

# Cellular and Molecular Biology of the Neuron

## Part II

# 神经系统细胞生物学（二）

Yan Zhang  
张研

# Cellular Information Transfer

## 细胞的信息传递

1、直接接触的细胞：细胞连接；细胞识别

*Directly contacted cells: cellular junctions and recognition*

2、未接触的细胞：化学通讯

*Non-contacted cells: chemical communication*

具有调节细胞生命活动的化学  
物质称为**信息物质**

Chemicals regulating cellular life activities are called **signaling molecules**.

## 化学信号转导的一般步骤

General steps of chemical information transduction

特定的细胞释放信息物质

Certain cells release signaling molecules



信息物质经扩散或血循环到达靶细胞

Signaling molecules reach target cells  
by diffusion or blood circulation

与靶细胞的受体特异性结合

Bind to receptors of target cells specifically



受体对信号进行转换并启动细胞内信使系统

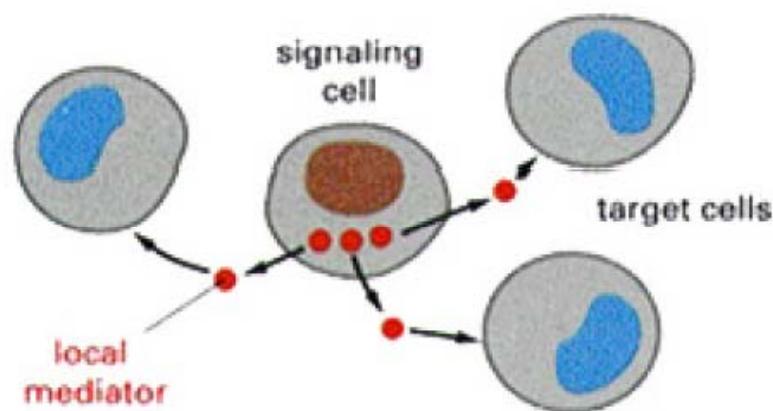
Receptors transduce signals and activate intracellular messenger system



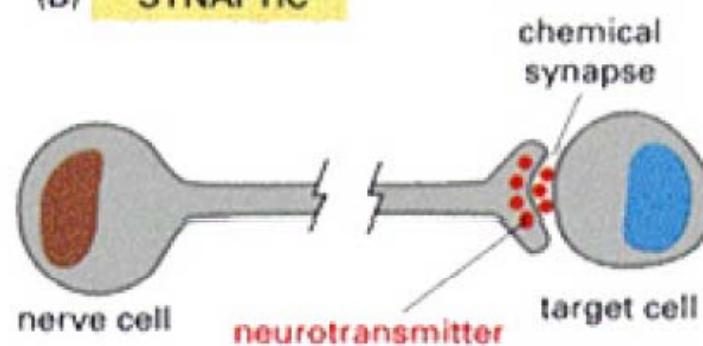
靶细胞产生生物学效应

Target cells trigger biological effects

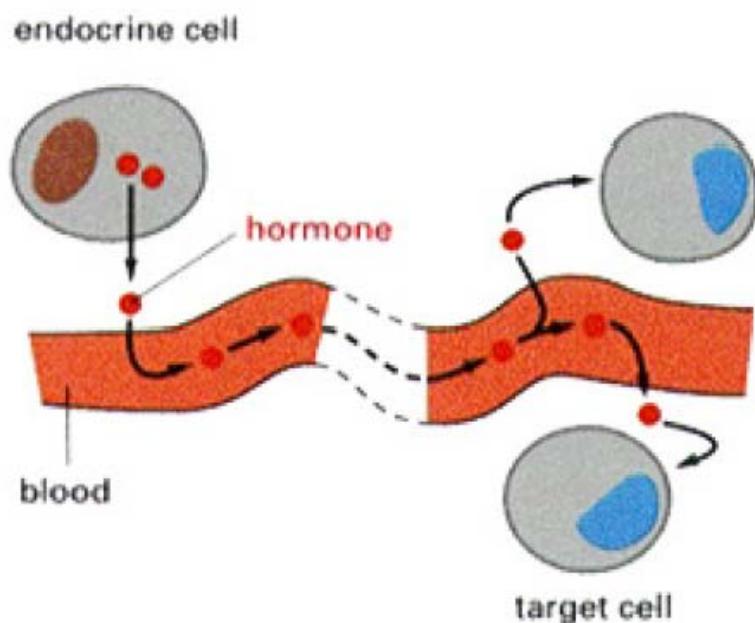
**(A) PARACRINE**



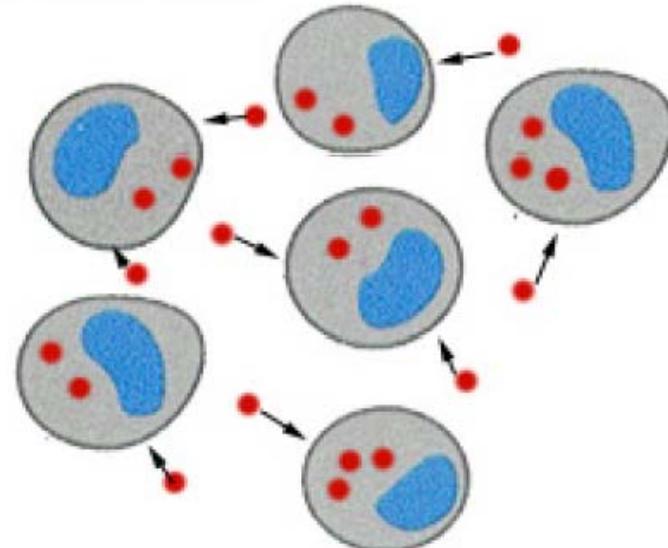
**(B) SYNAPTIC**



**(C) ENDOCRINE**



**(D) AUTOCRINE**



## (一) 细胞间信息物质 (extracellular signal molecule)

➤ 细胞间信息物质：配体 (ligand) 或第一信使  
Extracellular signaling molecules: ligand or first messenger

➤ 由细胞分泌的调节靶细胞生命活动的化学物质  
Chemicals secreted by cells to regulate life activities of target cells

(1) 特点：少量、短寿、高效、特异  
Low dosage, short lifespan, high efficiency and high specificity

(2) 作用类型：自分泌、旁分泌、内分泌  
Types: autocrine, paracrine and endocrine

(3) 化学性质：蛋白质和肽类；氨基酸及其衍生物；类固醇激素；脂酸衍生物；气体

chemicals: proteins and polypeptides, amino acids and their derivatives, steroid hormones, fatty acid derivatives and gas

(4) 溶解性质：水溶性；脂溶性；气体  
solubleness: water-soluble, liposoluble and gas

细胞受第一信使刺激后产生的在细胞内起传递信息作用的化学分子

Chemicals transmitting intracellular information after first messenger stimulation

### ❖第二信使(secondry messenger)

在细胞内传递信息的小分子物质，如： $\text{Ca}^{2+}$ 、DAG、 $\text{IP}_3$ 、Cer、cAMP、cGMP、花生四烯酸及其代谢产物等。

Secondary messengers:

Small molecules transmitting information intracellularly, such as  $\text{Ca}^{2+}$ , DAG,  $\text{IP}_3$ , Cer, cAMP, cGMP, arachidonic acid and its metabolites.

### ❖第三信使(third messenger)

负责细胞核内外信息传递的物质，是一类可与靶基因特异序列结合的核蛋白，能调节基因的转录，又称为DNA结合蛋白。

Third messengers:

Molecules transmitting information through the nucleus. They are nucleoproteins binding to specific sequences of target genes and are called DNA binding proteins as well.

# 化学性质

## Chemical properties

无机离子：如 **Ca<sup>2+</sup>**

Inorganic ions: such as Ca<sup>2+</sup>

脂类衍生物：如**DAG、Cer**

Fat derivatives: such as DAG and Cer

核苷酸：如**cAMP、cGMP**

Nucleotides: such as cAMP and cGMP

糖类衍生物：如**IP<sub>3</sub>**

Sugar derivatives: such as IP<sub>3</sub>

信号蛋白分子

Signaling proteins

# CNS neurotransmitters 中枢递质

1.概念: 中枢神经系统中参与突触传递的化学物质统称。

Concept: chemicals involved in synaptic transmission in the central nervous system (CNS)

神经递质的标准:

Qualifications:

- 突触前神经元内具有合成神经递质的物质及酶系统，能够合成该递质。

Producible in pre-synaptic neurons containing its raw materials and enzymic systems

- 递质贮存于突触小泡，冲动到达时能释放入突触间隙。

Stored in synaptic vesicles and released to the synaptic clefts when impulsion arrives

- 能与突触后膜受体结合发挥特定的生理作用。

Bind to post-synaptic receptors to trigger specific physiological effects

- 存在能使该递质失活的酶或其它环节（如重摄取）。

Able to be inactivated by enzymes or other approaches such as reuptaking

- 用递质拟似剂或受体阻断剂能加强或阻断递质的作用。

Its effects can be enhanced by neurotransmitter mimics and blocked by antagonists

## 2. 神经递质分类 Types of neurotransmitters

分类

家 族 成 员

Types

Members

胆碱类

乙酰胆碱

Cholines

Acetylcholine (Ach)

单胺类

Monoamines

儿茶酚胺: 多巴胺、去甲肾上腺素 (NE) 、肾上腺素 (E)

Catecholamine: dopamine, norepinephrine and epinephrine

吲哚胺: 5-HT

Indoleamine: 5-HT

氨基酸类

谷氨酸、门冬氨酸、甘氨酸、GABA

Amino acids:

glutamic acid, aspartic acid, glycine and GABA

肽类

下丘脑调节肽、ADH、催产素、阿片肽、脑-肠肽、心房钠尿肽等

Peptides:

hypothalamus regulatory peptide, ADH, oxytocin, opioid, brain-gut peptide, atrial natriuretic peptide.

嘌呤类

腺苷、ATP

Purines:

adenosine, ATP

气体

NO、CO

Gas:

NO, CO

脂类

PG类

Lipids:

PG

### 3. 受体学说 Receptor doctrine

(1) 概念: 嵌在细胞膜中大分子蛋白质分子, 能识别特定的递质, 并与之结合而产生生理效应, 改变细胞膜对某些离子的通透性。

Concept: macromolecular proteins set in cellular membrane, recognizes and binds to specific transmitters, triggers physiological effects and alters the cell membrane permeability of certain ions.

配体 { 激动剂 Agonist  
ligand { 拮抗剂 Antagonist

(2) 受体与配体结合的特性: 特异性; 饱和性; 可逆性。

Binding specificity of receptors and ligands: specificity, saturability, reversibility

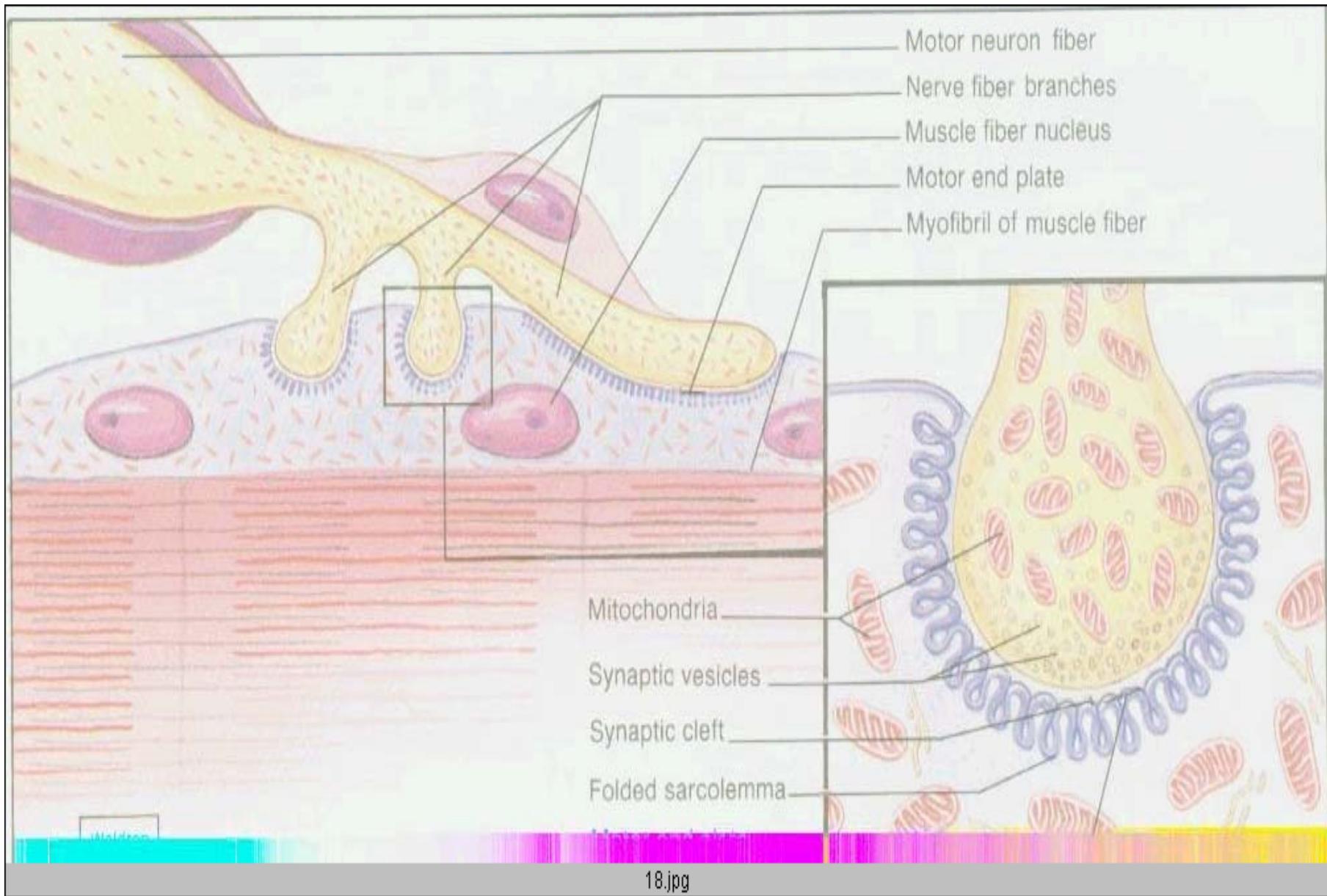
(3) 分类: Sorted by:

{ 分布部位分 Position: 突触前受体 突触后受体 pre- and post-synaptic  
生物效应分: 与离子通道耦联受体 coupled to ion channels  
Biological effects 激活G蛋白和蛋白激酶途径受体  
activate G proteins and protein kinase receptors  
结合递质分: 胆碱能受体 cholinergic receptors  
Binding transmitters 肾上腺素能受体 adrenergic receptors  
突触前受体 presynaptic receptors  
中枢递质的受体: 5-HT受体、氨基酸类受体等  
CNS transmitter receptors:  
5-HT receptors, amino acid receptors

## 主要的递质、受体系统 Major transmitter-receptor systems

| 递质<br>Transmitter | 受体<br>Receptor  | 第二信使<br>Second messenger         | 拮抗剂<br>Antagonist            | 通道效应<br>Channel effect                                   | 递质主要分布<br>Major distribution   |
|-------------------|---|----------------------------------|------------------------------|--|--|
|                   | $N_1$<br>(肌肉型烟碱受体)<br>Muscle-type nicotinic receptor  |                                  | 筒箭毒<br>十烃季铵<br>Decamethonium | $\uparrow \text{Na}^+$<br>和其他<br>小离子                     | 外周:<br>所有自主神经节前纤维、大多数副交感<br>神经节后纤维、少数交感神经节后纤维、骨<br>骼肌神经纤维等。  |
|                   | $N_2$<br>(神经元型烟碱受体)<br>Neuron-type nicotinic receptor |                                  | 筒箭毒<br>六烃季铵<br>Hexamethonium | $\uparrow \text{Na}^+ \text{and}$<br>other<br>small ions | PNS:<br>All autonomic nerve preganglionic fibers, most<br>parasympathetic postganglionic fibers, a few<br>sympathetic postganglionic fibers, skeletal<br>muscle fibers   |
| ACh               |   |                                  |                              |  |  |
|                   | $M_1$   | $\uparrow \text{IP}_3/\text{DG}$ | 阿                            | $\uparrow \text{Ca}^{2+}$                                | 中枢:<br>脊髓前角运动神经元、丘脑后部腹侧的<br>特异感觉投射神经元、脑干网状结构上行激<br>动系统、纹状体、边缘系统等。  |
|                   | $M_2$<br>(心 Cardiac)                                  | $\downarrow \text{cAMP}$         | 托                            | $\downarrow \text{K}^+$                                  | CNS:<br>Spinal cord anterior horn motor neurons,<br>posterior ventral thalamus specific sensory<br>projection neurons, brain stem reticular<br>structure ascending exciting system, striatum,<br>limbic system |
|                   | $M_3$   | $\downarrow \text{cAMP}$         | 品                            |  |  |
|                   | $M_4$<br>(腺体)   | $\uparrow \text{IP}_3/\text{DG}$ | Atropine                     |  |  |

| 递质<br>Transmitter                                  | 受体<br>Receptor                             | 第二信使<br>Second messenger       | 拮抗剂<br>Antagonist                        | 通道效应<br>Channel effect                                     | 递质主要分布<br>Major distribution  |
|--|--|--------------------------------|--|--|---|
| NE (小肠<br>Presynaptic membrane<br>small intestine) | $\alpha_1$                                 | $\uparrow$ IP <sub>3</sub> /DG | 酚妥拉明<br>Phentolamine                     | $\downarrow$ K <sup>+</sup>                                | 外周:<br>多数副交感神经节后纤维;<br>中枢:<br>低位脑干及上行投射到皮层、边缘前脑、下丘脑以及下行到达脊髓后角、侧角、前角的纤维。   |
|  | $\alpha_2$<br>突触前膜<br>Presynaptic membrane | $\downarrow$ cAMP              | 酚妥拉明<br>Phentolamine<br>育亨宾<br>Yohimbine | $\uparrow$ K <sup>+</sup><br>$\downarrow$ Ca <sup>2+</sup> | PNS:<br>Most parasympathetic postganglionic fibers<br>CNS:<br>Lower brainstem and ascending fibers projecting to the cortex, limbic forebrain, hypothalamus and descending fibers projecting to posterior/lateral/ anterior horn of the spinal cord |
|  | $\beta_1$<br>(心<br>Cardiac)                | $\uparrow$ cAMP                | 心得宁<br>Practolol<br>阿提洛尔<br>Atenolol     |  |   |
|  | $\beta_2$                                  |                                | 丁氧胺<br>butoxamine                        |  |   |
| 多巴胺<br>Dopamine                                    | $D_1, D_5$                                 | $\uparrow$ cAMP                |  |  | 黑质-纹状体、结节-漏斗、中脑边缘系统。<br>Substantia nigra-striatum, tubero-infundibular system, midbrain limbic system   |
|  | $D_2, D_3, D_4$                            | $\downarrow$ cAMP              |  | $\uparrow$ K <sup>+</sup><br>$\downarrow$ Ca <sup>2+</sup> |   |
| 5-HT   | 5-HT <sub>1</sub>                          | $\downarrow$ cAMP              |  | $\uparrow$ K <sup>+</sup>                                  | 中缝核内及上行投射到纹状体、下丘脑等以及下行到脊髓背角、侧角、前角。 Inside raphe nuclei and ascending fibers projecting to striatum, hypothalamus etc. and descending fibers to to posterior/lateral/ anterior horn of the spinal cord   |
|  | 5-HT <sub>2</sub>                          | $\uparrow$ IP <sub>3</sub> /DG |  | $\downarrow$ K <sup>+</sup>                                |   |



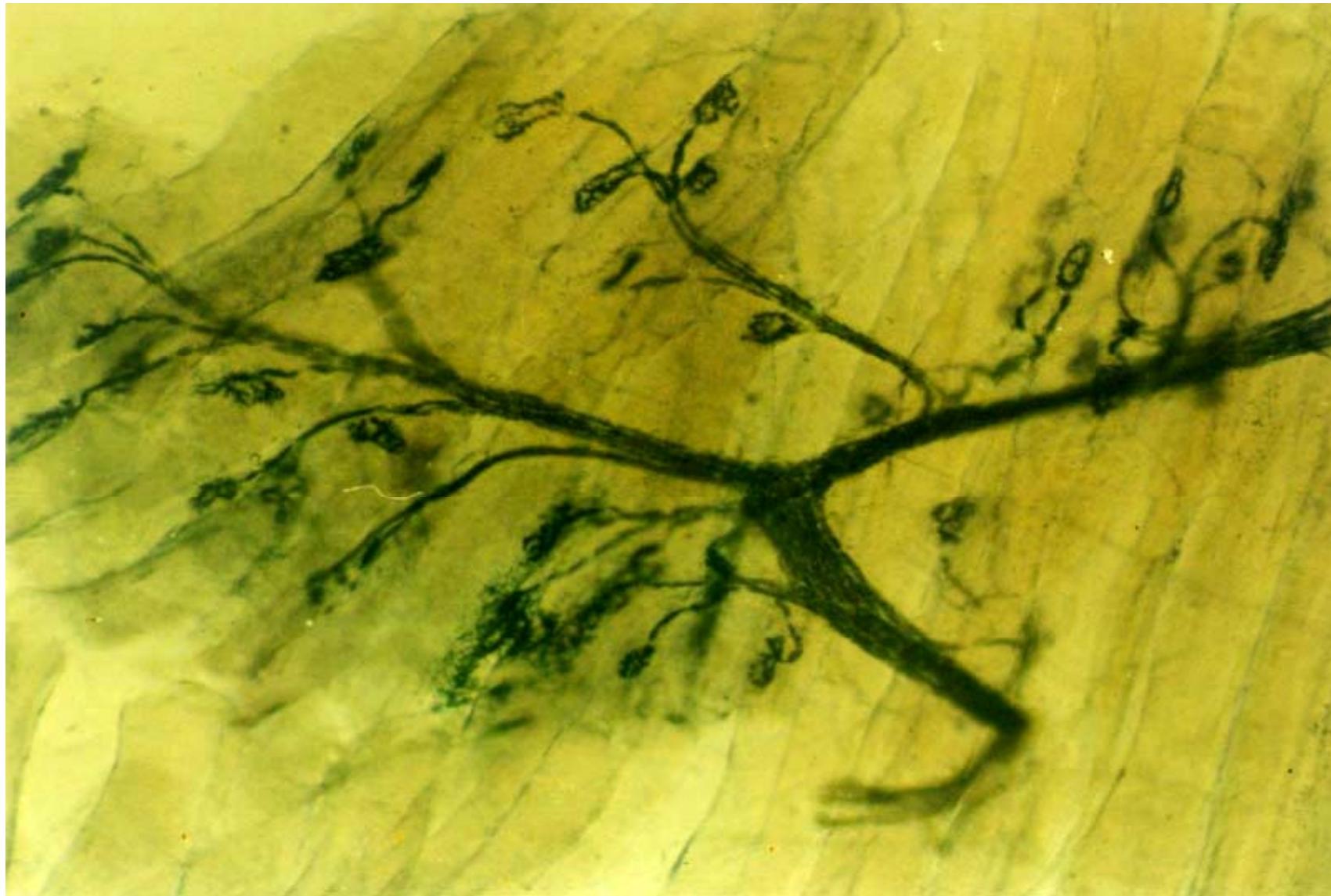
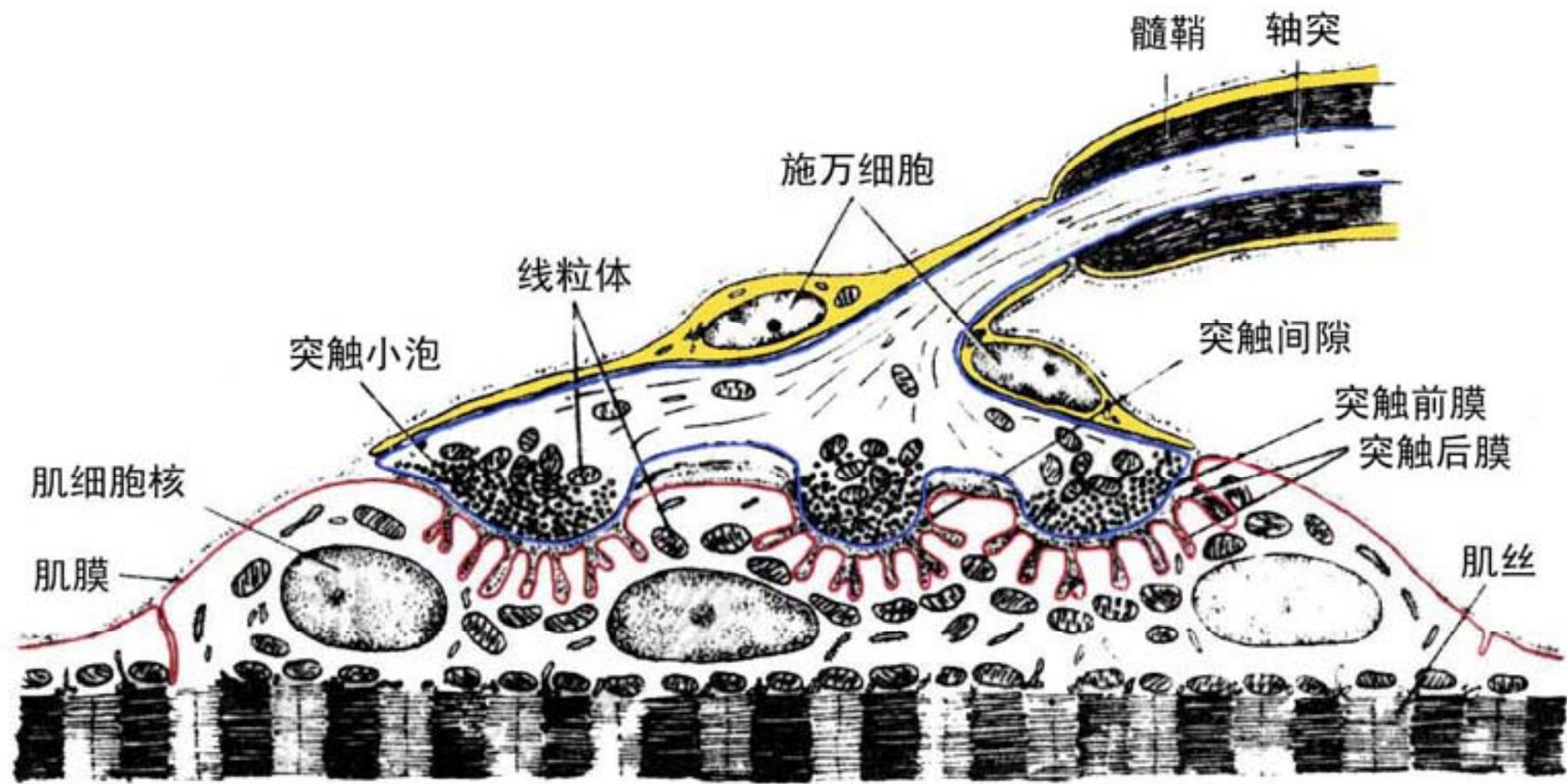
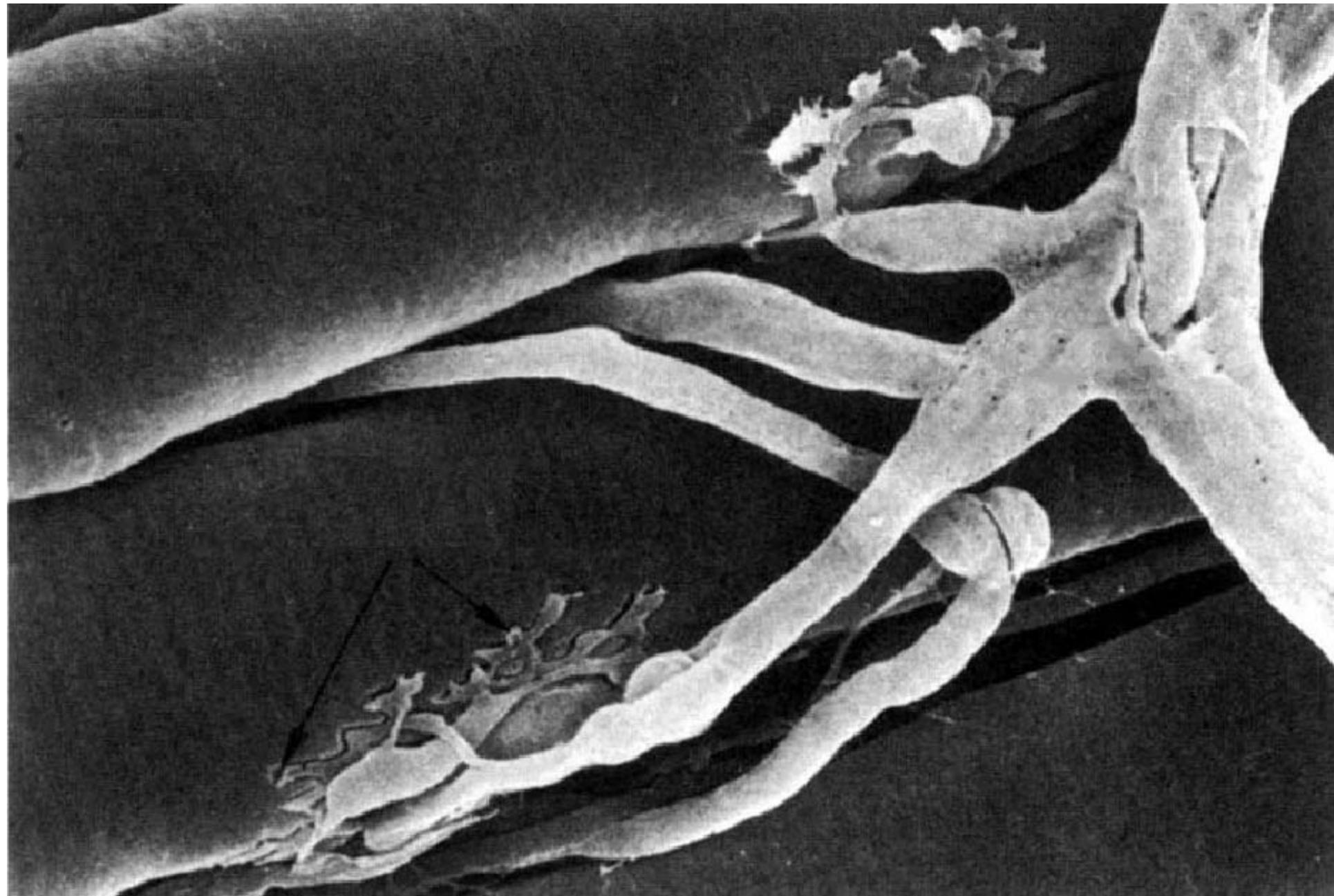


图45 运动终板光镜像 (氯化金染色)  
Motor endplate microscopy ( $\text{AuCl}_3$  staining)

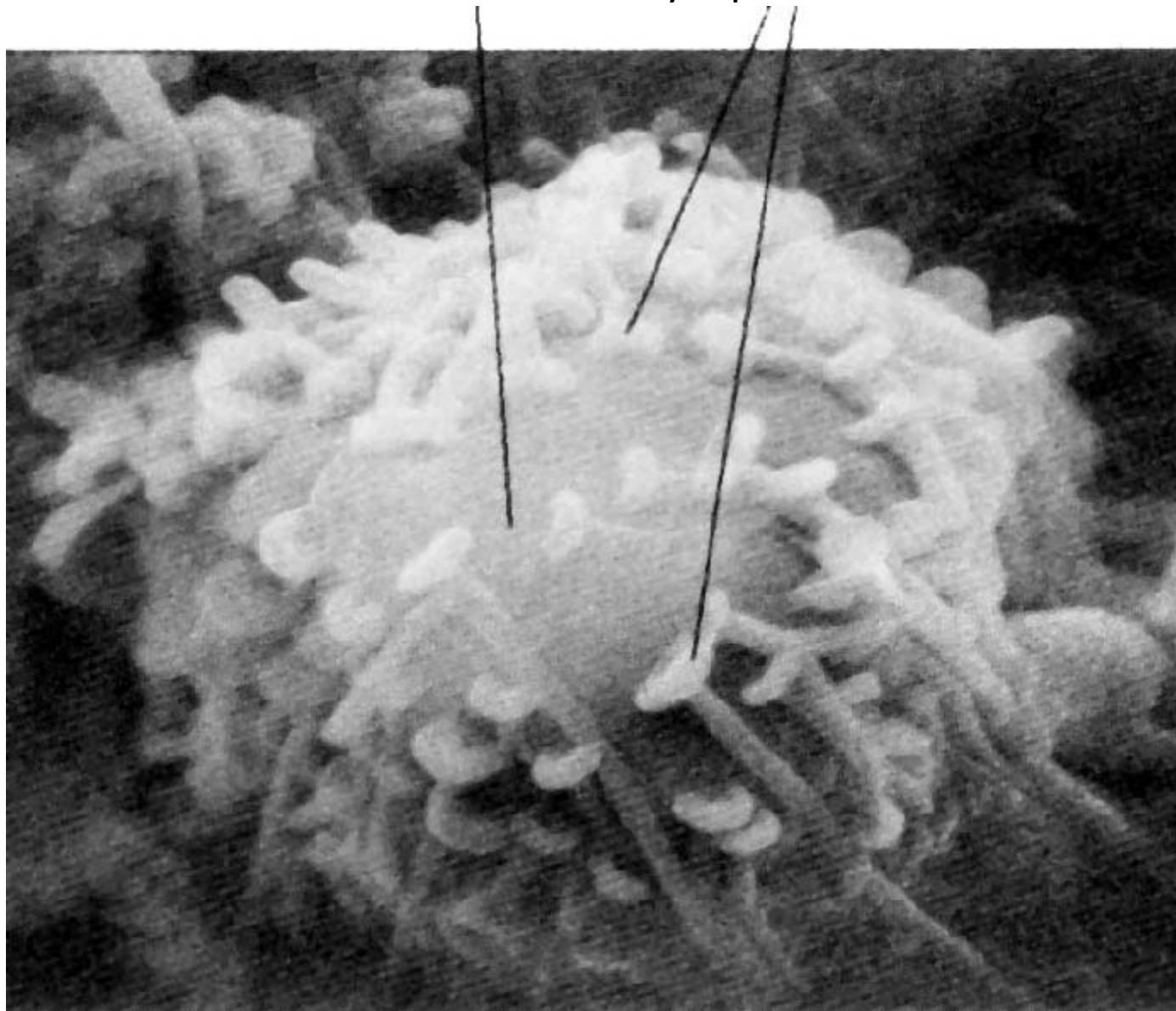


运动终板超微结构模式图  
Motor endplate ultrastructure

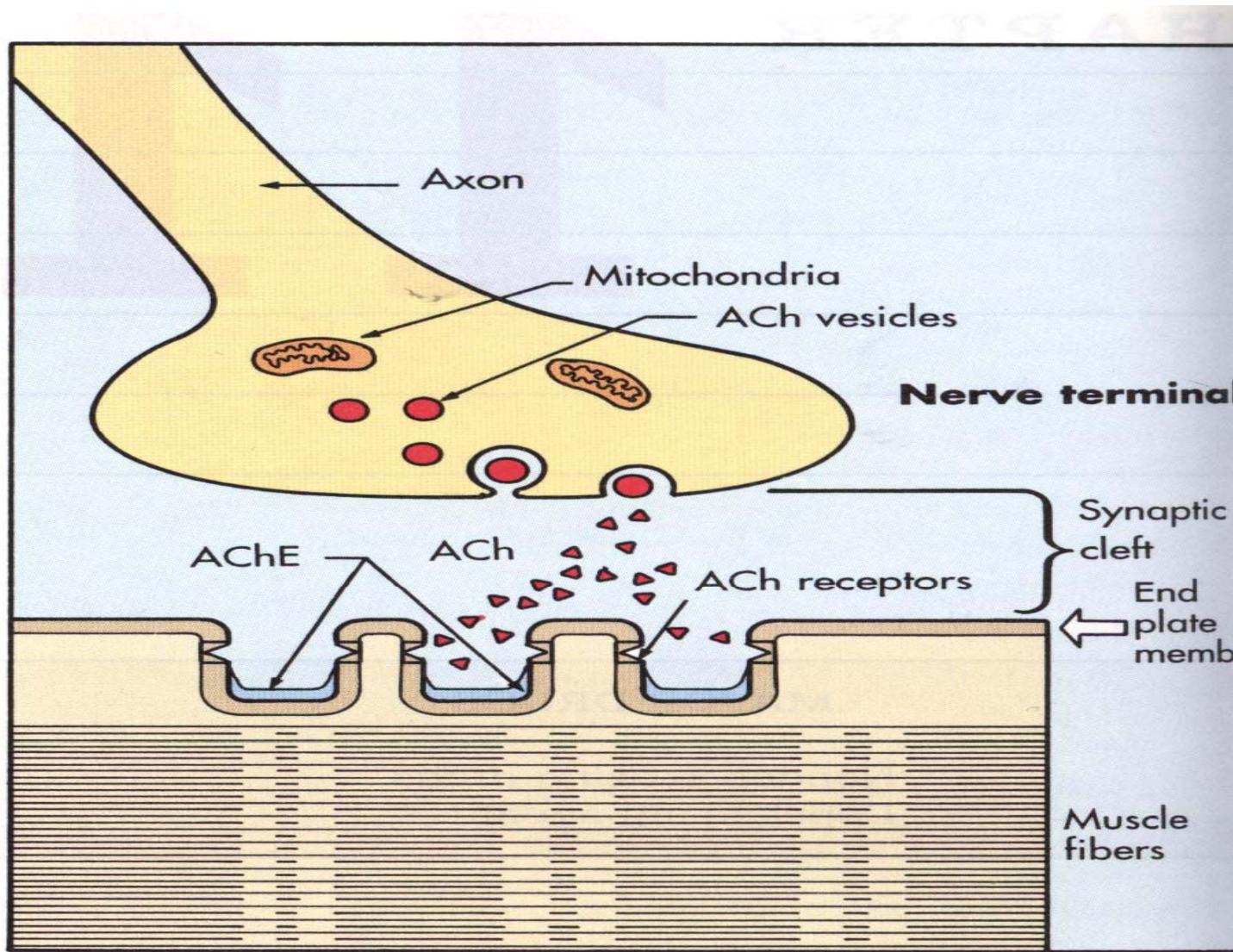


运动终板扫描电镜像  
Motor endplate SEM image

神经元胞体 突触小体  
Neuronal soma Synaptic knob



神经元胞体及表面的突触小体扫描电镜像  
Neuronal soma and superficial synaptic knobs by SEM



**FIGURE 11-1** Acetylcholine (*ACh*) release, diffusion across synaptic cleft, binding to receptors on end-plate membrane, hydrolysis by acetylcholinesterase (*AChE*) in the absence blocking drugs.

# The mechanism signal molecules act on targeting cells 信号分子对靶细胞的作用机理

## 一、受体 Receptors

### 1. 受体的概念 Concept

是指细胞膜上或细胞内能识别生物活性分子（激素、神经递质、毒素、药物等）并与之结合的生物大分子。

Macromolecules in cellular membranes or cytoplasm that recognize and bind bioactive molecules (hormones, neurotransmitters, toxins and drugs).

大多是蛋白质，少量糖脂

Majorly proteins and minorly glycolipids

受体大多位于膜上（膜受体，多为镶嵌糖蛋白），

少部分在胞内（胞内受体，均为DNA结合蛋白）

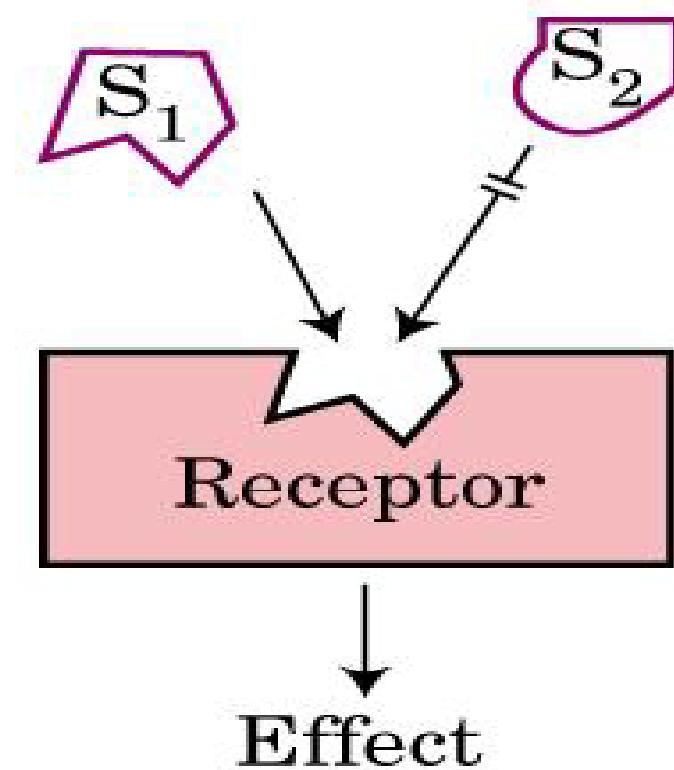
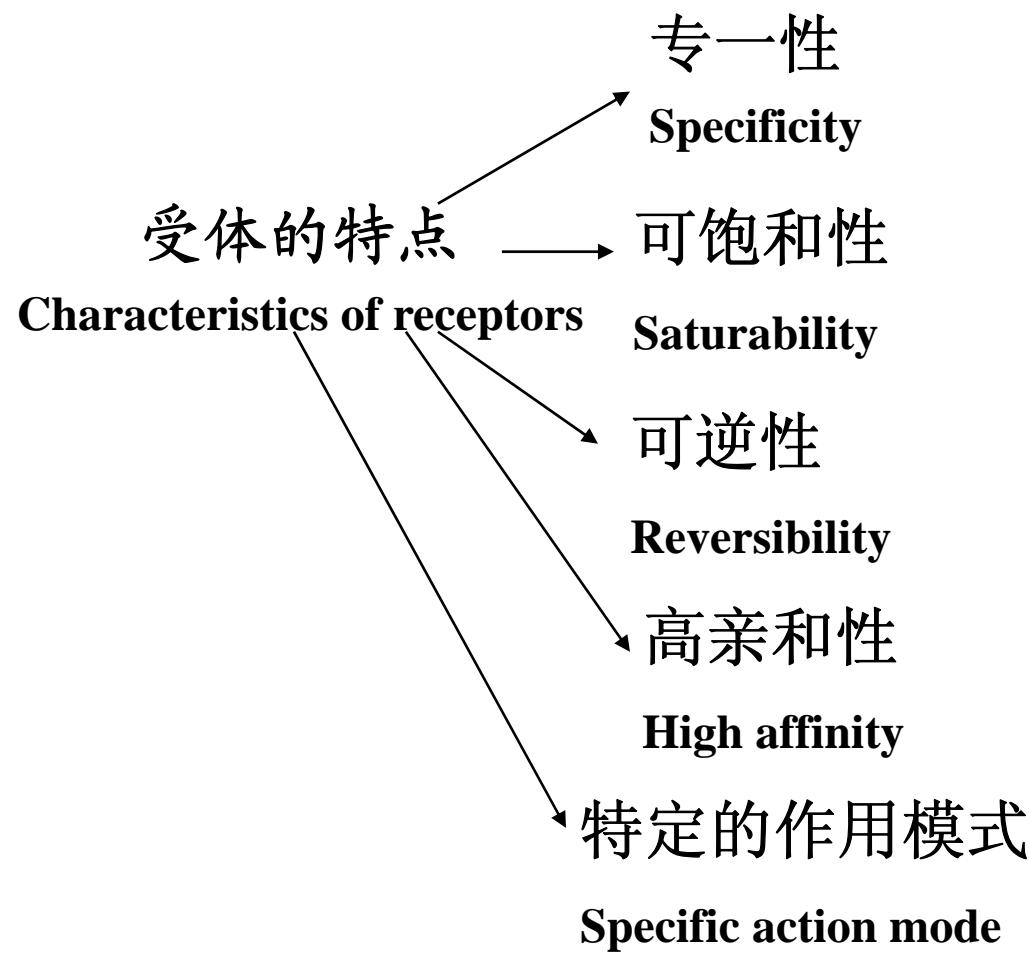
Receptors are majorly located in the membrane (membrane receptors, majorly integral glycoproteins) and minorly in the cytoplasm (intracellular receptors, all are DNA binding proteins).

配体 (ligand)

与受体结合的活性分子。是信息的载体，也称第一信使。

Bioactive molecules binding to receptors. They're carriers of information and are also called first messengers.

## 2、受体的特点 Characteristics of receptors

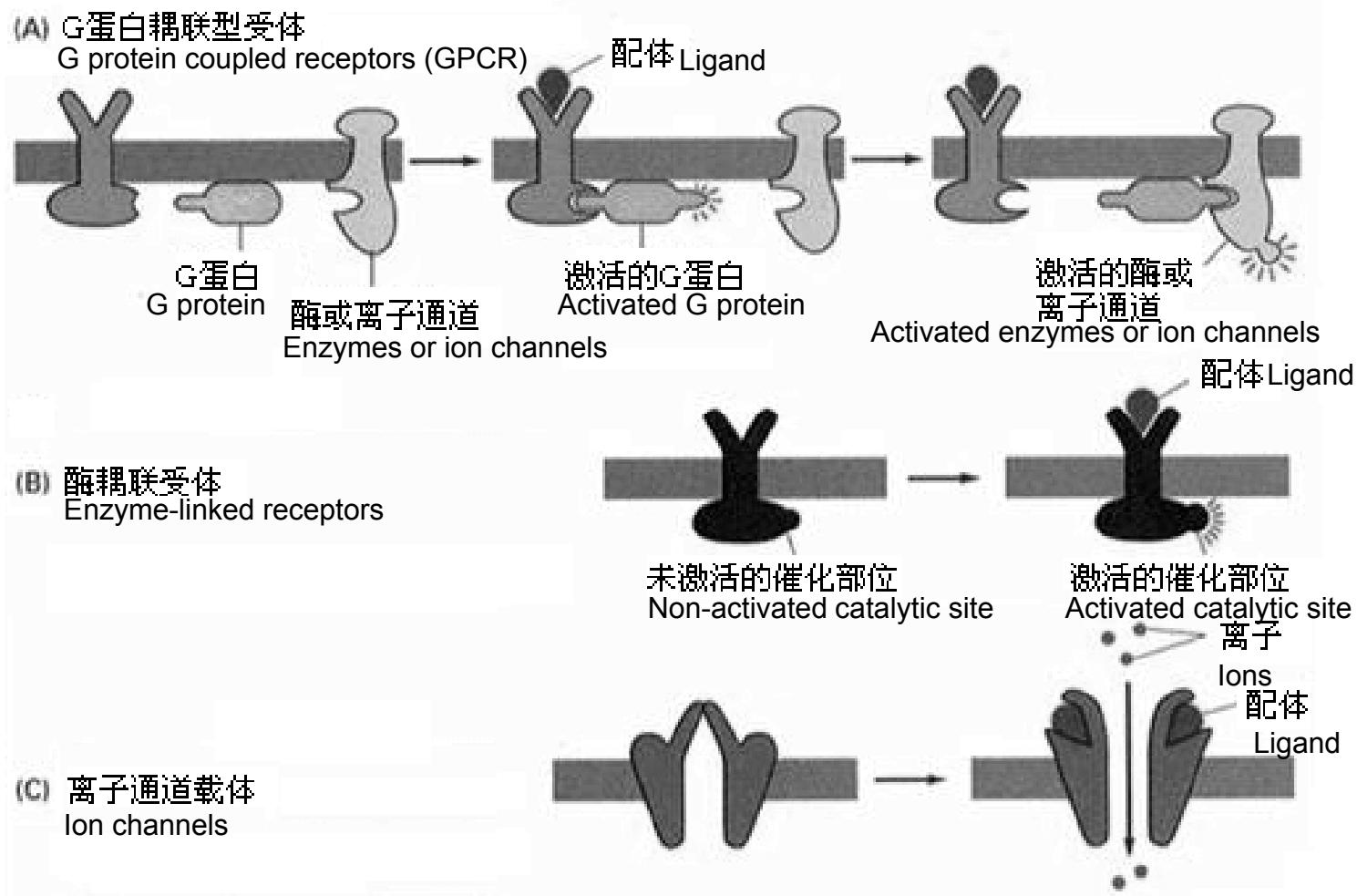


### 3、膜受体的分类 Classification of membrane receptors

G-蛋白耦联型 GPCR: 肾上腺素epinephrine, 糖原glycogen

酶耦联型 Enzyme-linked receptors: 生长因子 growth factors

离子通道型 Ion channelreceptors: 乙酰胆碱 Acetylcholine



胞外信息分子与膜受体结合，将信息传递至胞浆或核内，调节靶细胞功能的过程。

Extracellular signal molecules bind to membrane receptors and transduce information into the cytoplasm or nucleus, regulating functions of targeting cells.

◆ G蛋白(G protein)：位于细胞膜上胞浆侧，可与GTP/GDP结合的一种外周蛋白，它是一种转导体，可将外来的信号转化为传向细胞内的信号，其活性与GTP/GDP密切相关，故而得名。

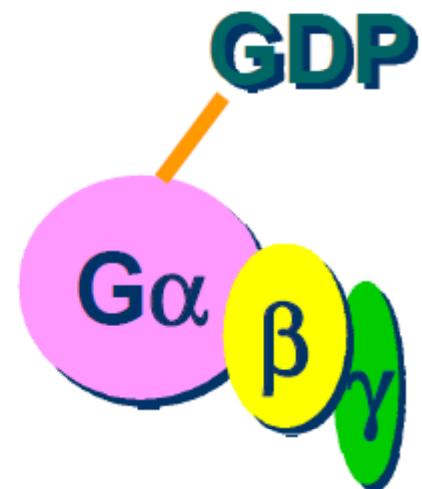
G protein: an peripheral protein located in the cytoplasm and binding to GTP/GDP, transducing extracellular information to intracellular information and named after its close relationship with GDP/GTP.



# 分类 (Classification)

- $\alpha$ 、 $\beta$ 和 $\gamma$ 亚单位  
组成的异三聚体

Heterotrimer composed of  $\alpha/\beta/\gamma$  subunits



- 小分子G蛋白

Small molecule G protein



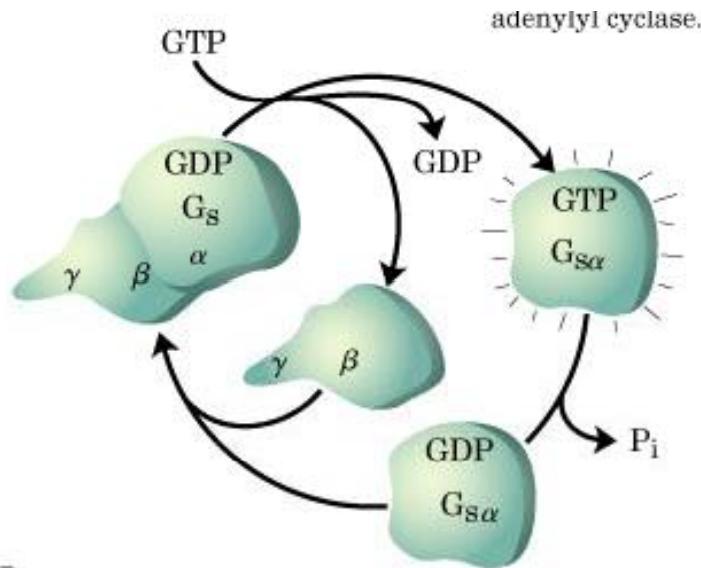
## 二、G蛋白耦联型受体系统 GPCR system

(一) G 蛋白：全称为GTP结合调节蛋白。是一类和GTP或GDP相结合的蛋白。

$\alpha$   $\beta$   $\gamma$  三个亚基组成。

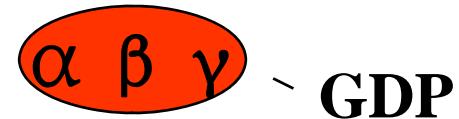
G protein: GTP-binding regulatory protein. Binds to GTP/GDP.

Composed of  $\alpha$  /  $\beta$  /  $\gamma$  subunits.



• 两种构象: Two conformations

非活化型:



Non-activated

活化型:



Activated

分布极广，参与细胞物质代谢的调节和基因转录的调控

Widely distributed and involved in regulations of material metabolism and gene transcription.

## 2、常见G蛋白的类型

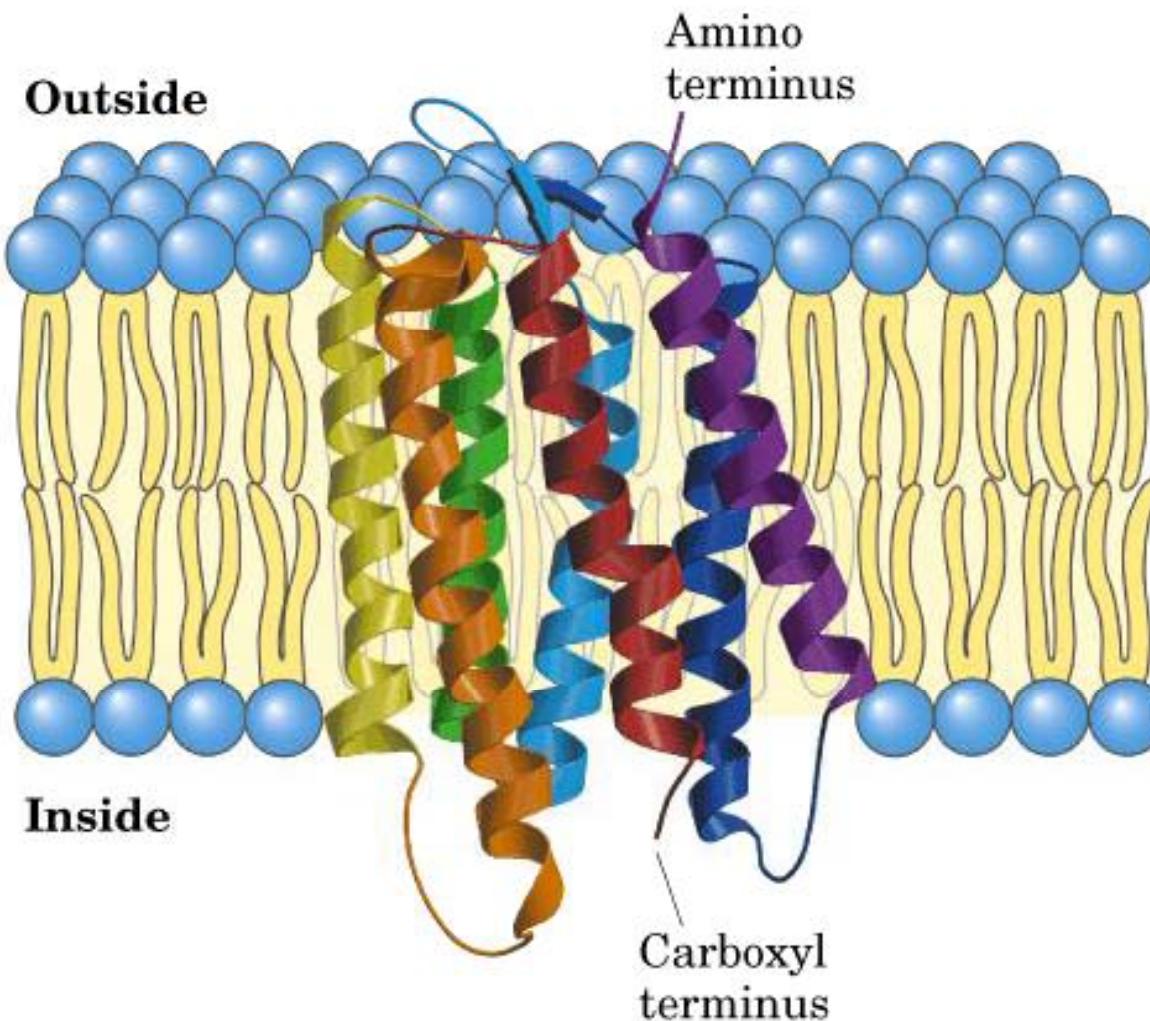
Common G protein types

| G蛋白的类型<br>Type | $\alpha$ 亚基<br>$\alpha$ subunit | 功 能<br>Function  |
|----------------|---------------------------------|--|
| $G_s$          | $\alpha_s$                      | 激活腺苷酸环化酶<br>Activate adenylate cyclase                                   |
| $G_i$          | $\alpha_i$                      | 抑制腺苷酸环化酶<br>Inhibit adenylate cyclase                                    |
| $G_p$          | $\alpha_p$                      | 激活磷脂酰肌醇的特异磷脂酶 C<br>Activate phosphatidylinositol phospholipase C         |
| $G_o^*$        | $\alpha_o$                      | 大脑中主要的G蛋白,可调节离子通道<br>Major G protein in brain and regulates ion channels |
| $G_T^{**}$     | $\alpha_T$                      | 激活视觉<br>Activate vision  |

\*<sub>0</sub>表示另一种(other) \* \* T：传导素 (transductin)

G蛋白相耦联的受体：一条肽链形成的跨膜蛋白，有7个跨膜  
 $\alpha$ -螺旋肽段往返于质膜的脂质双层中

GPCR: single-chain transmembrane peptide, with 7  
transmembrane  $\alpha$  helices shuttling in the membrane



## (二) G蛋白耦联受体信号转导的主要途径

### Major pathways of GPCR signal transduction

受体-G蛋白-AC（腺苷酸环化酶）途径：

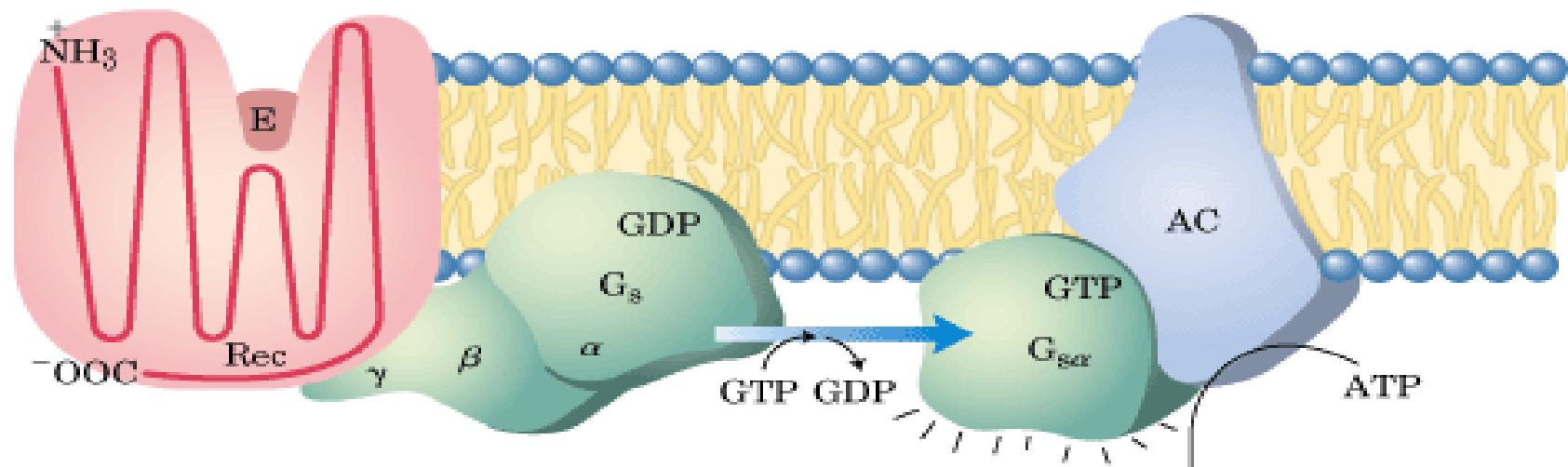
**Receptor-G protein-AC (adenylate cyclase) pathway**

以靶细胞内cAMP浓度改变和激活蛋白激酶A（protein kinase A,PKA）为主要特征，是激素调节物质代谢的主要途径

**Characterized by cAMP concentration alterations in target cells and PKA activation, major way for hormones to regulate material metabolism**

**功能：** 调节物质代谢、基因表达

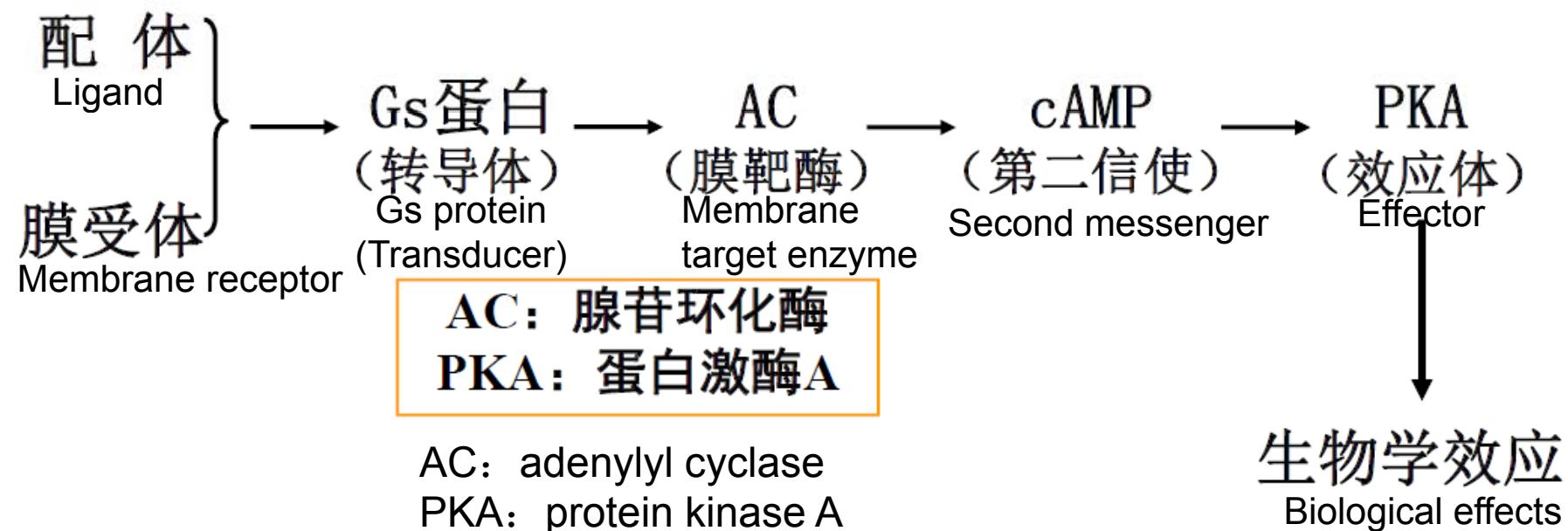
**Function:** regulations of material metabolism and gene transcription

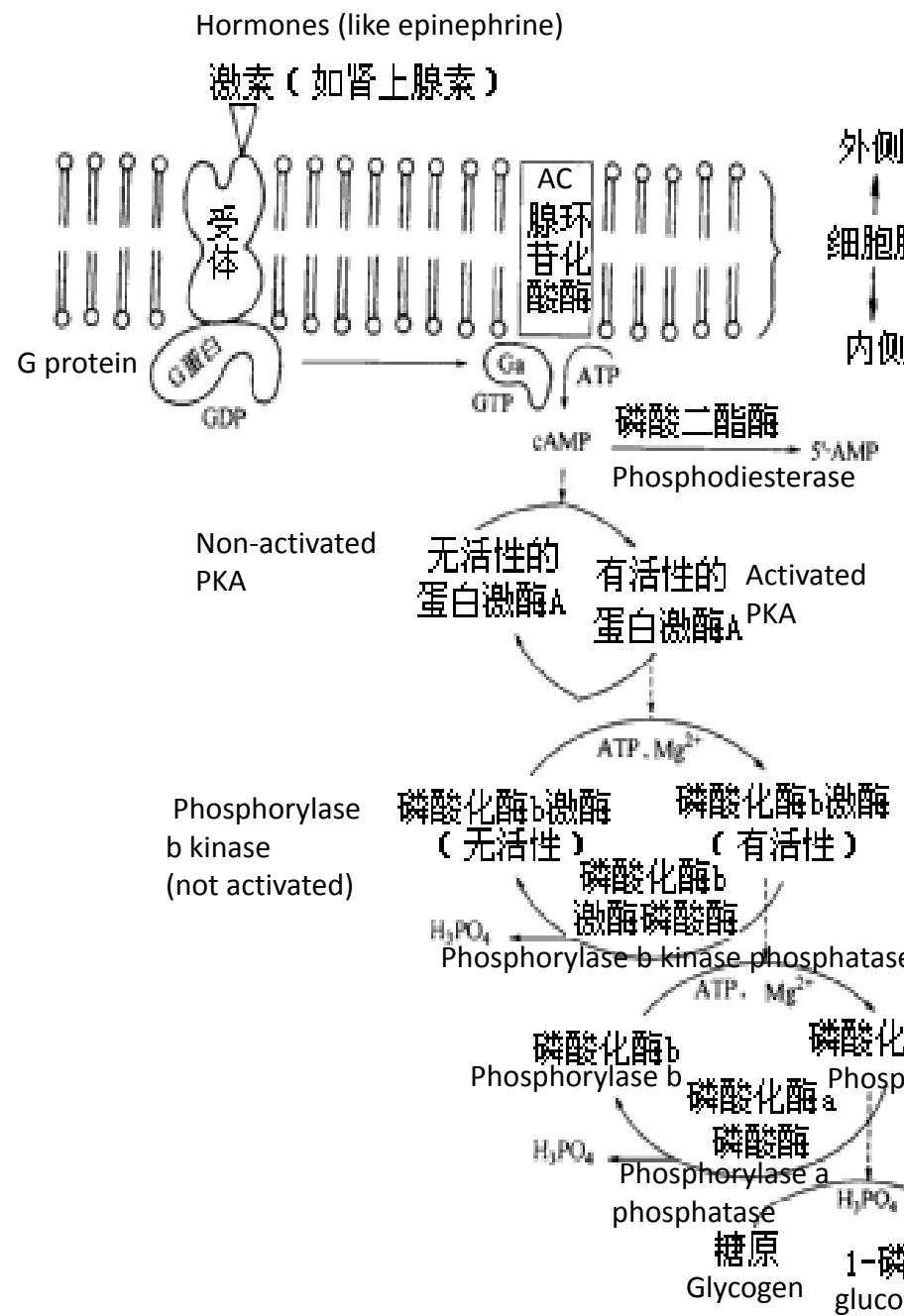


# (一) cAMP信息传递途径 (A激酶通路)



cAMP signal transduction pathway (PKA pathway)





## 配体与受体结合 Ligand binds to receptors

## 配体与受体结合 Ligand binds to receptors

## 交换GTP/GDP (G蛋白活化)

#### Exchange GTP/GDP (G protein activation)

## 结合并激活AC（腺苷酸环化酶） Bind and activate AC (adenylate cyclase)

Bind and activate AC (adenylyl cyclase)

se 生成cAMP (第二信使)  
Generate cAMP (second messenger)

Generate cAMP (second messenger)

激活 PKA  
Activate PKA

## ACTIVE FRAMES

发挥作用

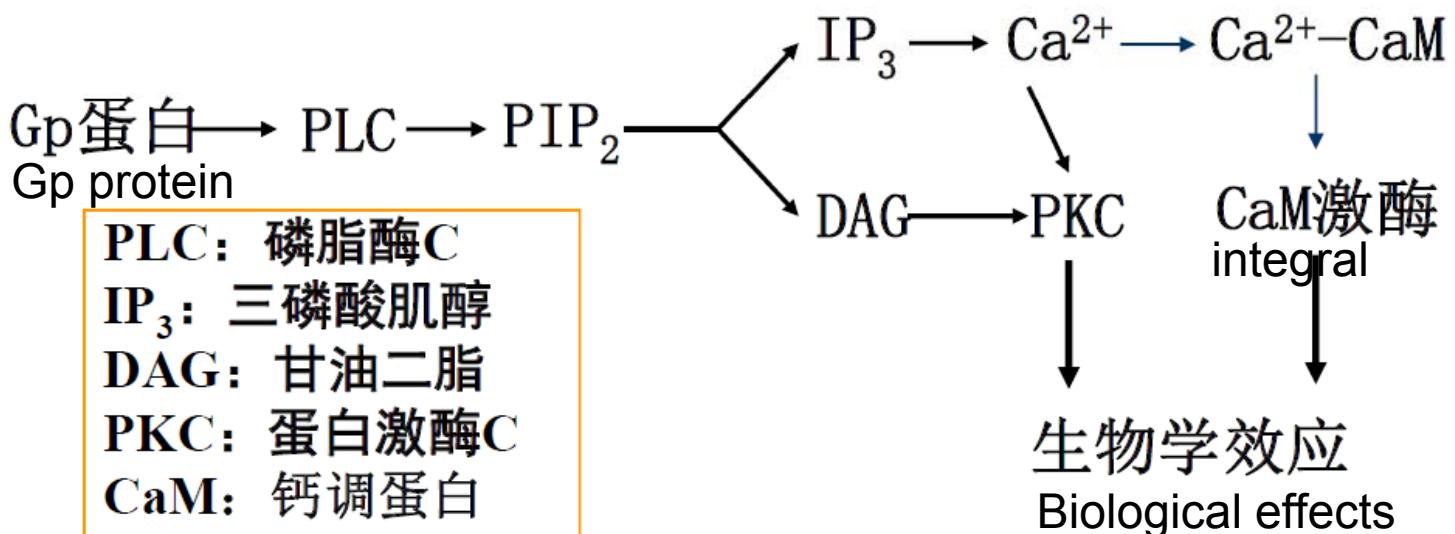
### Corresponding effects

## (二) PLC信息传递途径 (C激酶通路)

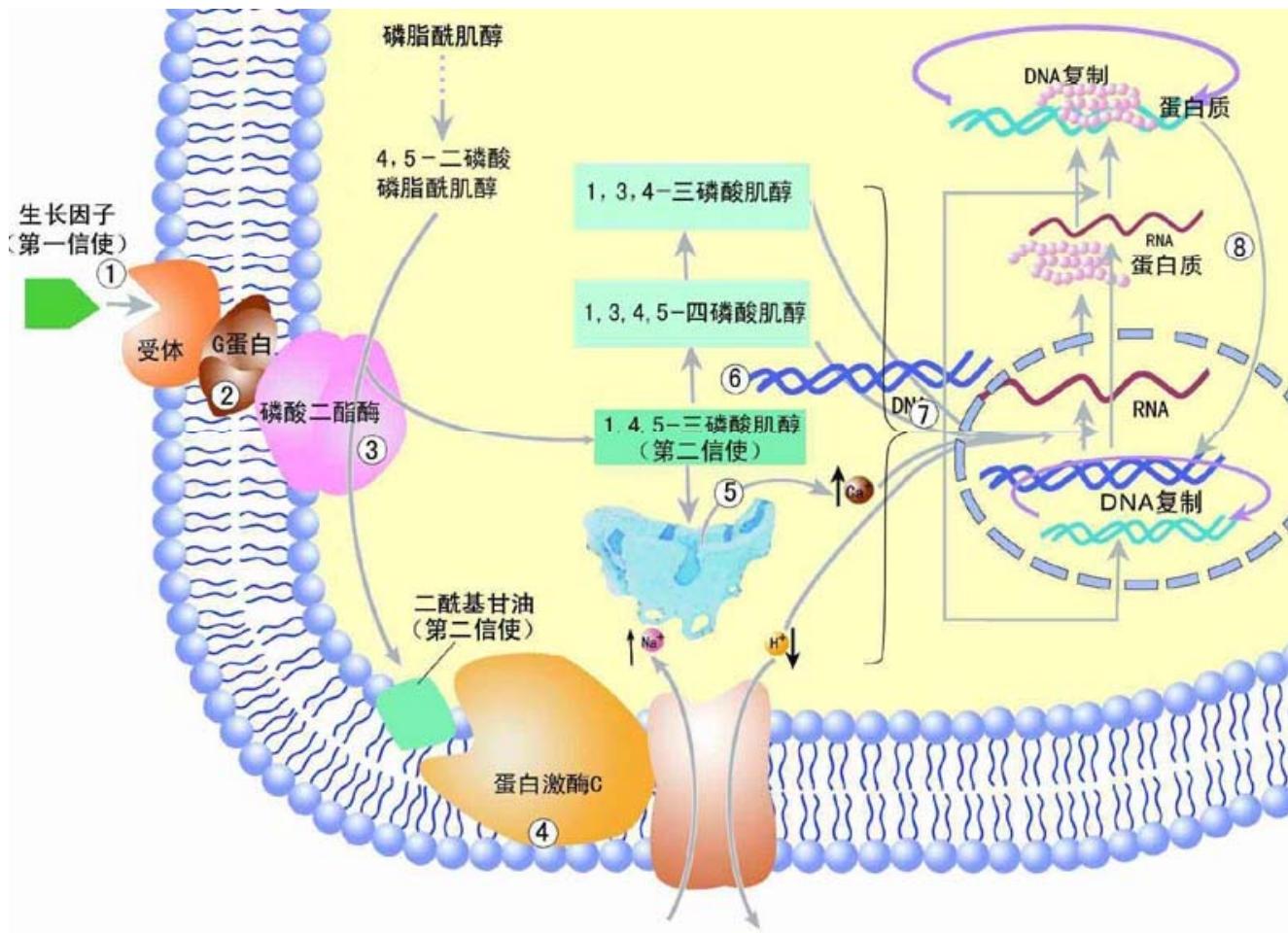
PLC signal transduction pathway (PKC)



配体  
Ligand  
膜受体  
Membrane receptors



PLC: phospholipase C  
IP<sub>3</sub>: Inositol triphosphate  
DAG: diacylglycerol  
PKC: protein kinase C  
CaM: calmodulin



1. 生长因子（第一信使）与受体结合。2. 结合后使与之偶连的G蛋白构象发生变化，从而激活与G蛋白偶连的磷酸二酯酶。3. 底物4, 5-二磷酸磷脂酰肌醇断裂成两个第二信使-二酰基甘油和1, 4, 5-三磷酸肌醇。4. 二酰基甘油通过蛋白激酶C活化 $\text{Na}^+/\text{H}^+$ 交换，使细胞内 $\text{H}^+$ 减少， $\text{pH}$ 升高。5. 1, 4, 5-三磷酸肌醇动员内质网中的 $\text{Ca}^{2+}$ 释放到细胞质，细胞质中 $\text{Ca}^{2+}$ 浓度升高。6. 1, 4, 5-三磷酸肌醇还可以转化成1, 3, 4, 5-四磷酸肌醇和1, 3, 4-三磷酸肌醇。7.  $\text{Ca}^{2+}$ 浓度和 $\text{pH}$ 的升高，以及1, 3, 4, 5-四磷酸肌醇都能够启动基因转录和蛋白质的合成。8. 最终导致DNA的合成。

### 三、酶耦联受体介导的信号转导系统

Enzyme-linked receptor mediated signal transduction system

酶耦联受体具有和G蛋白耦联受体完全不同的分子结构和特性，其胞质侧自身具有酶的活性，或者可直接结合并激活胞质中的酶而不需要G蛋白的参与。

Enzyme-linked receptors are distinctive from GPCRs in molecular structures and characteristics, whose cytoplasmic side acts as an enzyme or binds directly and activates cytoplasmic enzymes without G proteins.

已知的六类酶耦联型受体有：①受体酪氨酸激酶、②受体鸟苷酸环化酶、③受体酪氨酸磷脂酶、④受体丝氨酸/苏氨酸激酶⑤酪氨酸激酶连接的受体、⑥组氨酸激酶连接的受体（与细菌的趋化性有关）。

6 types of known enzyme-linked receptors: ① receptor tyrosine kinase ② receptor guanylate cyclase ③ receptor tyrosine phospholipase ④ Receptor serine/threonine kinase ⑤ Tyrosine kinase linked receptor ⑥ Histidine kinase linked receptor (related to the chemotaxis of bacteria)

下面主要介绍受体酪氨酸激酶和受体鸟苷酸环化酶。

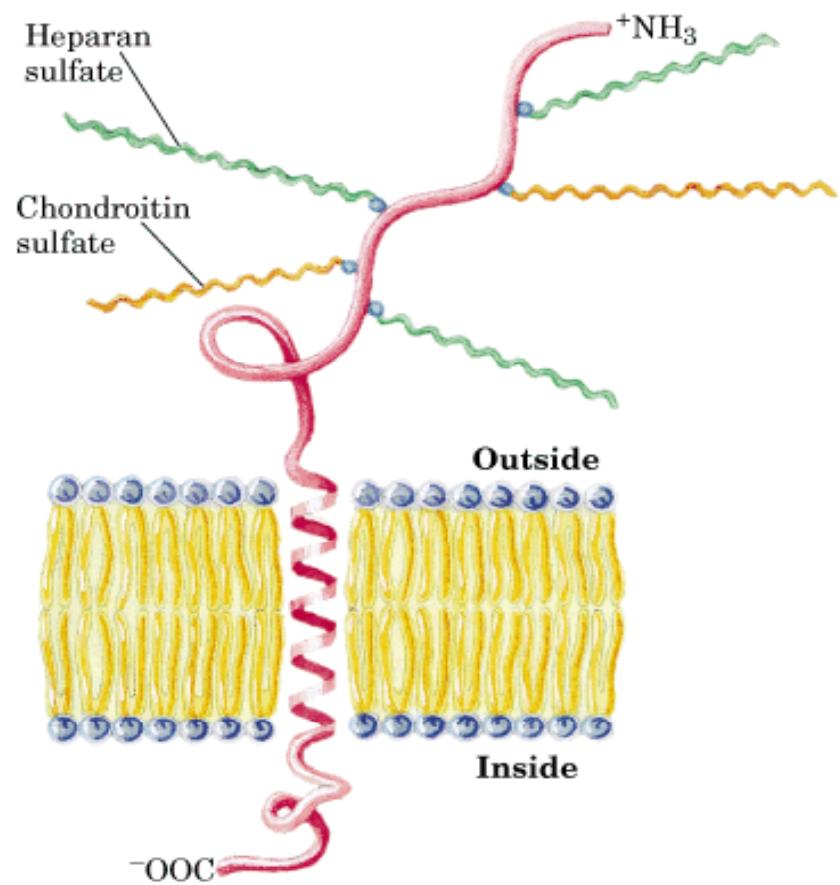
Following is mainly on receptor tyrosine kinase and receptor guanylate cyclase .

# 受体酪氨酸激酶

## Receptor tyrosine kinase

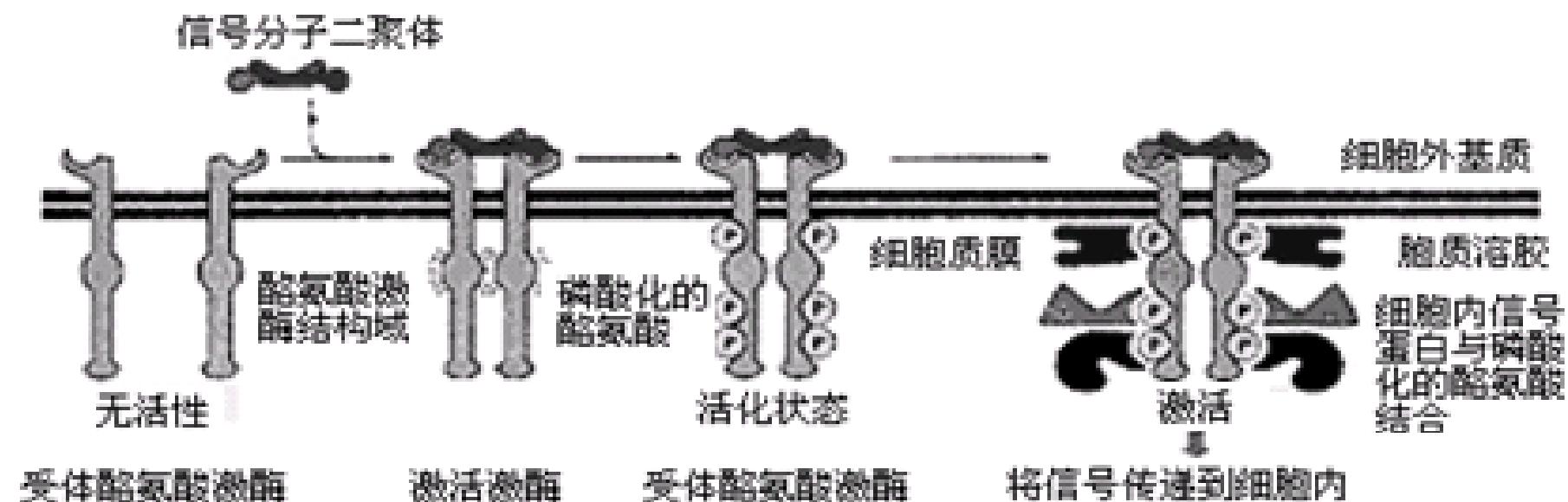
受体酪氨酸激酶（receptor protein tyrosine kinases, RPTKs）是最大的一类酶耦联受体。RPTKs都由三部分组成：细胞外结构域、单次跨膜的疏水 $\alpha$ 螺旋区、细胞内结构域。受体酪氨酸激酶的胞外区是结合配体结构域，配体是可溶性或膜结合的多肽或蛋白类激素，包括胰岛素和多种生长因子。胞内段是酪氨酸蛋白激酶的催化部位，并具有自磷酸化位点。

Receptor protein tyrosine kinases are the largest type of enzyme-linked receptors. RPTKs are made of 3 compartments: extracellular domain, single-pass hydrophobic  $\alpha$ -helix and intracellular domain. The extracellular domain of RPTKs is ligand-binding region, and the ligand is soluble or membrane-bound peptide or protein hormones including insulin and various growth factors. The intracellular domain is the catalytic site of tyrosine protein kinase and owns autophosphorylation sites.



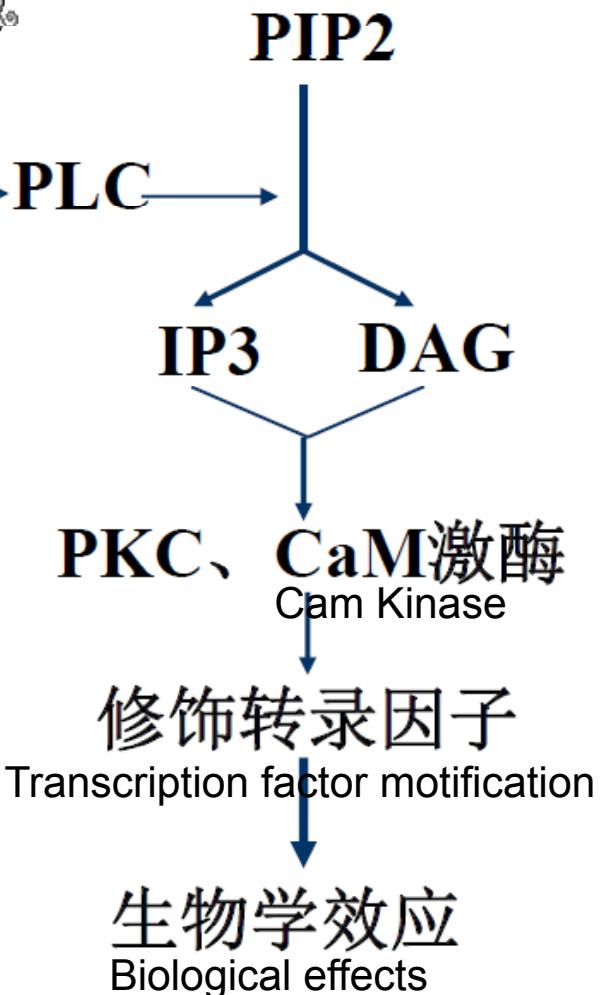
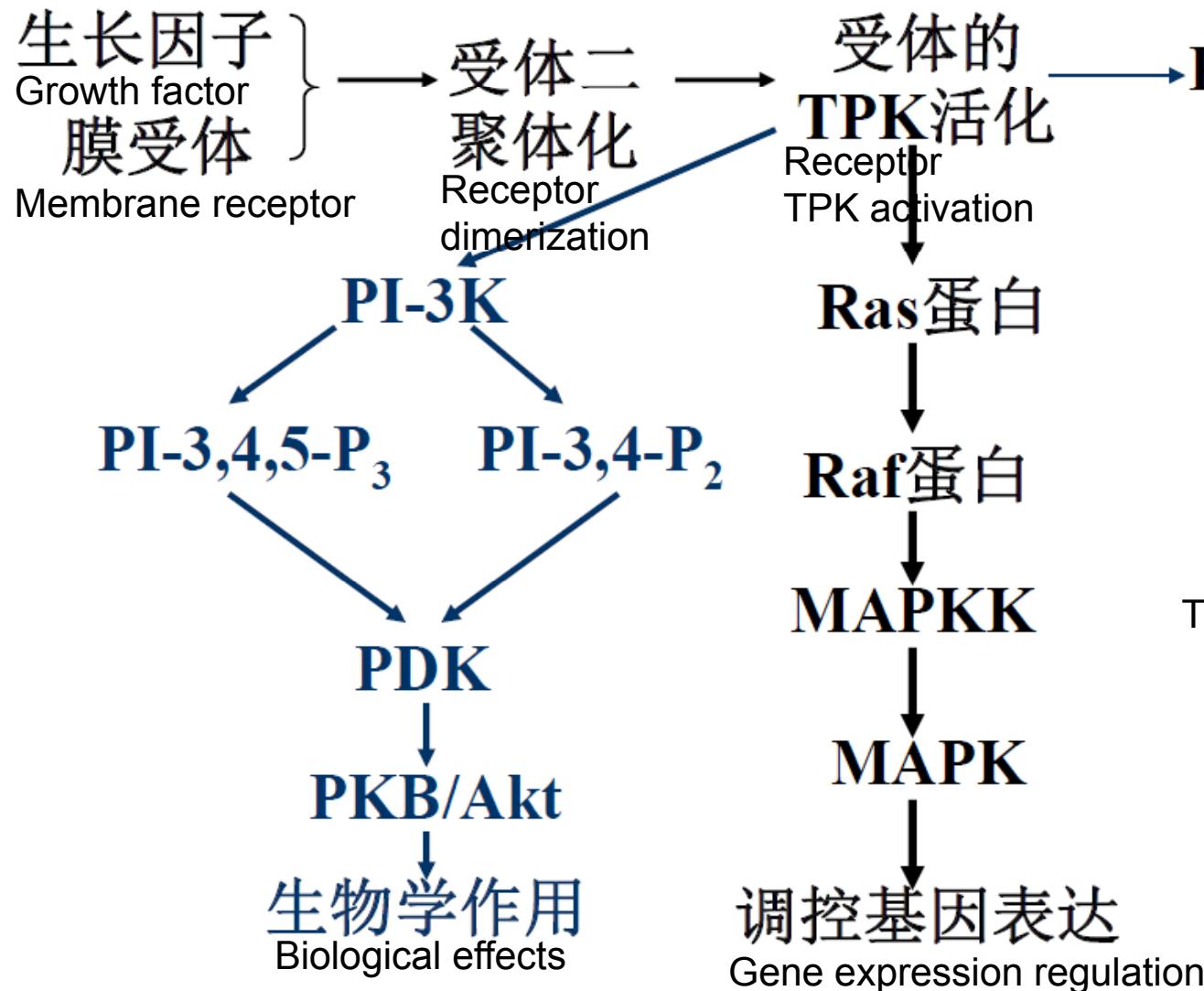
配体（如EGF）在胞外与受体结合并引起构象变化，导致受体二聚化形成同源或异源二聚体，在二聚体内彼此相互磷酸化胞内段酪氨酸残基，激活受体本身的酪氨酸蛋白激酶活性，二聚体的细胞内结构域装配成一个信号转导复合物。

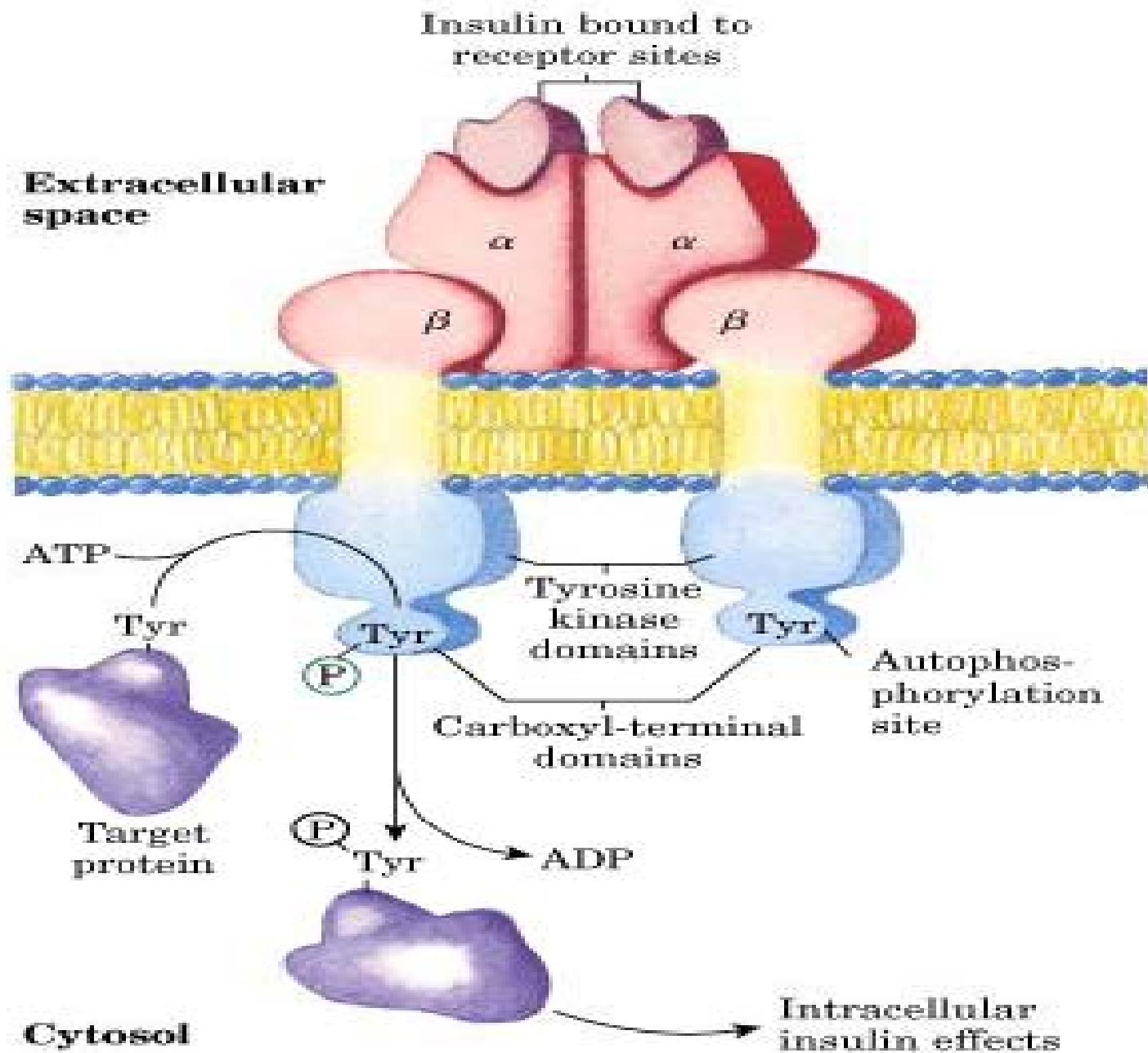
The ligand (such as EGF) binds to the receptor in the extracellular domain and triggers conformational changes, leading to receptor dimerization and formation of a homodimer or heterodimer and causing autophosphorylation in the intracellular tyrosine residues ,thus activating their tyrosine protein kinase activity. The intracellular domains of the dimer form a signal transduction complex.



# 1、受体型TPK-Ras-MAPK途径

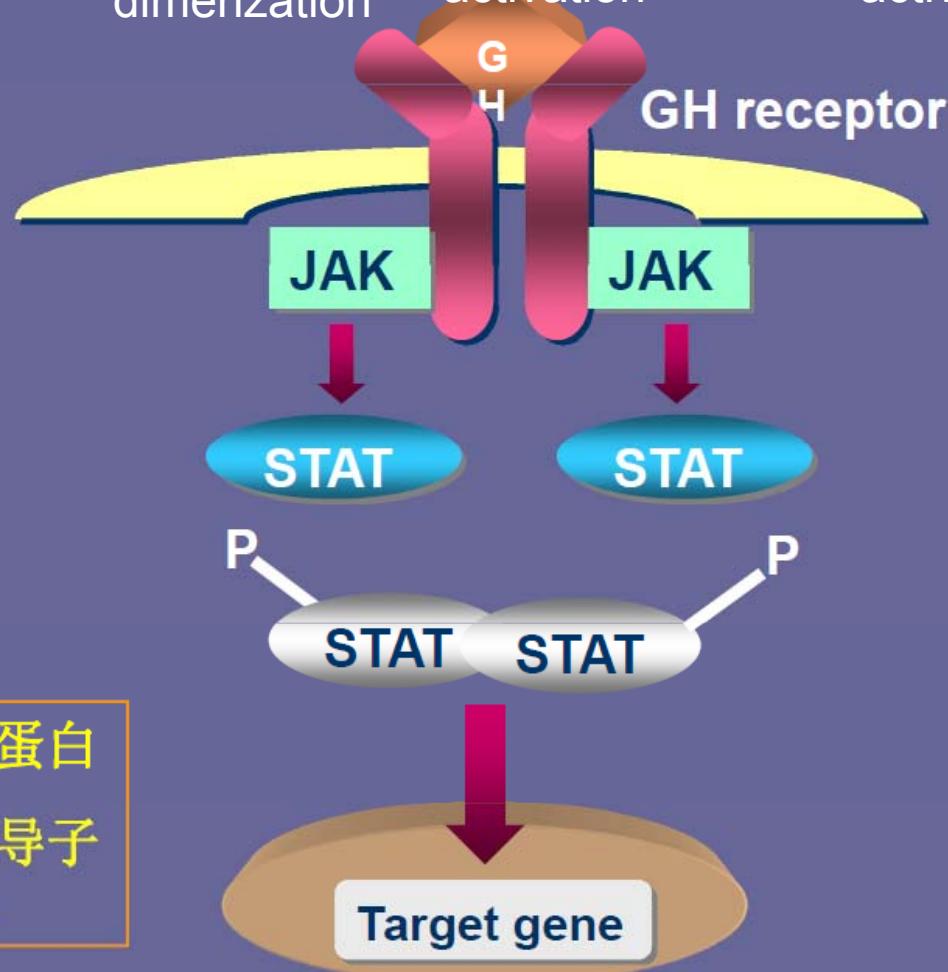
Receptor TPK-Ras-MAPK pathway





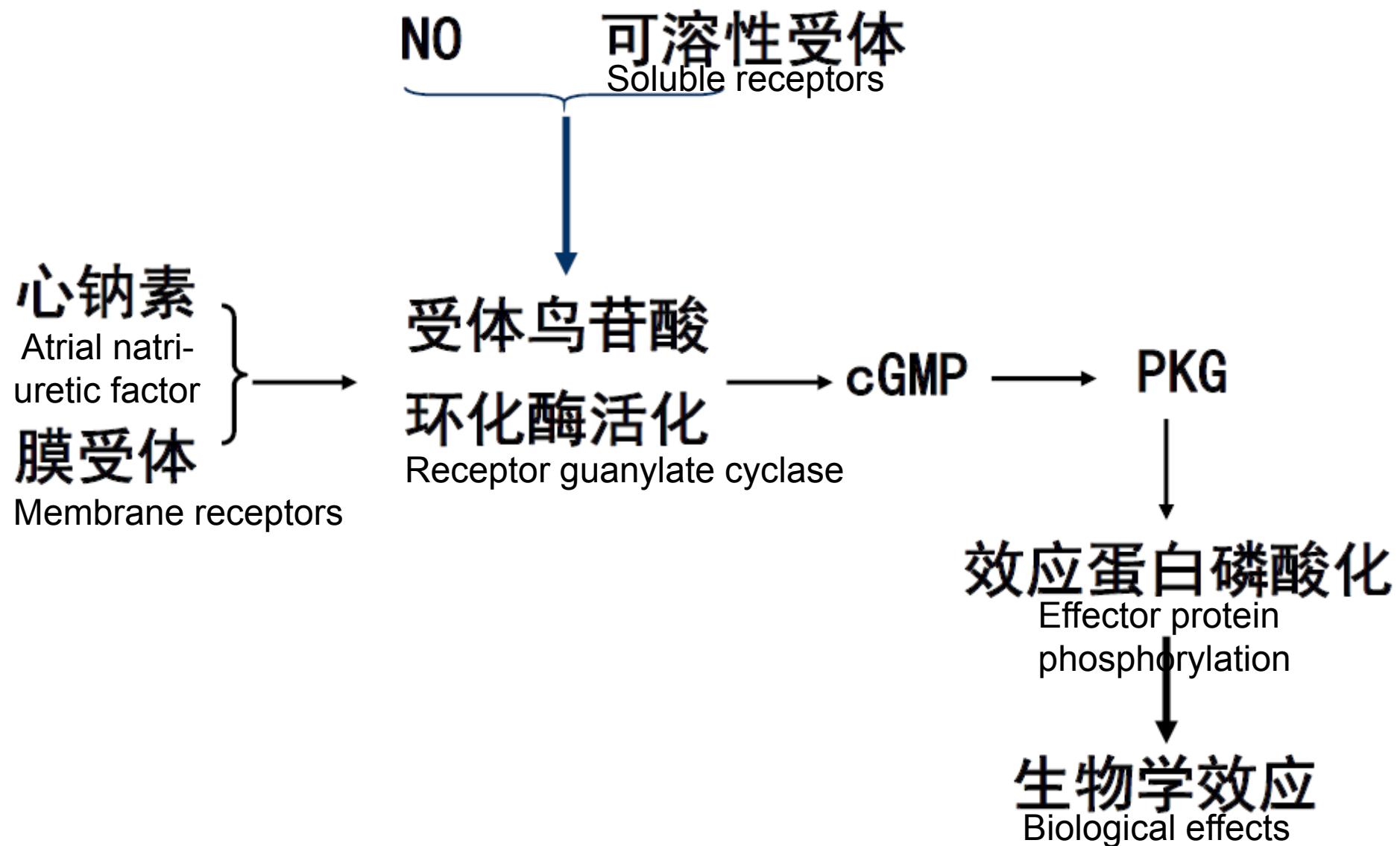
## 2、JAKs/STAT途径

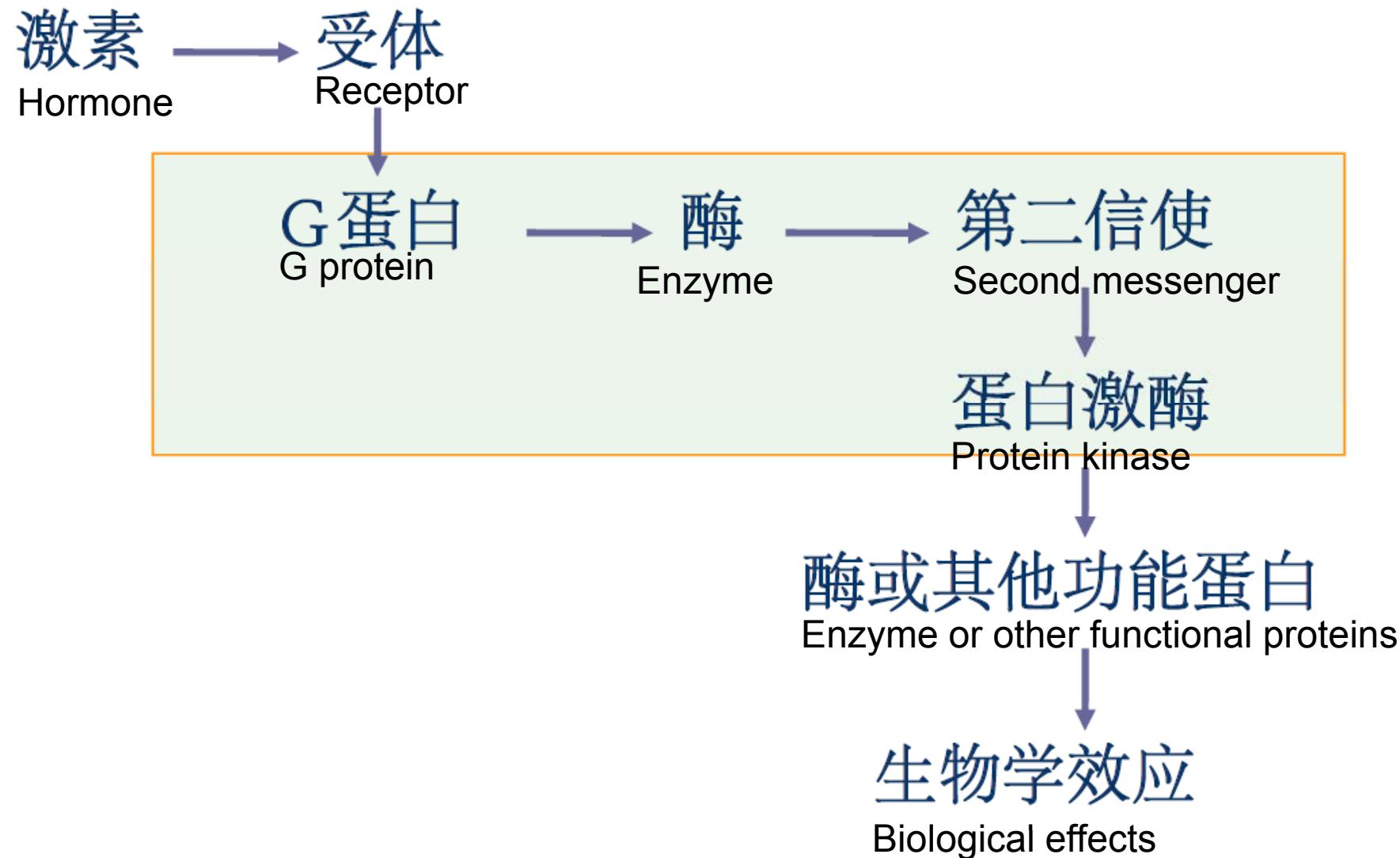
JAKs/STAT pathway



JAK: 连接物蛋白

STAT: 信号转导子  
和转录激动子





## 四、离子通道受体介导的信号转导

### **Ion channel receptor-mediated signal transduction**

离子通道型受体是一类自身为离子通道的受体，离子通道的开放和关闭，称为门控(gating)。

**Ion channel receptors are a type of receptors also functioning as ion channels. The opening and closing of a channel is called gating.**

根据门控机制的不同，将离子通道主要分为三大类：(1)化学门控通道，(2)电压门控通道，(3)机械门控通道，这3种通道蛋白质使不同细胞对外界相应的刺激起反应，完成跨膜信号转导。

**Ion channels are classified into 3 types according to gating mechanisms: (1)chemically gated channels (2)voltage-gated channels (3) mechanically-gated channels. These 3 types of channel proteins enable different cells to react to environmental stimulations and conduct transmembrane signal transductions.**

离子通道受体介导的信号转导的特点：不需要产生其它的细胞内信使分子，信号转导的速度快，对外界作用出现反应的位点较局限。

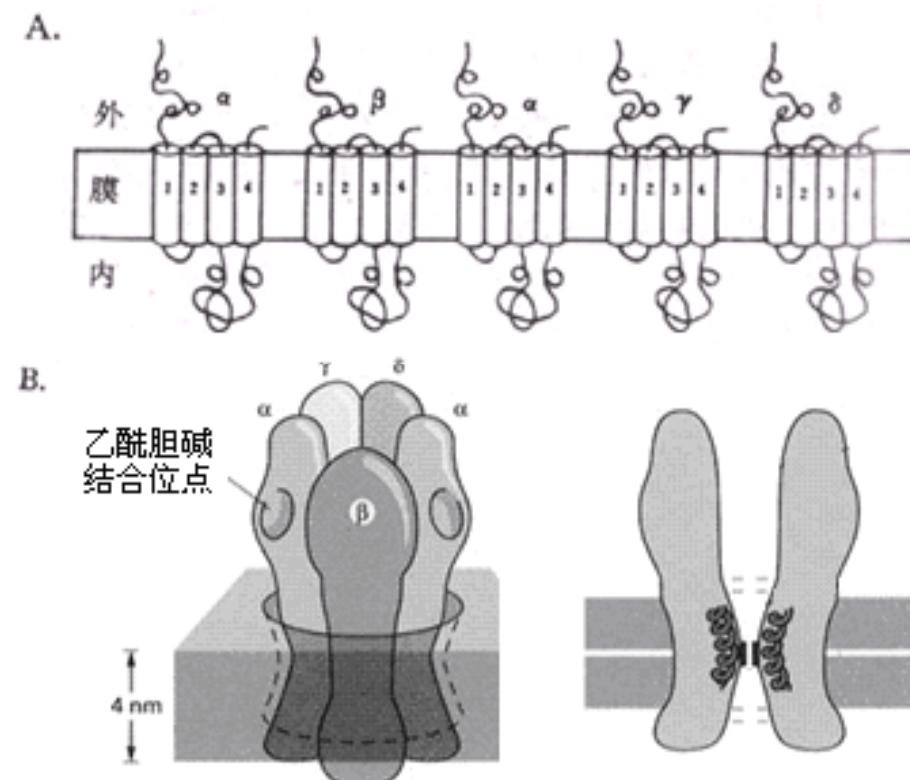
**Ion channel receptor-mediated signal transduction doesn't need to generate other intracellular messengers and are quick and site-limited.**

# (一) 化学门控通道 Chemically-gated ion channel

化学门控通道又称配体门控性离子通道: 由某些化学物质控制其开或关的通道称, 以递质受体命名, 如乙酰胆碱受体通道、谷氨酸受体通道、门冬氨酸受体通道等。Chemically-gated ion channels are also called ligand-gated ion channels and are named by corresponding transmitters such as acetylcholine receptor channels, glutamine receptor channels and aspartate receptor channels.

N2型Ach受体阳离子通道是由4种不同的亚单位组成的5聚体蛋白质, 形成一种结构为 $\alpha_2\beta\gamma\delta$ 的梅花状通道样结构; 每个亚单位的肽链都要反复贯穿膜4次; 在5个亚单位中, Ach的结合位点在 $\alpha$ 亚单位上, 结合后可引起通道结构的开放, 然后靠相应离子的易化扩散而完成跨膜信号转导。

N2 Ach receptor cation channels are made of 5 subunits of 4 types, forming a  $\alpha_2\beta\gamma\delta$  pentagon shaped channel . Every subunit passes through the membrane 4 times; Ach binding site is located in the  $\alpha$  subunit and its binding forces the channel to open and facilitated diffusion of the ions helps to finish the signal transduction process.



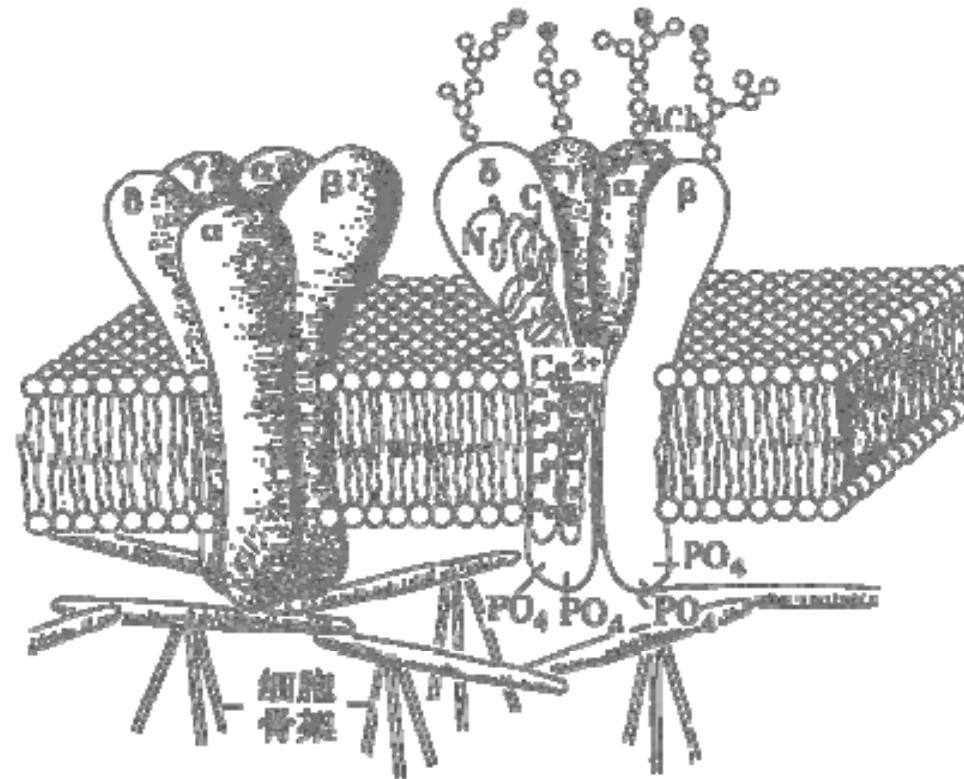


图 5-5  $N_2$  烟碱受体

5个亚基各含约450个氨基酸,此5个肽链形成一个跨膜的环,在细胞内固定于细胞骨架上,每一肽链跨膜4次,N端和C端都位于胞外部(如δ亚单位侧面所示)。

肽链在胞外被糖基化,在胞内被磷酸化,导致受体脱敏,2个α单位各有1个ACh结合位点,二者都结合1分子ACh后,钠通道即开放,细胞除极兴奋

## (二) 电压门控通道 Voltage-gated ion channels

电压门控通道又称电压依赖性或电压敏感性离子通道:因膜电位变化而开启和关闭, 以最容易通过的离子命名, 如 $K^+$ 、 $Na^+$ 、 $Ca^{2+}$ 、 $Cl^-$ 通道4种主要类型, 各类型又分若干亚型。

Voltage-gated ion channels are also called voltage-dependent or voltage-sensitive ion channels, and they open and close depending on the changes of the membrane potential and are named after the ions passing through most easily such as  $K^+$ 、 $Na^+$ 、 $Ca^{2+}$ 、 $Cl^-$  channels and they are further divided into several subtypes.

分子结构与化学门控通道类似, 但分子结构中存在一些对跨膜电位的改变敏感的结构域或亚单位, 诱发整个通道分子功能状态的改变。

Their molecular structure is similar to chemical channels but there are some domains sensitive to transmembrane potential changes and triggers the changes of the whole channel.

## (三) 机械门控通道 Mechanically-gated channels

机械门控通道又称机械敏感性离子通道:是一类感受细胞膜表面应力变化, 实现胞外机械信号向胞内转导的通道, 根据通透性分为离子选择性和非离子选择性通道, 根据功能作用分为张力激活型和张力失活型离子通道。

Mechanically-gated channels are also called mechanosensitive channels and they are a type of channels sensing variation of superficial cellular membrane stresses and thus transduce extracellular mechanical signals to intracellular signals. They are classified to ion-selective and non-selective channels by permeability and to stretch-activated and stretch-inactivated channels by function.

## 二、胞浆/核内受体及其信息传递



Cytosolic and intranuclear receptors and their signal transduction

Intranuclear receptors

胞内受体

配体进入细胞  
Ligands enter cells

配体 - 受体复合物  
Ligand-receptor complex

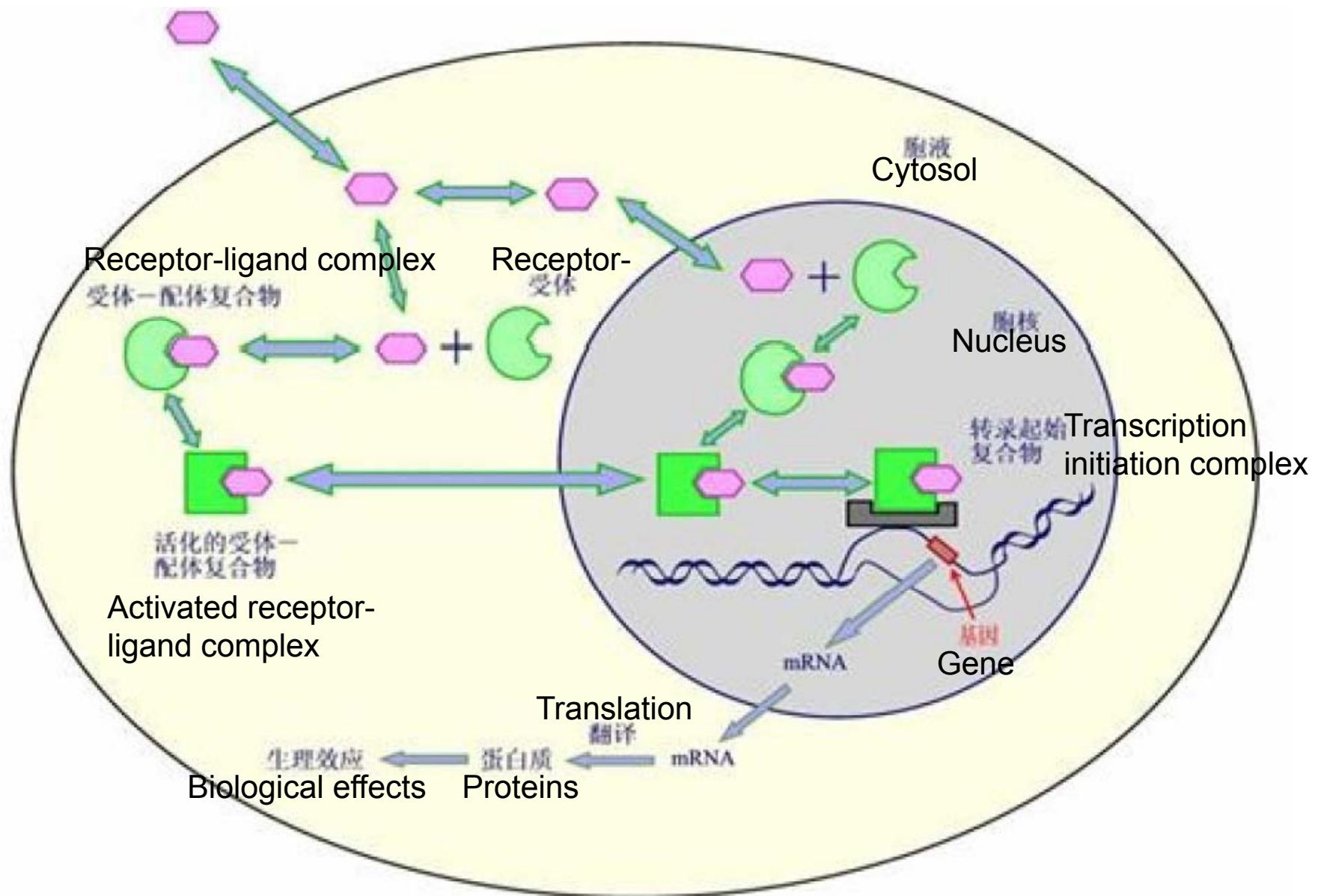
配体 - 受体二聚体化  
Ligand-receptor dimerization

Bind to intranuclear hormone response elements

与核内的激素反应元件结合

调节基因表达  
Gene expression regulation



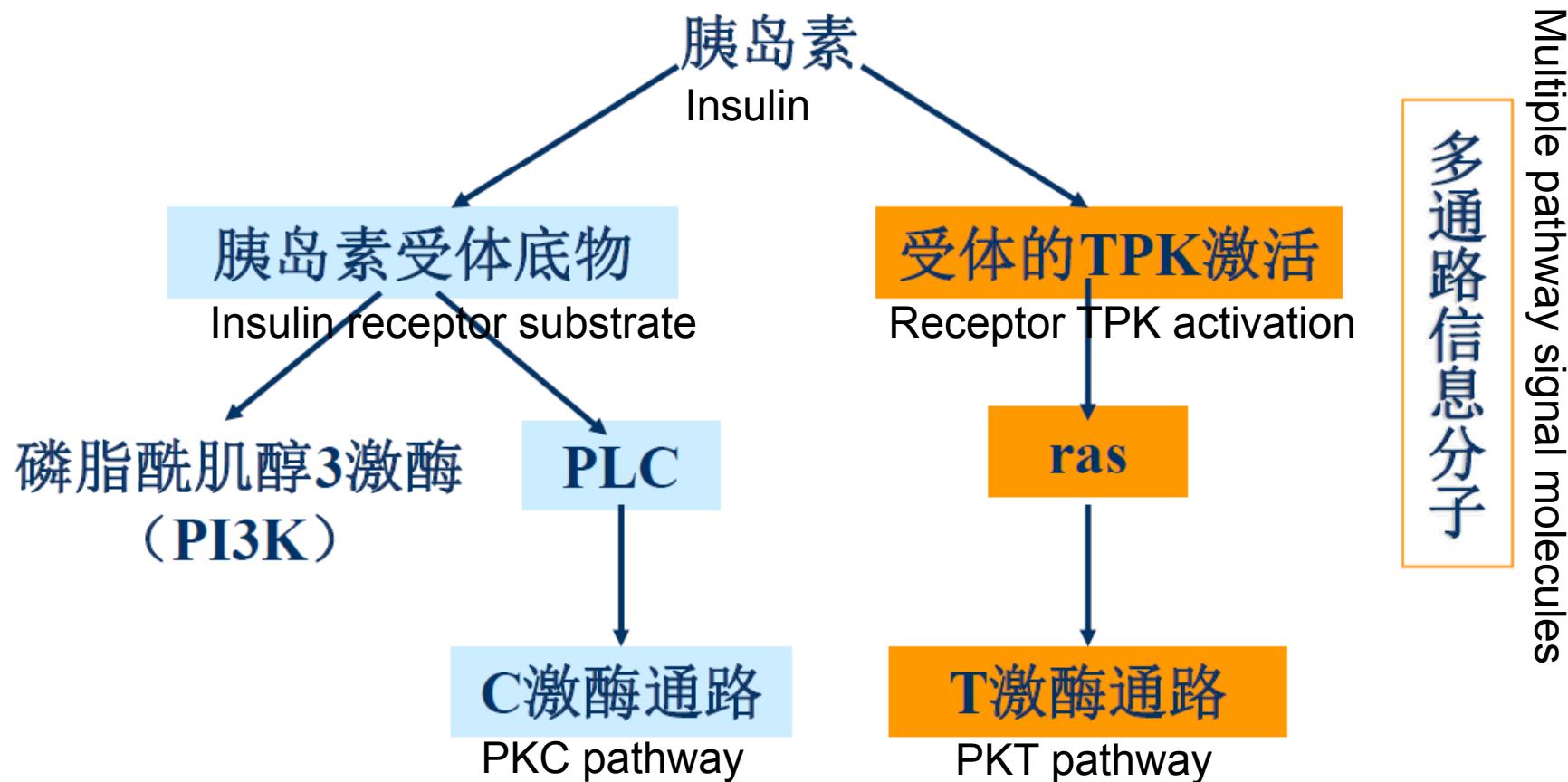


# 细胞信号传递途径之间的联系

Crosstalk of cellular signal transduction pathways

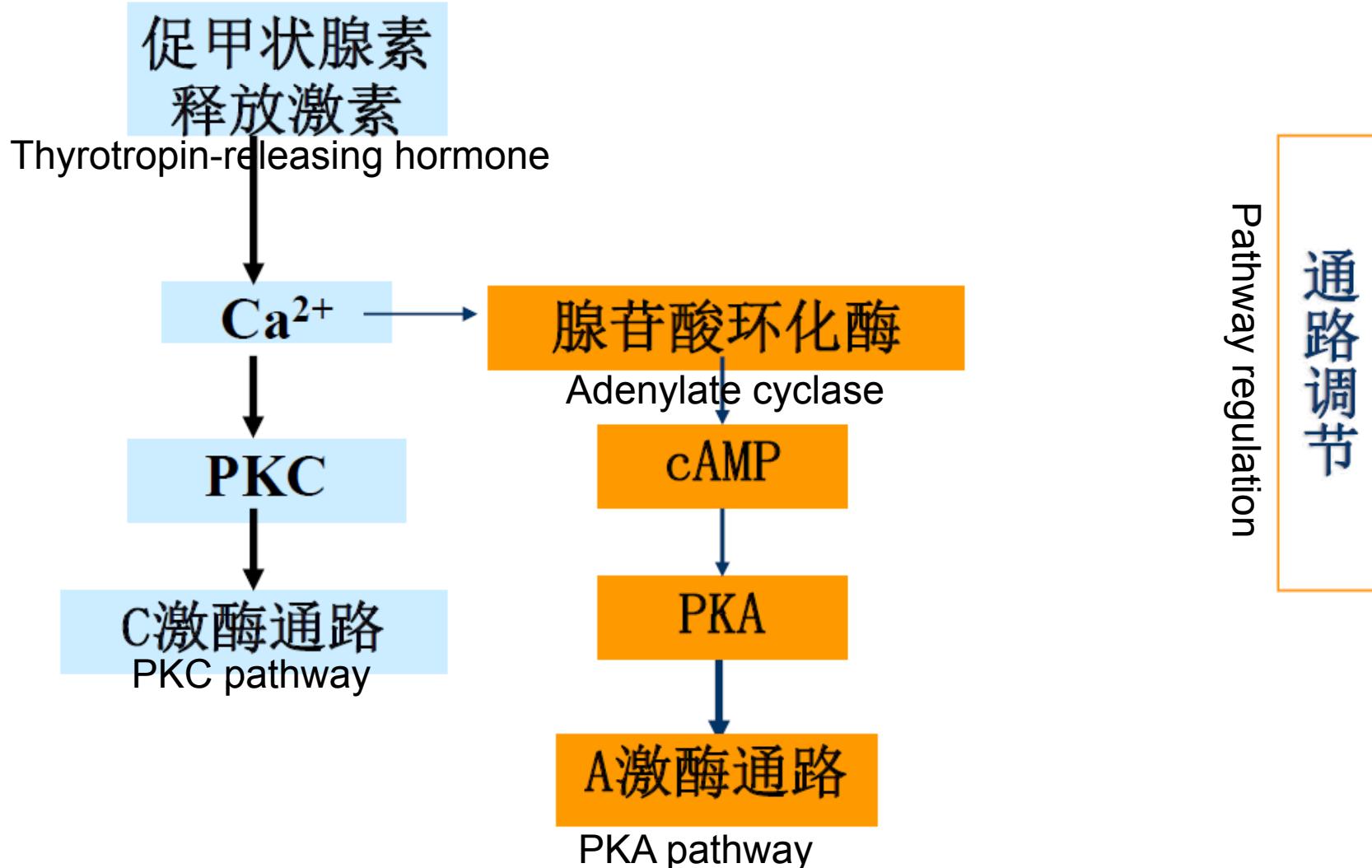
## 一、一种信息作用多条通路

Single piece of information acts on multiple pathways



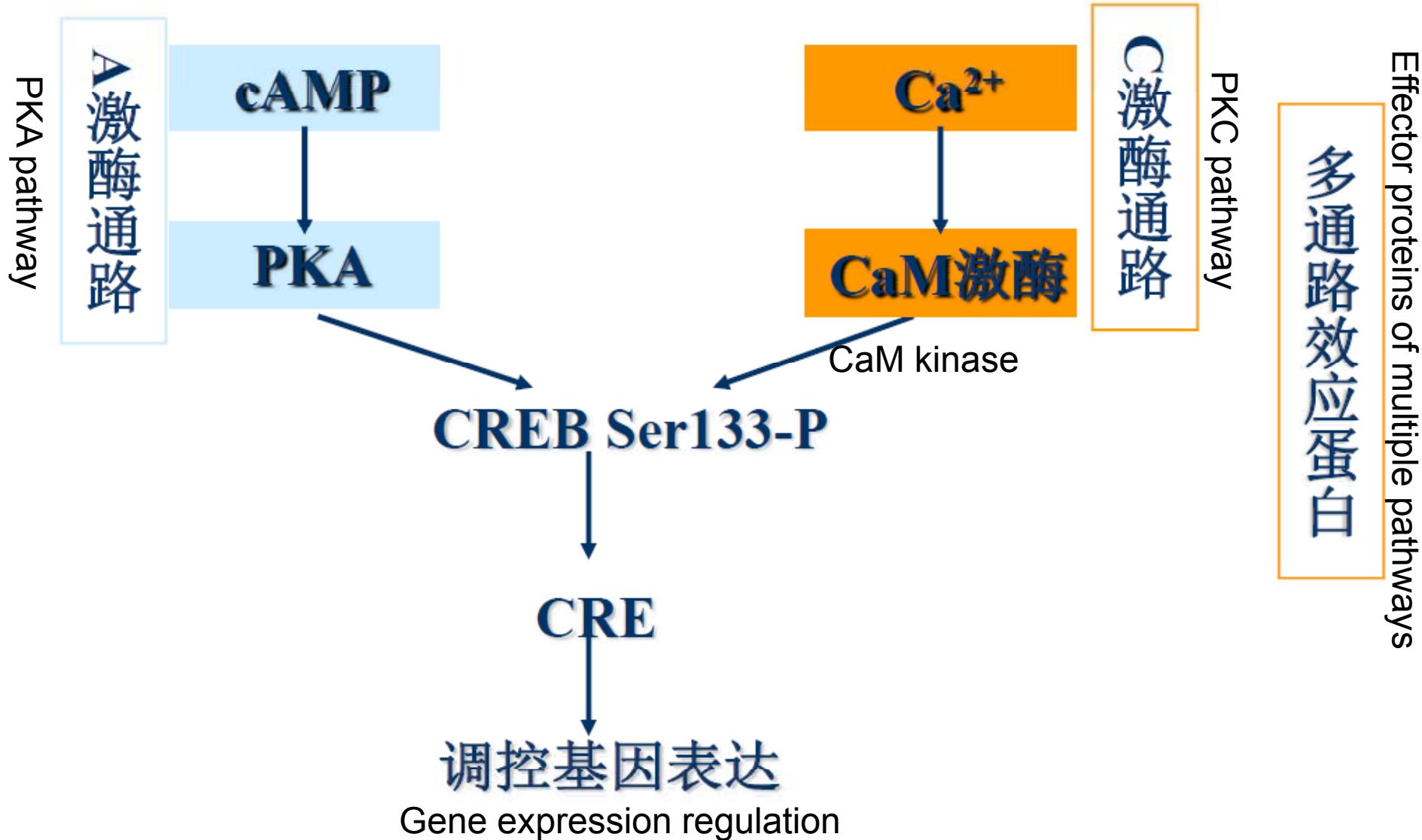
## 二、一种通路的组分调节另一条通路

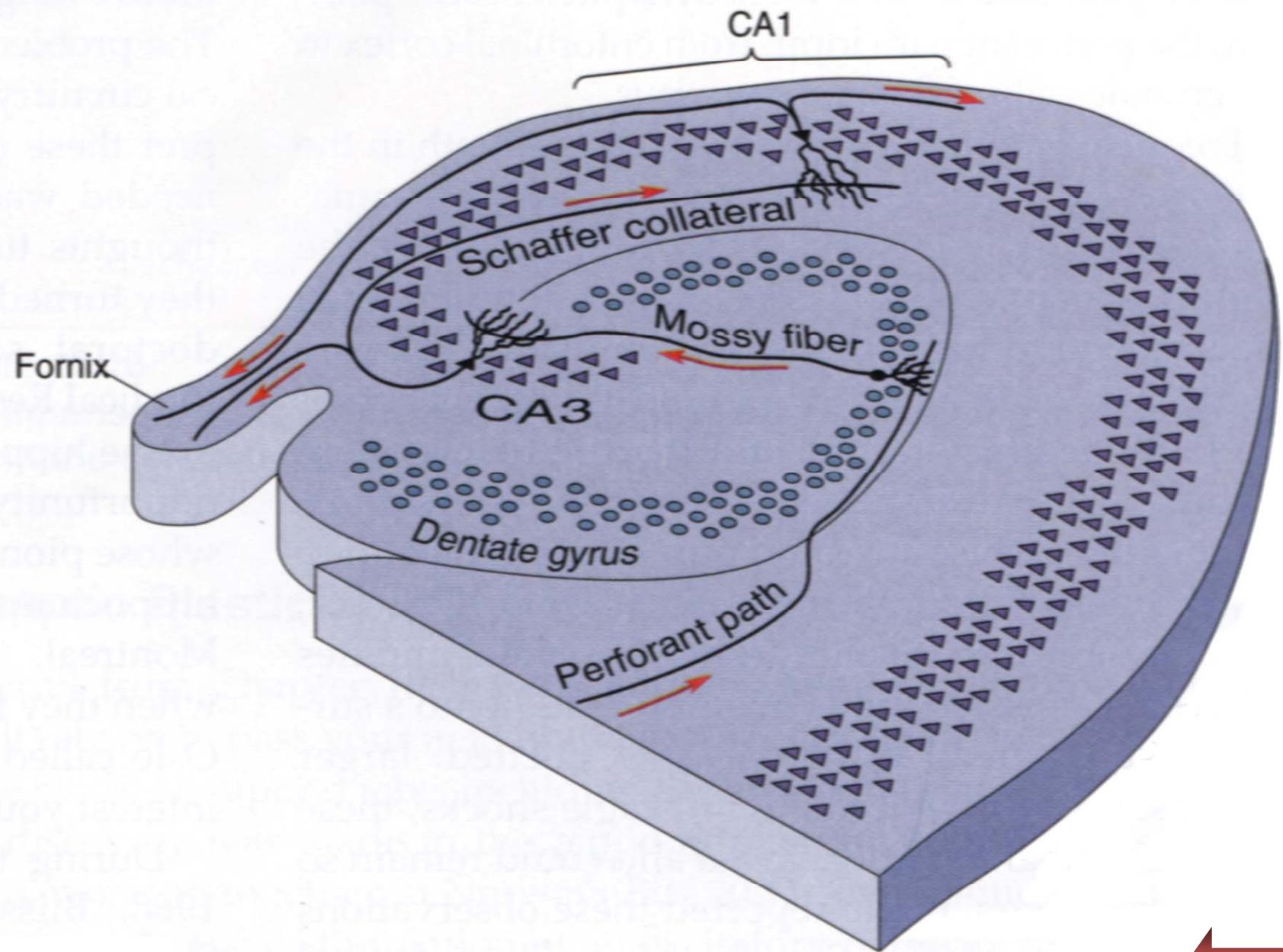
Components of a single pathway regulates another pathway



### 三、不同通路调节同一蛋白

Distinctive pathways regulates the same protein





- LTP产生的必要条件

**Requirements of LTP generation**

Activation of synapse

Strong depolarization of postsynaptic cell in CA1

- 引起突触后神经元去极化的条件

**Requirements to trigger depolarization of the postsynaptic neuron**

As high as enough frequency—EPSP temporal summation

As many as enough synapse—EPSP spatial summation

- 诱导CA1 LTP产生的突触后因素

**Postsynaptic factors to trigger CA1 LTP**

postsynaptic depolarization

activation of NMDA receptors

influx of  $\text{Ca}^{2+}$

activation by  $\text{Ca}^{2+}$  of several second-messenger systems in the postsynaptic cell

## LTP Has a Transient Early and a Consolidated Late Phase

LTP有瞬时早期和巩固后期

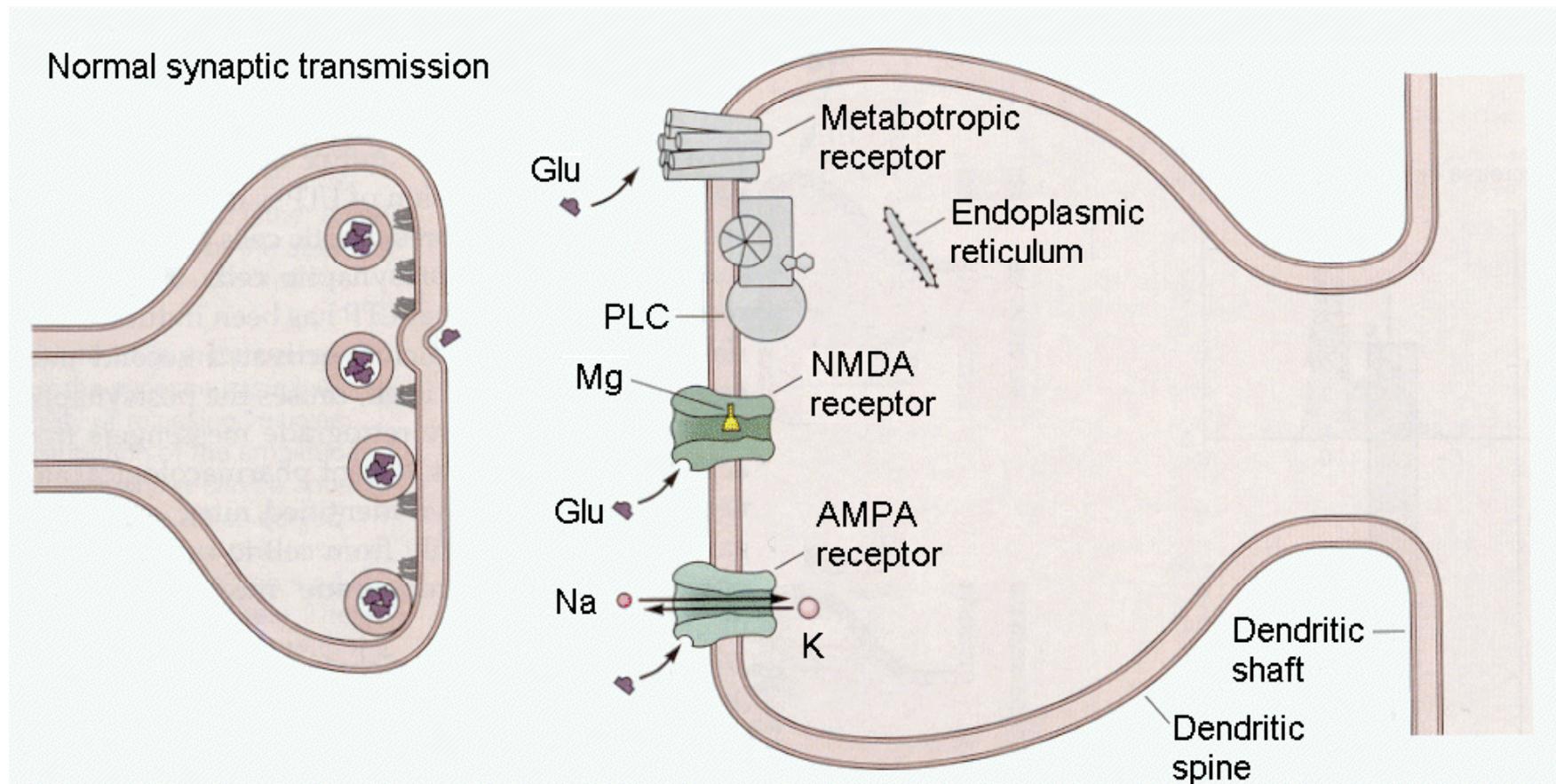
**Early LTP**-- one stimulus train produces an early, short term phase of LTP, lasting 1-3 hours-No new protein synthesis

早期LTP——一个刺激队列产生早期、短暂的LTP，持续1-3小时，没有新蛋白合成。

**Late LTP**-- Four or more trains induce a more persistent phase of LTP that lasts at least 24 hours—requires new protein and RNA synthesis

后期LTP——4或更多个队列诱发一个更稳固时期的LTP，持续至少24小时，需新蛋白质和RNA合成。

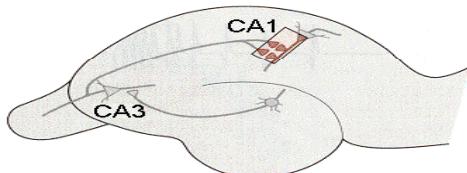
# Control 控制



(Kandel, ER, JH Schwartz and TM Jessell (2000)  
*Principles of Neural Science*. New York: McGraw-Hill.)

# Early and late phases of LTP

## 早/后期LTP



The late phase 后期

Presynaptic site: activation ,perhaps the growth,  
of additional machinery for transmitter  
release

突触前: 激活, 可能生长, 有额外的递质释  
放机制

Postsynaptic site: insertion of new clusters of  
receptors

突触后: 新受体簇插入

The early phase 早期

Presynaptic site: increase in probability of  
transmitter release, without structure  
changes.

: 递质释放可能性增加, 没有结构

aptic site:

:  
ynaptic depolarization

后去极化  
ation of NMDA receptors

A受体激活  
: of calcium  
流

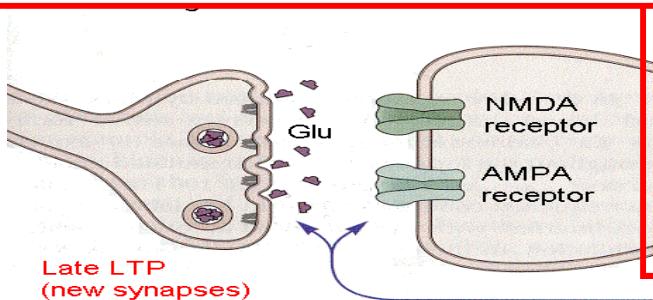
ation of several second messenger

systems by calcium

几种第二信使系统被钙激活

Increase the sensitivity and number of the  
postsynaptic AMPA receptors

增加突触后AMPA受体的敏感性和数量



(Kandel, ER, JH Schwartz and TM Jessell (2000)  
*Principles of Neural Science*. New York: McGraw-Hill.)

# Mechanisms of Early LTP 早期LTP机制

Single train → depolarization of the membrane of postsynaptic cell

单个队列→突触后细胞膜去极化

Remove the blockage of  $Mg^{2+}$  to NMDA receptor  
 $Mg^{2+}$  对NMDA受体的阻塞移除

$Ca^{2+}$  influx in postsynaptic cell → activation of protein kinases  
突触后细胞 $Ca^{2+}$ 内流→蛋白激酶的激活

Activity changes of AMPA receptor  
AMPA受体活性变化

Retrograde signal generator  
逆行信号发生器

NO?

Glu is released from presynaptic cell  
突触前细胞释放谷氨酸

Influx of  $Na^+$   
 $Na^+$ 内流

AMPA receptor  
AMPA受体

NMDA receptor  
NMDA受体

# Mechanisms of Late LTP 后期LTP机制

Repeated trains → depolarization of the membrane of postsynaptic cell

重复队列→突触后细胞膜去极化

Remove the blockage of  $Mg^{2+}$  to NMDA receptor  
 $Mg^{2+}$  对NMDA受体的阻塞移除

$Ca^{2+}$  influx in postsynaptic cell →  $Ca^{2+}/calmodulin$   
突触后细胞 $Ca^{2+}$ 内流 →  $Ca^{2+}/$ 钙调蛋白

Adenylyl cyclase 腺苷酸环化酶 → cAMP → cAMP kinase activation  
cAMP激酶激活

MAP kinase MAP激酶

New synapse  
新突触

Effectors  
效应器  
(tPA, BDNF)

Regulators  
调节器  
(C/EBP $\beta$ )

PCREB-1

Regulators  
调节器  
(C/EBP $\beta$ )

CRE

# Molecular mechanism of learning and memory

## 学习记忆的分子基础

- cAMP

海兔缩鳃反射的习惯化和敏化过程中cAMP的作用是关键性的

cAMP信号通路在LTP的蛋白合成依赖性时相中起关键性作用

cAMP plays a key role in the habituation and sensitization of the gill-withdraw reflex of sea slug aplysia.

cAMP signaling pathway is crucial in protein-synthesis dependent phase of LTP

- 蛋白激酶

CaMKII的持续活化对LTP的诱导及维持起重要作用

The permanent activation of CaMKII is critical in induction and maintenance of LTP

PKA在长时敏化中起重要作用

PKA is critical in long-term sensitization

- CREB

影响长时记忆

Impact on long-term memories

## 调控基因表达

Gene expression regulation

cAMP activate protein

kinase A, which

phosphorylate CREB

(CRE binding protein )

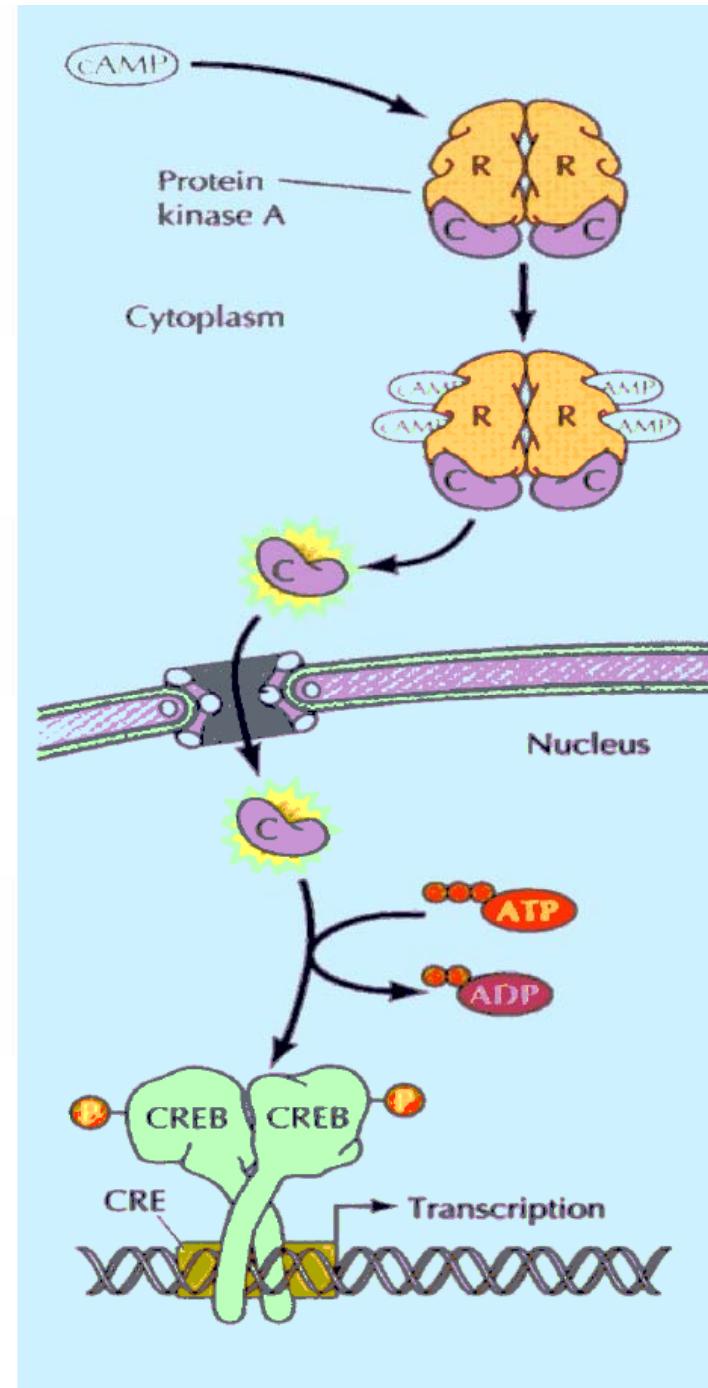
protein and initiate gene

transcription.

**CRE is cAMP response  
element in DNA.**

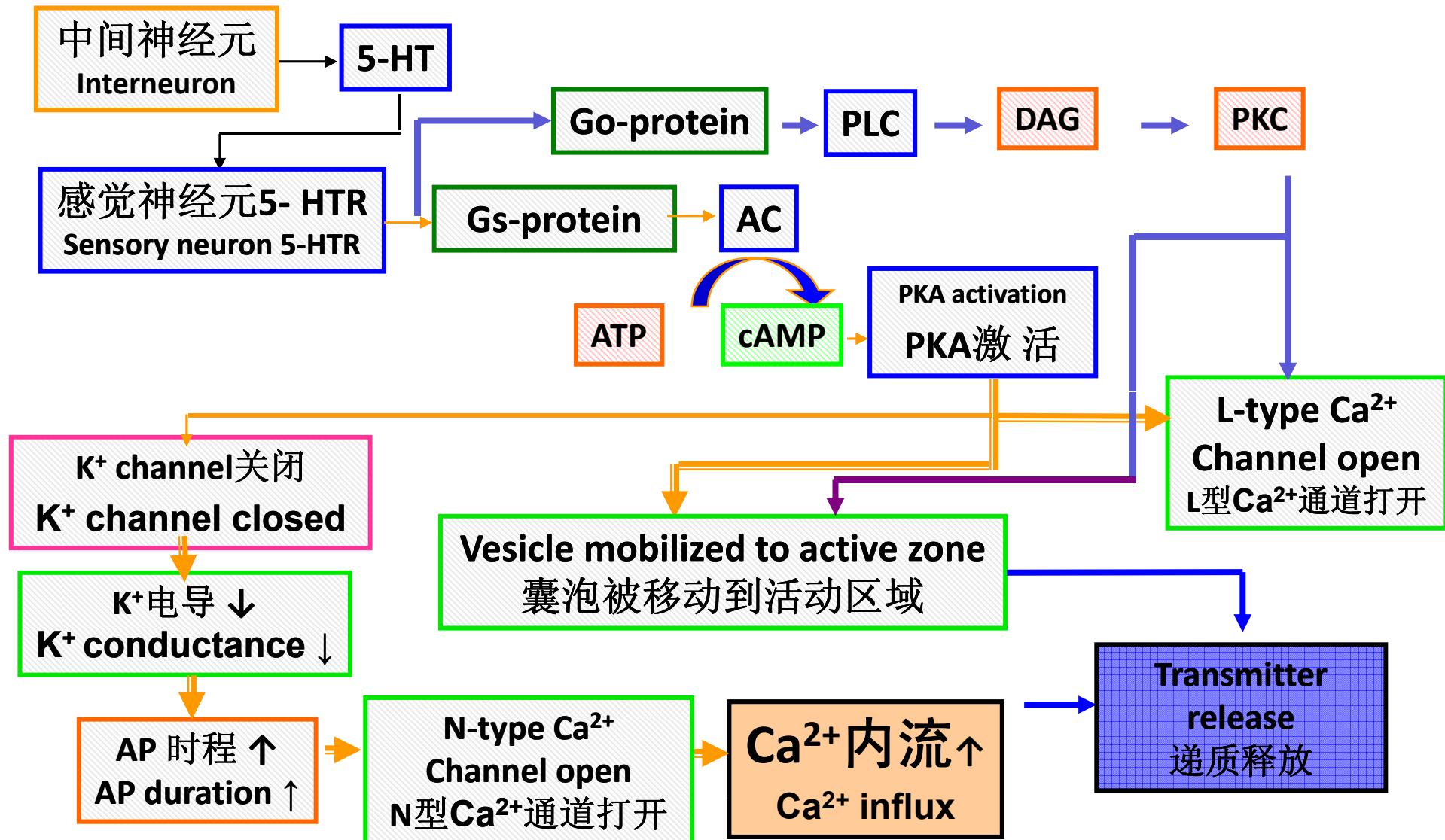
cAMP活性蛋白激酶A磷酸化  
CREB (CRE结合蛋白), 起始基因  
转录。

CRE是DNA中cAMP的响应元件。



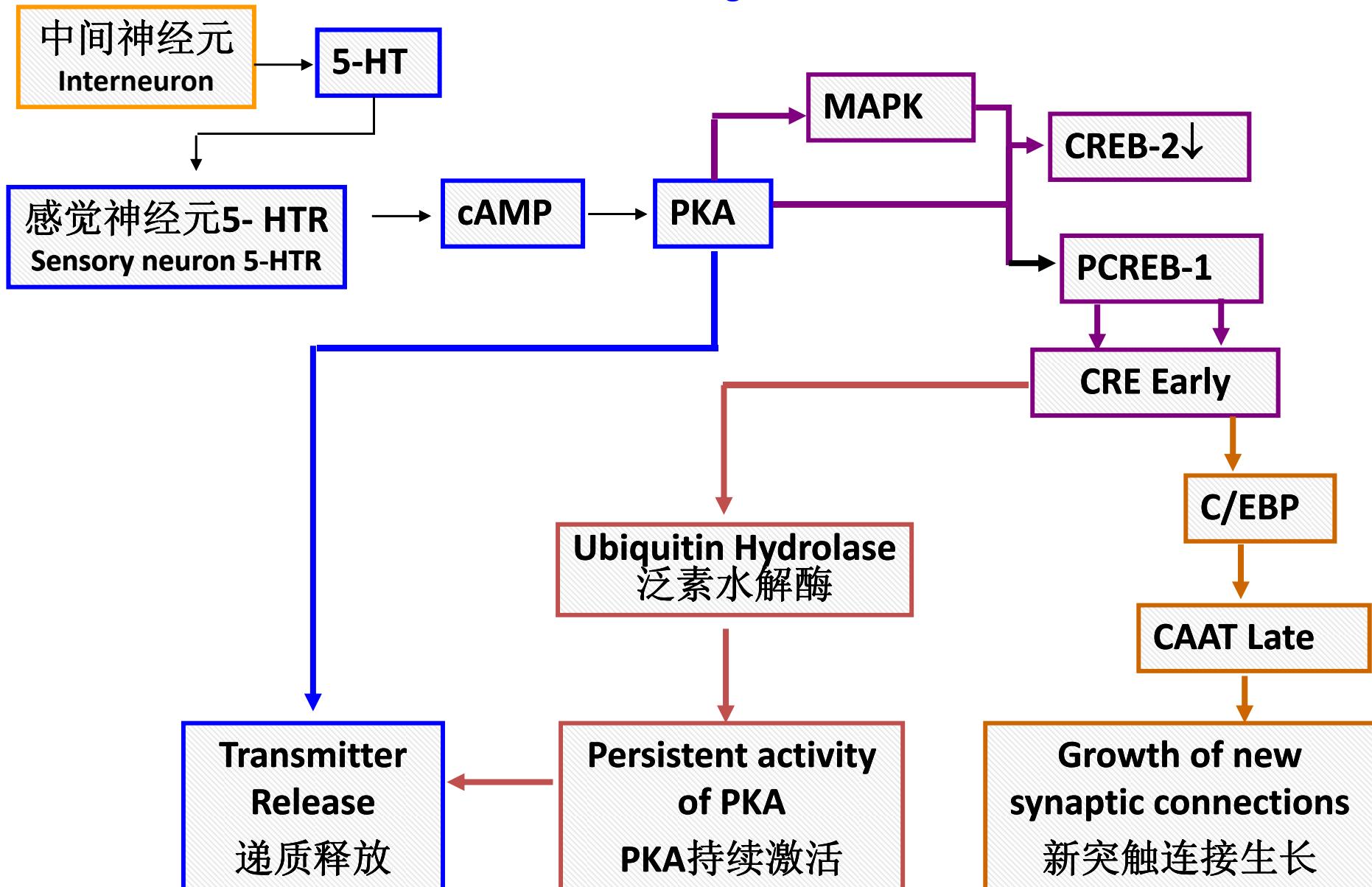
# 敏化的机制

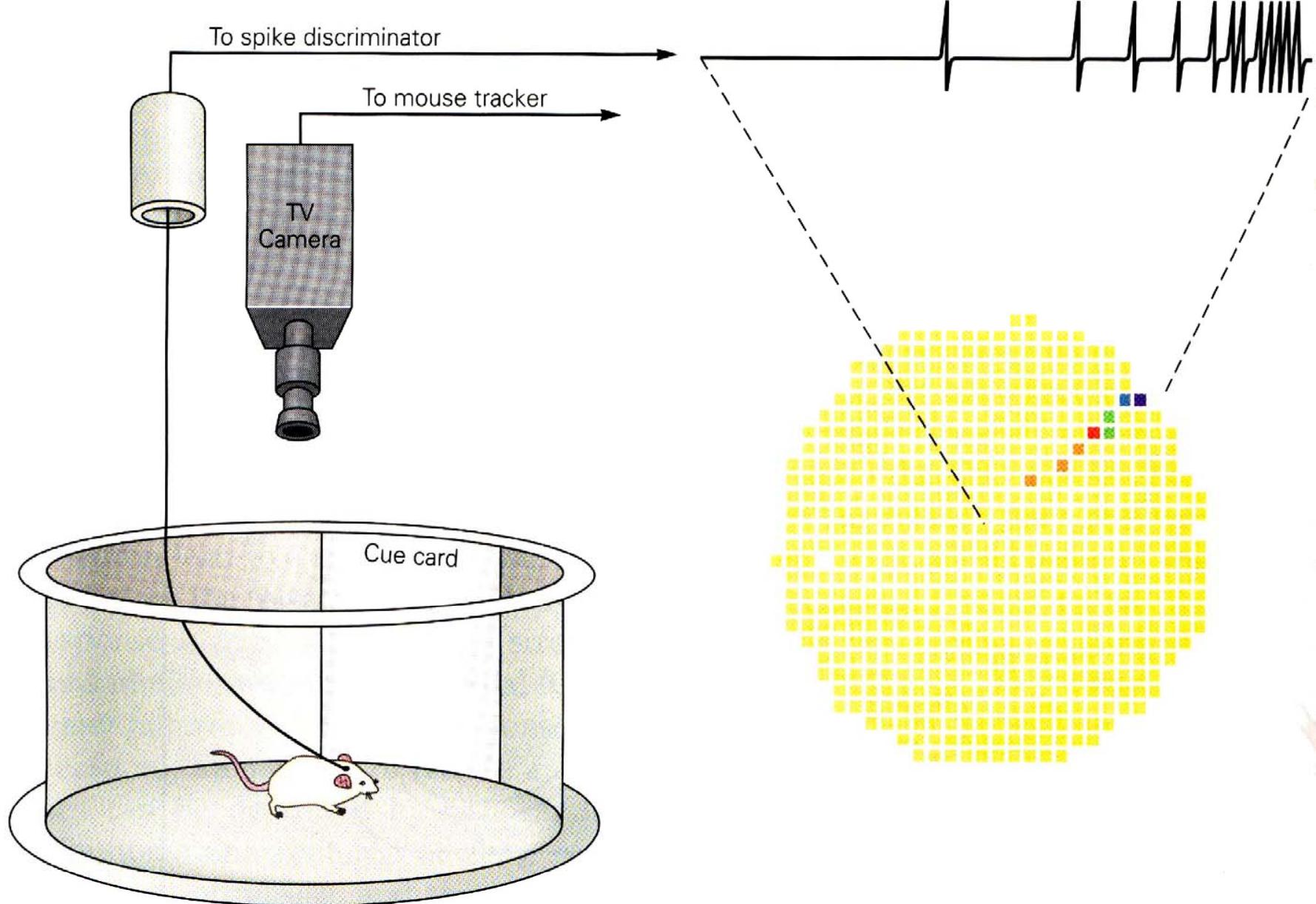
## Mechanisms of Short Term Sensitization



# 参与长时敏化的分子链

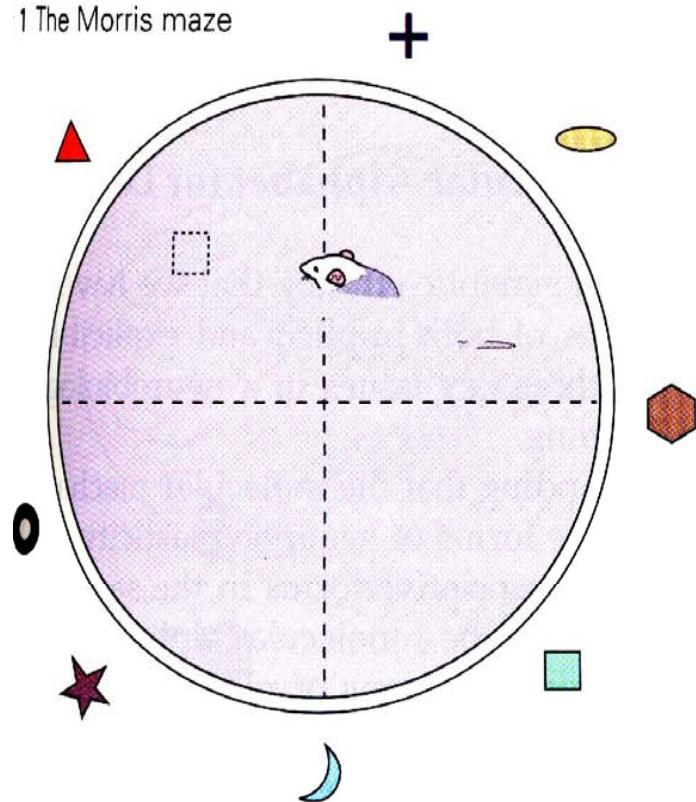
Molecules involved in long Term Sensitization



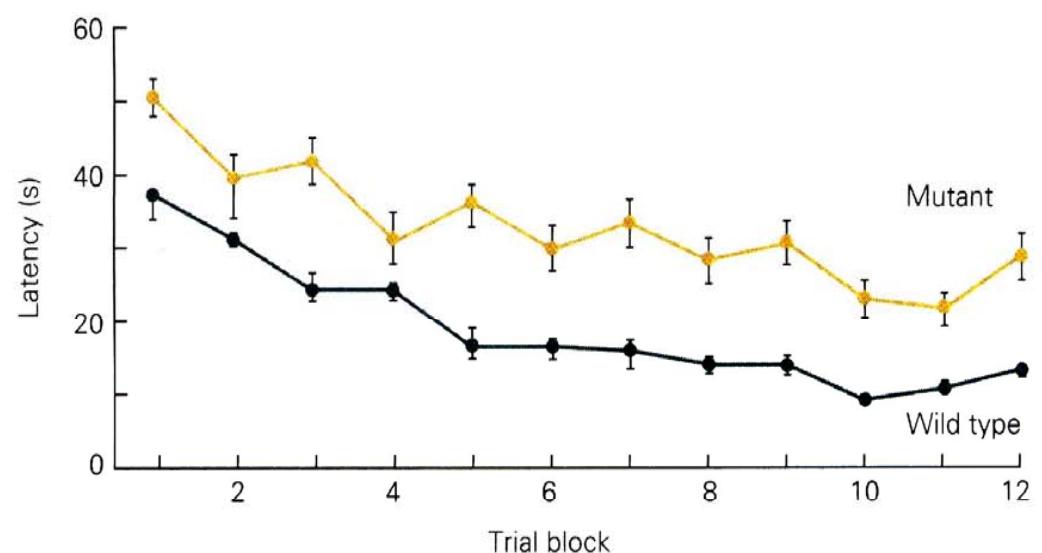


**B Spatial memory defects**

1 The Morris maze

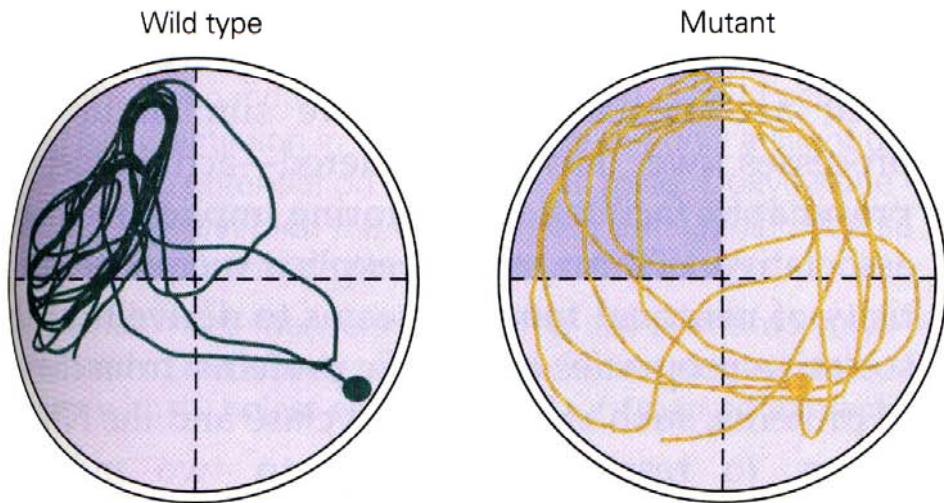


2 Escape latencies



### 3 Transfer test of Morris maze

#### a Movement patterns



#### b Search time

