Overview of Receptor

Receptor

- Receptors are protein molecules, embedded in either the plasma membrane (cell surface receptors) or the cytoplasm or nucleus (nuclear receptors) of a cell, to which one or more specific kinds of signaling molecules may attach. A molecule which binds (attaches) to a receptor is called a ligand, and may be a peptide (short protein) or other small molecule, such as a neurotransmitter, a hormone, a pharmaceutical drug, or a toxin. Through binding to a receptor, these signals direct a cell to do something—for example to divide or die, or to allow certain molecules to enter or exit.

受体的概念

- 定位：细胞膜或细胞内；
- 性质：蛋白质单体、同多聚体或异多聚体，有配体结合域和转导信号的功能域；
- 作用：特异识别并结合信息分子；将信息分子携带的信号转变成细胞的反应，引起生物学效应

Defining a Receptor

1.Specificity – a receptor must be able to distinguish between often closely-related signals.

2. High affinity – signals are often present in low concentrations – effective receptors can often detect nM to pM concentrations.

3. Saturability – a cell has a finite number of receptors and, thus there is a limit to the number of ligand molecules a cell can bind.

4. Reversibility – ligand-receptor association is not covalent – as the ligand concentration drops the complex can dissociate.

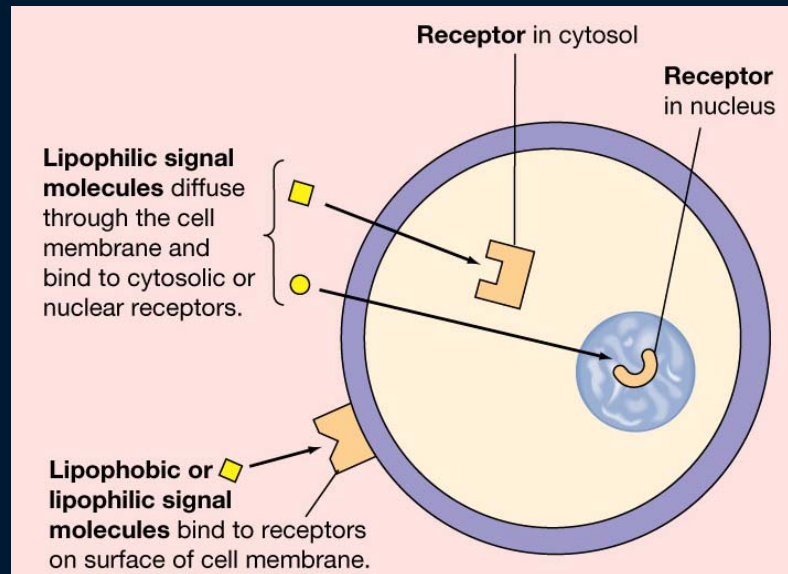
5. **Coupling** – the receptor transfers a signal from ligand to cell.

It is this last feature, more than any other that distinguishes a receptor from a binding protein .

Receptor Classes(by anatomy location)

- 分类
  - 解剖学定位
    - 细胞膜受体
      - 门控离子通道
      - 与G蛋白偶联
      - PTK连接
    - 细胞内受体
  - 药理学特性

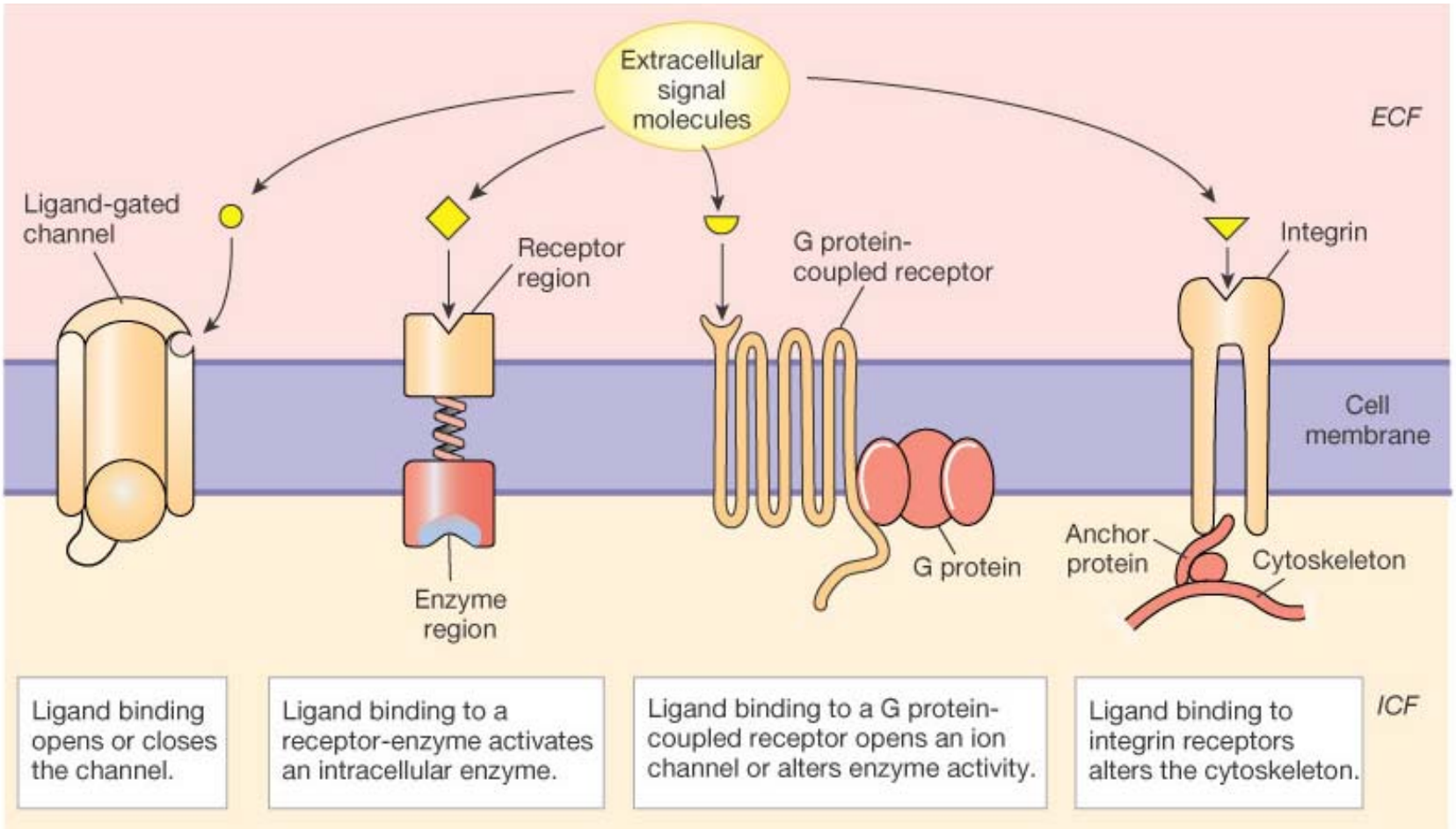
按受体跨膜信息转导机制



Membrane Receptor Classes(by transmembrane signal transduction)

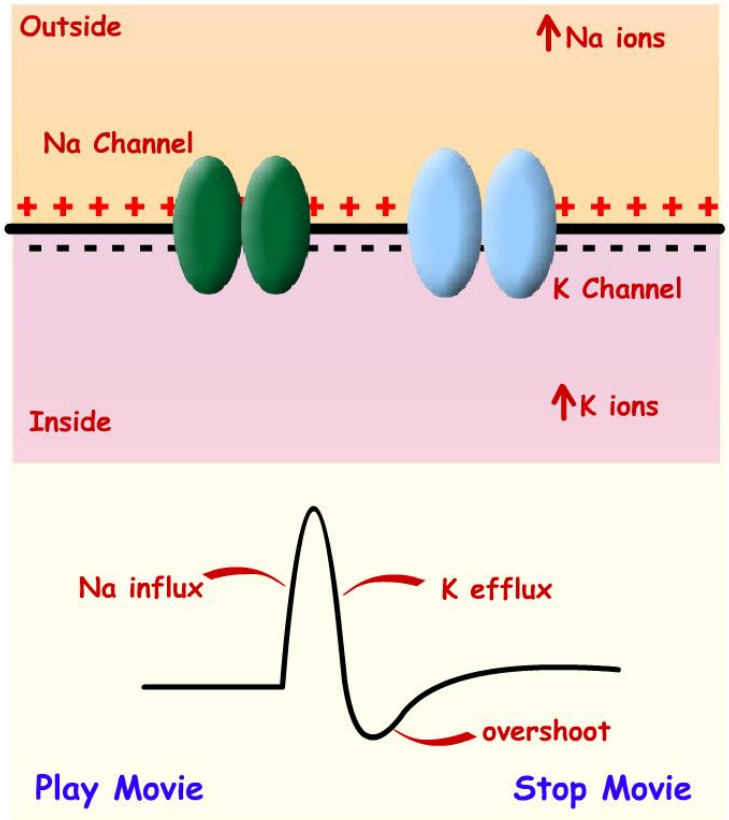
- **Ligand- gated channel**
- **G-protein-coupled**
- **Receptor enzymes**
- **Integrins**

Membrane Receptor Classes



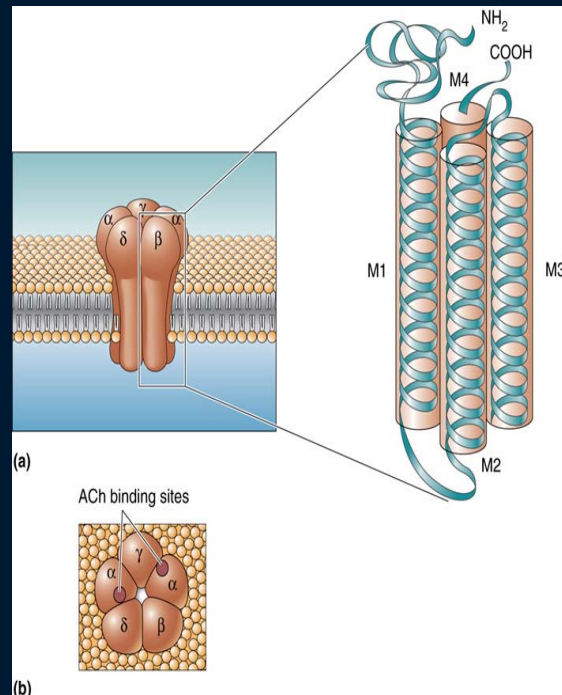
配体门控离子通道
Ligand- gated channel

Ion channels are signaling proteins



配体门控离子通道
Ligand- gated channel

- 是一类具有能与特异配体结合的离子通道所组成的受体，是由若干亚单位组成的寡聚体，当与配体结合后可导致离子通道开放，促进细胞内外离子的跨膜流动，产生去极化或超极化；通道对离子电荷的选择性取决于通道入口处氨基酸残基的特性。



为什么离子不能通过脂质双分子层而必须通过离子通道？

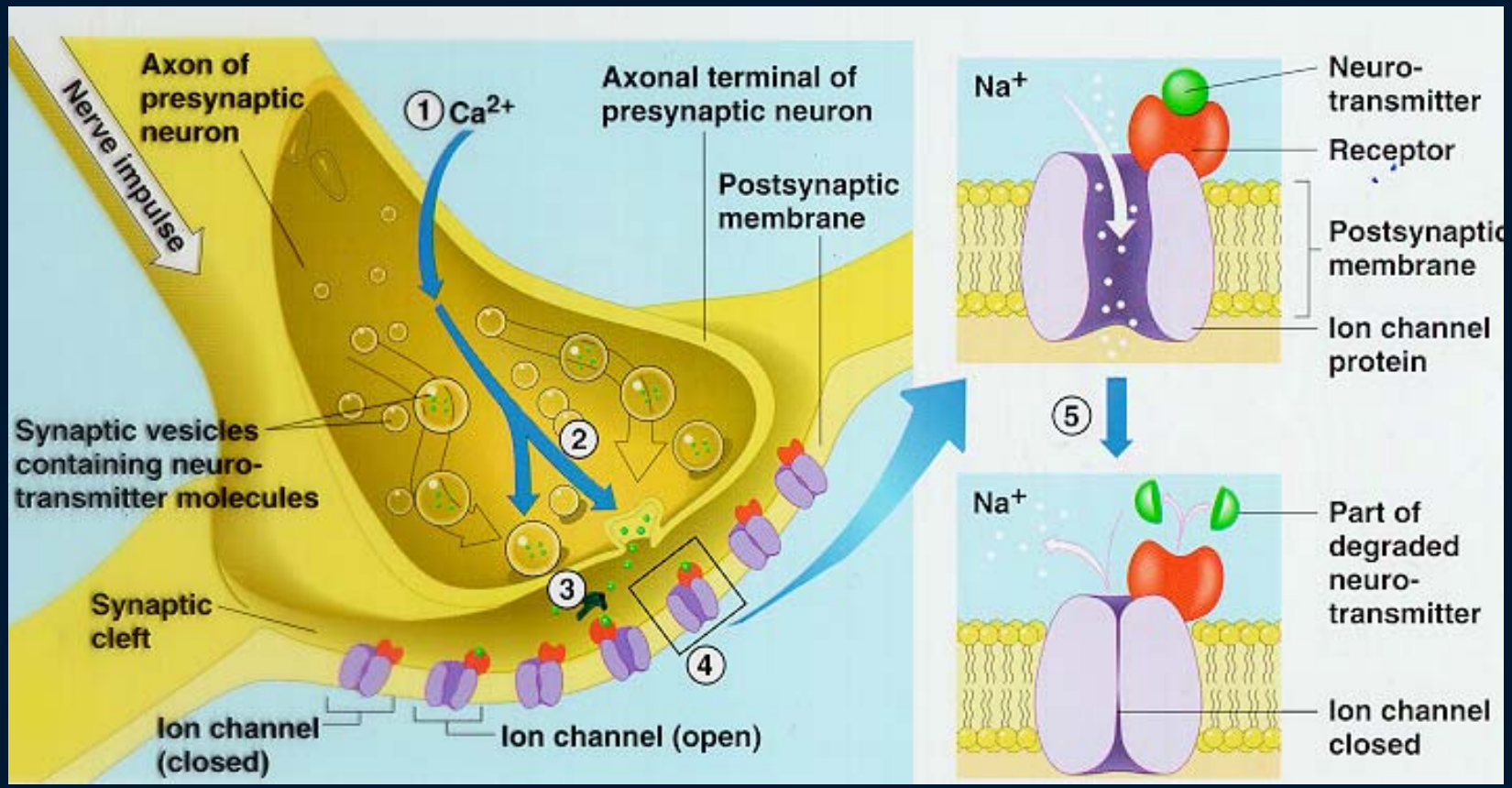
水分子是双极性分子，氧原子吸引电子带负电荷，氢原子趋向失去电子带正电荷。

水溶液是一种极性环境，阳离子吸引在氧原子上，阴离子吸引在氢原子上。离子与水相互吸引，离子被带静电的水包绕着，被水包绕着的离子与细胞膜中的疏水区是不相溶的不可能从膜中自由通过

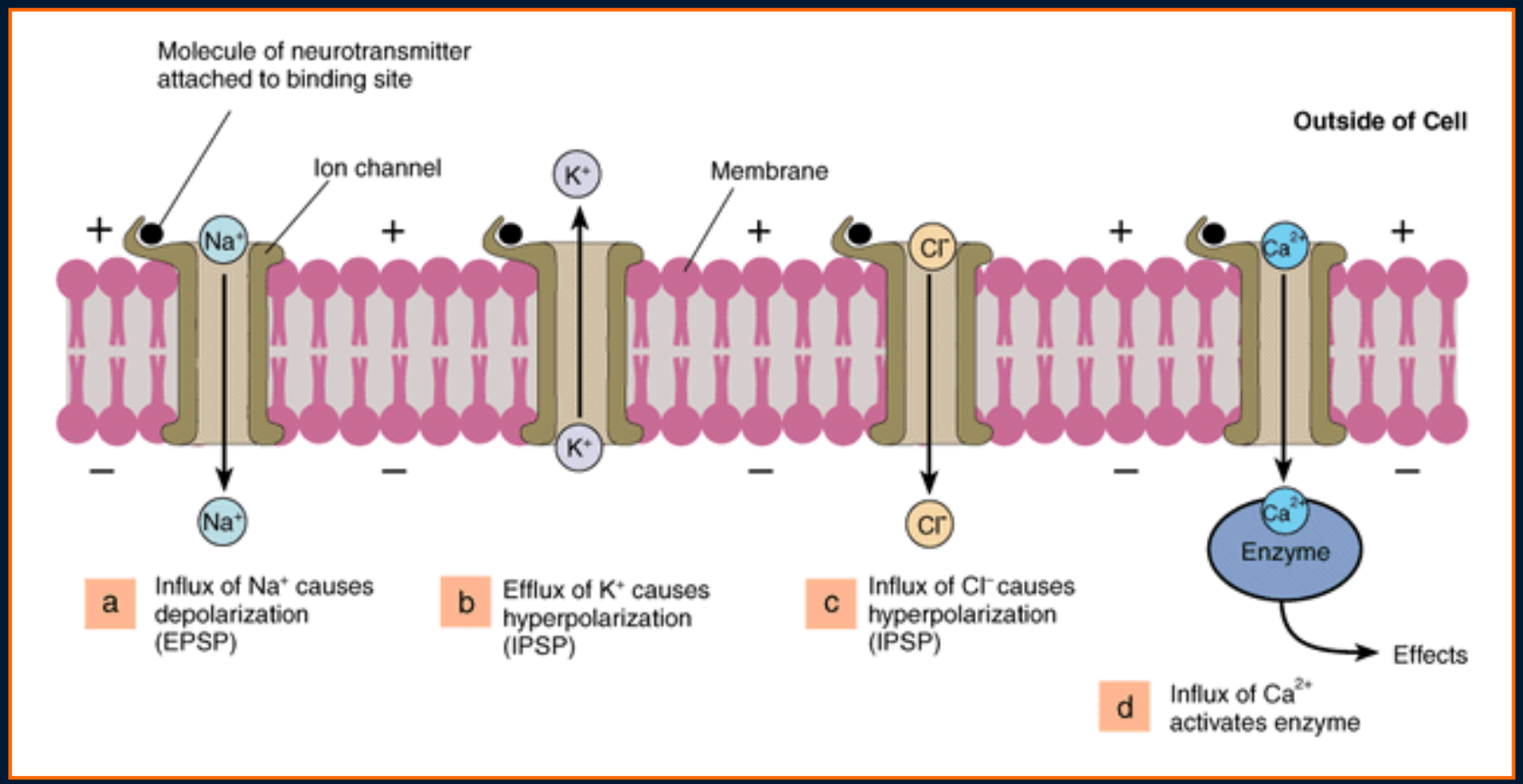
配体门控通道特性

- 受体与配体结合具有像酶一样的特异性
- 不同类型的通道具有不同的离子选择性

LGIC mediate fast synaptic transmission.

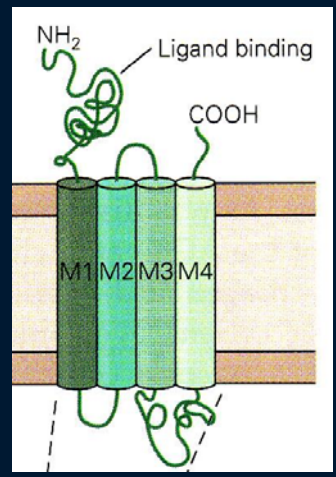


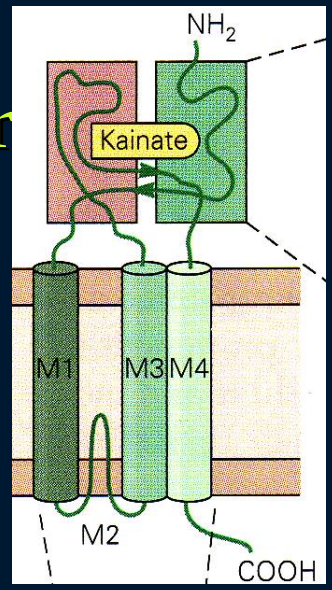
LGICs are responsible for changing a chemical signal in the synapse (neurotransmitter) to either an inhibitory or excitatory post synaptic potential in the post synaptic cell.

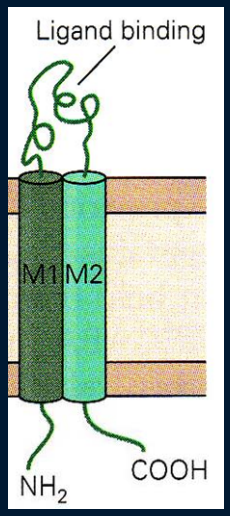


Families of Ligand-Gated Ion Channels

- Cys-loop receptors
  - Nicotinic Acetylcholine receptor
  - $GABA_A$ and $GABA_C$ Receptors
  - Glycine Receptor
  - $5\text{-}HT_3$ Receptor
- Ionotrophic Glutamate Receptor
  - NMDA
  - AMPA
  - Kainate
- P2X Receptors







Kandel, Schwartz & Jessel, *Principles of Neural Science* 4th Ed. (2000)

Cystine-Loop Superfamily of Ligand-Gated Ion Channels

Cystine-Loop Superfamily of Ligand-Gated Ion Channels

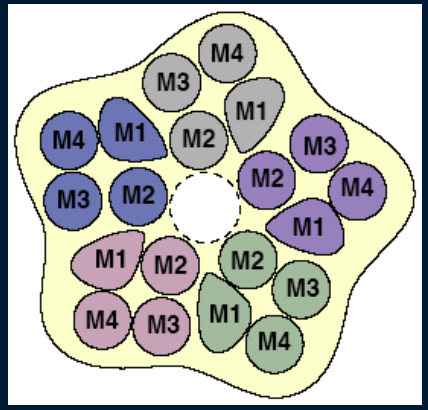
Heteromeric or homomeric pentamers （异质性或同源五聚体）

Characterized by a large N-terminal loop cross-linked by cystine bridges

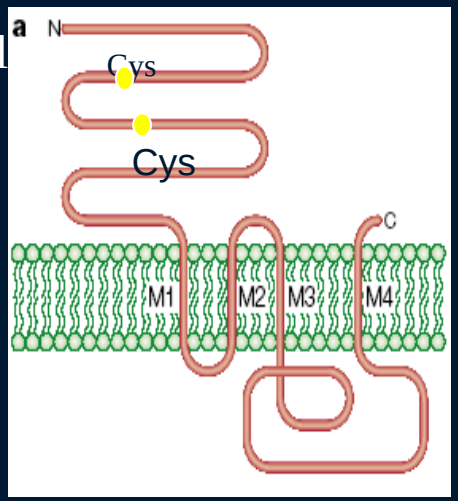
Each subunit is made up of 4 membrane spanning helices （四个跨膜结构域）

The large intracellular M3-M4 linker is the site for many cytoskeletal protein-protein interactions.

M2 lines the pore



Keramidas et al., 2004.

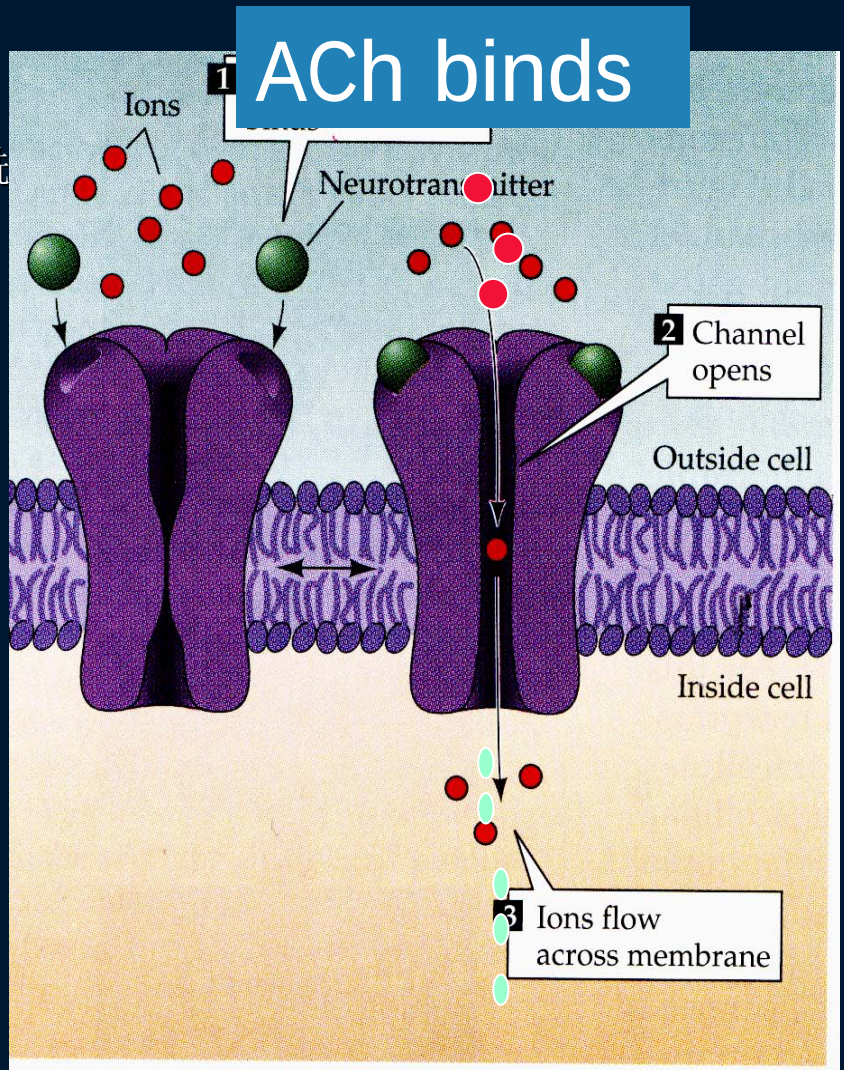


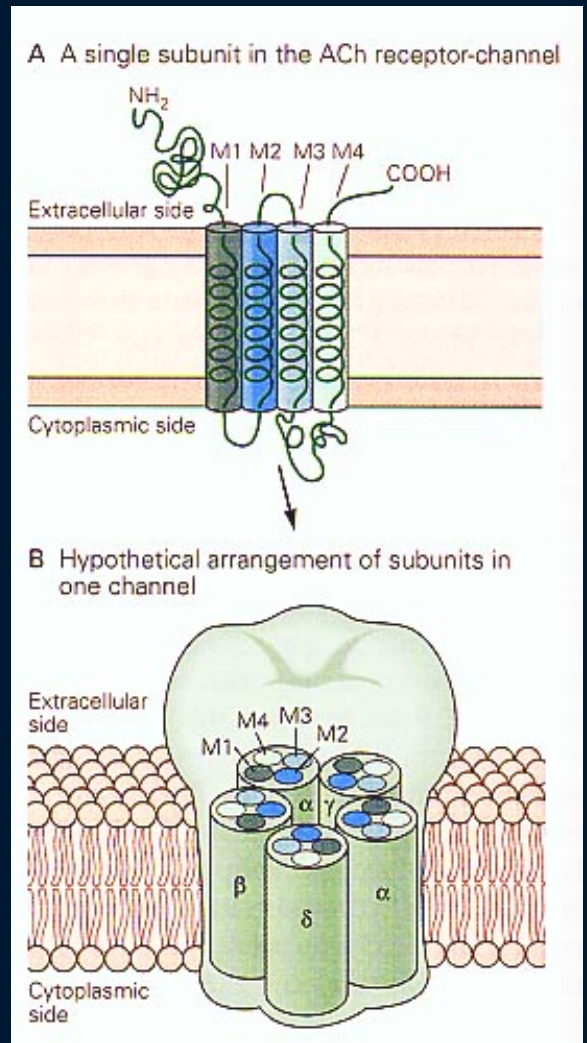
Ashcroft 2000

Cystine-Loop Superfamily of Ligand-Gated Ion Channels

nAChR

- Activated by Acetylcholine （乙酰胆碱） and Nicotine （尼古丁）
- Blocked by curare （箭毒） and some general anesthetics （麻醉药）.
- Non-selective cation channel including sodium, potassium and calcium.





N-AChR

- 突触前N-AChR：正反馈调节

  自身受体：位于突触区或临近突触的末梢前部位，增加ACh的释放

  异源受体：在脑内，增加NA、DA、Glu和GABA的释放

- 正反馈调节机制：

  ①受体激活后，Na＋内流使膜去极化，开放电压依赖性Ca2＋通道

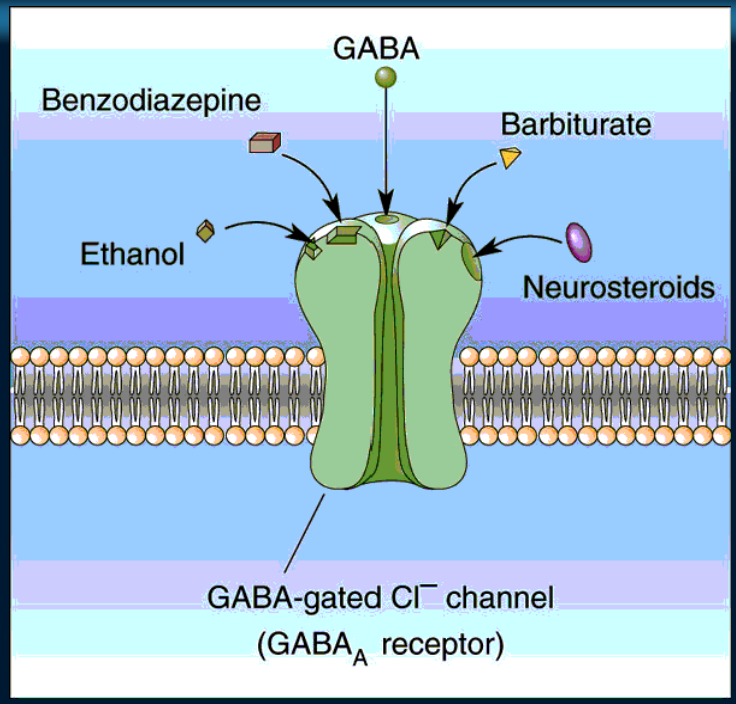
  ②某些类型N-AChR对Ca2+高度通透性，如α7型

N-AChR

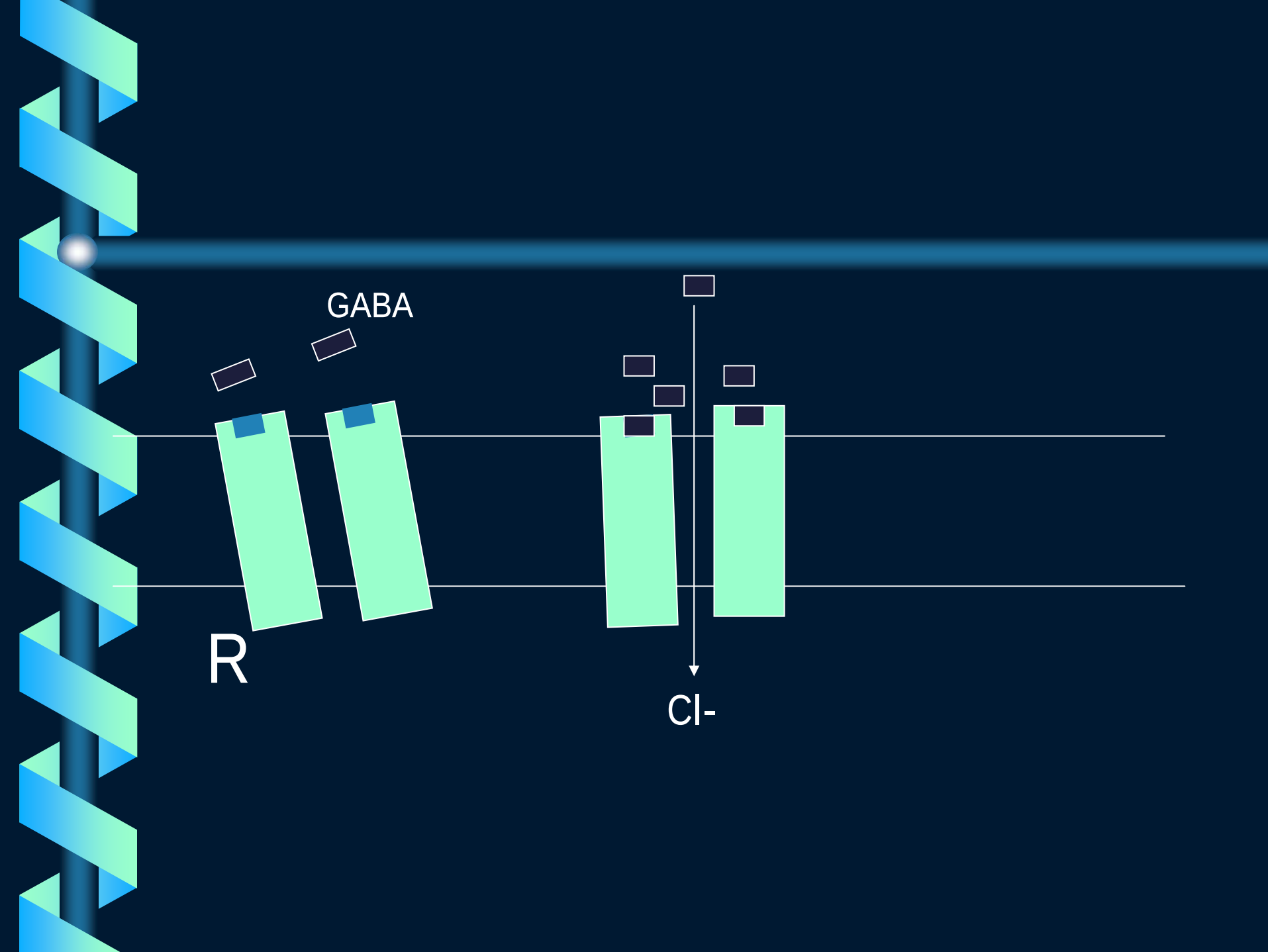
- 突触后N-AChR

介导快速兴奋性突触传递，有利于神经系统结构和功能发生长时程变化，如感觉皮质的发育、学习记忆的建立。

$GABA_A$型受体



- The receptors are multimers made up of five individual protein subunits, each of which contributes to the pore of the ion channel


GABA
R
Cl-

Ionotrophic Glutamate Receptors

The Tetrameric Structure of a Glutamate Receptor Channel

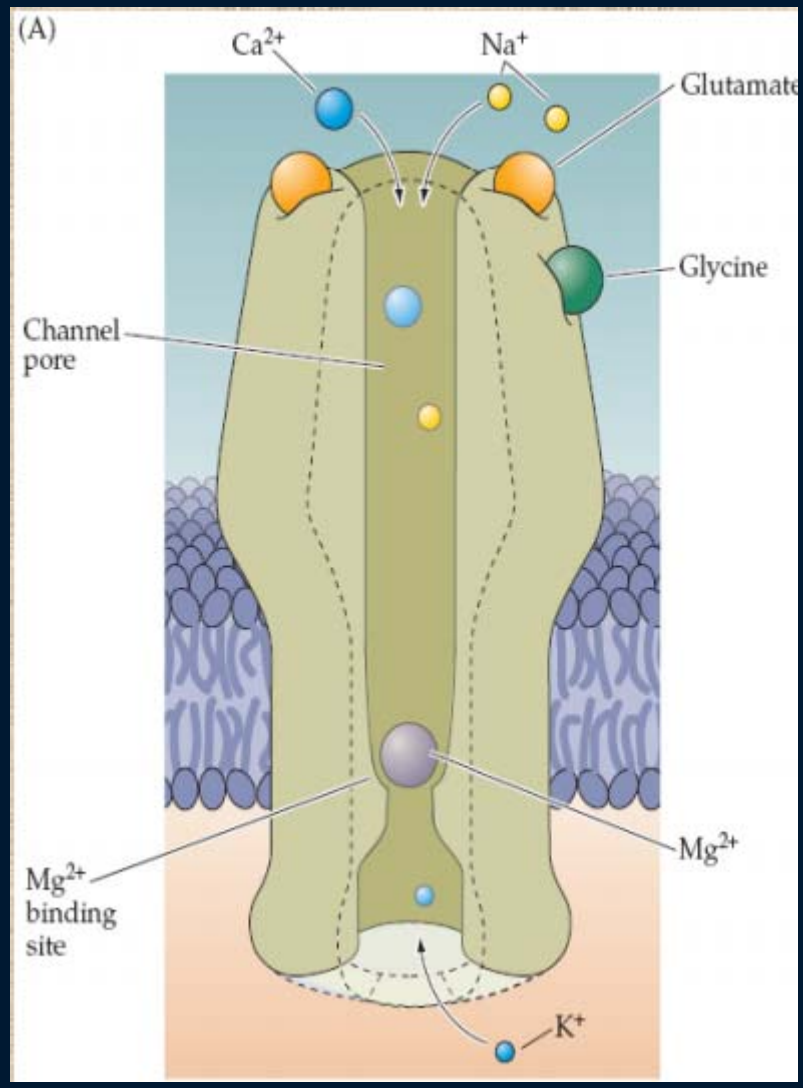
Christian Rosenmund, Yael Stern-Bach, Charles F. Stevens*

SCIENCE • VOL. 280 • 5 JUNE 1998 • www.sciencemag.org

How many subunits make up an ionotrophic glutamate receptor?

NMDAR

- 由4个亚单位构成，每个亚单位3次跨膜，第二个跨膜段没有完全跨膜，形成一个环，构成通道内壁



NMDAR的特点

Na+/K+/Ca2+阳离子通透性受体

- • Na+、Ca2+内流，K+外流，引起突触后膜去极化；通道开放后，Ca2+的内流和细胞内Ca2+浓度增加激活一系列Ca2+依赖的生化过程
- • 通道呈簇状开放，持续时间可达75～90ms，产生慢时程EPSP，有利于突触反应的时间总和
- • NMDAR过度兴奋导致细胞内Ca2+超载，对神经元也会产生毒性作用

NMDAR的特点

NMDAR通道的开放与激活受配体和膜电位的双重调节

- • 即激动剂的结合和突触后膜去极化
- 在正常膜电位水平，受体通道被被细胞外Mg2+阻滞，此阻滞作用随膜去极化而减少，通道电流随之增大，该现象称为受体通道的电压依赖性。
- • 70%的兴奋性突触同时存在NMDAR和非NMDAR，20%的突触仅有非NMDAR，10%的突触仅有NMDAR
- 两类受体毗邻分布，非NMDAR提供NMDAR激活的膜去极化条件

NMDAR的特点

- **NMDAR参与兴奋性突触传递的长时程增强**

  高频刺激突触前神经元，使突触传递效率随之增加，在突触后神经元产生EPSP的长时程增强

NMDAR受多种内源性物质或药物的调制

- • Glu位点：NMDAR的激动剂和竞争性拮抗剂的作用位点
- • Mg2+作用位点：生理浓度的Mg2+以电压依赖的方式阻滞NMDAR通道，表现为单通道的开放时程明显缩短，开放频率减少
- • Gly作用位点： Gly是NMDAR激活的辅助激动剂，能增强NMDA诱发的电流反应；其增强作用在1umol/L已达饱和，接近与脑脊液中甘氨酸的正常水平

NMDAR受多种内源性物质或药物的调制

- 多胺的作用位点：复杂的作用,包括增强和抑制

- ·增强作用：

①依赖Gly的增强作用，在Gly浓度未饱和时，增加NMDAR对Gly的亲和性

②不依赖Gly的增强作用，在Gly浓度饱和时，通过自身多价阳离子，屏蔽H+作用部位，解除H+对NMDAR的紧张性抑制，改变通道蛋白构象，增大通道的开放频率

- 抑制作用：

①在通道外口形成电流屏障，减小通道电导，或在Mg2＋作用部位阻滞通道开放

②减小NMDAR对激动剂的亲和性

NMDAR受多种内源性物质或药物的调制

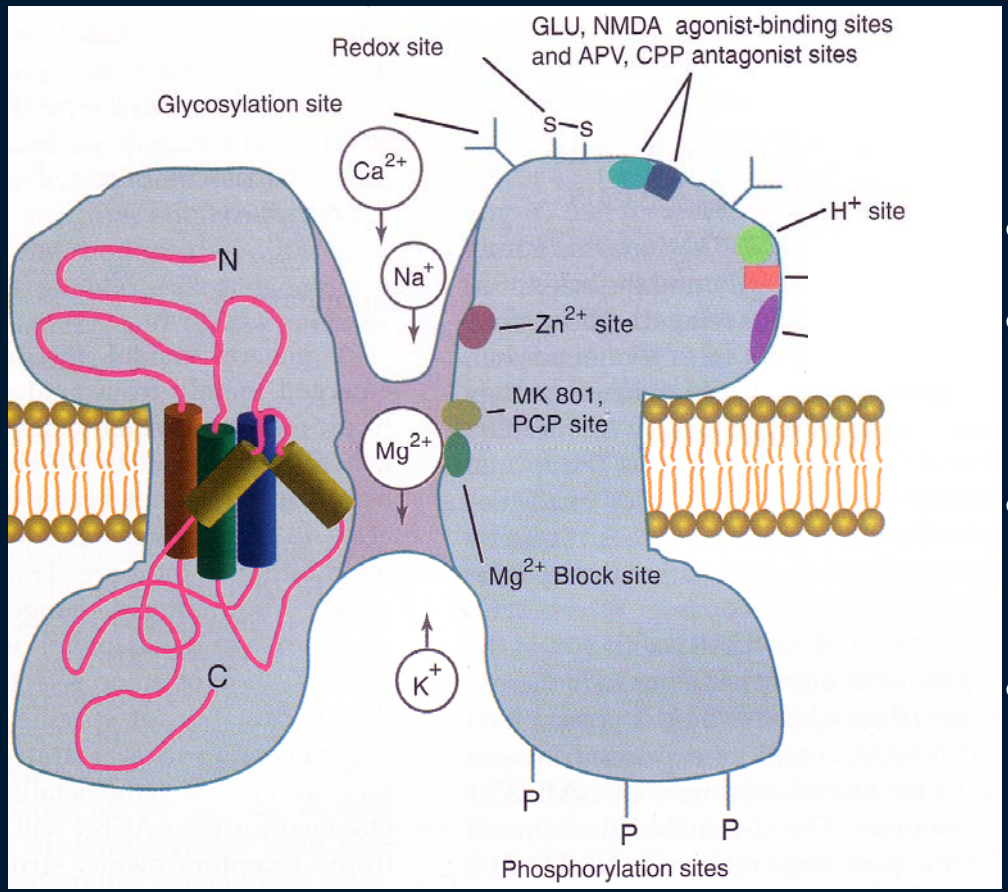
NMDAR受多种内源性物质和药物的调制

- • 非竞争性拮抗剂作用位点：开放通道阻滞剂(openchannel bloker)，作用部位在NMDAR通道的内部，当受体激活，通道开放时，药物才能到达或离开其作用部位
- • H+作用位点：非竞争性抑制，不依赖于膜电位，pH为7.4时，NMDAR的活动已部分被抑制，pH为6.6时，抑制作用达50％
- • Zn2+或Cd2+也有阻滞作用，Zn2+作用位点位于NMDAR通道外口附近

NMDA受体的两大特性

- 1.具有电压依赖的Mg2+阻滞的特性
- 2 .对**Na+/K+/Ca2+**阳离子通透

NMDA receptor and Mg2+



- Blocks channel at rest
- Depolarization --> Mg^{2+} ion leaves the pore
- Glu + depolarization = Coincidence Detector
- Other channel blockers: PCP, ketamine, MK801

Zigmond et al. 1999

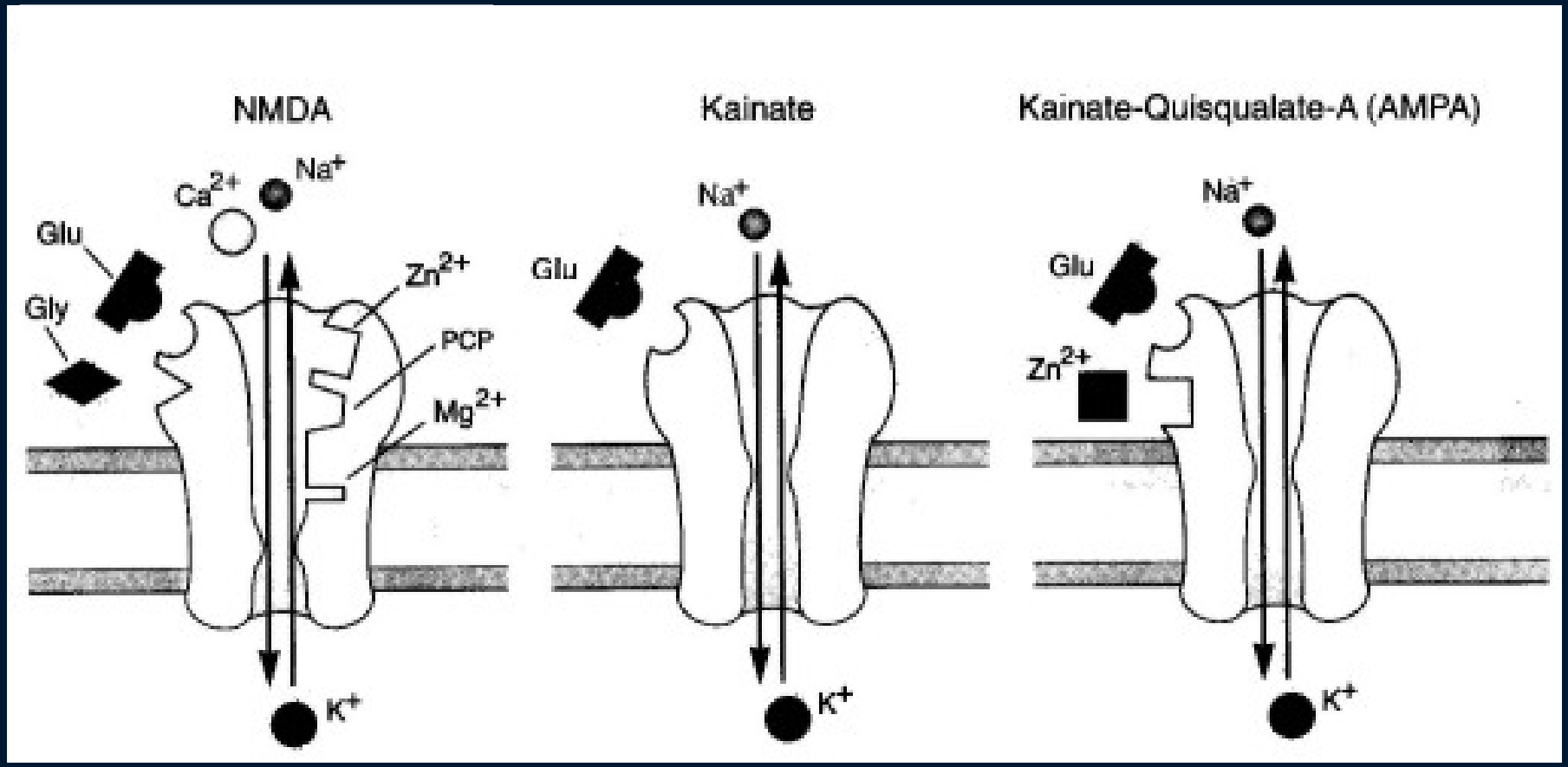
Ionotrophic Glutamate Receptors AMPA and Kainate Receptors

- AMPAR和KAR
- • Na+/K+阳离子通透性受体，对Ca2+多数不通透，少数AMPAR受体对Ca2+通透
- • 与NMDAR协调介导兴奋性的突触传递
- • KAR作为自身受体，负反馈调节Glu的释放；也可作为GABA的异源受体，减少GABA的释放，抑制其介导的IPSP

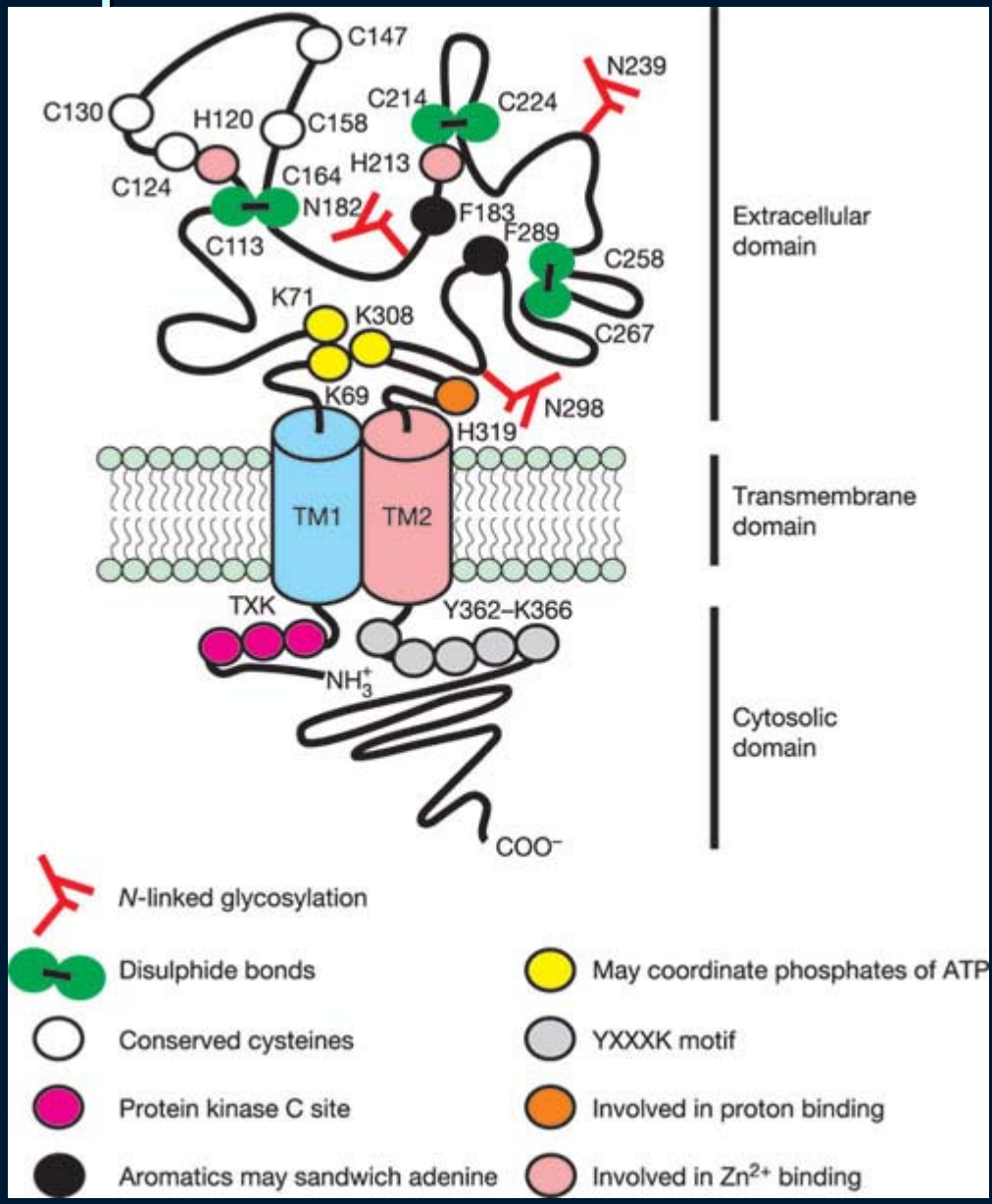
Ionotrophic Glutamate Receptors
AMPA and Kainate Receptors

Ionotrophic Glutamate Receptors
AMPA and Kainate Receptors
Activate rapidly
Desensitize within a few milliseconds
Kainate – GluR5-7, KA1-2
AMPA – GluR1-4

- With GluR2 subunit: permeable only to K+ and Na+
- Without GluR2 subunit: **Ca2+**-permeable
- AMPA = alpha-**a**mino-3-hydroxy-5-**m**ethyl-4-isoxazole**p**ropionic **a**cid


NMDA
Kainate
Kainate-Quisqualate-A (AMPA)
Ca2+
Na+
Glu
Gly
Zn2+
PCP
Mg2+
K+
Na+
Glu
K+
Na+
Glu
Zn2+
K+

P2X Receptors

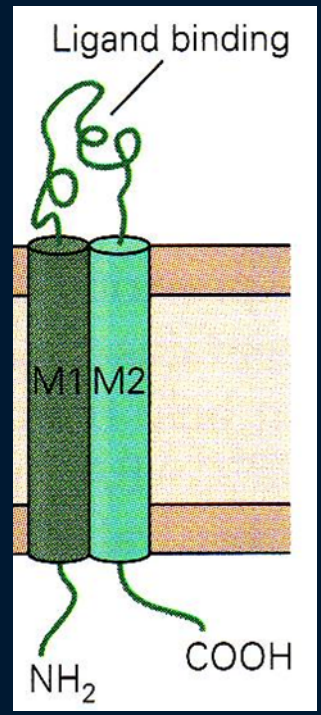


P2X receptors as cell-surface ATP sensors in health and disease

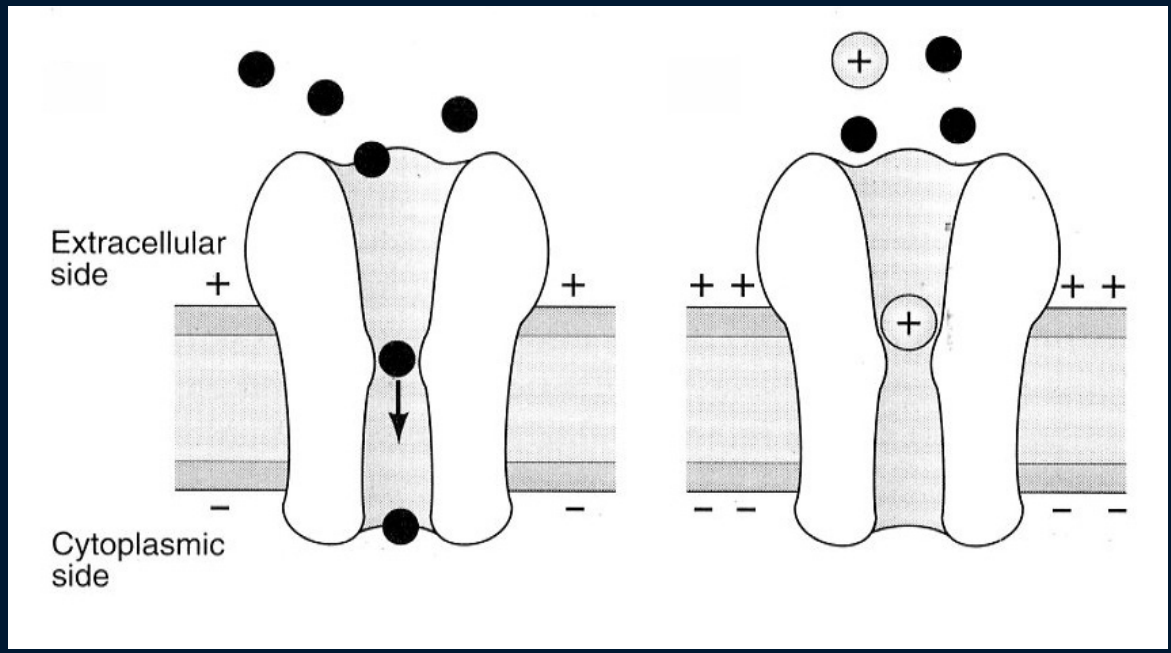
Nature **442**, 527-532

P2X Receptors

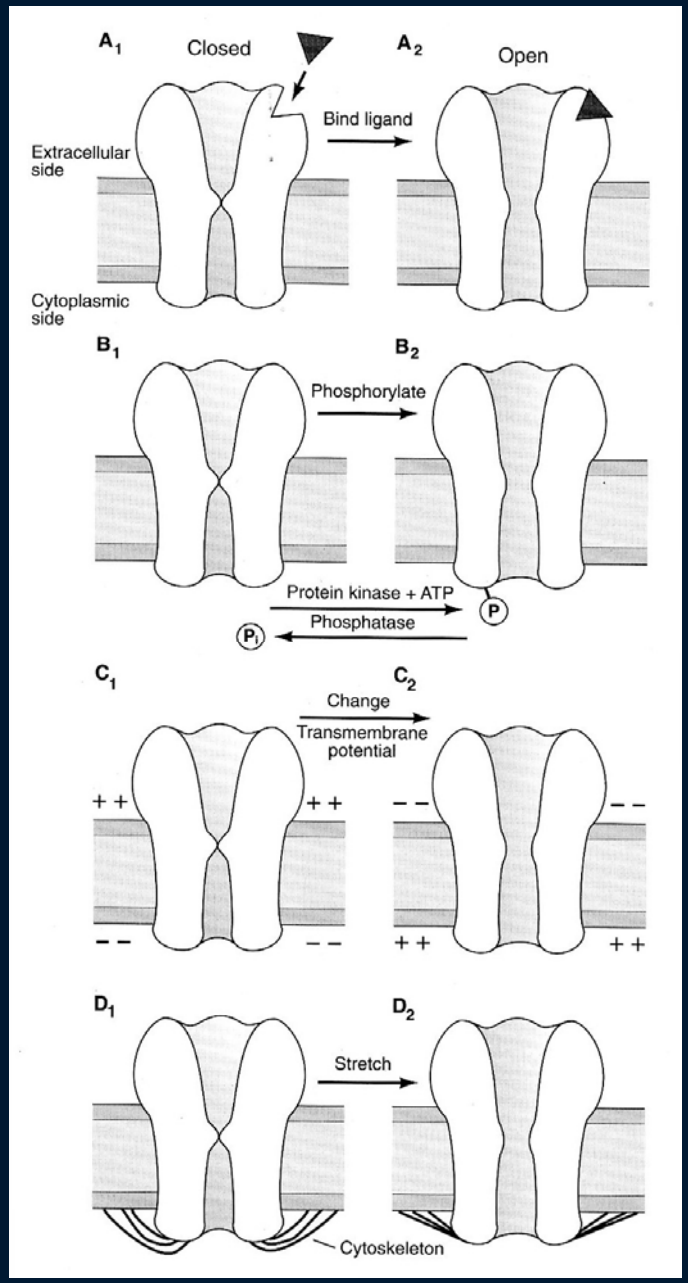
- Gated by extracellular ATP
- Trimeric arrangement determined by crosslinking and agonist binding studies
- 7 subtypes, heteromultimers produce a variety of kinetic outcomes
- M1 is involved in gating, M2 lines the pore
- Intracellular N and C termini are important for protein-protein interactions



It is possible to block ion channels using pharmacologic techniques



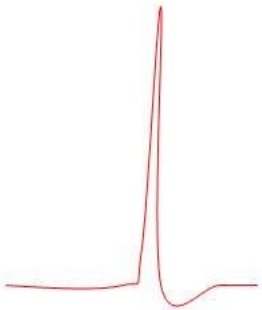
Many stimuli can open (or close) ion channels



离子通道研究历史性的贡献

—— 获得三次诺贝尔奖

① 1963



② 1991

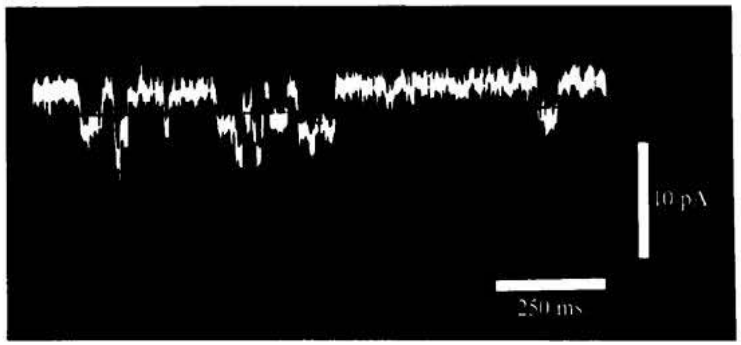
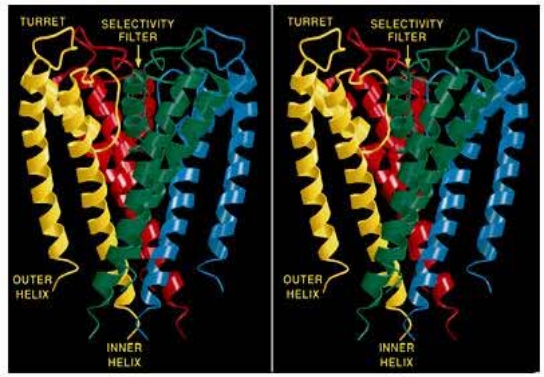


Figure 2. Early single-channel currents from denervated frog *(Rana pipiens)* cutaneous pectoris

③ 2003

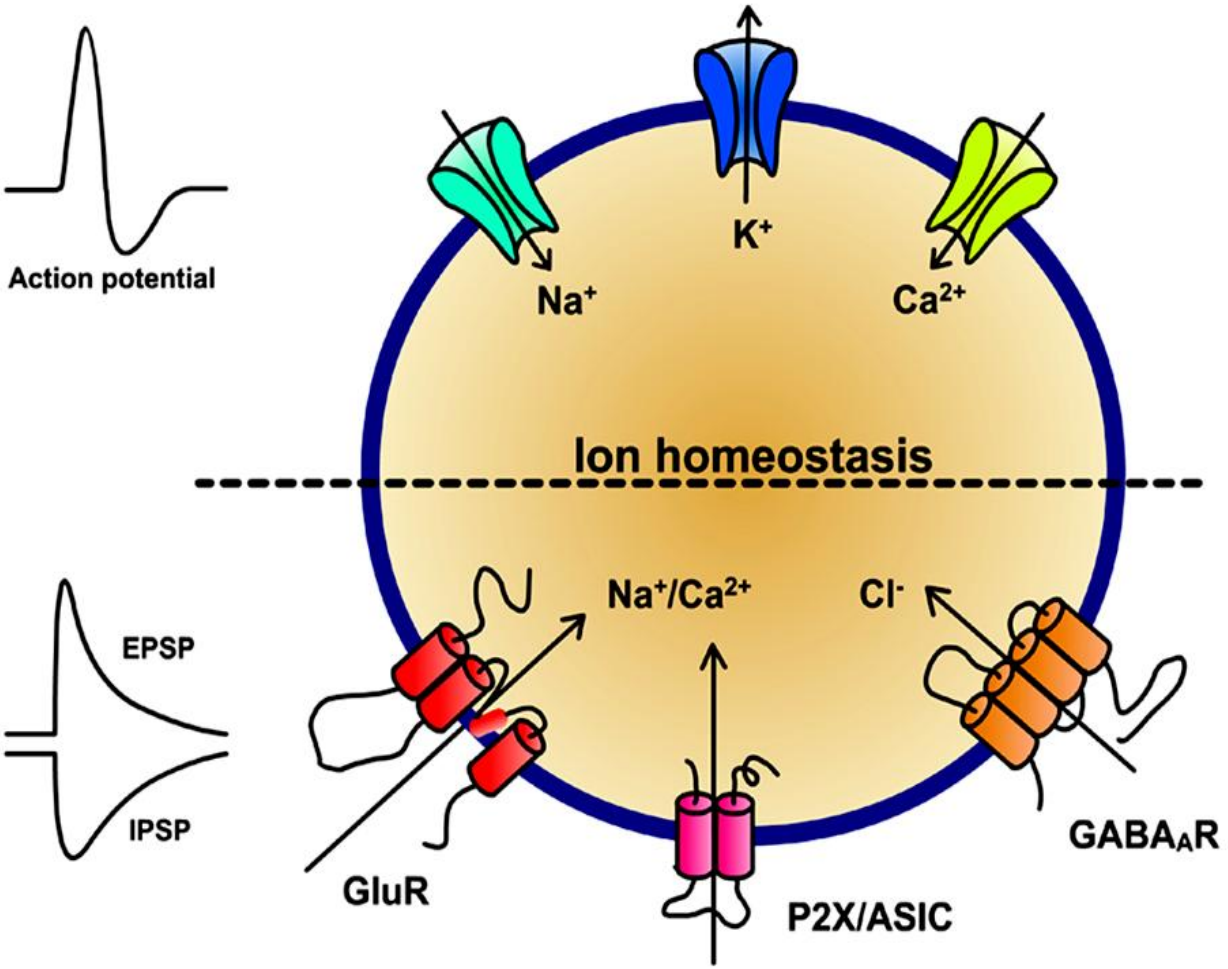


① 动作电位的离子机制—神经信号的物质基础

② 发明膜片钳技术—从单通道记录到突触传递

③ 晶体结构解析—从可视化到蛋白质动态行为

离子通道与神经科学



- 膜兴奋性
- 突触传递
- 思维记忆
- 感觉运动
- 疾病靶点
- 药理靶点

G-protein-Coupled receptors are metabotropic receptors

- 是一类由受体、G蛋白和效应酶三部分组成的信号偶联系统。这类受体激活后，只有通过G蛋白的转导，才能将信号传递至效应系统。

清华客座教授获2012年诺贝尔化学奖

罗伯特·莱夫科维茨

布莱恩·克比尔卡

因在G蛋白偶联受体（G Protein Coupled Receptors）方面的卓越成就获得2012年度诺贝尔化学奖。

G-protein-Coupled receptors

细胞表面的聪明受体

莱夫科维茨从1968年便开始利用放射性碘来寻找细胞接受信号的物质，这种物质后来被称为“G蛋白偶联受体”。

2007年，科比尔卡首次用T4溶菌酶融合法解析了β-肾上腺素受体的结构，该方法后来成为获取G蛋白偶联受体三维结构的常规手段。2011年，他又在这个受体被激活并向细胞发送信号时获得了三维图像。

莱夫科维茨和克比尔卡的研究对于理解G蛋白偶联受体如何起作用至关重要。此外，在2011年，克比尔卡还取得了另一项突破：他和研究团队在一个精确的时刻——β-肾上腺素受体被激素激活并向细胞发送信号——获得了β-肾上腺素受体图像。这一图像是一个分子杰作，可谓几十年辛苦研究的成果。

ARTICLE

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Crystal structure of the β_2 adrenergic receptor–Gs protein complex

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G protein–coupled receptors (GPCRs) are responsible for the majority of cellular responses to hormones and neurotransmitters as well as the senses of sight, olfaction and taste. The paradigm of GPCR signalling is the activation of a heterotrimeric GTP binding protein (G protein) by an agonist-occupied receptor. The β_2 adrenergic receptor (β_2AR) activation of Gs, the stimulatory G protein for adenylyl cyclase, has long been a model system for GPCR signalling. Here we present the crystal structure of the active state ternary complex composed of agonist-occupied monomeric β_2AR and nucleotide-free Gs heterotrimer. The principal interactions between the β_2AR and Gs involve the amino- and carboxy-terminal α-helices of Gs, with conformational changes propagating to the nucleotide-binding pocket. The largest conformational changes in the β_2AR include a 14 Å outward movement at the cytoplasmic end of transmembrane segment 6 (TM6) and an α-helical extension of the cytoplasmic end of TM5. The most surprising observation is a major displacement of the α-helical domain of Gαs relative to the Ras-like GTPase domain. This crystal structure represents the first high-resolution view of transmembrane signalling by a GPCR.

Introduction

The β_2 adrenergic receptor (β_2AR) has been a model system for the large and diverse family of G protein-coupled receptors (GPCRs) for over 40 years. It was one of the first GPCRs to be characterized by radioligand binding, and it was the first neurotransmitter receptor to be cloned[1] and structurally determined by crystallography[2,3]. The β_2AR was initially identified based on its physiological and pharmacological properties, but it was not known if receptors and G proteins were separate entities, or parts of the same protein[4]. Subsequent biochemical studies led to the isolation and purification of functional β_2AR and Gs, the stimulatory G protein that activates adenylyl cyclase, and the reconstitution of this signalling complex in phospholipid vesicles[5,6]. The cooperative interactions of β_2AR and Gs observed in ligand binding assays formed the foundation of the ternary complex model of GPCR activation[7,8]. In the ternary complex consisting of agonist, receptor and G protein, the affinity of the receptor for agonist is enhanced and the specificity of the G protein for guanine nucleotides changes in favour of GTP over GDP. The GPCR field has evolved markedly since these initial studies. Isolation of the genes and cDNAs for the β_2AR and other GPCRs using protein sequencing and expression cloning led to the expansion of the family by homology cloning. More recently, sequencing of the human genome led to the identification of over 800 GPCR genes[9]. Experimental tools for identifying protein–protein interactions and for expression and silencing of genes have revealed a complex network of cellular signalling and regulatory pathways including G protein-independent activation of cytosolic kinases[10,11]. Nevertheless, the β_2AR continues to be a relevant model for most aspects of GPCR pharmacology, signalling and regulation.

Notwithstanding the remarkable advances in this field, we still know relatively little about the structural basis for transmembrane signalling by GPCRs. Figure 1 shows the G protein cycle for the β_2AR–Gs complex. Agonist binding to the β_2AR promotes interactions with GDP-bound Gsαβγ heterotrimer, leading to the exchange of GDP for GTP, and the functional dissociation of Gs into Gα-GTP and Gβγ subunits. The separate Gα-GTP and Gβγ subunits can modulate the activity of different cellular effectors (channels, kinases or other enzymes). The intrinsic GTPase activity of Gαs leads to hydrolysis of GTP to GDP and the reassociation of Gα-GDP and Gβγ subunits, and the termination of signalling. The active state of a GPCR can be defined as that conformation that couples to and stabilizes a nucleotide-free G protein. In this agonist-β_2AR–Gs ternary complex, Gs has a higher affinity for GTP than GDP, and the β_2AR has an approximately 100-fold higher affinity for agonists than does β_2AR alone. In an effort to understand the structural basis for GPCR signalling, we crystallized the β_2AR–Gs complex.

Crystallization of the β_2AR–Gs complex

The first challenge for crystallogenesis was to prepare a stable β_2AR–Gs complex in detergent solution. The β_2AR and Gs couple efficiently in lipid bilayers, but not in detergents used to solubilize and purify these proteins. We found that a relatively stable β_2AR–Gs complex could be prepared by mixing purified GDP-Gs (approximately 100 μM final concentration) with a molar excess of purified β_2AR bound to a high affinity agonist (BI-167107, Boehringer Ingelheim)[12] in dodecylmaltoside solution. Apyrase, a non-selective purine pyrophosphatase, was added to hydrolyse GDP released from Gs on forming a complex with the β_2AR. Removal of GDP was essential because both GDP and GTP

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G-PROTEIN-COUPLED RECEPTORS ("metabotropic receptors")

- sites for action of about 45% of drugs
- for slow synaptic transmission (seconds - minutes)
-examples: beta-adrenergic receptors,
muscarinic receptors
- "coupling":

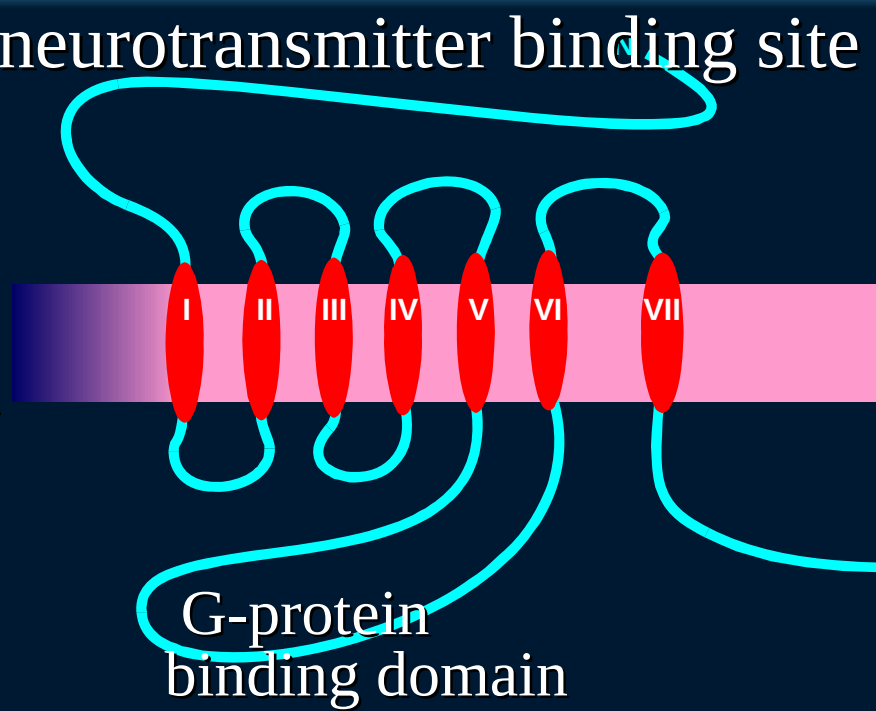
RECEPTOR serpentine receptors: a polypeptide chain traverses the membrane seven times

G PROTEIN

EFFECTOR

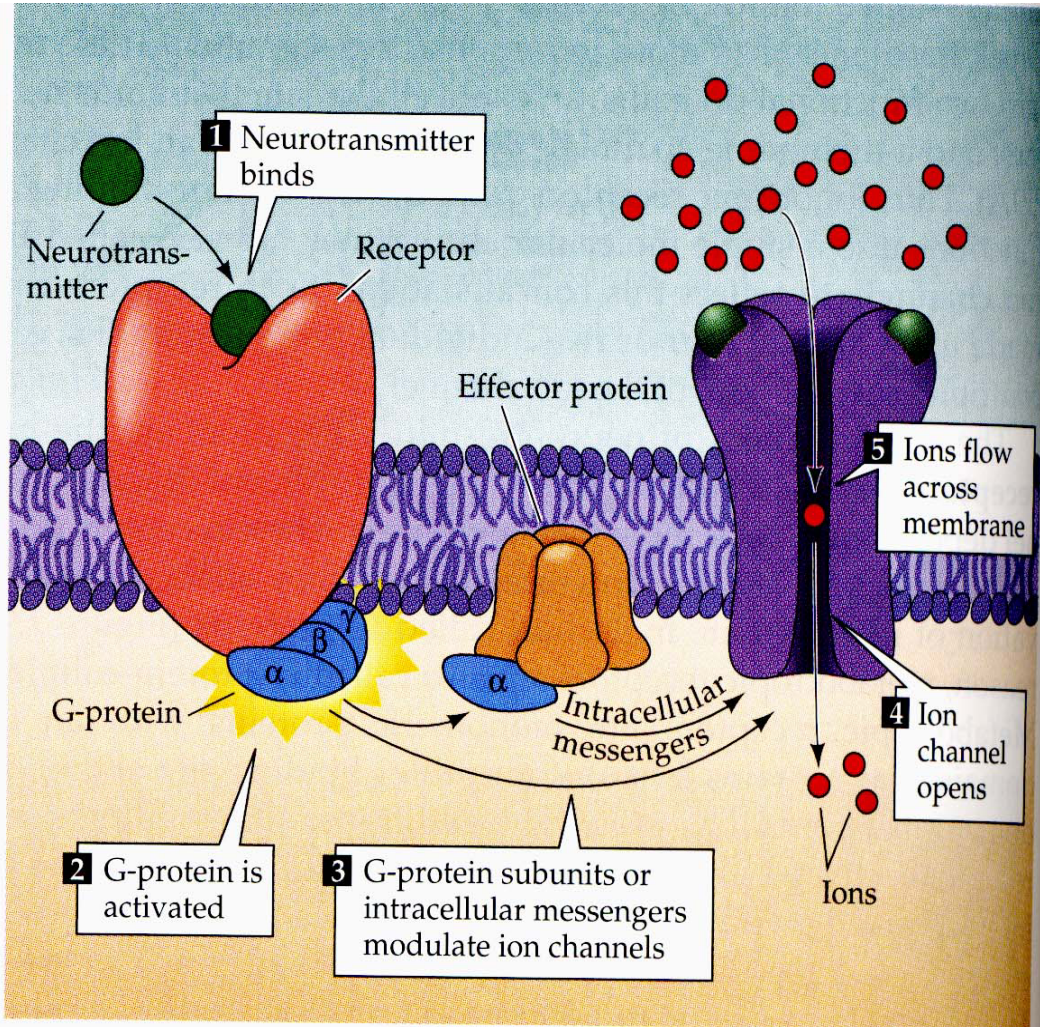
G-protein-Coupled receptors are metabotropic receptors

- The receptors are monomeric proteins with an extracellular domain that contains a neurotransmitter binding site and an intracellular domain that binds to G-protein
- G-proteins can be thought of as transducers that couple neurotransmitter binding to the regulation of postsynaptic ion channels.



G-protein-Coupled receptors are metabotropic receptors

- These receptors do not have ion channels as part of their structure; instead, they affect channels by the activation of intermediate molecules called G-protein
- The ion movement through a channel depends on one or more metabolic steps. So G-protein-Coupled receptors are also called metabotropic receptors



G-Protein-coupled Receptors

- Hundreds of types
- Main signal transducers
  - Activate enzymes
  - Open ion channels
  - Amplify:
    - adenyl cyclase-cAMP

Many neurotransmitter receptors are G-protein-Coupled receptors

- M-AChR
- mGluR
- $GABA_BR$
- $5\text{-}HT_{1\text{-}7}R$（except $5\text{-}HT_3R$）
- DA R

G-PROTEIN-COUPLED RECEPTORS („metabotropic receptors“)

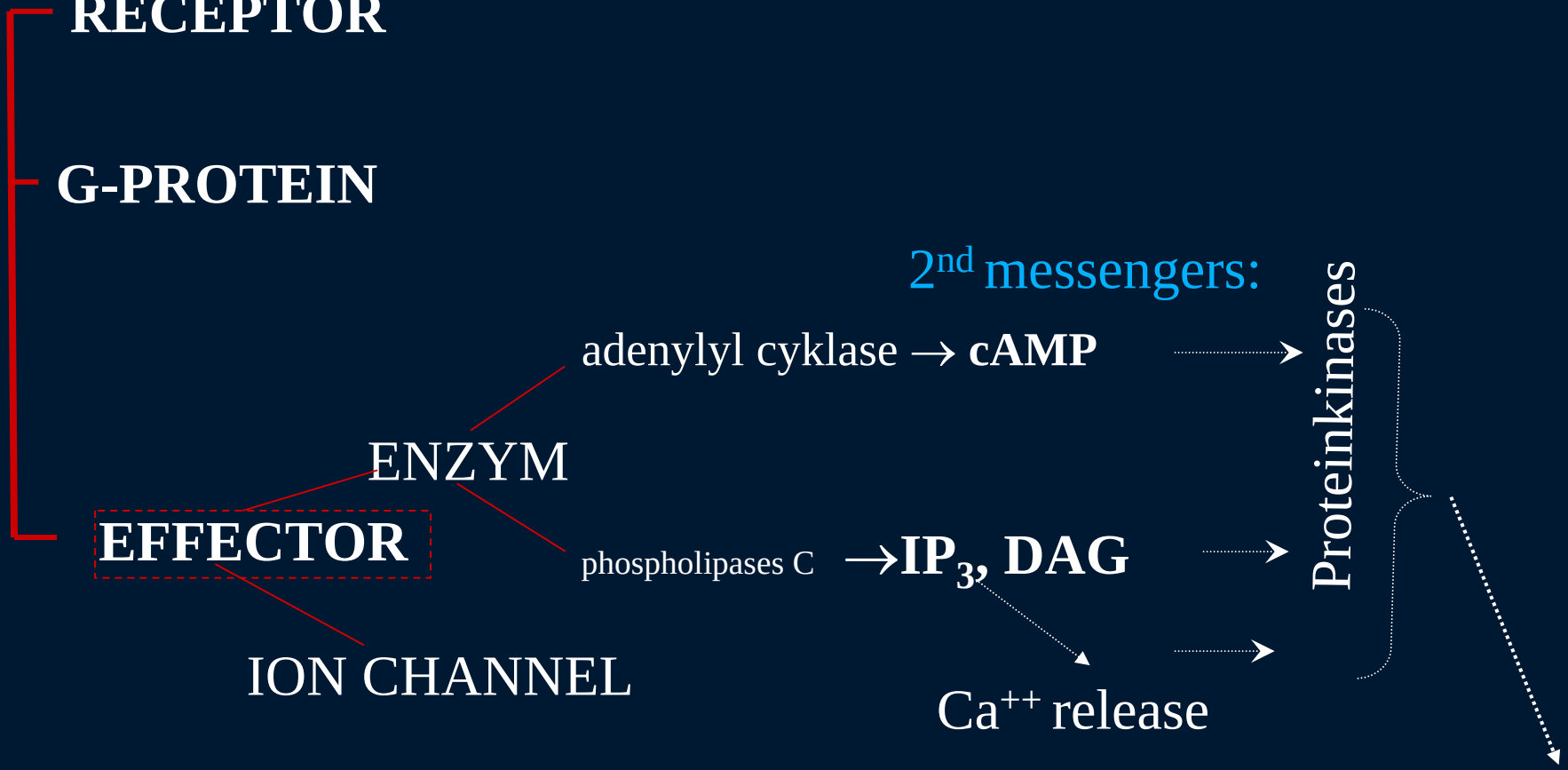
RECEPTOR

G PROTEIN - trimer, ✂, ✍, ☎ subunits

✂ subunit: GDP↔GTP, GTPase aktivity
stimulation (G_S) , inhibition (G_I) of the effector

EFFECTOR

G-PROTEIN-COUPLED RECEPTORS
(“metabotropic receptors”)



Activation/inhibition of cellular functions

eg. contractile proteins, enzymes, transporters, ion channels

G 蛋白：

是鸟苷酸结合蛋白（guanosine nucleotide-binding protein）的简称，是指能与 GTP 或 GDP 结合，与膜受体偶联而具有信号转导作用的蛋白质。

G 蛋白的发现和意义

Rodbell 等在 **20** 世纪 **70** 年代发现跨膜信号转导需要 **GTP** 存在。

1977年，Gilman发现了G蛋白。

1981年，Gilman纯化了G蛋白。

1994年，Gilman 和 Rodbell 获医学和生理学诺贝尔奖。

吉尔曼（**Alfred G. Gilman**）

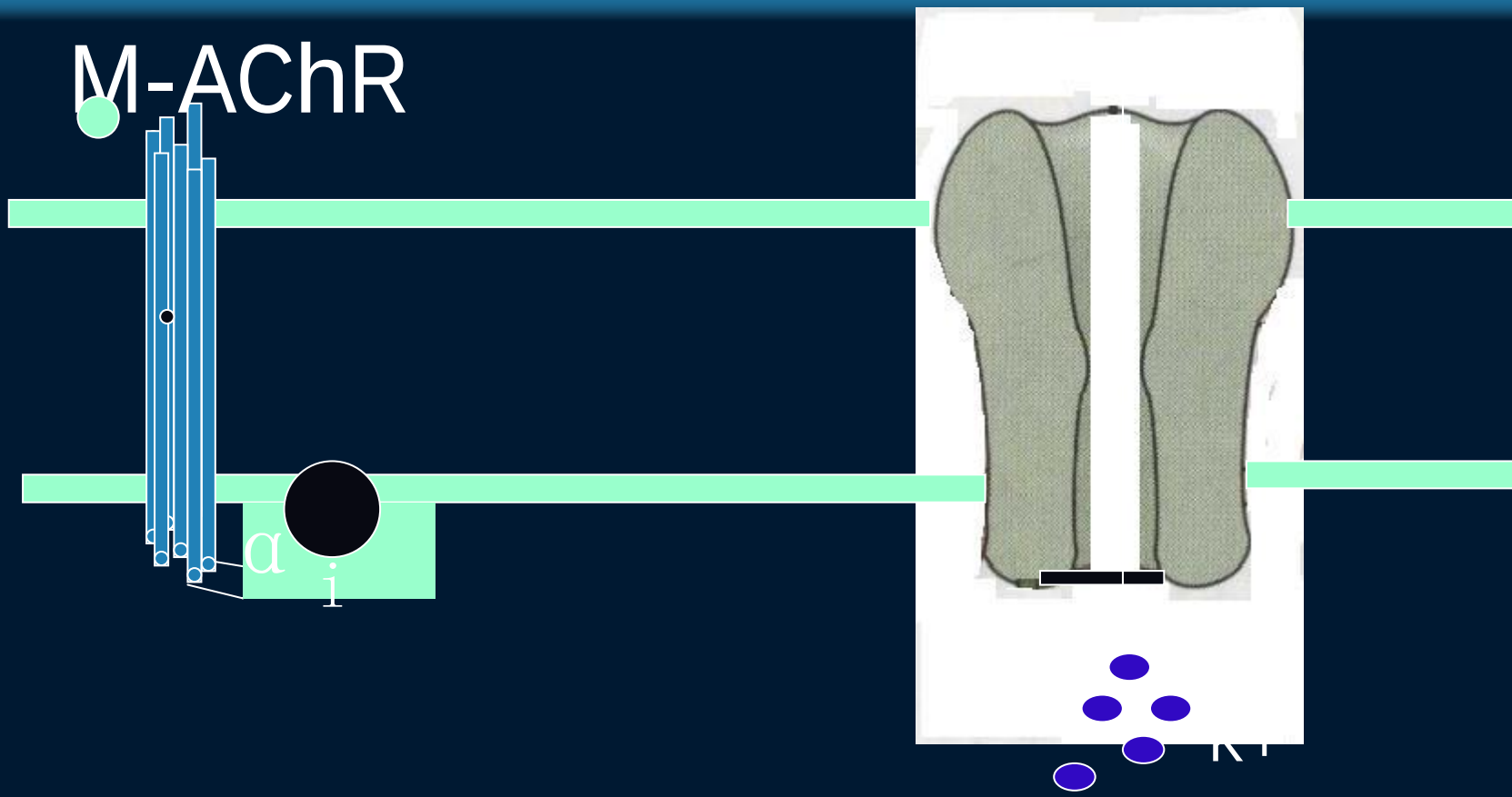
1941.7.1~

德克萨斯大学西南医学中心药学系

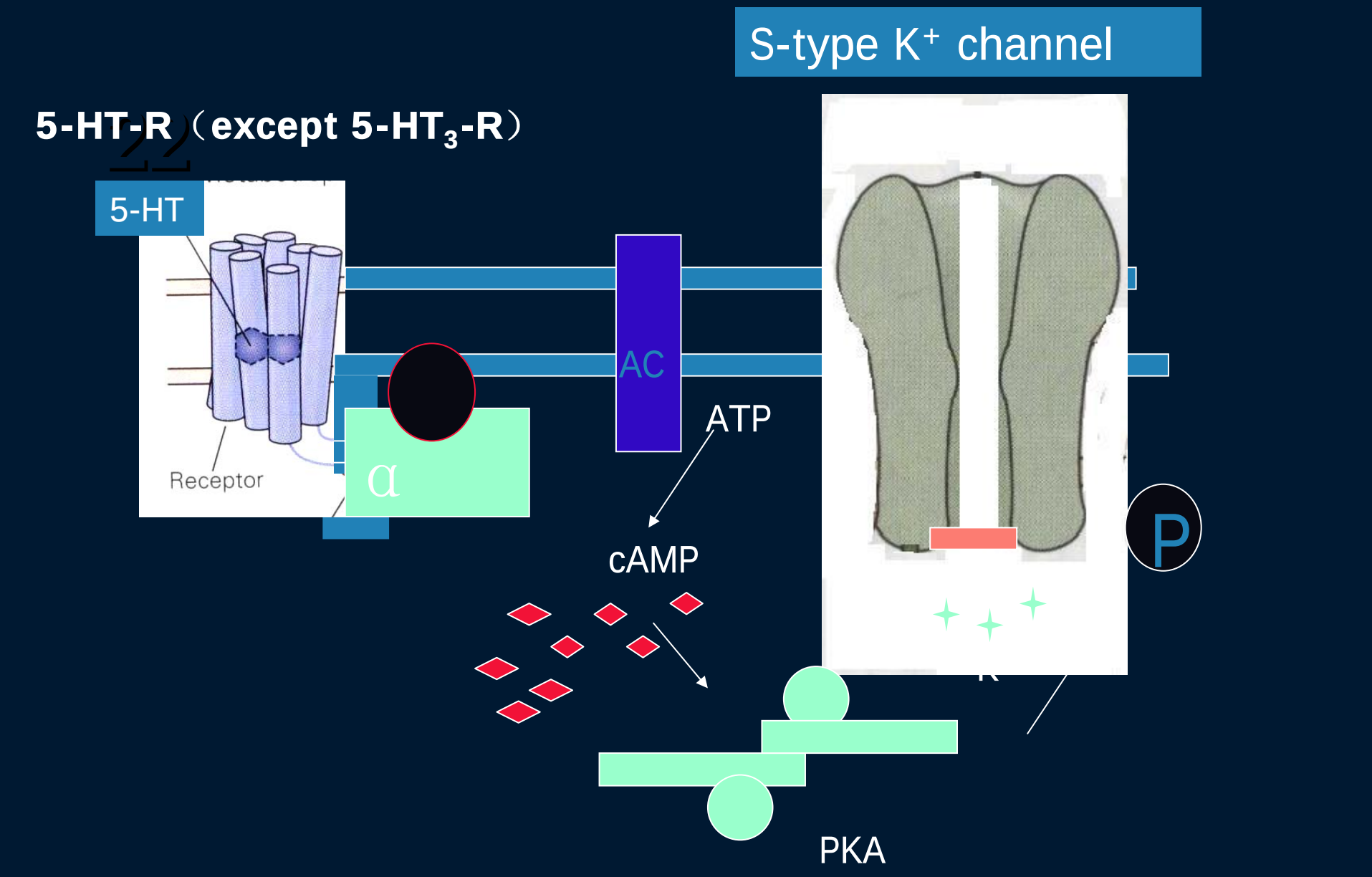
发现G蛋白的意义：

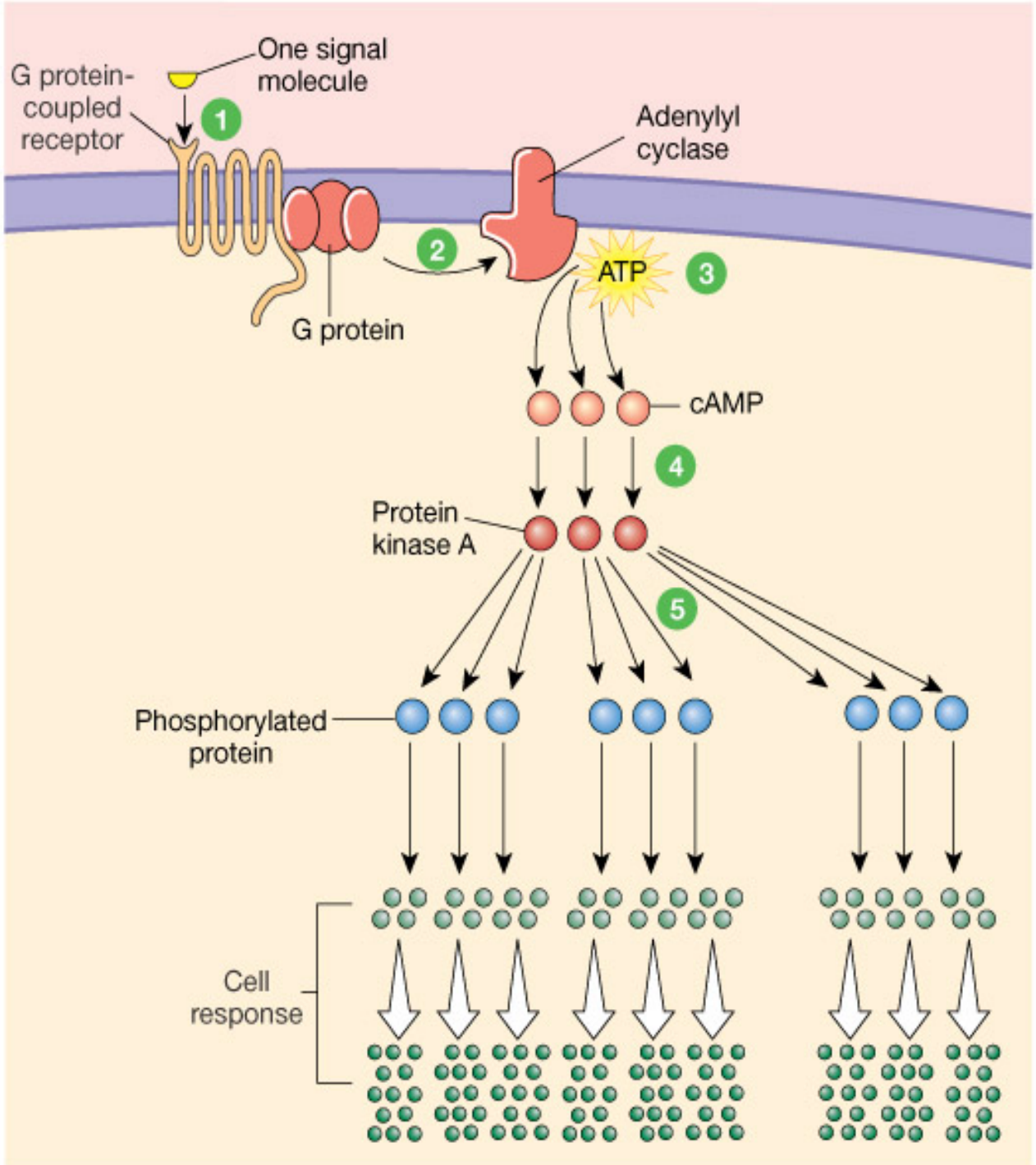
它揭示了细胞外信号如何转换为细胞内信号的真正机制，从而开辟了细胞信号跨膜转导研究的新时代。

G protein can open ion channels directly without employing second messengers



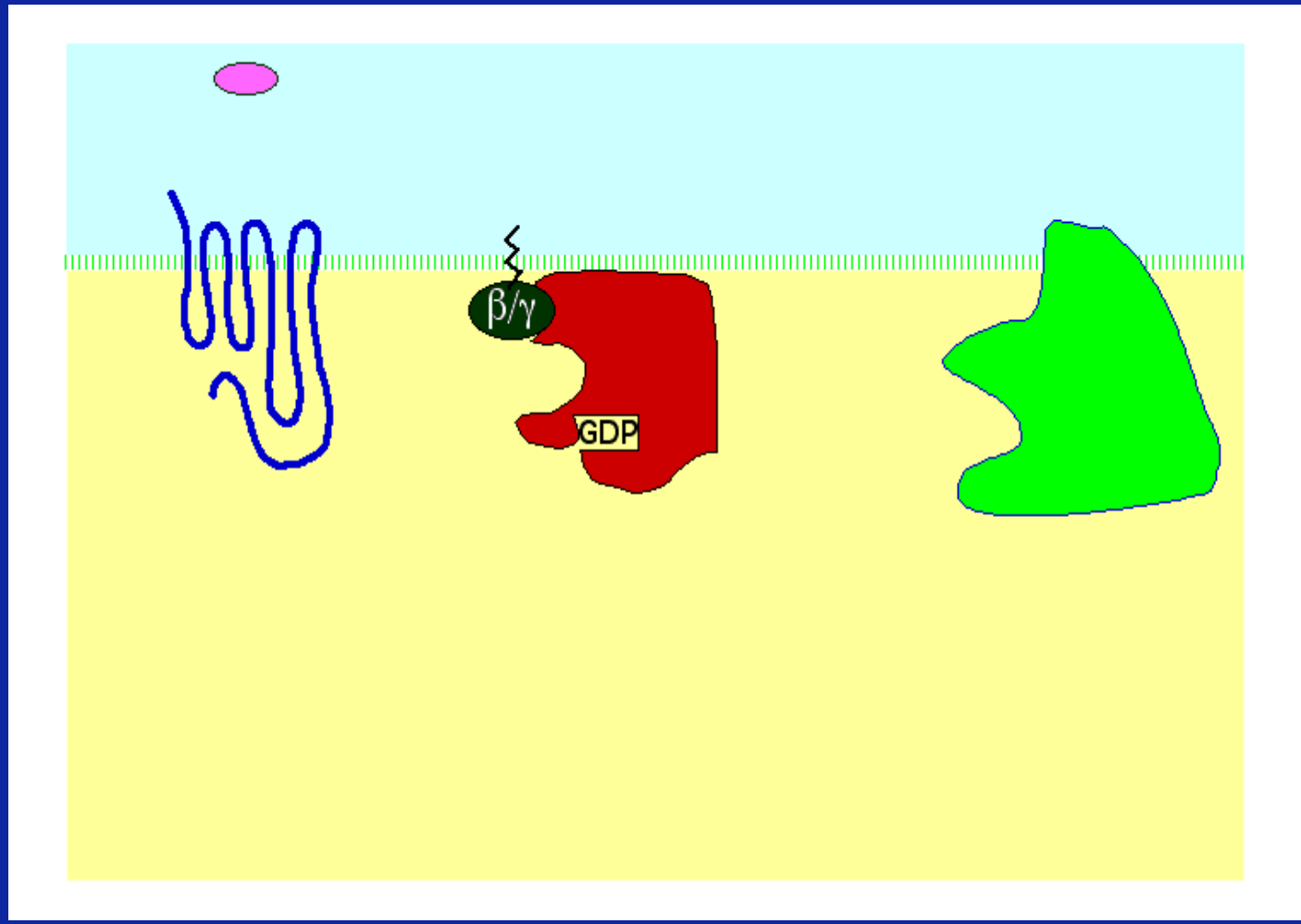
G protein can open ion channels indirectly with employing second messengers



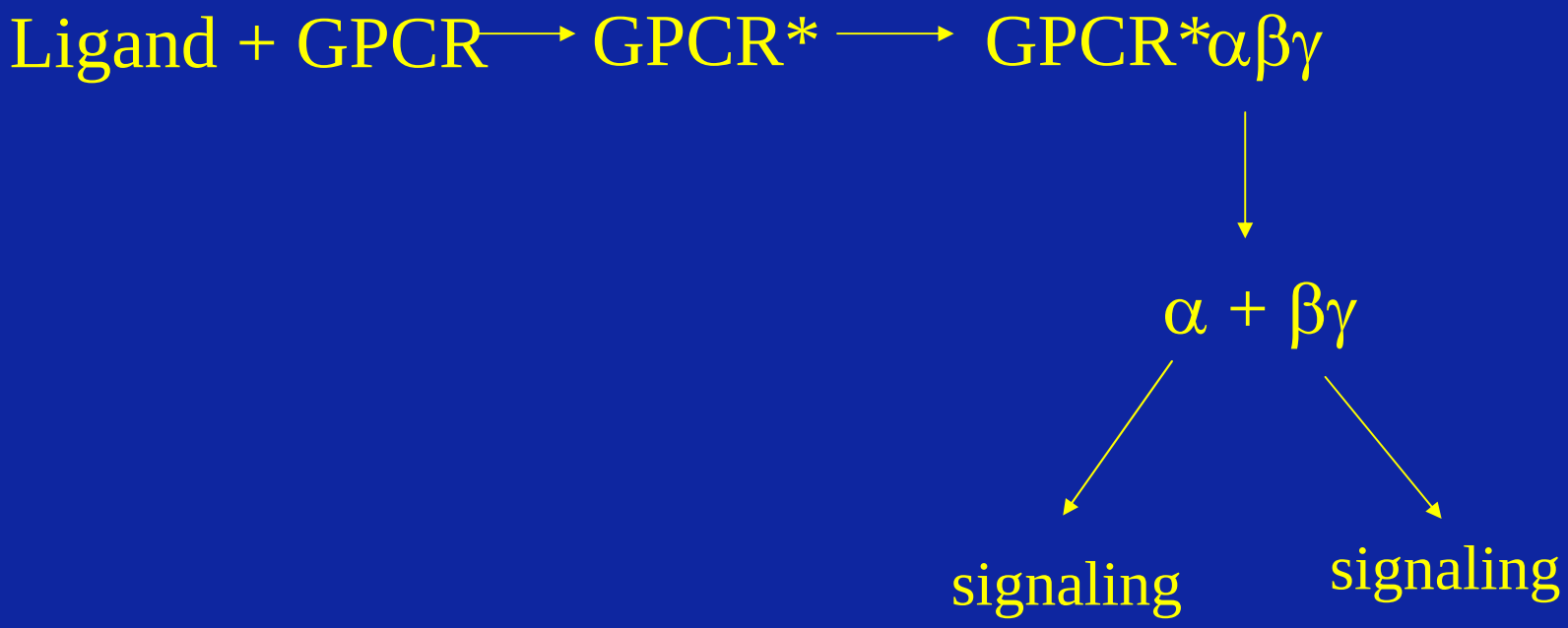


1. Signal molecule binds to G protein-linked receptor, which activates the G protein.
2. G protein turns on adenylyl cyclase, an amplifier enzyme.
3. Adenylyl cyclase converts ATP to cyclic AMP.
4. cAMP activates protein kinase A.
5. Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.

A depiction of how GPCRs activate signaling



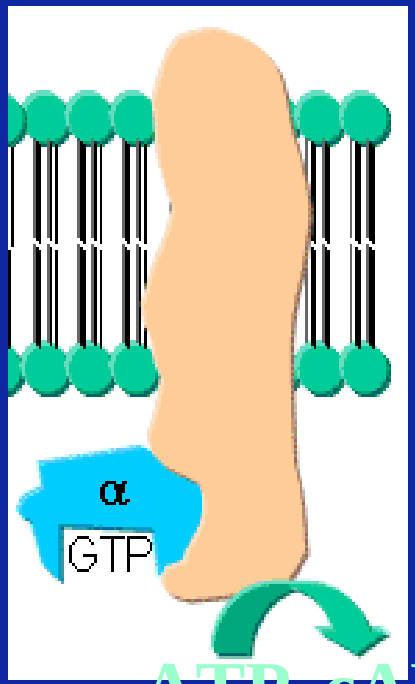
Another depiction of how GPCRs activate signaling



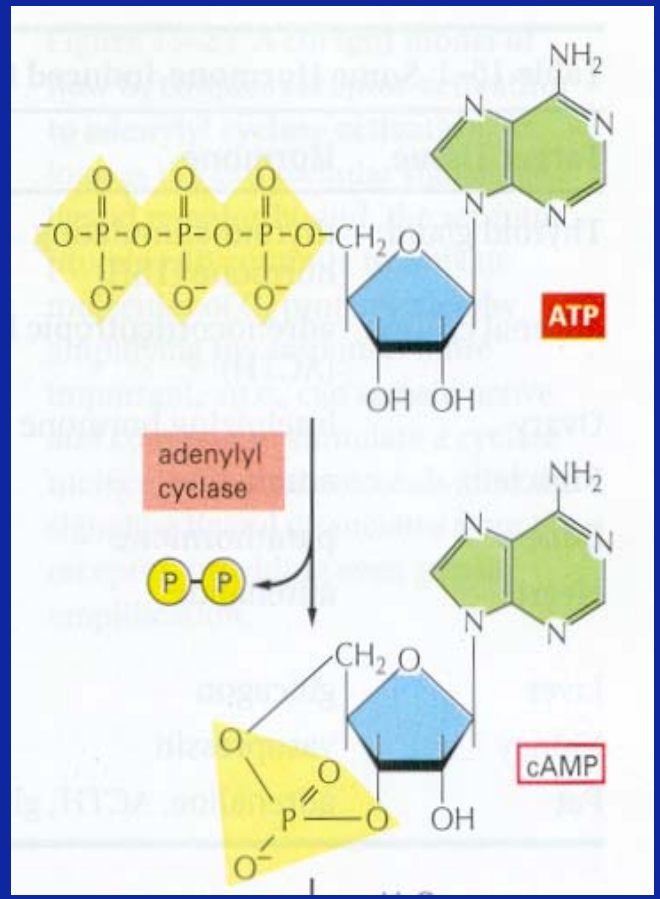
GPCR G-protein coupled receptor

αβγ Heterotrimeric GTP-binding protein (G protein)

Adenylate cyclase



ATP cAMP



Membrane protein
makes cAMP from ATP

Three major families of G-proteins

G_s	couples to Adenylate Cyclase stimulates AC activity increases cAMP activates Protein Kinase A
G_i	couples to Adenylate Cyclase inhibits AC activity decreases cAMP inhibits Protein Kinase A
G_q	couples to Phospholipase C increases diacylgyclerol(DAG) increases IP3 increases intracellular Ca^{2+} activates Protein Kinase C

G-protein	Receptor examples	Signaling pathway
Gs	β-adrenergic receptor ACTH receptor FSH receptor	↑ cAMP ↑ PKA activity
Gi	α_2-adrenergic receptor M2 muscarinic receptor	↓ cAMP ↓ PKA activity
Gq	α_1-adrenergic receptor M1, M3 muscarinic receptors Angiotensin receptor	↑ PLC activity ↑ DAG, IP3 ↑ Ca^{2+} ↑ PKC activity

Same receptor, same signaling pathway, produces specific effects in different tissues

β1-adrenergic receptors acting on skeletal muscle:

AC ↑ cAMP ↑ PKA ↑ phosphorylase kinase ↑ glycogen phosphorylase

↓

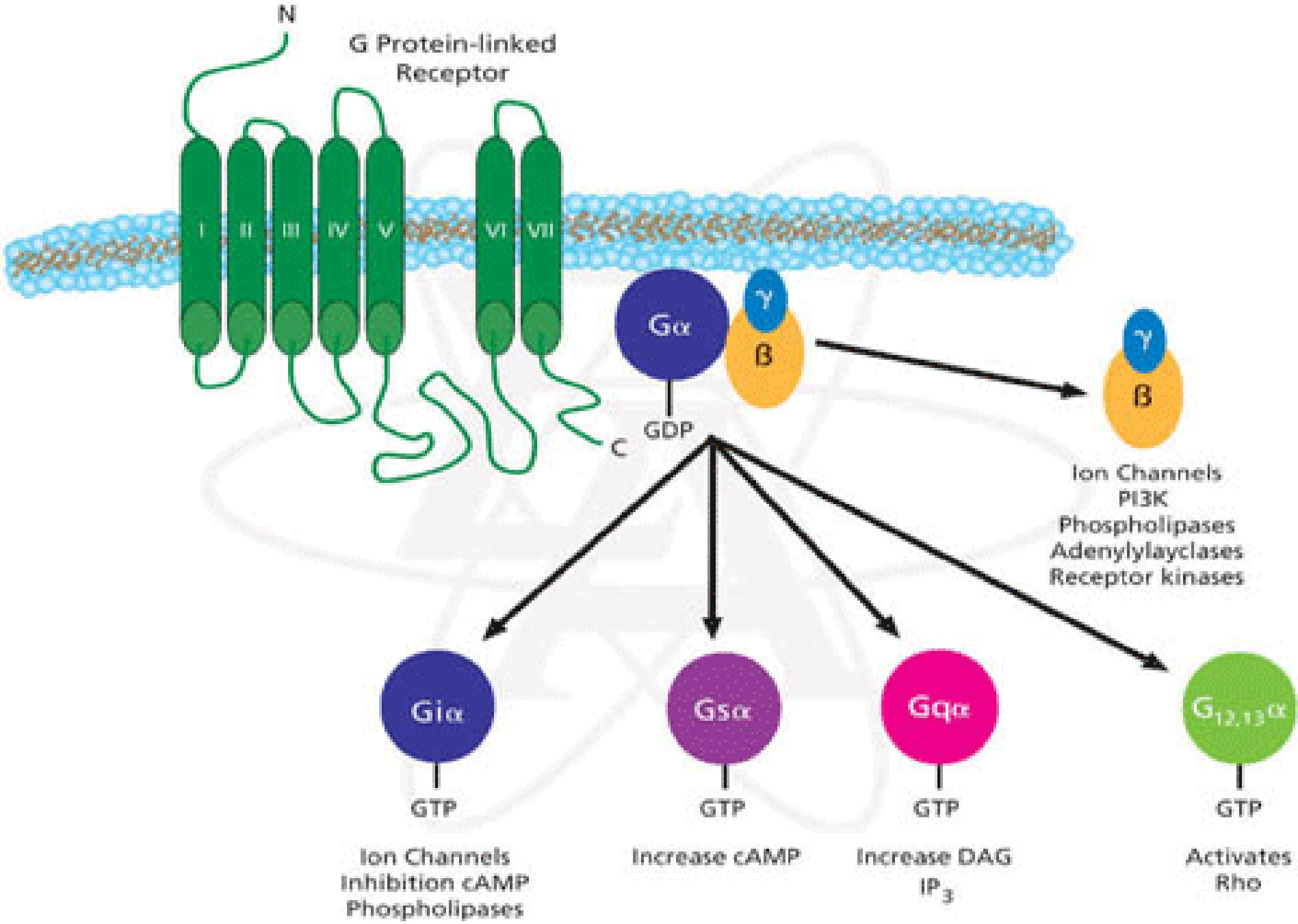
glycogen → glucose 1-phosphate

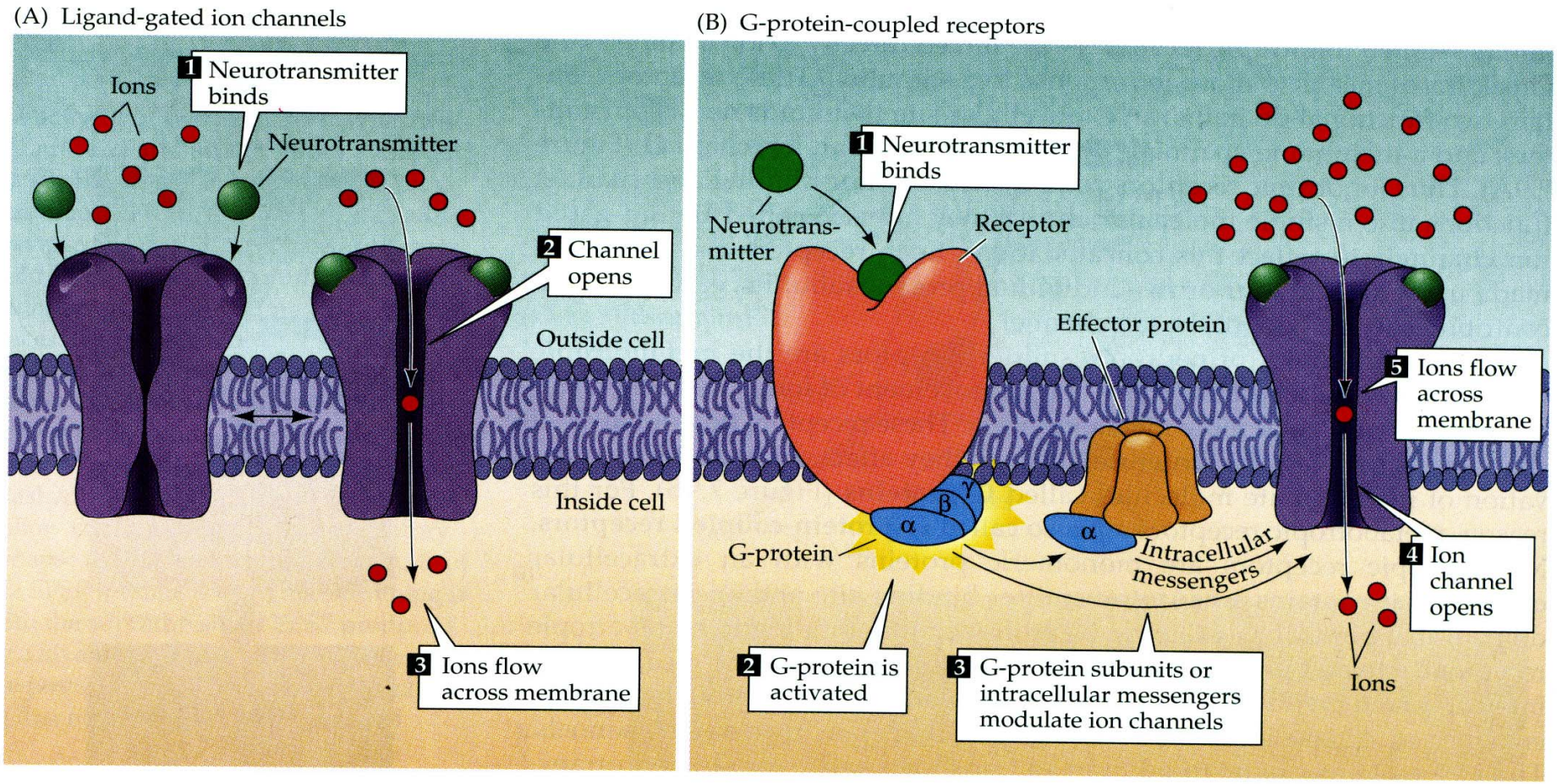
β1-adrenergic receptors acting on cardiac muscle:

AC ↑ cAMP ↑ PKA ↑ L-type calcium channel ↑ calcium influx

↓

contraction


N
G Protein-linked
Receptor
I
II
III
IV
V
VI
VII
C
Gα
γ
β
GDP
γ
β
Ion Channels
PI3K
Phospholipases
Adenylylayclases
Receptor kinases
Giα
GTP
Ion Channels
Inhibition cAMP
Phospholipases
Gsα
GTP
Increase cAMP
Gqα
GTP
Increase DAG
IP3
G12,13α
GTP
Activates
Rho


(A) Ligand-gated ion channels
Ions
1 Neurotransmitter binds
Neurotransmitter
2 Channel opens
Outside cell
Inside cell
3 Ions flow across membrane
(B) G-protein-coupled receptors
1 Neurotransmitter binds
Neurotrans-mitter
Receptor
Effector protein
5 Ions flow across membrane
γ
β
α
α
G-protein
Intracellular messengers
4 Ion channel opens
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels
Ions

Distinguishing properties of ionotropic receptors **and** metabotropic receptors

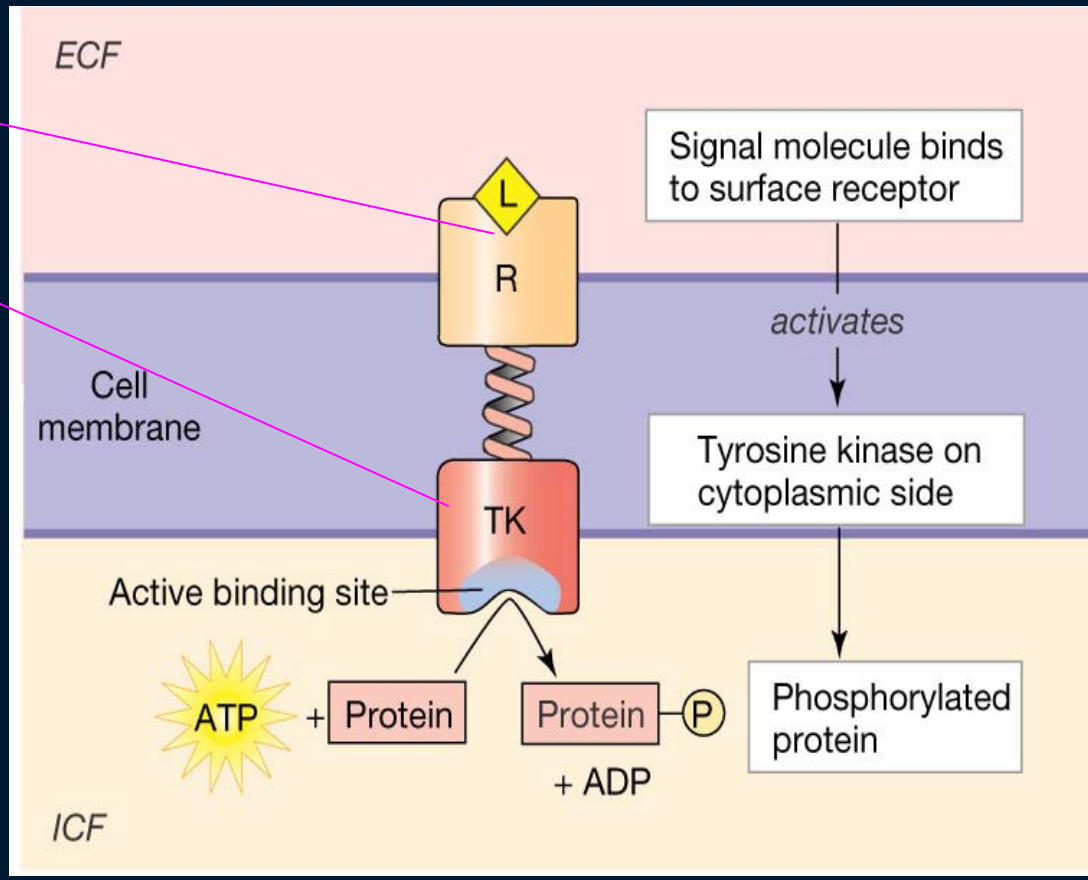
ionotropic receptors	metabotropic receptors
Multimers	**monomer**
forms an ion channel	do not have ion channels
Rapid postsynaptic effects (ms)	slow (seconds to minutes)
Need not G-proteins	need G-proteins
Rapid behavior (stretch reflex)	Modulate neural circuitry mediated behavior

Receptor Enzymes (Enzyme-linked receptors)

Two domain
extracellular binding domain

intracellular domain is enzyme

often tyrosine kinases



Subfamilies of Receptor Tyrosine Kinases

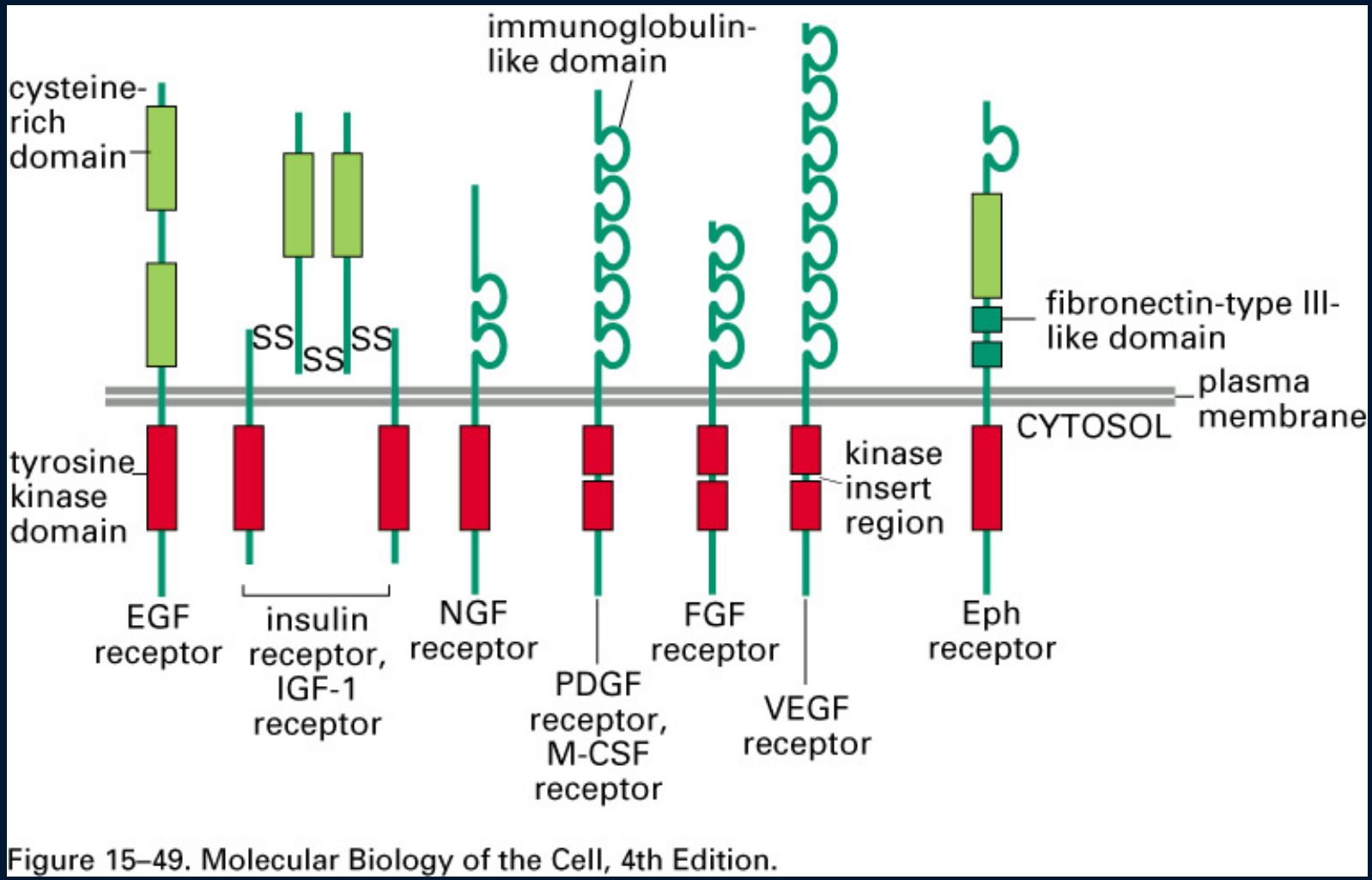
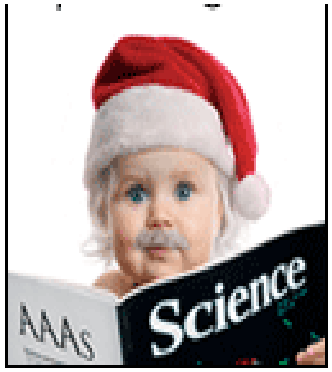


Figure 15–49. Molecular Biology of the Cell, 4th Edition.

The tyrosine kinase pathway differ from G protein-coupled receptors in two way

- 1.They span the membrane only once.
- 2.Their cytoplasmic domain contains a protein kinase activity that phosphorylates proteins on tyrosine residues.



Thank you!