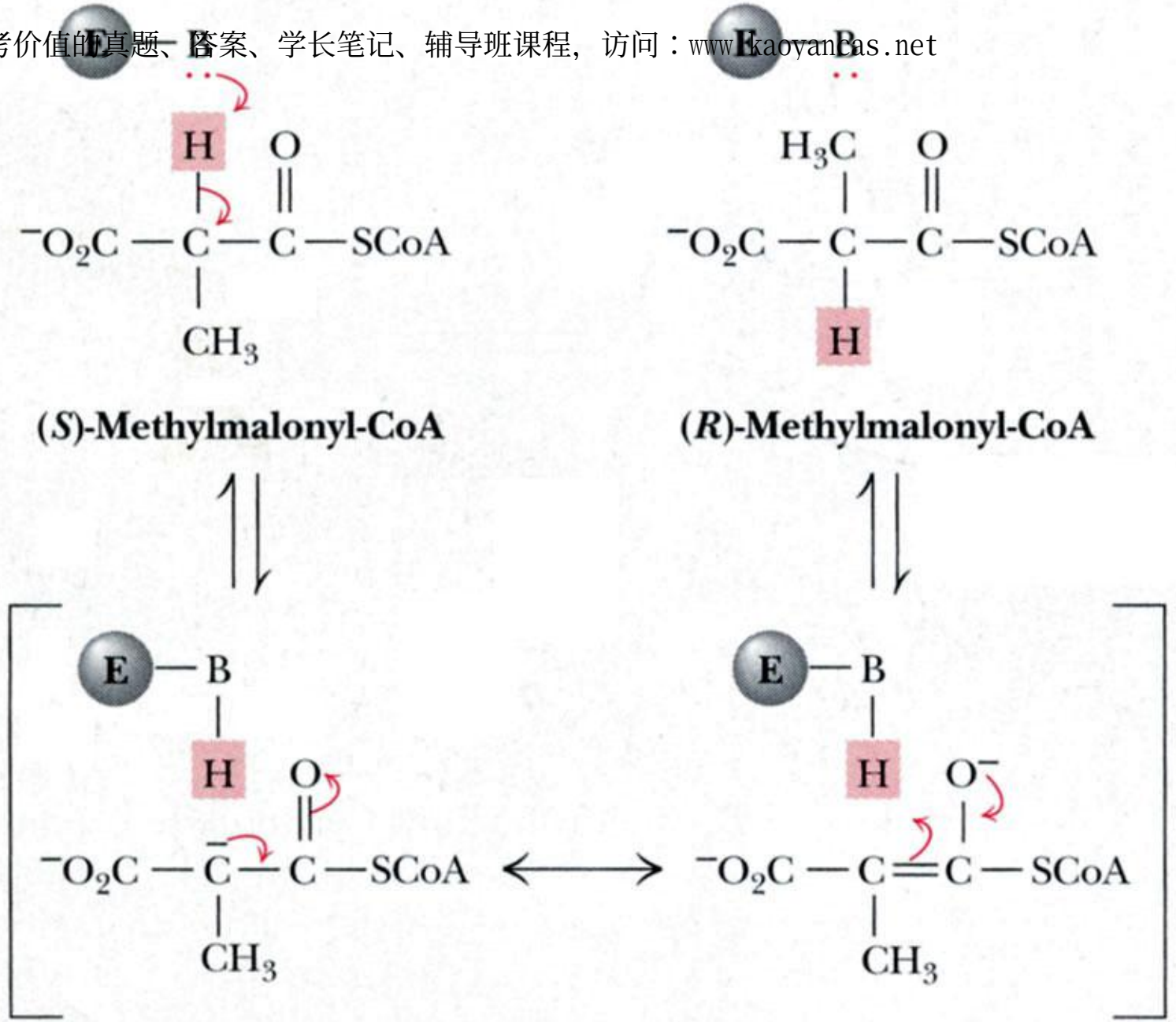


（六）奇数碳原子脂肪酸的氧化生成丙酰-CoA

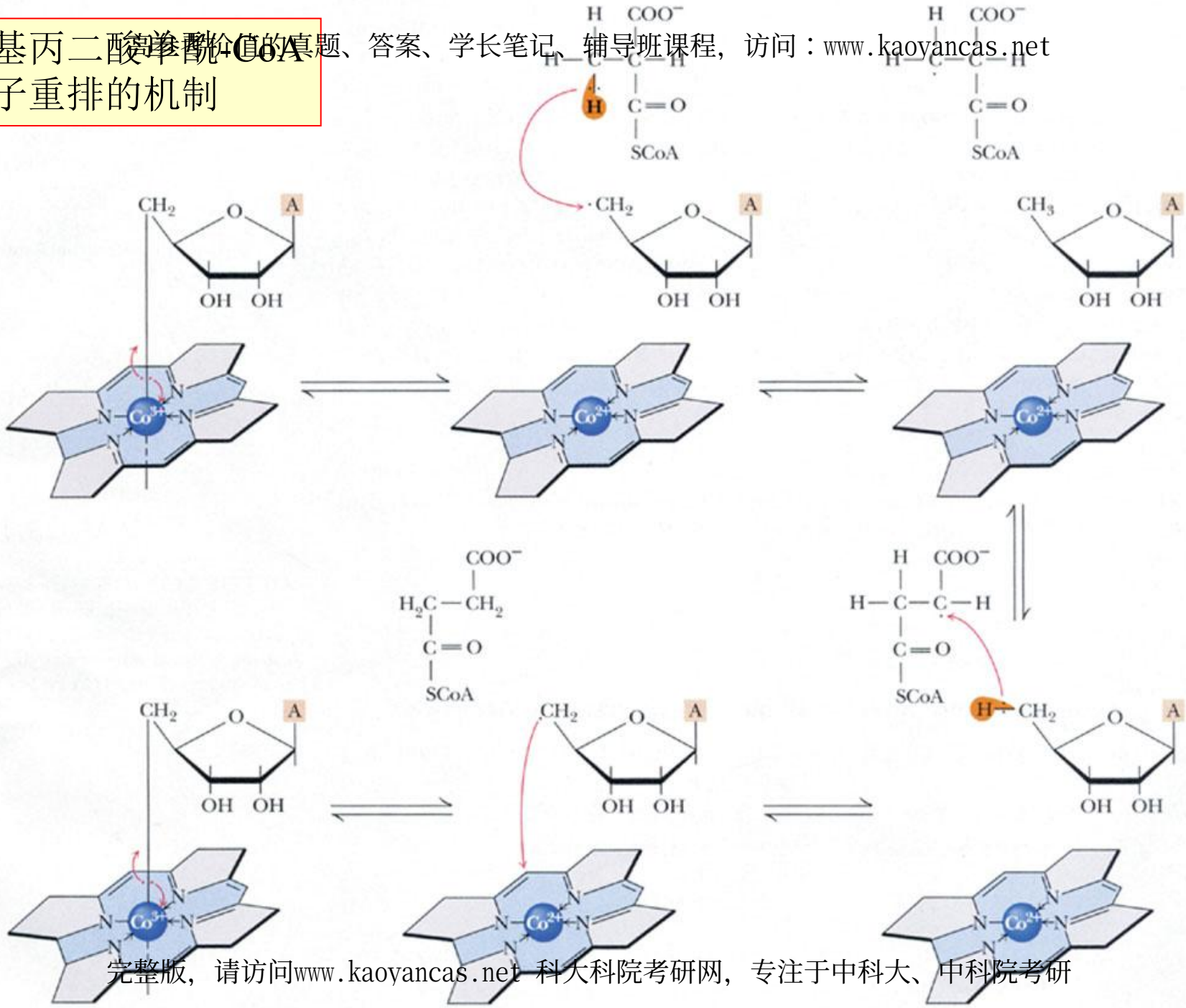




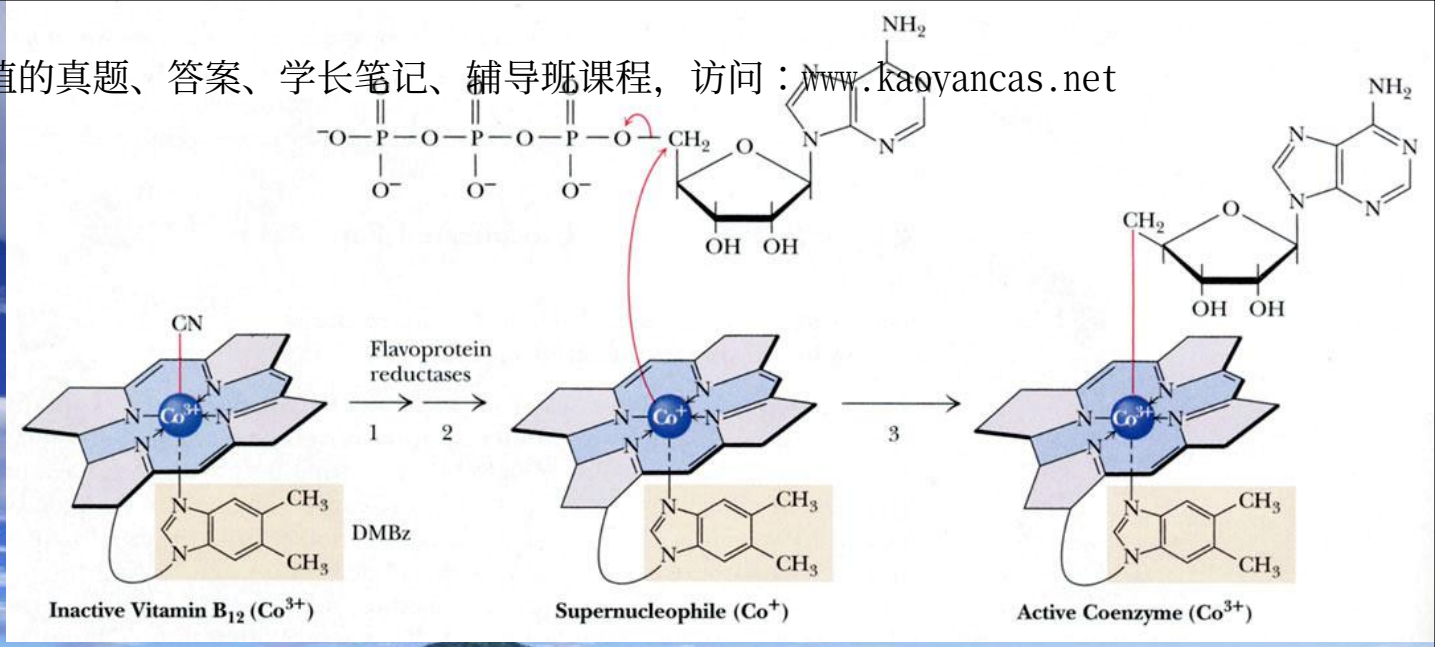
丙酰-CoA的共振形式



甲基丙二酸单酰-CoA分子重排的机制



维生素B_{12}活化的机制



The Nobel Prize in Chemistry 1964

"for her determinations by X-ray techniques of the structures of important biochemical substances"

Presentation Speech

Dorothy Crowfoot Hodgkin

Great Britain

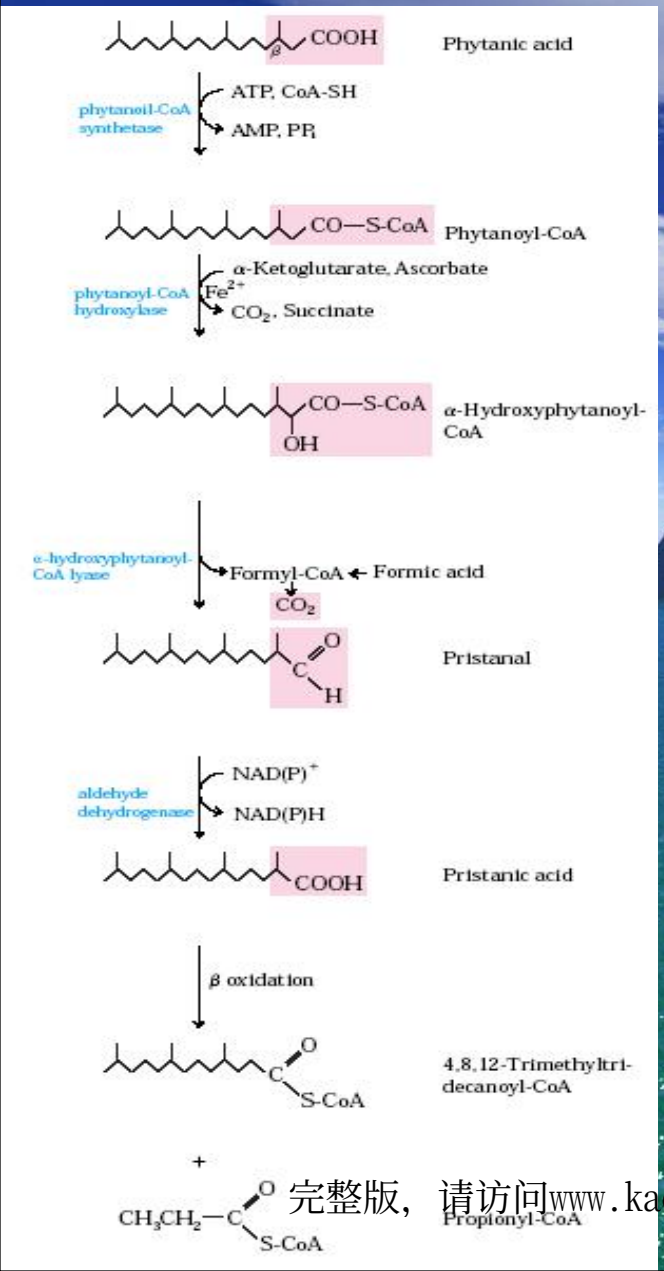
Royal Society
Oxford University
Oxford, Great Britain

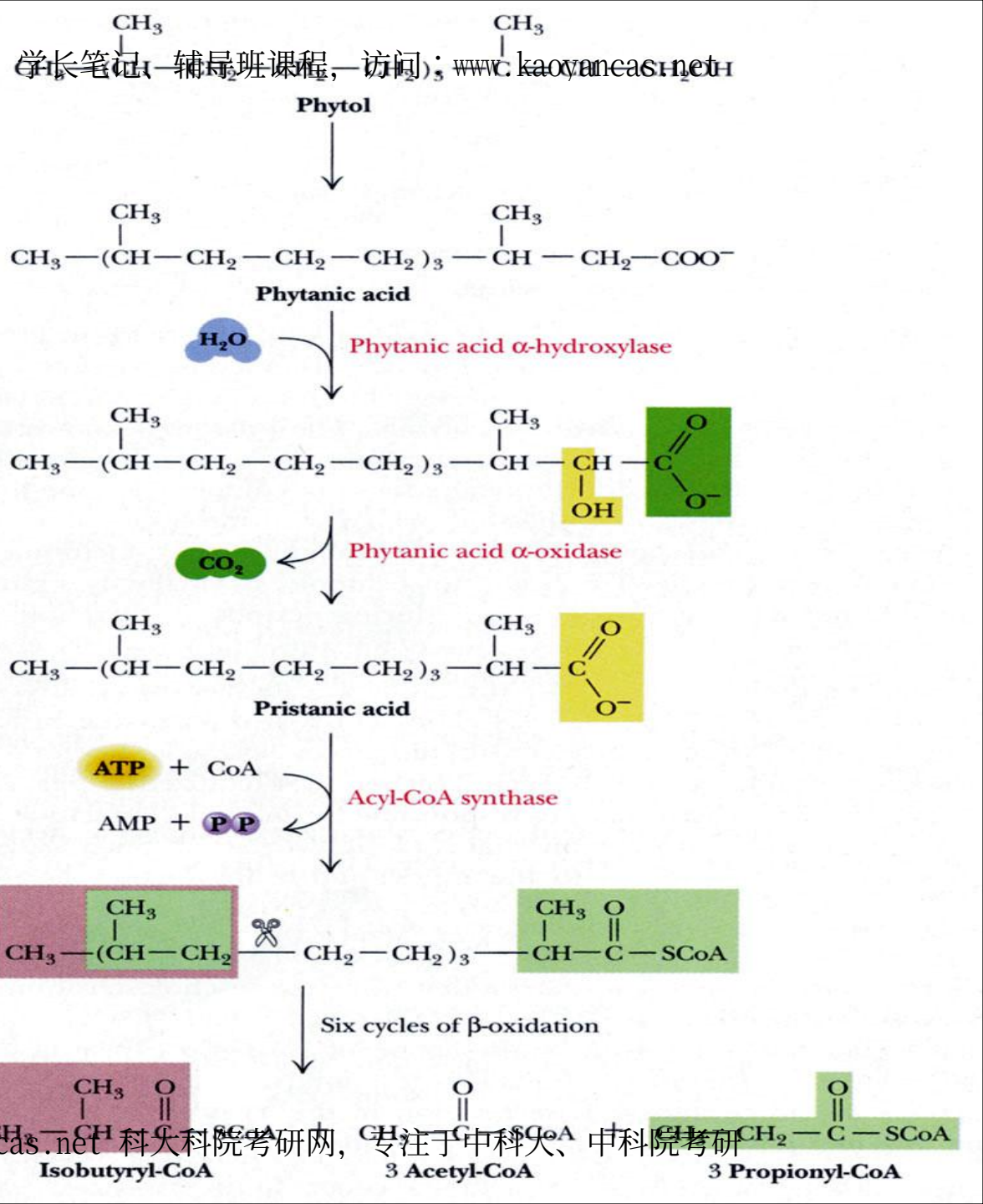
1910 - 1994

Biography

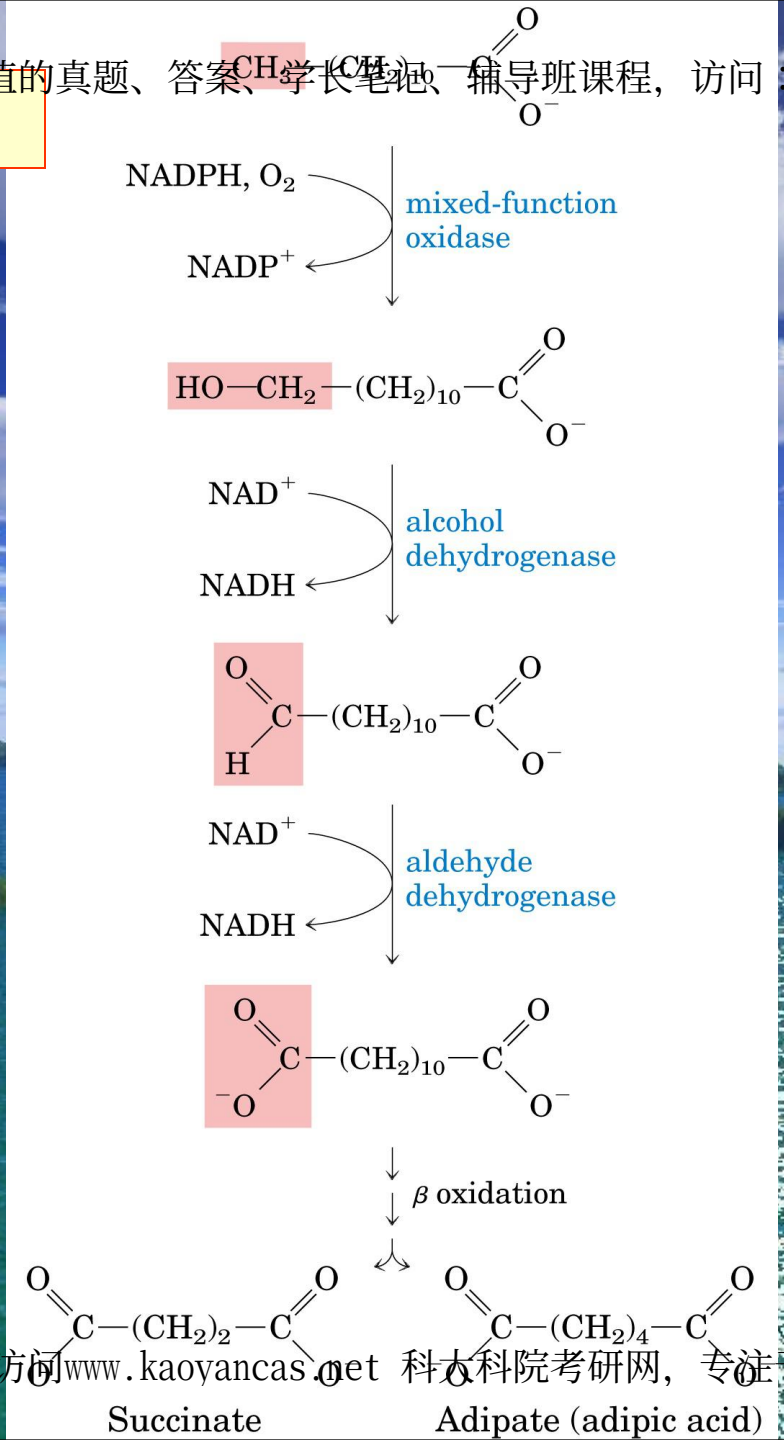
3-D structure of coenzyme B_{12} and penicillin.

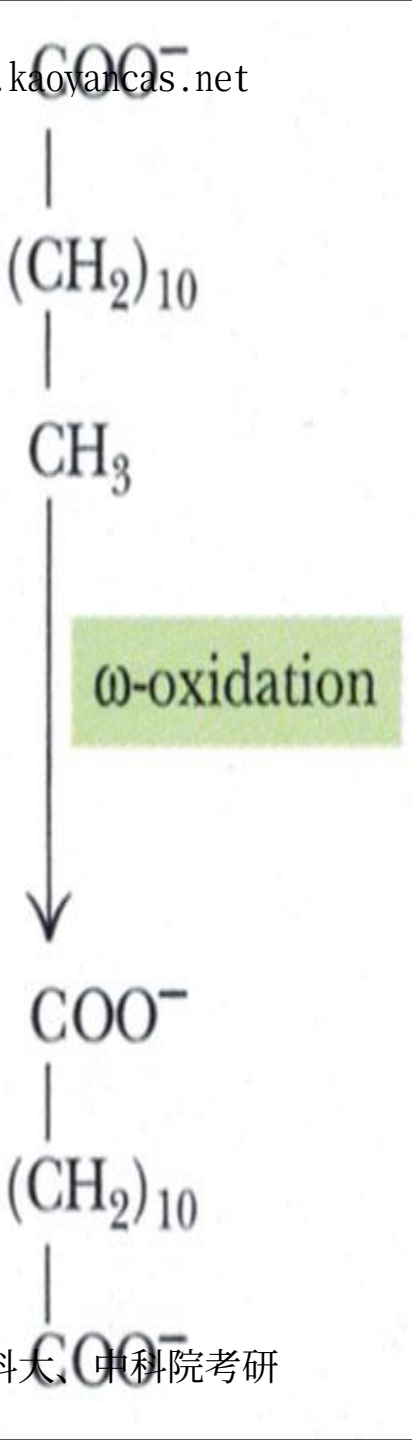
（七）α-氧化





（八）ω-氧化





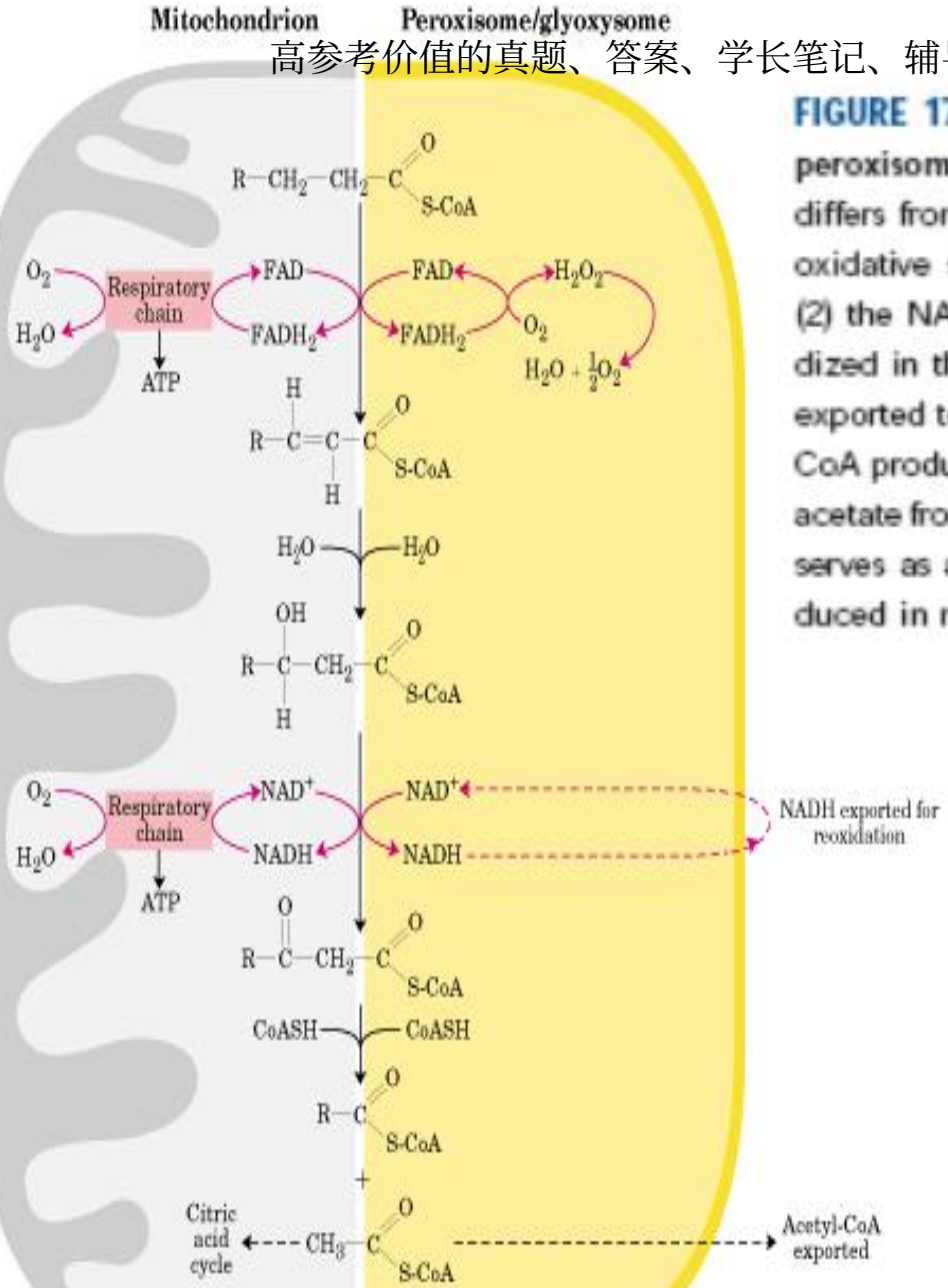
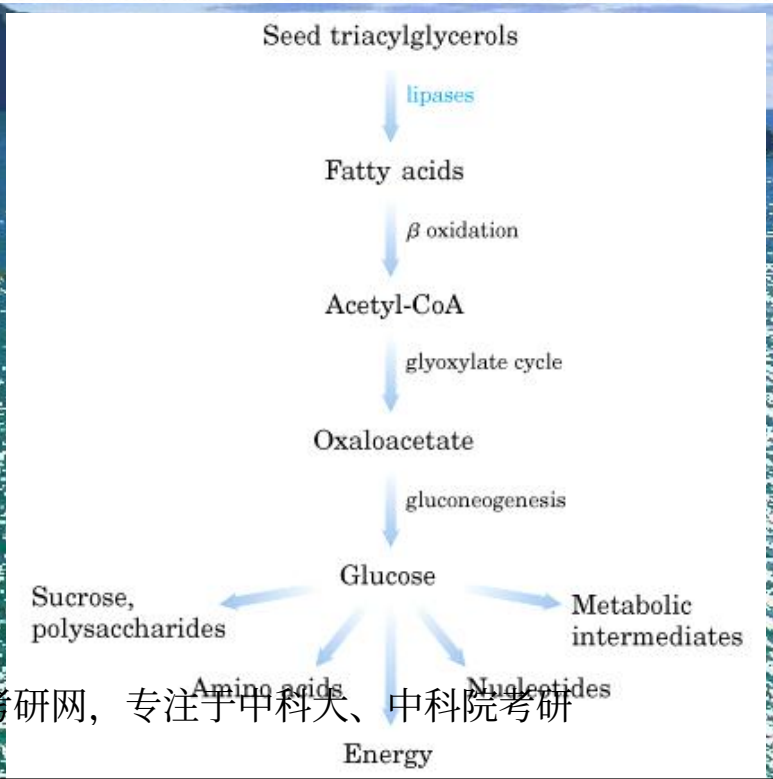


FIGURE 17–13 Comparison of β oxidation in mitochondria and in peroxisomes and glyoxysomes. The peroxisomal/glyoxysomal system differs from the mitochondrial system in two respects: (1) in the first oxidative step electrons pass directly to O_2, generating H_2O_2, and (2) the NADH formed in the second oxidative step cannot be reoxidized in the peroxisome or glyoxysome, so reducing equivalents are exported to the cytosol, eventually entering mitochondria. The acetyl-CoA produced by peroxisomes and glyoxysomes is also exported; the acetate from glyoxysomes (organelles found only in germinating seeds) serves as a biosynthetic precursor (see Fig. 17–14). Acetyl-CoA produced in mitochondria is further oxidized in the citric acid cycle.

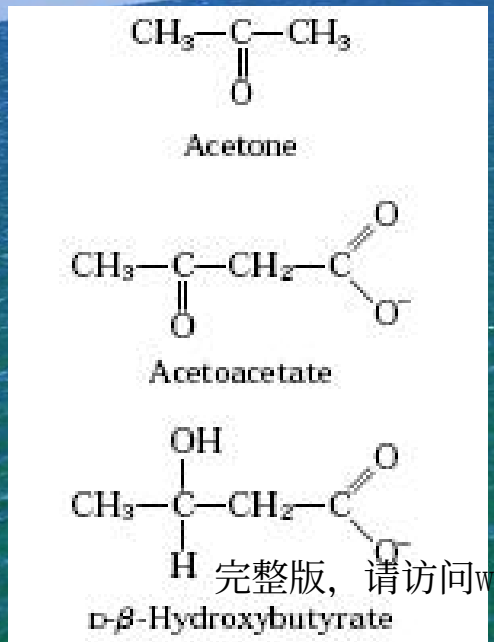


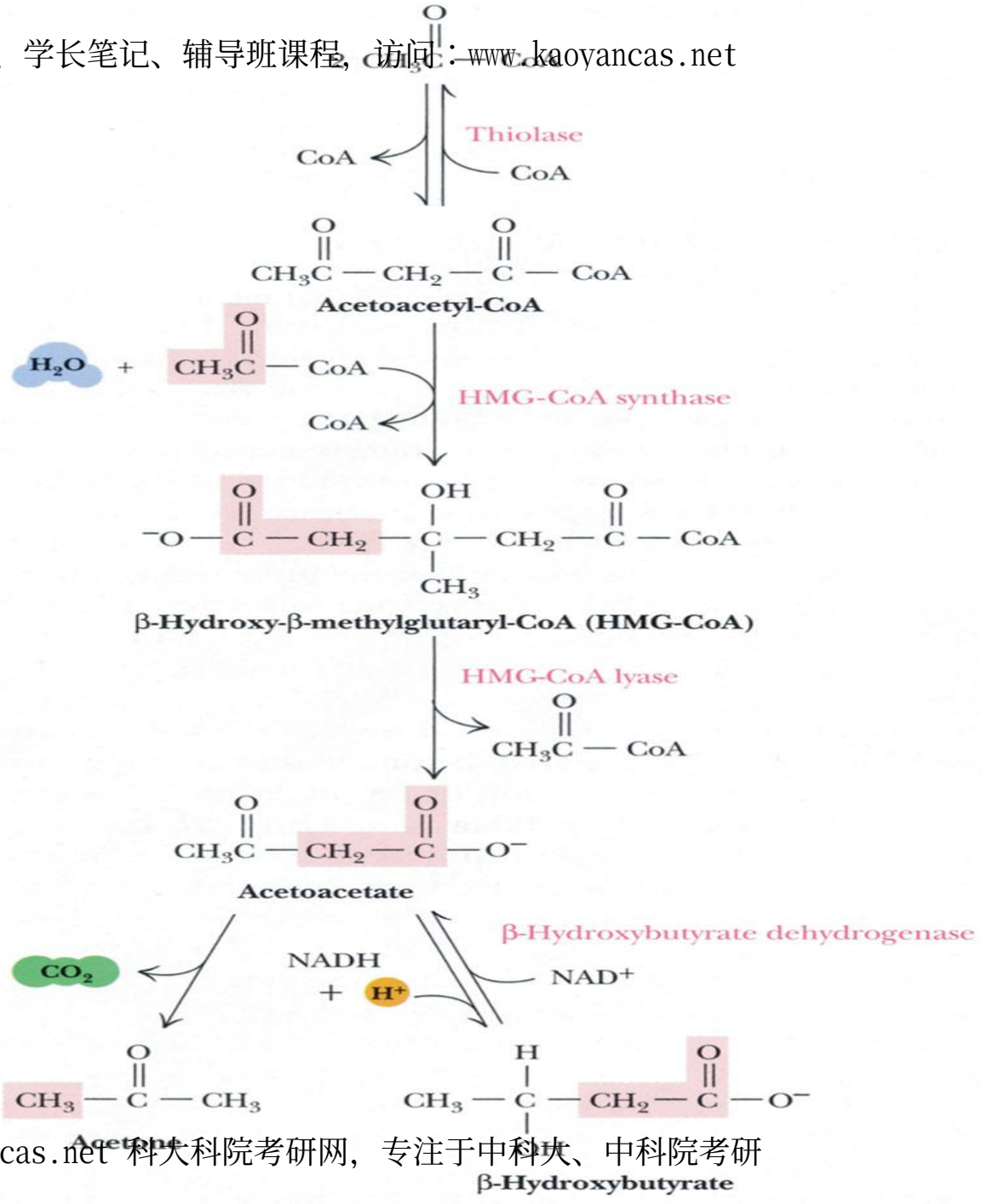
（九）酮体

1.乙酰-CoA的代谢结局

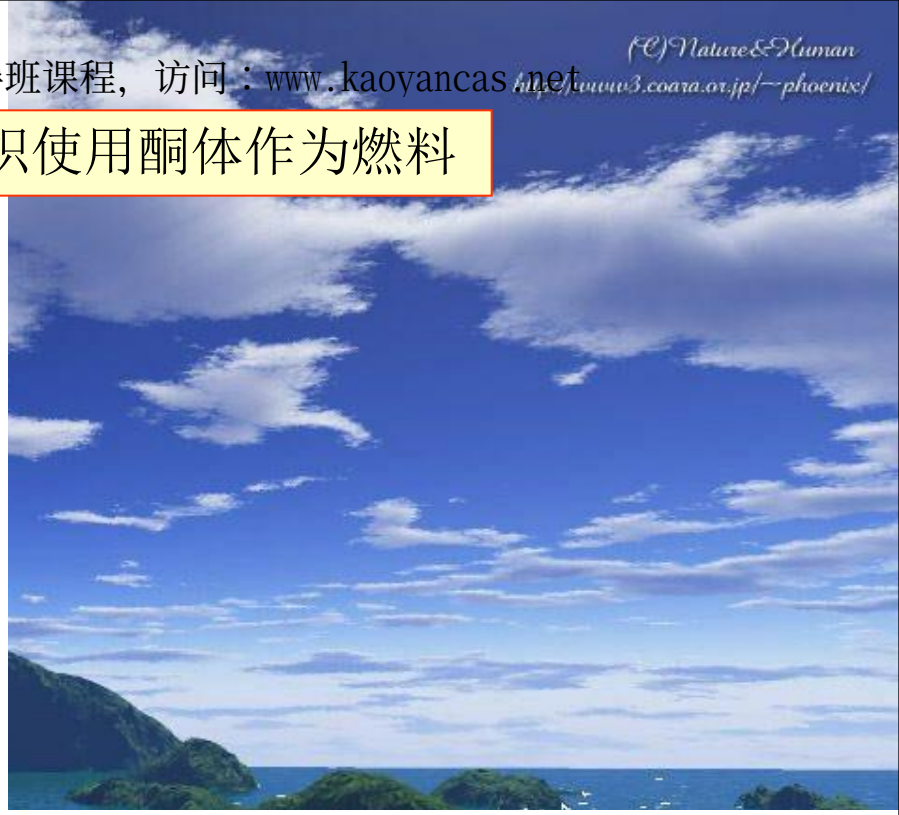
进入柠檬酸循环；合成固醇类；合成脂肪酸；合成酮体。

2.肝脏中酮体的形成





3.肝外组织使用酮体作为燃料



β-Hydroxybutyrate

NAD⁺ ⇌ NADH + H⁺

β-Hydroxybutyrate dehydrogenase

Acetoacetate

Succinyl-CoA → Succinate

β-Ketoacyl-CoA transferase

Acetoacetyl-CoA

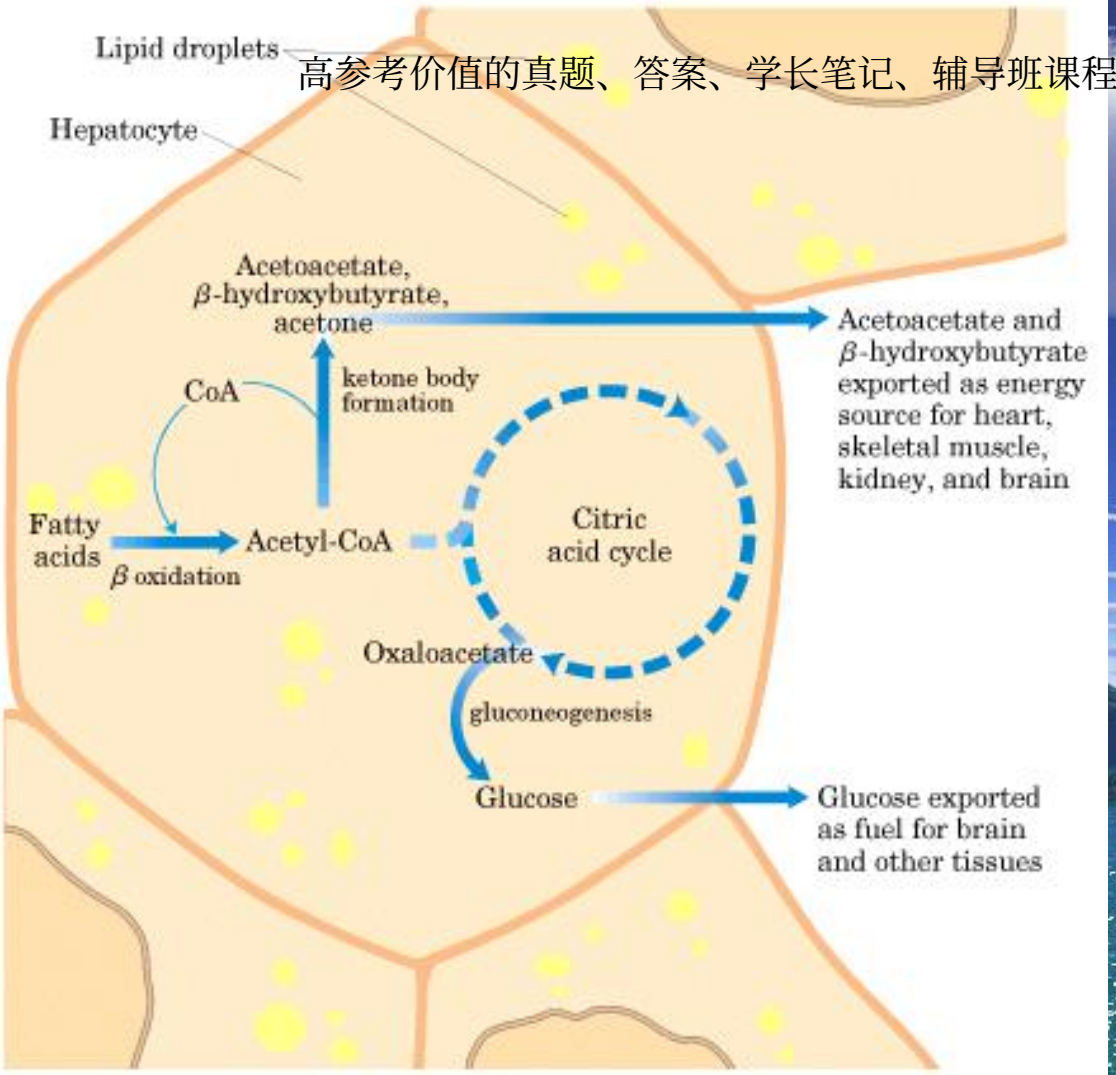
CoA → CoA

Thiolase

2 Acetyl-CoA

FIGURE 17–19 D-β-Hydroxybutyrate as a fuel. D-β-Hydroxybutyrate, synthesized in the liver, passes into the blood and thus to other tissues, where it is converted in three steps to acetyl-CoA. It is first oxidized to acetoacetate, which is activated with coenzyme A donated from succinyl-CoA, then split by thiolase. The acetyl-CoA thus formed is used for energy production.

丙酮很少被利用，主要通过呼吸系统或随尿液排出体外。



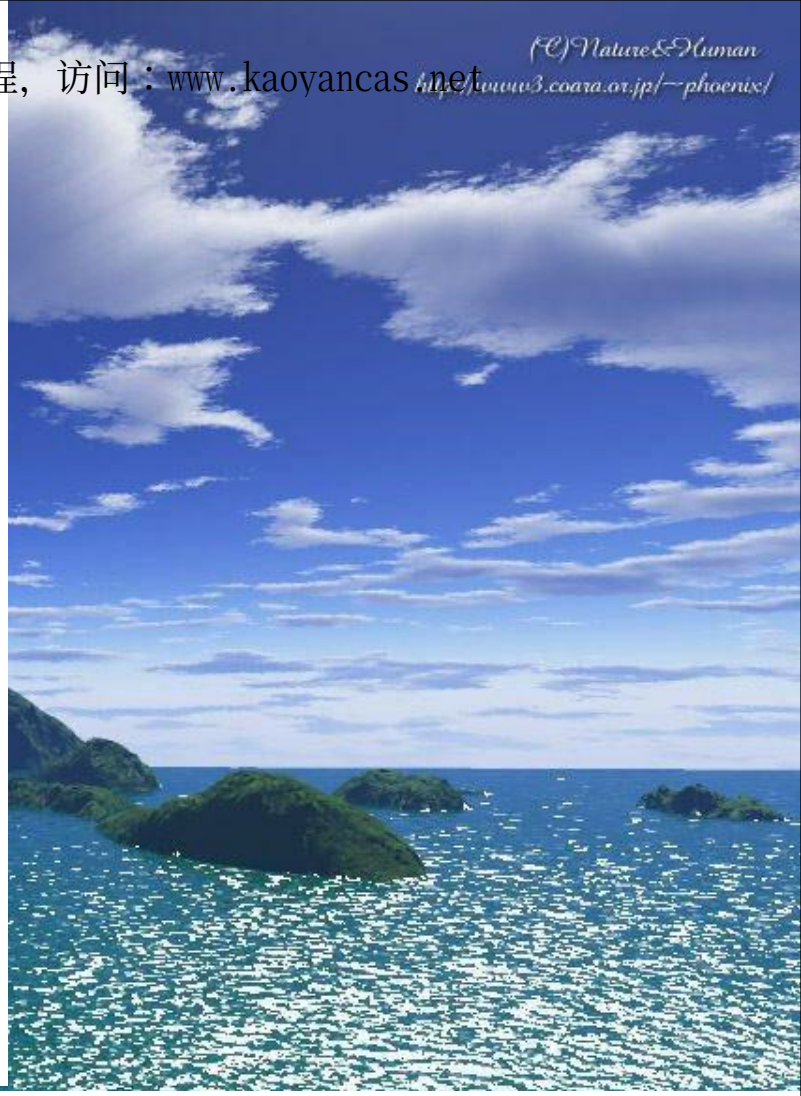


FIGURE 17–20 Ketone body formation and export from the liver. Conditions that promote gluconeogenesis (untreated diabetes, severely reduced food intake) slow the citric acid cycle (by drawing off oxaloacetate) and enhance the conversion of acetyl-CoA to acetoacetate. The released coenzyme A allows continued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

（十）脂肪酸代谢的调节

1. 脂肪酸进入线粒体的调控

肉碱酰基转移酶 受丙二酰-CoA的强烈抑制，丙二酰-CoA含量高有利于脂肪酸的合成。

2. 心脏中脂肪酸氧化的调节

心脏以脂肪酸的氧化为主要能源，若耗能减少，乙酰-CoA和NADH含量增高，抑制脂肪酸的氧化。

3. 激素对脂肪酸代谢的调节

肾上腺素和胰高血糖素使脂肪组织的cAMP含量增高，促进脂肪酸的氧化，抑制脂肪酸的合成。胰岛素促进脂肪酸的合成。

4. 根据机体代谢需要的调控

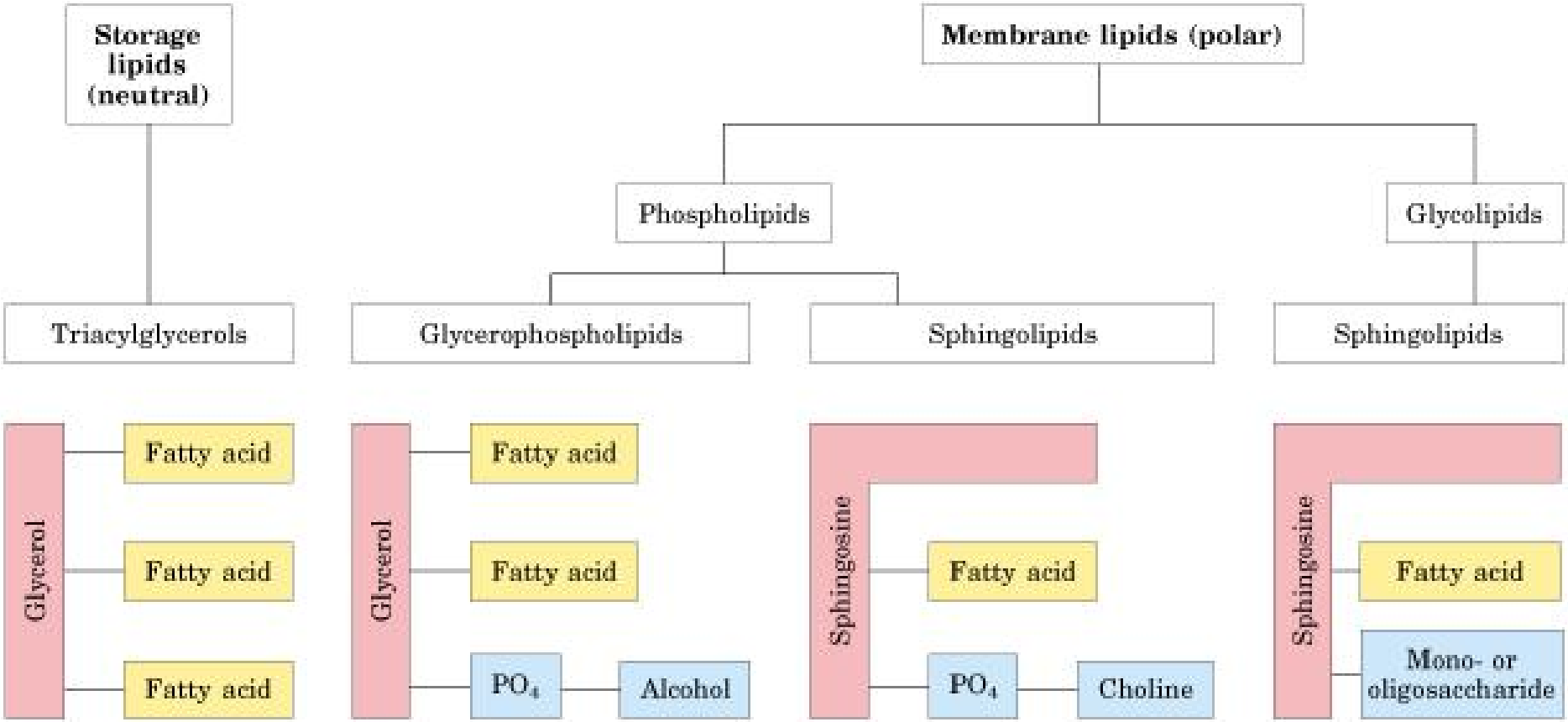
若软脂酰-CoA过量，会抑制脂肪酸的合成。柠檬酸过量促进脂肪酸的合成。

5. 长时间膳食的改变导致相关酶水平的调整

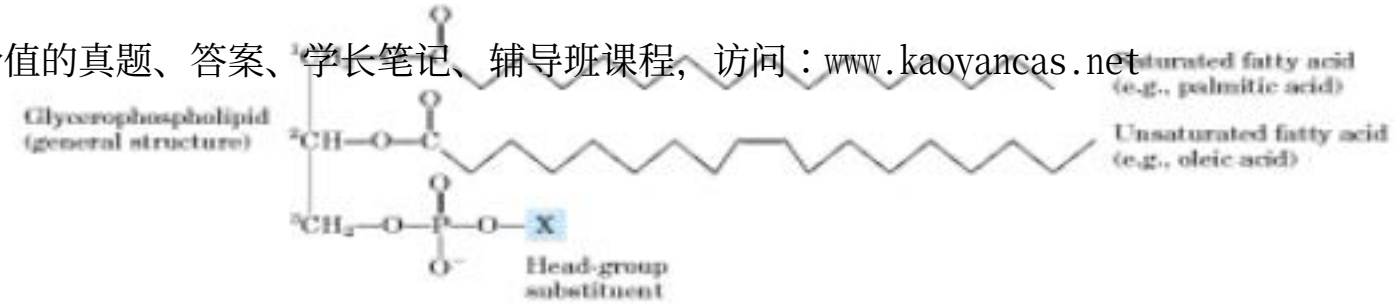
长时间食用低脂肪饲料的大鼠，乙酰-CoA羧化酶的活力会大幅度提高，可能是提高了基因转录的速度。

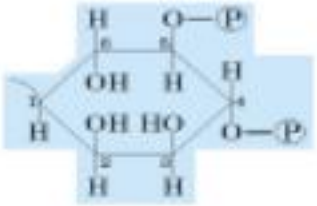
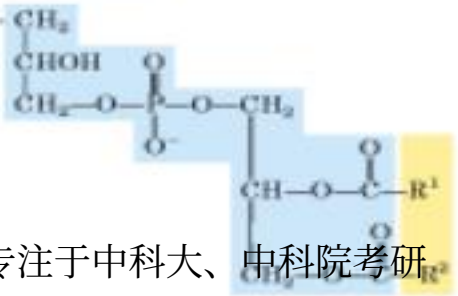
三、磷脂和甾醇的代谢

1.膜结构脂类:磷脂和糖脂

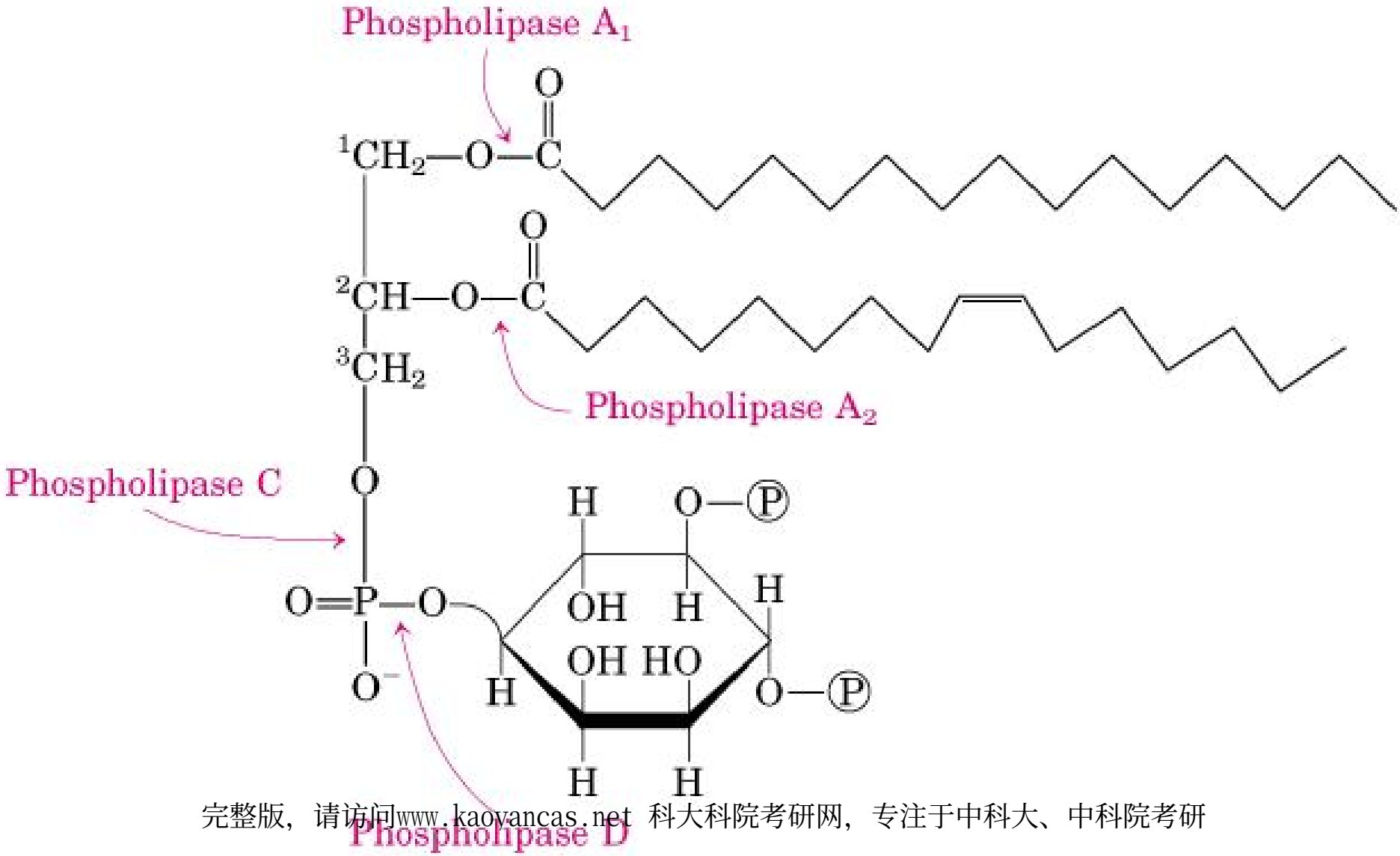


2.磷酸甘油酯是磷脂酸的衍生物



Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	—H	−1
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$	0
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$	0
Phosphatidylserine	Serine	$-CH_2-\underset{COO^-}{CH}-\overset{+}{N}H_3$	−1
Phosphatidylglycerol	Glycerol	$-CH_2-\underset{OH}{CH}-CH_2-OH$	−1
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate		−4
Cardiolipin	Phosphatidyl-glycerol		−2

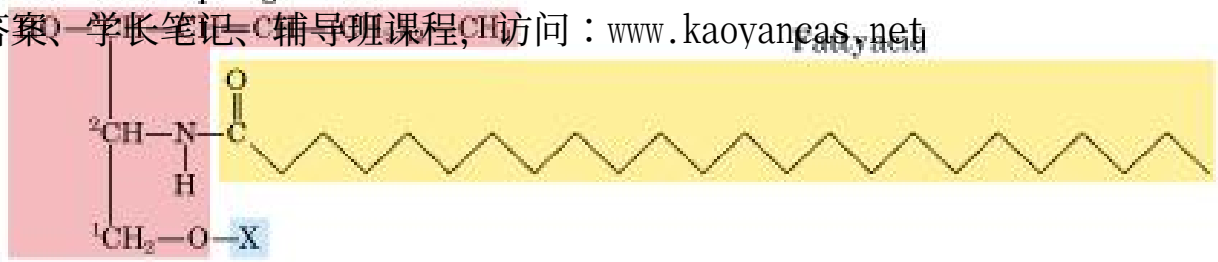
3.磷脂的分解代谢

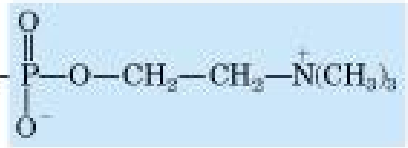
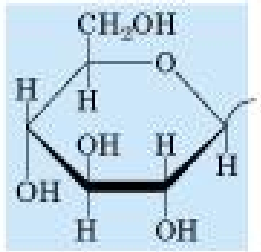
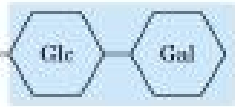
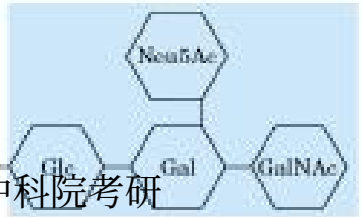


4.鞘磷脂的代谢

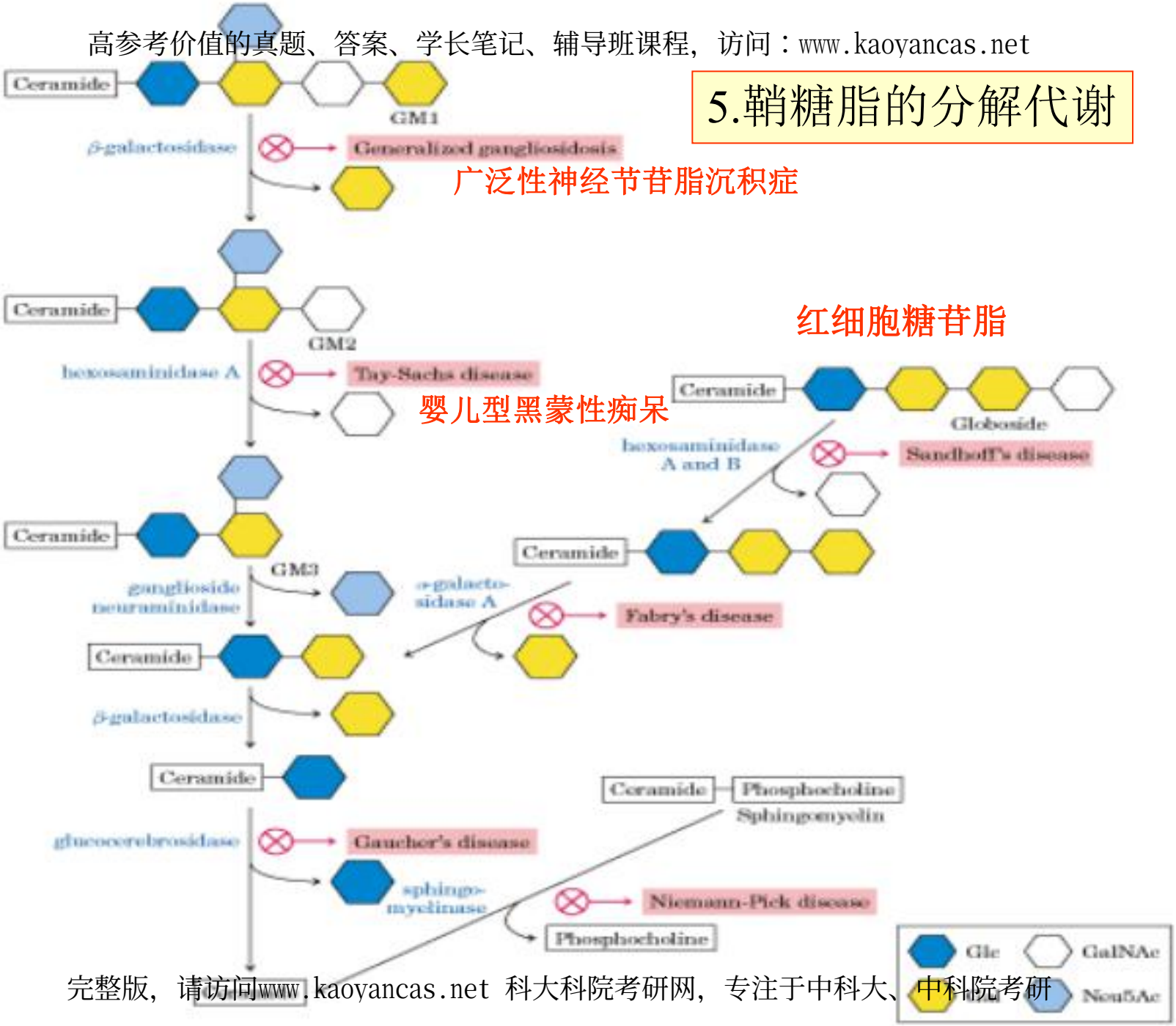
Sphingosine

Sphingolipid (general structure)

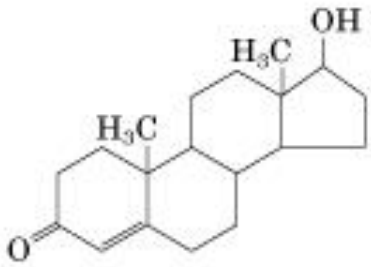


Name of sphingolipid	Name of X	Formula of X
Ceramide	—	—H
Sphingomyelin	Phosphocholine	
Neutral glycolipids Glucosylcerebroside	Glucose	
Lactosylceramide (a globoside)	Di-, tri-, or tetrasaccharide	
Ganglioside GM2	Complex oligosaccharide	

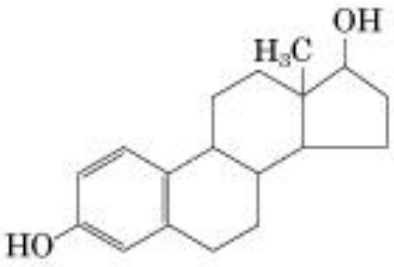
5.鞘糖脂的分解代谢



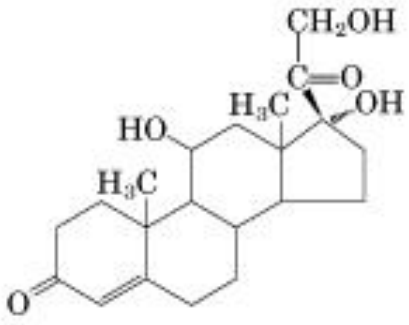
6.甾醇的代谢



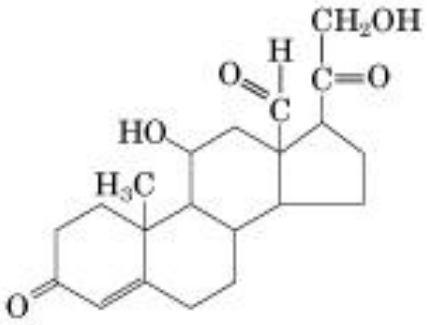
Testosterone



Estradiol



Cortisol



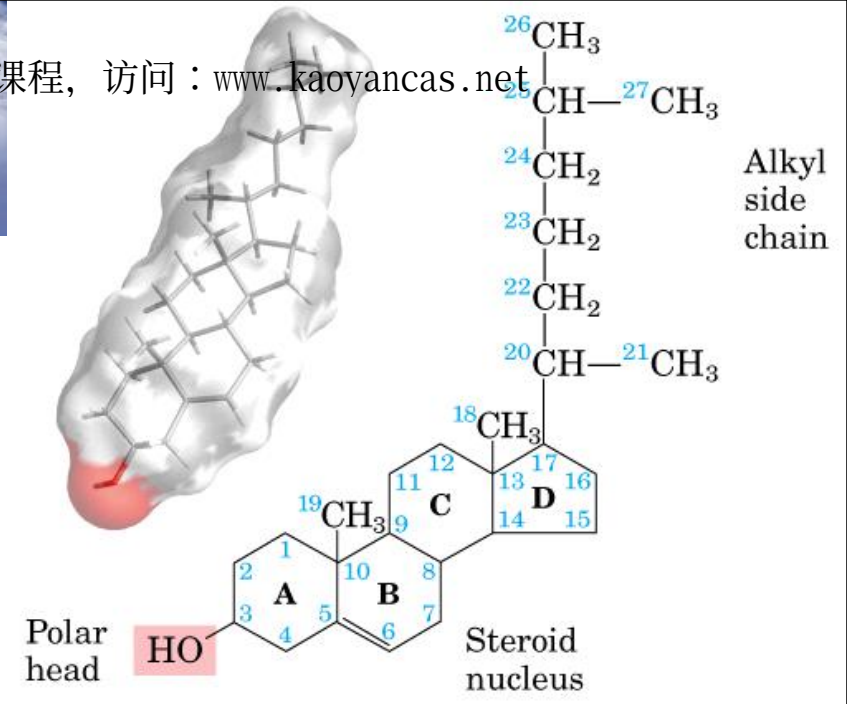
Aldosterone

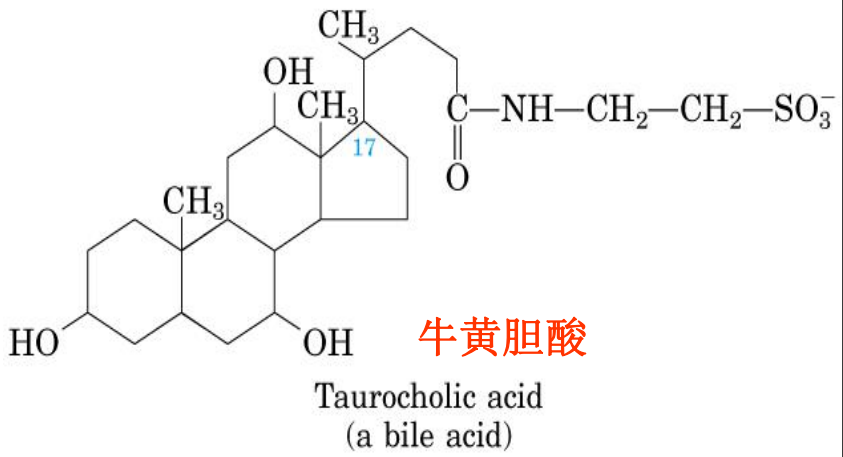
Prednisolone

强的松龙

Prednisone

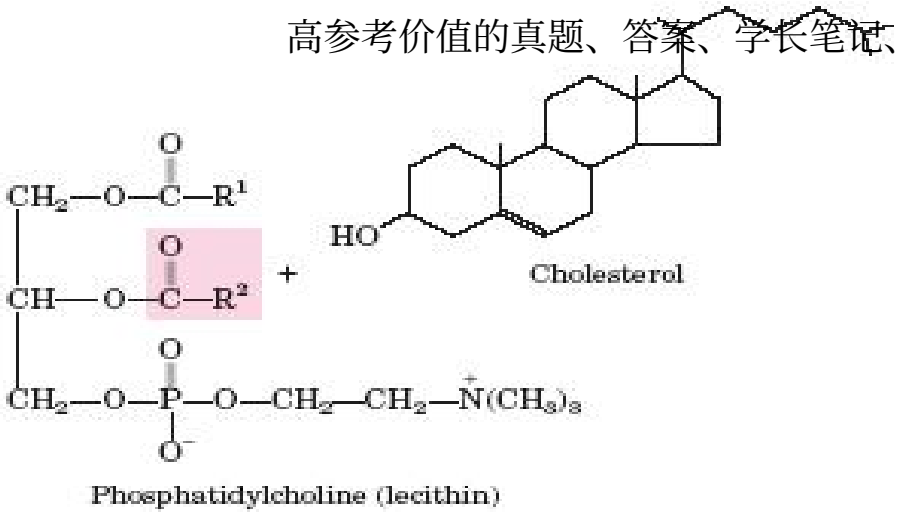
强的松

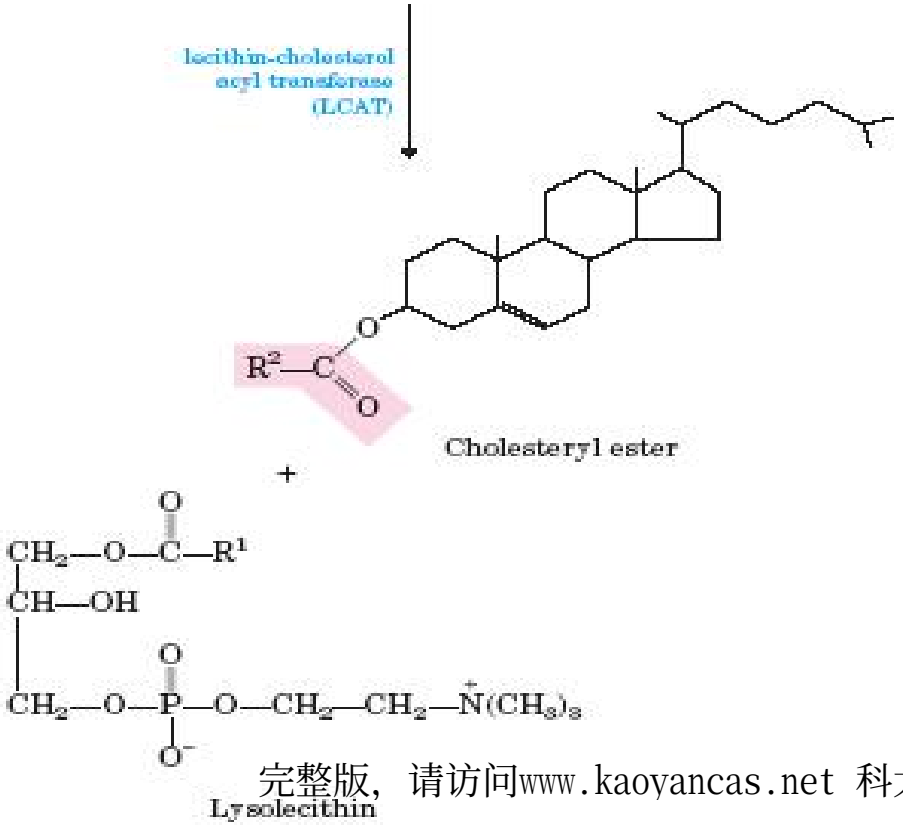


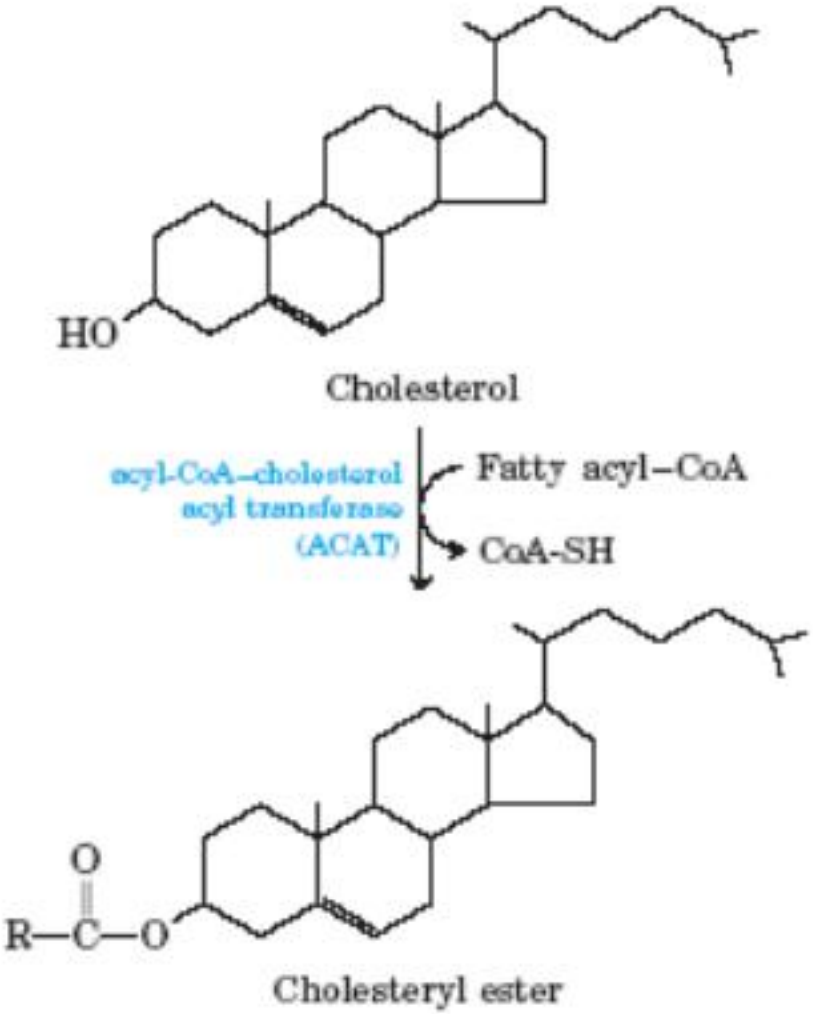


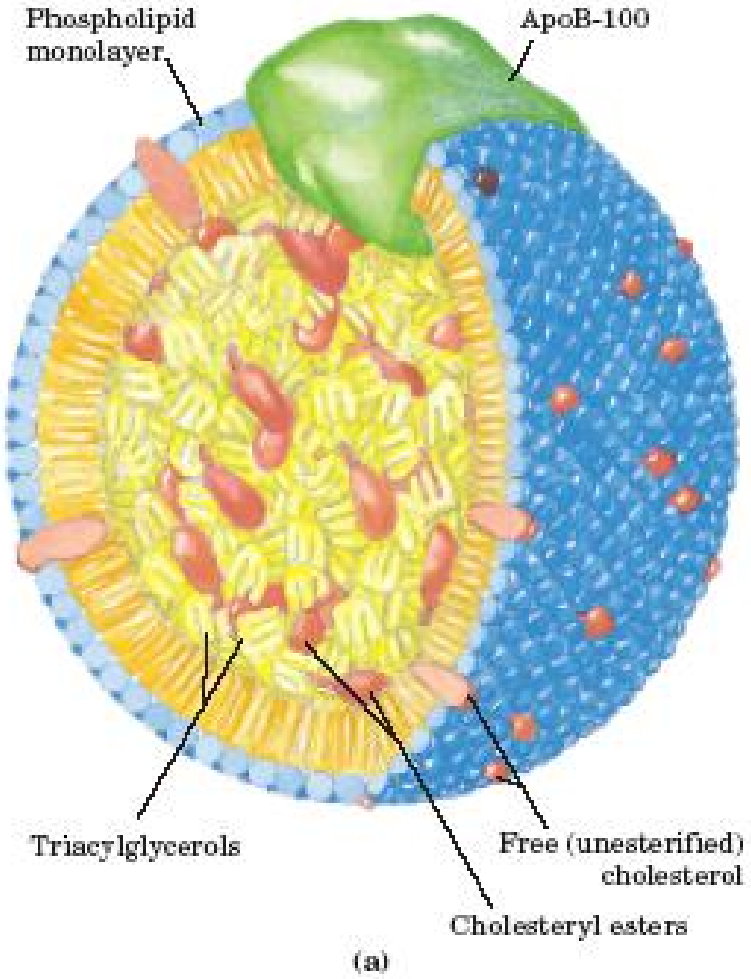
牛黄胆酸

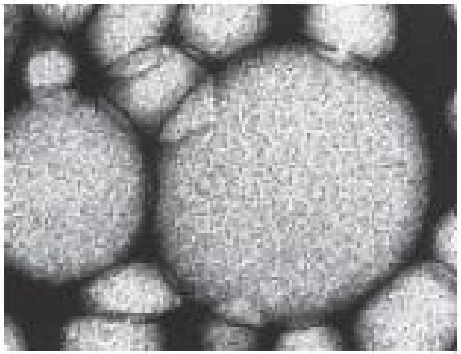
Taurocholic acid
(a bile acid)

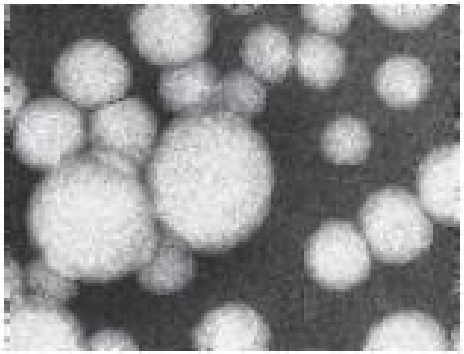


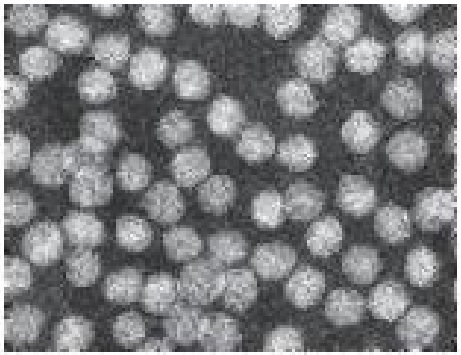


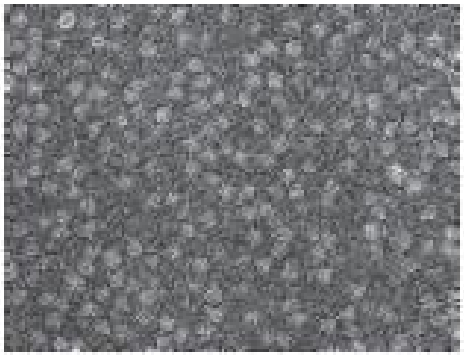





Chylomicrons (×60,000)


VLDL (×180,000)


LDL (×180,000)


HDL (×180,000)

(b)

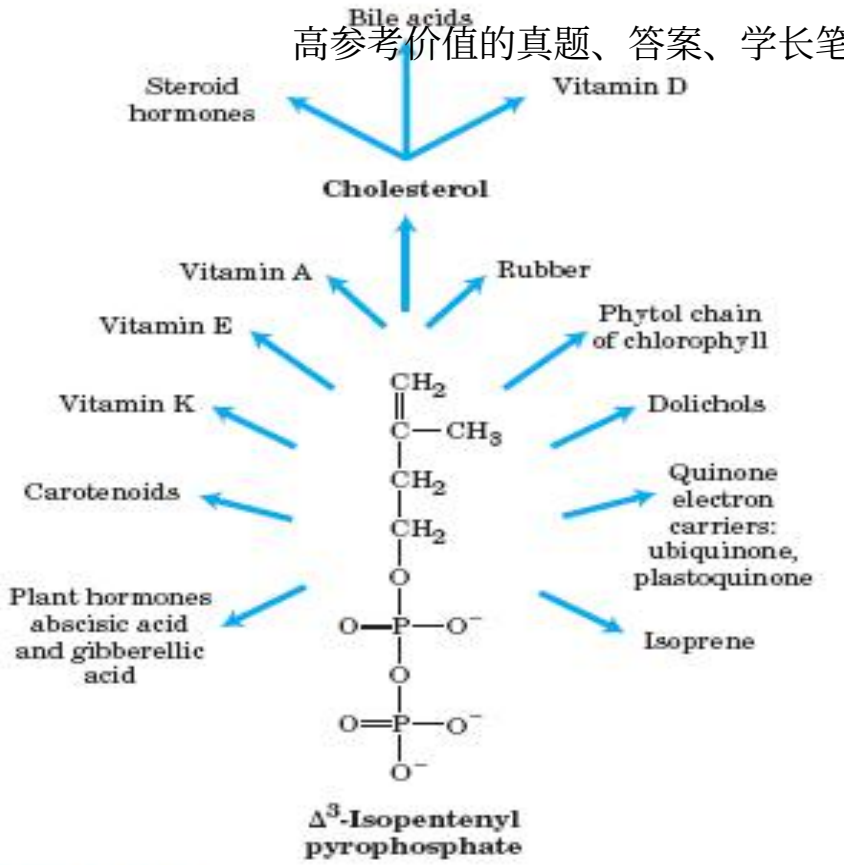
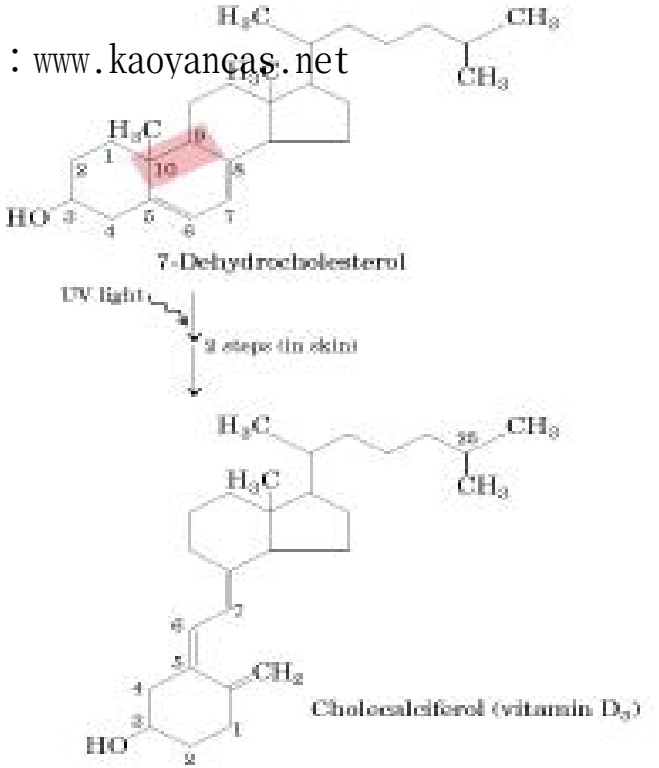
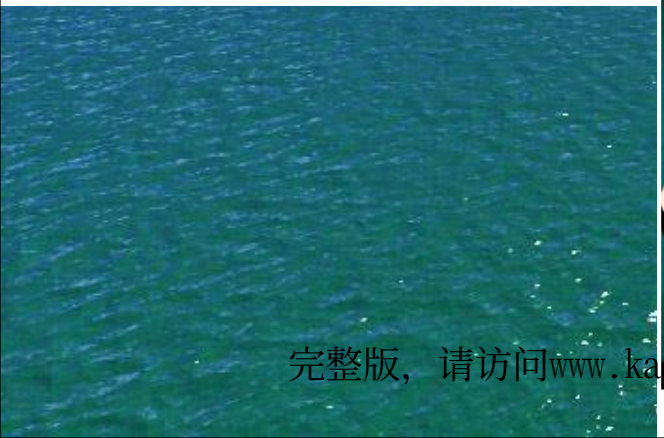
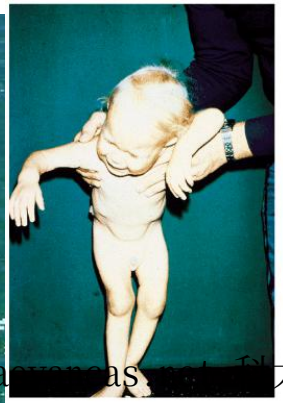


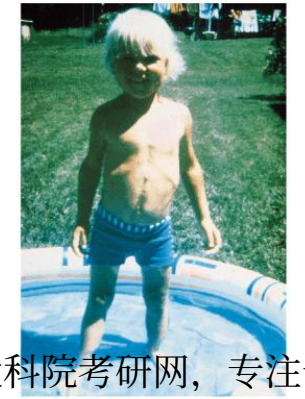
FIGURE 21-48 Overview of isoprenoid biosynthesis. The structures of most of the end products shown here are given in Chapter 10.





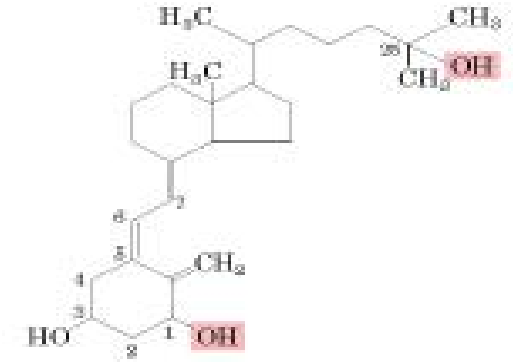


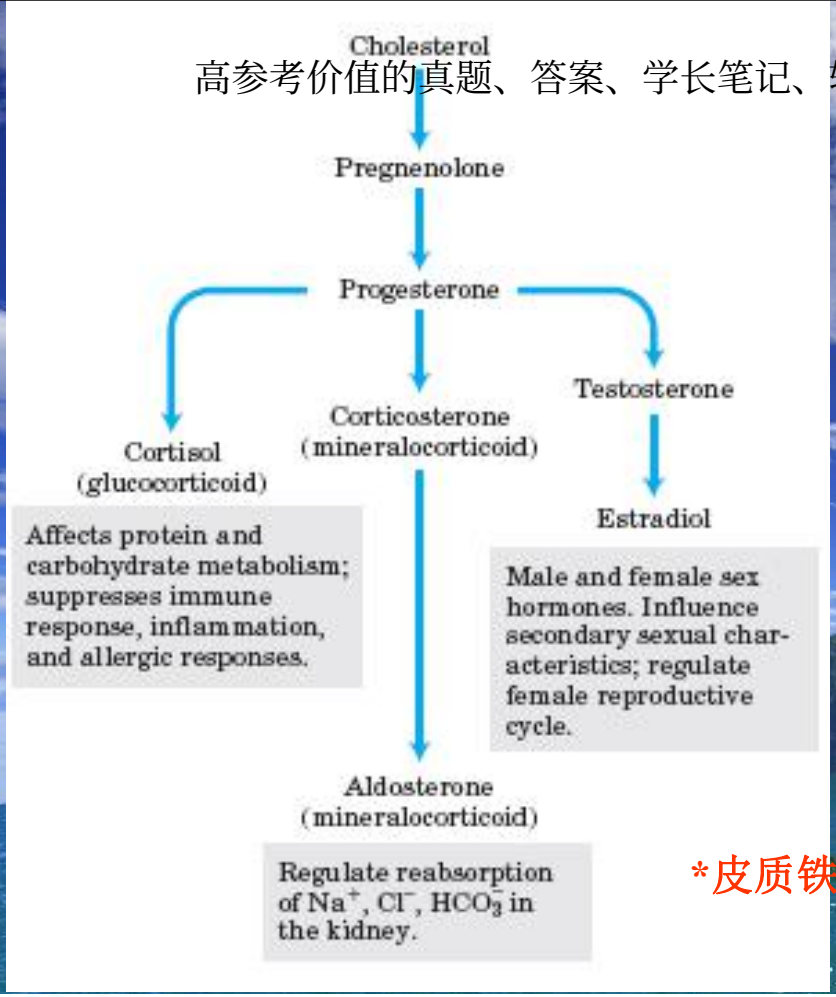
Before vitamin D treatment



After 14 months of vitamin D treatment

(b)





*皮质铁氧还蛋白

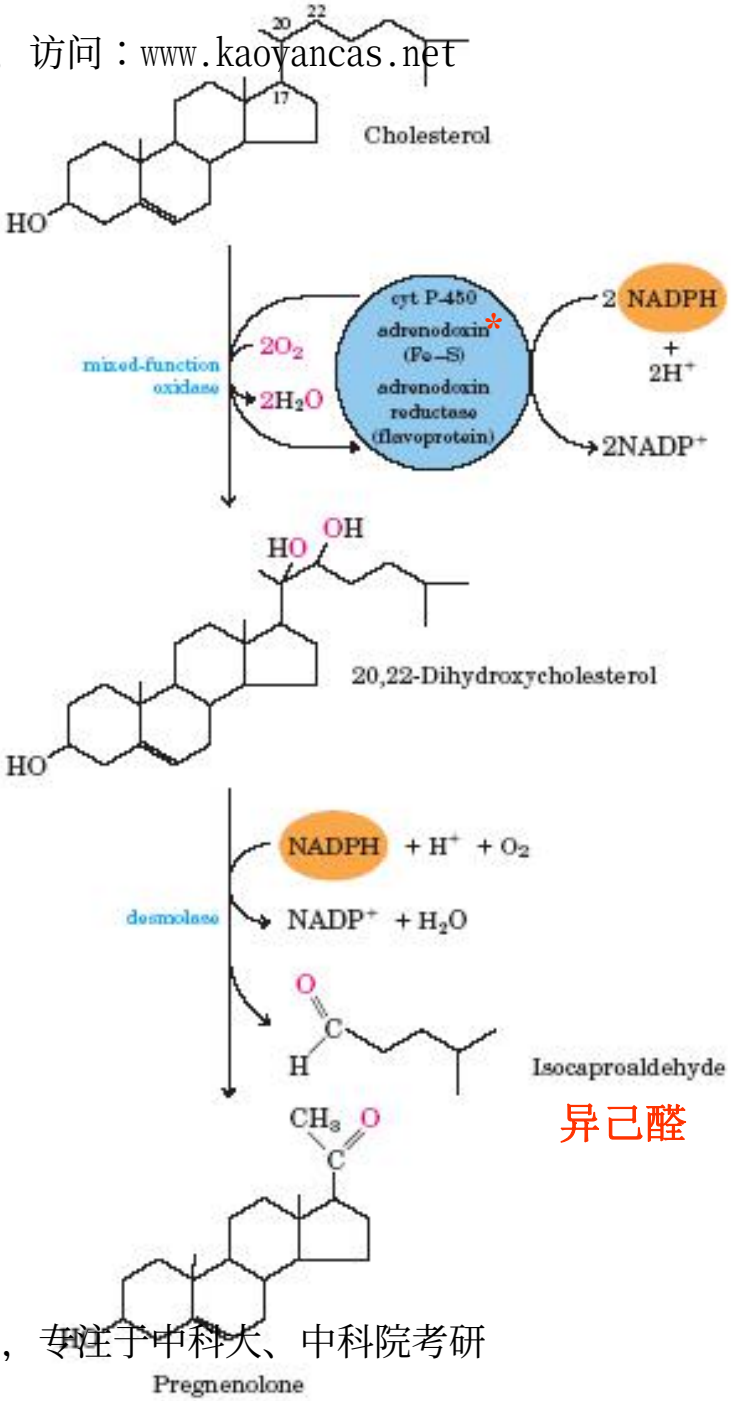


FIGURE 21–47 Side-chain cleavage in the synthesis of steroid hormones. Cytochrome P-450 acts as electron carrier in this mixed-function oxidase system that oxidizes adjacent carbons. The process also requires the electron-transferring proteins adrenodoxin* and adrenodoxin reductase. This system for cleaving side chains is found in mitochondria of the adrenal cortex, where active steroid production occurs. Pregnenolone is the precursor of all other steroid hormones (see Fig. 21–46).

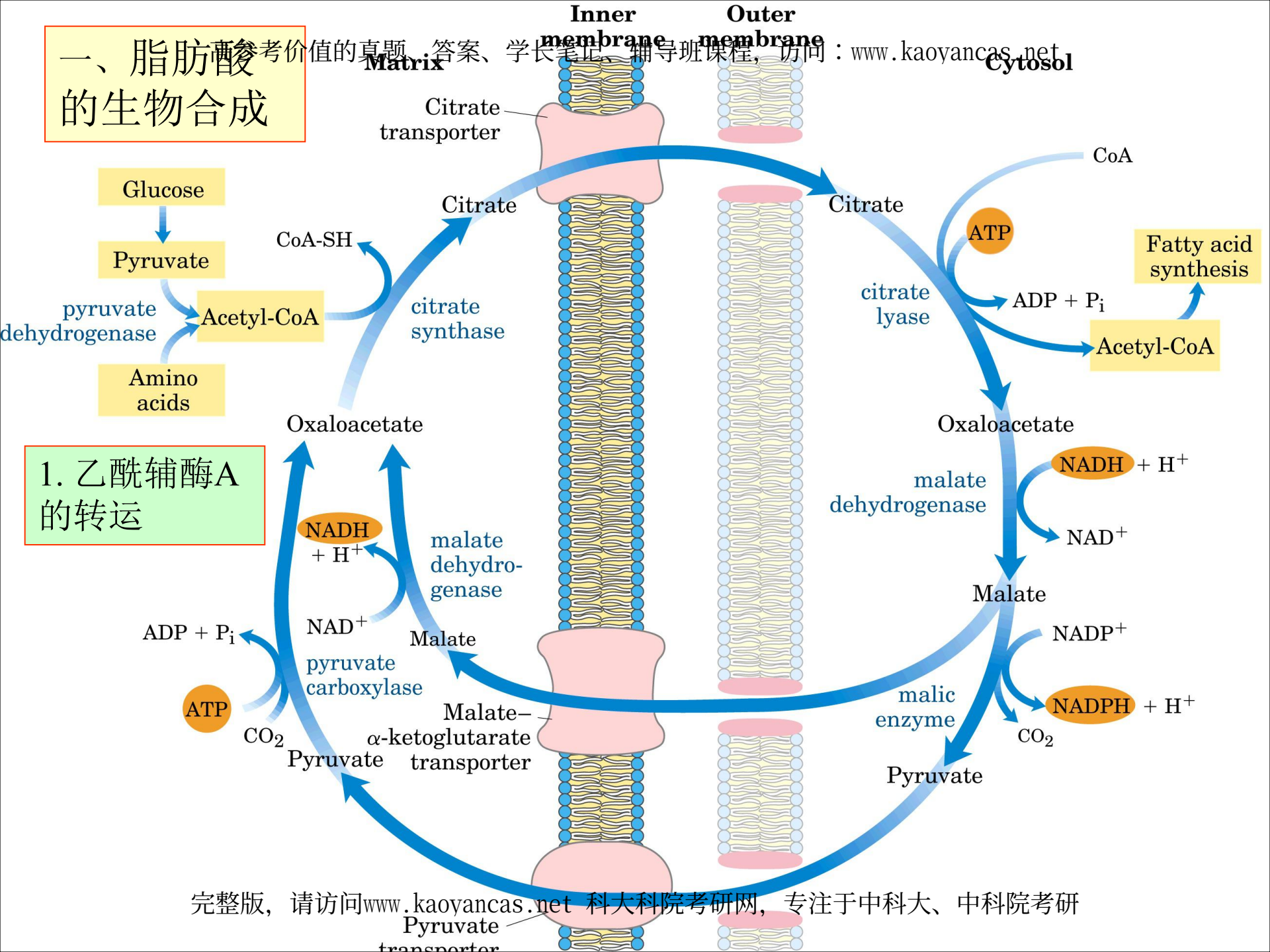
基本要求

1. 熟悉脂质的消化、吸收和传送。
2. 掌握饱和脂肪酸的氧化途径。（重点）
3. 熟悉不饱和脂肪酸的氧化途径。（难点）
4. 掌握酮体的生成、利用和生物学意义。（重点）
5. 熟悉磷脂、鞘脂类和甾醇的代谢。
6. 掌握脂肪酸代谢的调节。（重点）

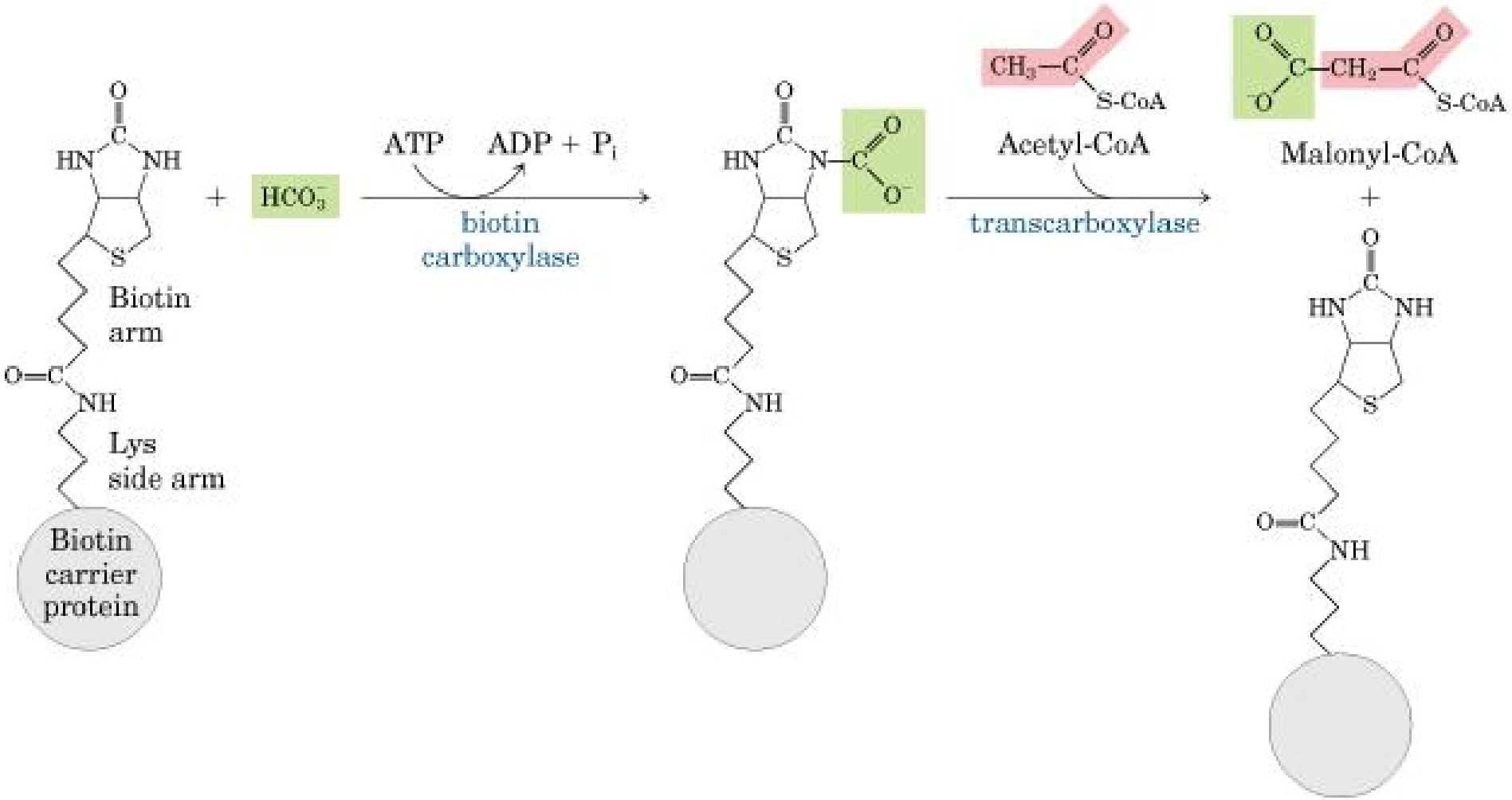
第29章 脂类的生物合成

一、脂肪酸的生物合成

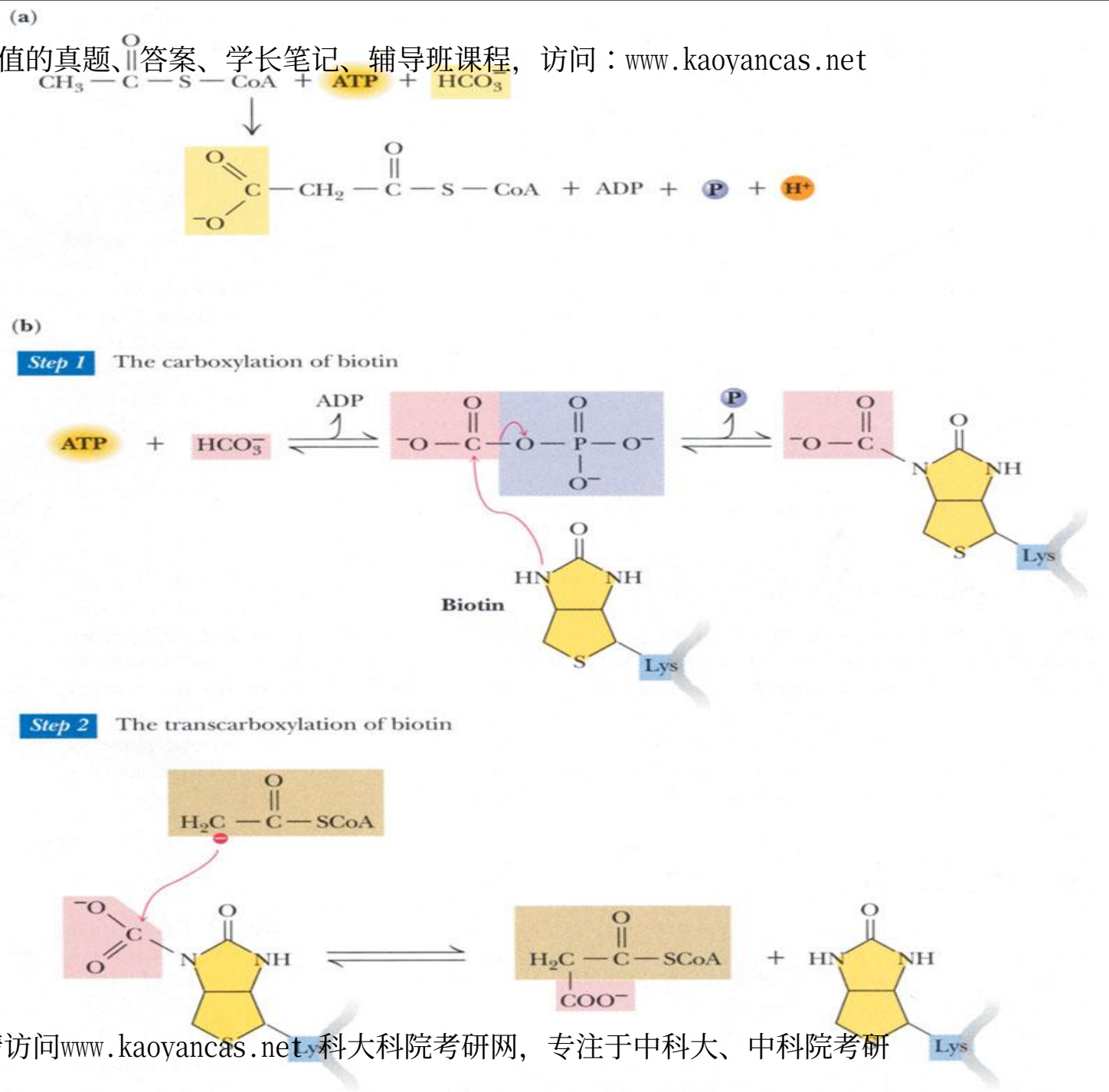
1. 乙酰辅酶A的转运



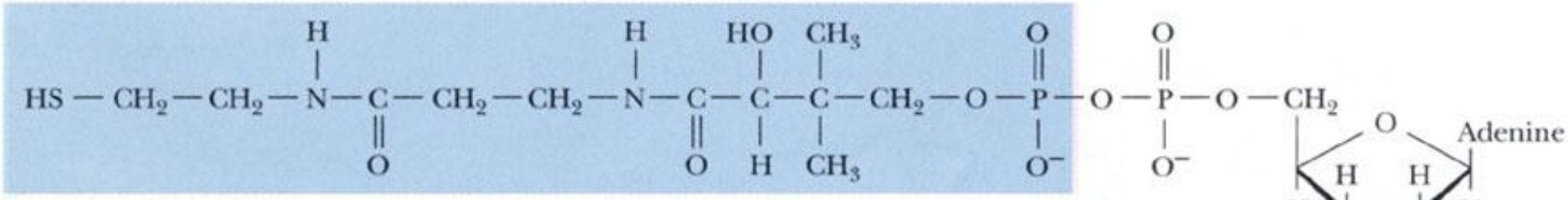
2. 乙酰辅酶A羧化酶催化的反应



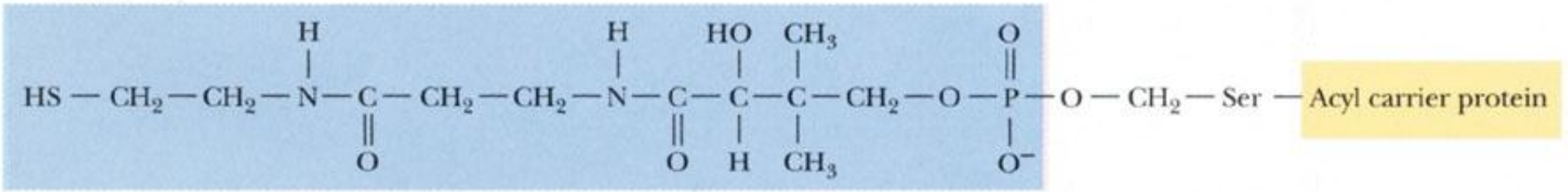
乙酰辅酶A羧化酶催化反应的机制



3. 脂肪酸可以与辅酶A或ACP连接



Phosphopantetheine group of coenzyme A



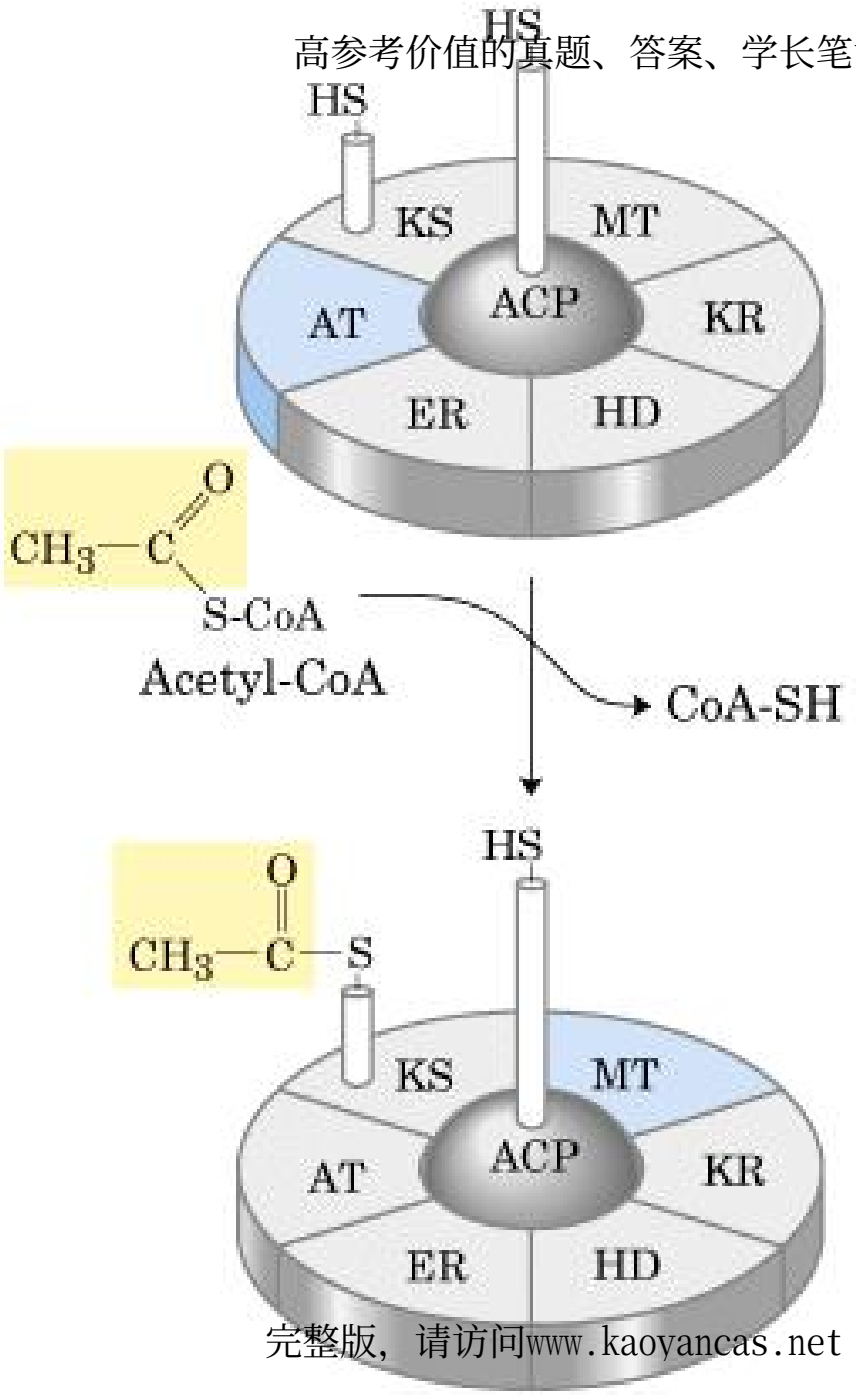
Phosphopantetheine prosthetic group of ACP

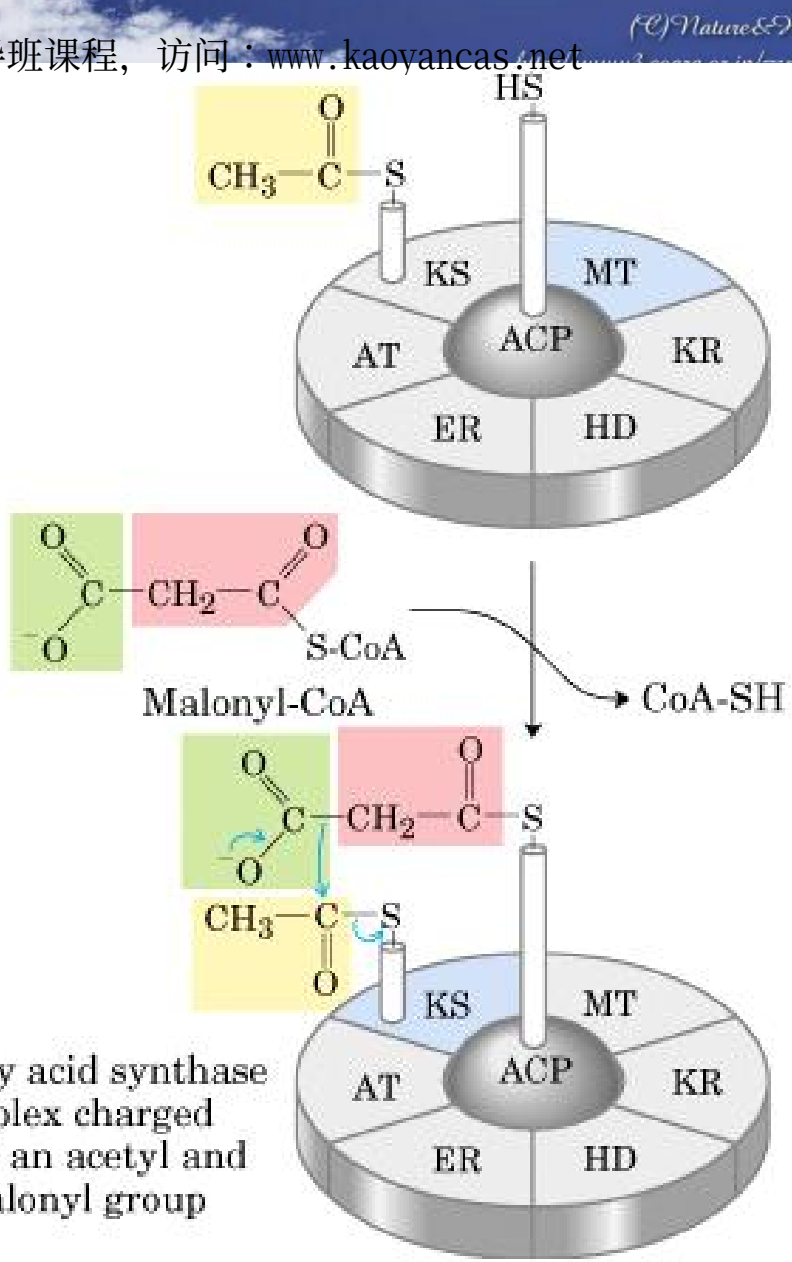
4. 软脂酸合成的途径

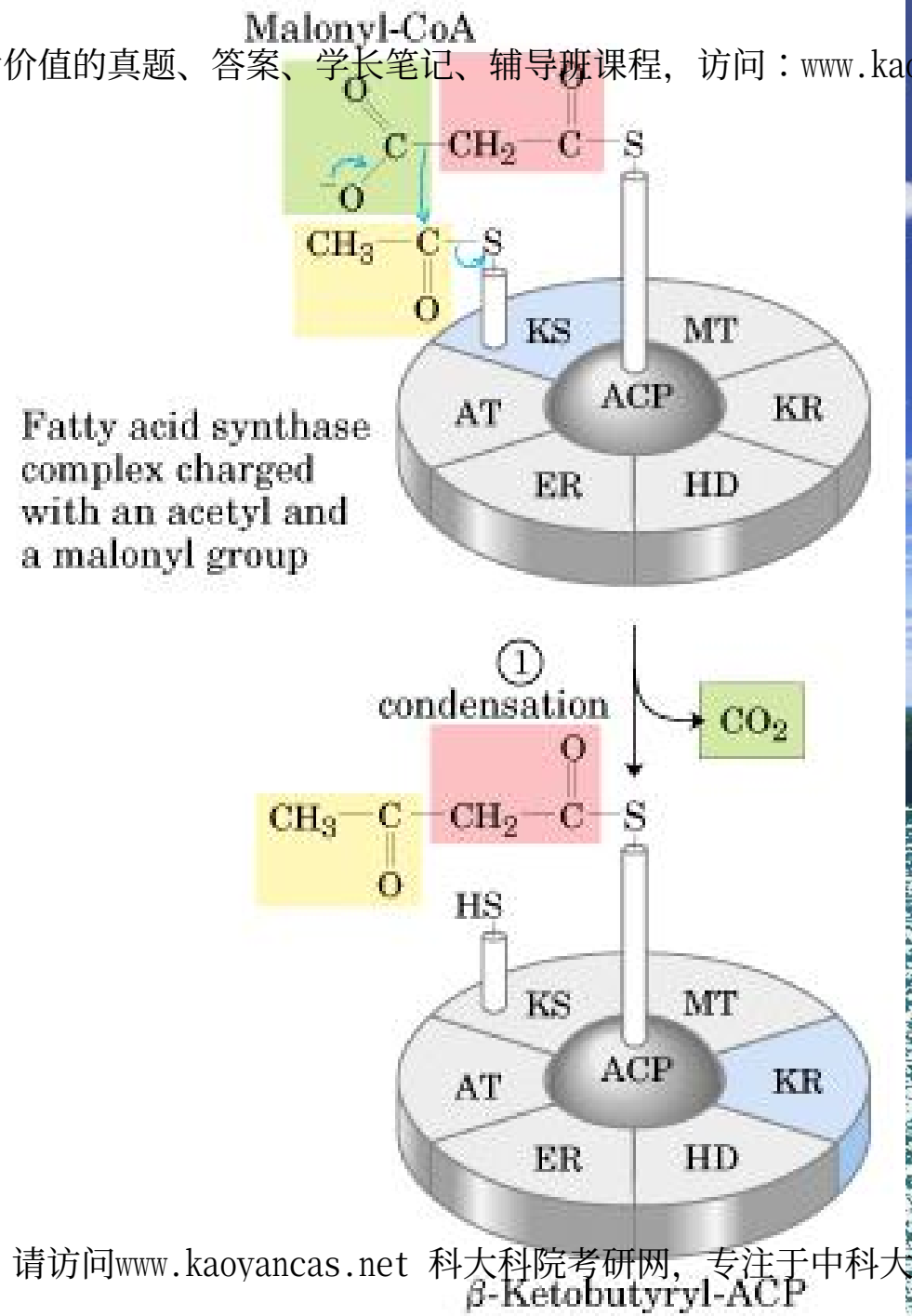
table 21–1

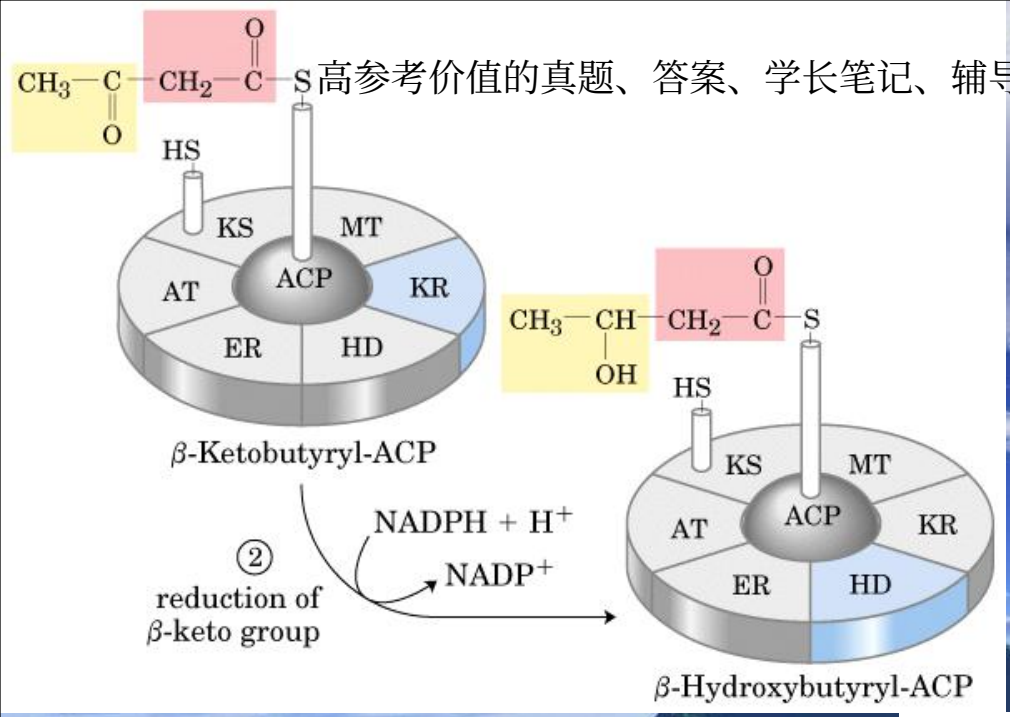
Proteins of the Fatty Acid Synthase Complex of *E. coli*

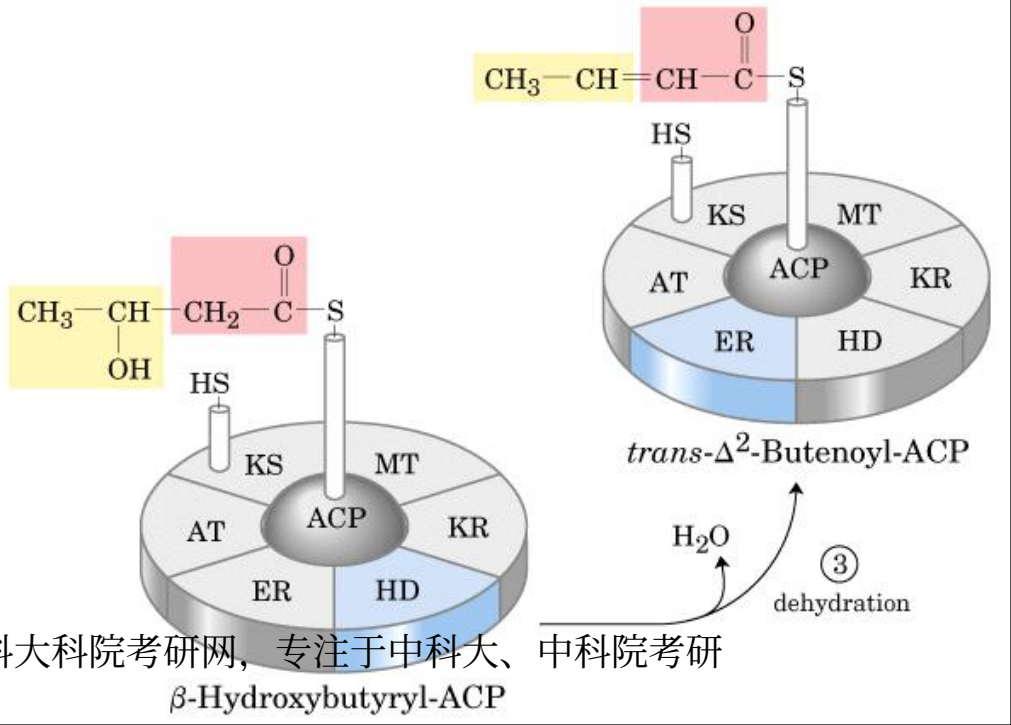
Protein	Role
Acyl carrier protein (ACP)	Carries acyl groups in thioester linkage
Acetyl-CoA–ACP transacetylase (AT)	Transfers acyl group from CoA to Cys residue of KS
β-Ketoacyl-ACP synthase (KS)	Condenses acyl and malonyl groups (there are at least three isozymes of KS)
Malonyl-CoA–ACP transferase (MT)	Transfers malonyl group from CoA to ACP
β-Ketoacyl-ACP reductase (KR)	Reduces β-keto group to β-hydroxy group
β-Hydroxyacyl-ACP dehydratase (HD)	Removes H_2O from β-hydroxyacyl-ACP, creating double bond
Enoyl-ACP reductase (ER)	Reduces double bond, forming saturated acyl-ACP

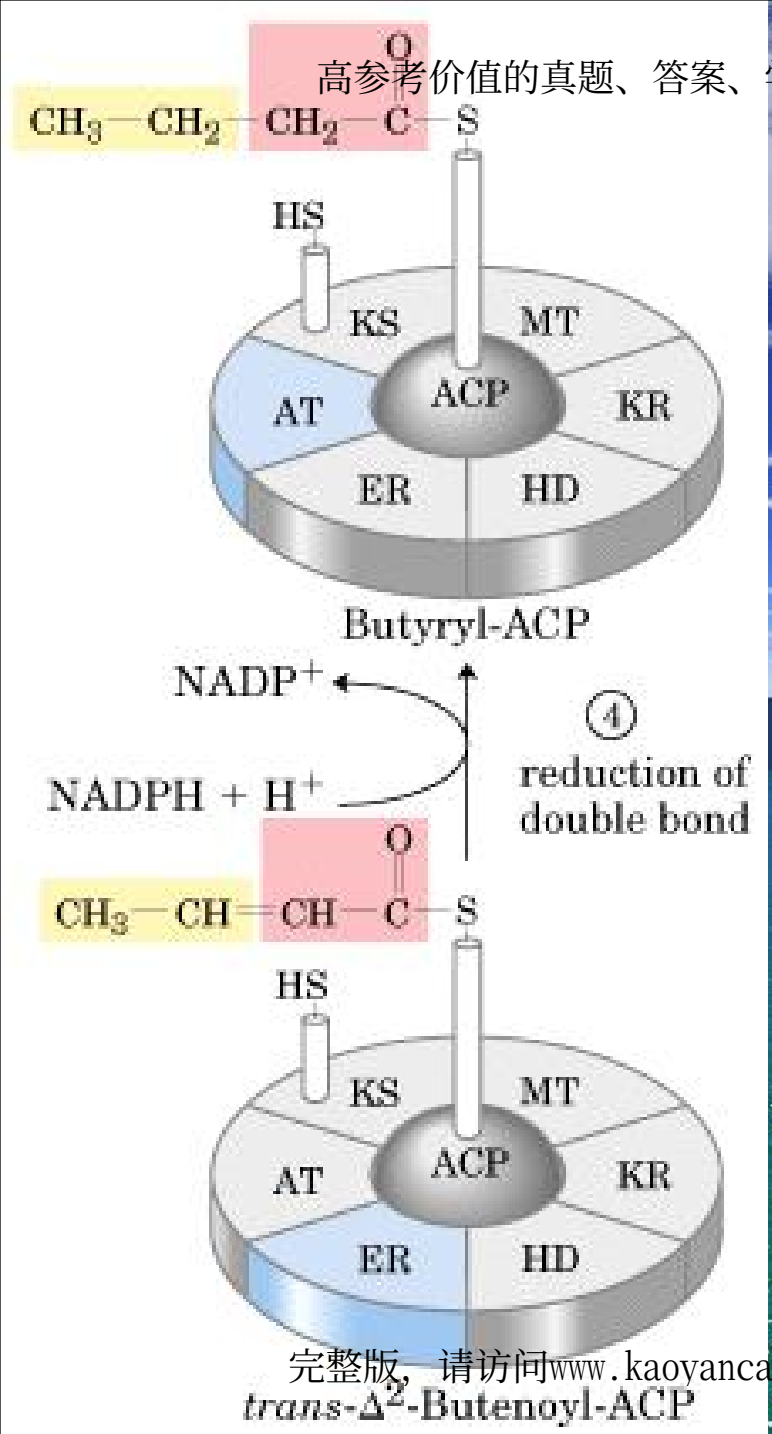


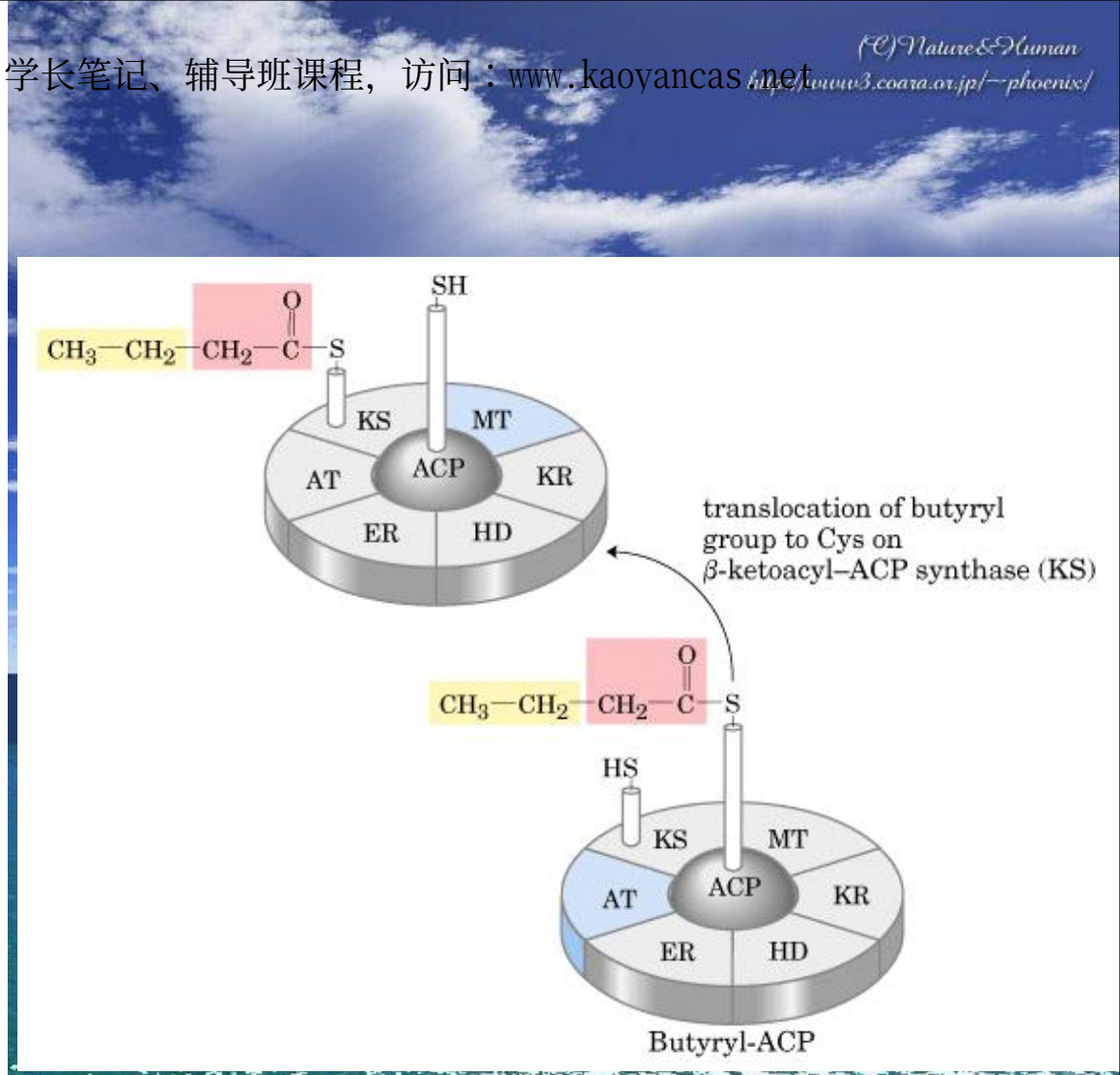


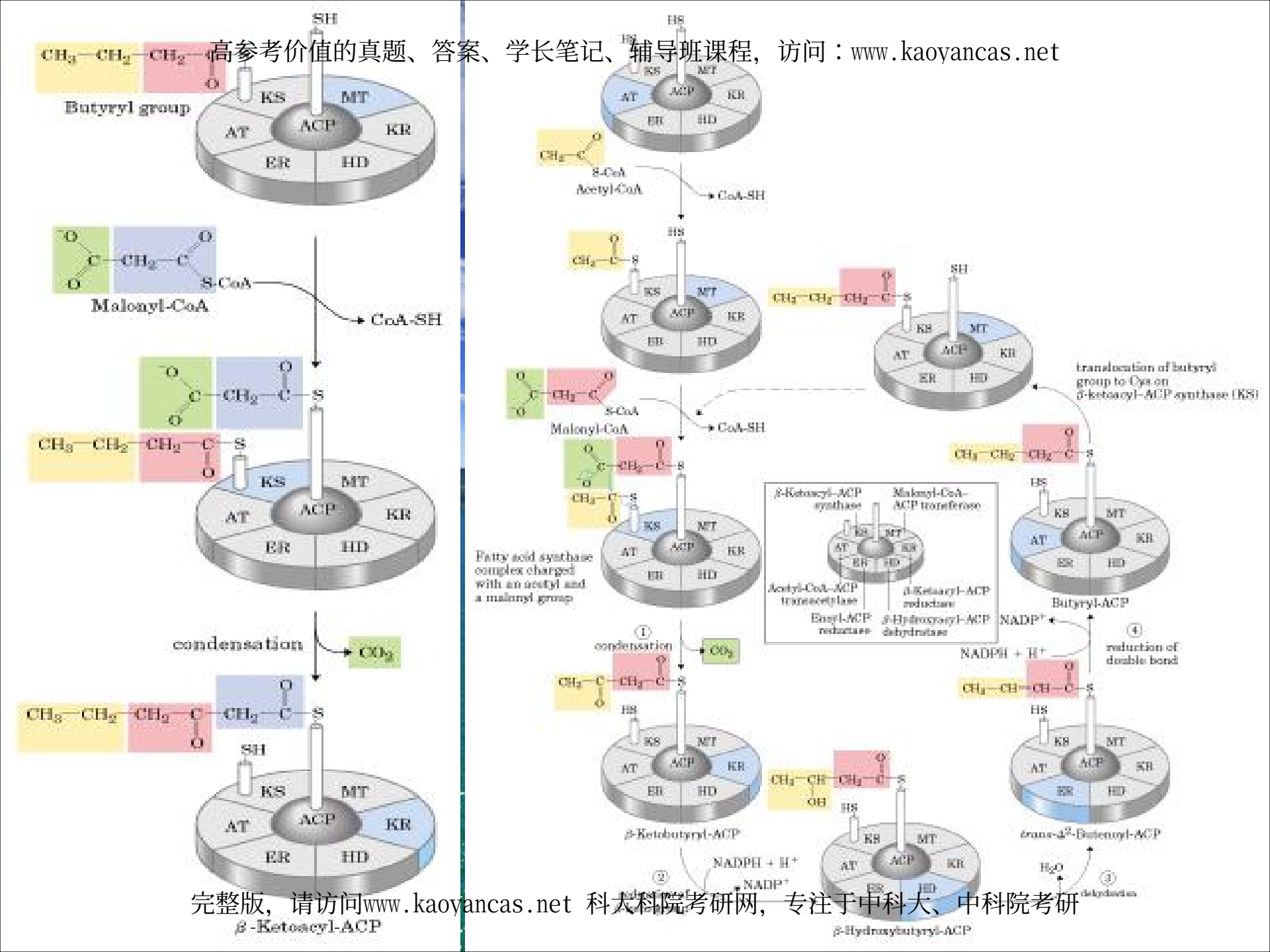




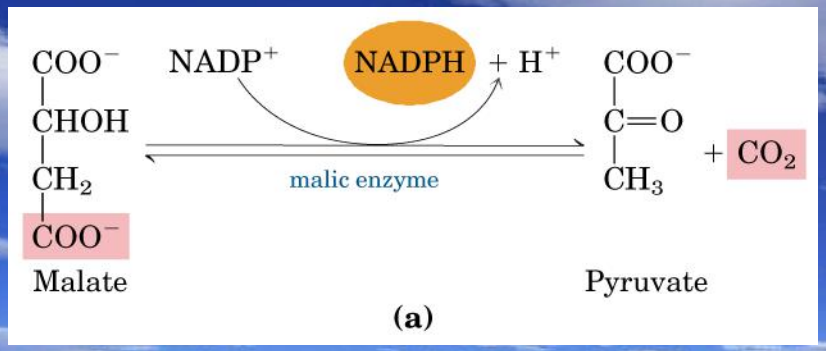


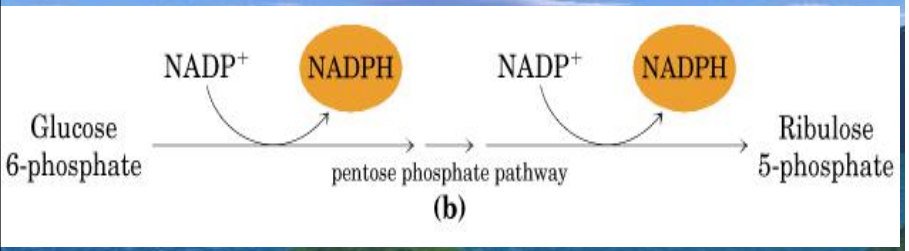






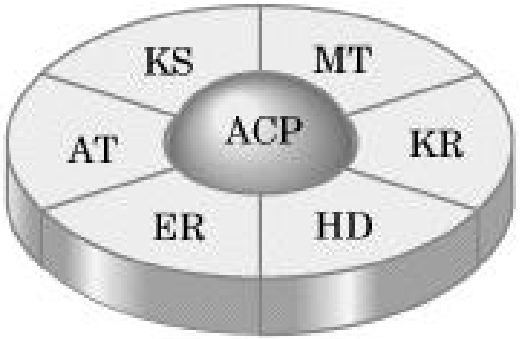
5.NADPH的来源



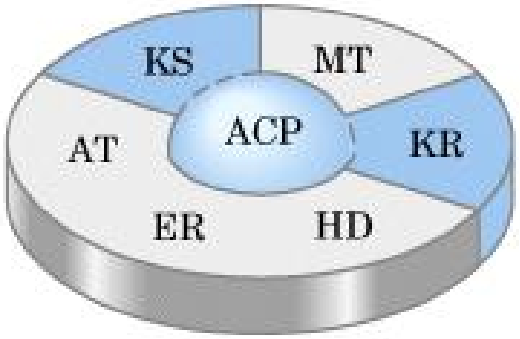


6.不同生物脂肪酸合成酶的结构

Bacteria, Plants
Seven activities in seven separate polypeptides

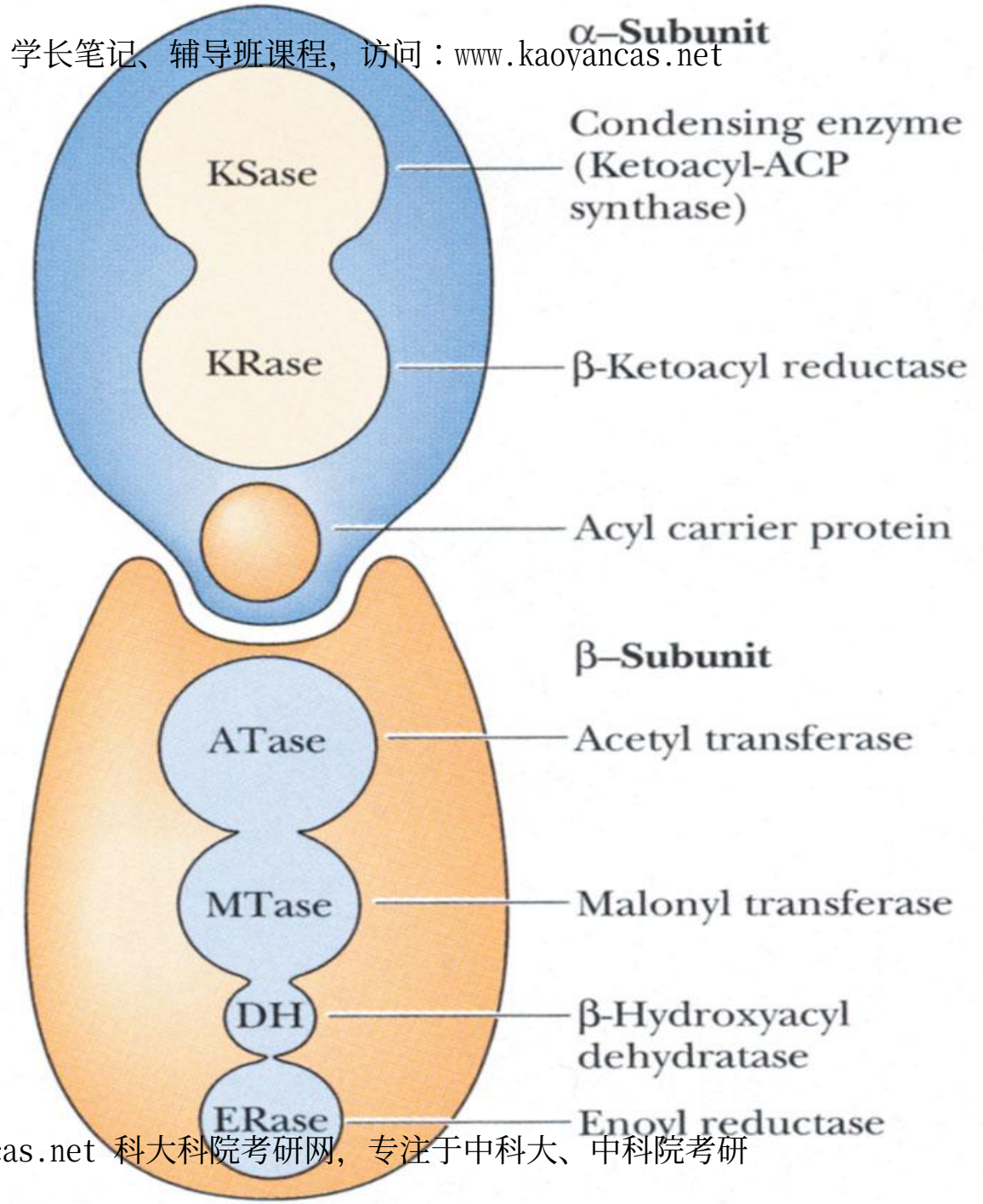


Yeast
Seven activities in two separate polypeptides

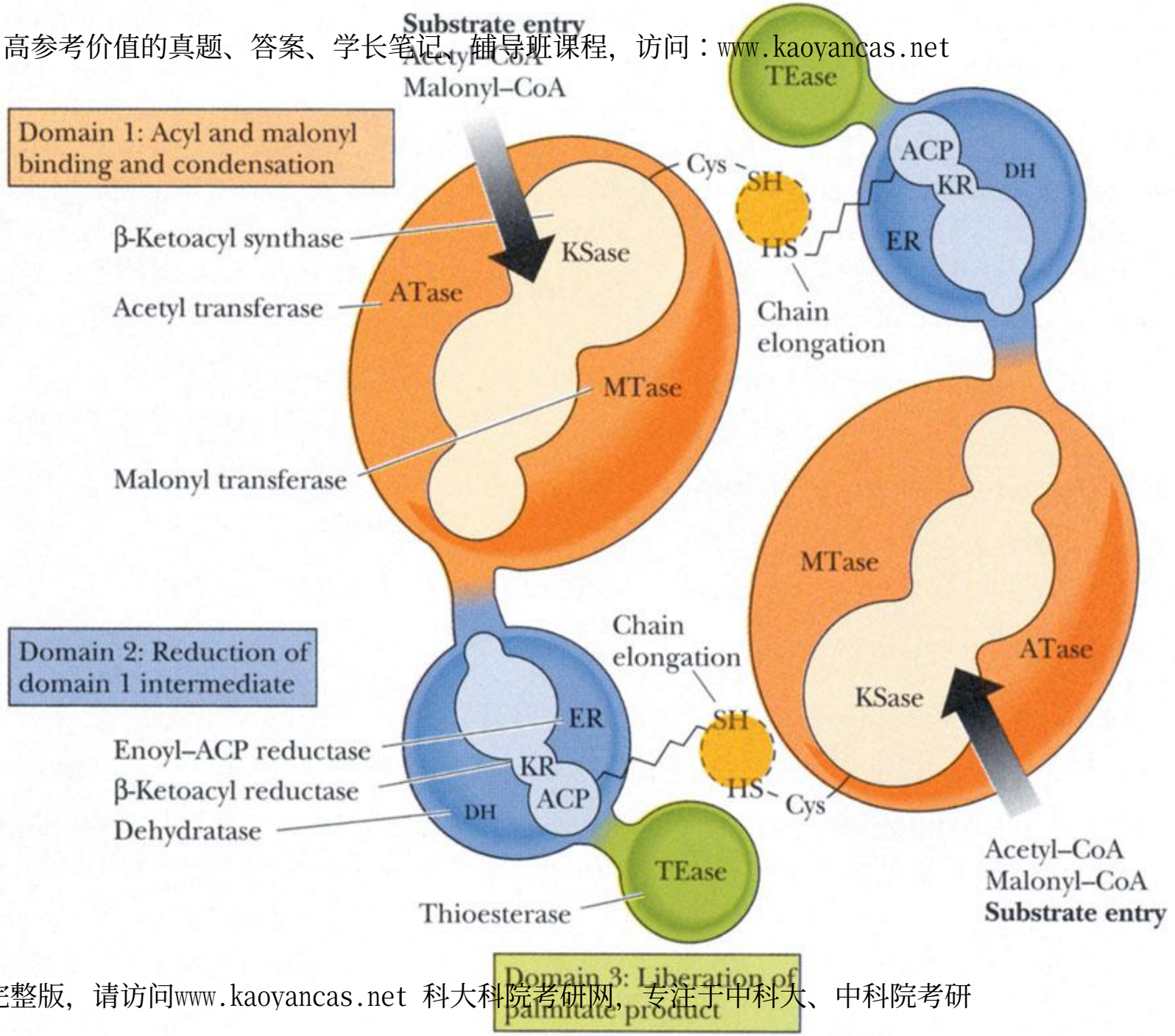


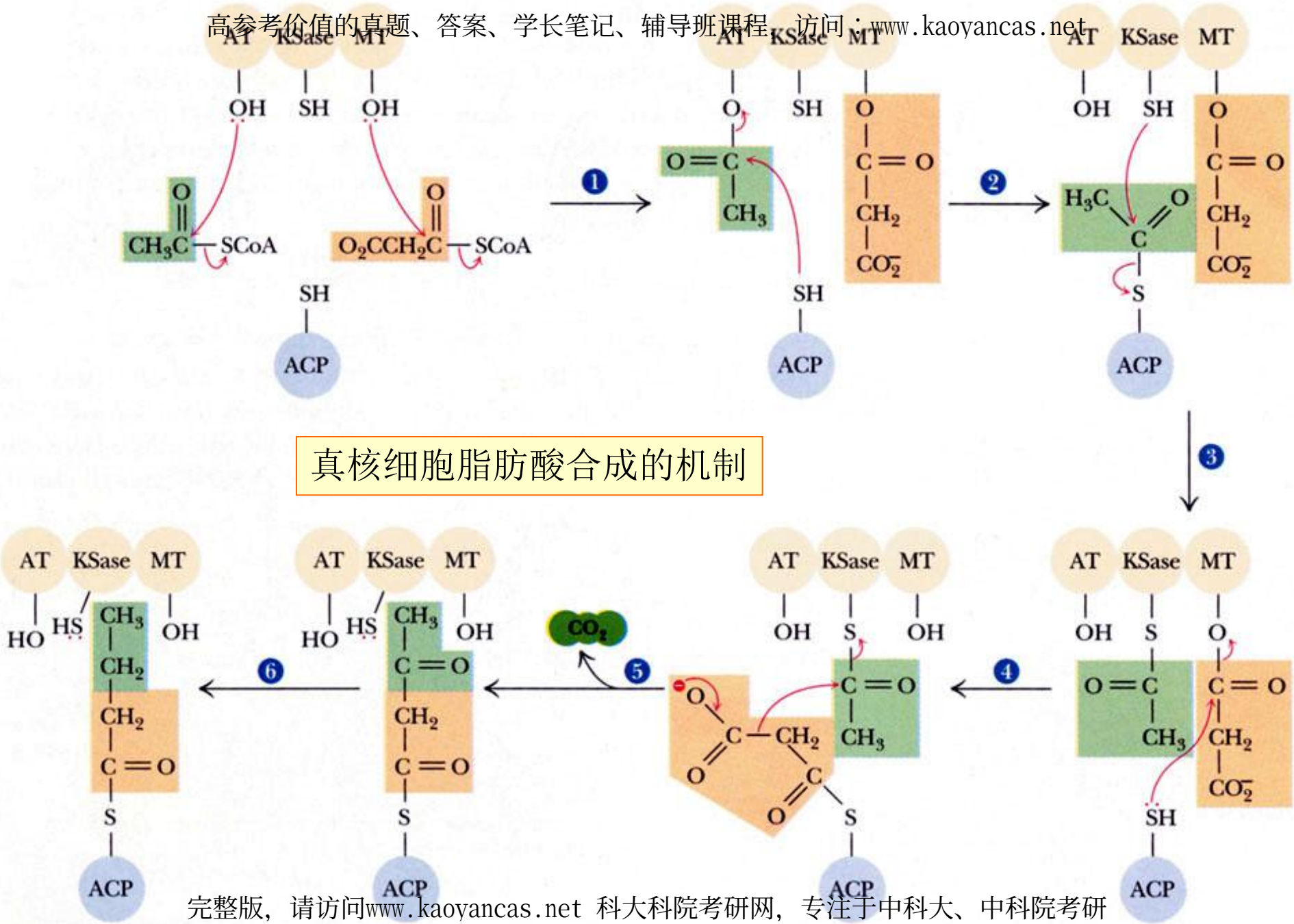
Vertebrates
Seven activities in one large polypeptide

酵母脂肪酸合成酶的结构



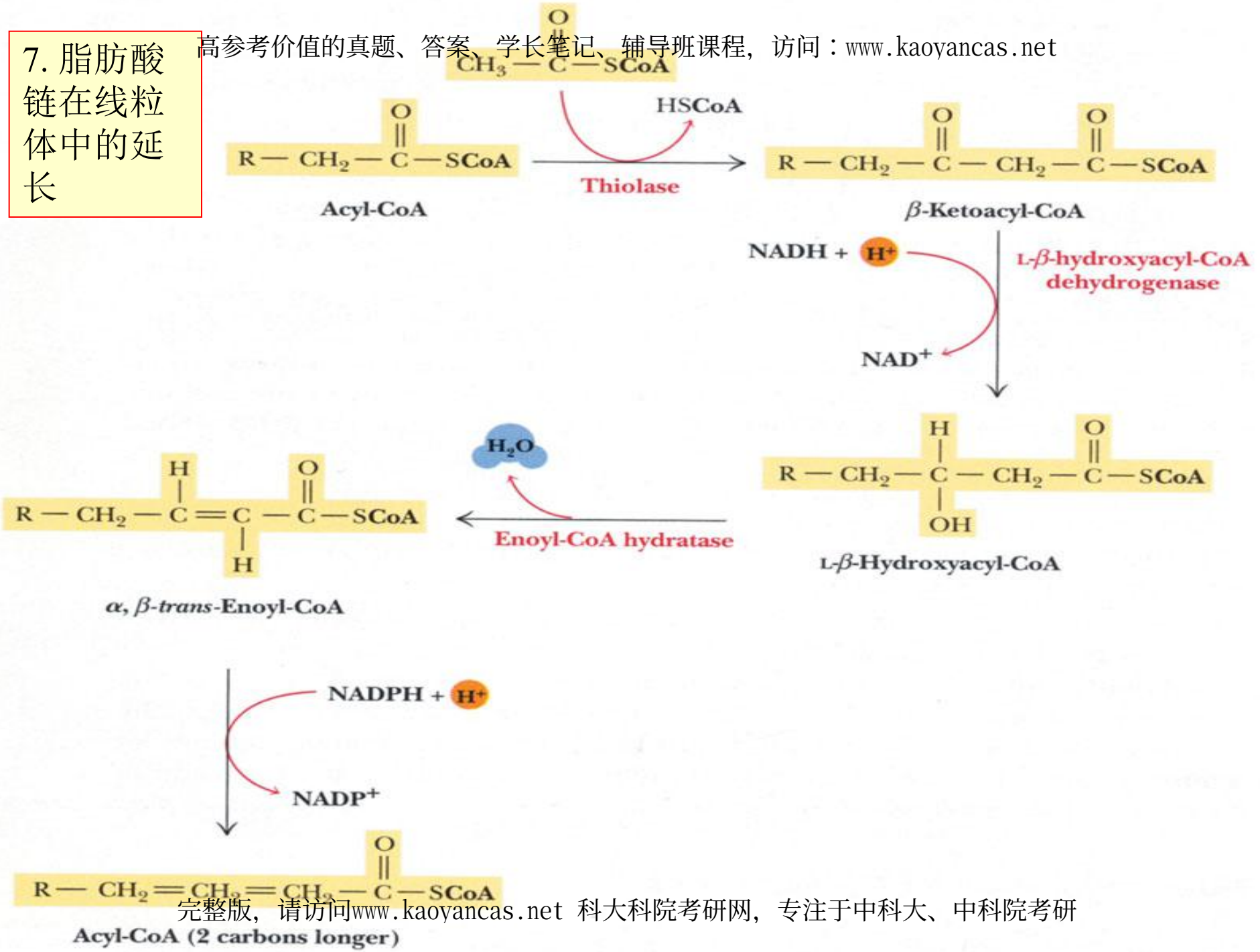
动物细胞脂肪酸合成酶的结构





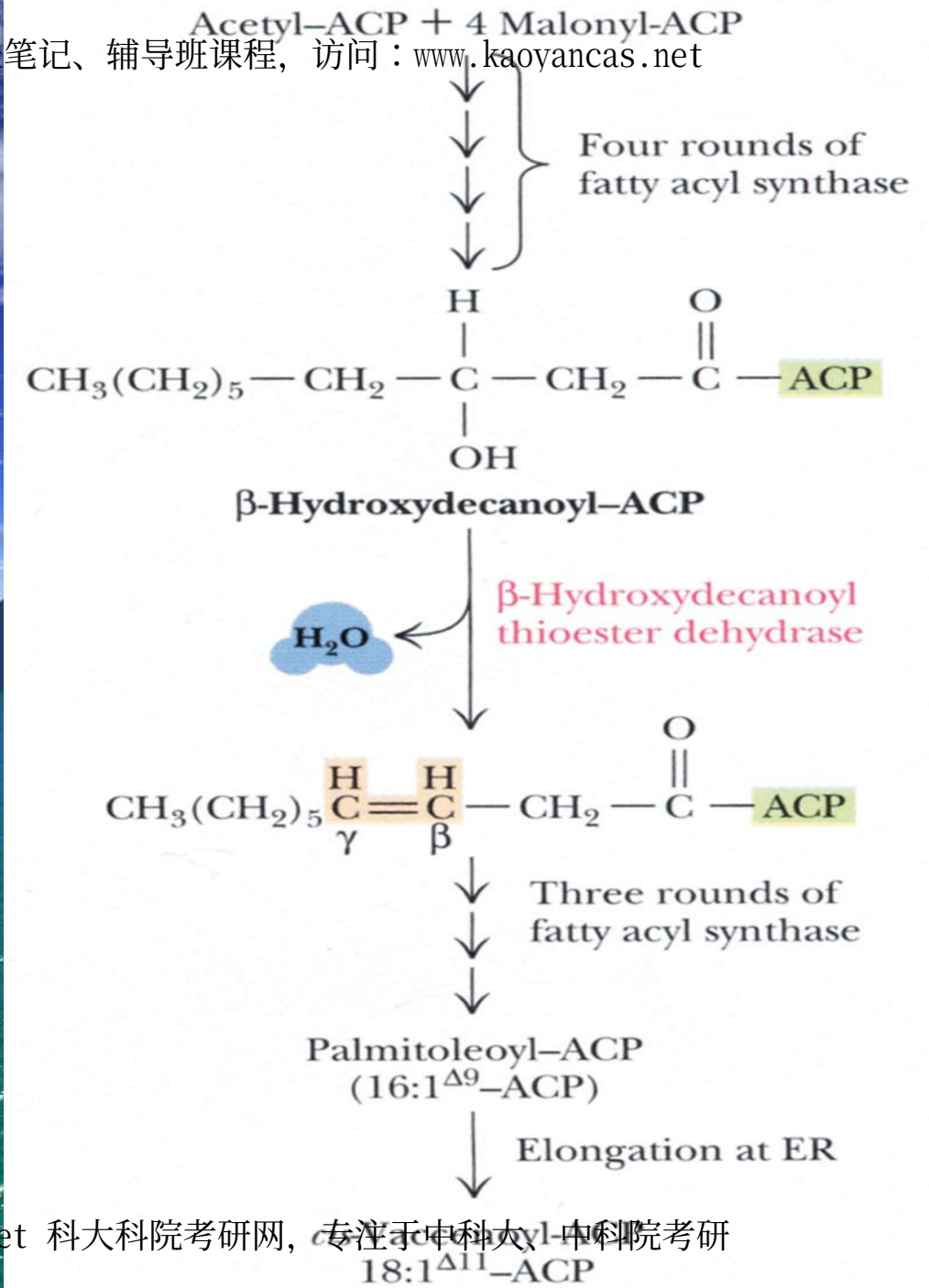
真核细胞脂肪酸合成的机制

7. 脂肪酸链在线粒体中的延长

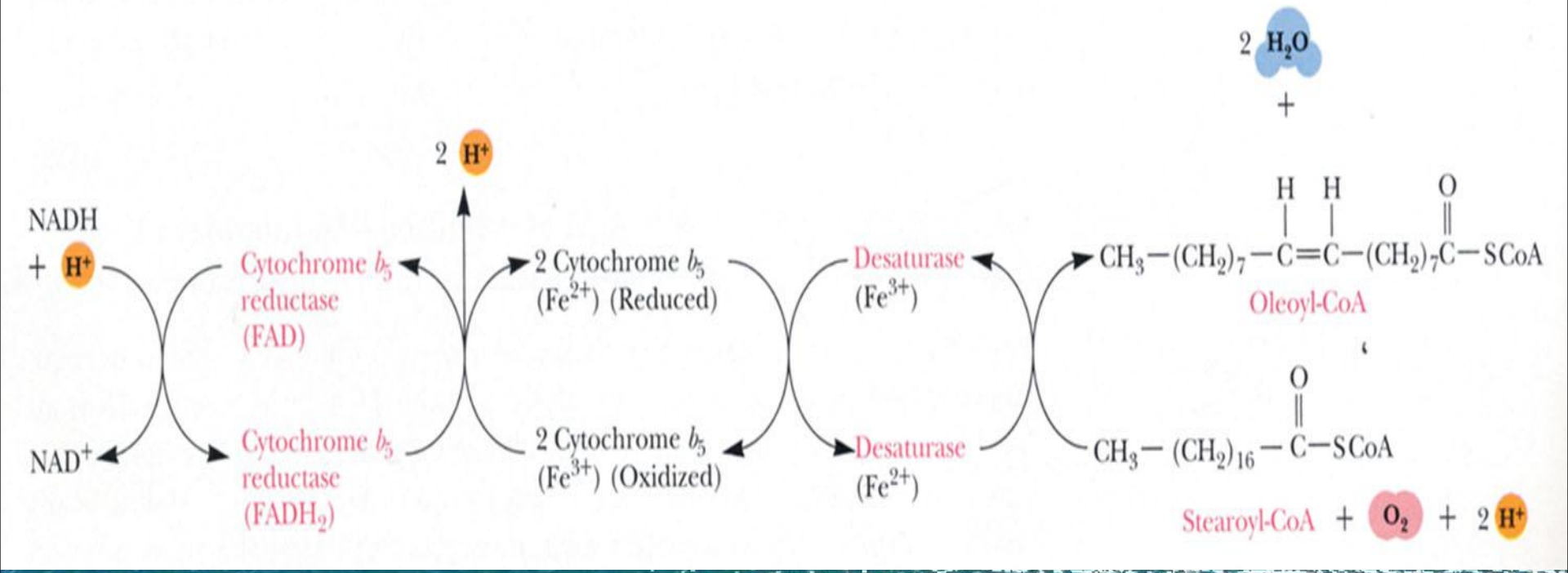


8. 不饱和脂肪酸的合成

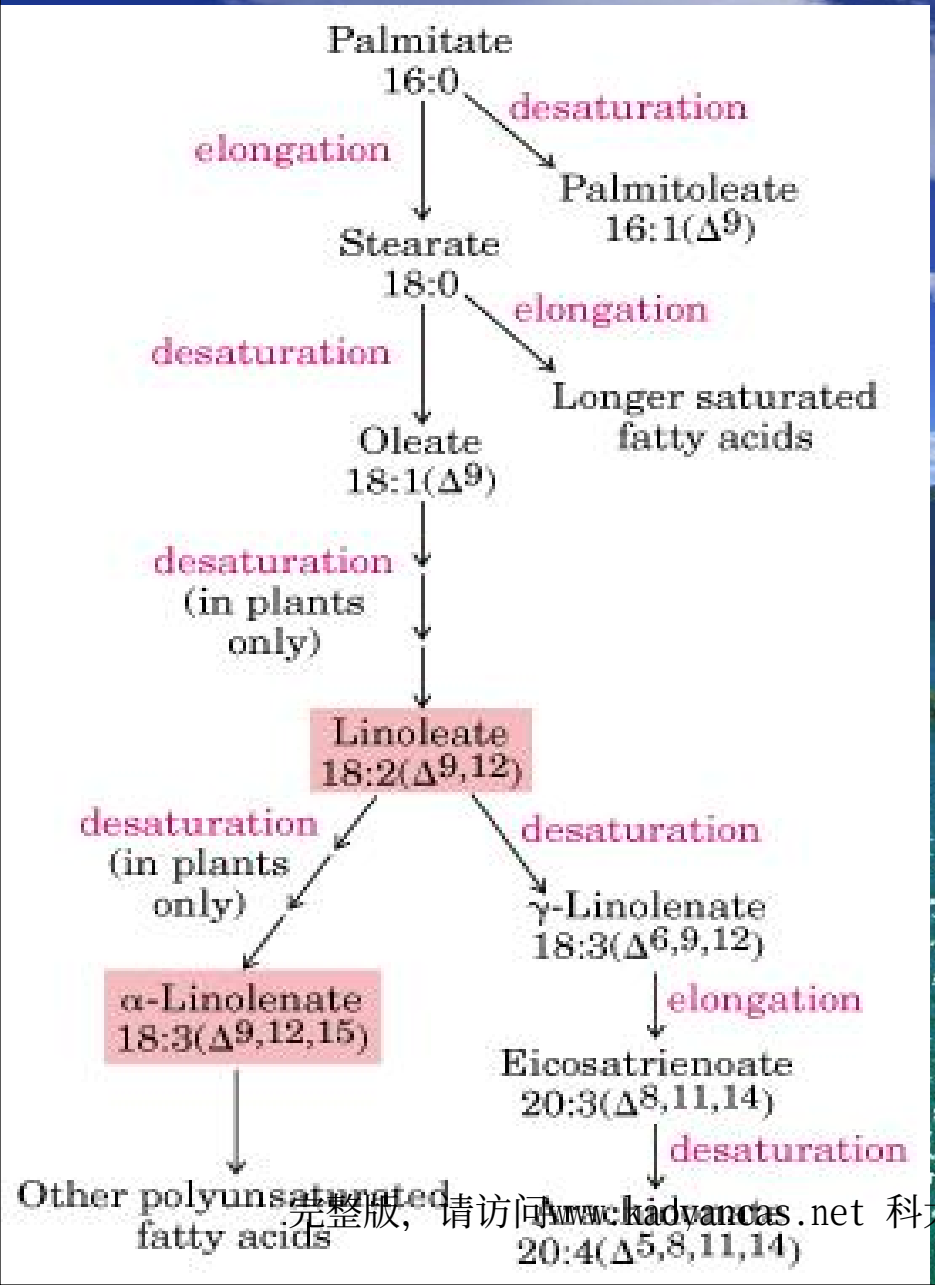
在大肠杆菌中，特定的脱水酶将双键引入延长中的脂肪酸链。

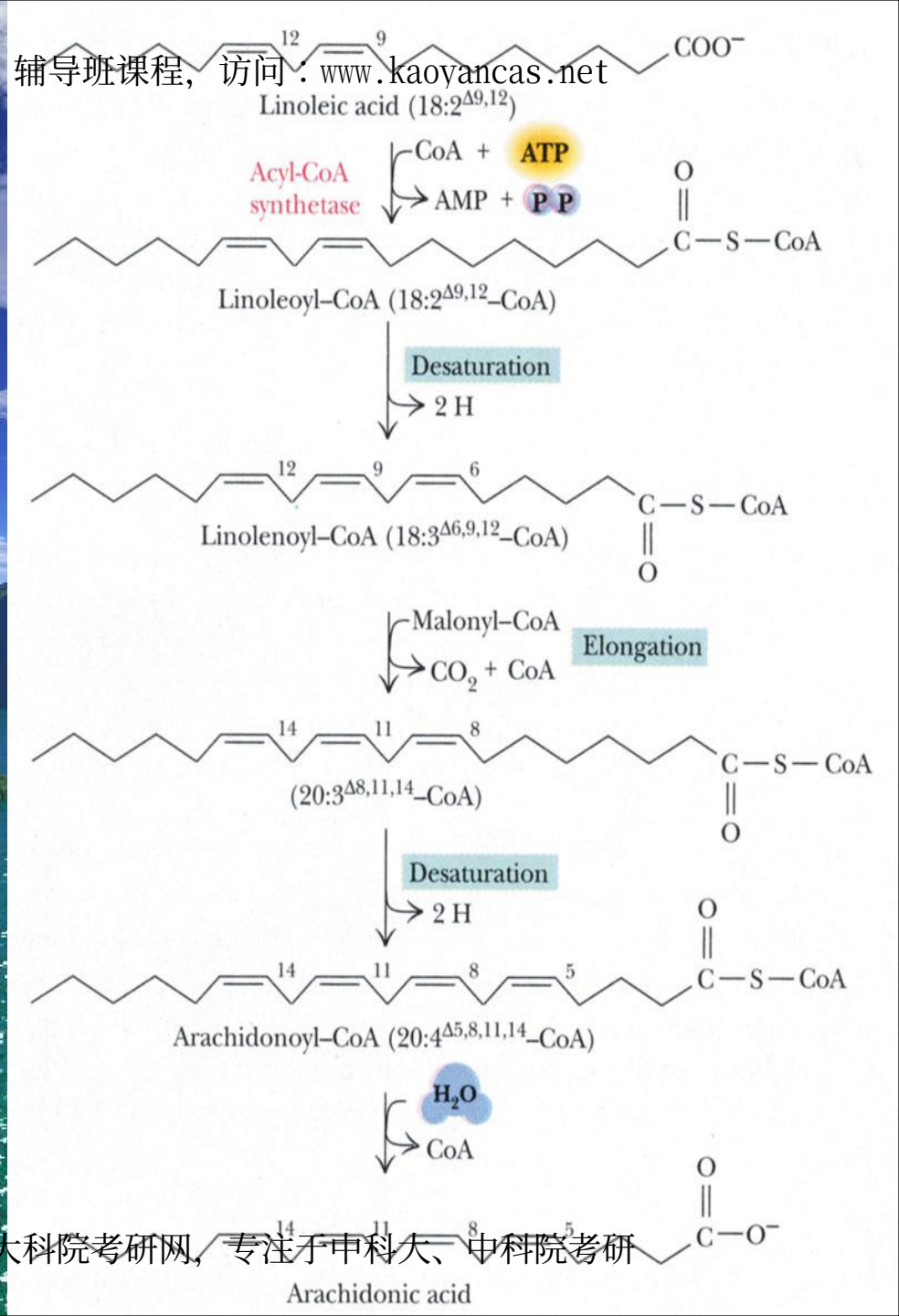


在真核细胞中， 将双键引入脂肪酸链的机制。

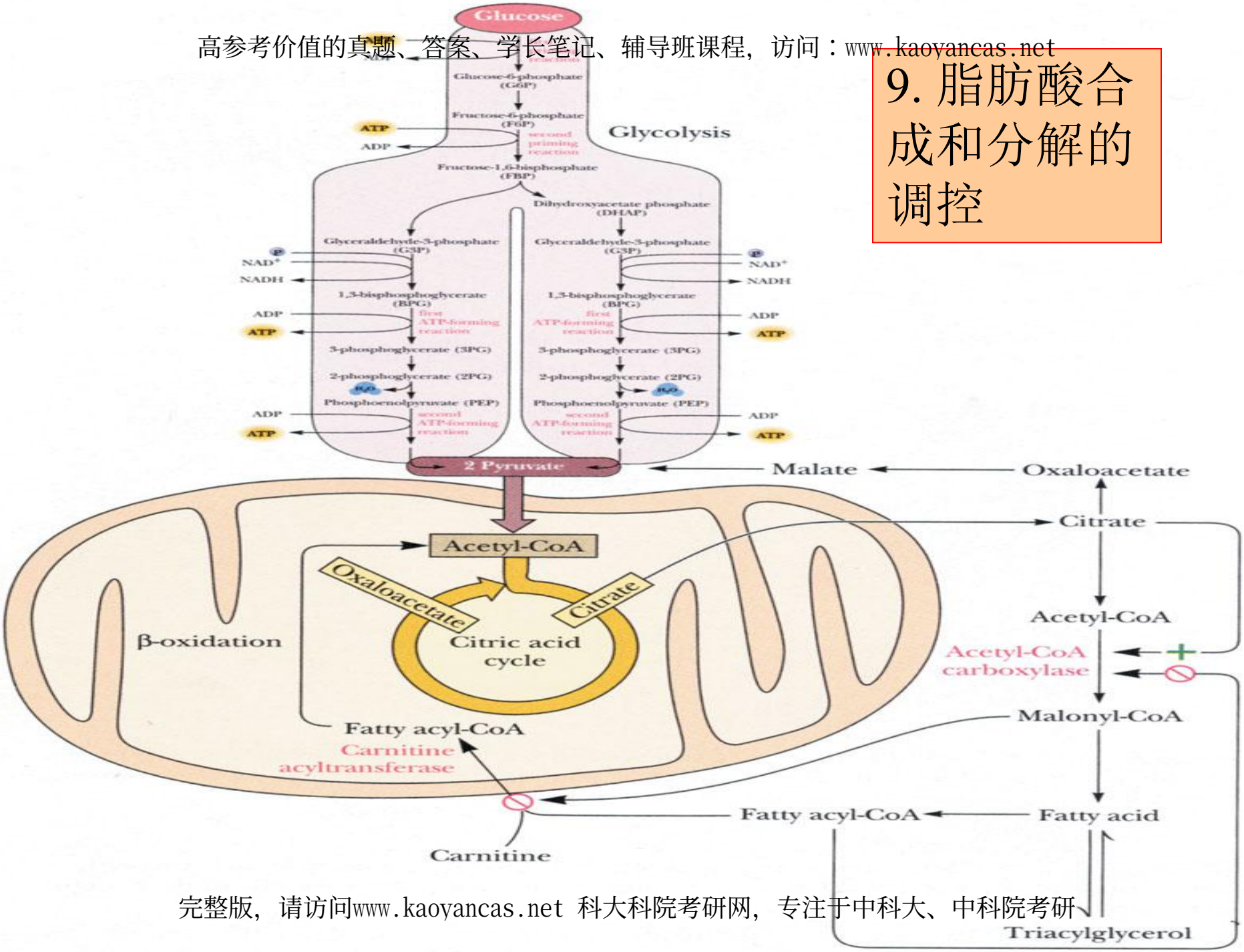


花生四烯酸合成的机制

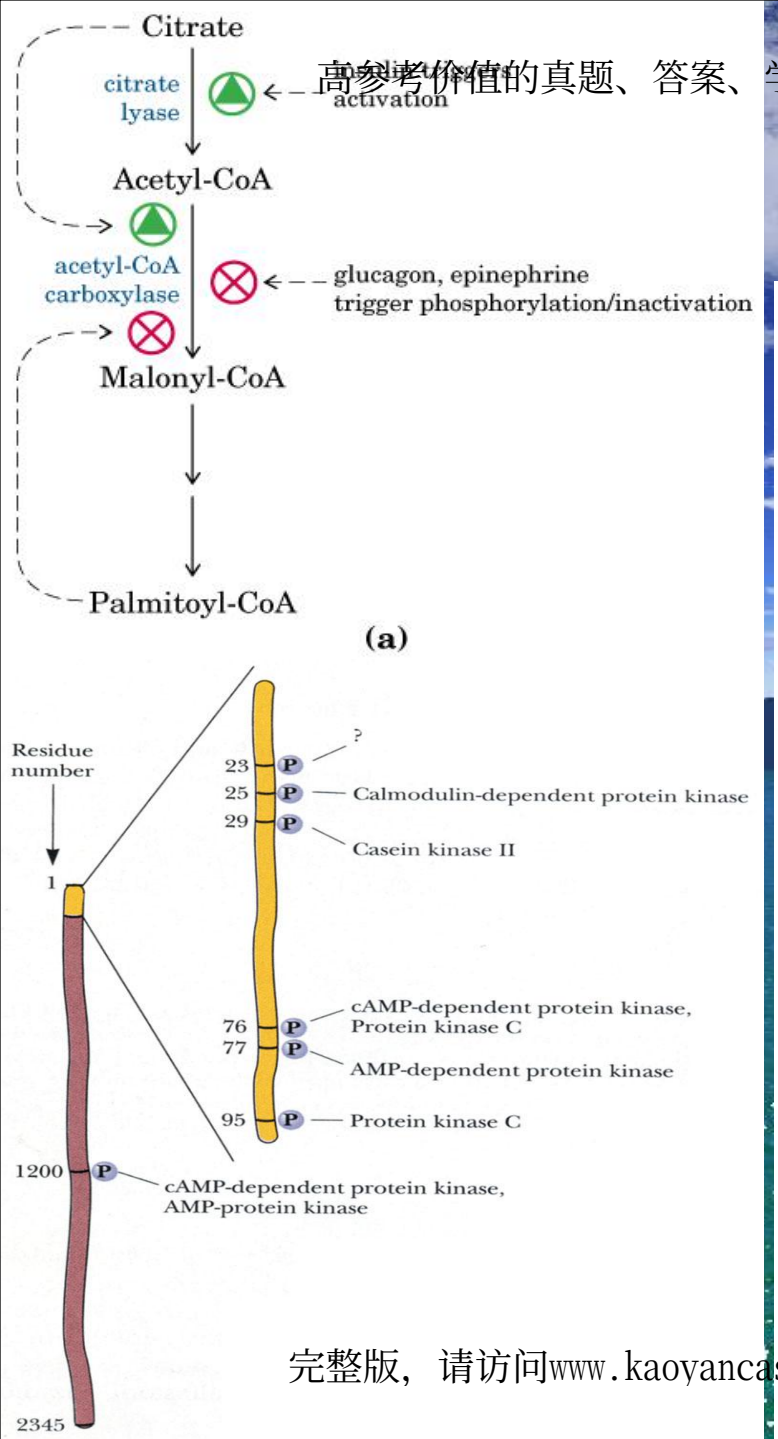


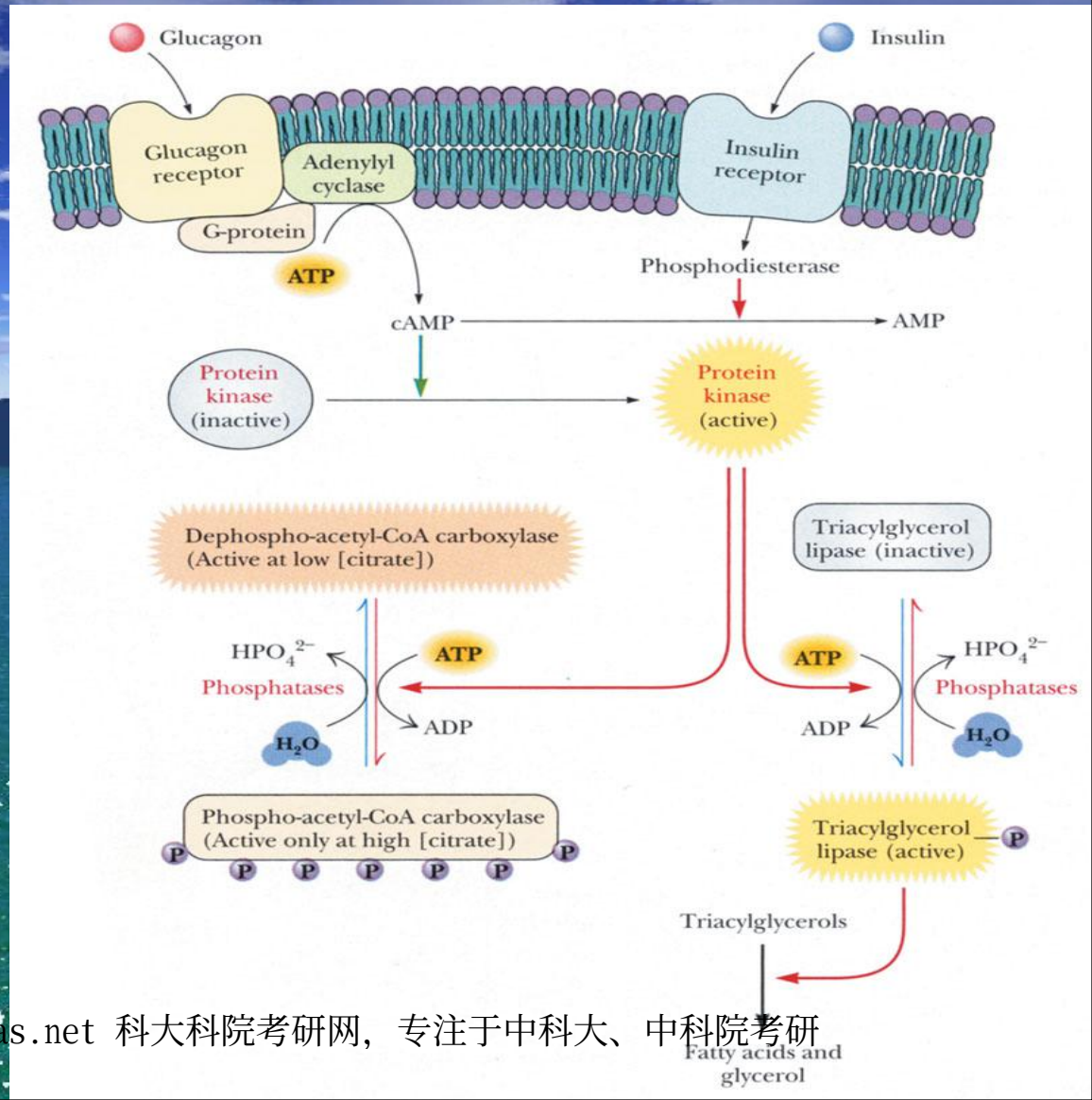


9. 脂肪酸合成和分解的调控

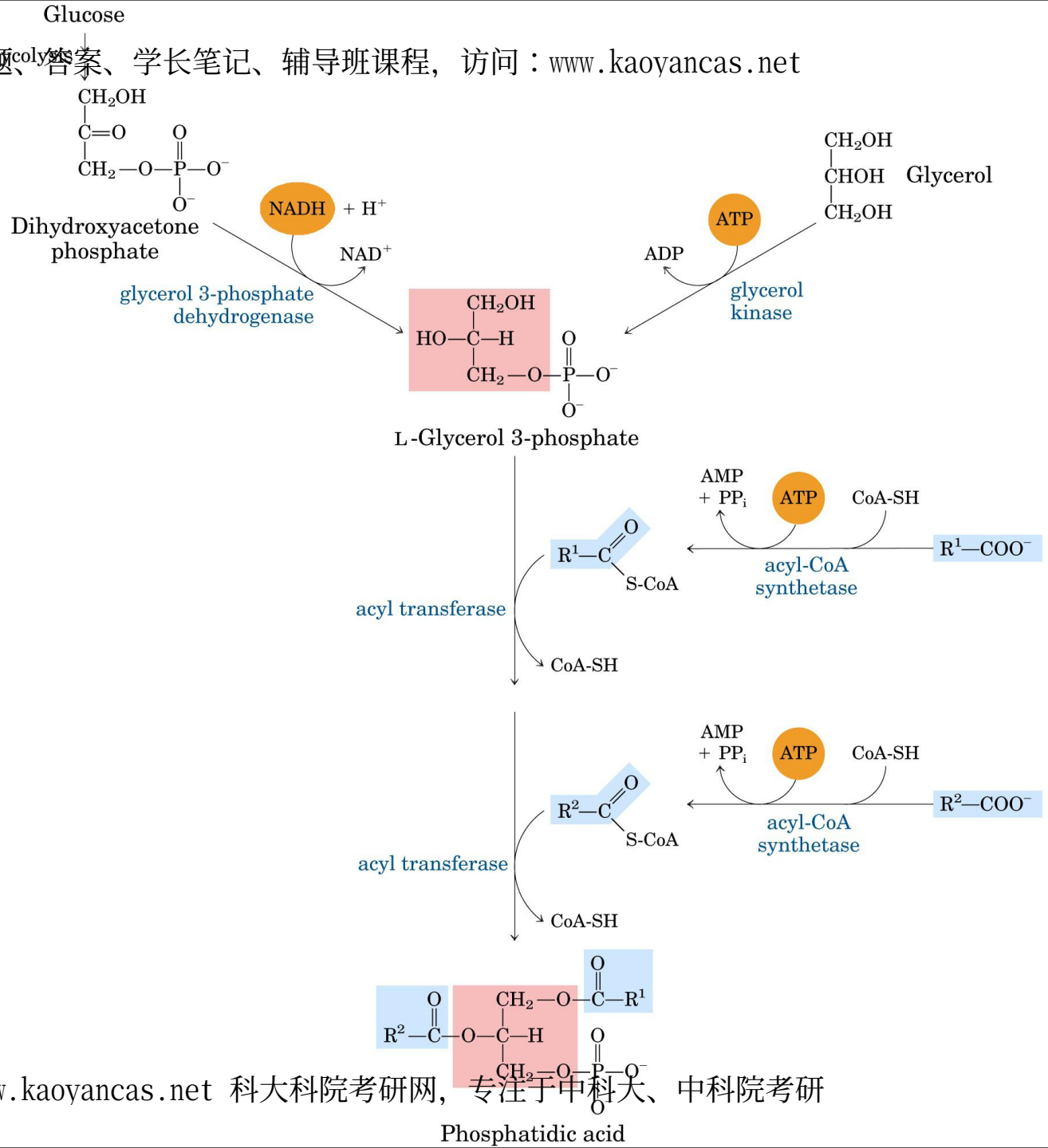


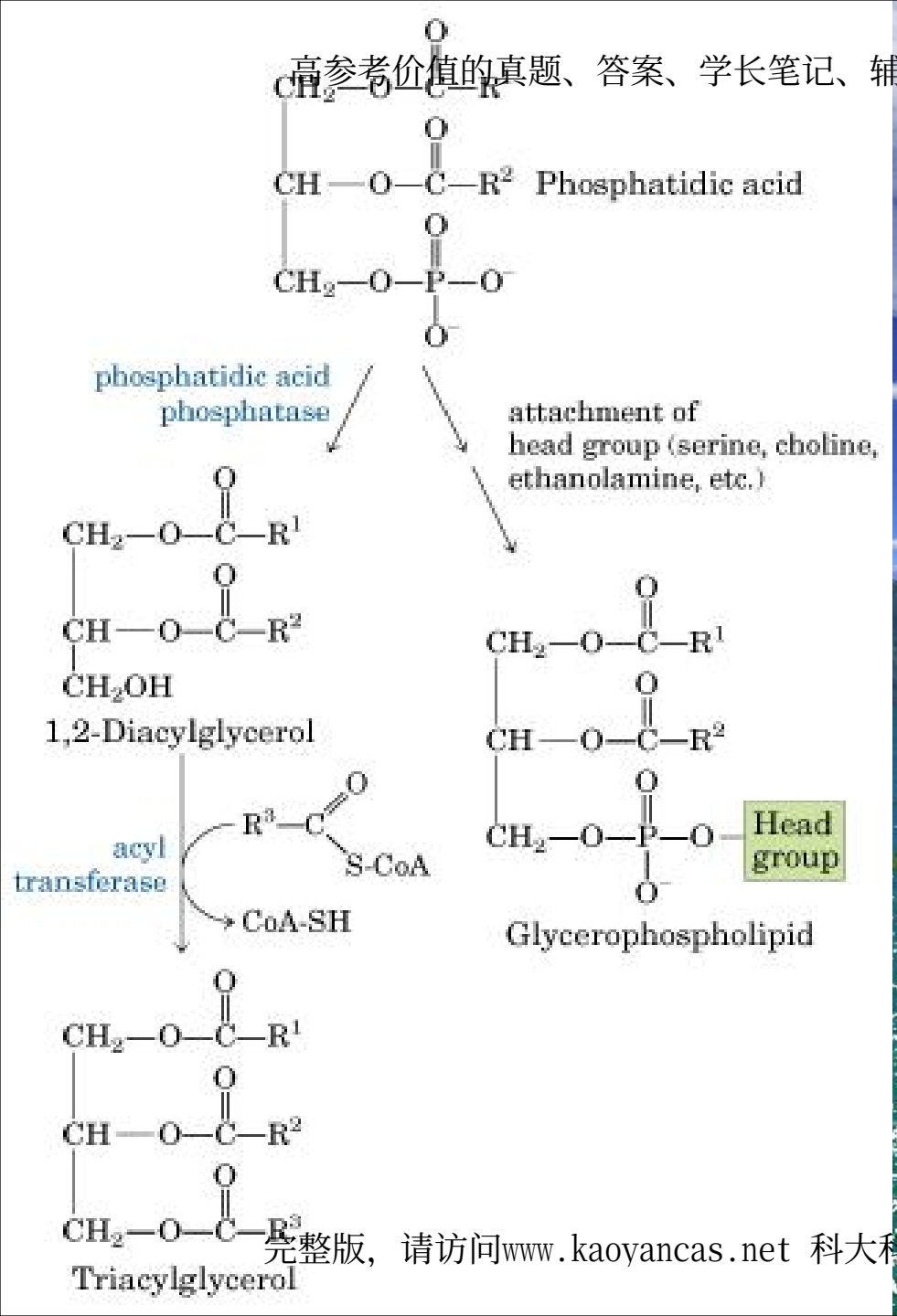
激素对脂肪酸合成和获取三酰甘油的调控

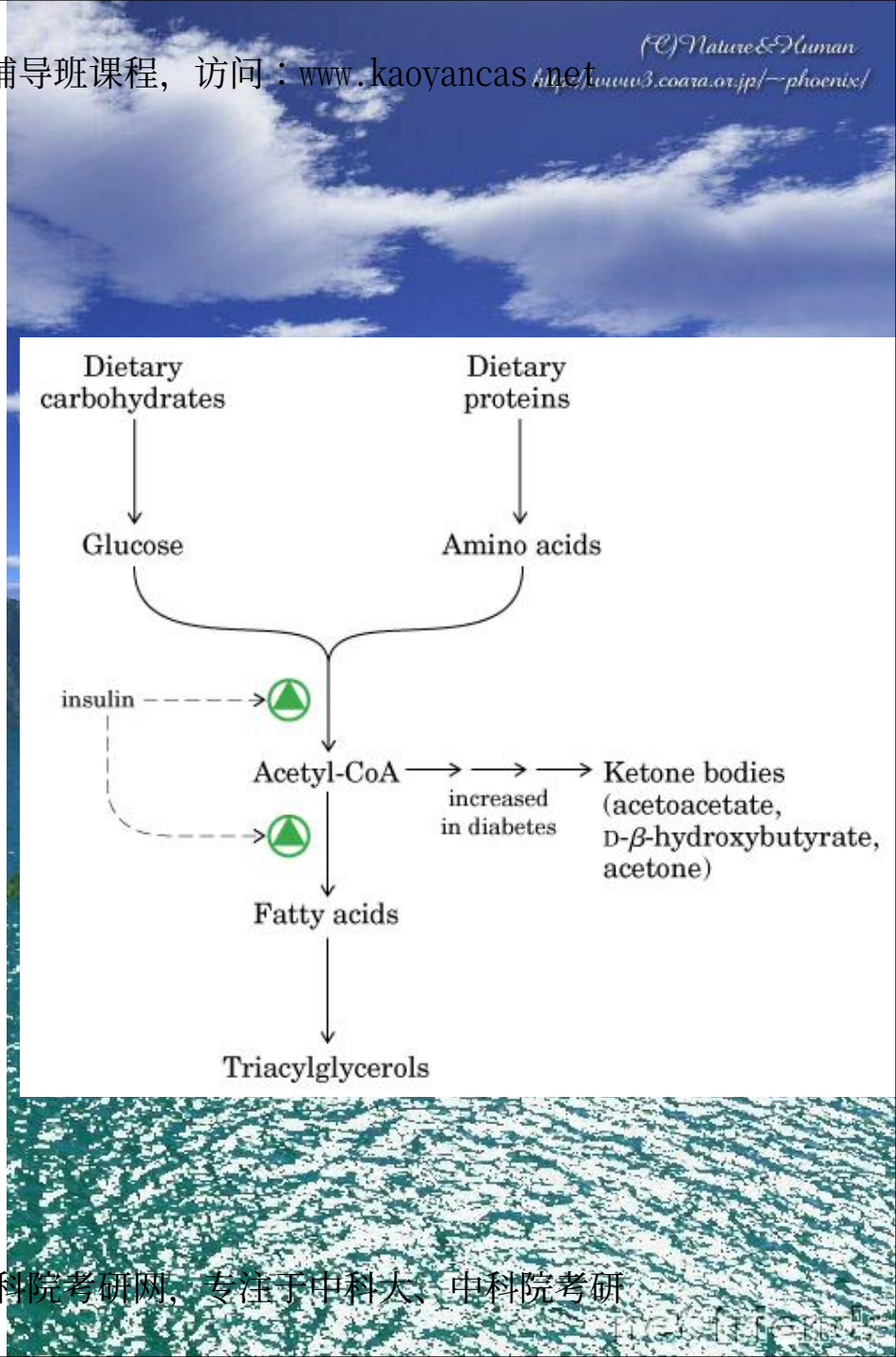




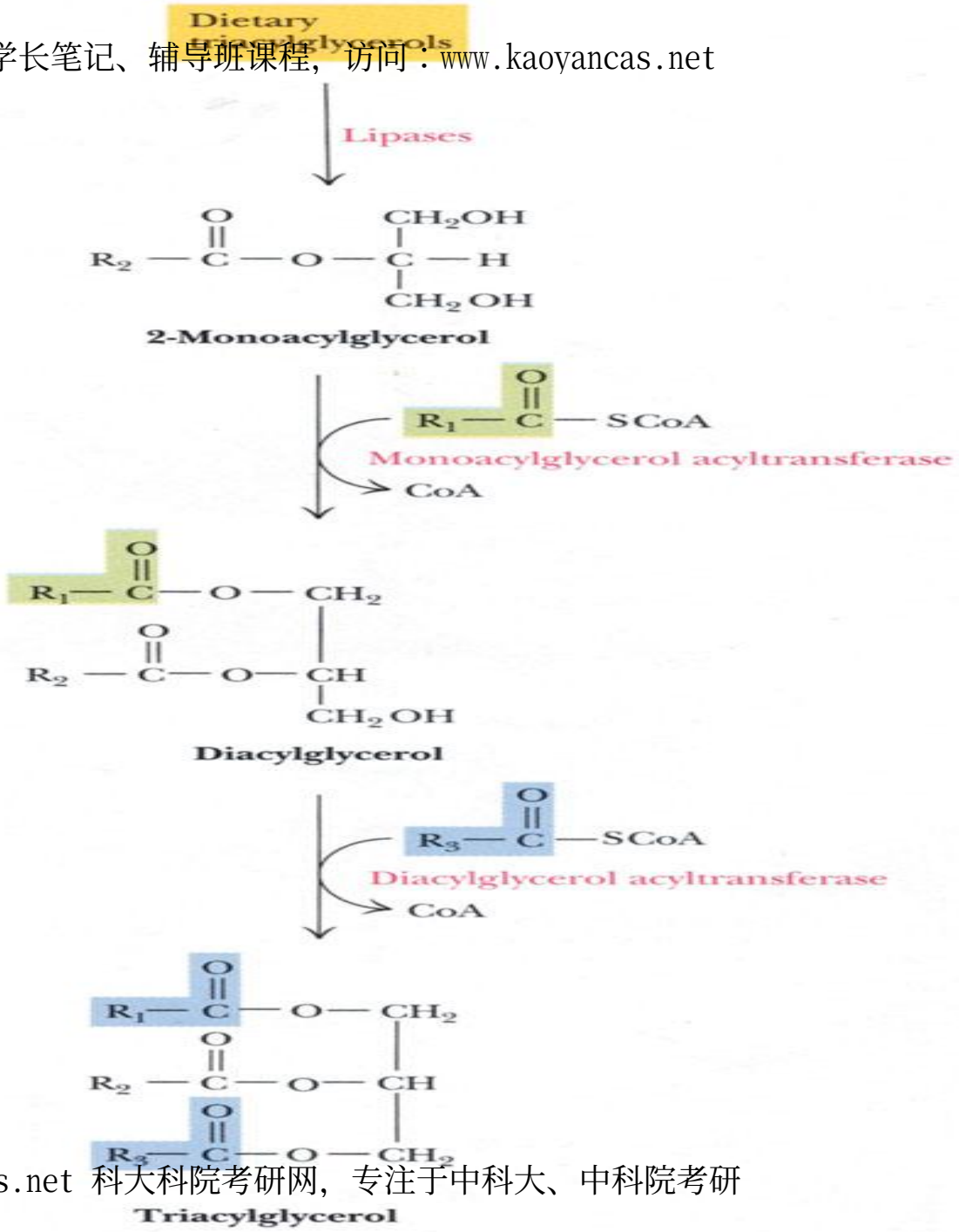
二、 其他脂类的生物合成



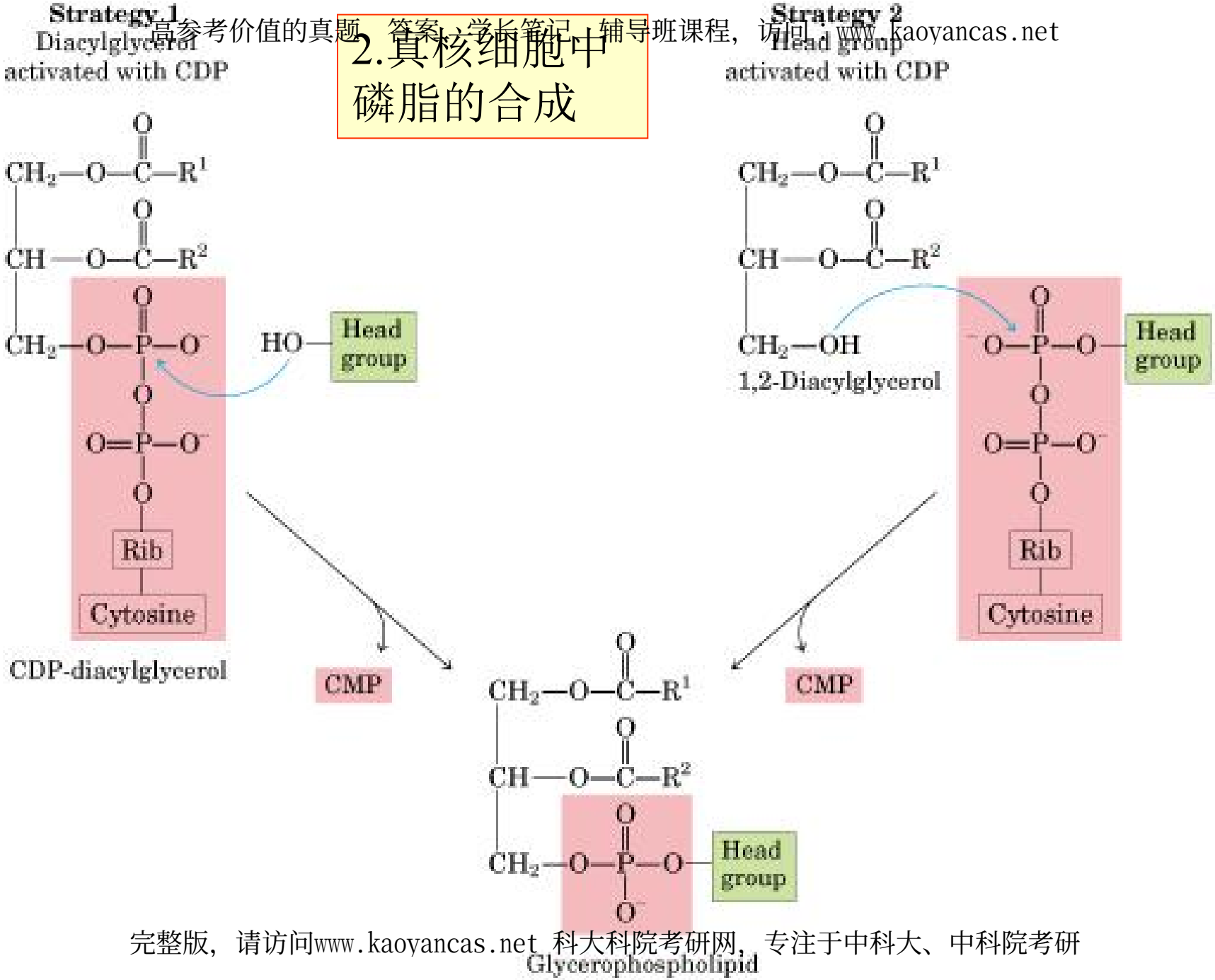


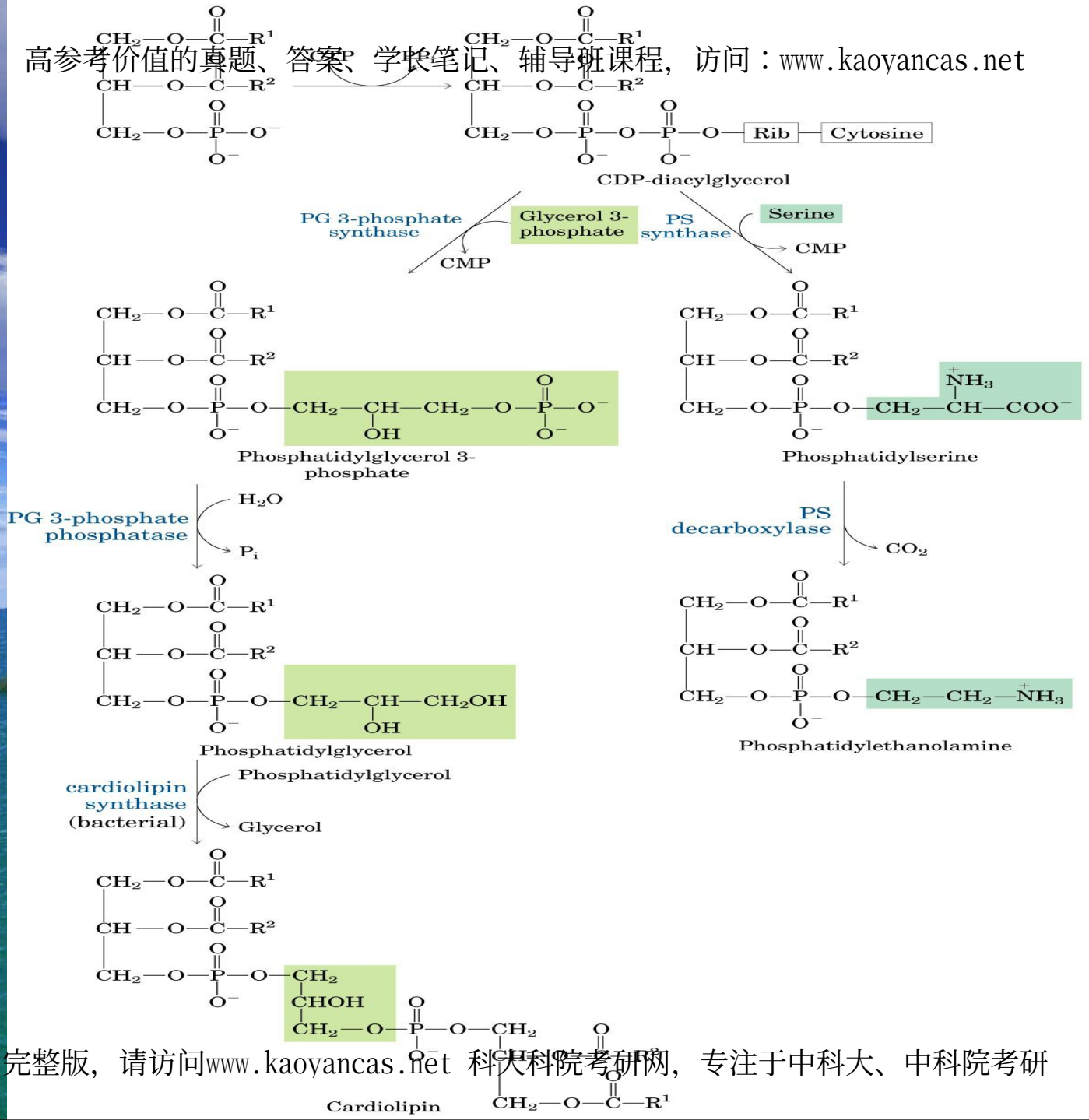


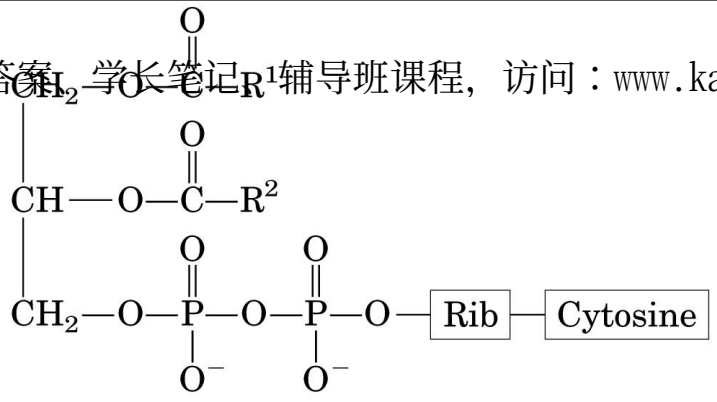
1.三酰甘油的合成



2.真核细胞中磷脂的合成







CDP-diacylglycerol

Phosphatidylglycerol

cardiolipin synthase

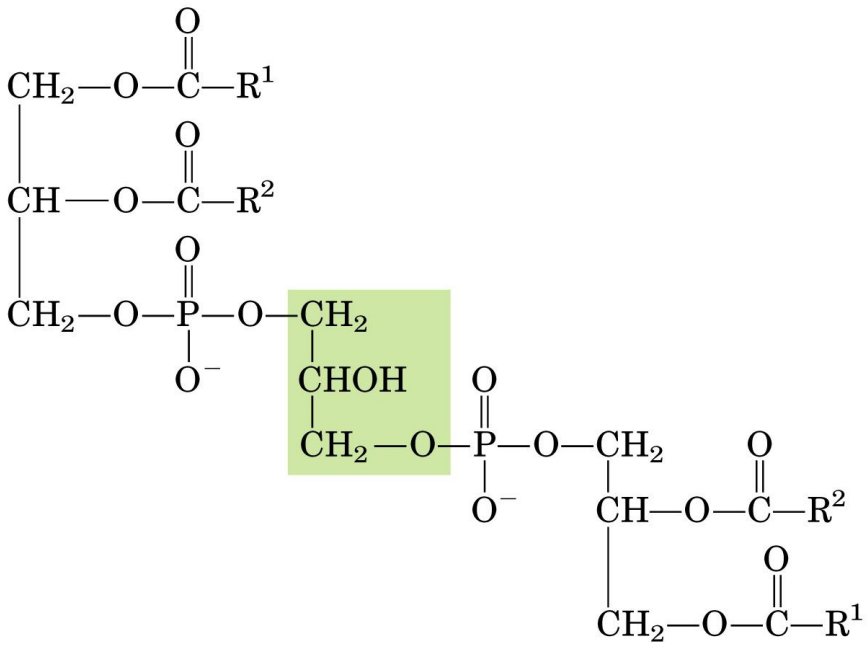
(eukaryotic)

CMP

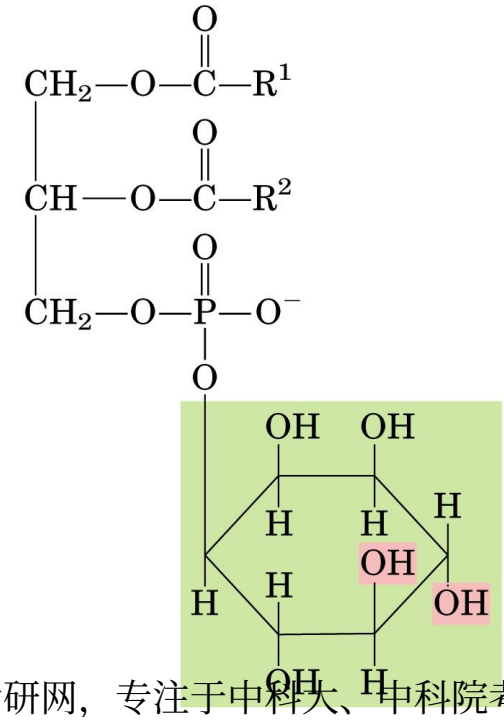
PI synthase

Inositol

CMP

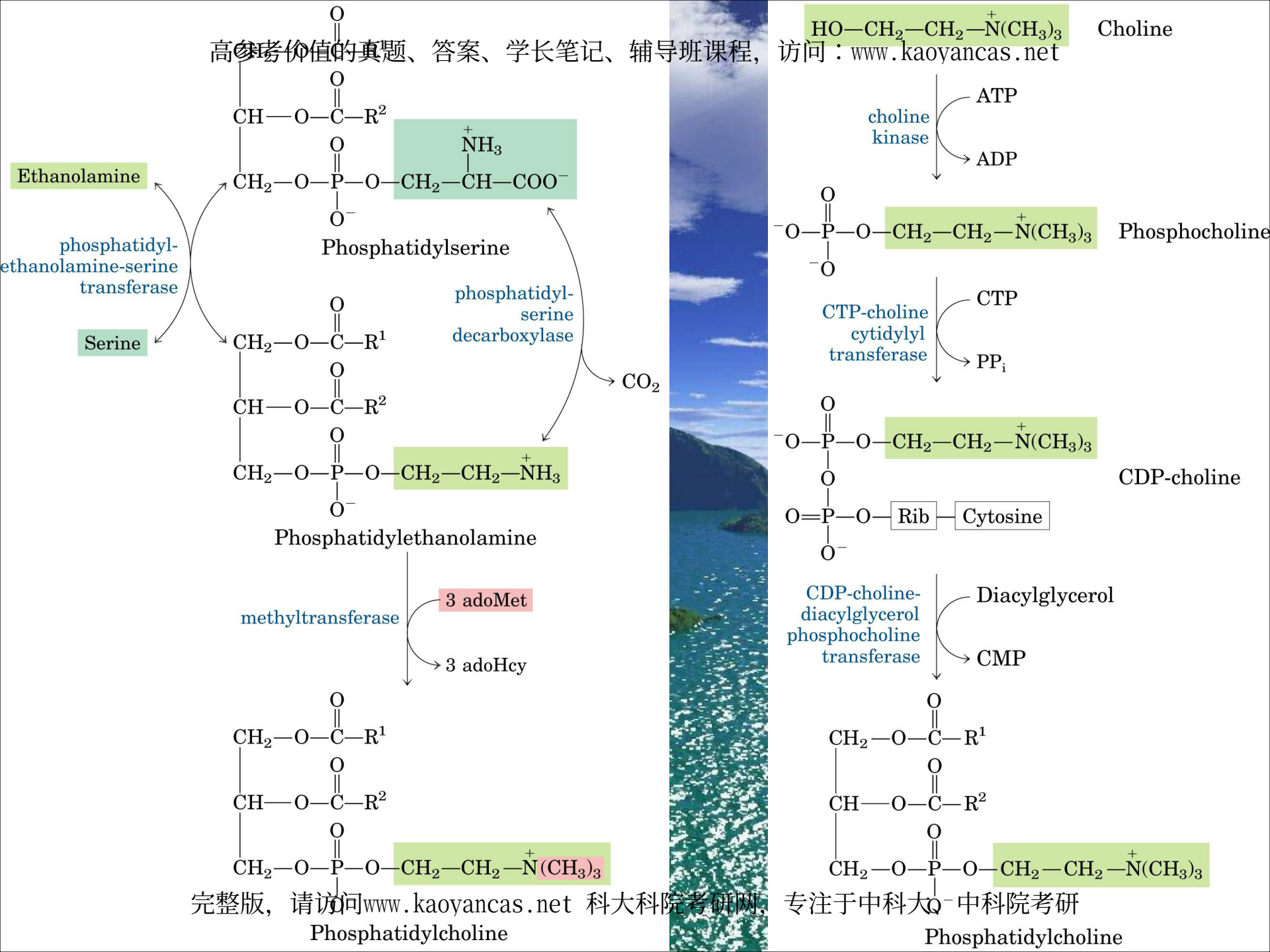


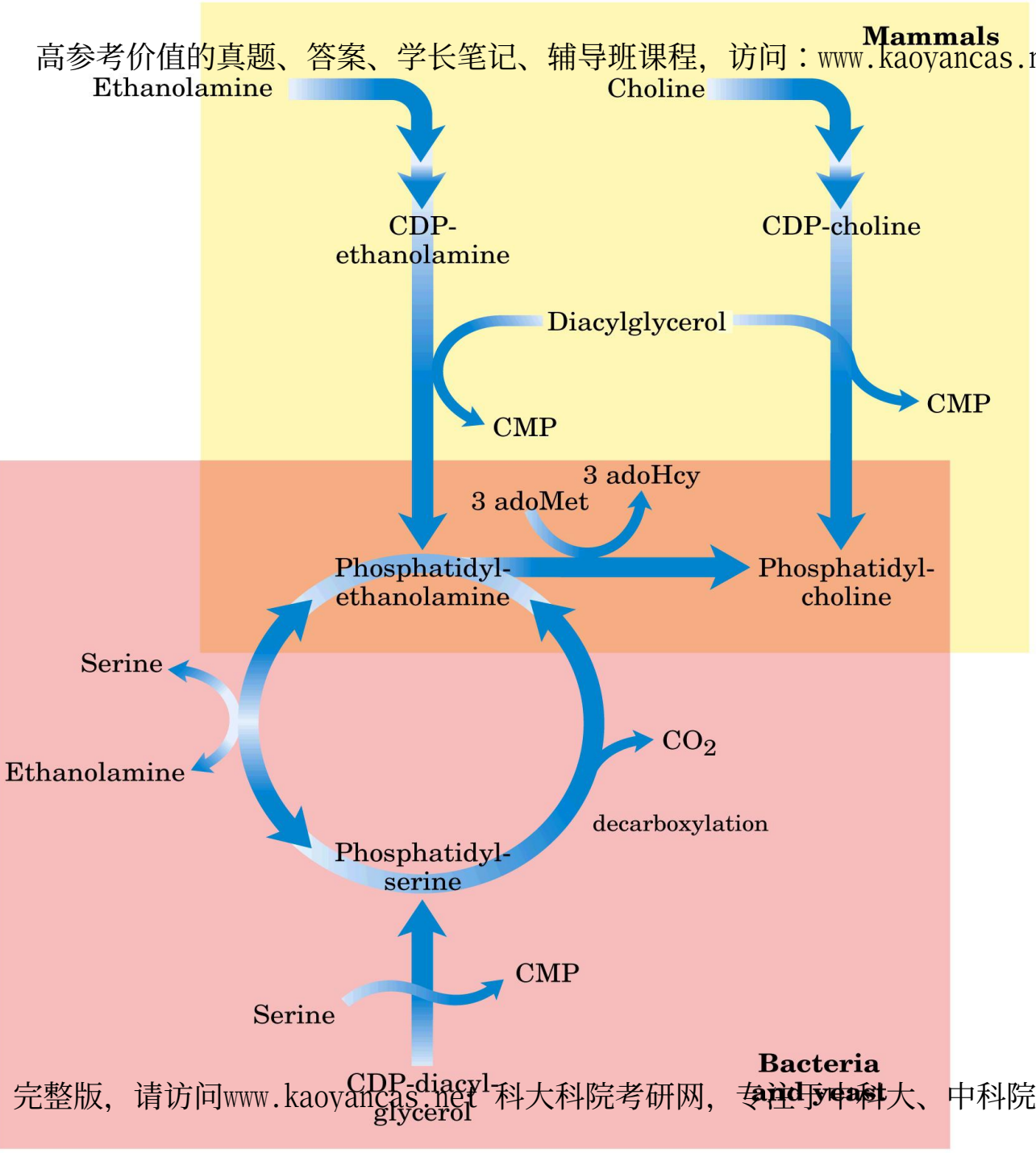
Cardiolipin



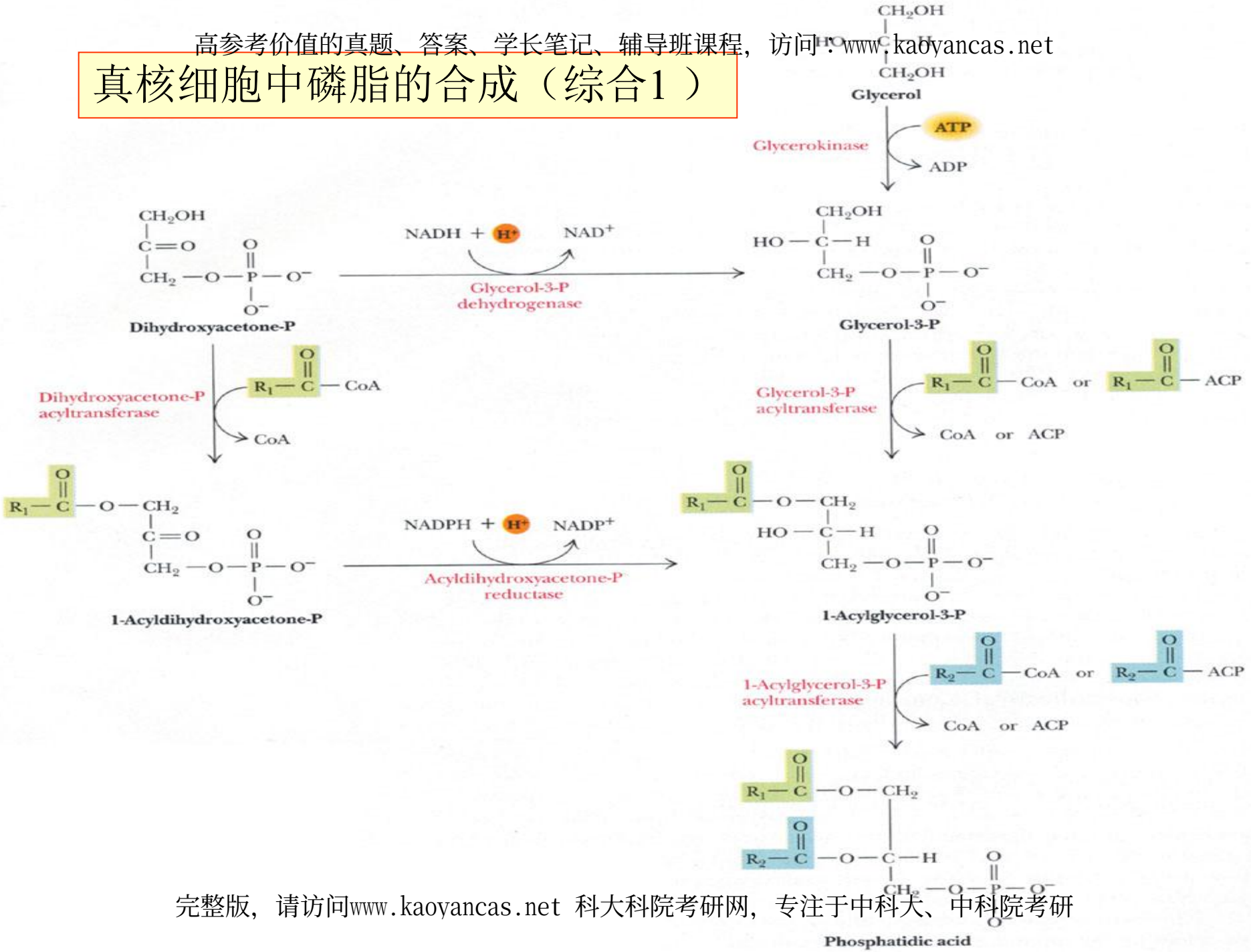
Phosphatidylinositol

These —OH groups can also be esterified with $—PO_3^{2-}$.

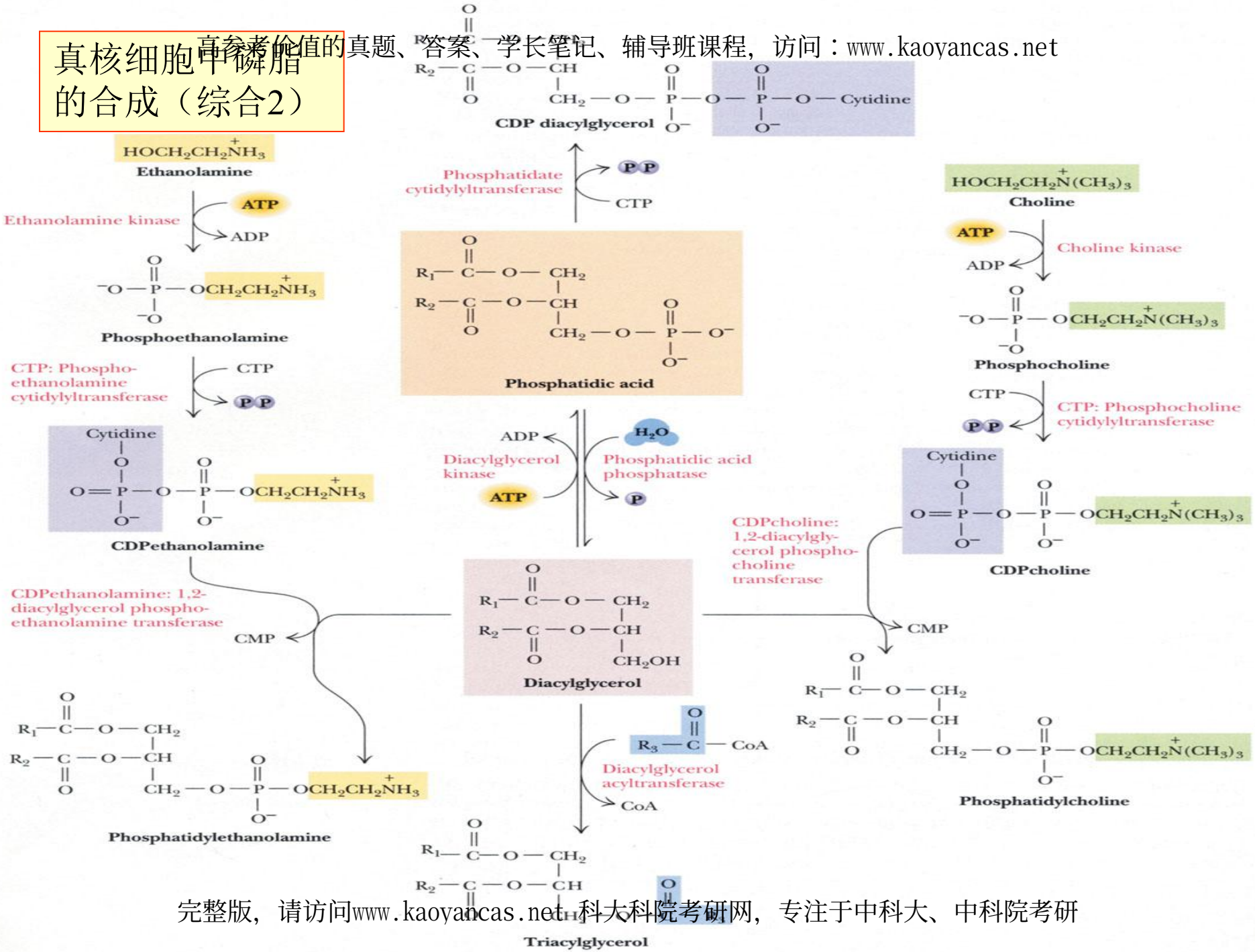




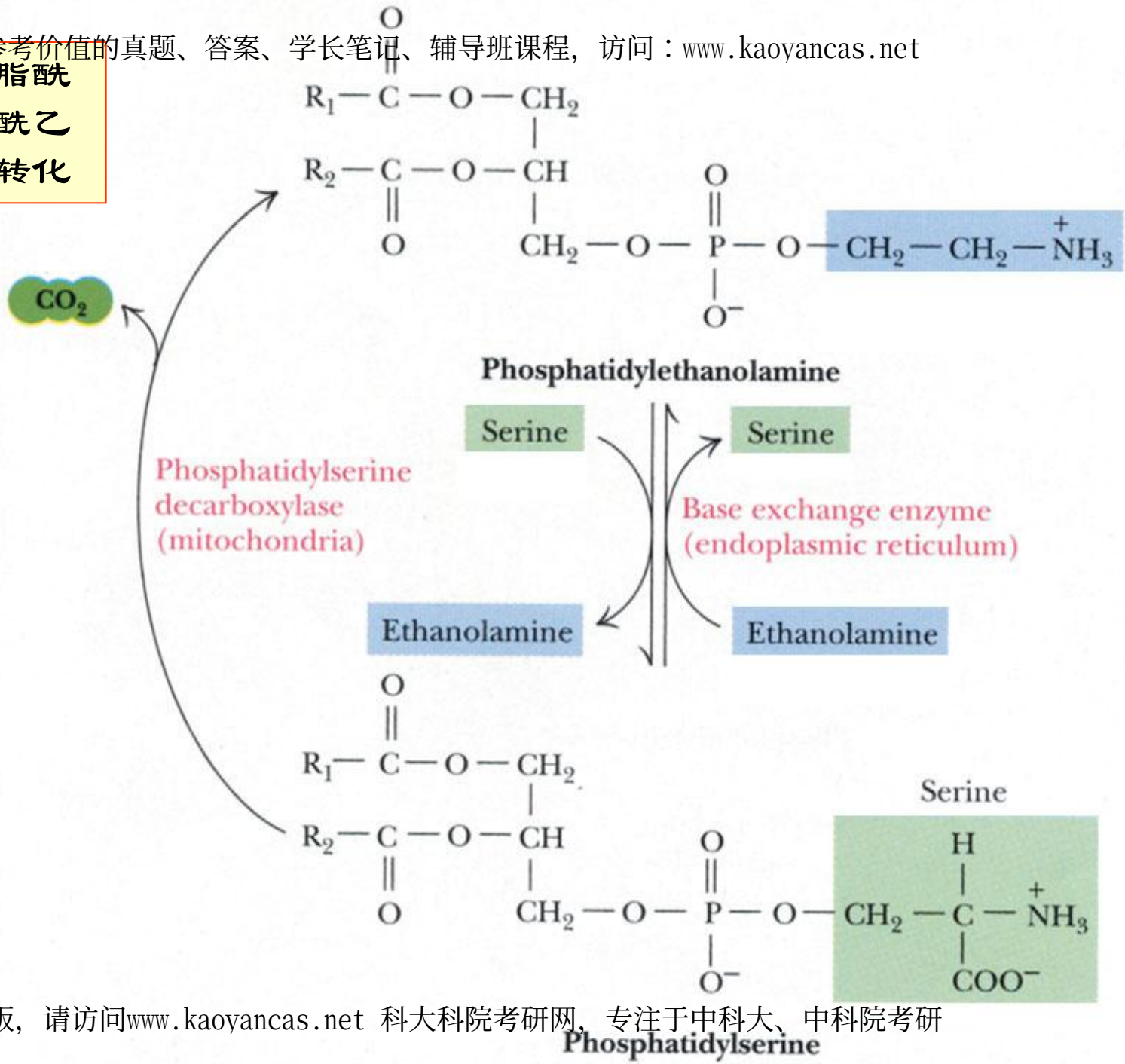
真核细胞中磷脂的合成（综合1）

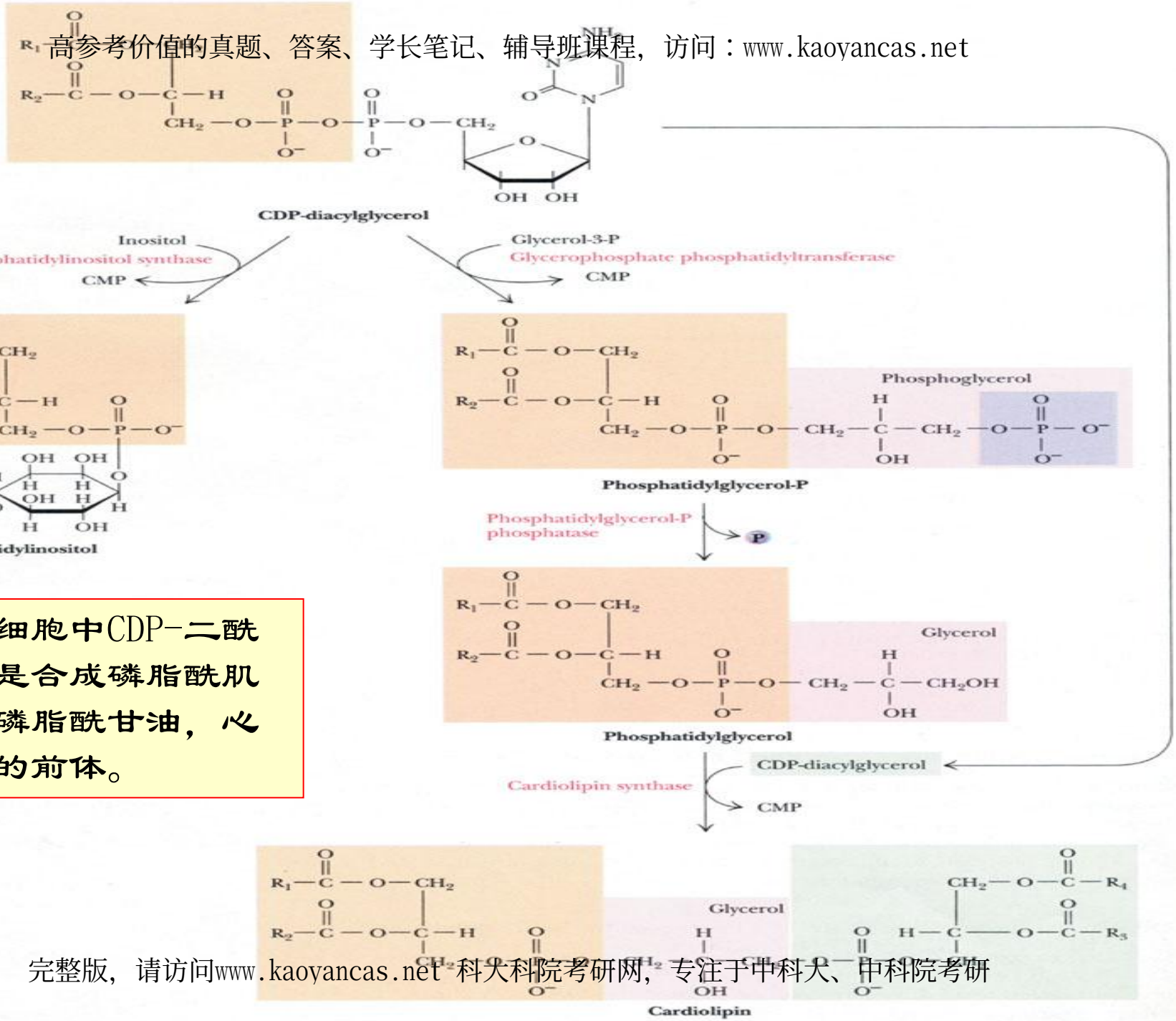


真核细胞中磷脂的合成（综合2）



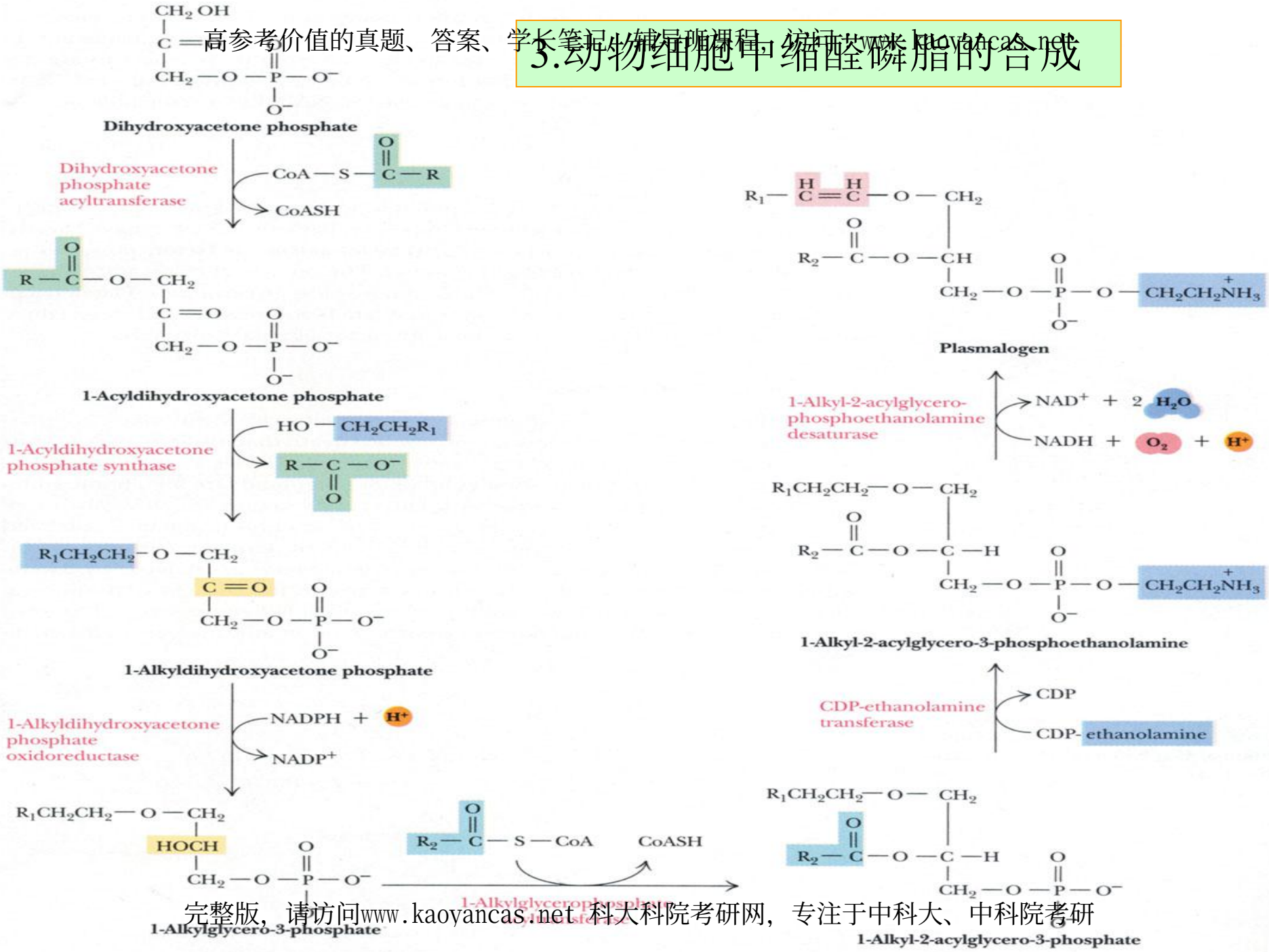
哺乳动物磷脂酰胆碱和磷脂酰乙醇氨的相互转化

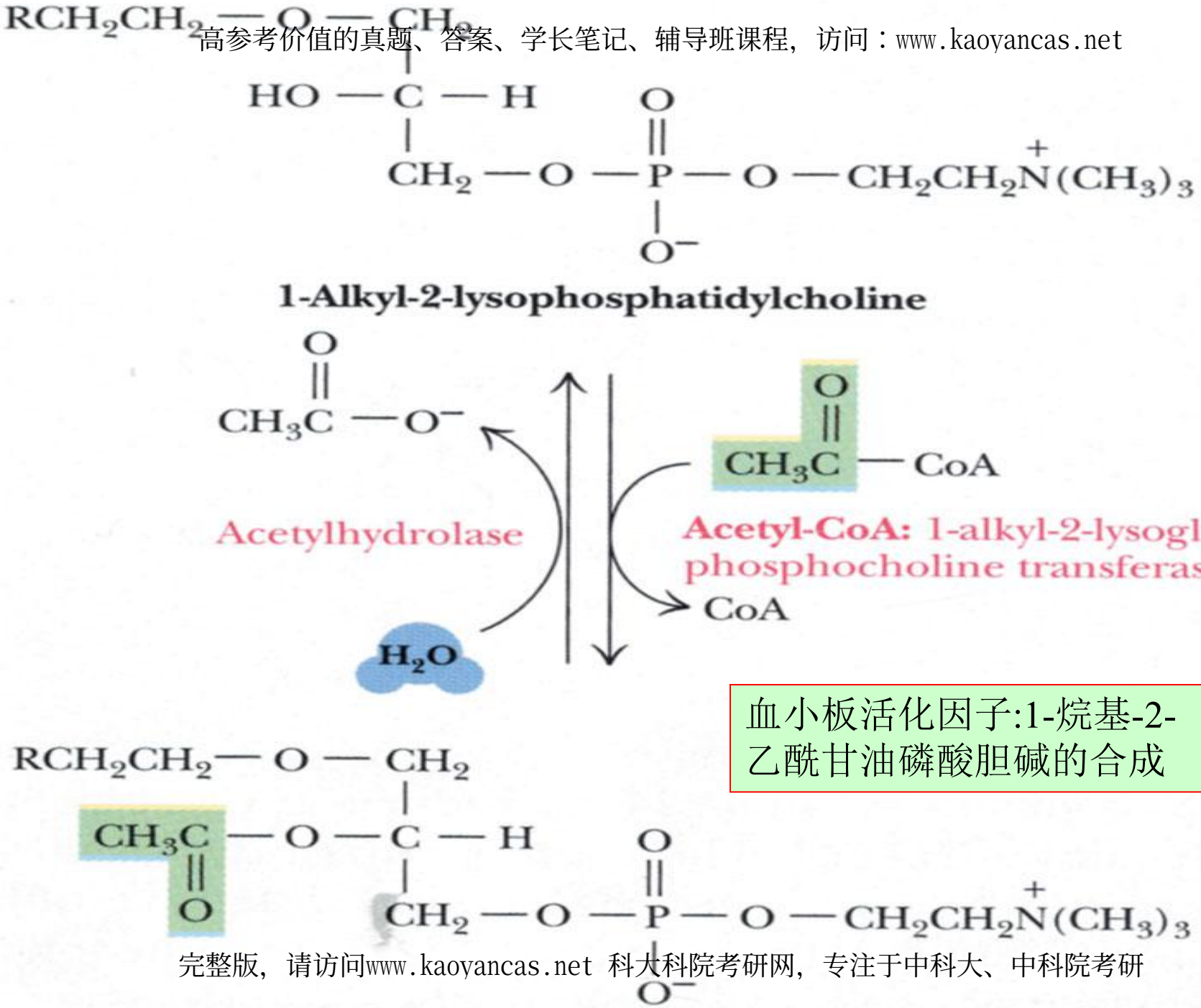




真核细胞中CDP-二酰甘油是合成磷脂酰肌醇，磷脂酰甘油，心磷脂的前体。

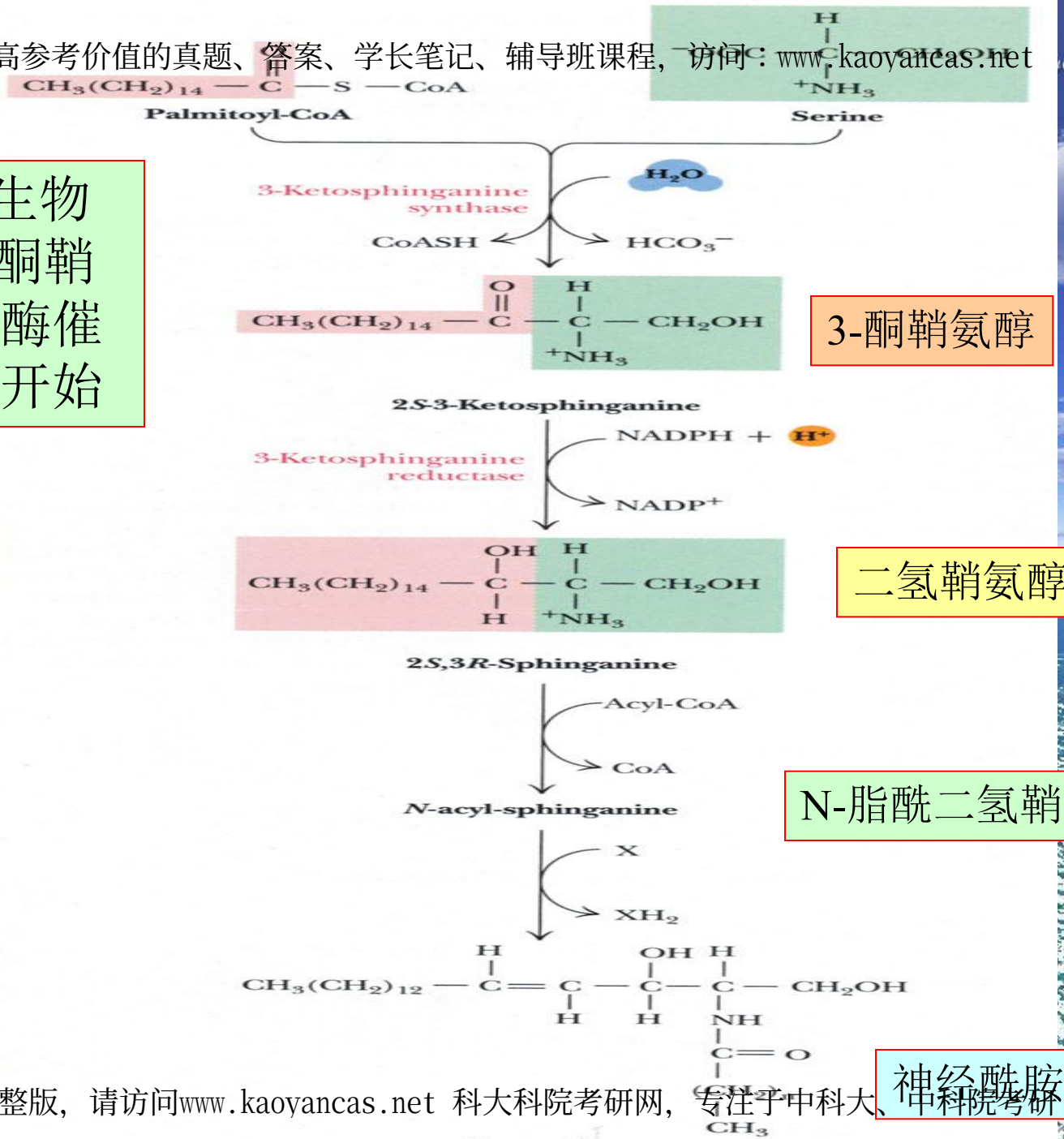
3.动物细胞中缩醛磷脂的合成





血小板活化因子:1-烷基-2-乙酰甘油磷酸胆碱的合成

4.鞘脂的生物合成由3-酮鞘氨醇合成酶催化的反应开始

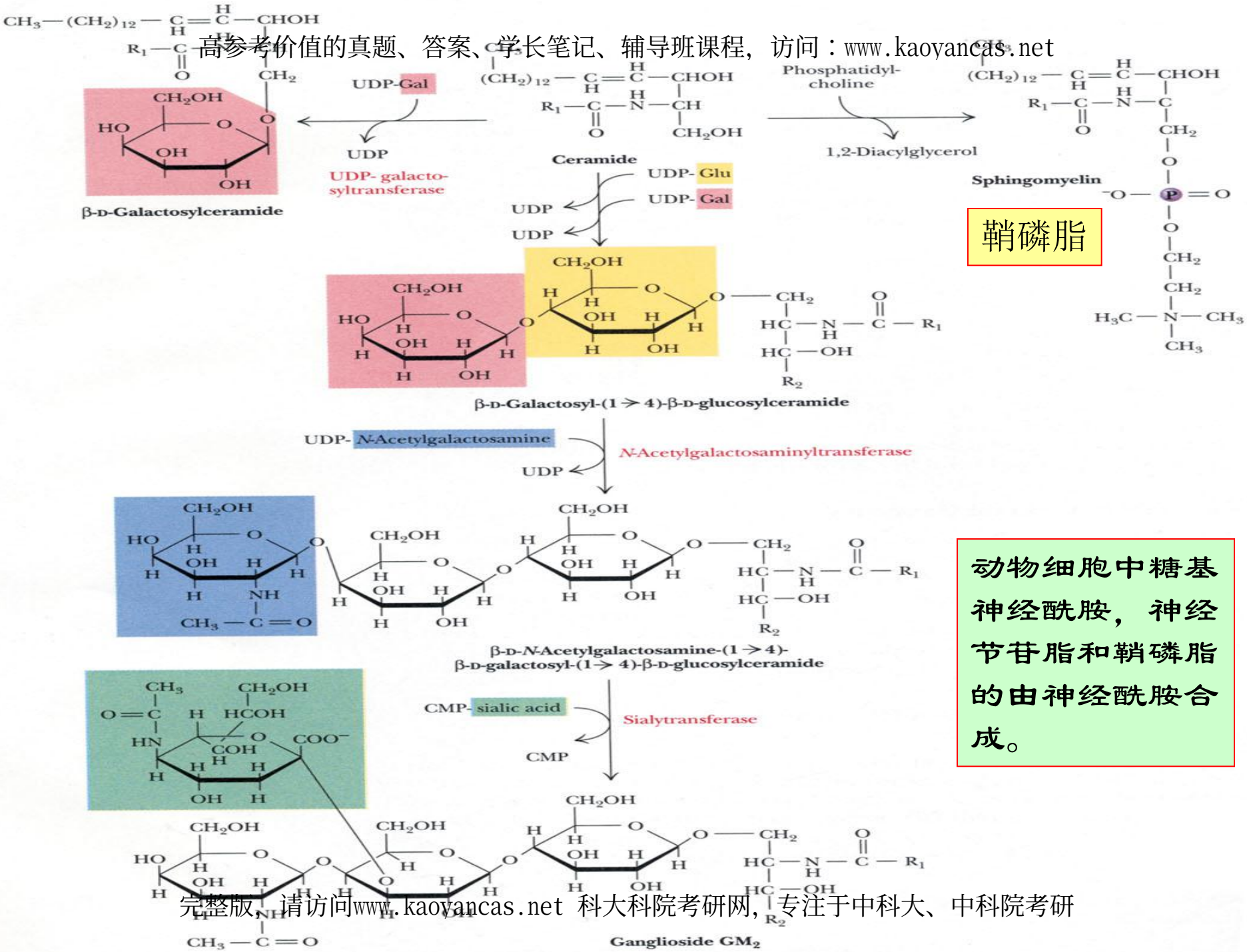


3-酮鞘氨醇

二氢鞘氨醇

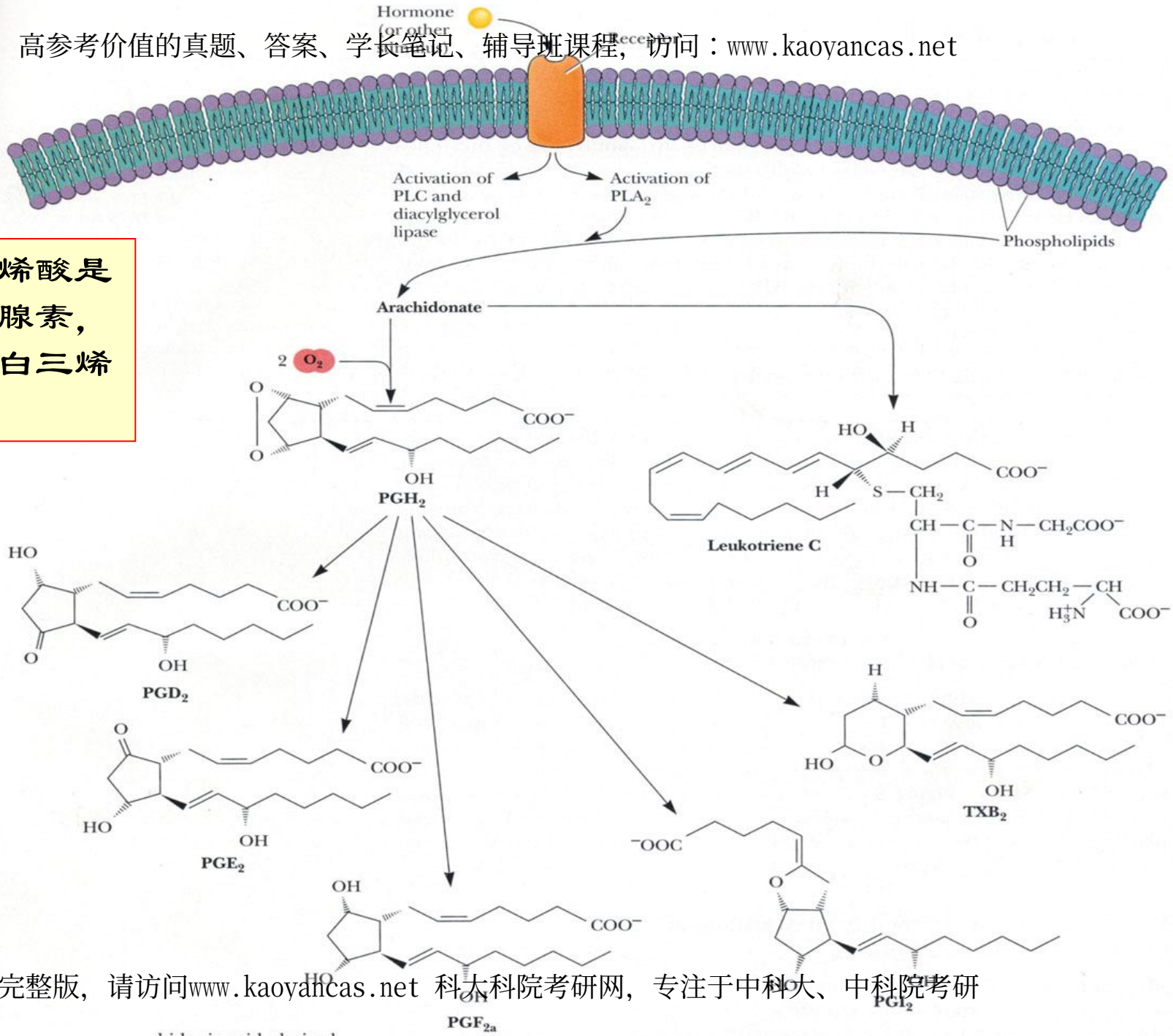
N-脂酰二氢鞘氨醇

神经酰胺

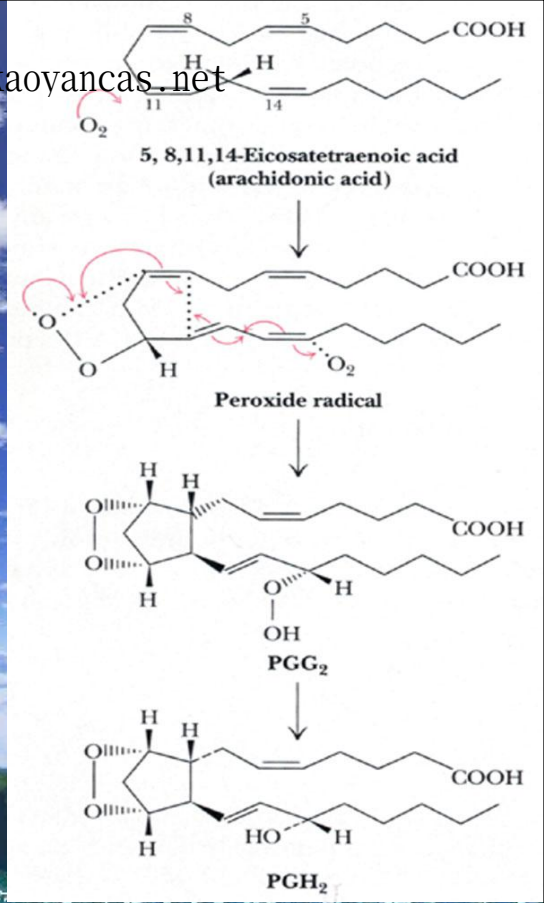


动物细胞中糖基神经酰胺，神经节苷脂和鞘磷脂的由神经酰胺合成。

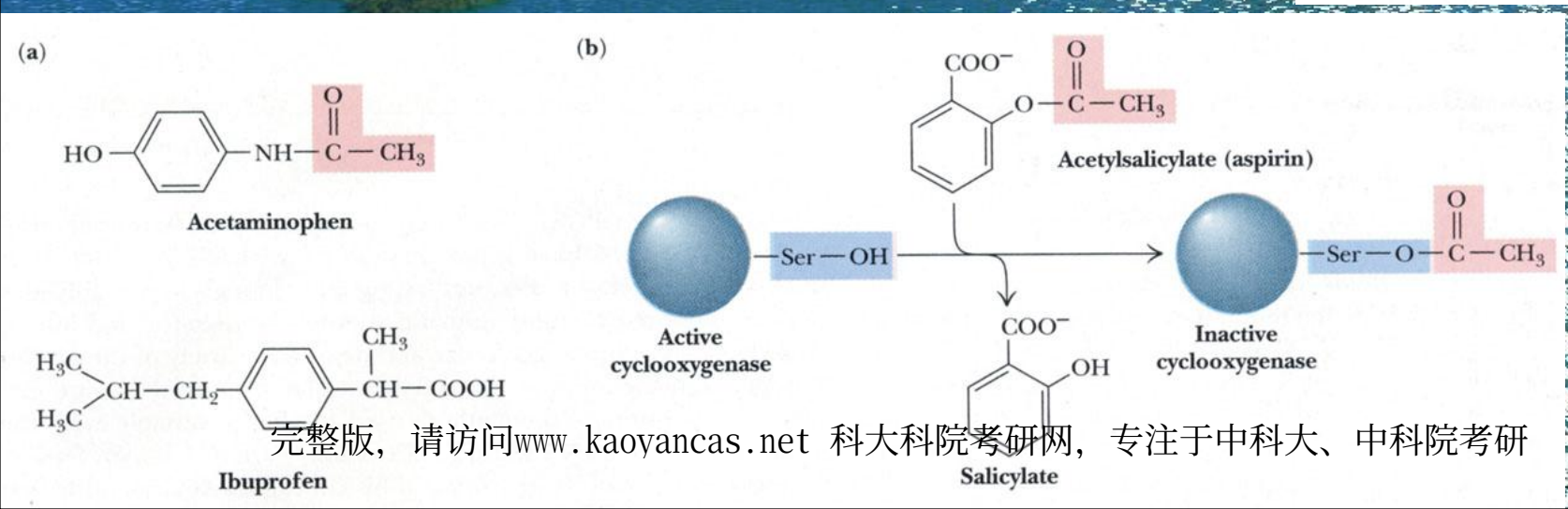
4. 花生四烯酸是合成前列腺素，血拴烷和白三烯的前体。



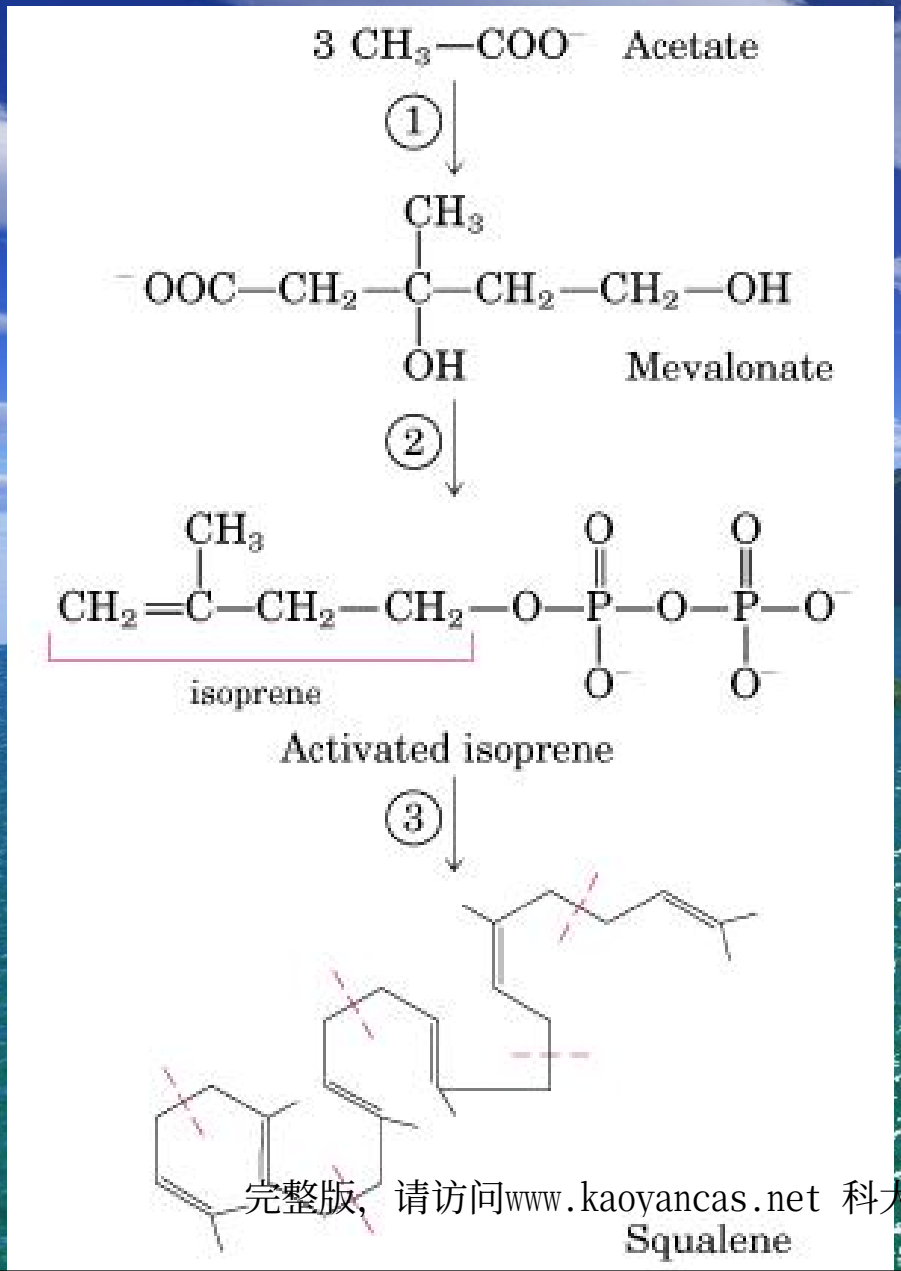
前列腺素内过氧化物合成酶催化PGH_2的合成

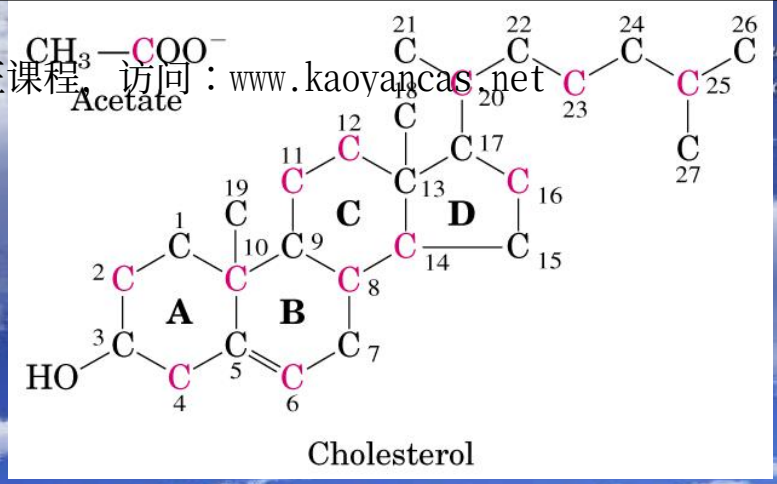


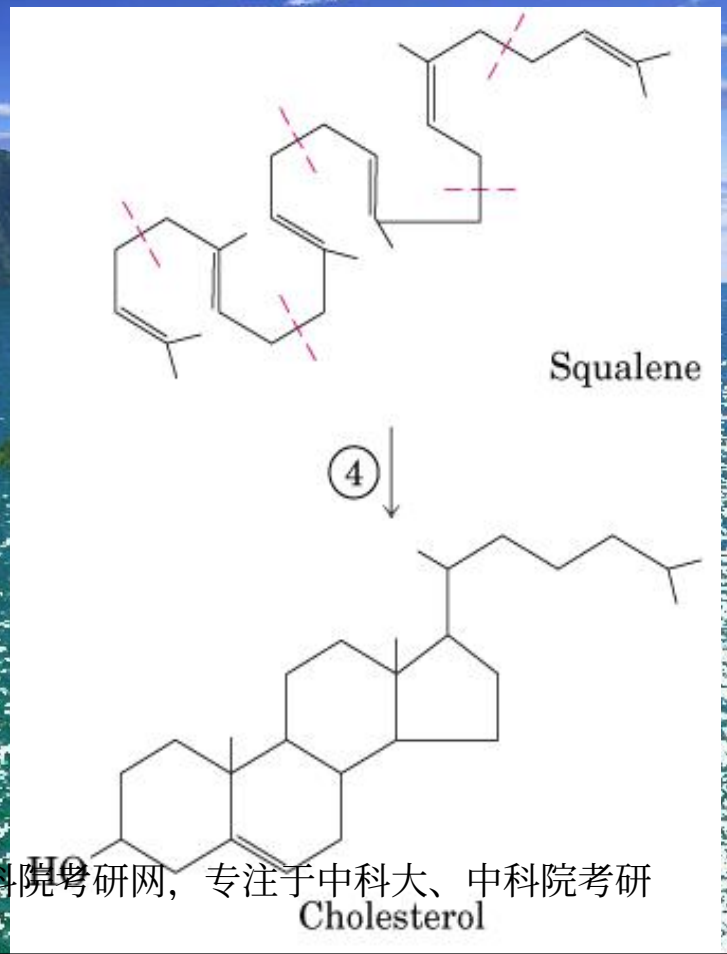
阿斯匹林使环加氧酶失活



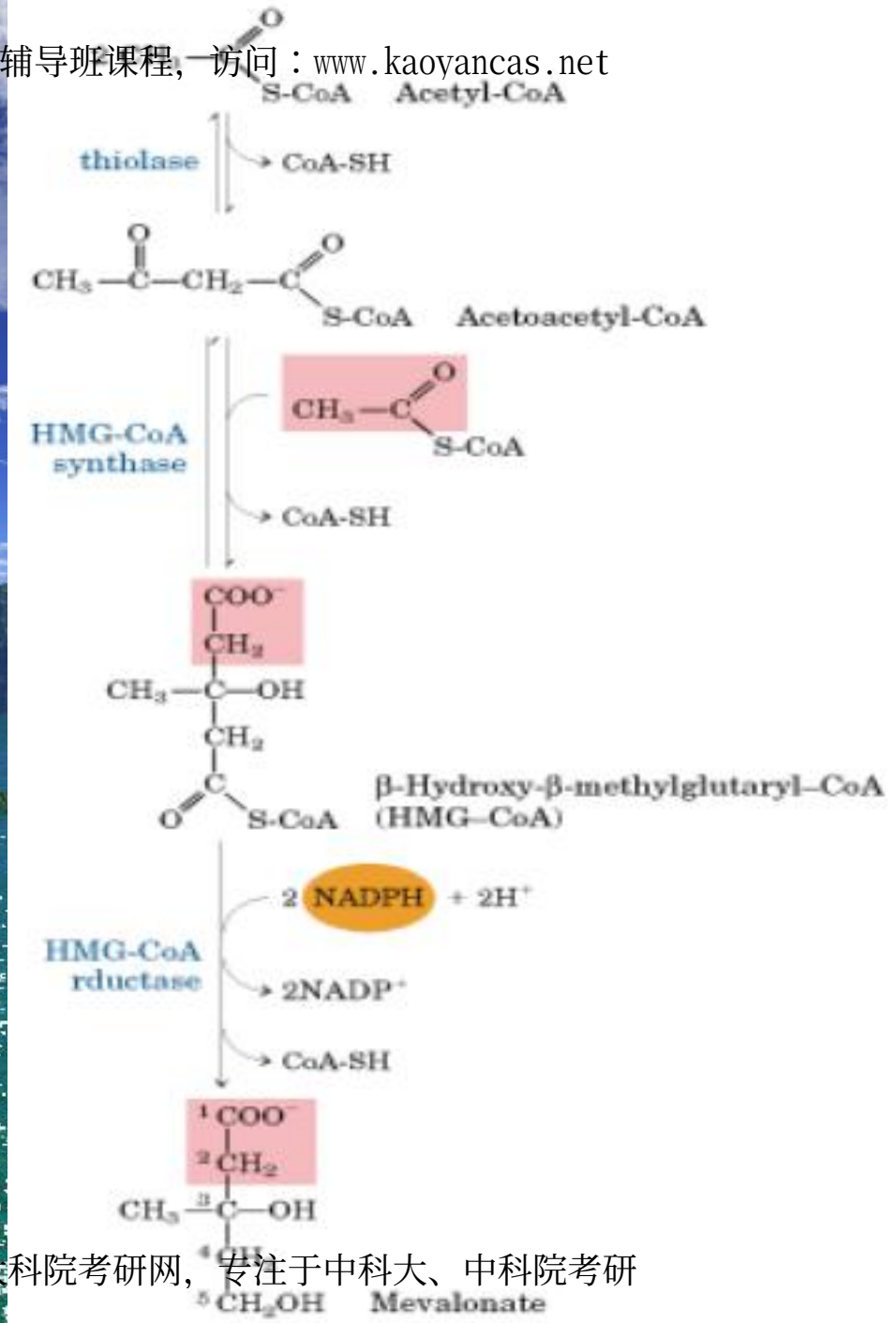
5.胆固醇的合成





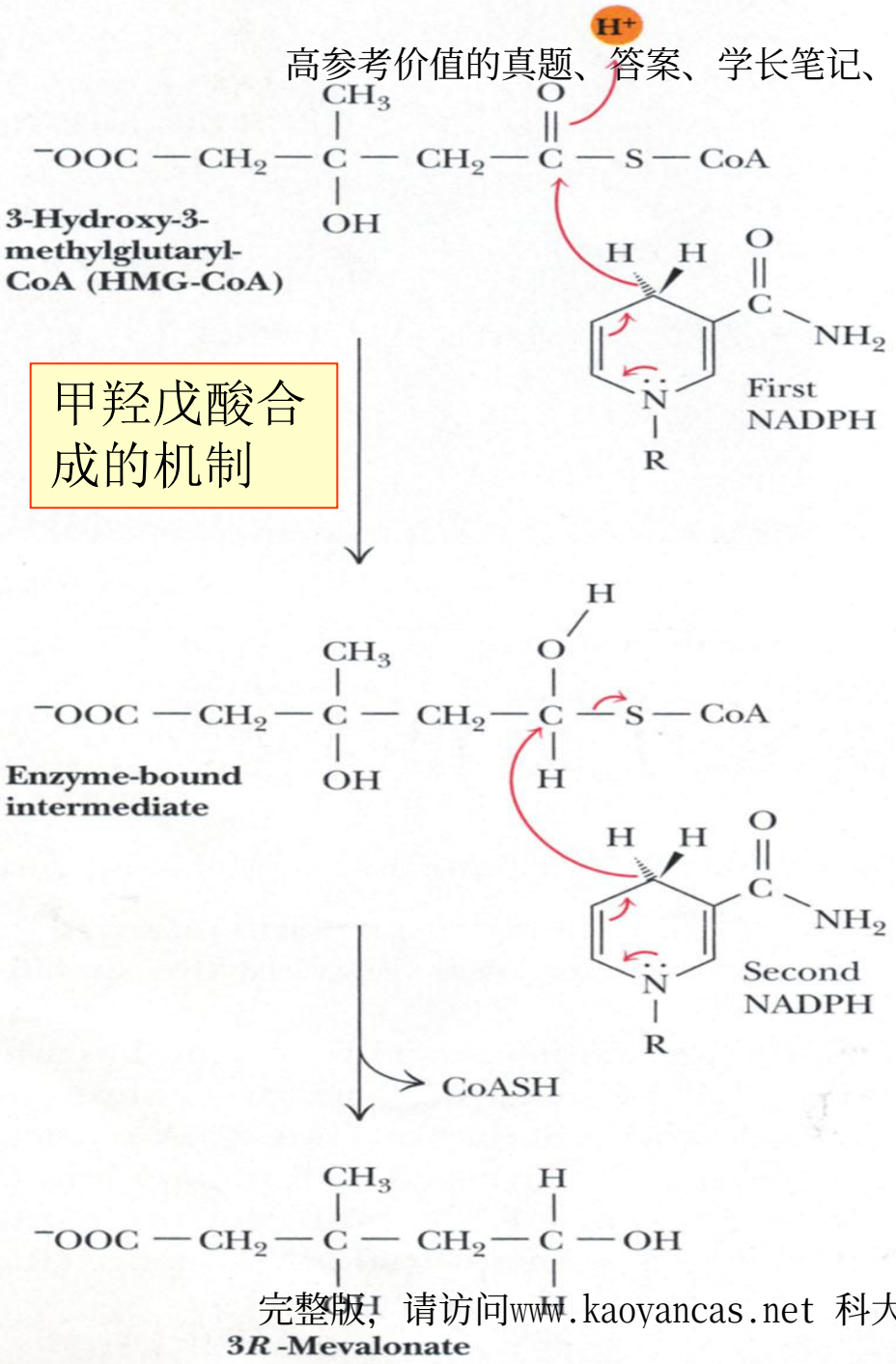


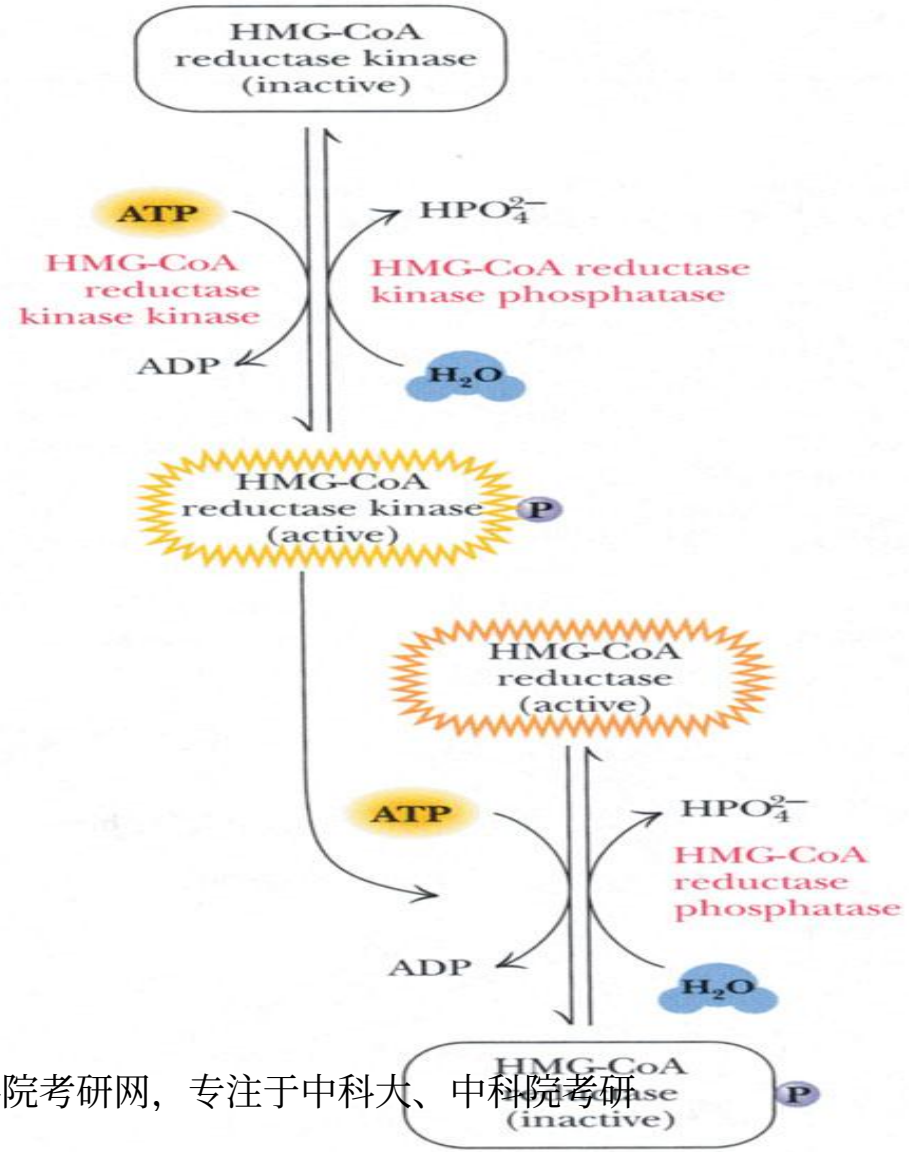
甲羟戊酸的合成



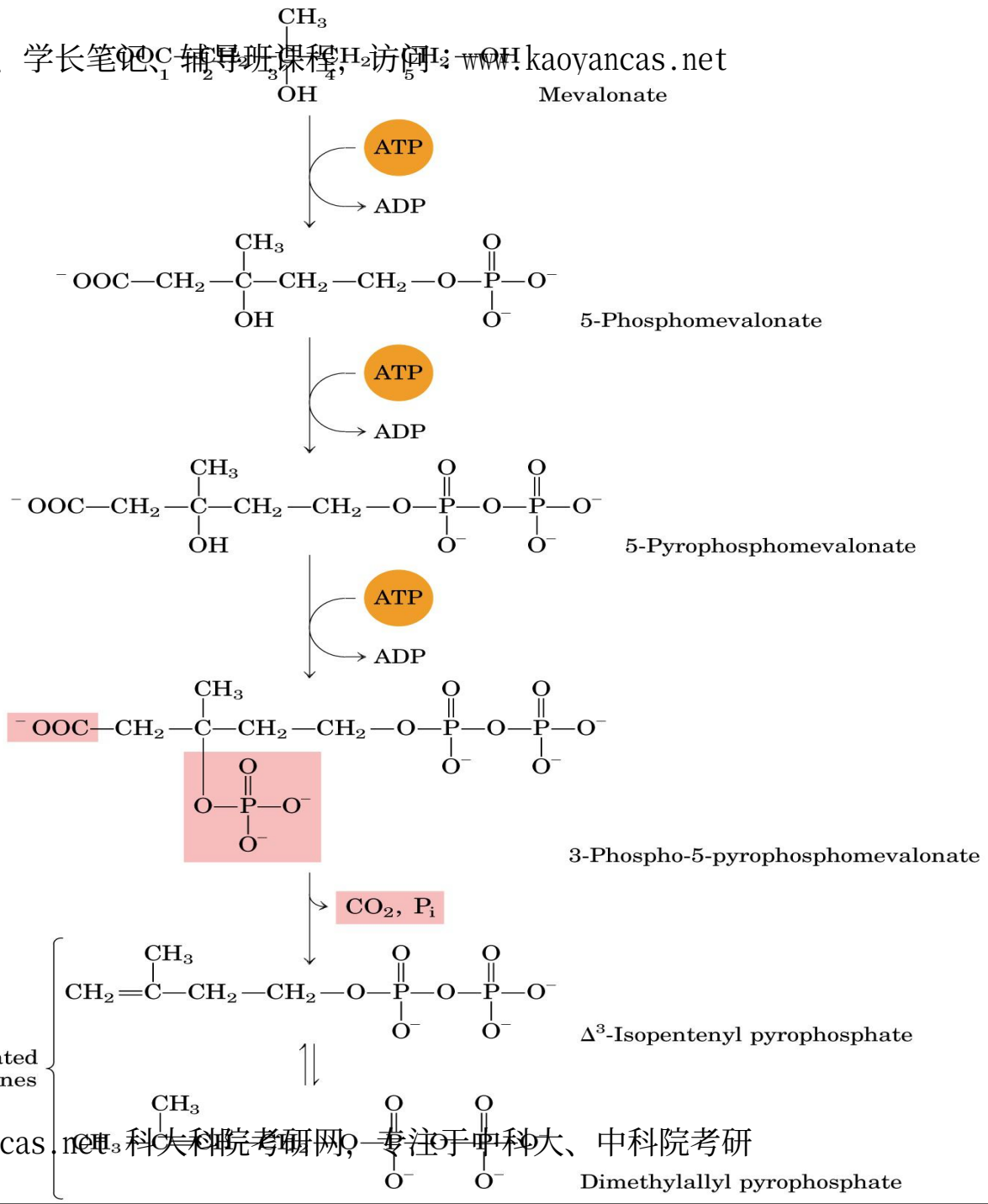
HMG-CoA还原酶的活力受合成速度、降解速度及磷酸化和脱磷酸调控。

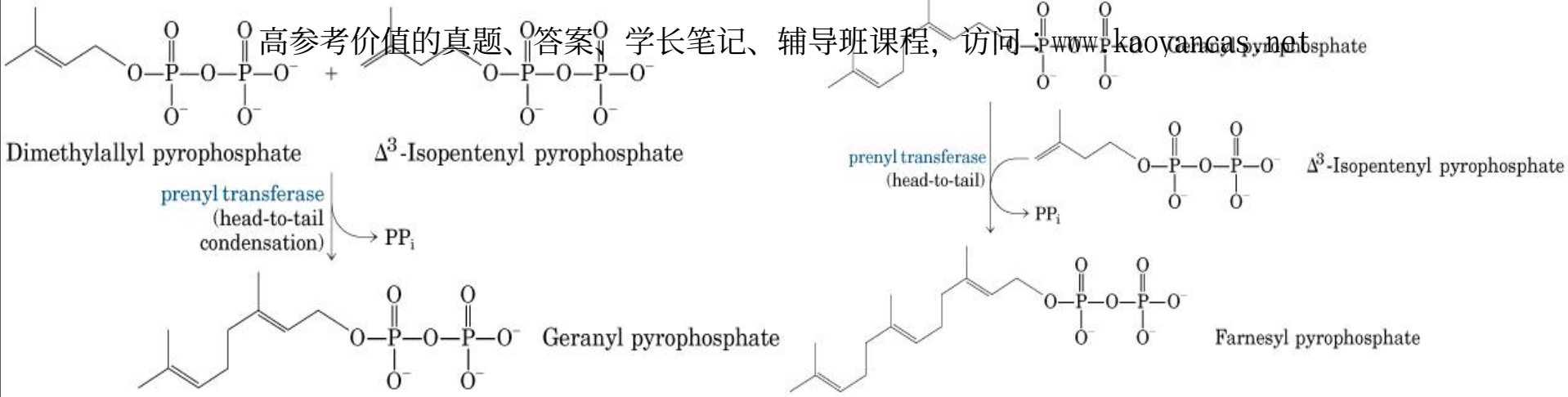
甲羟戊酸合成的机制

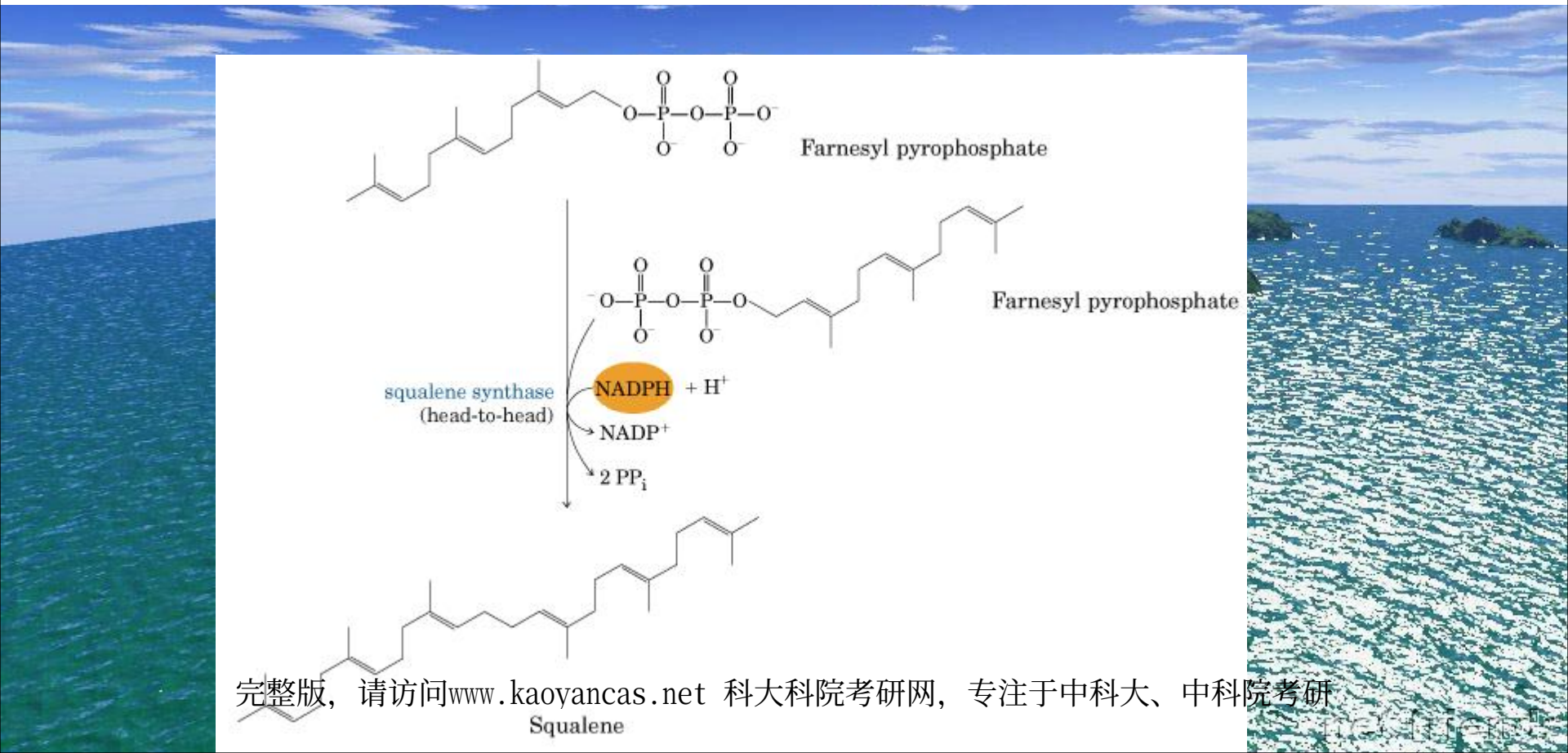




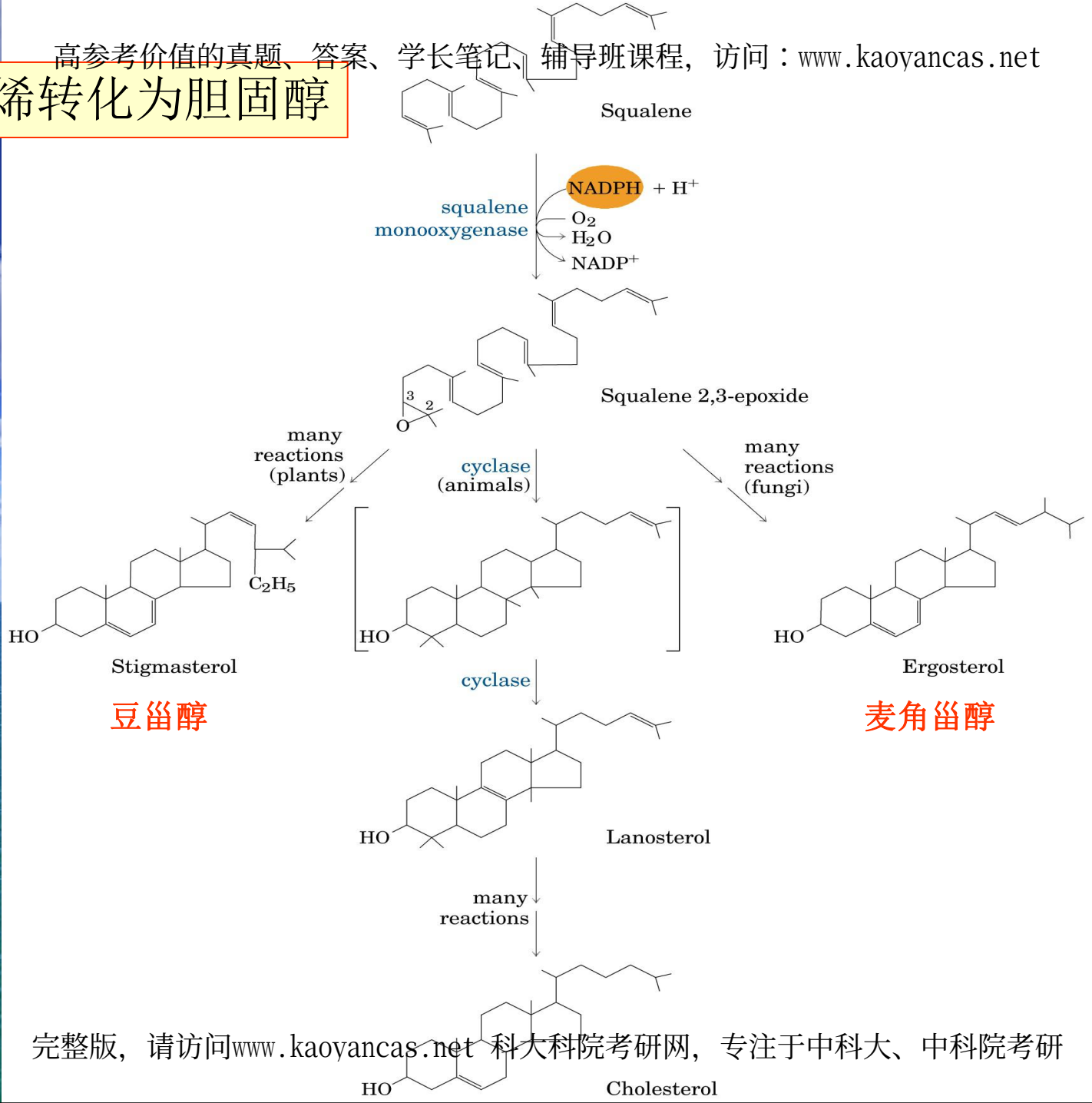
甲羟戊酸到鲨烯的转化

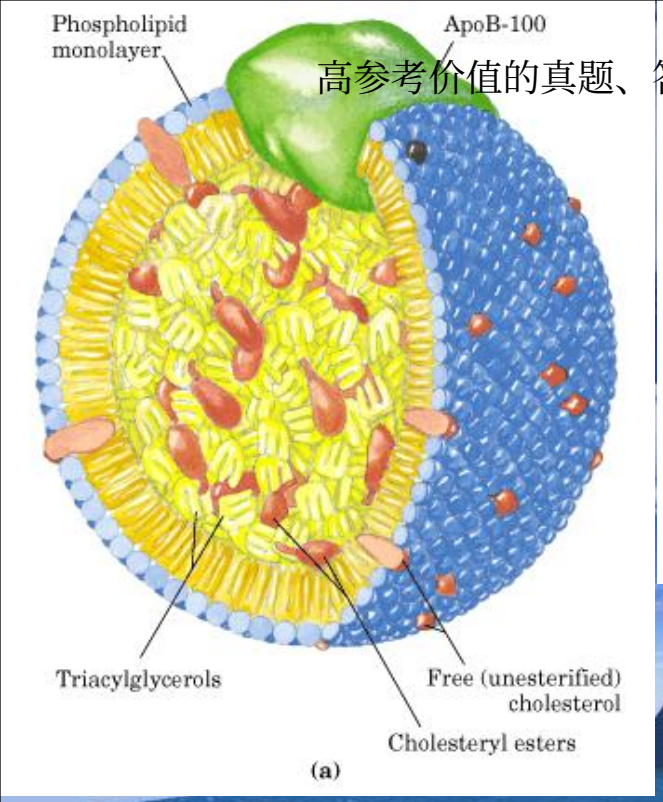


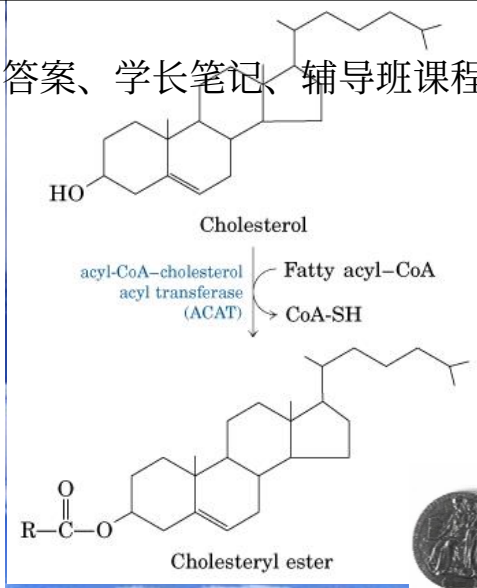




由鲨烯转化为胆固醇







The Nobel Prize in Physiology or Medicine 1964

"for their discoveries concerning the mechanism and regulation of the cholesterol and fatty acid metabolism"

Presentation Speech

Konrad Bloch

USA

Harvard University
Cambridge, MA, USA

1912 -

Biography

Feodor Lynen

Germany

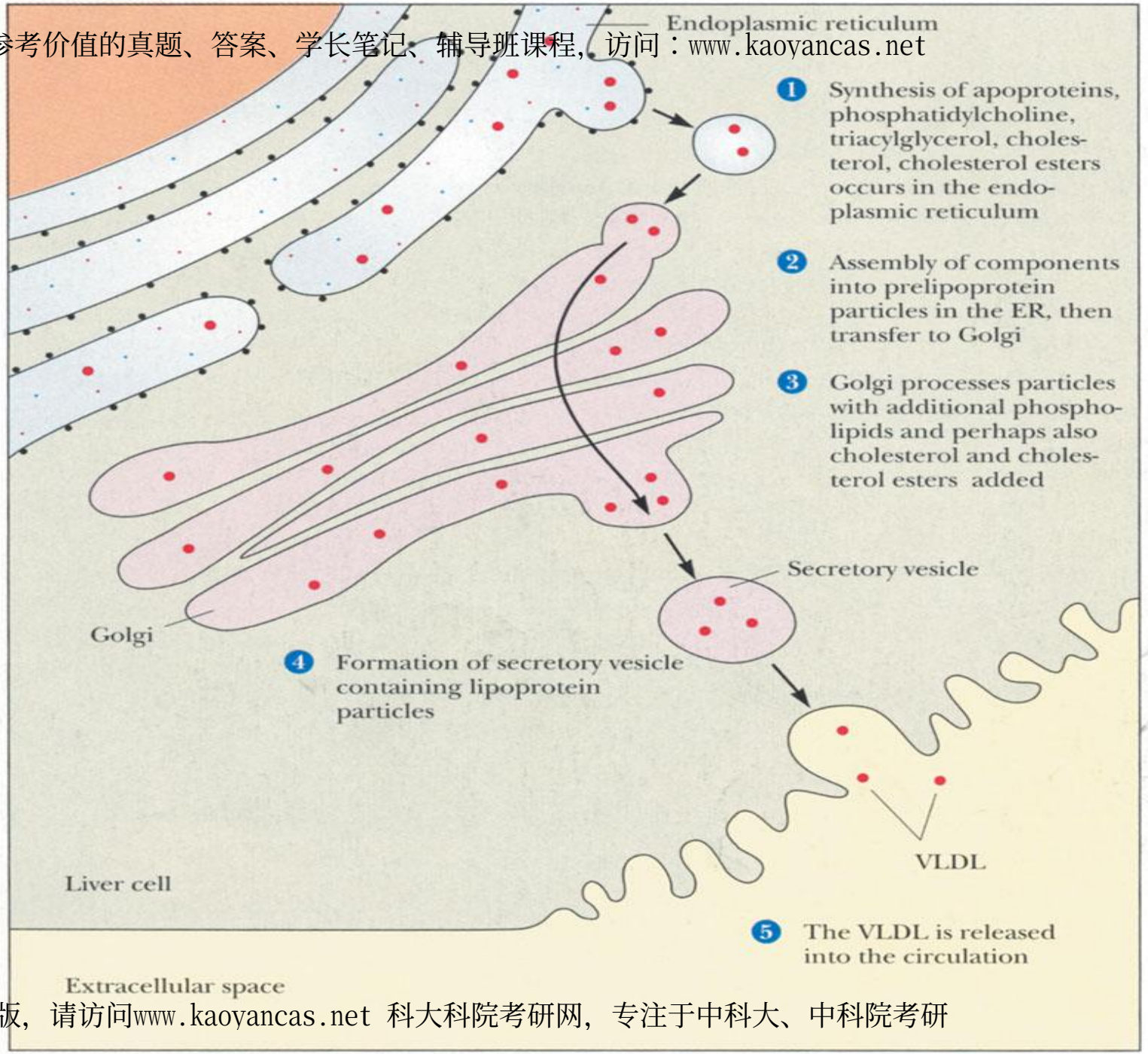
Max-Planck-Institut f r Zellchemie
Munich, Germany

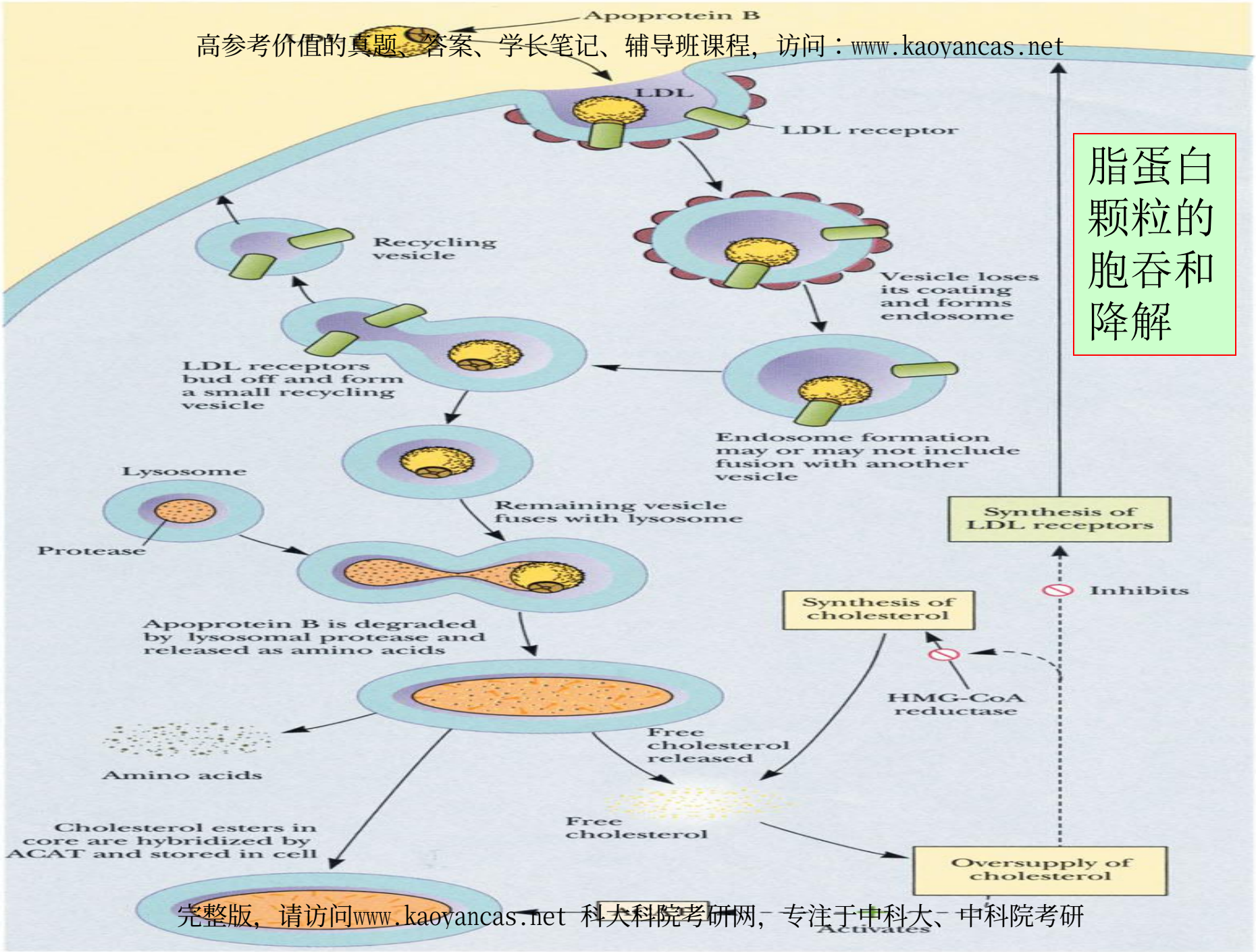
1911 - 1979

Biography

胆固醇的合成是一个高度耗能的过程，合成一个胆固醇需18个乙酰辅酶A，36个ATP，16个NADPH。能源物质过剩时，胆固醇的合成速度加快，午夜时，合成速度较快，膳食固醇类，特别是植物固醇可抑制胆固醇的合成。

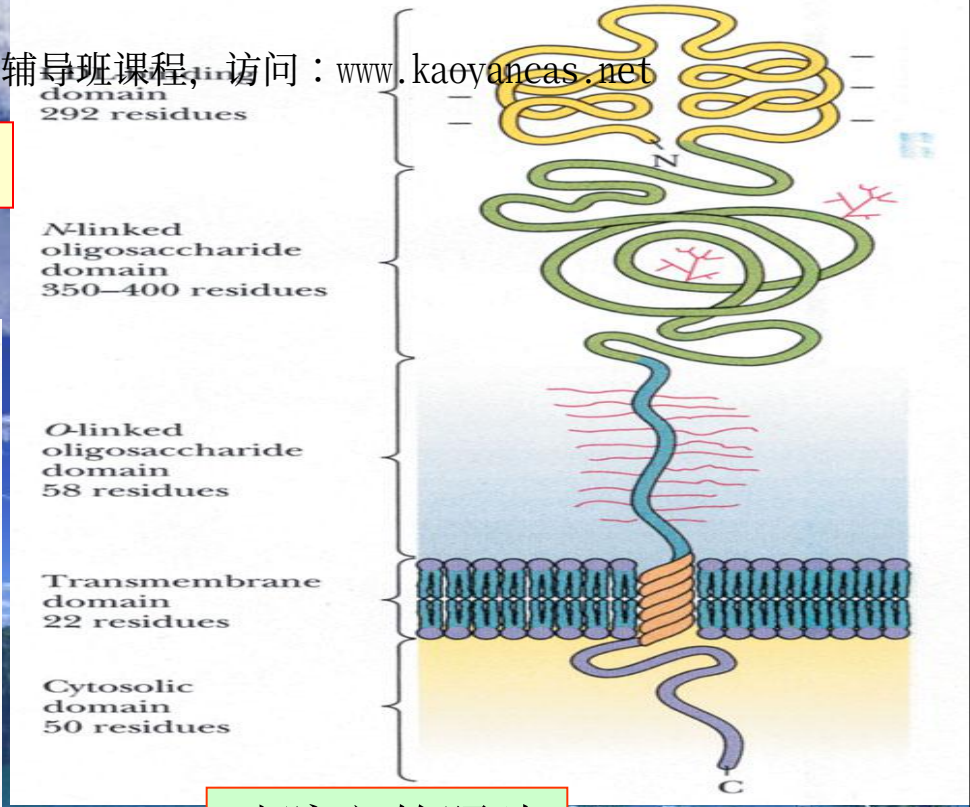
载脂蛋白在肝细胞内质网合成，在内质网组装成脂蛋白颗粒，在高尔基体加工，包装成分泌小泡，分泌到肝细胞外。





脂蛋白颗粒的胞吞和降解

LDL受体的结构



The Nobel Prize in Physiology or Medicine 1985

"for their discoveries concerning the regulation of cholesterol metabolism"

Press release

Michael S. Brown

USA

University of Texas Health
Science Center at Dallas
Dallas, TX, USA

1941 -

Biography

Joseph L. Goldstein

USA

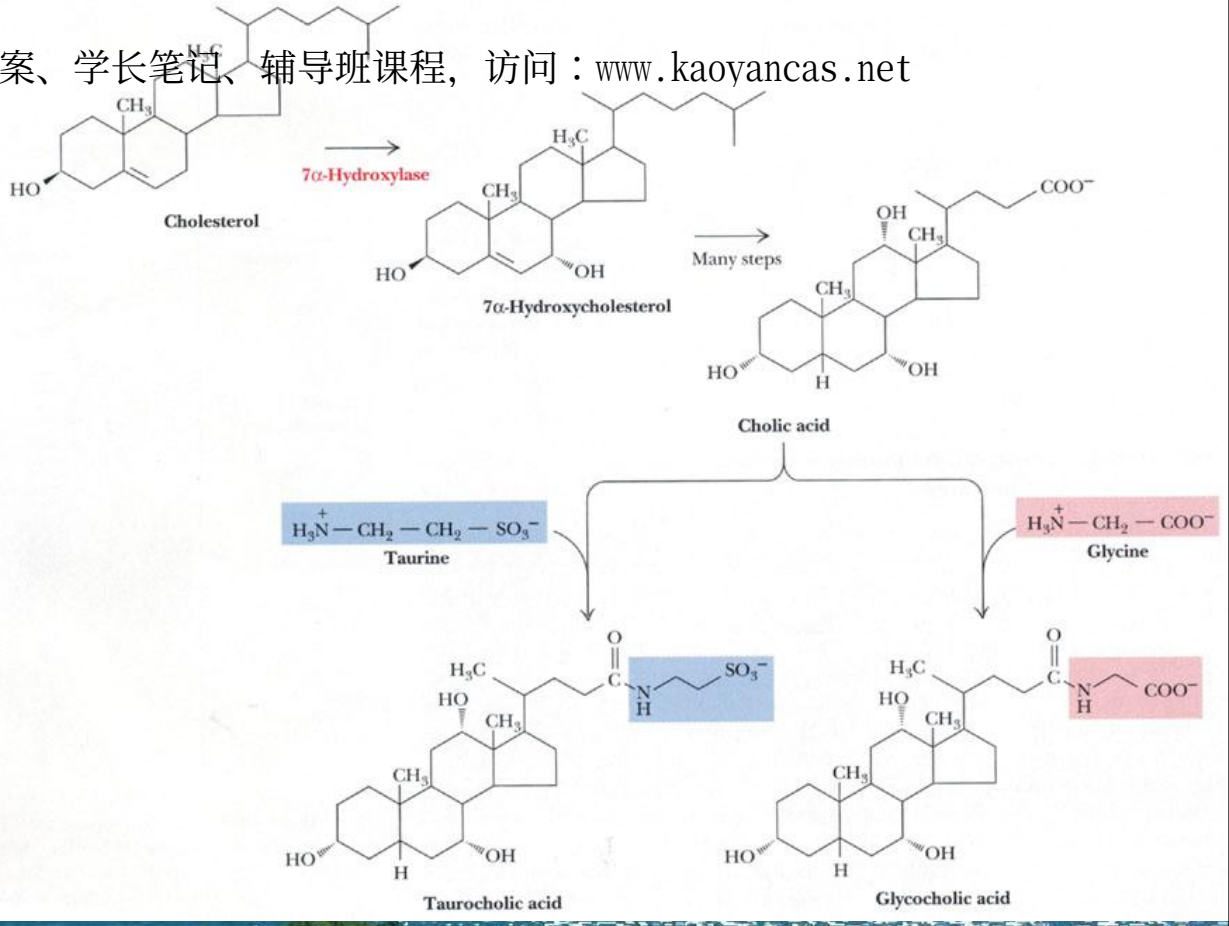
University of Texas Health
Science Center at Dallas
Dallas, TX, USA

1940 -

Biography

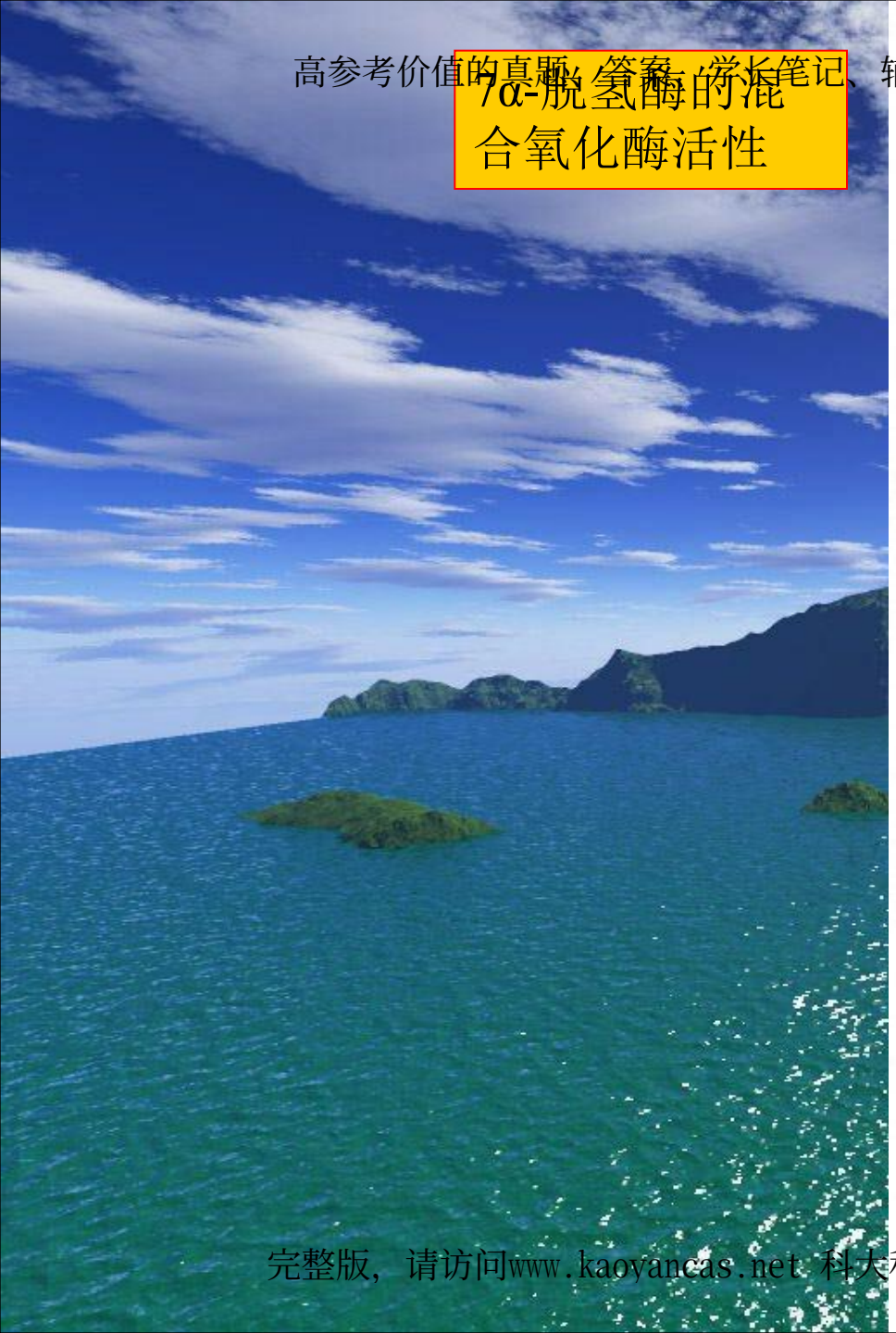
动脉斑的照片

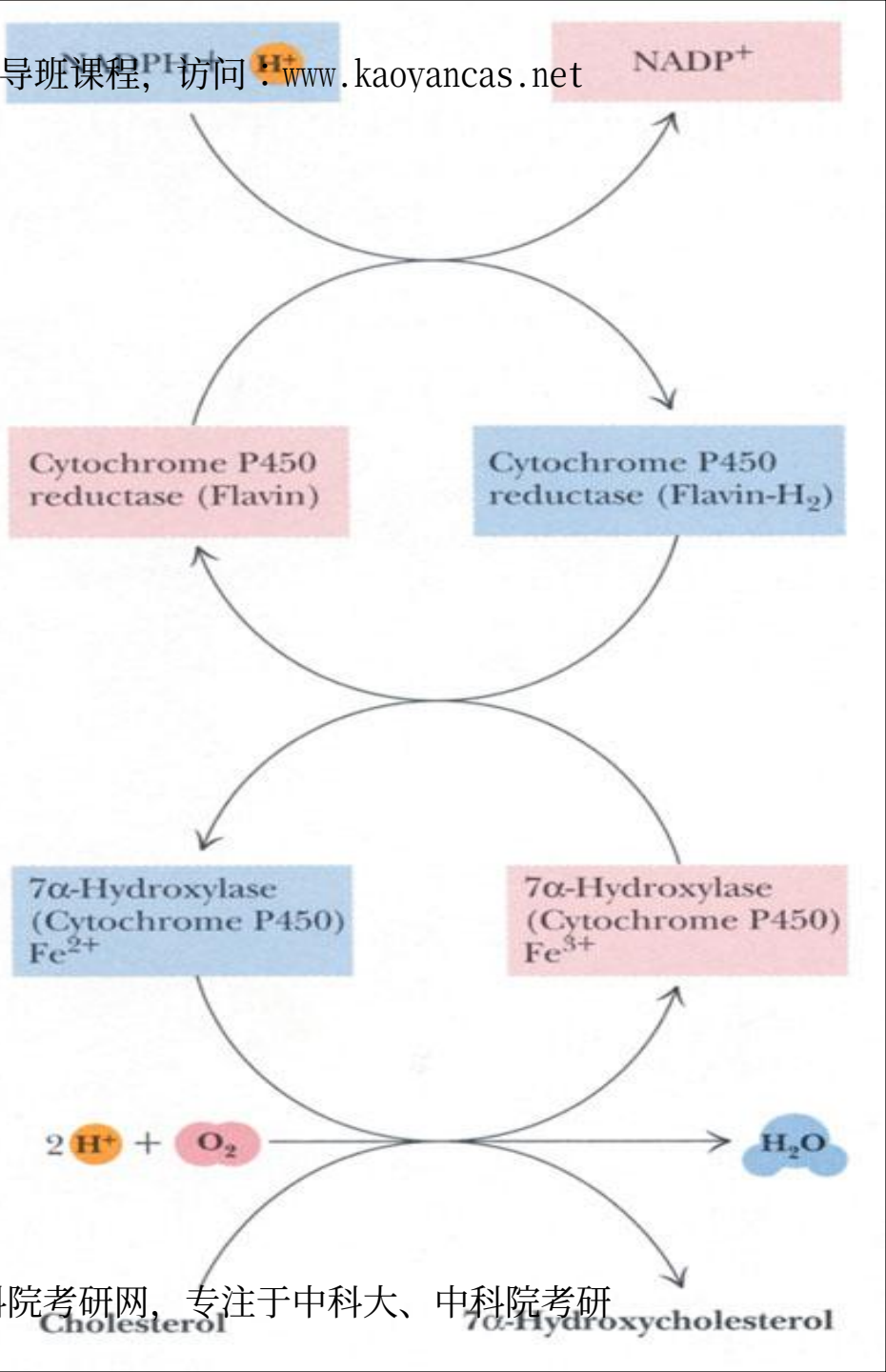
胆酸和胆酸盐的合成

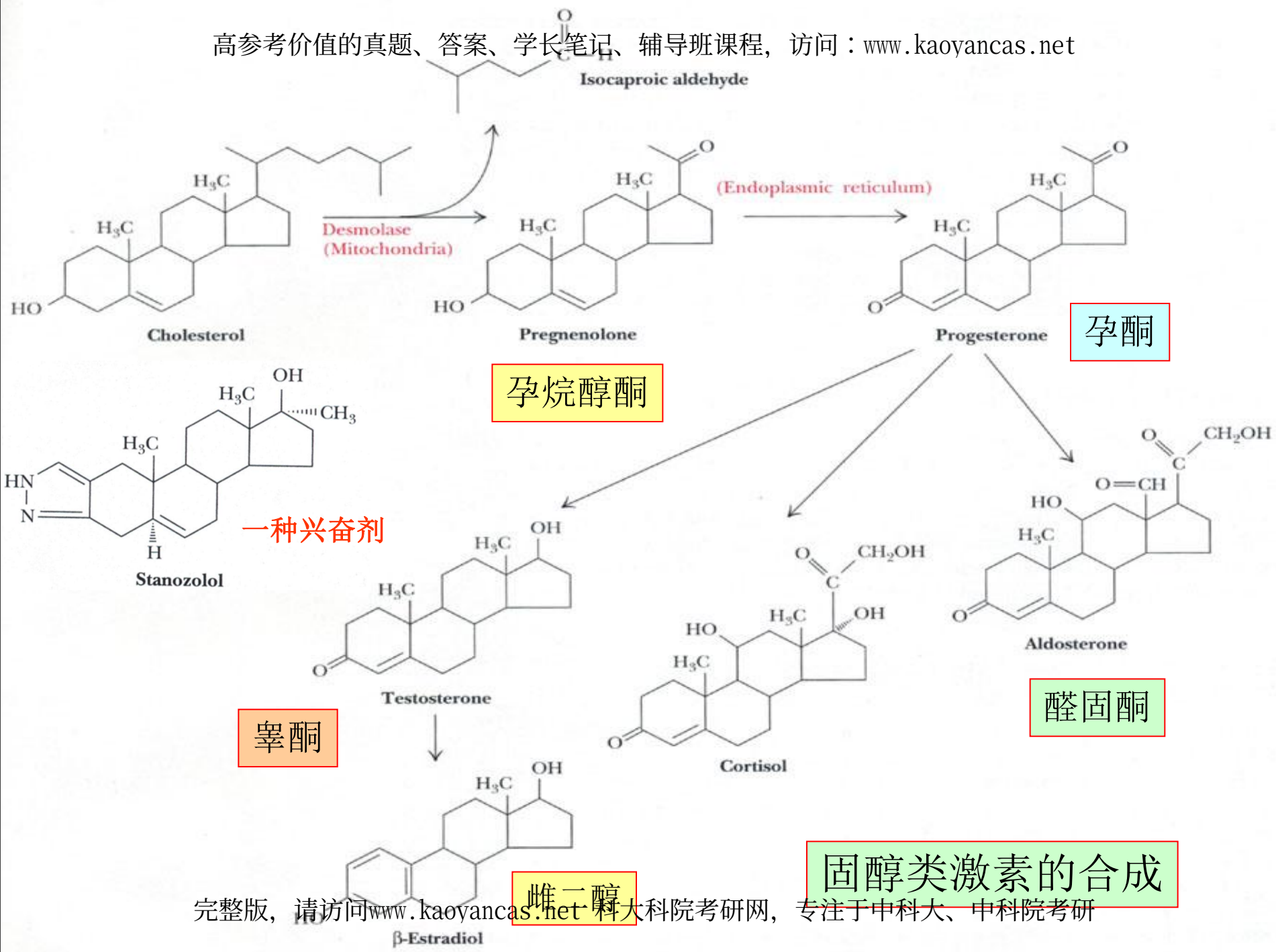


降低血清胆固醇的药物

7α-脱氢酶的混合氧化酶活性







基本要求

1. 掌握饱和脂肪酸的合成途径及调控。（重点）
2. 熟悉不饱和脂肪酸的合成途径及调控。
3. 熟悉磷脂、鞘脂类和甾醇的合成途径及调控。