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第32章

核苷酸代谢

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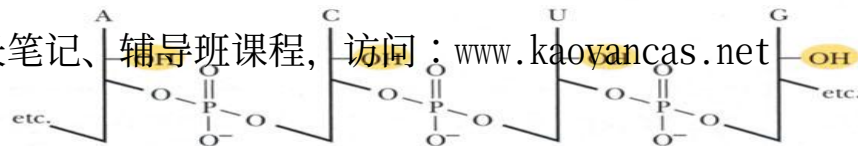


一、核酸和核苷酸的分解代谢

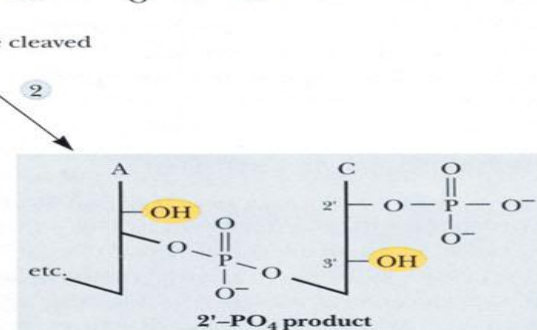
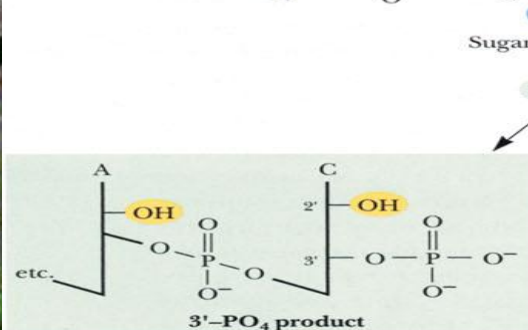
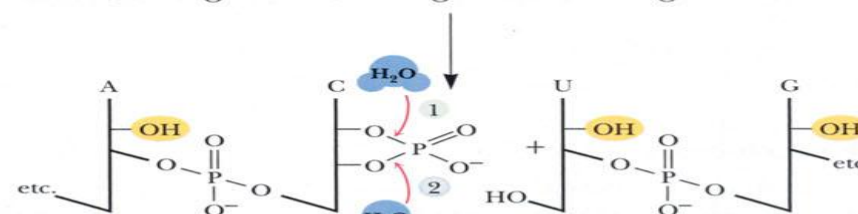
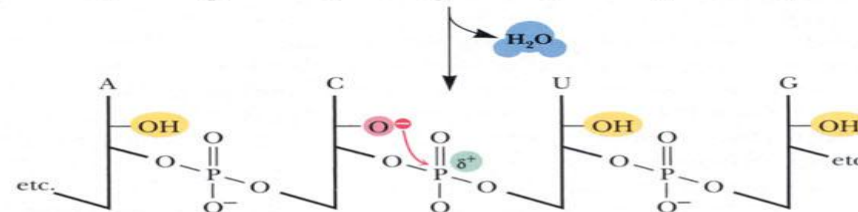
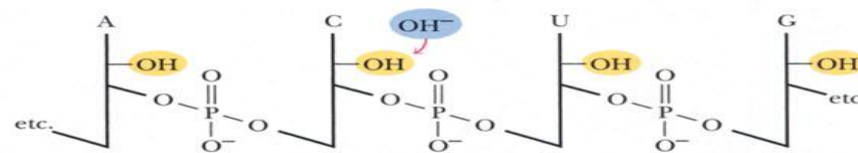
(一) 核酸的水解

核酸的碱水解

RNA:

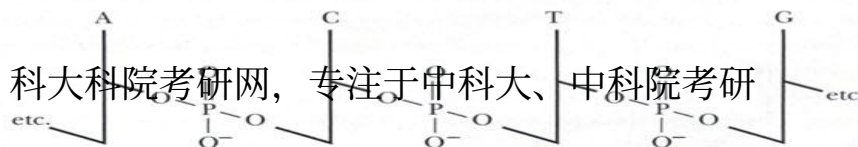


A nucleophile such as OH^- can abstract the H of the 2'-OH, generating 2'-O $^-$ which attacks the δ^+ P of the phosphodiester bridge:



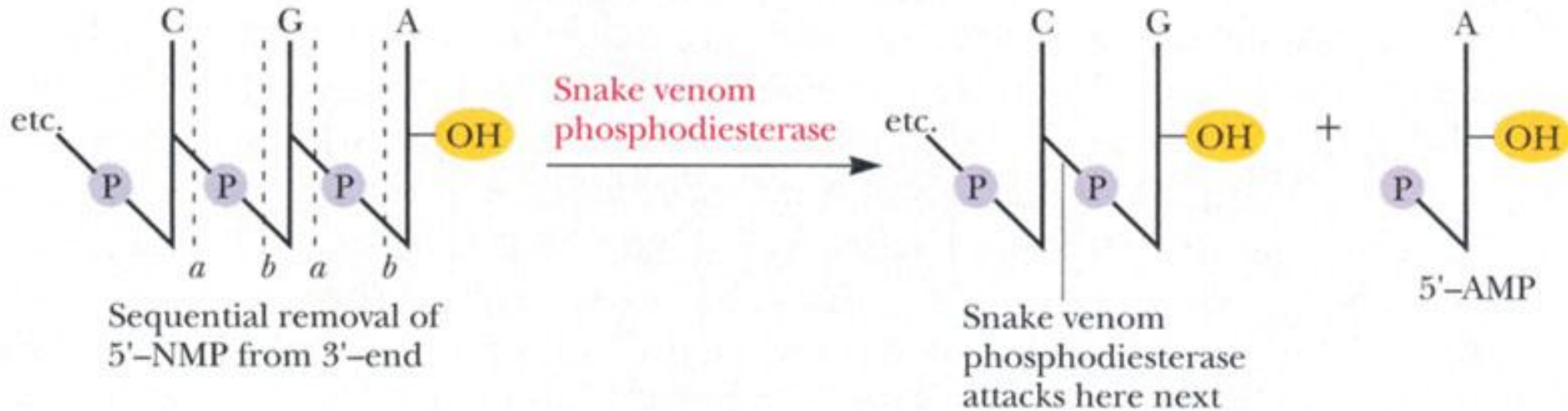
Complete hydrolysis of RNA by alkali yields a random mixture of 2'-NMPs and 3'-NMPs.

DNA: no 2'-OH; resistant to OH^- :

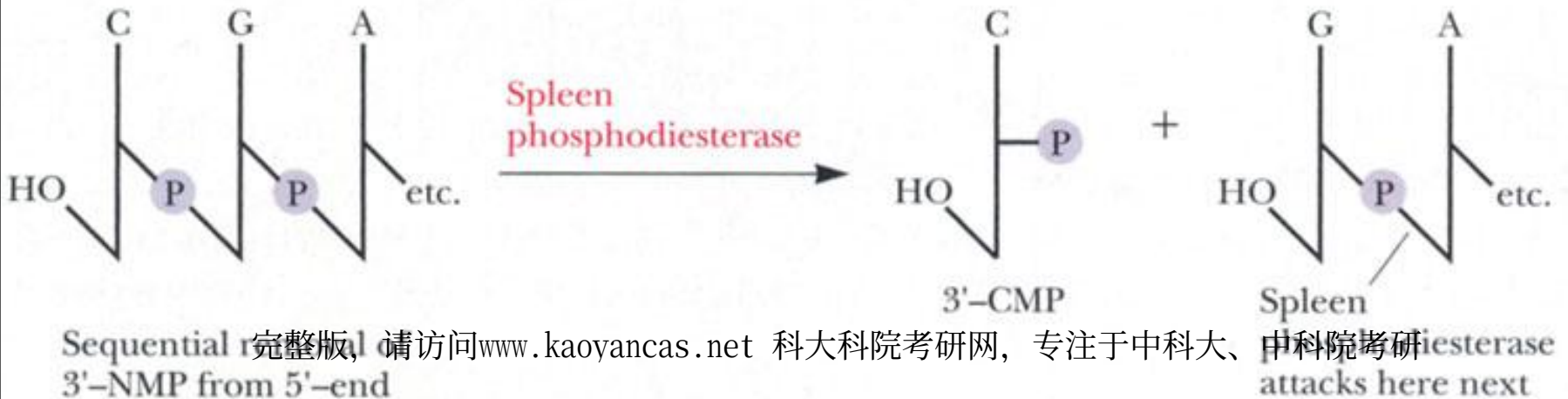


核酸的酶水解

Snake venom phosphodiesterase: an "a" specific exonuclease:



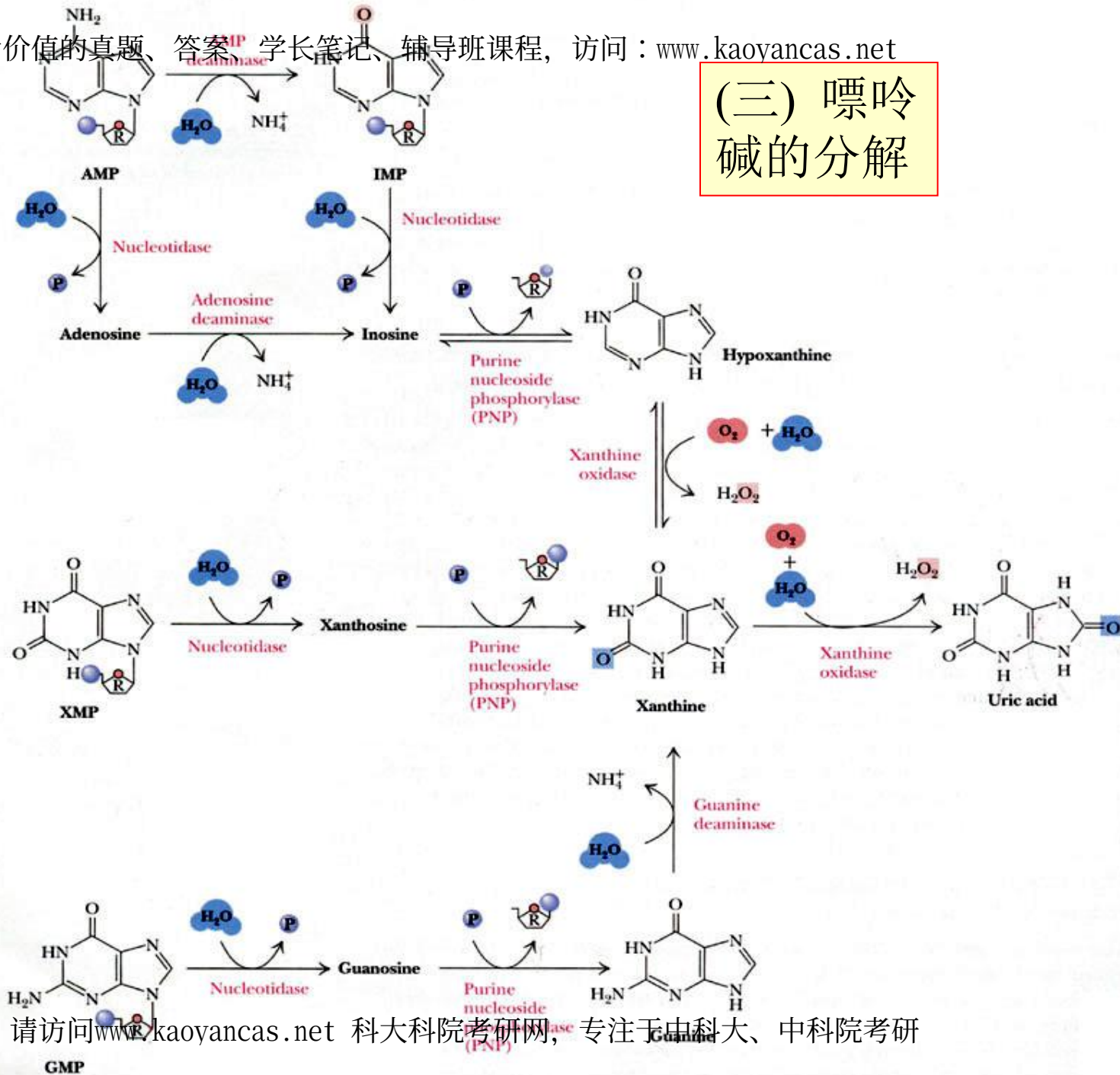
Spleen phosphodiesterase: a "b" specific exonuclease:



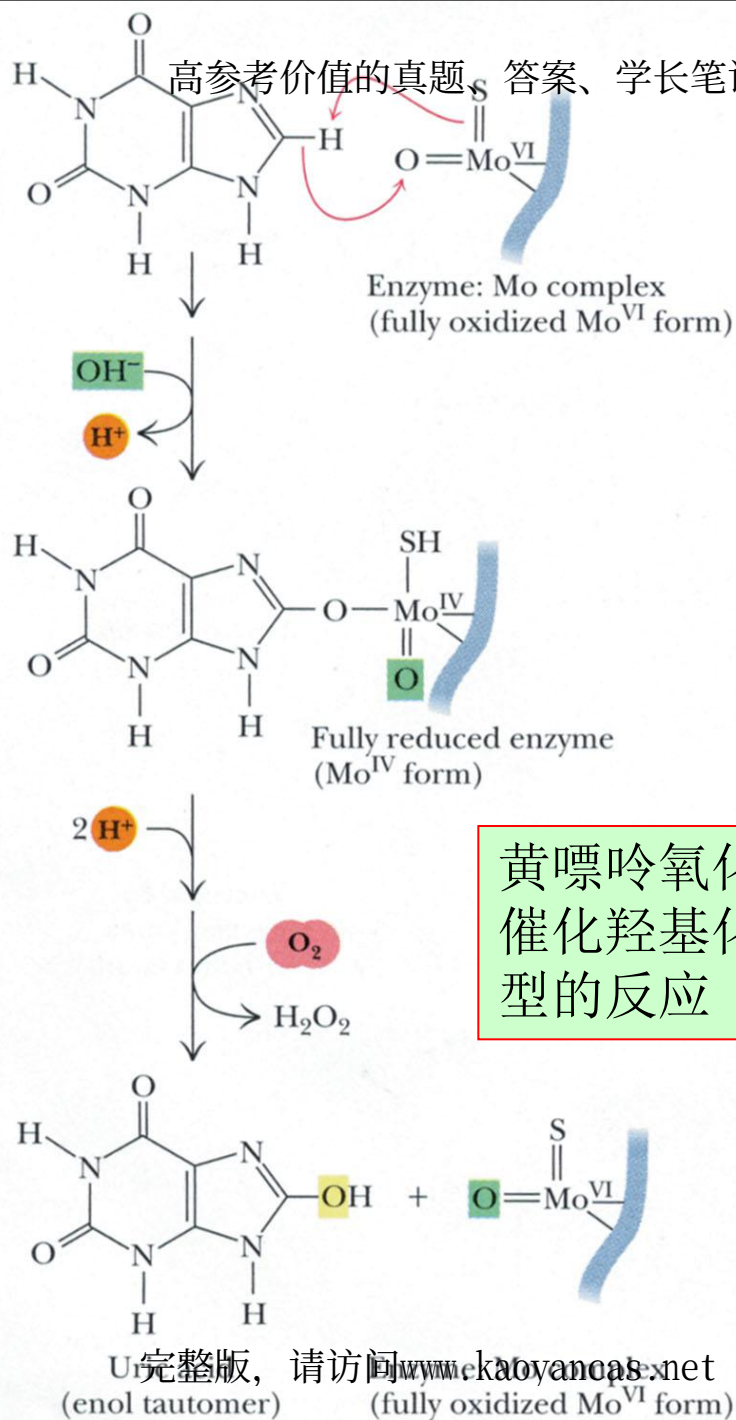
(二) 核苷酸的降解

核苷酸在核苷酸酶作用下，水解为核苷和磷酸。

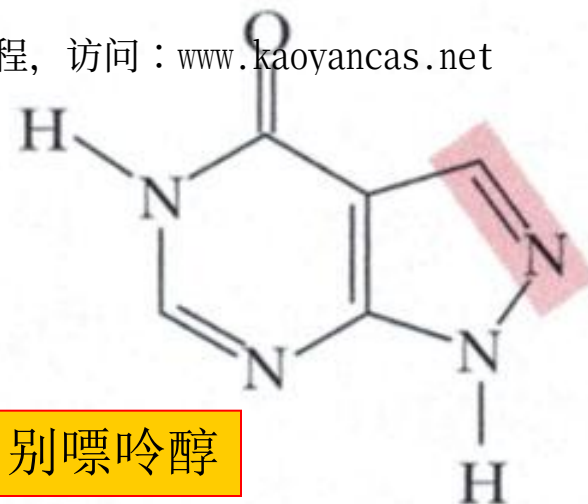
在核苷磷酸化酶的作用下，核苷分解为碱基和戊糖-1-磷酸；在核苷水解酶的作用下，核苷水解为碱基和戊糖。



(三) 嘌呤碱的分解



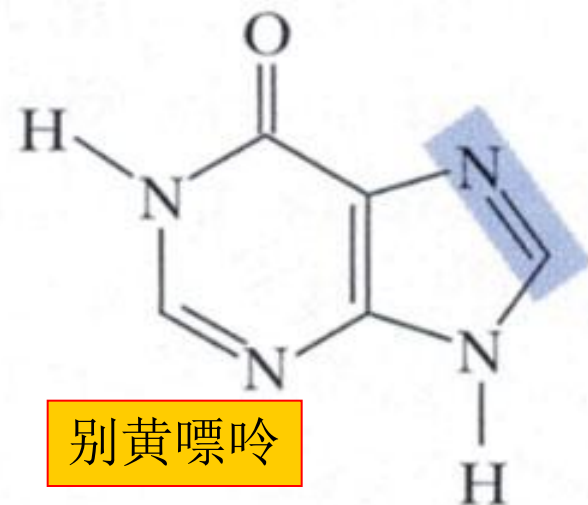
黄嘌呤氧化酶
催化羟基化类
型的反应



别嘌呤醇

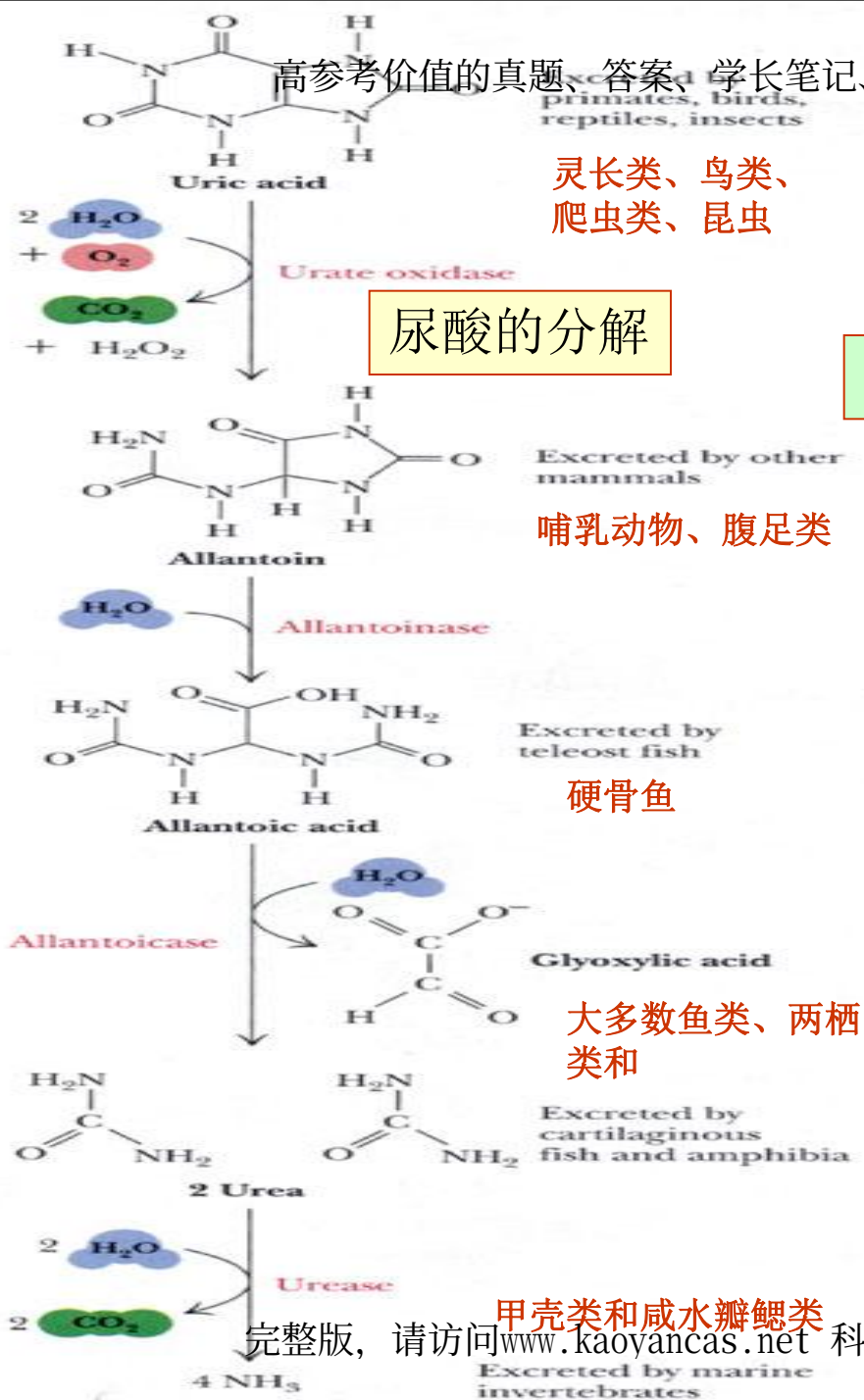
Allopurinol

黄嘌呤氧化酶的抑制剂

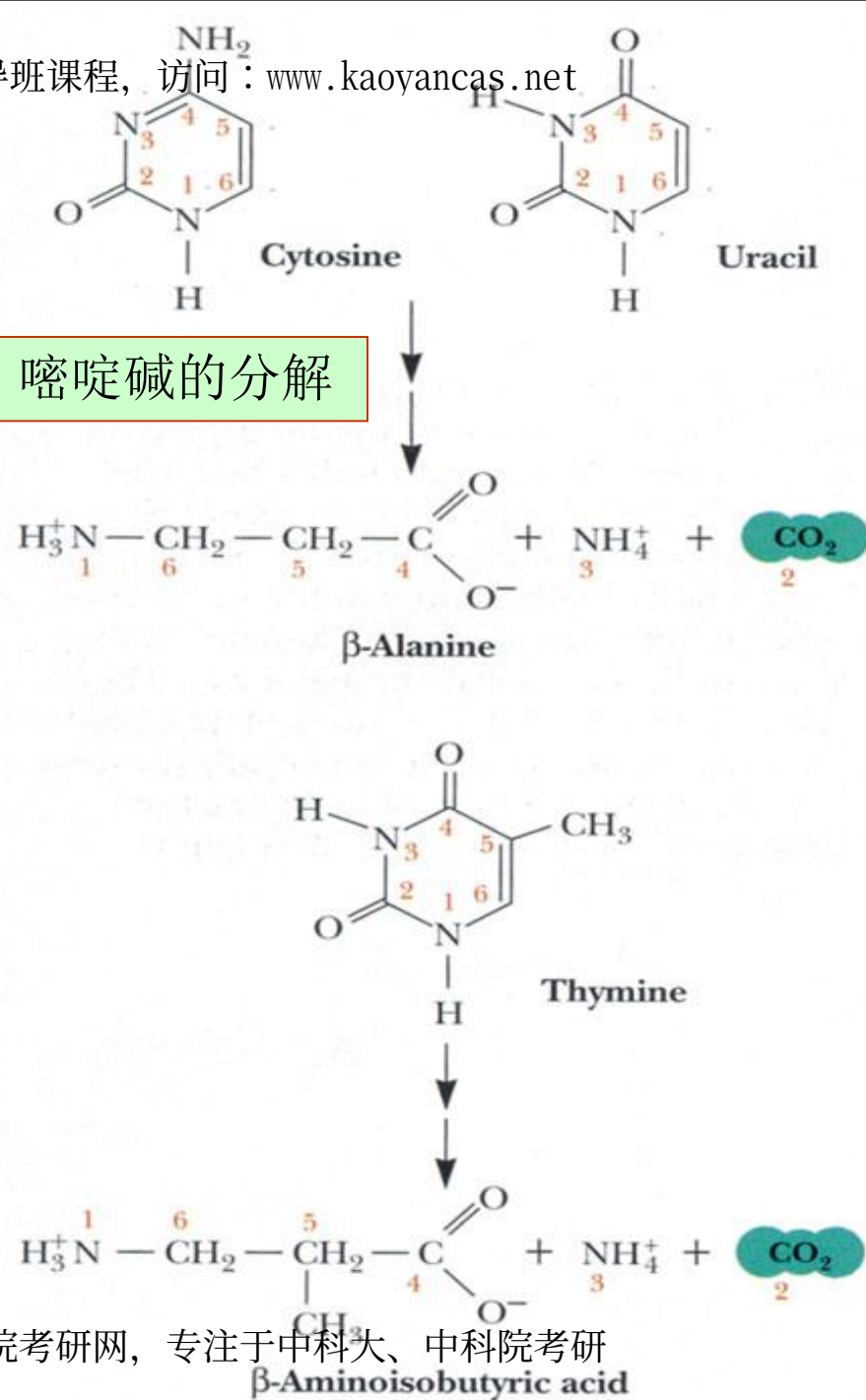


别黄嘌呤

Hypoxanthine



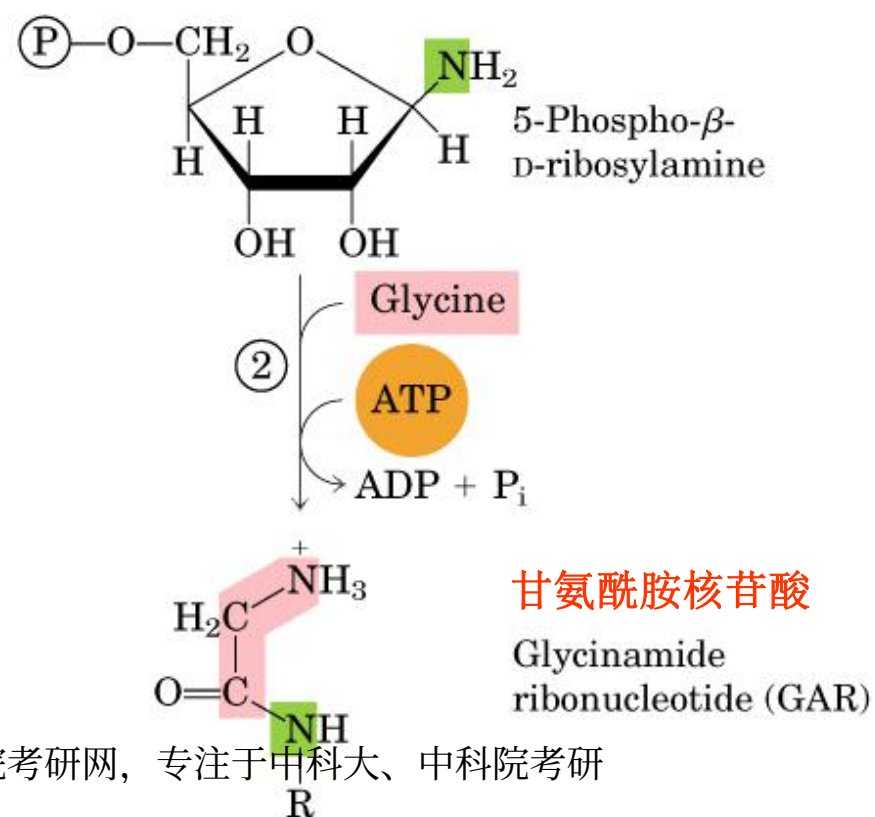
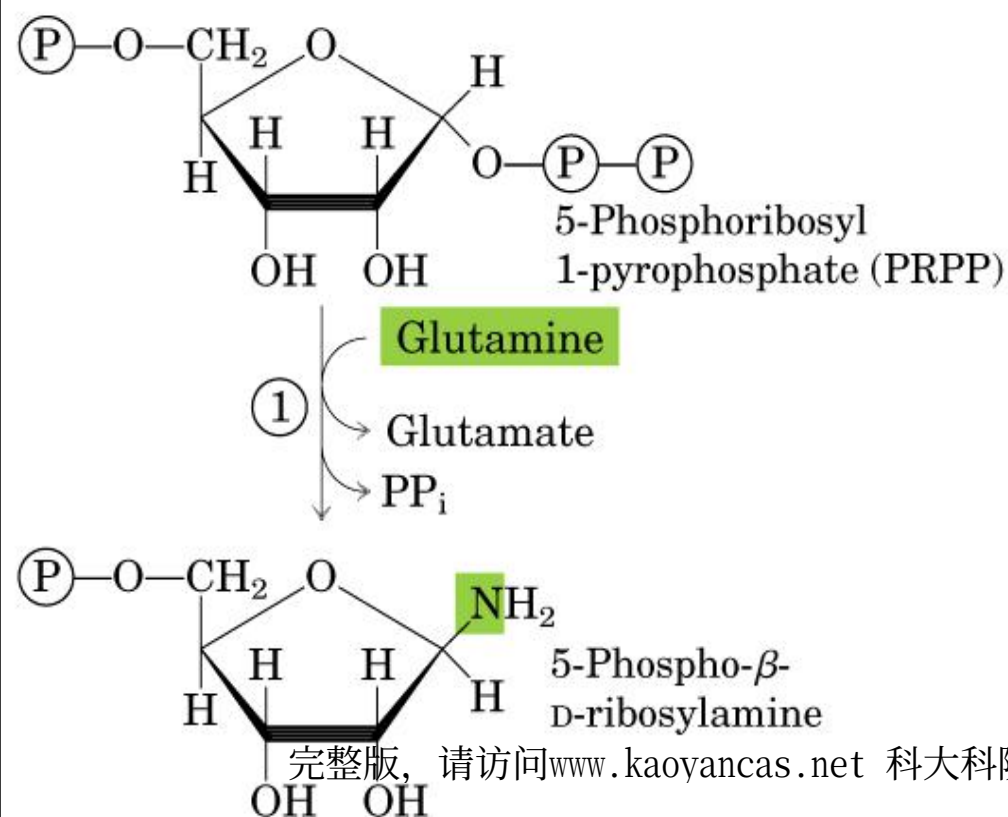
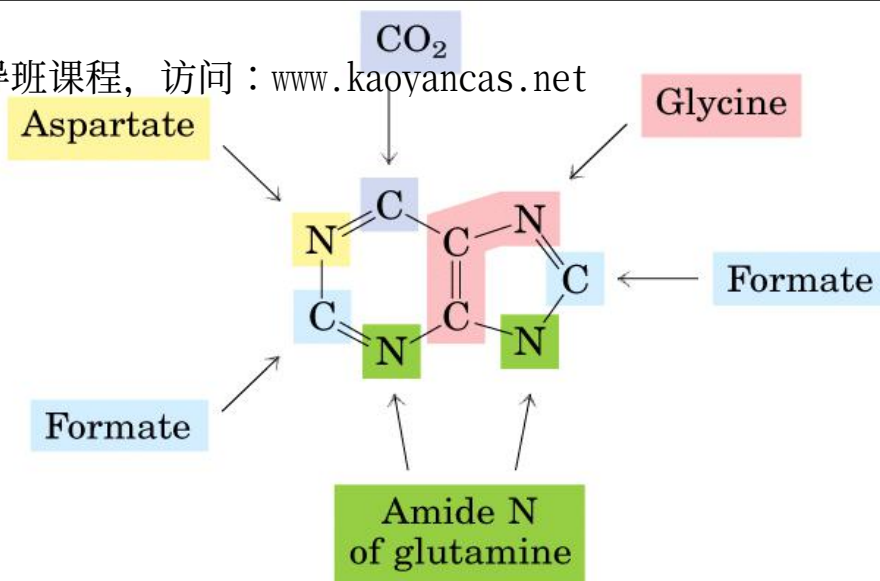
(四) 嘧啶碱的分解

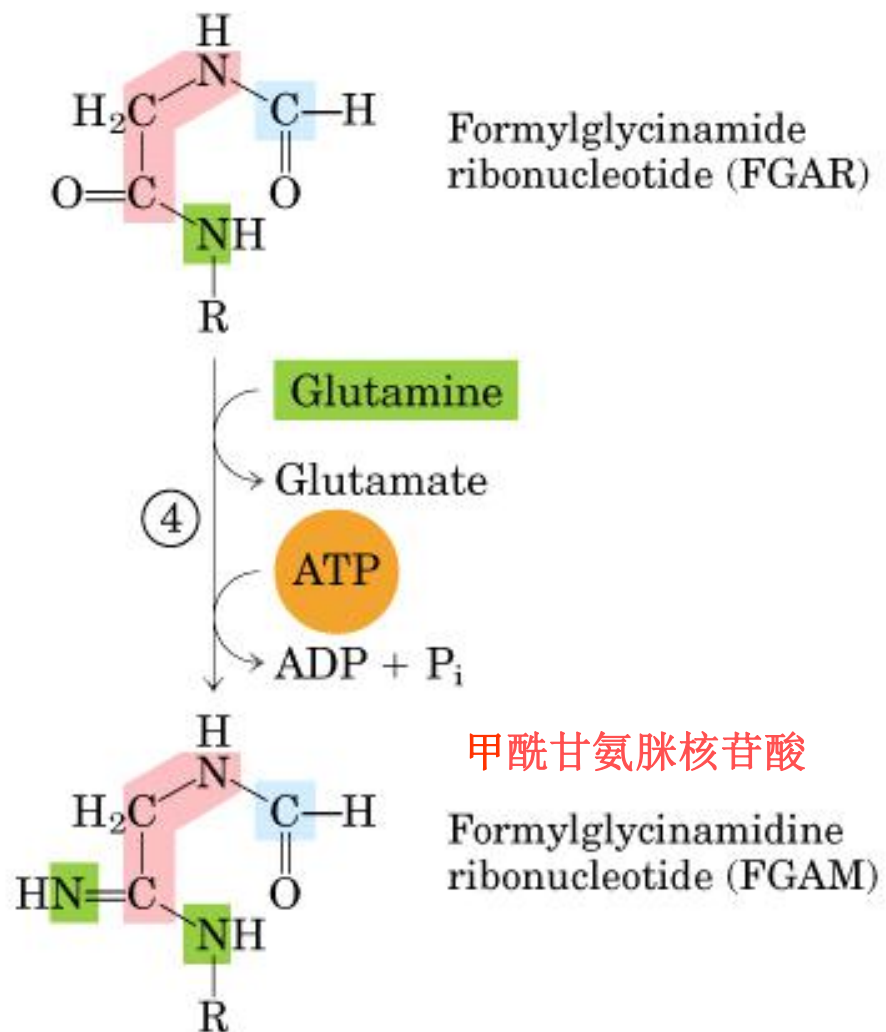
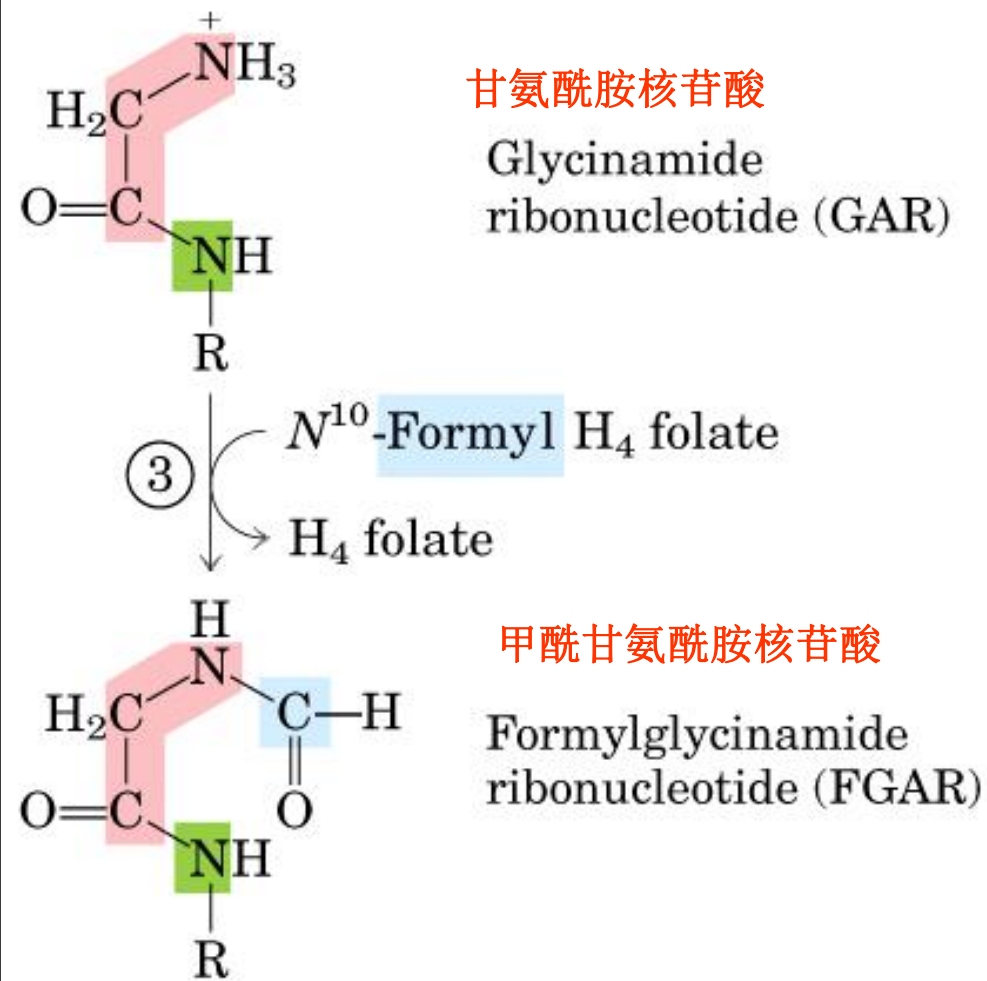


二、核苷酸的生物合成

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(一) 嘌呤核糖核苷酸的合成

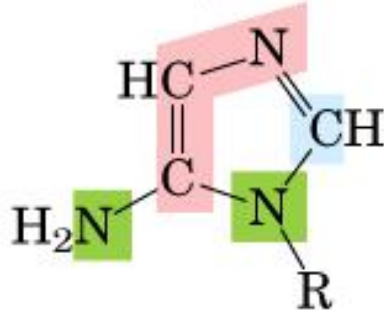
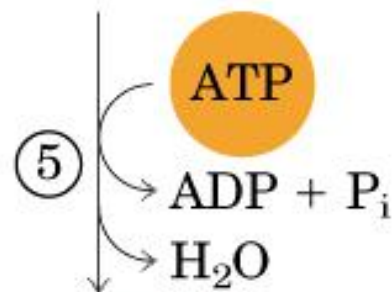






甲酰甘氨酸核苷酸

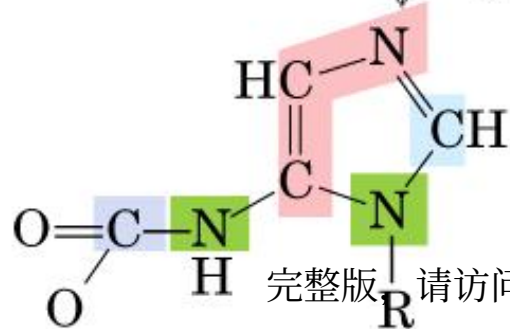
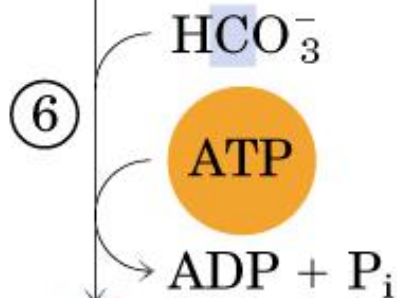
Formylglycinamidine
ribonucleotide (FGAM)



5-Aminoimidazole
ribonucleotide (AIR)

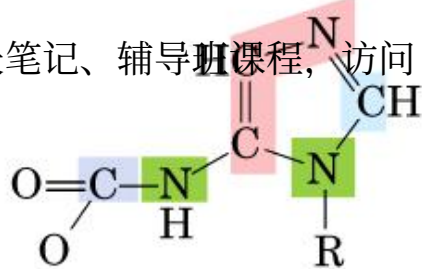
5-氨基咪唑核苷酸

AIR



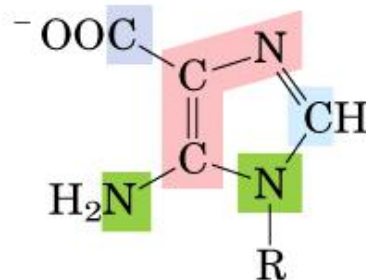
N⁵-Carboxyaminoimidazole
ribonucleotide
(N⁵-CAIR)

N⁵-羧基氨基咪唑核苷酸



N^5 -Carboxyaminoimidazole
ribonucleotide
(N^5 -CAIR)

N^5 -羧基氨基咪唑核苷酸

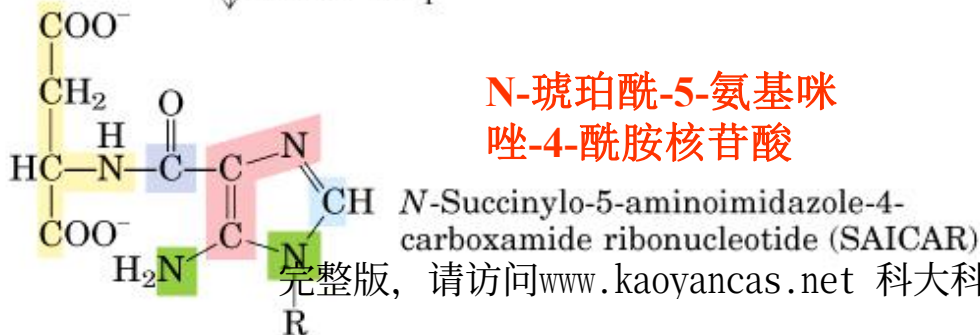
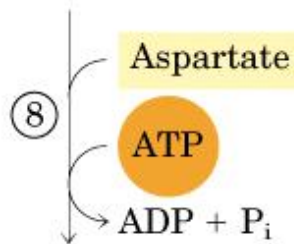


5-Amino-4-carboxyamino-
imidazole ribonucleotide

5-氨基-4-羧酸咪唑核苷酸



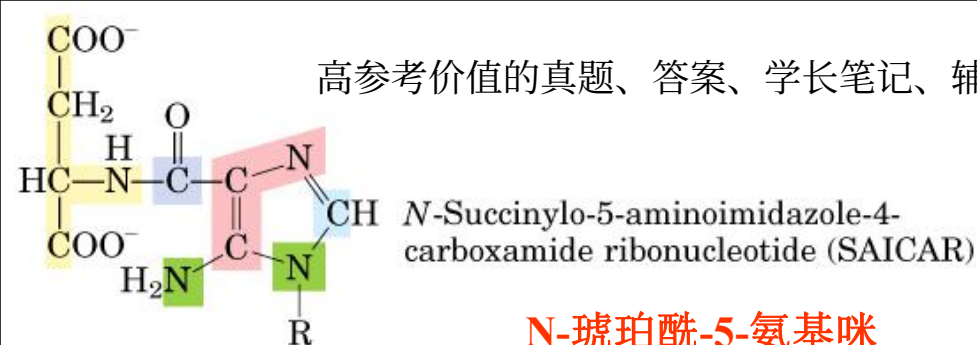
5-Amino-4-carboxyamino-
imidazole ribonucleotide



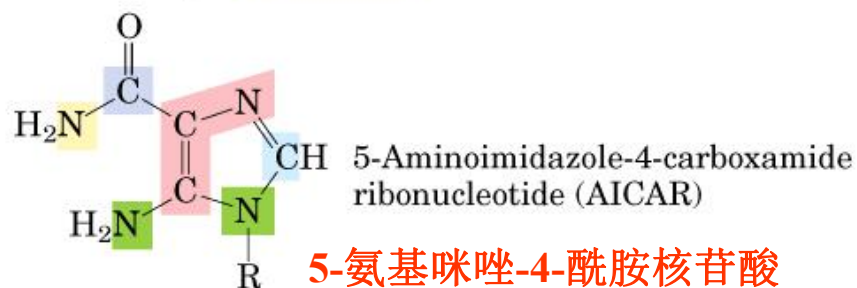
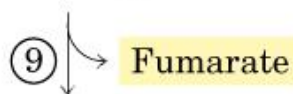
**N-琥珀酰-5-氨基咪
唑-4-酰胺核苷酸**

N -Succinyl-5-aminoimidazole-4-
carboxamide ribonucleotide (SAICAR)

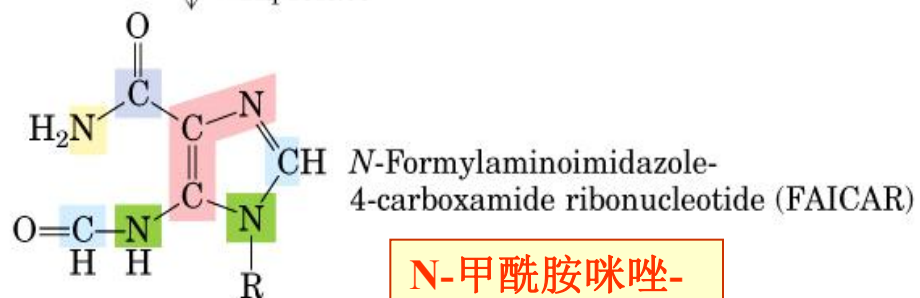
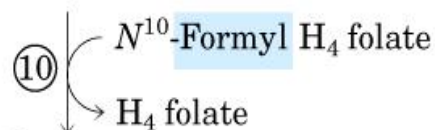
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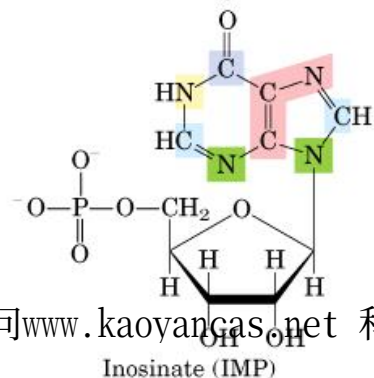
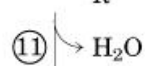
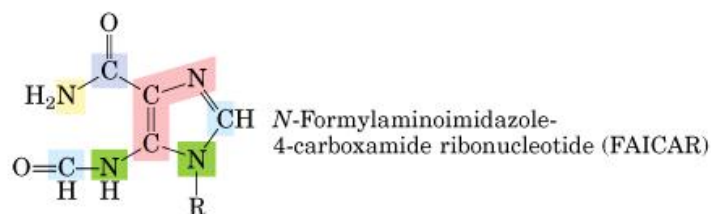
N-琥珀酰-5-氨基咪唑-4-酰胺核苷酸



5-氨基咪唑-4-酰胺核苷酸



N-甲酰胺咪唑-4-酰胺核苷酸



次黄嘌呤核苷酸

Inosine monophosphate (IMP)

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α -D-Ribose-5-phosphate

ATP AMP

5-Phosphoribosyl- α -pyrophosphate (PRPP)

Glutamine + H_2O Glutamate + $P-P$ Gln: PRPP amidotransferase

Phosphoribosyl- β -amine

Glycine + ATP ADP + P GAR synthetase

Glycinamide ribonucleotide (GAR)

$N^{\delta 0}$ -Formyl-THF GAR transformylase

Formylglycinamide ribonucleotide (FGAR)

ATP + Glutamine + H_2O ADP + Glutamate + P FGAM synthetase

Formylglycinamide ribonucleotide (FGAM)

ATP ADP + P AIR synthetase

11 H_2O IMP synthase

N -formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)

THF $N^{\delta 0}$ -Formyl-THF AICAR transformylase

5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)

Fumarate Adenylosuccinate lyase

N -succinyl-5-aminoimidazole-4-carboxamide ribonucleotide (SAICAR)

8 ADP + P Aspartate + ATP SAICAR synthetase

Carboxyaminoimidazole ribonucleotide (CAIR)

7 CO_2 ATP ADP + P AIR carboxylase

5-Aminoimidazole ribonucleotide (AIR)

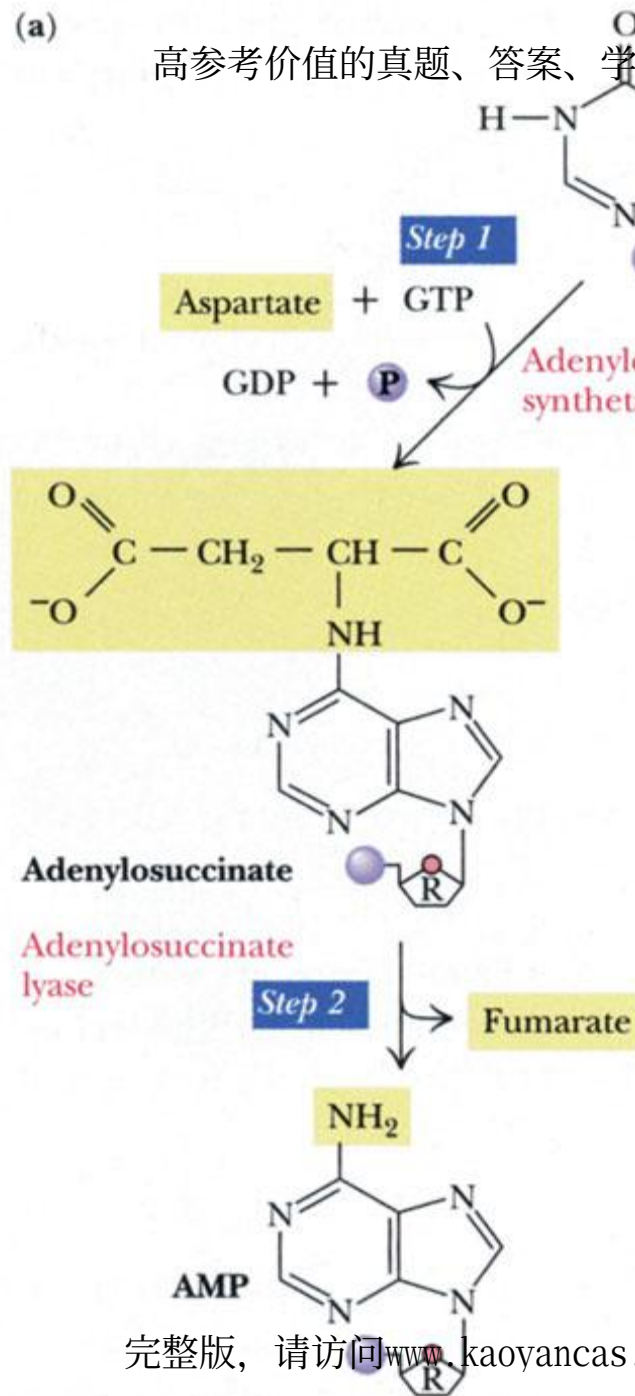
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(a)

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由IMP合成AMP和GMP

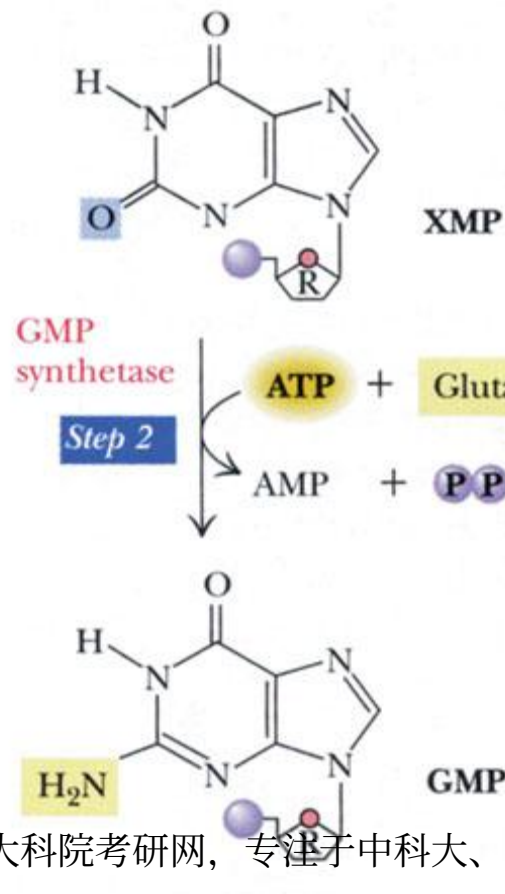
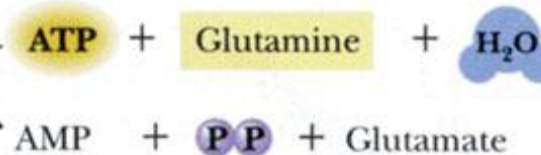
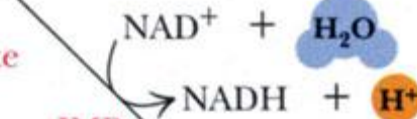


(b)

IMP dehydrogenase

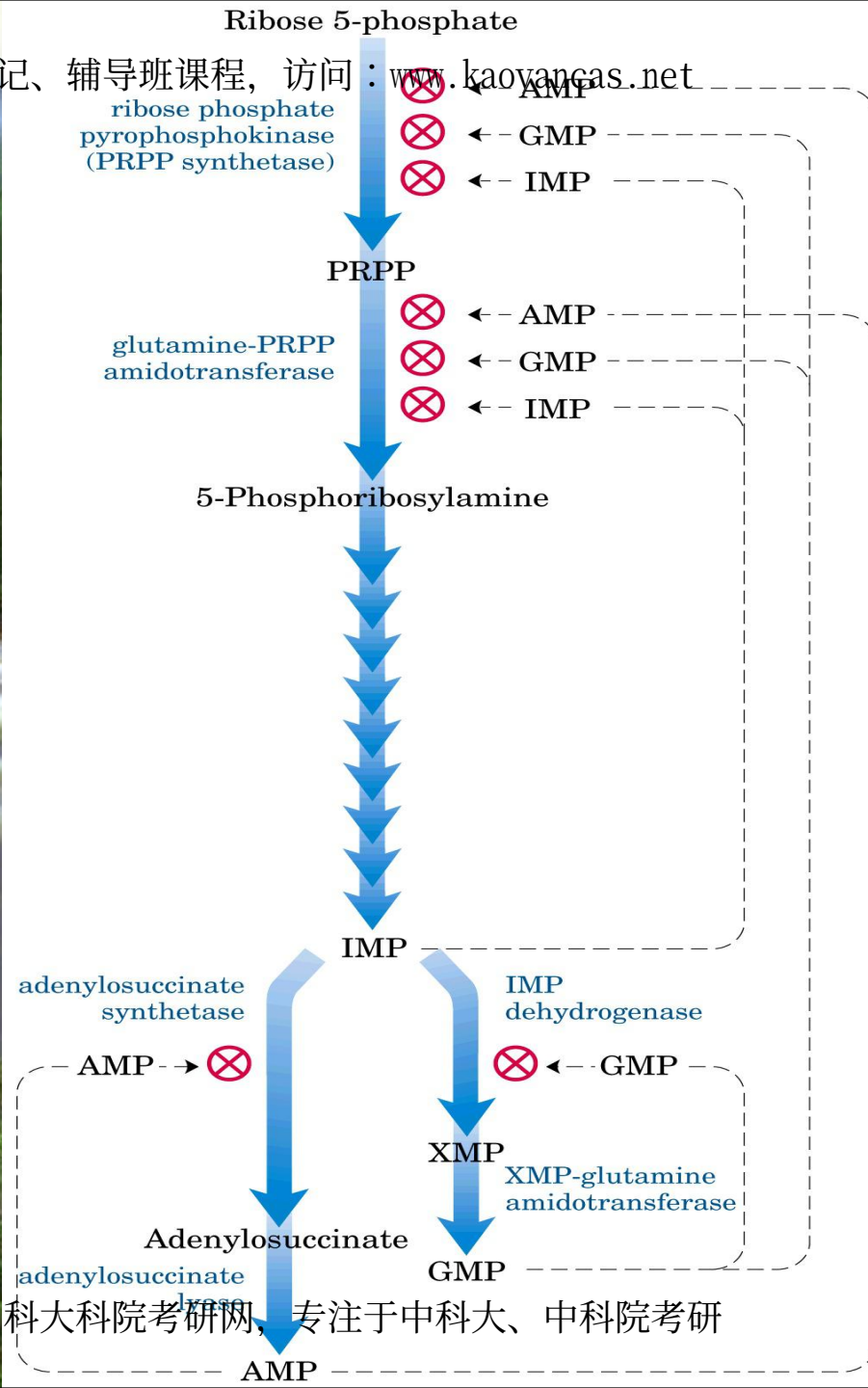
GMP synthetase

Step 2

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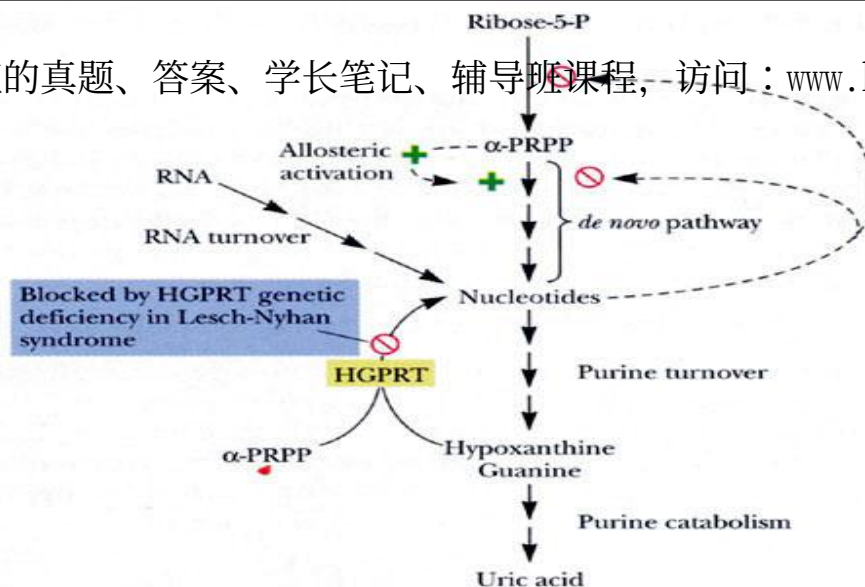
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嘌呤核苷酸合成的调控

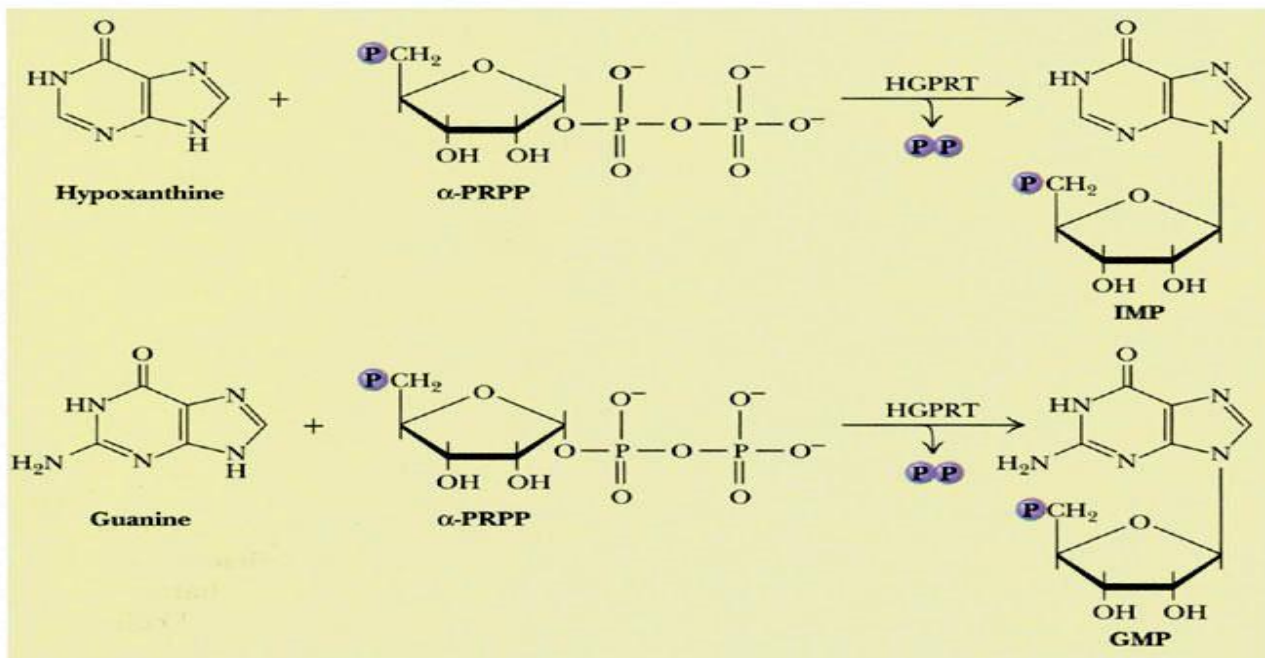


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嘌呤核苷酸合成的补救合成



缺少次黄嘌呤-鸟嘌呤磷酸核糖转移酶（HGPRT）会导致自毁面容症。

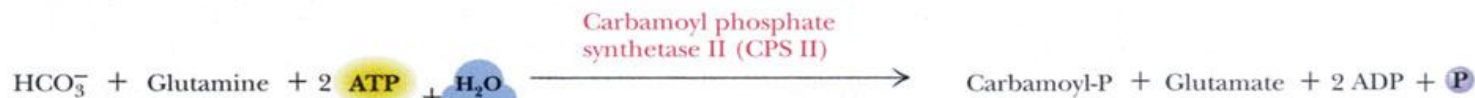
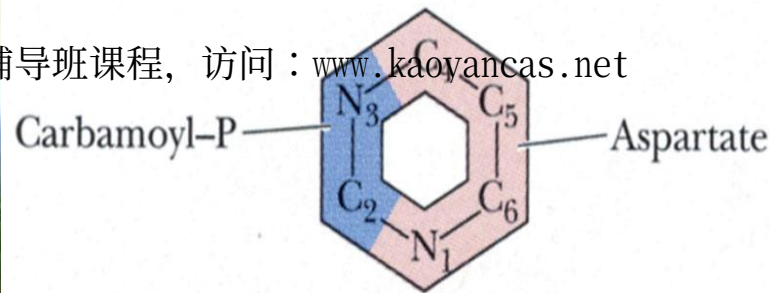


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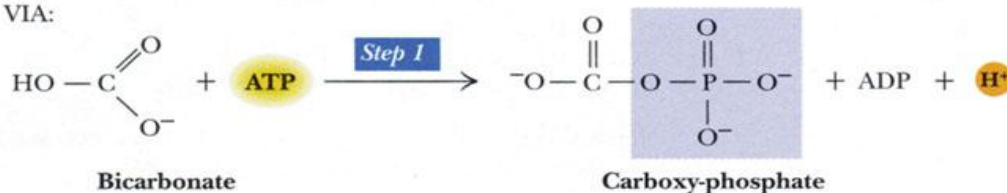


(二) 嘧啶核糖核苷酸的合成

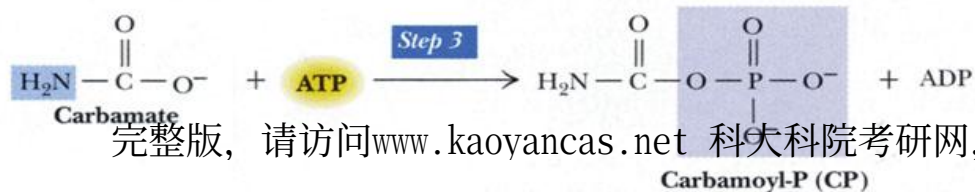
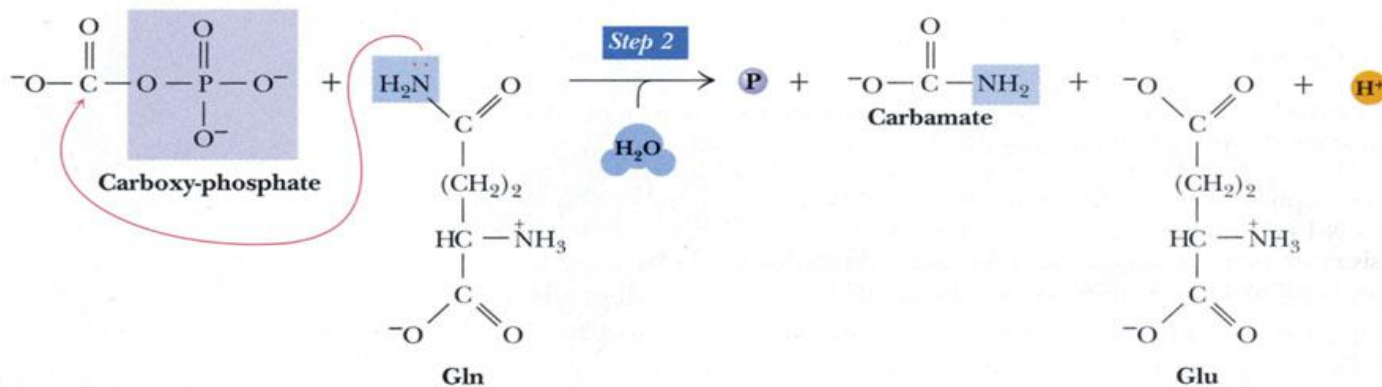
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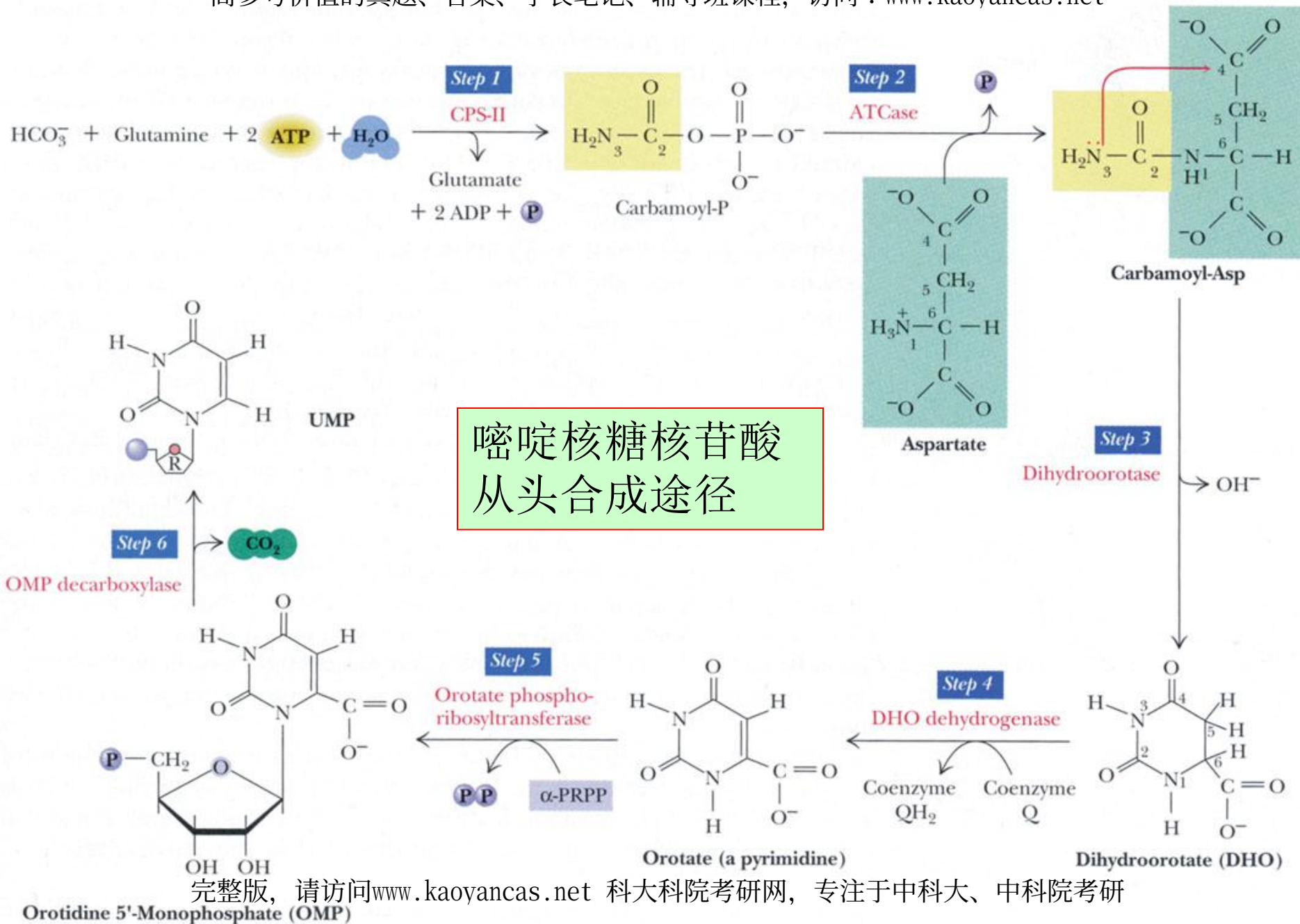
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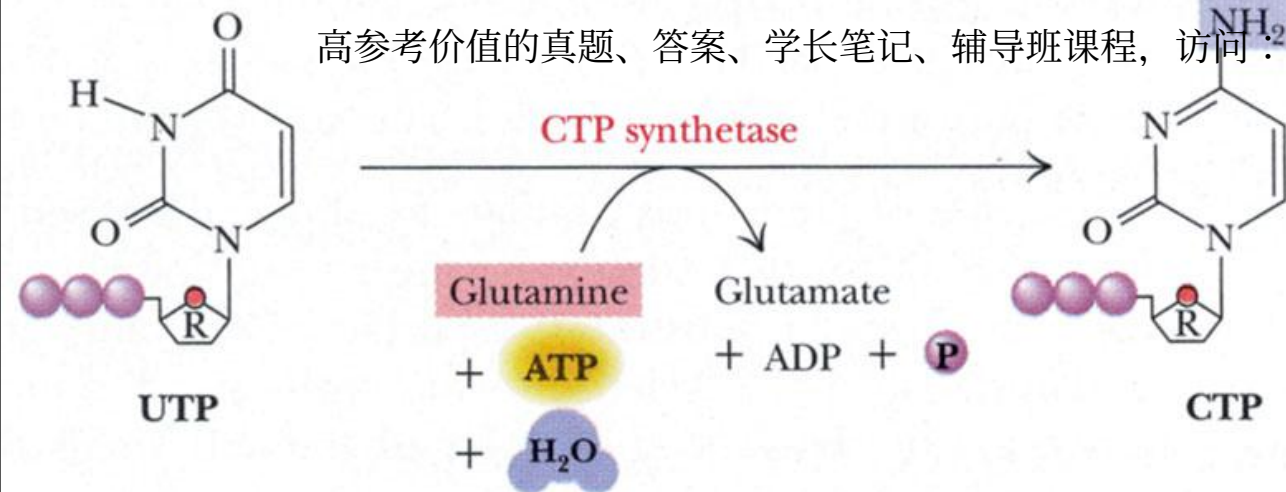


氨甲酰磷酸合成酶催化的反应

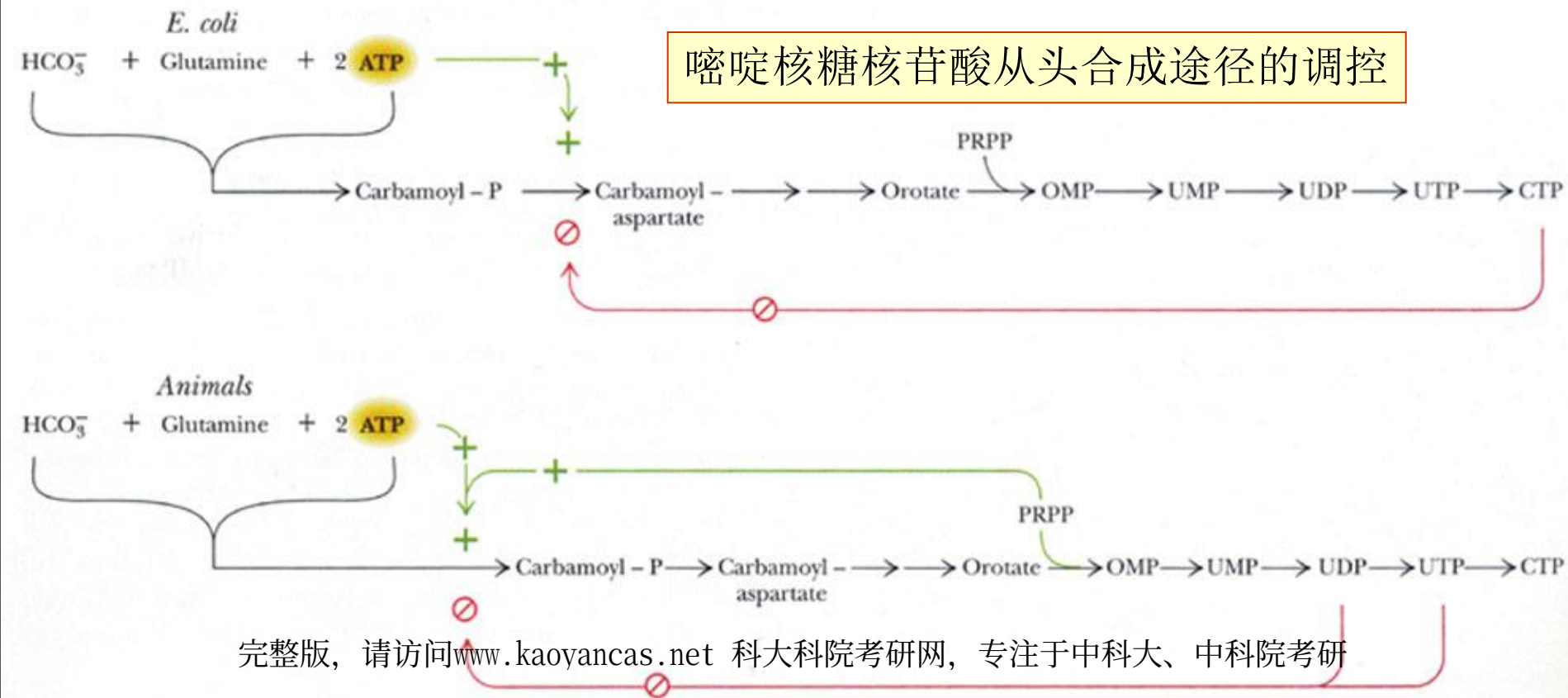


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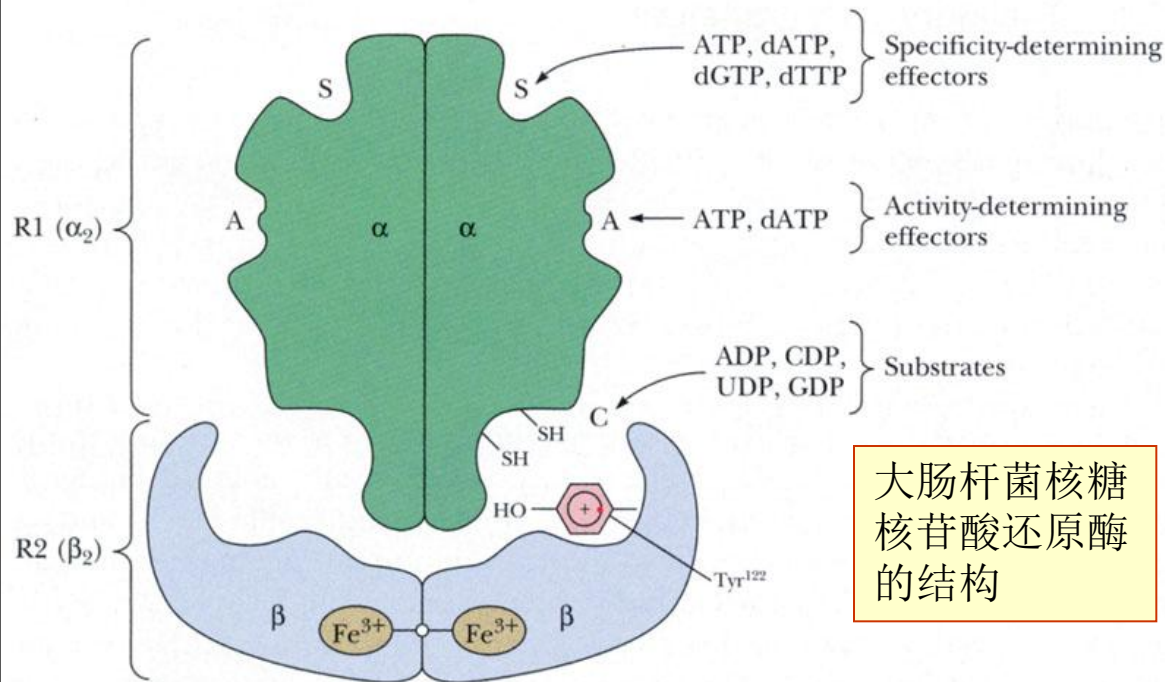
嘧啶核糖核苷酸从头合成途径的调控



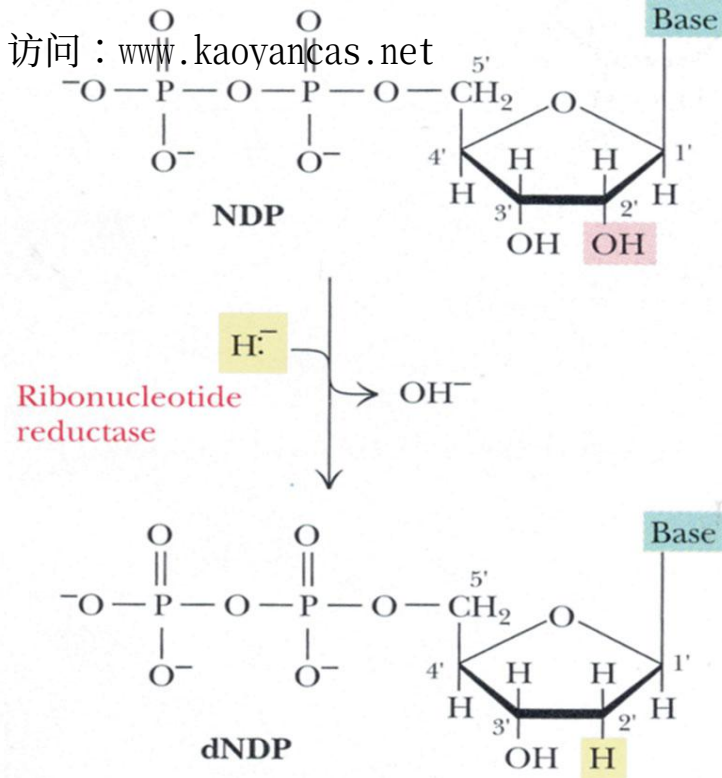
(三) 脱氧核糖核苷酸的合成

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大肠杆菌核糖核苷酸还原酶的结构



脱氧核糖核苷酸生物合成的调控

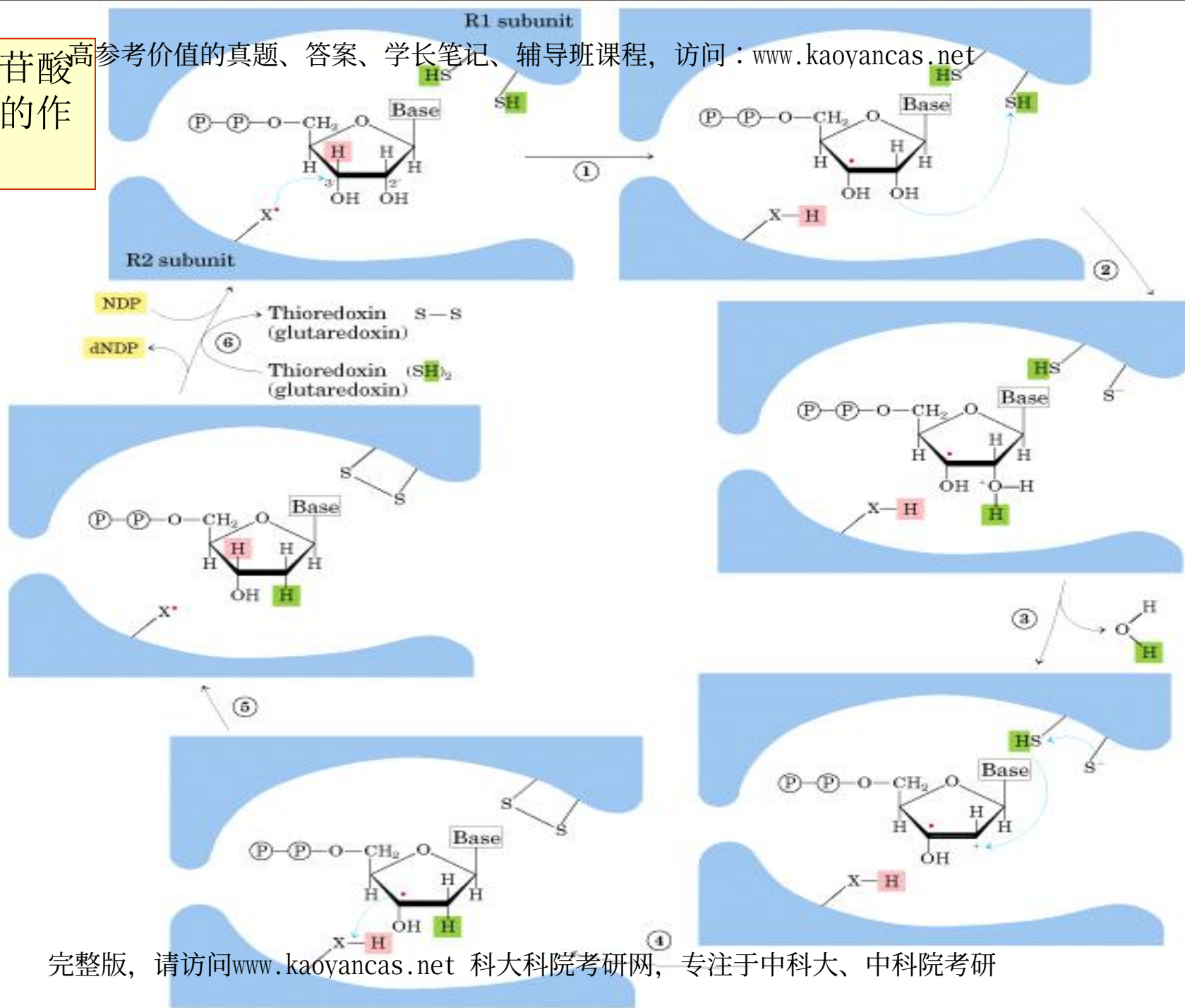
Energy status of cell is robust; [ATP] is high. Make DNA:

- 1 ATP occupies activity site A: ribonucleotide reductase *ON*
- 2 ATP in specificity site S favors CDP or UDP in catalytic site C $\rightarrow [dCDP], [dUDP] \uparrow$
- 3 $dCDP \rightarrow dUMP \rightarrow dTMP \rightarrow dTTP$
- 4 dTTP occupies specificity site S, favoring GDP or ADP in catalytic site C $GDP \rightarrow dGDP \rightarrow dGTP$
- 5 dGTP occupies specificity site S, favoring ADP in catalytic site C $\rightarrow [dADP] \uparrow$
- 6 dATP replaces ATP in activity site A: ribonucleotide reductase *OFF*

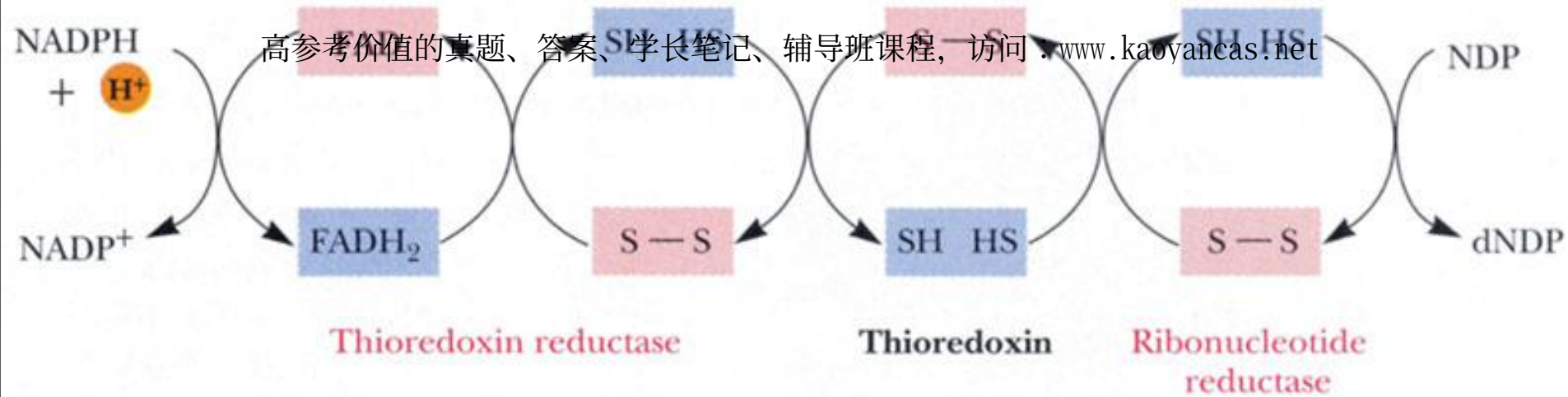
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核糖核苷酸还原酶的作用机制

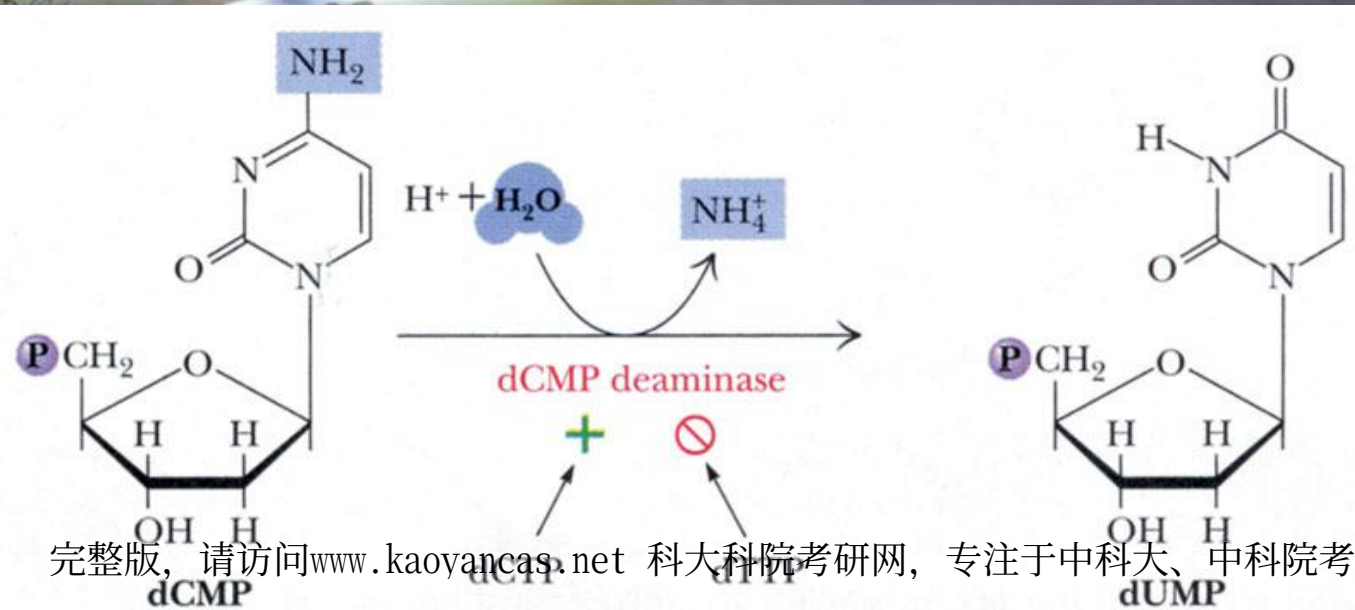
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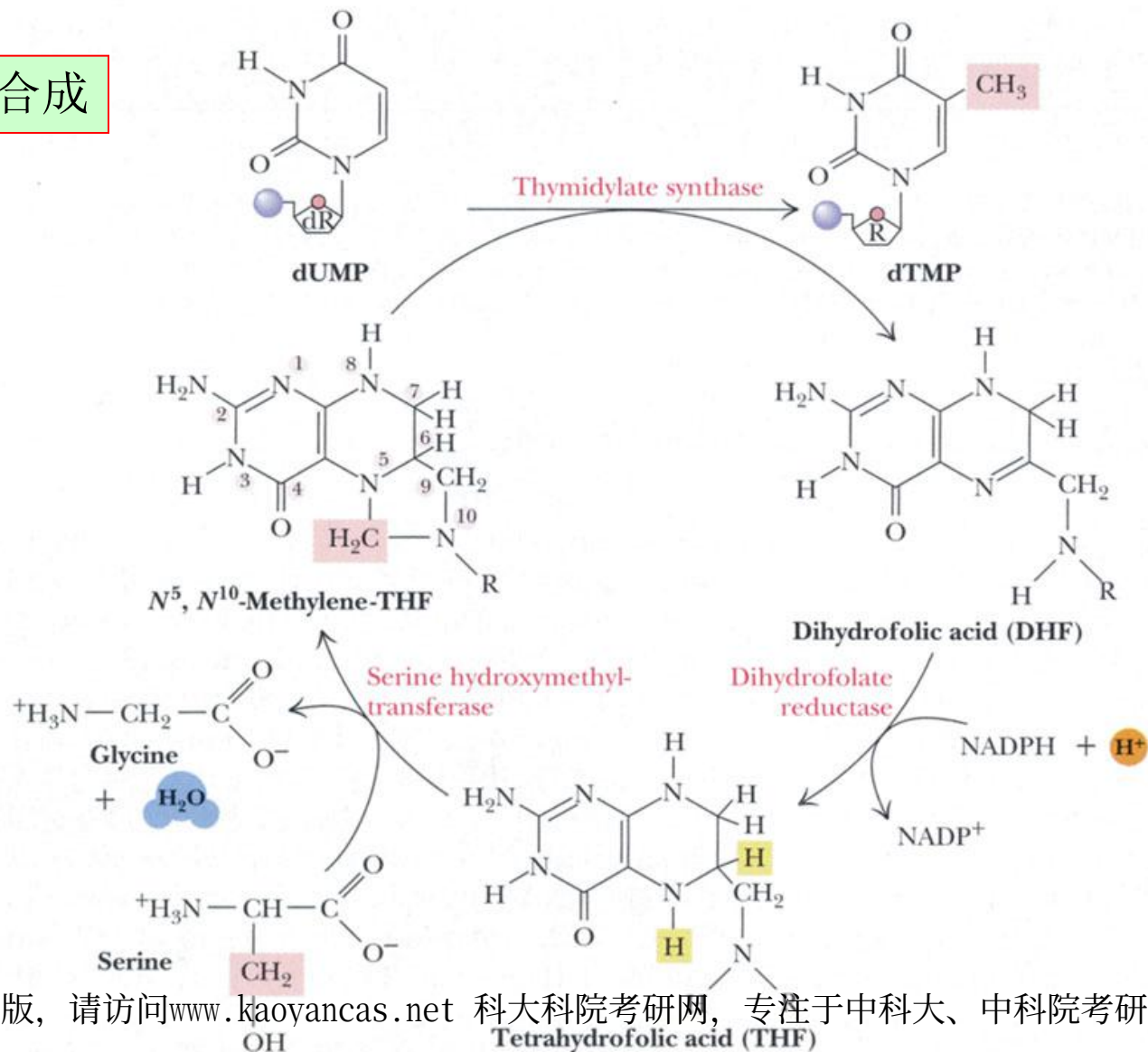


核糖核苷酸还原酶相关的氧化还原循环

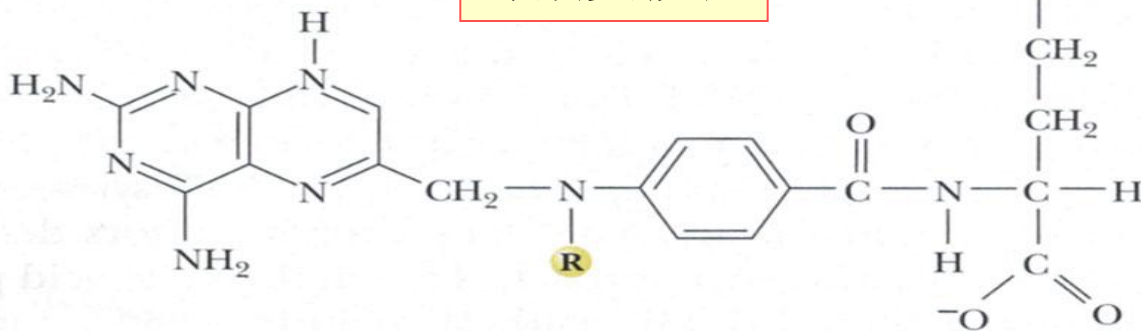


From dUDP: dUDP $\longrightarrow$ dUMP $\longrightarrow$ dTMP
 From dCDP: dCDP $\longrightarrow$ dCMP $\longrightarrow$ dUMP $\longrightarrow$ dTMP

胸腺嘧啶的合成



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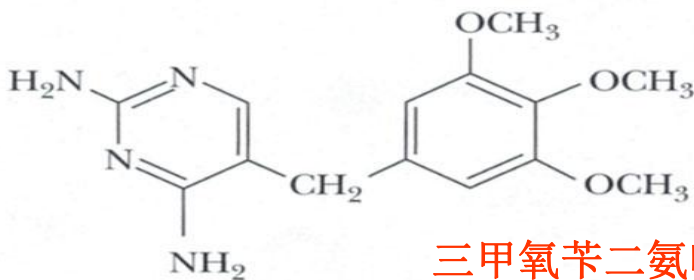
2-Amino, 4-amino analogs of folic acid

$R = H$ Aminopterin

$R = CH_3$ Amethopterin (methotrexate)

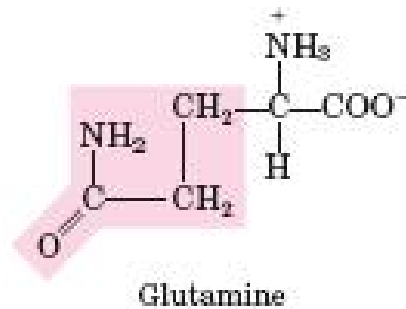
氨基蝶呤

氨甲蝶呤



三甲氧苄二氨嘧啶

Trimethoprim



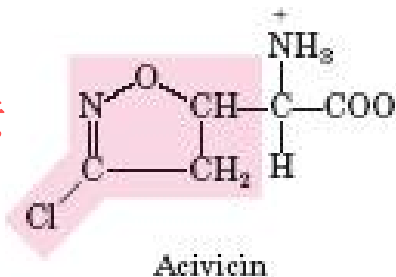
Glutamine



重氮丝氨酸

Azaserine

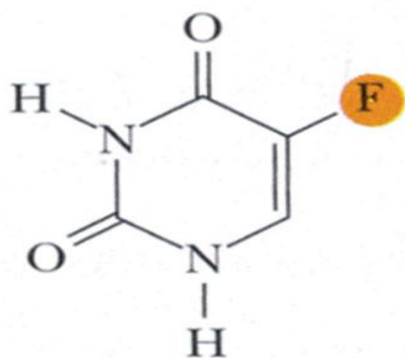
阿雪维菌素



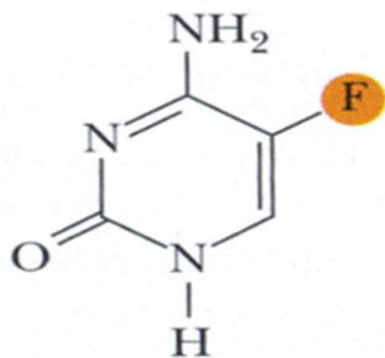
Acivicin

FIGURE 22-48 Azaserine and acivicin, inhibitors of glutamine amidotransferases. These analogs of glutamine interfere in a number of amino acid and nucleotide biosynthetic pathways.

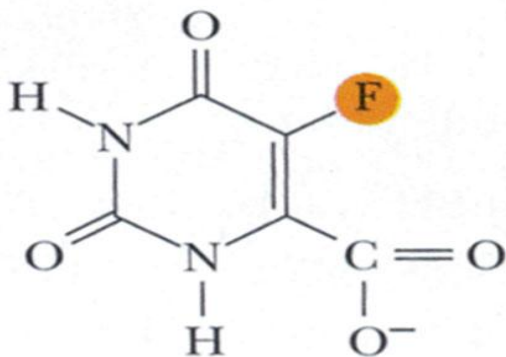
嘌呤类似物如次黄嘌呤，6-巯基嘌呤和嘧啶类似物可抑制核苷酸合成



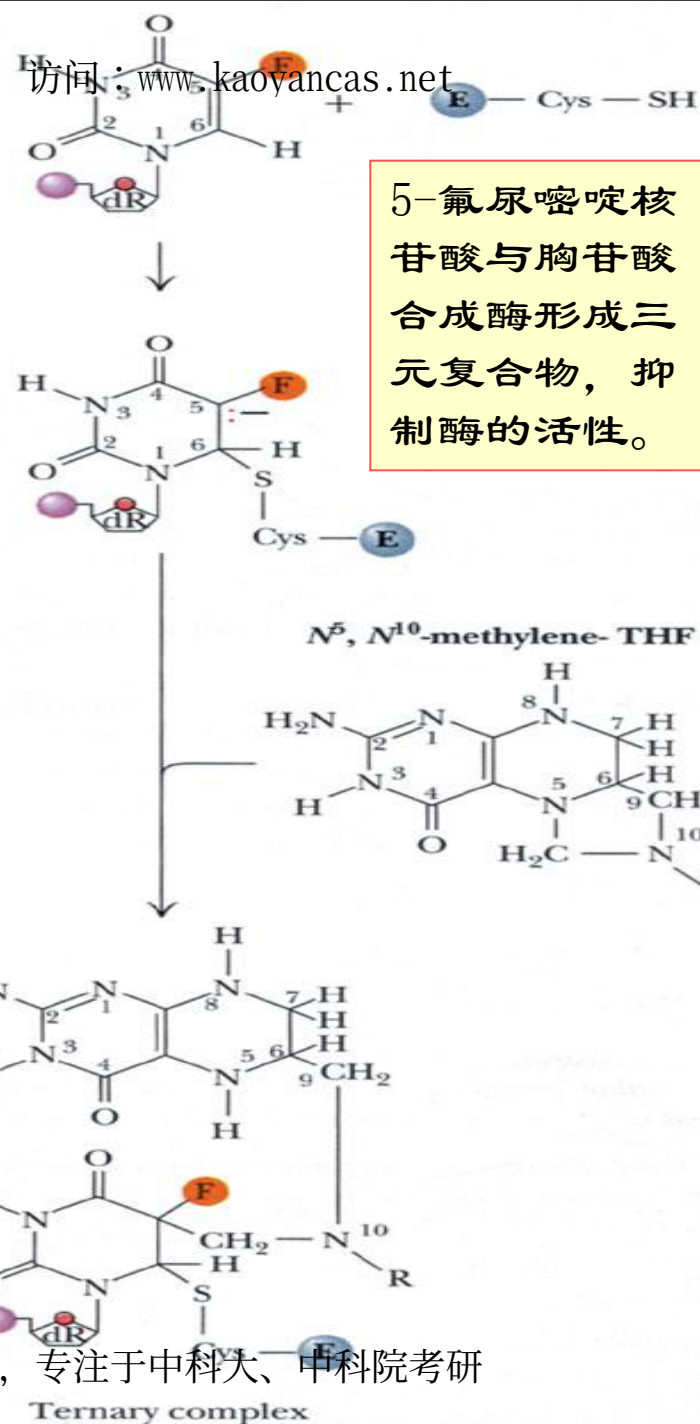
5-Fluorouracil



5-Fluorocytosine



5-氟乳清酸 5-Fluoroorotate



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(四) 辅酶核苷酸的生物合成

1. 烟酰胺核苷酸的合成

烟酸 + 5-磷酸核糖焦磷酸 $\rightarrow$ 烟酸单核苷酸 + PPi (烟酸单核苷酸焦磷酸化酶)

烟酸单核苷酸 + ATP $\rightarrow$ 脱酰胺-NAD + PPi (脱酰胺-NAD焦磷酸化酶)

脱酰胺-NAD + 谷氨酰胺 + ATP $\rightarrow$ NAD + 谷氨酸 + AMP + PPi (NAD合成酶)

NAD + ATP $\rightarrow$ NADP + ADP (NAD激酶)

2. 黄素核苷酸的合成

核黄素 + ATP $\rightarrow$ FMN + ADP (黄素激酶)

FMN + ATP $\rightarrow$ FAD + PPi (FAD焦磷酸化酶)

3. 辅酶A的合成 (结构式见p403)

泛酸 + ATP $\rightarrow$ 4'-磷酸泛酸 + ADP (激酶)

4'-磷酸泛酸 + 半胱氨酸 + ATP (CTP) $\rightarrow$ 4'-磷酸泛酰半胱氨酸 + ADP (CDP) (合成酶)

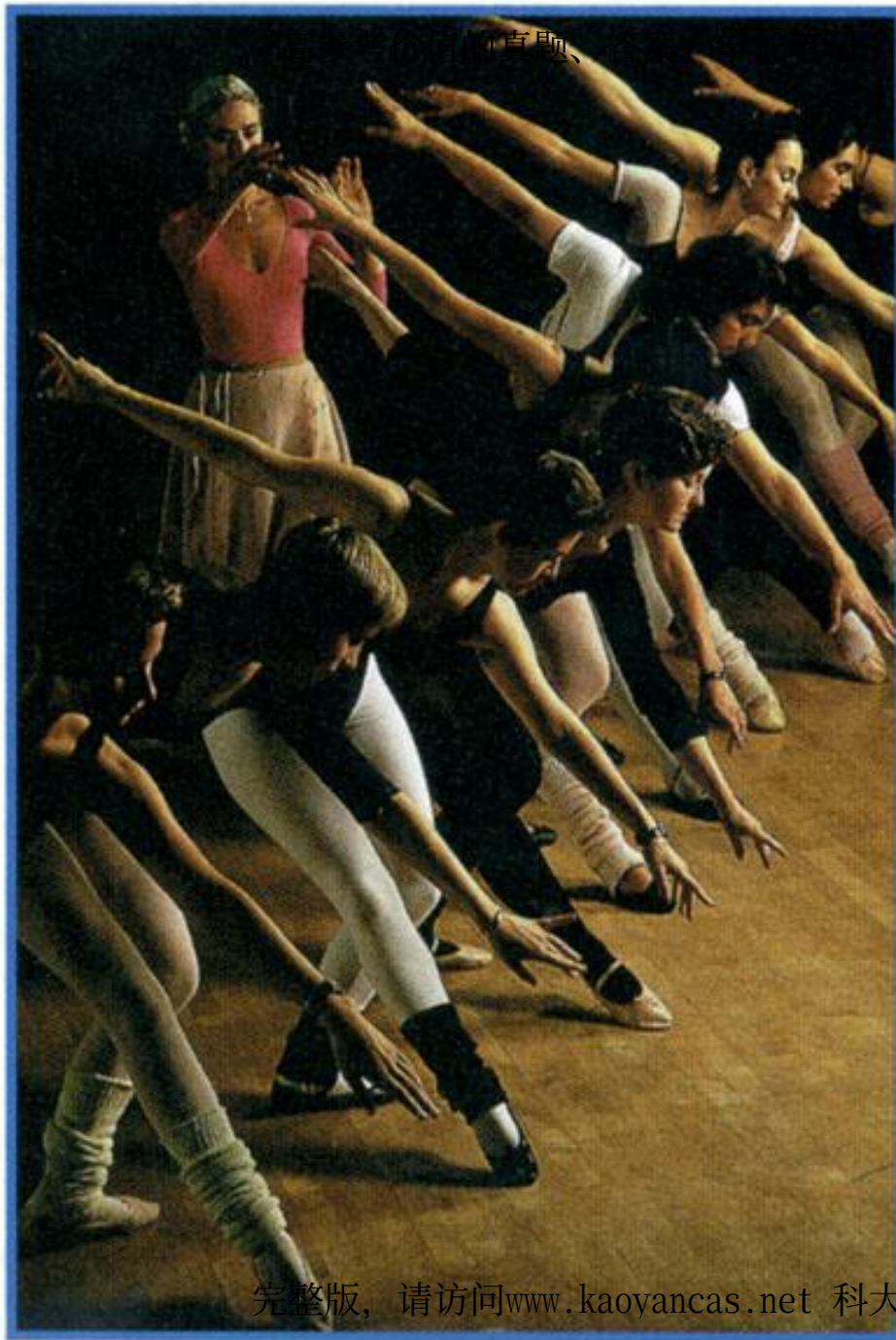
4'-磷酸泛酰半胱氨酸 + ATP $\rightarrow$ 4'-磷酸泛酰巯基乙胺 + CO₂ (脱羧酶)

4'-磷酸泛酰巯基乙胺 + ATP $\rightarrow$ 脱磷酸辅酶A + PPi (焦磷酸化酶)

脱磷酸辅酶A + ATP $\rightarrow$ 辅酶A + ADP (激酶)

基本要求

1. 熟悉核苷酸的分解代谢。
2. 熟悉核苷酸的生物合成途径。
3. 掌握有关的抗代谢物及与抗癌药的关系。 **(重点，教材叙述不够系统)**



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第33章

细胞代谢的调节

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一、细胞代谢的调节网络

1. 代谢途径交叉形成网络

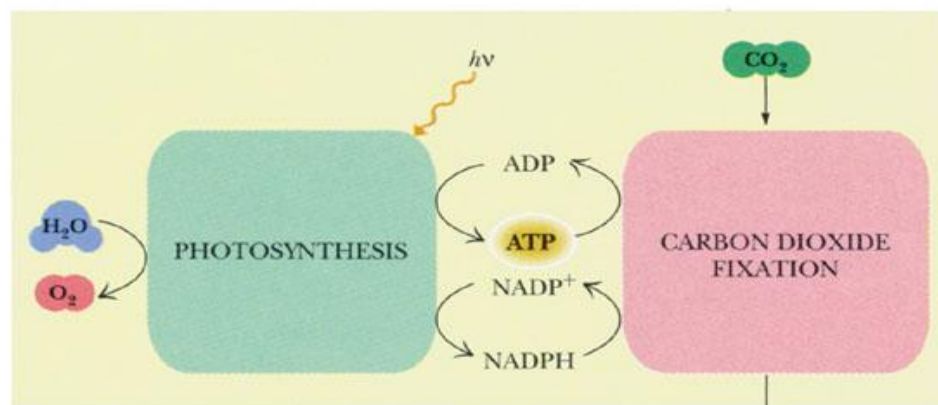
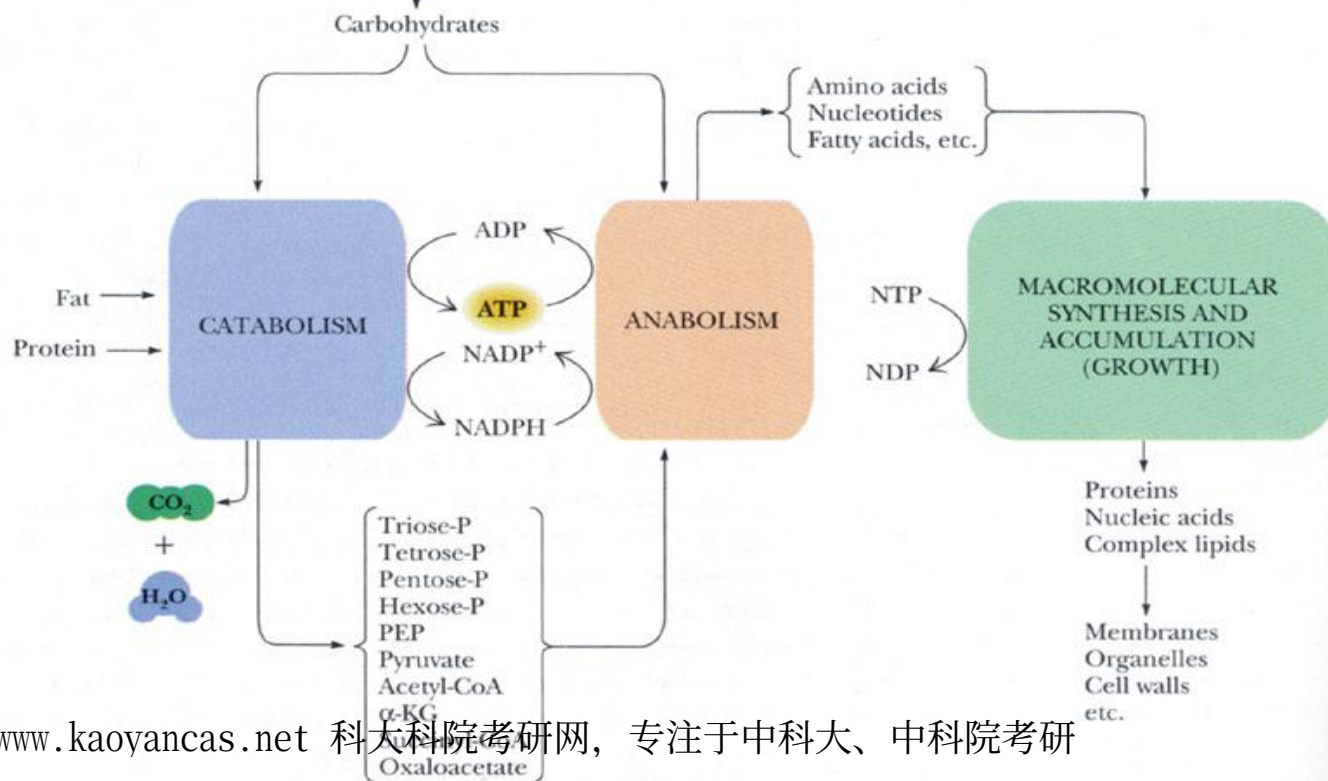


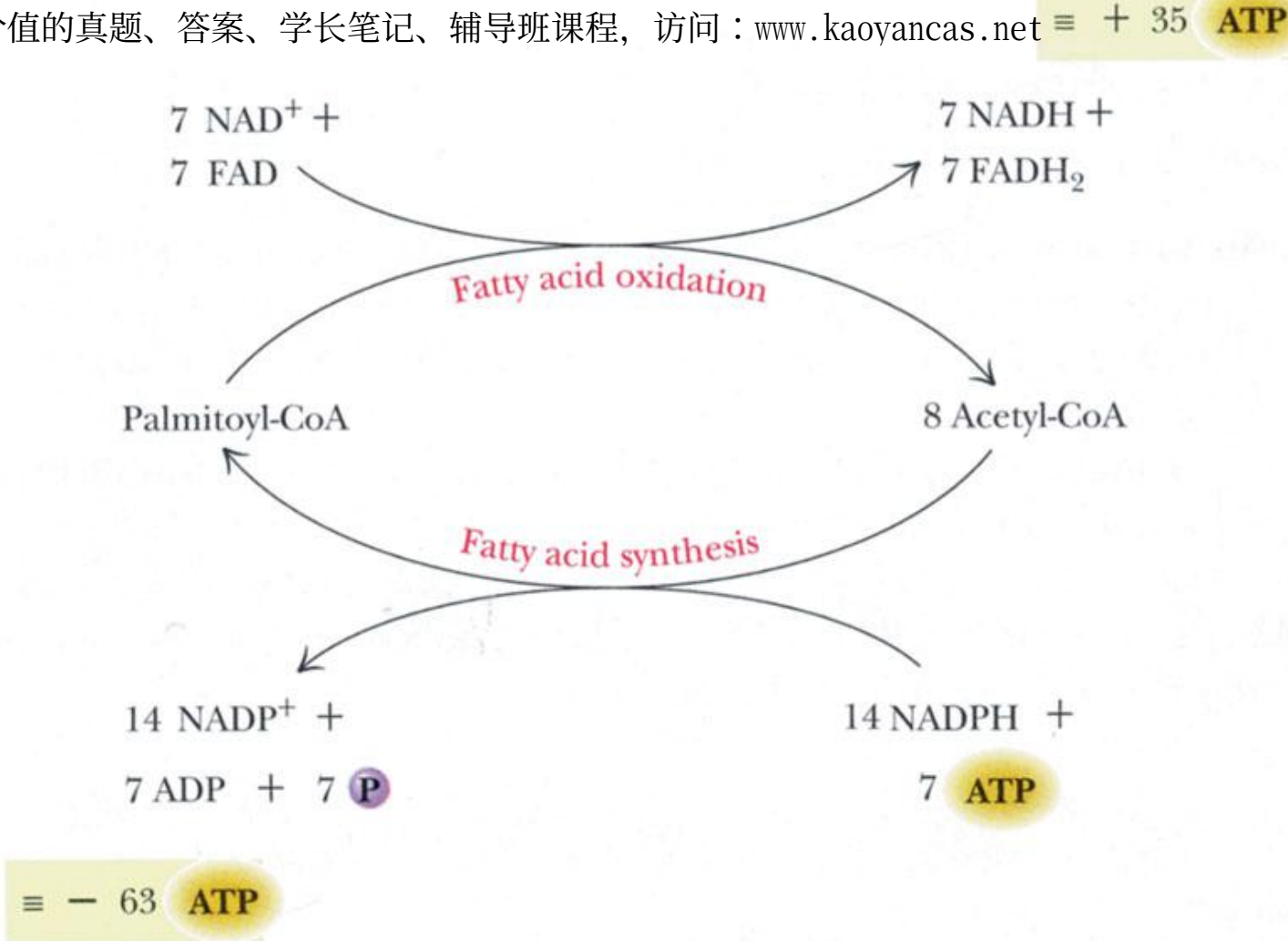
FIGURE 28.1 • Block diagram of intermediate metabolism.

中间代谢的方框图解



2. 分解代谢和合成代谢的单向性

(1) 细胞的能量状态决定代谢的方向

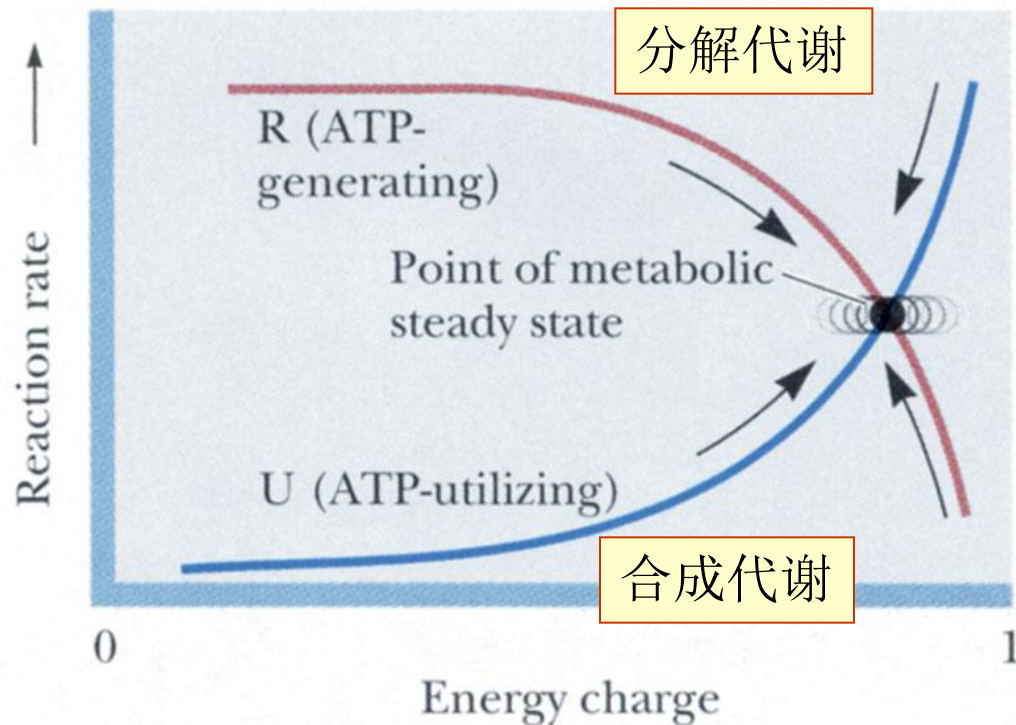
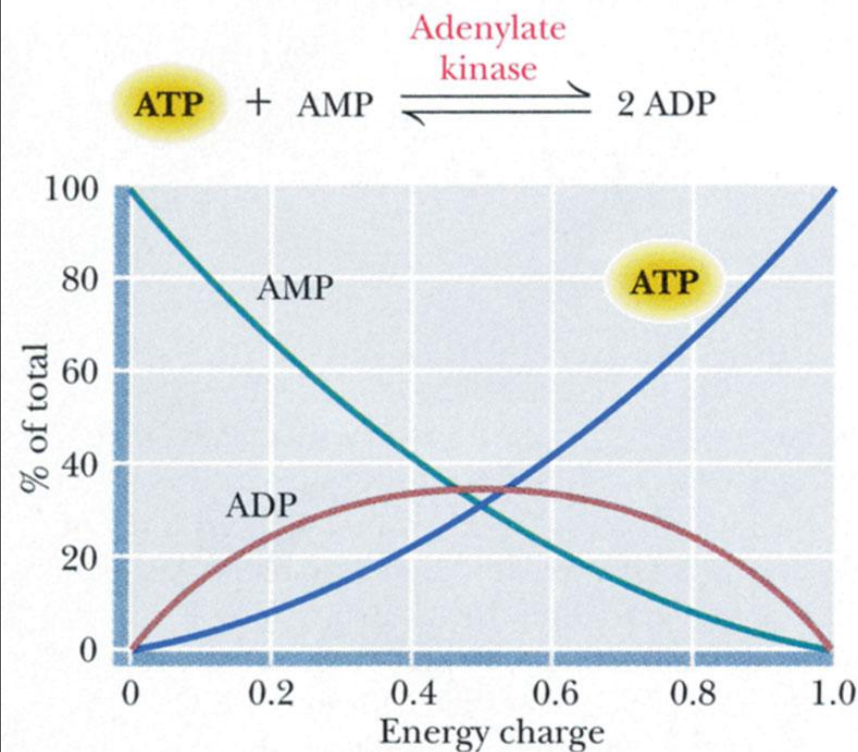


按照旧算法，NADH相当于3个ATP，FADH₂相当于2个ATP，NADPH相当于4个ATP，能量供应充足则合成脂肪酸，能量供应不足则分解脂肪酸

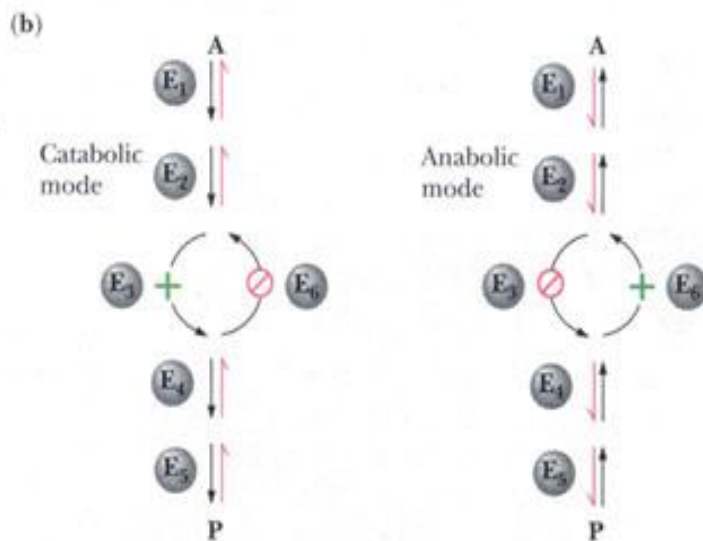
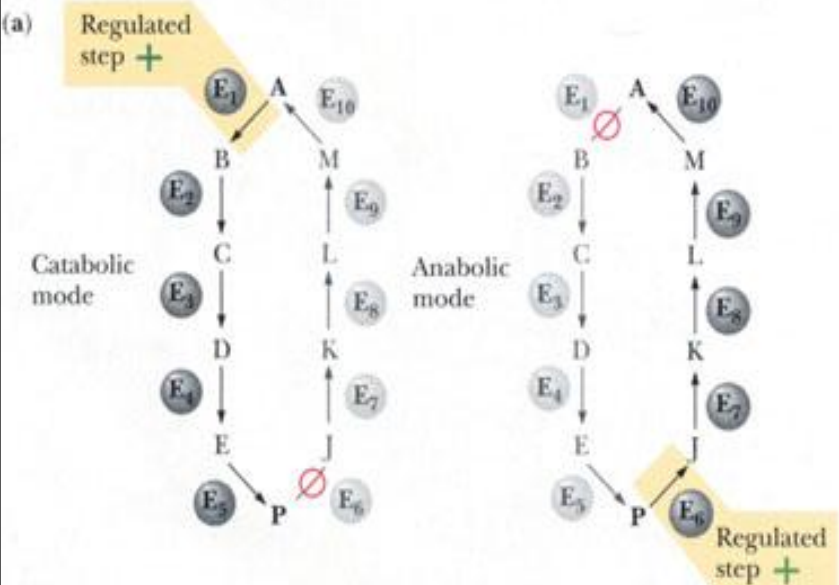
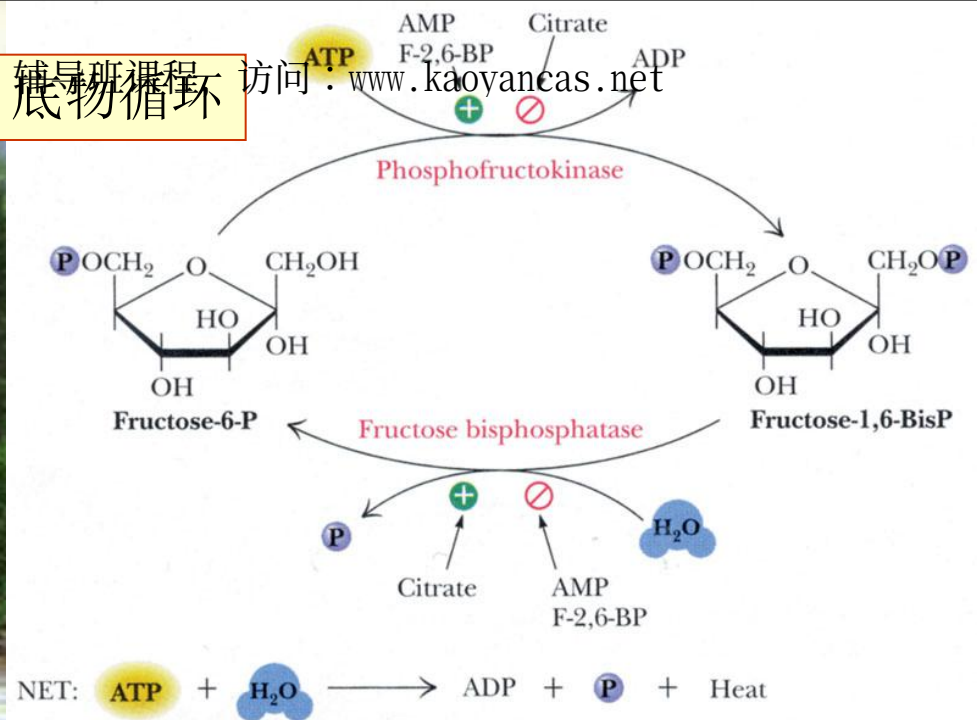
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ATP与能荷

能荷在代谢稳态点周围振荡



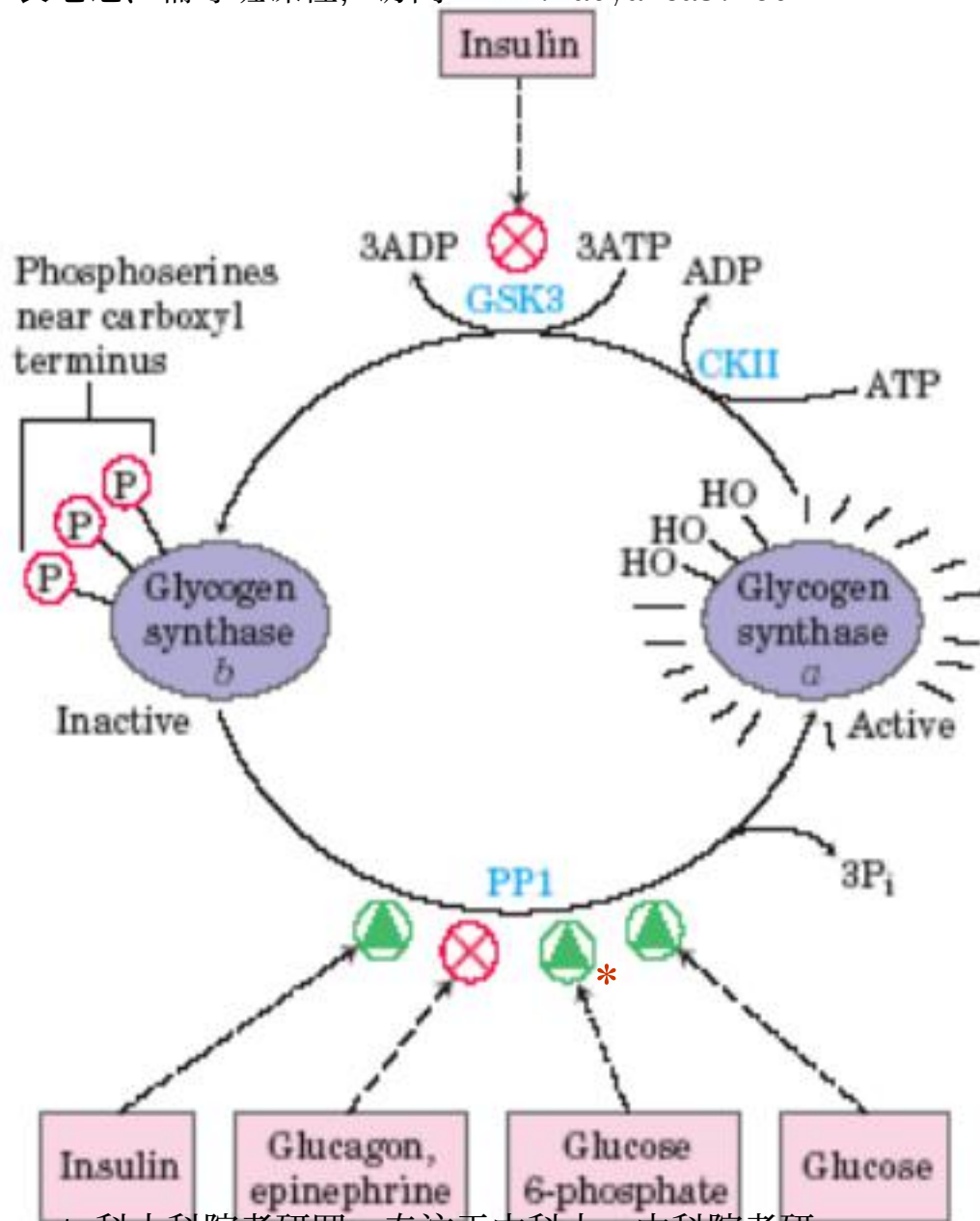
(2) 关键的调控步骤决定代谢的方向



3.酶活性的调节

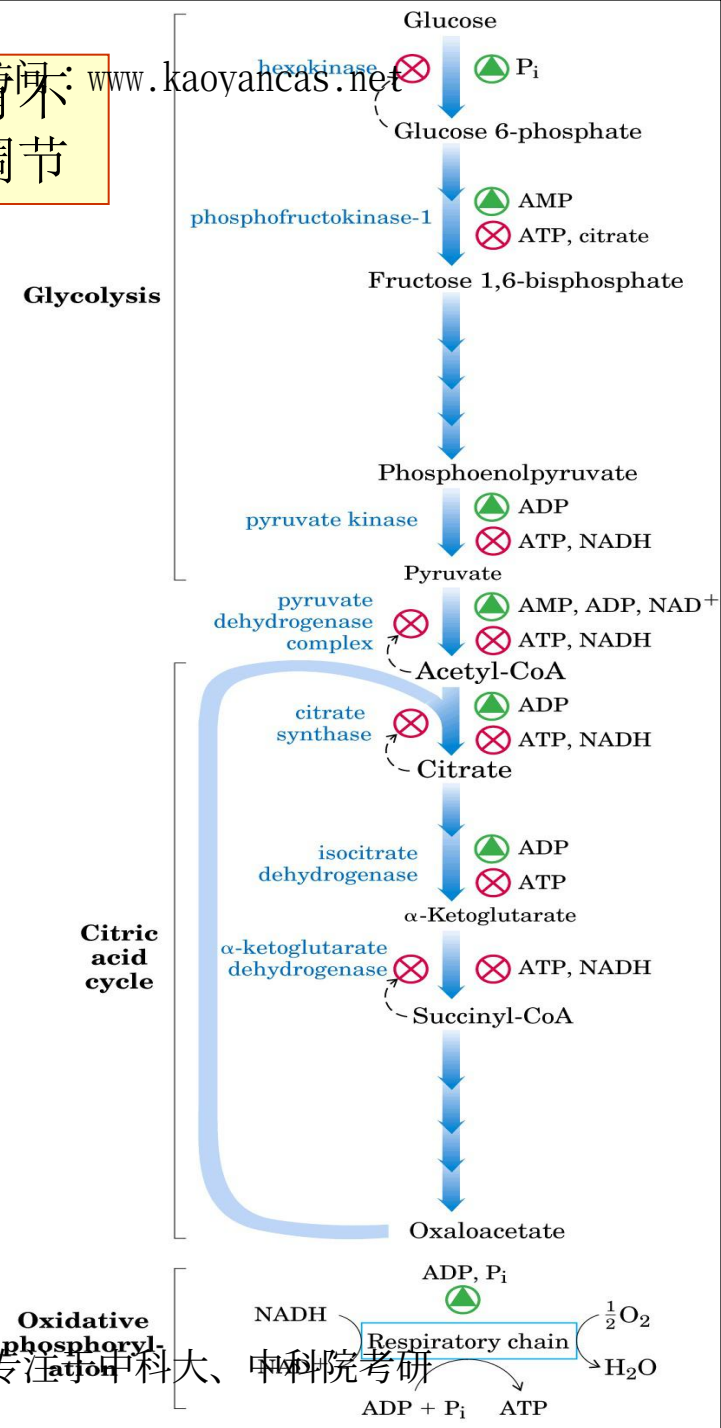
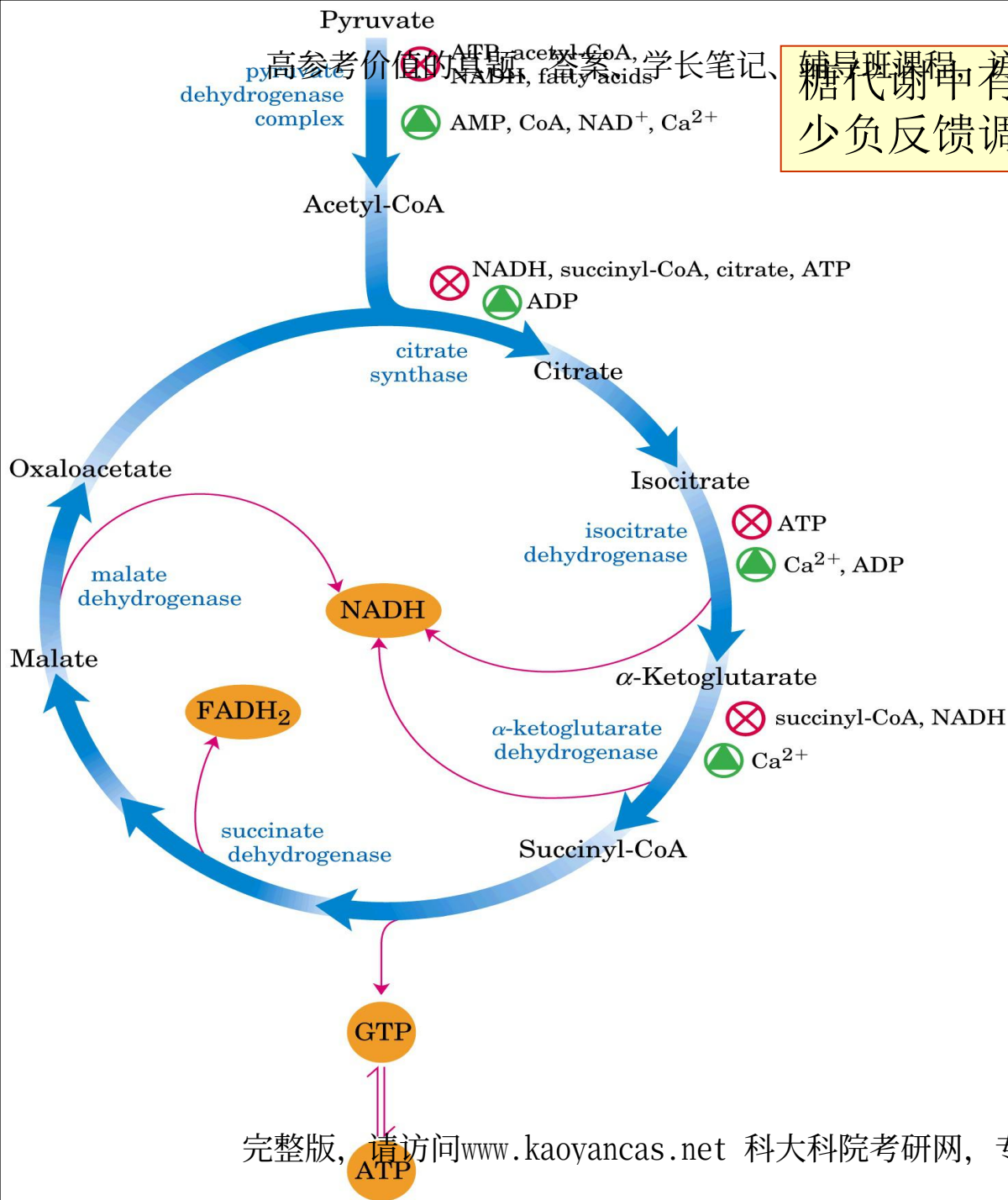
(1) 酶促反应的前馈和反馈

葡萄糖-6-磷酸对糖原合成酶的激活作用属于正前馈调节。



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糖代谢中不少负反馈调节



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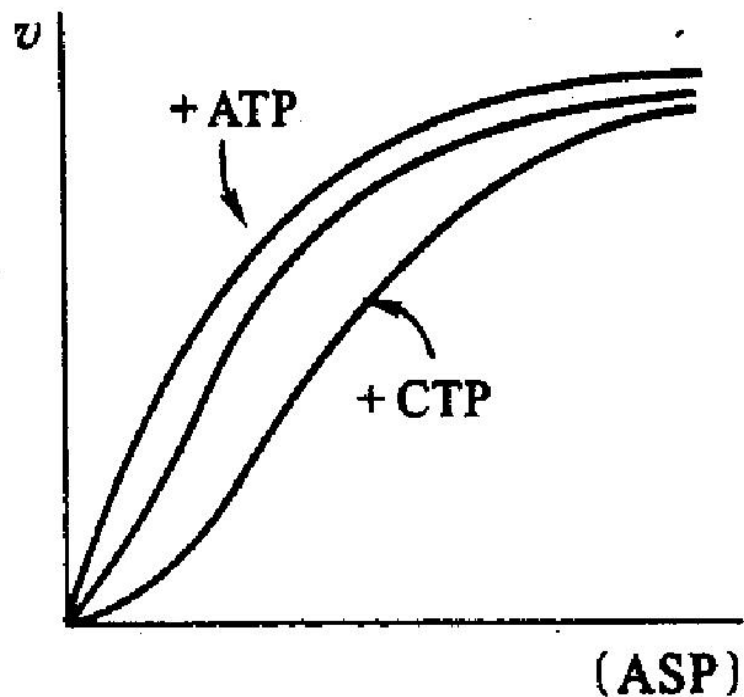
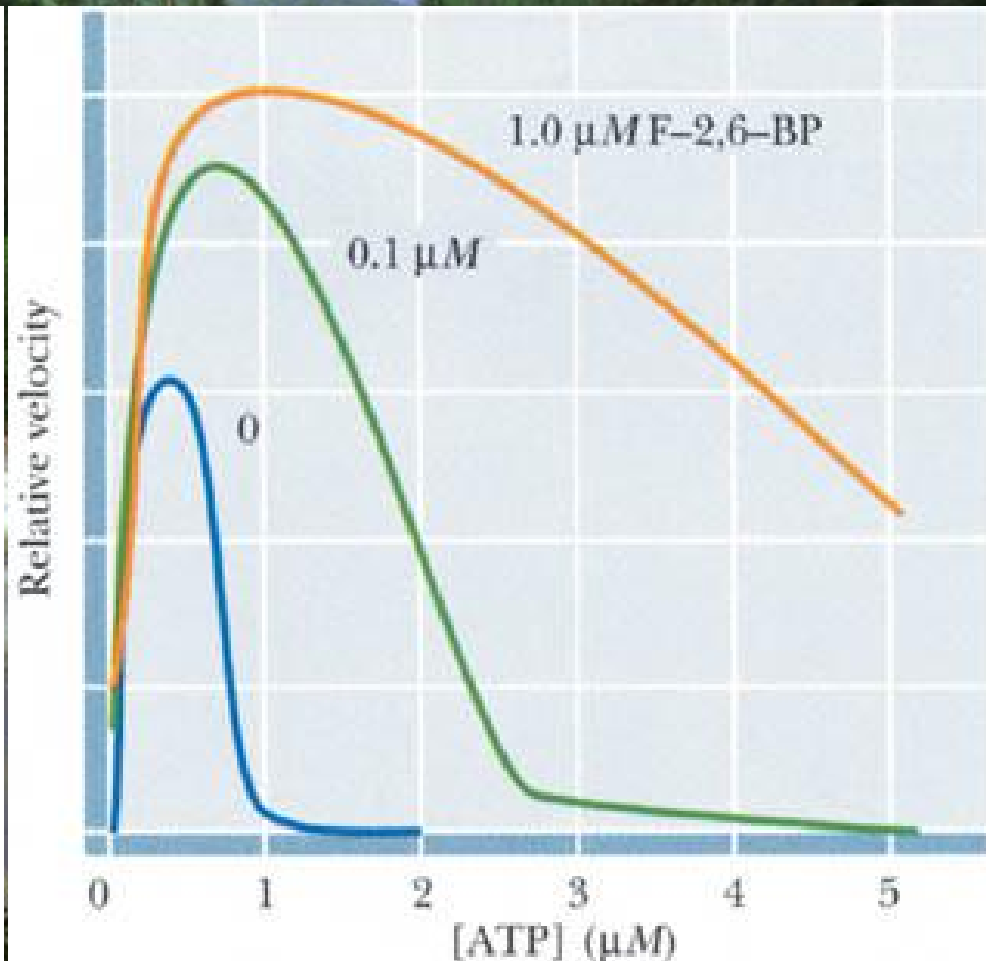


图 10-46 ATCase 的别构效应
ATP 是激活剂而 CTP 是抑制剂



果糖磷酸激酶的调控

(3) 蛋白酶对酶活性的影响 (参见酶原的激活)

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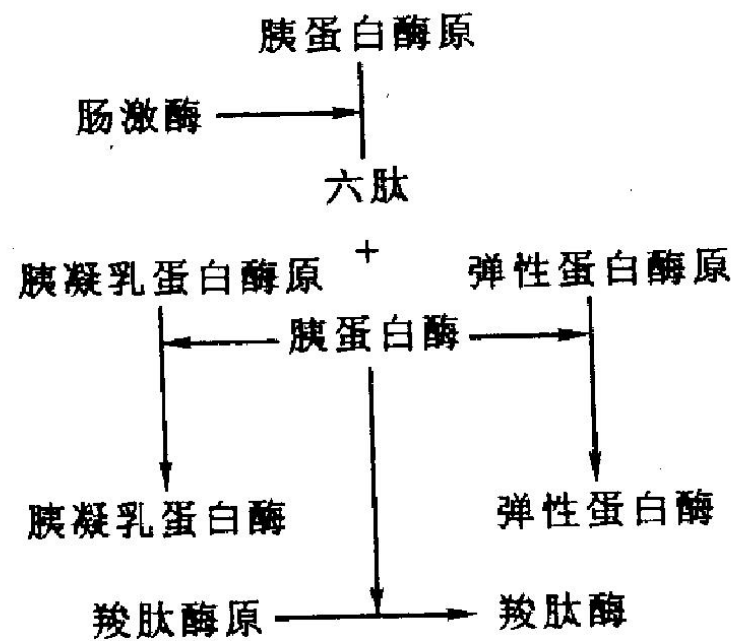
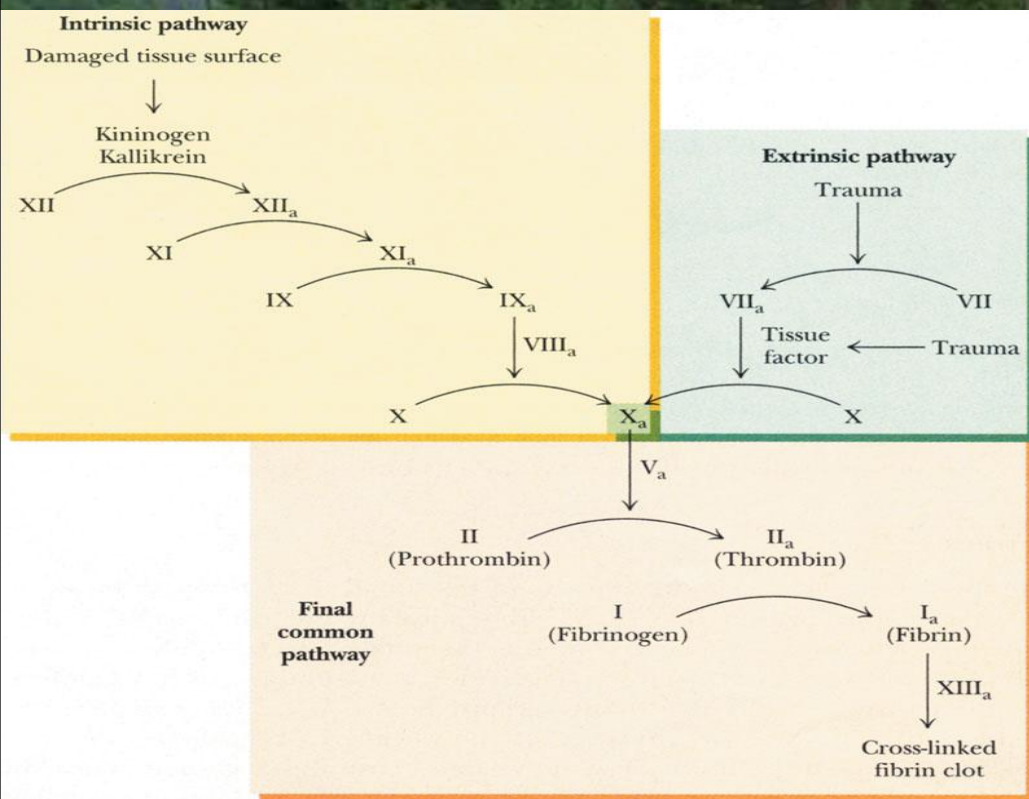
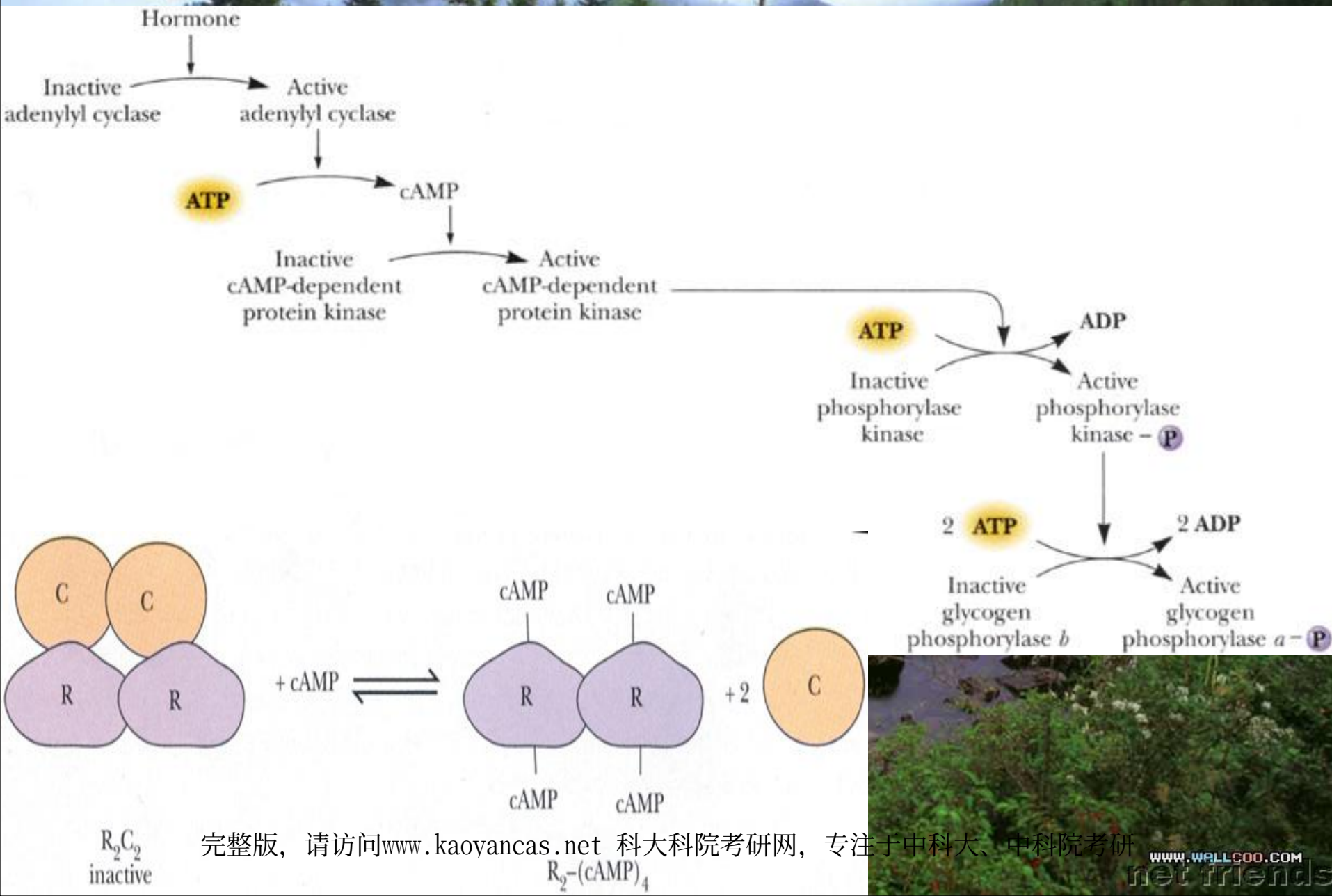


图 10-65 胰蛋白酶对各种胰脏蛋白酶原的激活作用

(4) 酶的共价修饰与连续激活 (参考酶的共价修饰和细胞信号的传导)



二、细胞结构对代谢途径的分隔控制

1. 细胞结构和酶的空间分布

细胞膜控制细胞与环境之间的物质、能量和信息交换；

核膜将细胞分为细胞核和细胞质两部分，细胞核贮存遗传信息，进行基因复制、转录和转录后的加工；

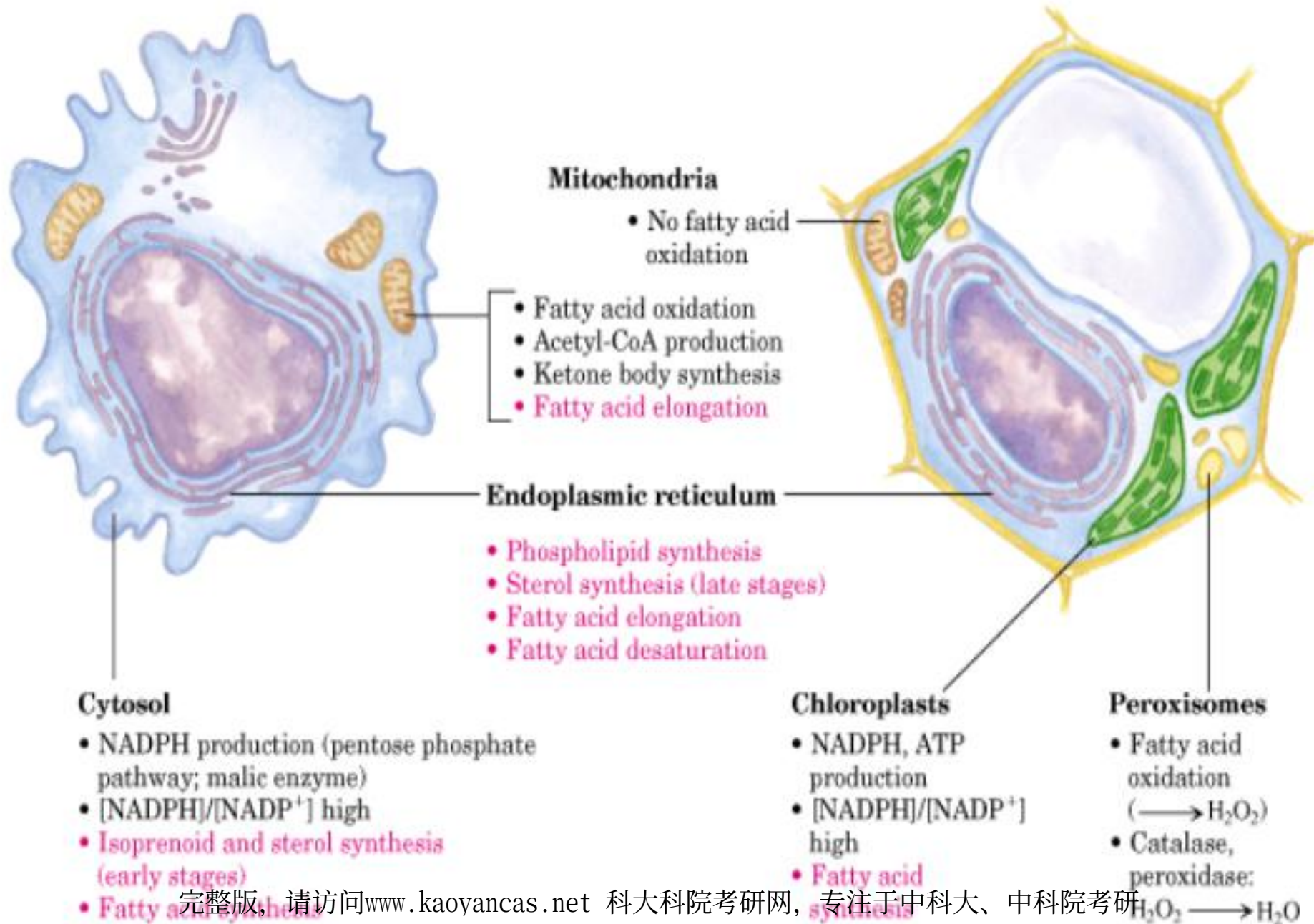
胞液是细胞质的连续水相部分，糖酵解、糖原异生、磷酸葡萄糖途径，及糖、脂肪酸、氨基酸、核苷酸的生物合成主要在胞液中进行，胞液中悬浮着细胞器和细胞骨架；

粗面内质网合成分泌性蛋白质，光面内质网合成磷脂、糖脂、胆固醇，蛋白质的糖基化在内质网膜的内侧进行，通过运输泡与靶细胞器的膜融合后转向膜的外侧；

高尔基体参与细胞合成物和吸收物的加工、浓缩、包装、运输；

溶酶体分解细胞的吞噬物和老化的细胞内容物；

线粒体中进行柠檬酸循环、脂肪酸氧化、氨基酸分解、氧化磷酸化等产能反应。



2.细胞信号传递系统

(1) 门控离子通道和神经信号的传导

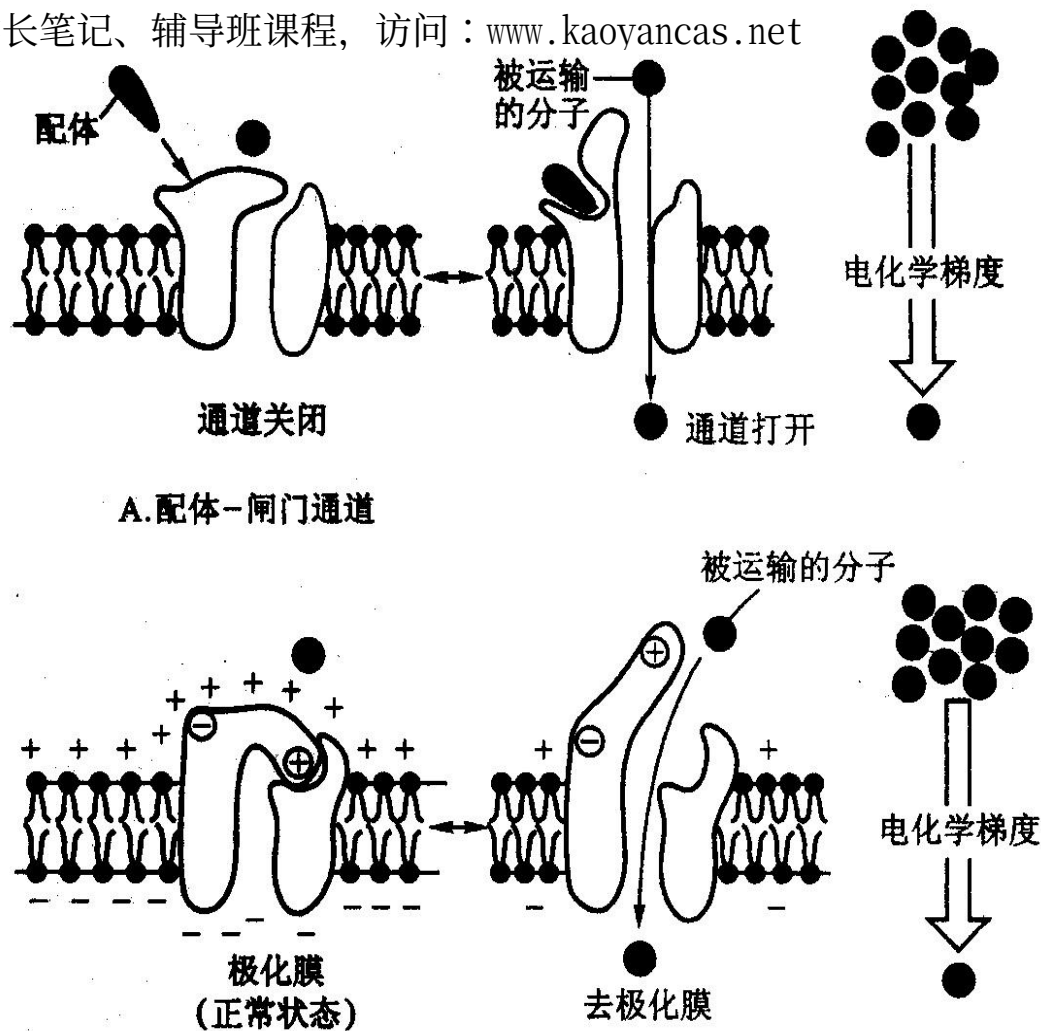


图 21-22 两种类型的闸门离子通道

只有当运输蛋白处于“开”的构型时，让离子顺电化学梯度通过。A. 中的通道“配体-闸门”通道，只有当细胞外的配体结合到运输蛋白（或膜结合蛋白）时，通道打开。B. 中的通道是“电压-闸门”通道，当膜去极化时则打开

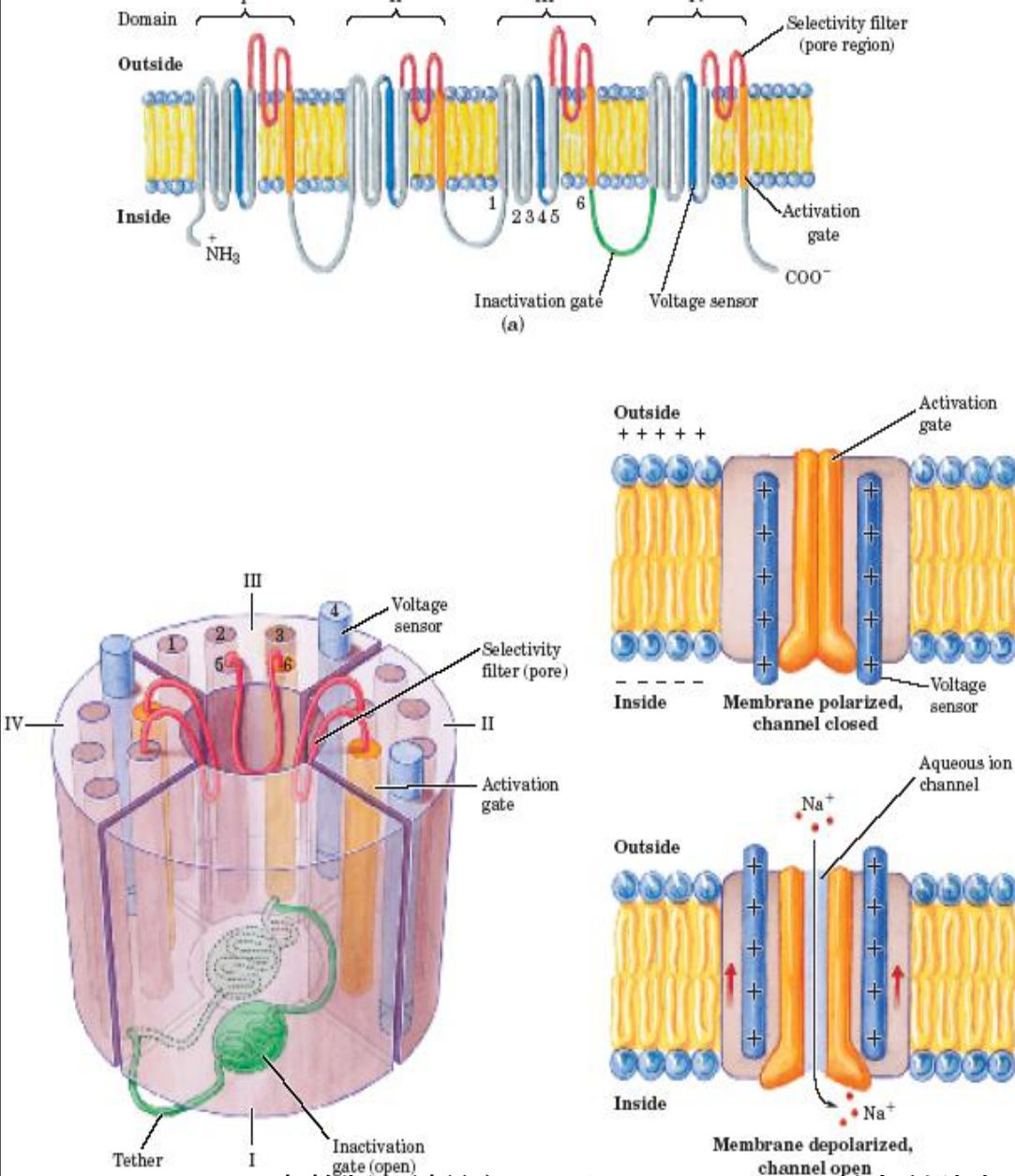


FIGURE 11-50 Voltage-gated Na⁺ channels of neurons. Sodium channels of different tissues and organisms have a variety of subunits, but only the principal subunit (α) is essential. (a) The α subunit is a large protein with four homologous domains (I to IV), each containing six transmembrane helices (1 to 6). Helix 4 in each domain (blue) is the voltage sensor; helix 6 (orange) is thought to be the activation gate. The segments between helices 5 and 6, the pore region (red), form the selectivity filter, and the segment connecting domains III and IV (green) is the inactivation gate. (b) The four domains are wrapped about a central transmembrane channel lined with polar amino acid residues. The segments linking helices 5 and 6 (red) in each domain come together near the extracellular surface to form the selectivity filter, which is conserved in all Na⁺ channels. The filter gives the channel its ability to discriminate between Na⁺ and other ions of similar size. The inactivation gate (green) closes (dotted lines) soon after the activation gate opens. (c) The voltage-sensing mechanism involves movement of helix 4 (blue) perpendicular to the plane of the membrane in response to a change in transmembrane potential. As shown at the top, the strong positive charge on helix 4 allows it to be pulled inward in response to the inside-negative membrane potential (V_m). Depolarization lessens this pull, and helix 4 relaxes by moving outward (bottom). This movement is communicated to the activation gate (orange), inducing conformational changes that open the channel in response to depolarization.

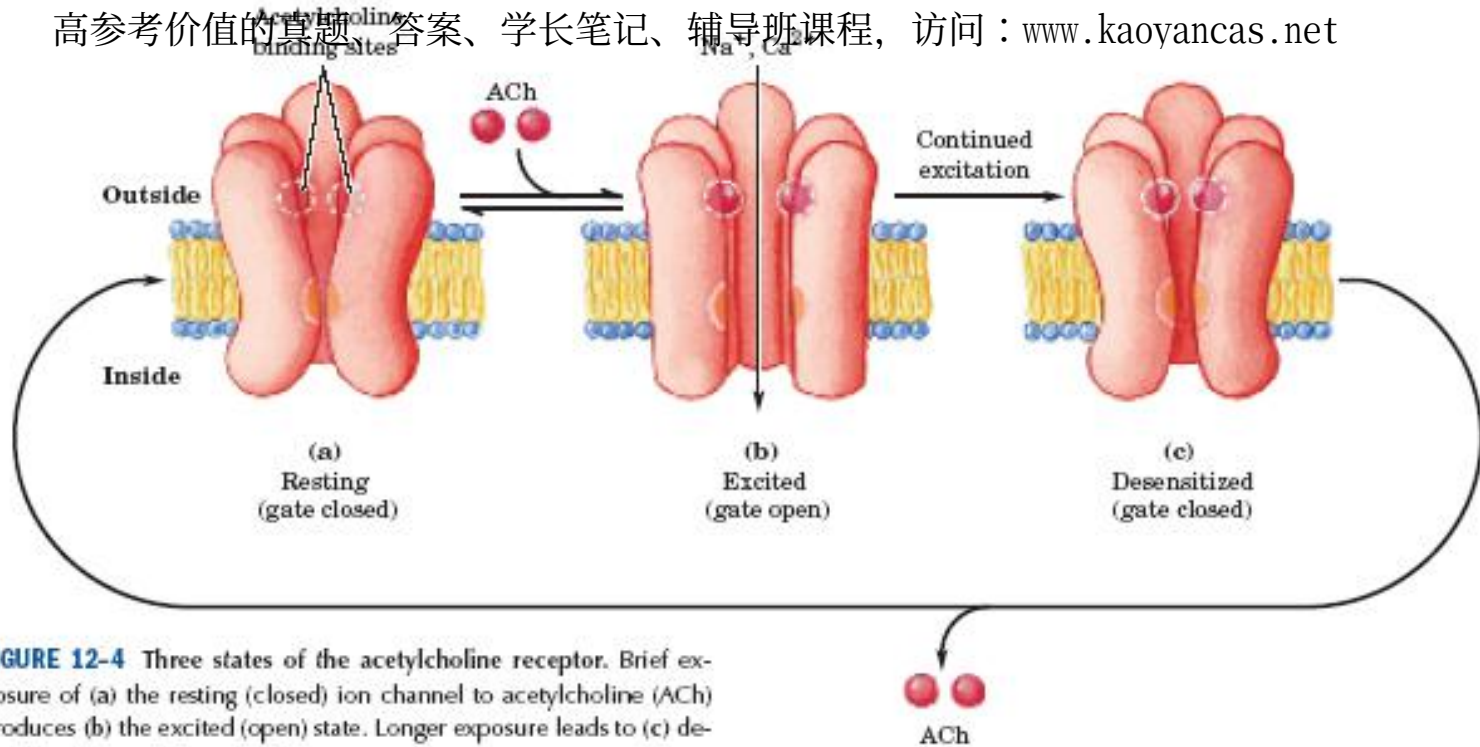
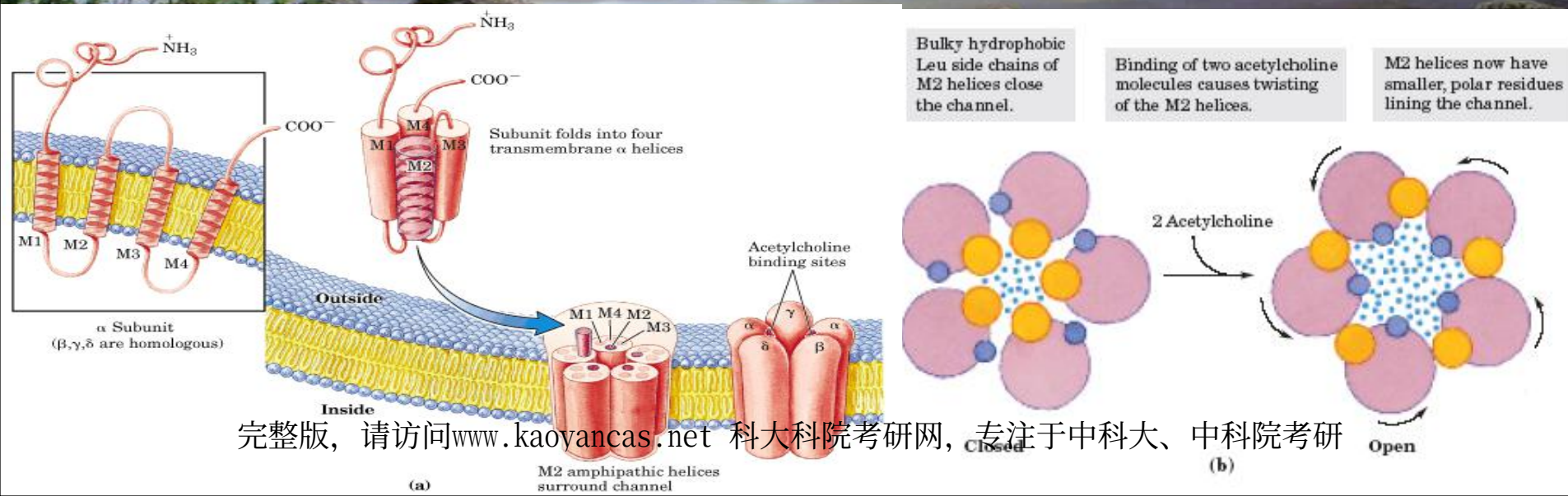


FIGURE 12-4 Three states of the acetylcholine receptor. Brief exposure of (a) the resting (closed) ion channel to acetylcholine (ACh) produces (b) the excited (open) state. Longer exposure leads to (c) desensitization and channel closure.



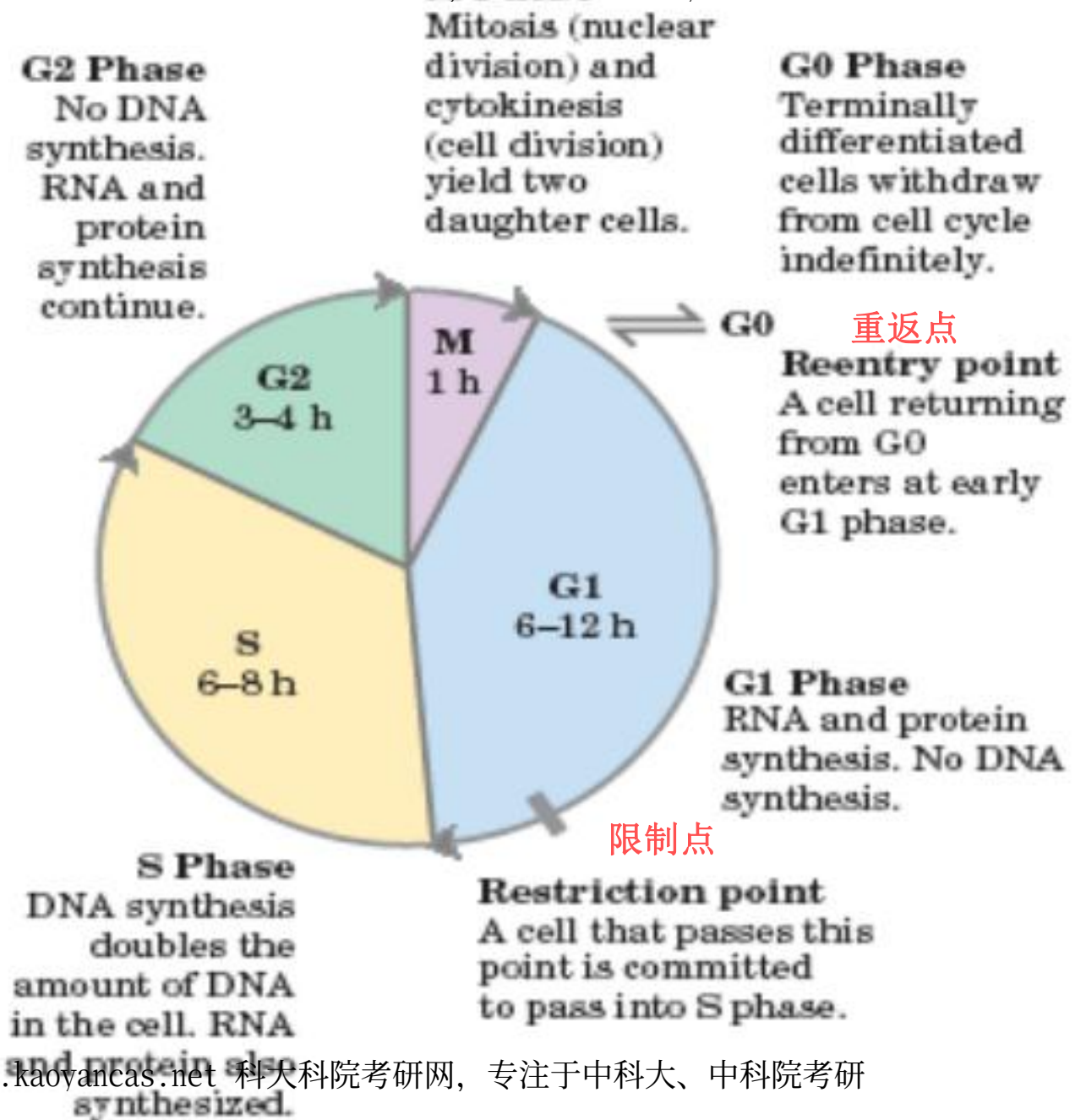
(2) 激素和递质受体的信号转导系统

G 蛋白参与的一些生理过程

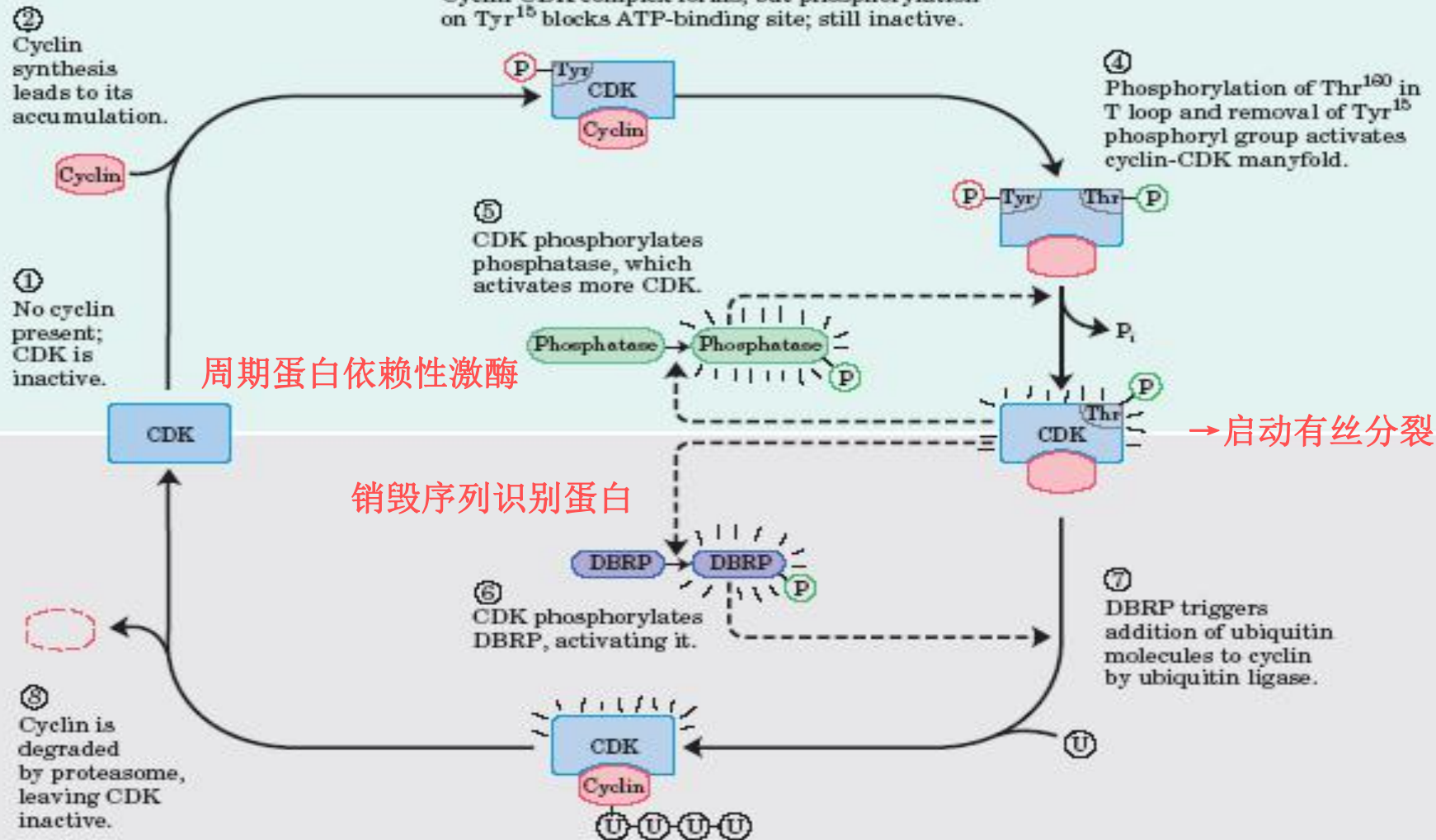
刺 激 物	受 体	G 蛋白	效 应 子	生 理 效 应
肾 上 腺 素	β -肾上腺素受体	G_s	腺苷酸环化酶	糖原降解
5-羟 色 胺	5-羟色胺受体	G_s	腺苷酸环化酶	海兔的行为敏感性及学习过程
光	视 紫 质	传导素 (transducin)	cGMP 磷酸二酯酶	视觉激动作用
IgE-抗原复合物	肥大细胞的 IgE 受体	G_{PLC}	磷脂酶 c	分 泌
f-蛋 氨 酸 肽	化学趋向性受体	G_{PLC}	磷脂酶 c	化学趋向性
乙 酰 胆 碱	蕁毒碱受体	G_K	K^+ 通道	减慢起搏活动

注： G_{PLC} 和 G_{PKC} 代表在这些级联中还未确定的 G 蛋白。
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(3) 细胞增殖的调节



(a)



(b)

FIGURE 12-44 Regulation of CDK by phosphorylation and proteolysis. (a) The cyclin-dependent protein kinase activated at the time of mitosis (the M phase CDK) has a "T loop" that can fold into the substrate-binding site. When Thr¹⁶⁰ in the T loop is phosphorylated, the loop moves out of the substrate-binding site, activating the CDK

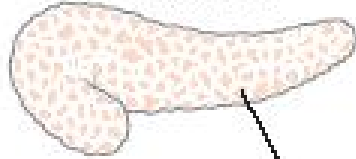
manyfold. (b) The active cyclin-CDK complex triggers its own inactivation by phosphorylation of DBRP (destruction box recognizing protein). DBRP and ubiquitin ligase then attach several molecules of ubiquitin (U) to cyclin, targeting it for destruction by proteasomes, proteolytic enzyme complexes.

(4) 人体主要器官的代谢系统

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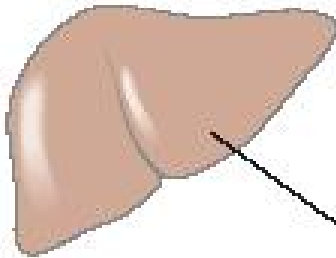
Secretes insulin and glucagon in response to changes in blood glucose concentration.

Pancreas



Processes fats, carbohydrates, proteins from diet; synthesizes and distributes lipids, ketone bodies, and glucose for other tissues; converts excess nitrogen to urea.

Liver



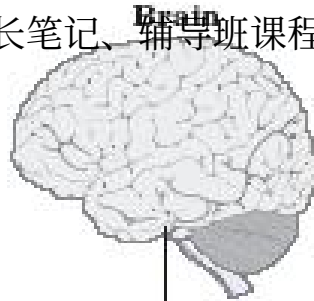
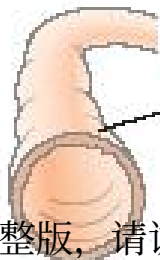
Carries nutrients from intestine to liver.

Portal vein



Small intestine

Absorbs nutrients from the diet, moves them into blood or lymphatic system.



Brain

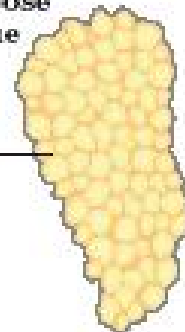
Transports ions to maintain membrane potential; integrates inputs from body and surroundings; sends signals to other organs.

Lymphatic system



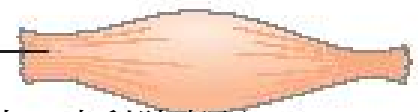
Carries lipids from intestine to liver.

Adipose tissue



Synthesizes, stores, and mobilizes triacylglycerols.

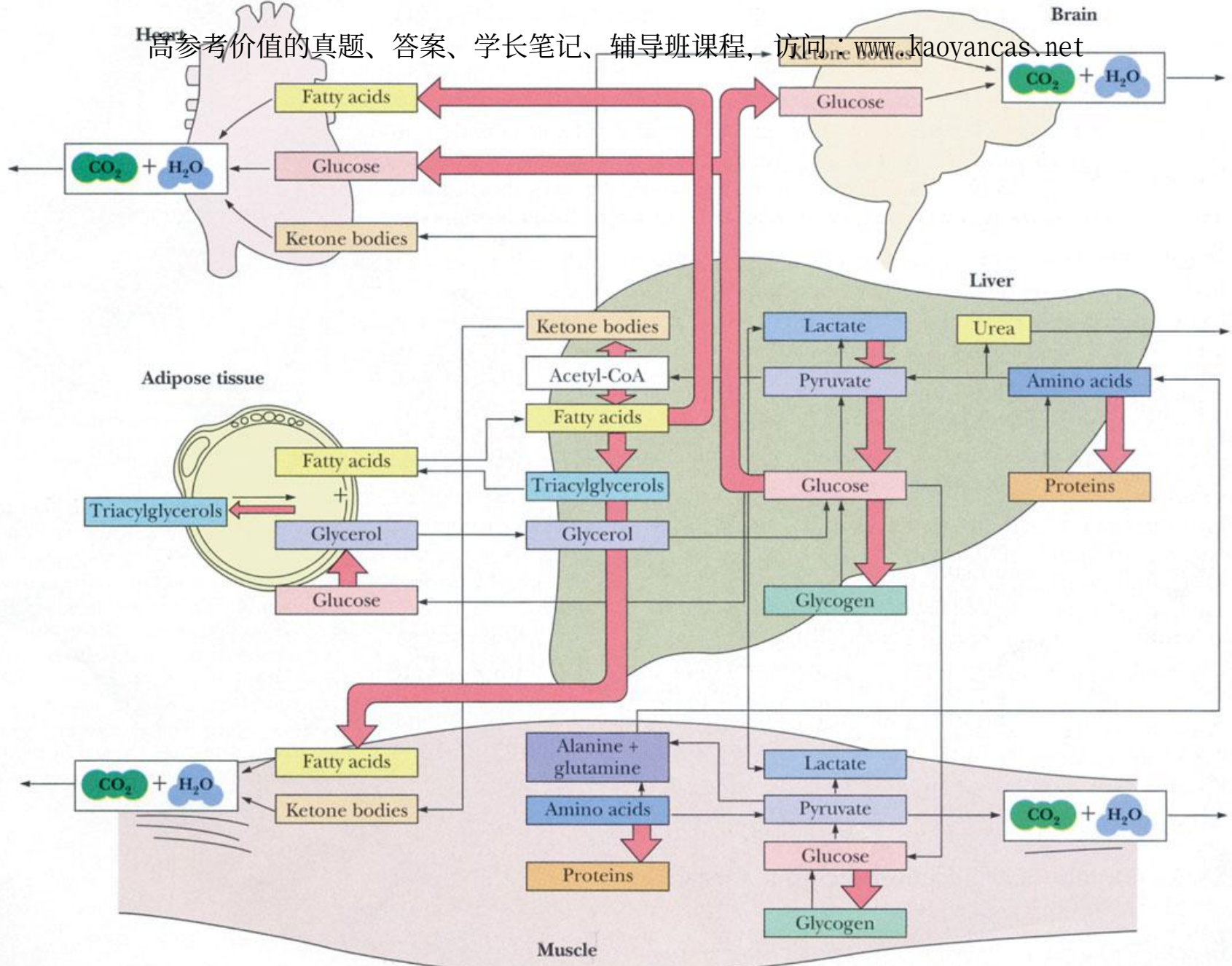
Uses ATP to do mechanical work.



Skeletal muscle

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基本要求

1. 掌握细胞代谢调节网络的特点。 (重点)
2. 掌握酶活性调节的主要途径。 (重点)
3. 熟悉细胞结构对代谢途径的分隔控制。
4. 熟悉细胞信号传递系统。 (难点、重点)