

# Farmacología y Farmacoterapia I

## Grado en Farmacia - UAH

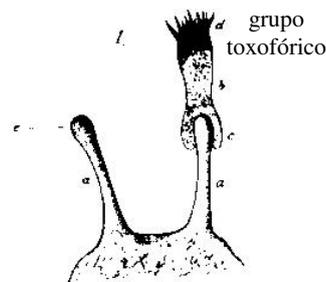
### Tema 5 (curso 2021-2022)

Clasificación de las principales dianas farmacológicas. Receptores farmacológicos. Mecanismos de transducción de señales. Receptores constitutivamente activados.

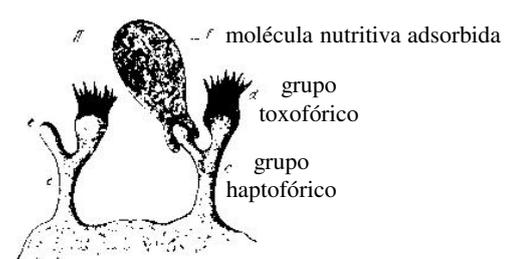
Prof. Federico Gago Badenas  
Universidad de Alcalá  
(federico.gago@uah.es)



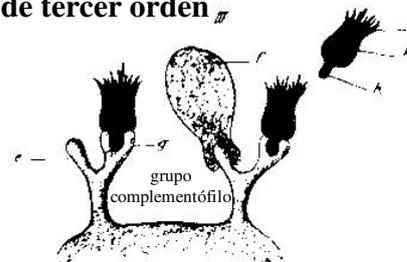
#### I. Receptor de primer orden



#### II. Receptor de segundo orden



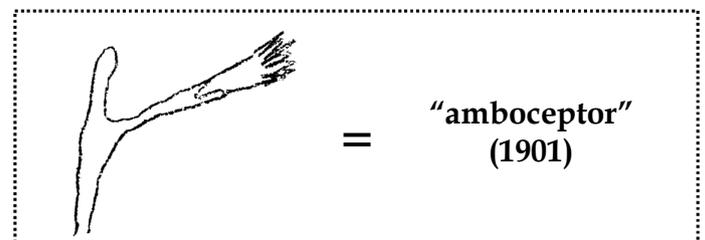
#### III. Receptor de tercer orden



*“Corpora non agunt nisi fixata”*

Paul Ehrlich

“Address in Pathology on Chemotherapeutics:  
Scientific Principles, Methods, and Results”  
Lancet II, 445 (1913)



**Principios del siglo XX:** estudio de las acciones de agonistas y antagonistas colinérgicos y adrenérgicos sobre diversos órganos diana.

*J. N. Langley: acciones de pilocarpina y atropina sobre la glándula salival del perro*  
*H. H. Dale: inversión del efecto de la adrenalina ("simpatina") por los alcaloides del cornezuelo del centeno, etc*

**1920-1970:** Desarrollo de las teorías clásicas de la acción de receptores basadas en la **aplicación de la ley de acción de masas** a datos obtenidos sobre preparaciones fisiológicas intactas.

*A. J. Clark, Ariëns, Stephenson, Black, Furchgott, etc*  
*R.P. Ahlquist: subclasificación de receptores adrenérgicos en alfa y beta*

**1960-1970:** Fusión entre la bioquímica y la farmacología de receptores.

*E. Sutherland: AMP cíclico como segundo mensajero*  
*Rodbell y Gilman: regulación de la actividad de la adenilil ciclase por nucleótidos de guanina.*

**TRES características de las acciones de los fármacos indican que son concentrados por las células sobre pequeñas áreas específicas conocidas como RECEPTORES:**

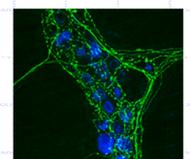
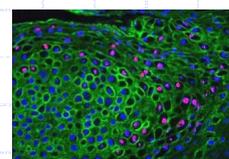
- ✓ la **alta dilución** (a menudo  $10^{-9}$  M) a la que mantienen su potencia disoluciones de muchos fármacos,
- ✓ la **alta especificidad química** de los fármacos, tan discriminante que incluso los isómeros d- y l- de una misma sustancia pueden tener acciones farmacológicas diferentes, y
- ✓ la **alta especificidad biológica** de los fármacos (= **selectividad**), e.g. la isoprenalina tiene un potente efecto sobre el músculo cardíaco pero muy escaso sobre el músculo estriado.

Técnicas que han contribuido a convertir el concepto "nebuloso" inicial de **RECEPTOR farmacológico** en entidades moleculares discretas que pueden ser ensayadas y manipuladas para conseguir un beneficio terapéutico (*orden cronológico*):

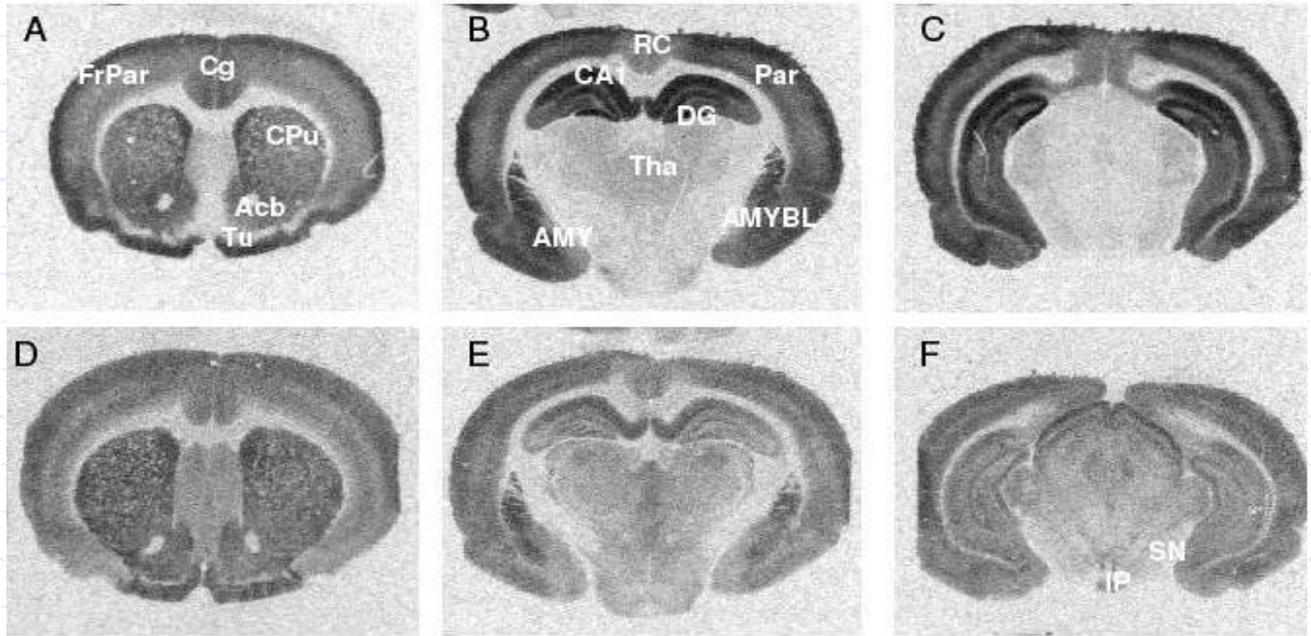
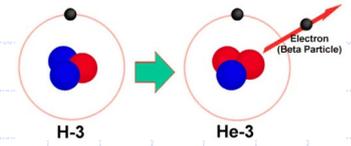
- ✓ Autorradiografías y ensayos de fijación/desplazamiento de radioligandos
- ✓ Etiquetado de fotoafinidad
- ✓ Solubilización y purificación (cromatografía de afinidad)
- ✓ Clonado y secuenciación de los receptores
- ✓ Reconstitución de sistemas receptoriales funcionales completos a partir de los componentes individuales purificados (transfección ADN<sub>c</sub>)
- ✓ Mutagénesis dirigida y receptores quiméricos
- ✓ Criomicroscopía electrónica, difracción de rayos X, espectroscopía de resonancia magnética nuclear (RMN)

## Localización de los neurotransmisores (NT) y las enzimas que los sintetizan

- ◆ Ensayos de fijación de radioligandos
  - Extracción de tejido del cuerpo
  - Homogeneización del tejido y extracción de las membranas celulares
  - Incubación de las membranas con el NT (o un agonista o antagonista del receptor) marcado radiactivamente
  - Lavado del material radioactivo no pegado a las membranas
  - Determinación de la radiactividad de la muestra en un contador de centelleo
- ◆ Ensayos de fijación *in situ* : **autorradiografía**
  - Preservar el tejido
  - Preparar rodajas o rebanadas del tejido
  - Exponer el tejido al NT (o un agonista o antagonista del receptor) marcado radiactivamente
  - Eliminar el material radioactivo no pegado a las membranas mediante lavado
  - Exponer la preparación a una película sensible a la radiación
- ◆ Tomografía de emisión de positrones (PET) o fotón único (SPECT) utilizando trazadores específicos
- ◆ Inmunohistoquímica e inmunocitoquímica
- ◆ Hibridización de ADN o ARN *in situ*

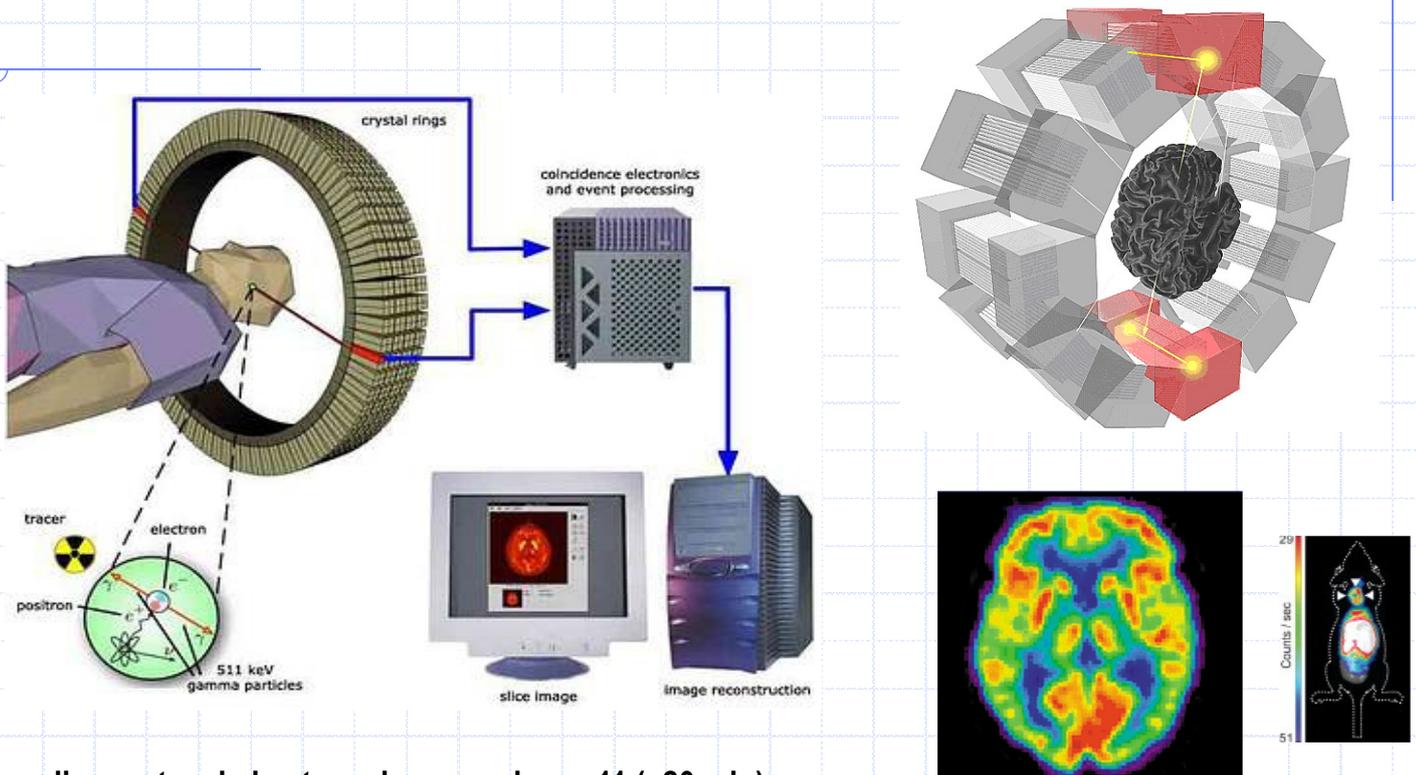


# Autorradiografía de receptores



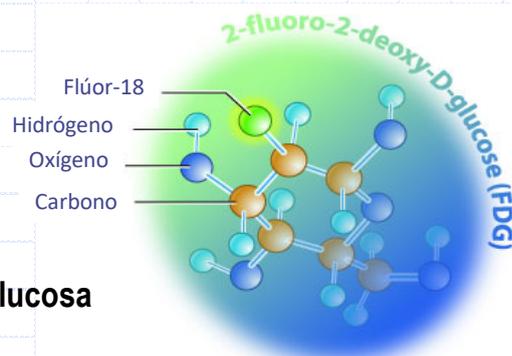
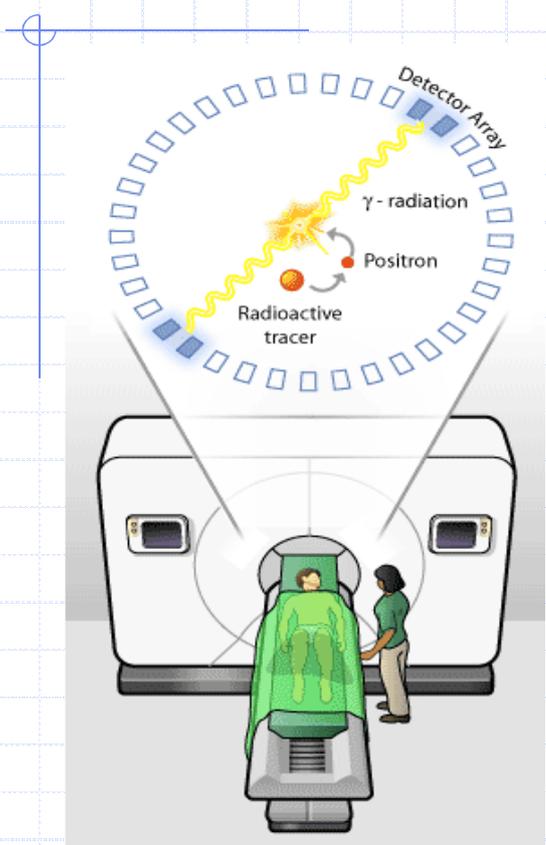
Imágenes autorradiográficas que muestran la distribución anatómica de la fijación de  $[^3\text{H}]$ pirenzepina (A, B, C) y  $[^3\text{H}]$  AF-DX384 (D, E, F) en secciones coronales del cerebro de rata. Estos radioligandos tienen como dianas a los receptores muscarínicos  $M_1/M_4$  y  $M_2/M_4$ , respectivamente.

# Tomografía de emisión de positrones (PET)

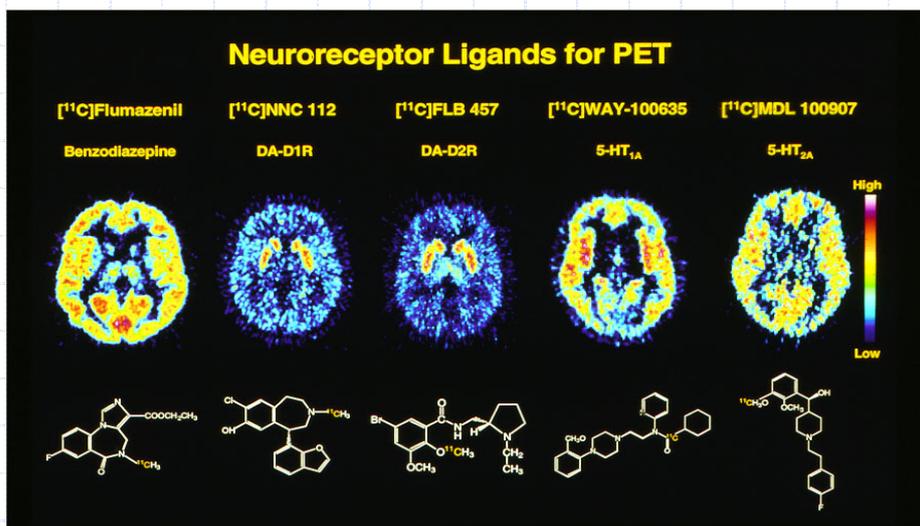


Vidas medias cortas de los trazadores: carbono-11 (~20 min), nitrógeno-13 (~10 min), oxígeno-15 (~2 min), y flúor-18 (~110 min).

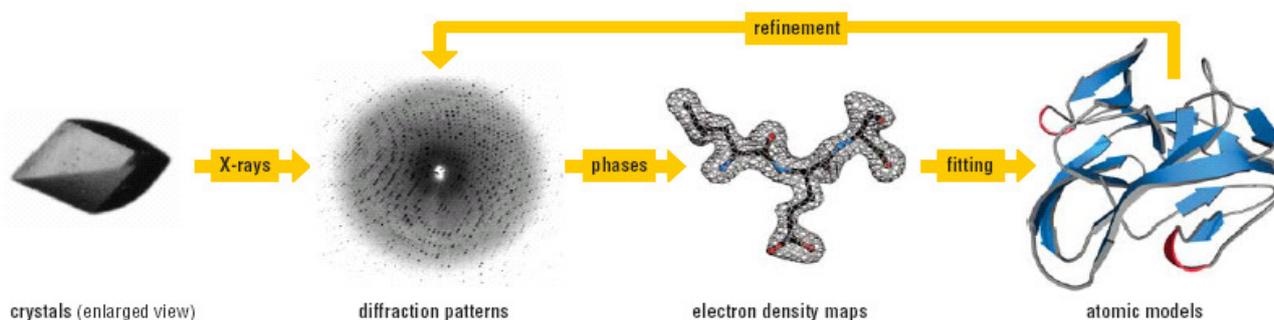
# Tomografía de emisión de positrones (PET)



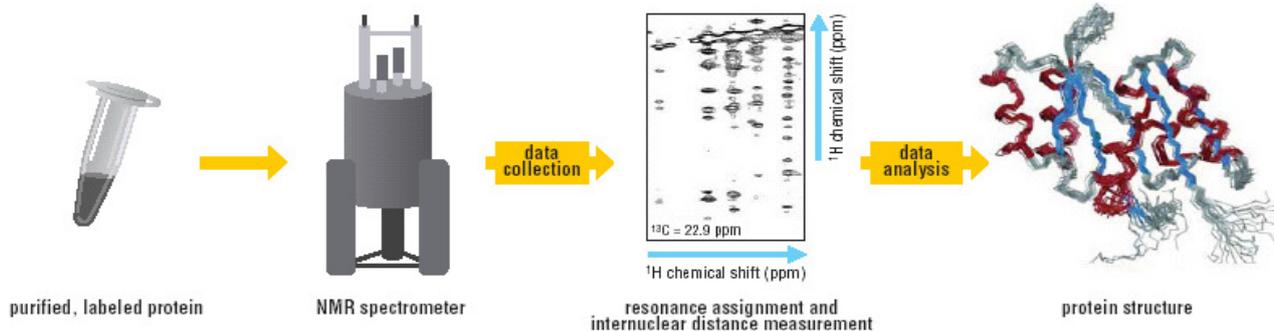
FDG: 2-F-desoxi-D-glucosa



## Determinación de Estructuras 3D por Cristalografía de Rayos X,



## Espectroscopía de RMN



## y (Crio)Microscopía Electrónica (Microscopía Electrónica 3D)

# Molecular Machinery: A Tour of the Protein Data Bank

Cells build many complex molecular machines that perform the biological jobs needed for life. Some of these machines are molecular scissors that cut food into digestible pieces. Others then use these pieces to build new molecules when cells grow or tissues need to be repaired. Some molecular machines form sturdy beams that support cells, and others are motors that use energy to crawl along these beams. Some recognize attackers and mobilize defenses against infection.

Researchers around the world are studying these molecules at the atomic level. These 3D structures are freely available at the Protein Data Bank (PDB), the central storage of biomolecular structures. A few examples from the ~100,000 structures held in the PDB are shown here at a magnification of about 3,500,000 times, with each atom represented as a small sphere. The enormous range of molecular sizes is illustrated here, from the water molecule (H<sub>2</sub>O) with only three atoms (shown on the left) to the ribosomal subunits with hundreds of thousands of atoms.

## Digestive Enzymes: breaking food into small nutrient molecules

1. Amylase 1mso
2. Phospholipase 1pse
3. Decarboxylase 2dca
4. Lipase 1lii
5. Pepsin 5pep
6. Trypsin 1tryp
7. Carboxypeptidase 5cpa
8. Ribonuclease 5rsa

## Blood Plasma Proteins: transporting nutrients and defending against injury

9. Factor X 1f10
10. Thrombin 1tbr
11. Fibrin 1fbr
12. Serum Albumin 1cra

## Viruses and Antibodies: engaging in constant battle in the bloodstream

13. Antibody 1igt
14. Ribonuclease 5rsa

## Hormones: carrying molecular messages through blood

15. Glucagon 1gcn
16. Insulin 1ins
17. Epidermal Growth Factor 1egf

## Channels, Pumps and Receptors: getting back and forth across the membrane

18. Ras Protein 5ras
19. Beta2 Adrenergic Receptor/Gs Protein 3bta
20. Acetylcholine Receptor 1acr
21. Epidermal Growth Factor Receptor 1egf
22. Rhodopsin 1rho
23. P-glycoprotein 1pdr
24. Na<sup>+</sup>/K<sup>+</sup> ATPase 1nka
25. Calcium Pump 1cnp
26. Cytochrome 5p9b

## Photosynthesis: harvesting energy from the sun

27. Photosystem II 1psa
28. Light harvesting Complex 1lhc
29. Photosystem I 1psi
30. Photosynthetic Reaction Center 1rc

## Enzymes: cutting and joining the molecules of life

31. Cytochrome C oxidase (Complex IV) 1co3
32. Cytochrome c 1cyt
33. Cytochrome bc<sub>1</sub> complex (Complex III) 1bc1
34. NADH:Ubiquinone Oxidoreductase (Complex I) 1n1o
35. ATP Synthase 1af7
36. Myoglobin 1mgb
37. Hemoglobin 4hhb
38. Fibrin 1fbr
39. Fatty Acid Synthase 2zuc
40. Bacterio Rhodospirillum Rubro Rubredoxin/Cytochrome 1fca
41. Green Fluorescent Protein 1gfl
42. Luciferase 1luc
43. Glutamine Synthase 2gls
44. Alcohol Dehydrogenase 2ahs
45. Dihydrofolate Reductase 1dhf
46. Nitrogenase 1nif
47. Leucine Aminopeptidase 1lap
48. Beta Lactamase 1blm
49. Catalase 1cat
50. Thymidylate Synthase 2thz
51. Tyrosinase 1tyr
52. Aspartate Carbonyltransferase 4art
53. Hexokinase 1hki
54. Phosphoglucomutase 1hgm
55. Phosphotransferase 4pfr
56. Alcohol dehydrogenase 2ahs
57. Isocitrate dehydrogenase 2icdh
58. Cytochrome 5p9b
59. Phosphoglucomutase 1hgm
60. Phosphoglucomutase 1hgm
61. Triose 1trp
62. Pyruvate Kinase 1pkm

## Scale:

1000 5000 10000  
1000 (nanometers)  
104 millimeters

Extracellular Protein Membrane Protein Intracellular Protein: Cytosol

## Energy Production: powering the processes of the cell

31. Cytochrome C oxidase (Complex IV) 1co3
32. Cytochrome c 1cyt
33. Cytochrome bc<sub>1</sub> complex (Complex III) 1bc1
34. NADH:Ubiquinone Oxidoreductase (Complex I) 1n1o
35. ATP Synthase 1af7
36. Myoglobin 1mgb
37. Hemoglobin 4hhb

## Storage: containing nutrients for future consumption

38. Fibrin 1fbr

## Infrastructure: supporting and moving cells

63. Actin 1act
64. Myosin 1myo
65. Microtubule 1tub
66. Collagen 1col

## Protein Synthesis: building new molecular machines

67. Transfer RNA 1tra
68. Val<sup>t</sup> tRNA Synthetase 1tas
69. Threonine tRNA Synthetase 1tth
70. Glutaminyl tRNA Synthetase 1tgn
71. Isobutyl tRNA Synthetase 1tib
72. Phenylalanyl tRNA Synthetase 1tph
73. Asparaginyl tRNA Synthetase 1tasn
74. Ribosome 1p91
75. Elongation factor Tu/EFNA 1tef
76. Elongation factor G/EF 1teg
77. Elongation factor Ts and Tu 1efu
78. Initiation 1itb
79. Chaperonin GroEL/ES 1aan
80. Protein-coupled Receptor 2pdr
81. Yeast Heat Shock Protein 1hsp26
82. Prionase 4hst
83. Ubiquitin 1ubq

## DNA: storing and reading genetic information

84. DNA 1dna
85. Inhibition Inducible Eosin 1ei
86. DNA Polymerase 1dna
87. Topoisomerase 1top
88. RNA Polymerase 2rho
89. Ice suppressor 1sh 1shs
90. Catalytic Core Activator Protein 1cap
91. RNA-binding Protein/Transcription Factor 1baf
92. DNA Helicase 1dnh
93. DNA Polymerase 1dna
94. Nucleosome 1nuc
95. HU Protein 1hup
96. Single-strand DNA-binding protein 1ssb

## Intracellular Protein: Nucleus

<http://www.rcsb.org/pdb/>

# How Do DRUGS Work?

Examples from the PDB archive

PROTEINS are tiny molecular machines that perform most of the tasks needed to keep cells alive. These machines are far too small to see, so you might imagine that it is impossible to affect their action. However, drugs can be used to turn proteins on or off. DRUGS are small molecules that bind to proteins and modify their actions. Some very powerful drugs, such as antibiotics or anticancer drugs, are used to completely disable a critical molecular machine. These drugs can kill a bacterial or cancer cell. Other molecules, such as aspirin, gently block less-critical proteins for a few hours. With the use of these drugs, we can make changes inside our own cells, such as the blocking of pain signals. Many structures of drugs that bind to proteins have been determined by scientists. These atomic structures allow us to see how drugs work, and perhaps how to modify them to improve their action. A few examples are shown here. Some of these drugs, like penicillin, were discovered in nature. Other drugs, such as HIV protease inhibitors, were created by using the target protein structure to design new drug molecules. These structures of proteins and drugs, along with many others, can be explored at the RCSB Protein Data Bank (PDB).

## Antibiotics & Antivirals

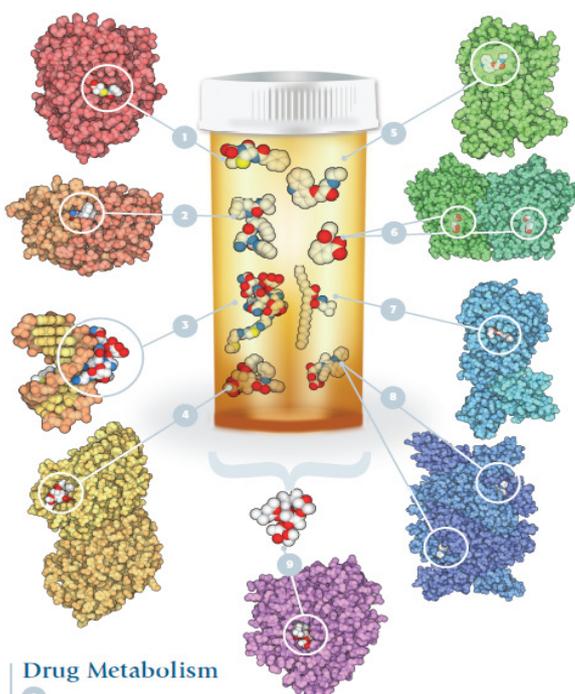
Antibiotics and antiviral drugs are specific poisons. They need to kill pathogenic organisms like bacteria and viruses without poisoning the patient at the same time. Often, these drugs attack proteins that are only found in the targeted bacterium or virus and which are crucial for their survival or multiplication. For instance, penicillin attacks the enzyme that builds bacterial cell walls, and HIV protease inhibitors like saquinavir attack an enzyme that is needed for HIV maturation.

1. D-alanyl-D-alanine carboxypeptidase with penicillin (1pwc)
2. HIV protease with saquinavir (1hsv)

## Anticancer Chemotherapy

Cancer cells grow and multiply without control. Since these cells are still similar to normal cells, it is difficult to kill them selectively with drugs that can't distinguish between the two. Many drugs currently used for cancer chemotherapy attack all growing cells, including cancer cells and normal cells. This causes the severe side effects of cancer chemotherapy, because the drugs attack rapidly-growing cells in hair follicles and the stomach. Two examples are shown here. Bleomycin attacks DNA in actively growing cells, often cleaving the DNA chain and killing the cell. Paclitaxel (taxol) binds to tubulin, preventing the action of microtubules during cell division.

3. DNA with bleomycin (1mka)
4. Tubulin with taxol (1tfx)



## Drug Metabolism

You have probably noticed that when you take drugs, the effects gradually wear off in a few hours. Enzymes like cytochrome P450 continually search for drugs and destroy them. This is important because it protects us from poisonous molecules in our diet and in the environment, but it means that we have to take multiple doses of drugs when being treated for a disease.

5. Cytochrome P450 3A4 with erythromycin (2jdo)

## Drugs of Signaling Proteins

Many drugs are designed to keep bodily processes at normal healthy levels. Much of the body's regulation is done through elaborate communications between cells, so some of the most widely prescribed drugs function by blocking the signaling proteins that allow cells to communicate. G-protein-coupled receptors, which transmit signals across cell membranes, are targets for many drugs. For instance, the drug loratadine (Claritin) is used to treat allergies because it blocks the histamine receptor. Losartan (Cozaar) is used to treat high blood pressure because it blocks the angiotensin II receptor, and carazolol is one of a large class of beta-blockers that bind to the adrenergic receptor, making it useful for treating heart disease. Signals can also be stopped by blocking the enzymes that create a signaling molecule. Aspirin blocks pain at the source by inhibiting the enzyme cyclooxygenase, which makes pain-signaling prostaglandin molecules.

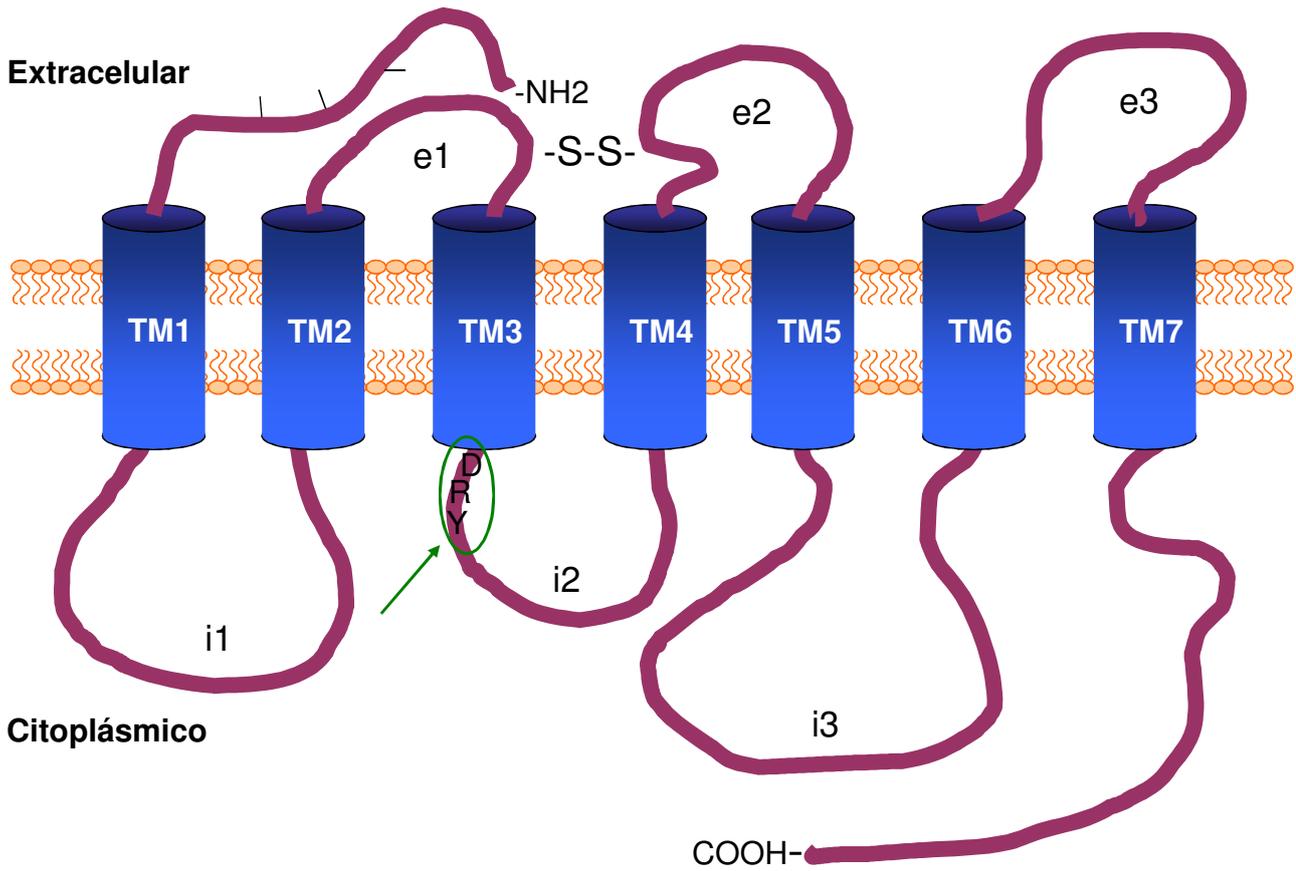
5. Adrenergic receptor with carazolol (2rh1)
6. Prostaglandin H2 synthase with aspirin (1pfa). The drug breaks into two pieces when it binds to the enzyme, and the smaller piece (an acetyl group) is attached to the enzyme with a covalent bond. The closeup shows the drug in one piece.

## Lifestyle Drugs

Pharmaceutical scientists have developed a number of drugs that help people modify their own health and bodily function. The drug orlistat (Xenical or alli) blocks the action of pancreatic lipase, and thereby reduces the amount of fat that is absorbed from food. Atorvastatin (Lipitor) and simvastatin (Zocor) lower cholesterol by blocking the action of HMG-CoA reductase, an enzyme involved in the synthesis of cholesterol. These drugs can be used, along with changes in diet and exercise, to help lose weight, regulate cholesterol levels, and control heart disease.

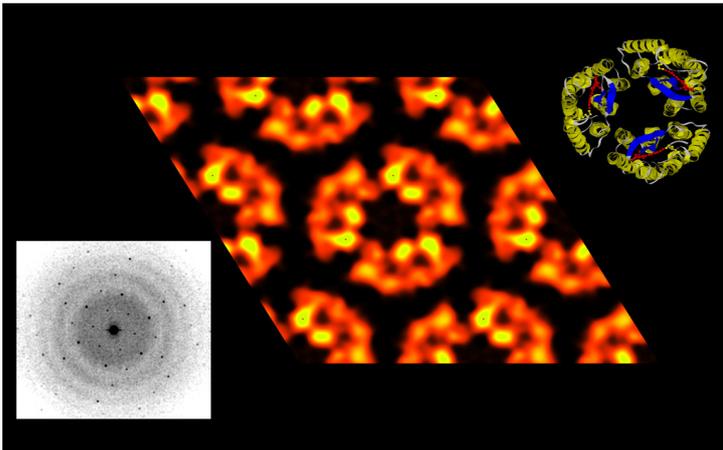
7. Pancreatic lipase with an allyl phosphonate inhibitor (1lpa). The drug orlistat shown on the right is similar to the inhibitor found in the crystal structure.
8. HMG-CoA reductase with atorvastatin (1hmk)

# RECEPTORES ACOPLADOS A PROTEÍNAS G (GPCR)



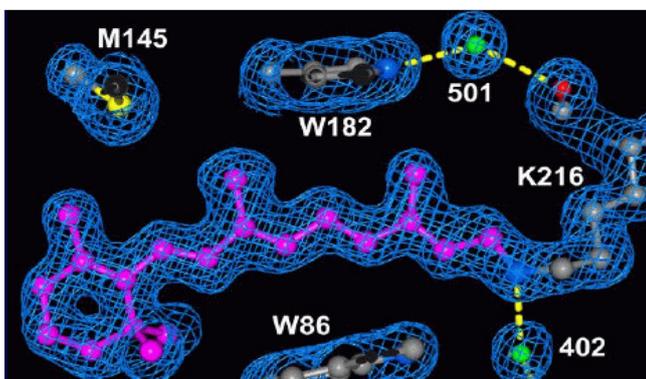
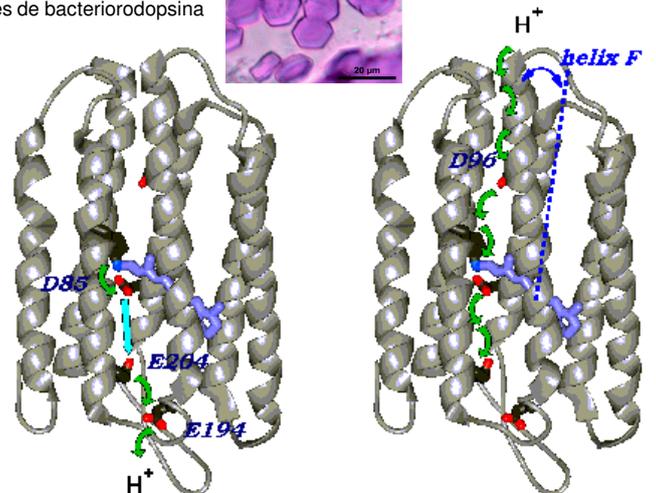
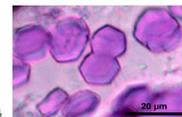
## BACTERIORODOPSINA

Una proteína de 7 segmentos transmembrana (con retinal como cofactor) que funciona como una bomba de protones cuando recibe un fotón de luz

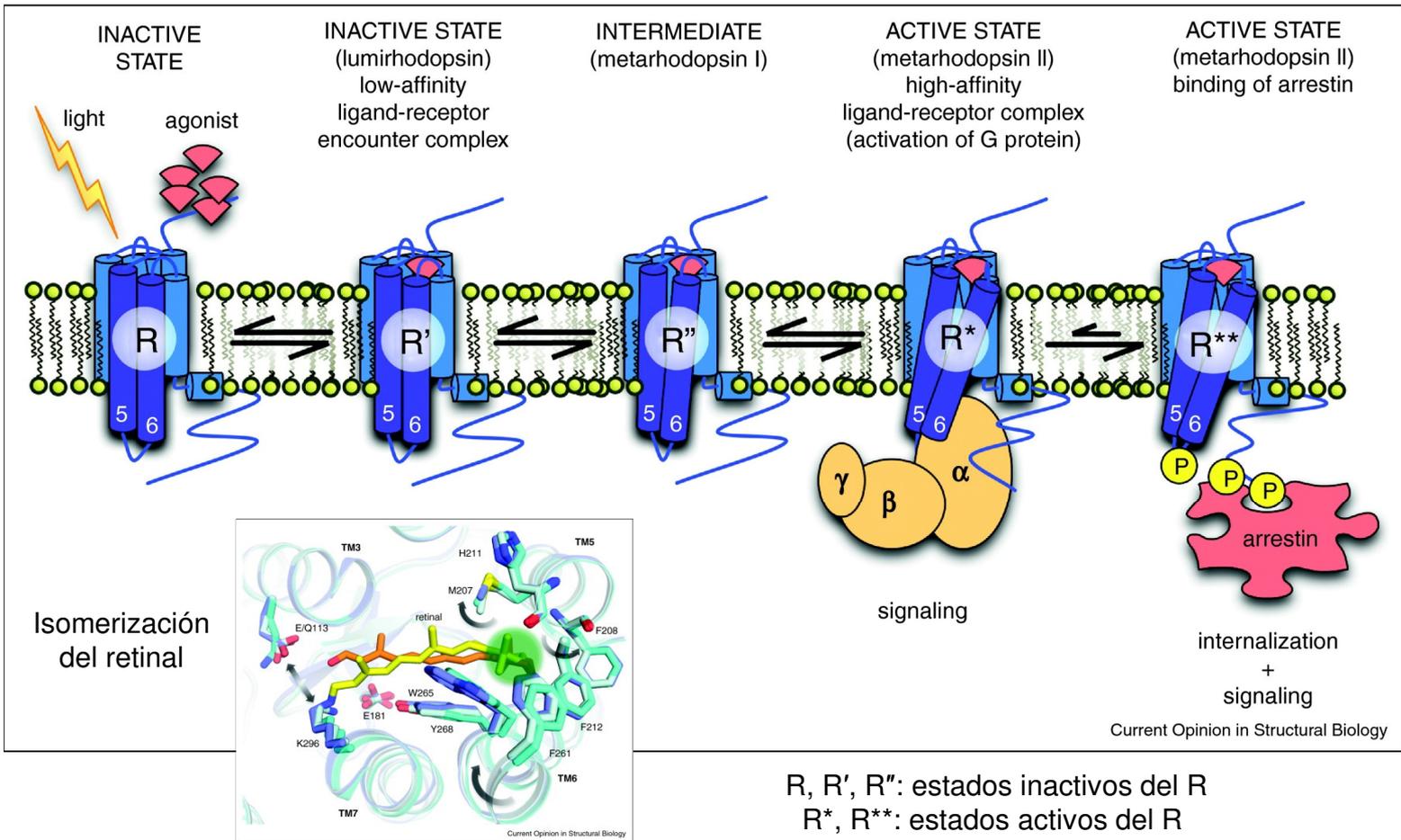


Salinas de Marchamalo (Murcia)

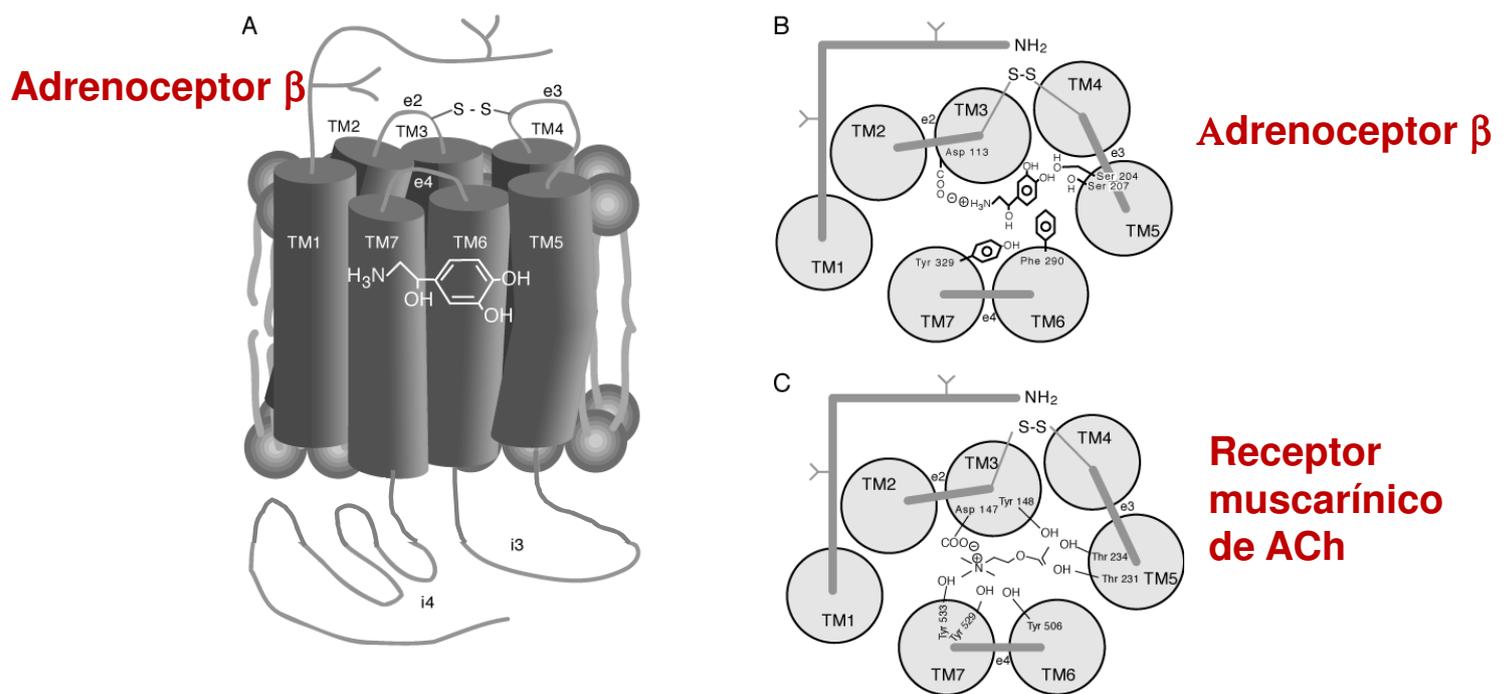
*Halobacterium salinarum*  
cristales de bacteriorodopsina



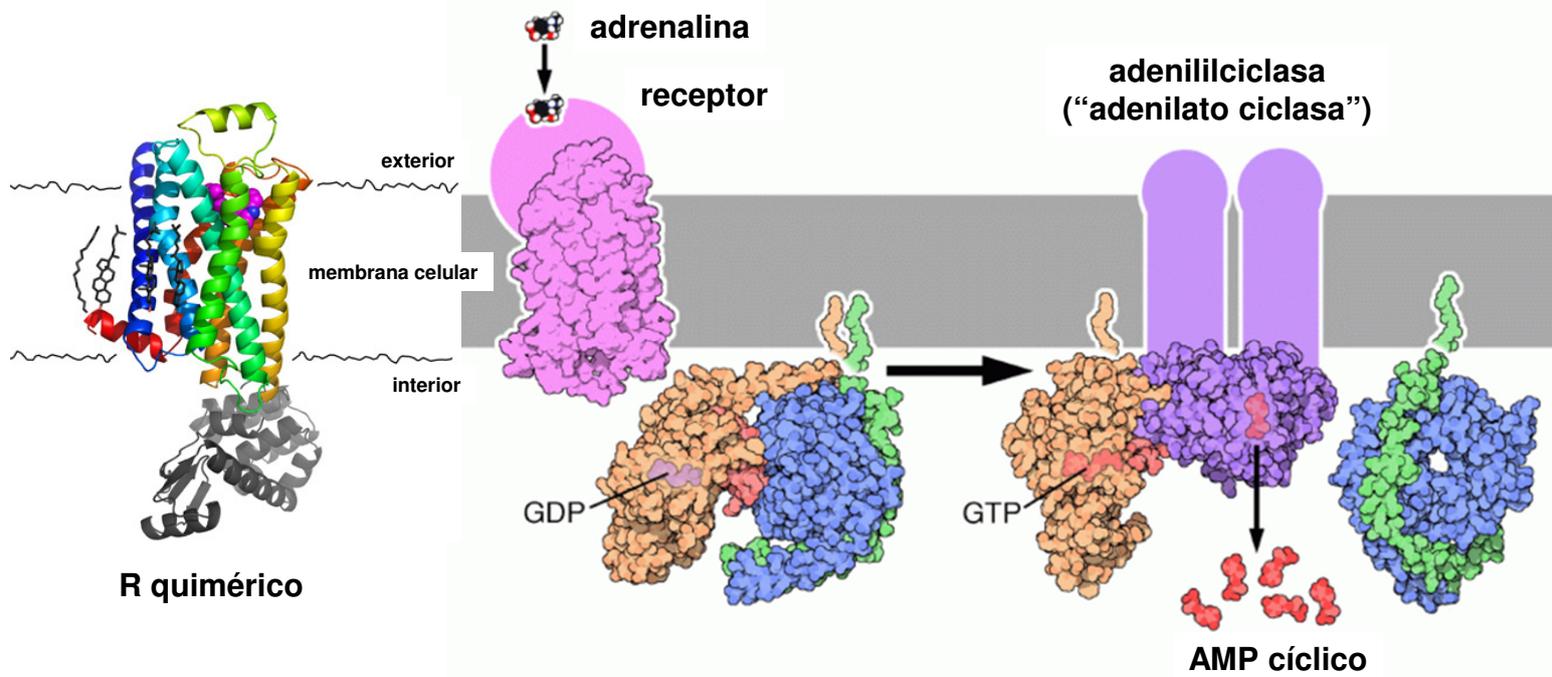
# Activación inducida por agonistas de los GPCRs de la clase A: similitudes con la activación de la rodopsina por la luz



## TOPOLOGÍA DE MEMBRANA PREDICHA PARA LOS GPCRs (antes de que se resolviese su estructura tridimensional)



Fundamental Neuroscience (1999) by M.J. Zigmond, F.E. Bloom, S.C. Landis, J.L. Roberts & L.R. Squire. Academic Press, San Diego CA, USA. ISBN: 0-12-780870-1



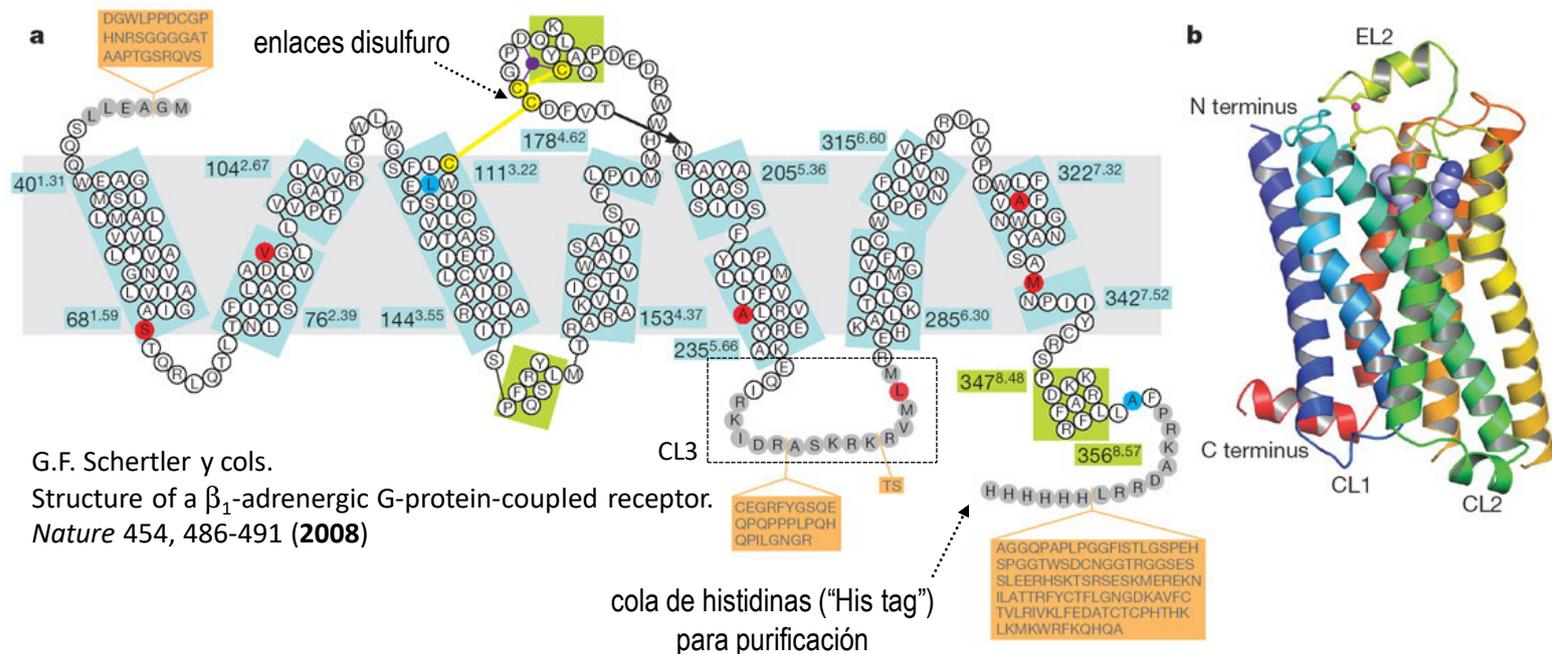
**Estructura tridimensional del receptor  $\beta_2$ -adrenérgico.** La proteína está coloreada como un arcoiris desde el azul de un extremo (el N-terminal) hasta el rojo en el otro (C-terminal). En una célula, las hélices  $\alpha$  atraviesan la membrana celular. La unión al receptor del agonista natural (adrenalina) dispara una serie de eventos que culminan en una respuesta celular.

**Protein Data Bank: 2RH1, 2R4R, 2R4S**

**Brian K. Kobilka** y cols.: "GPCR Engineering Yields High-Resolution Structural Insights into  $\beta_2$ -Adrenergic Receptor Function", publicado en *Science* 318, 1266-1273 (2007)

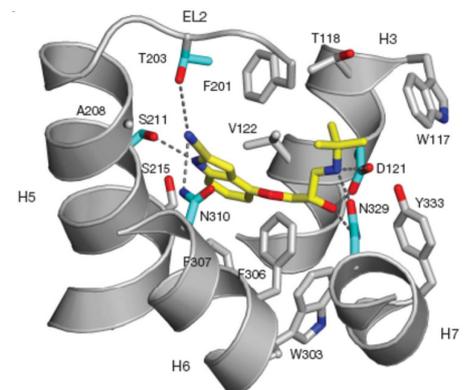
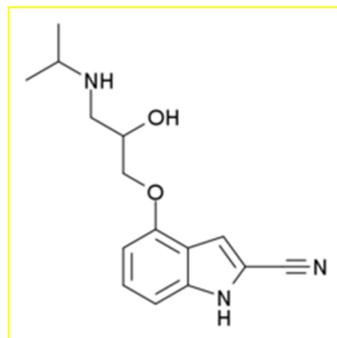
**Brian K. Kobilka** y cols.: "Crystal structure of the human  $\beta_2$  adrenergic G-protein-coupled receptor", publicado en *Nature* 450, 383-387 (2007)

**Premio Nobel de Química (2012)**



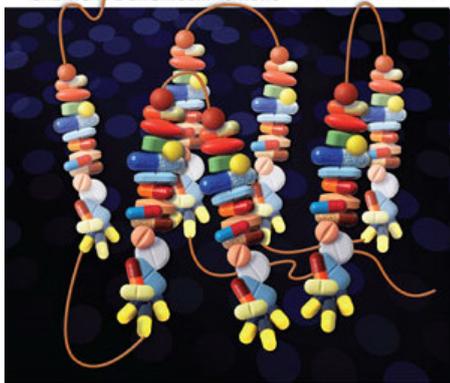
G.F. Schertler y cols.  
Structure of a  $\beta_1$ -adrenergic G-protein-coupled receptor.  
*Nature* 454, 486-491 (2008)

**Estructura tridimensional del receptor  $\beta_1$ -adrenérgico unido al antagonista de alta afinidad cianopindolol.**

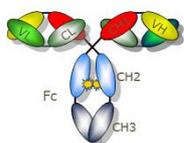


**Protein Data Bank: 2VT4**

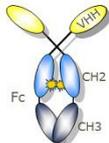
<http://www.rcsb.org/pdb/explore/explore.do?structureId=2VT4>



**TRANSMEMBRANE PROTEINS**  
 How GPCR structures help the drug hunt P.15



Anticuerpo convencional



Anticuerpo de camélido con solo la cadena pesada



Nanocuerpo (VHH)

**HISTORY LESSON**  
**A Winding Path For GPCRs**



**1900:** Parke-Davis patents an early GPCR-targeted drug—epinephrine, a pure form of naturally occurring adrenaline—which acts on adrenergic receptors.

**2000:** First X-ray structure of a GPCR, the retina pigment rhodopsin, is unveiled.



**2007:** Second GPCR X-ray structure, the β<sub>2</sub>-adrenergic receptor, debuts.

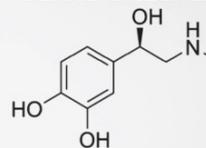
**2008:** First GPCR molecular modeling assessment kicks off.



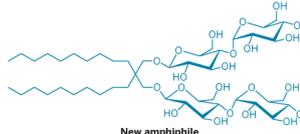
**Jan. 13, 2011:** Activate X-ray structures of the β<sub>2</sub>-adrenergic receptor are published. Llama antibodies help stabilize one structure.

**Jan. 27, 2011:** Receptos initiates human clinical trials of a GPCR-targeted drug developed with help from a crystal structure.

**ADRENALINE**

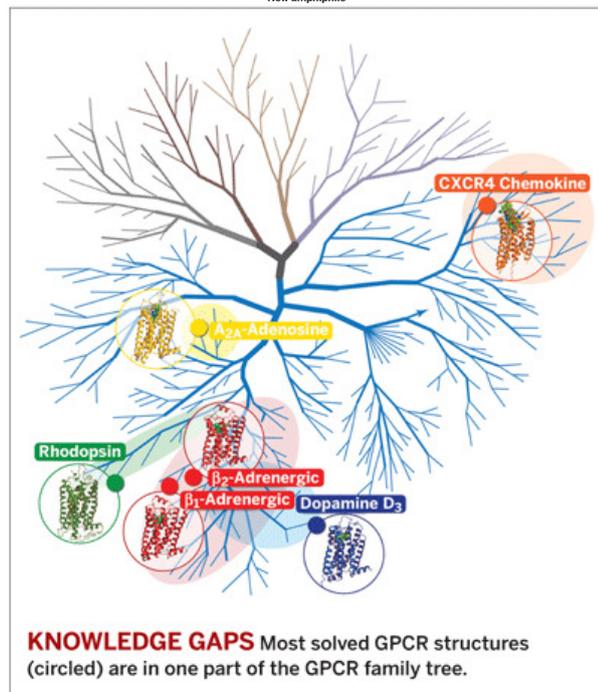


**A.K.A. EPINEPHRINE**

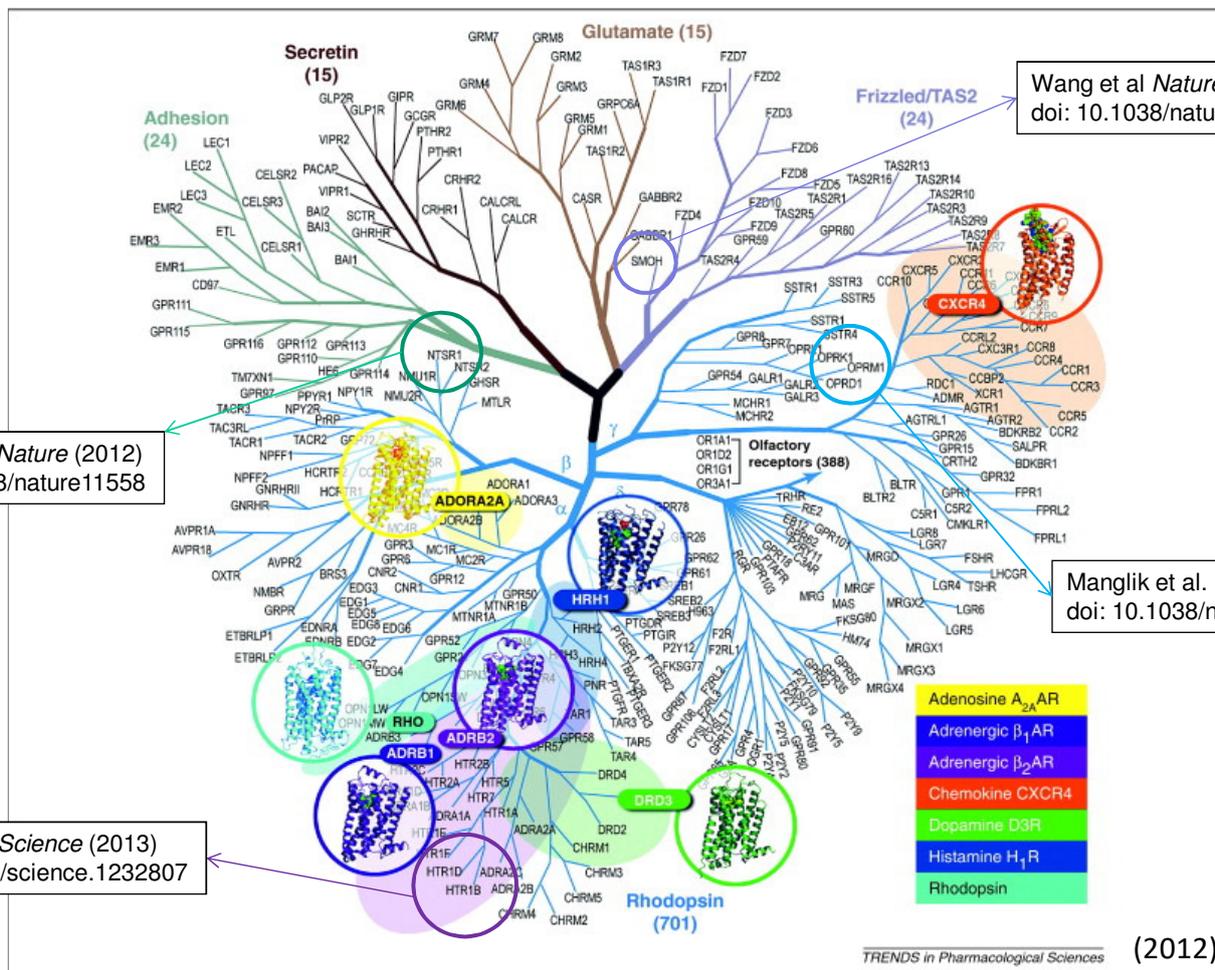


Tensoactivo

New amphiphile



**KNOWLEDGE GAPS** Most solved GPCR structures (circled) are in one part of the GPCR family tree.

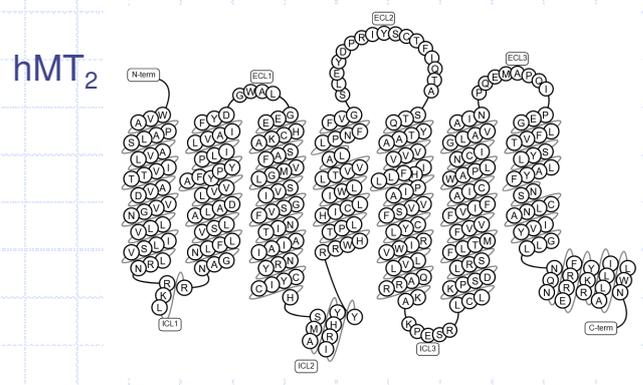
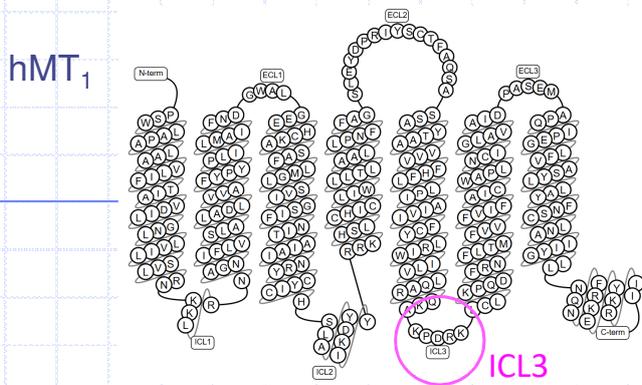
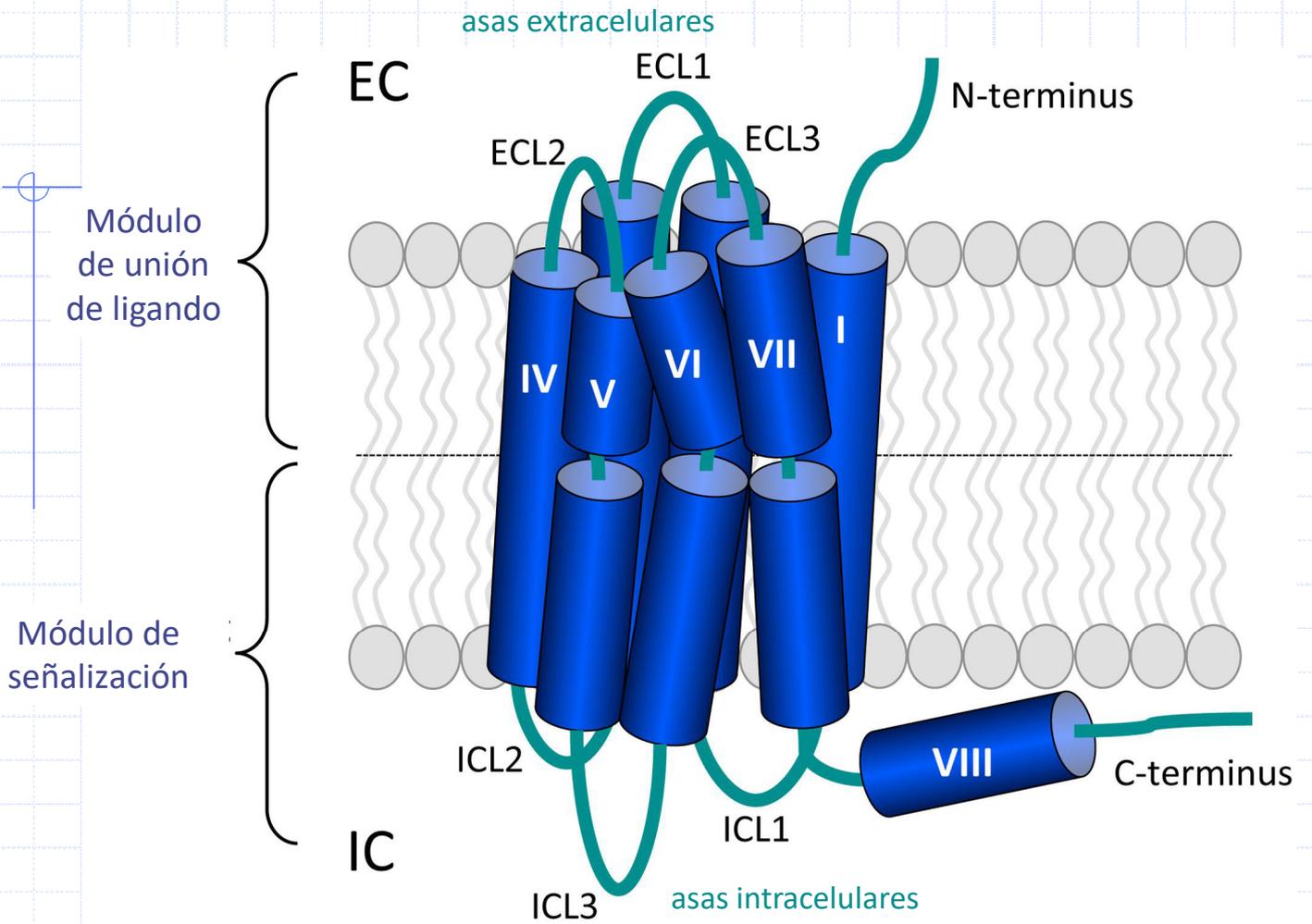


White et al *Nature* (2012)  
 doi: 10.1038/nature11558

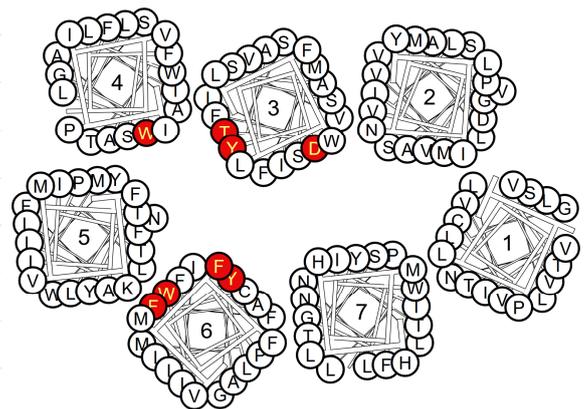
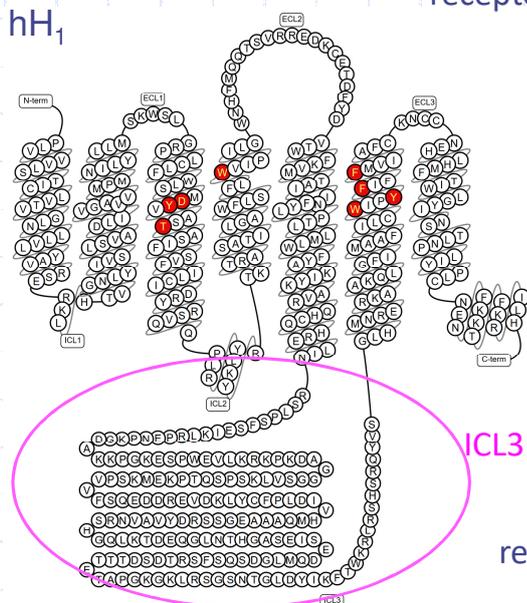
Wang et al *Nature* (2013)  
 doi: 10.1038/nature12167

Manglik et al. *Nature* (2013)  
 doi: 10.1038/nature10954

Wang et al. *Science* (2013)  
 doi: 10.1126/science.1232807



receptores humanos de melatonina



receptor H<sub>1</sub> humano de histamina

Los GPCRs son máquinas complejas, controladas no solo por sus ligandos farmacológicos...

sino también por colesterol, lípidos, iones sodio y fosfato, agua, etc.

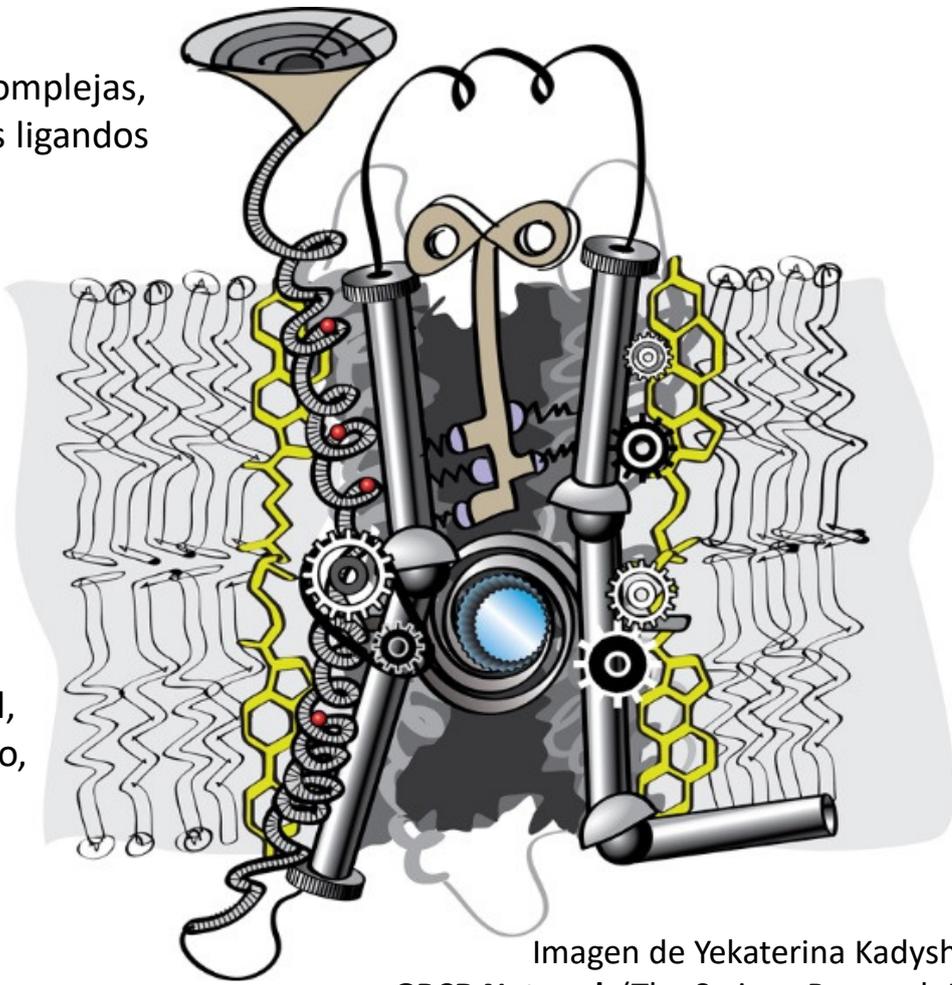
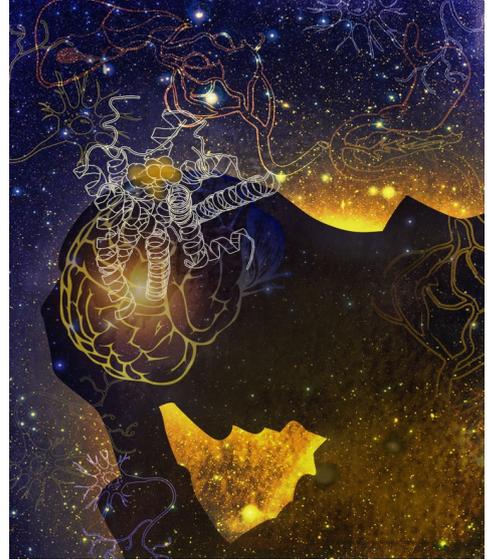
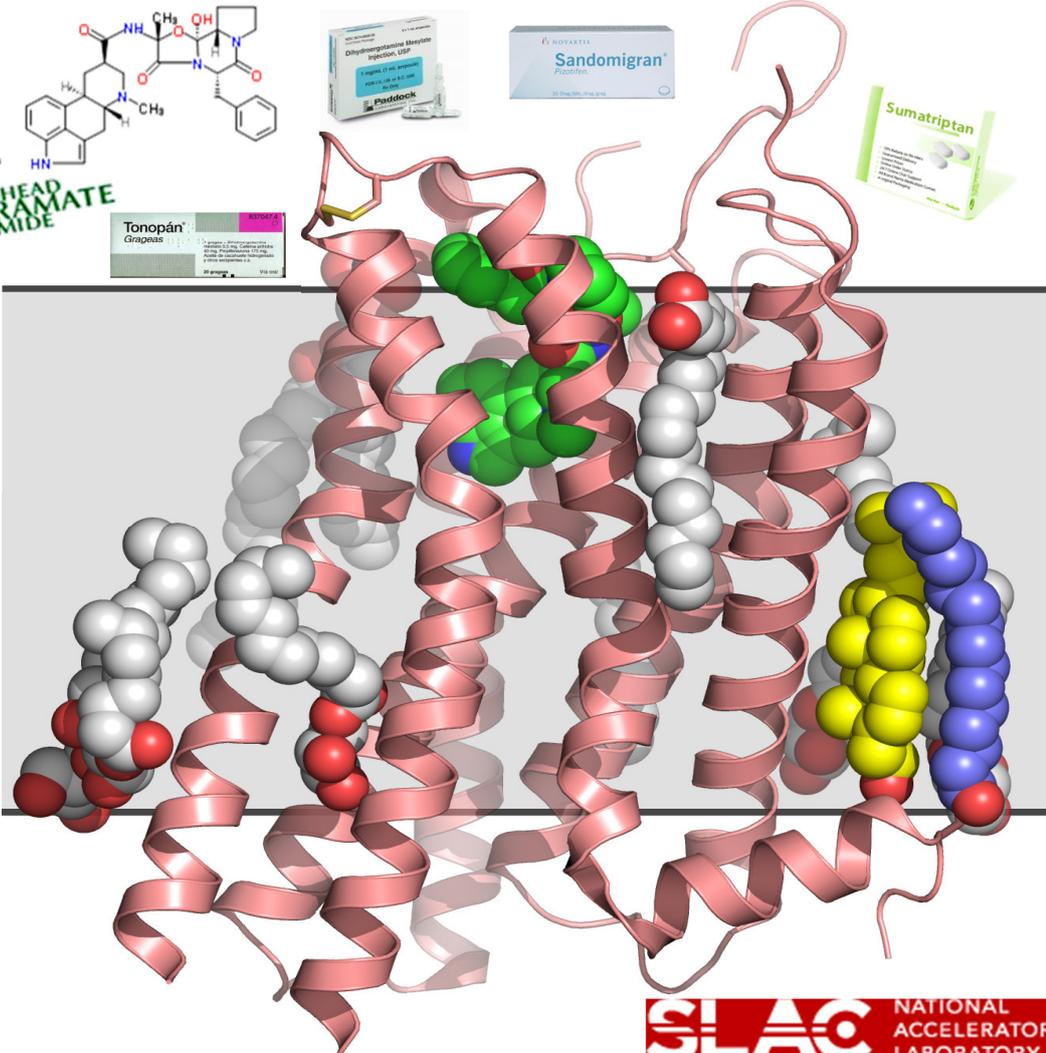
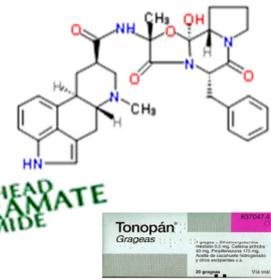
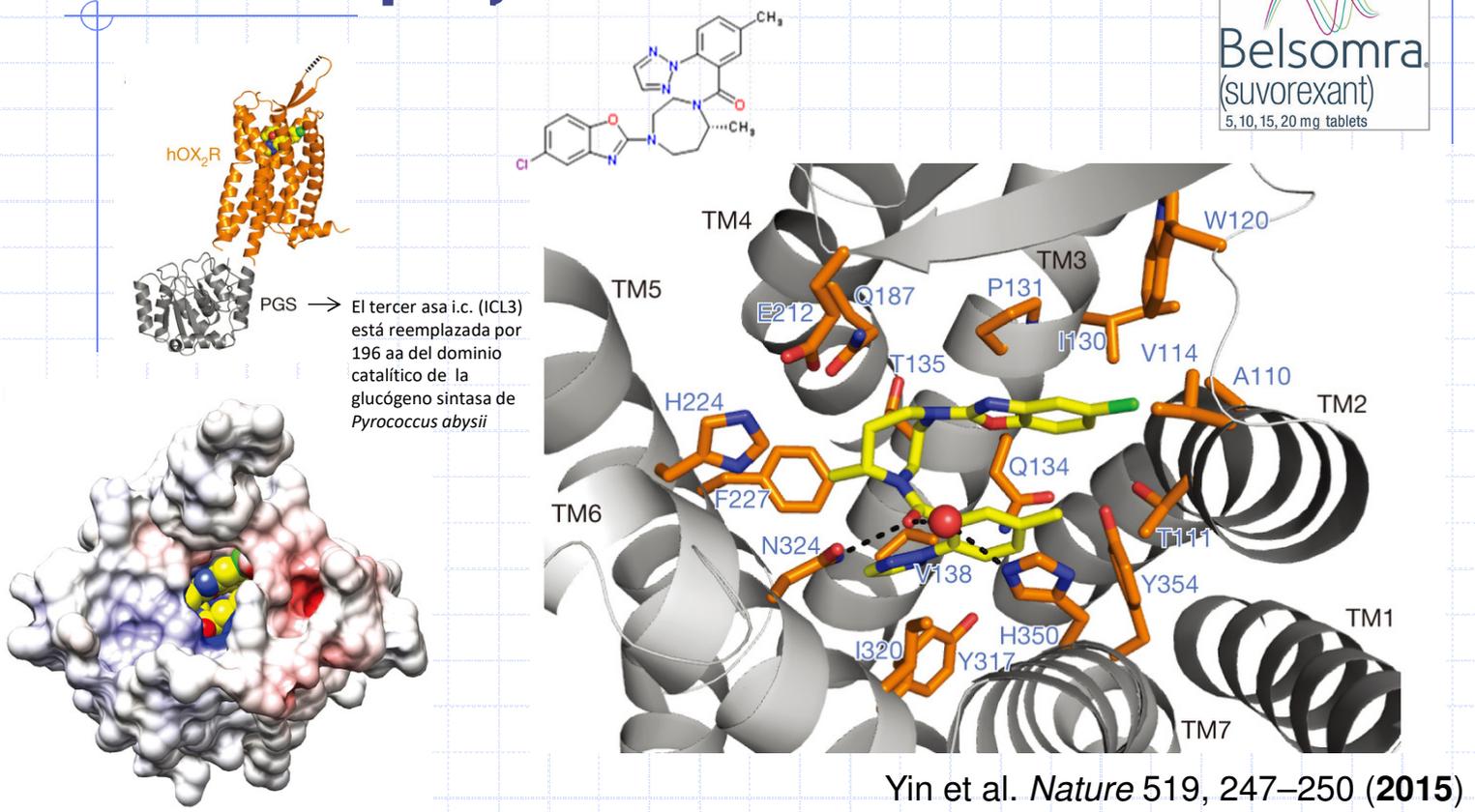


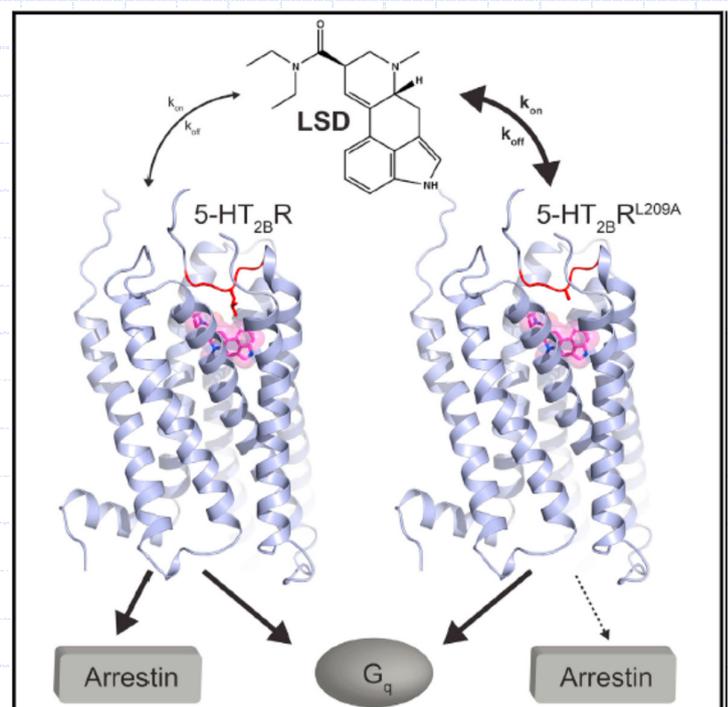
Imagen de Yekaterina Kadyshevskaya, GPCR Network (The Scripps Research Institute)



# El receptor humano de orexina OX<sub>2</sub> en complejo con suvorexant

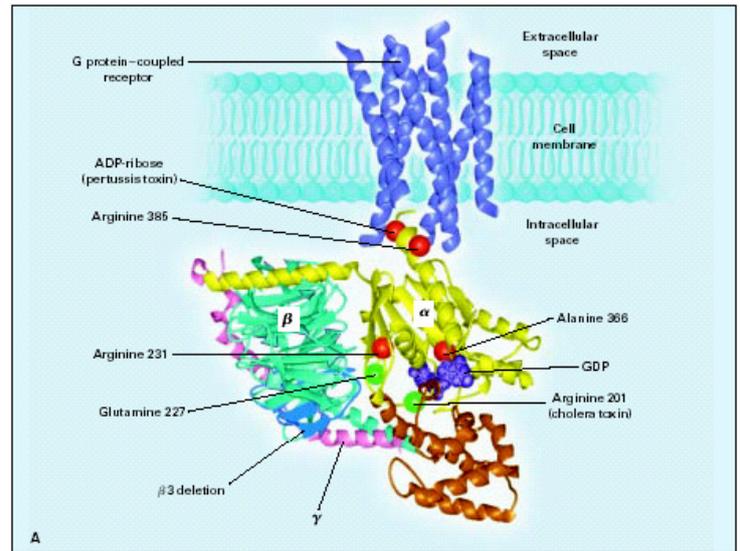
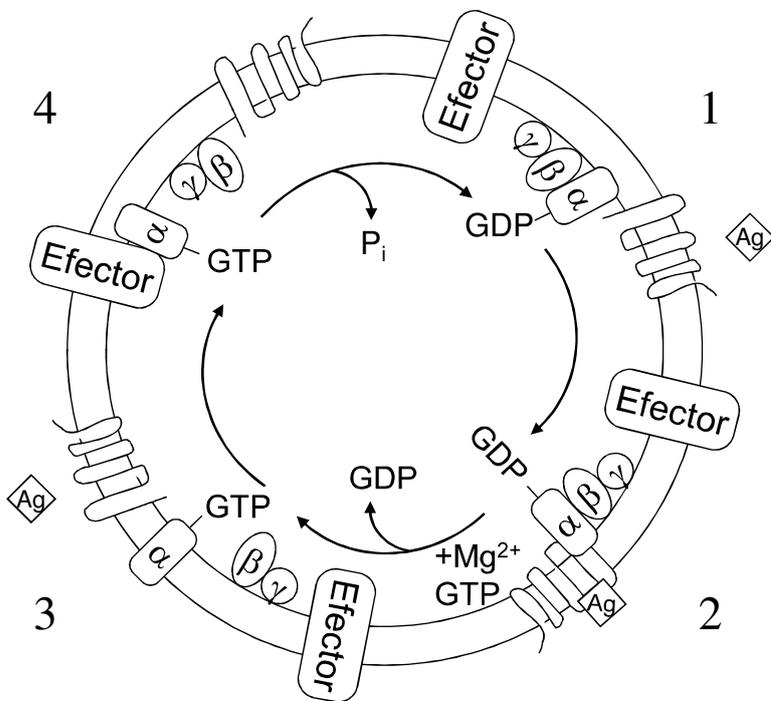


# El receptor humano de serotonina 5-HT<sub>2B</sub> en complejo con LSD



Protein Data Bank: 5TVN

Wacker et al. *Cell* 168, 377–389 (2017)



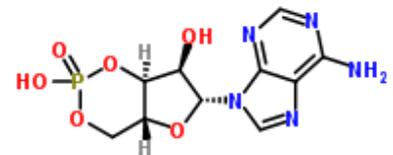
**Esquema explicativo de la transducción de señales mediada por las proteínas G:** 1) La ocupación de un **receptor 7TM** por un agonista (Ag) conduce a la formación de un complejo ternario con la **proteína G (αβγ)** en cuya subunidad α está unida una molécula de GDP; 2) el intercambio de GDP por GTP en presencia de iones  $Mg^{2+}$  conduce a la activación de la proteína G, a su separación del receptor, y a la disociación de  $\alpha \cdot GTP$  de  $\beta\gamma$ ; 3) el agonista también se disocia del receptor en su forma de baja afinidad; y 4)  $\alpha \cdot GTP$  y  $\beta\gamma$  activan a sus respectivos sistemas efectoros (aquí representado sólo para la primera que puede ser, por ejemplo, la **adenililciclasa**). La actividad GTPasa intrínseca de la subunidad  $\alpha$  hidroliza el GTP para dar GDP y fosfato inorgánico, tras lo cual se vuelve a formar la proteína G heterotrimérica.

## Ejemplos de sistemas de segundo mensajero

### ➤ Sistema del **AMP cíclico** como segundo mensajero

La enzima **ADENILIL CICLASA** (“adenilato ciclasa”) convierte ATP en AMPc cuando se activa por una proteína G del tipo  $G_s$ . Esta enzima está inhibida por las proteínas G de la clase  $G_i$ .

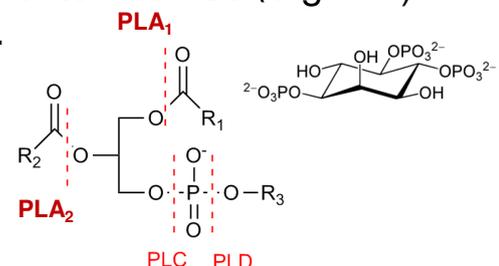
Ejemplos:            adrenoceptor  $\beta$              $\uparrow$  AMPc  
                           adrenoceptor  $\alpha_2$          $\downarrow$  AMPc



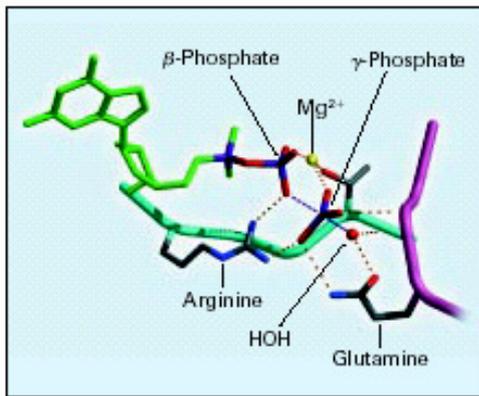
### ➤ Sistema del **fosfatidilinositol** como segundo mensajero

La enzima **FOSFOLIPASA C** hidroliza el fosfatidilinositol-4,5-bisfosfato ( $PIP_2$ ) para dar dos segundos mensajeros – el diacilglicerol (DAG) y el inositol trifosfato ( $IP_3$ ). DAG estimula a la enzima proteína quinasa C mientras que el  $IP_3$  promueve la liberación de  $Ca^{2+}$  a partir de depósitos de almacenamiento internos (e.g. RE). La fosfolipasa C se activa por una proteína G del tipo  $G_q$ .

Ejemplos:            muscarínico  $M_3$              $\uparrow$   $IP_3$  y DAG  
                           adrenoceptor  $\alpha_1$          $\uparrow$   $IP_3$  y DAG



# Clases de proteínas G definidas por su subunidad $\alpha$



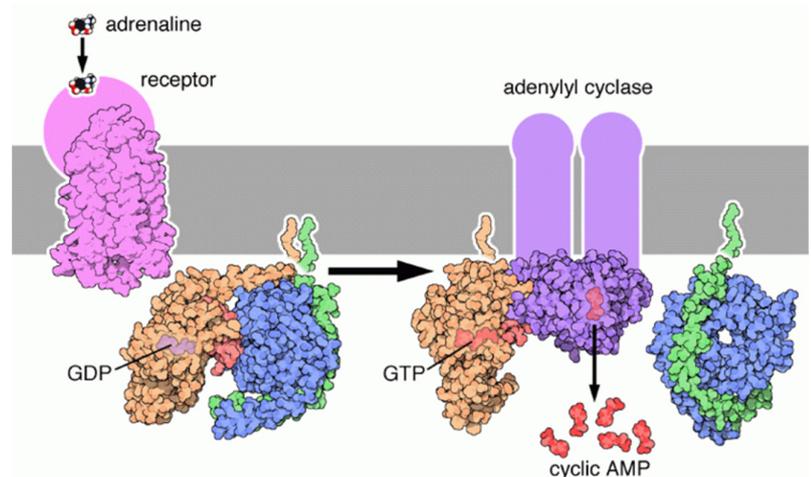
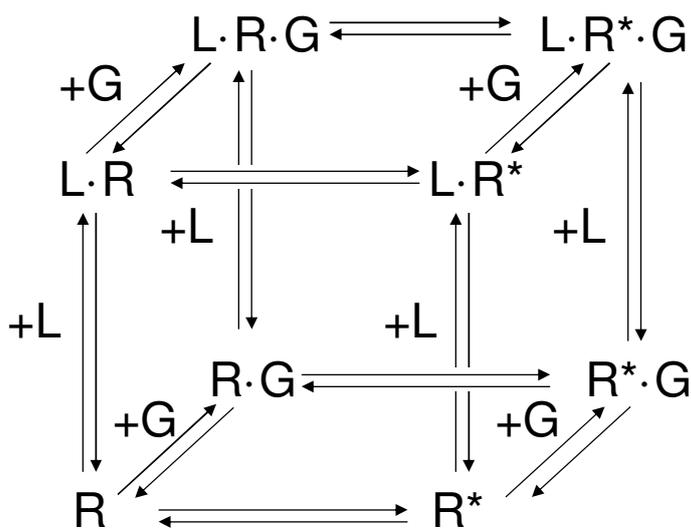
Hidrólisis del GTP

Clase	Subtipos	P.M. (kDa)
$\alpha_s$	4	45
$\alpha_{i/o}$	3	40
$\alpha_{q/11}$	5	40
$\alpha_{12}$	2	39

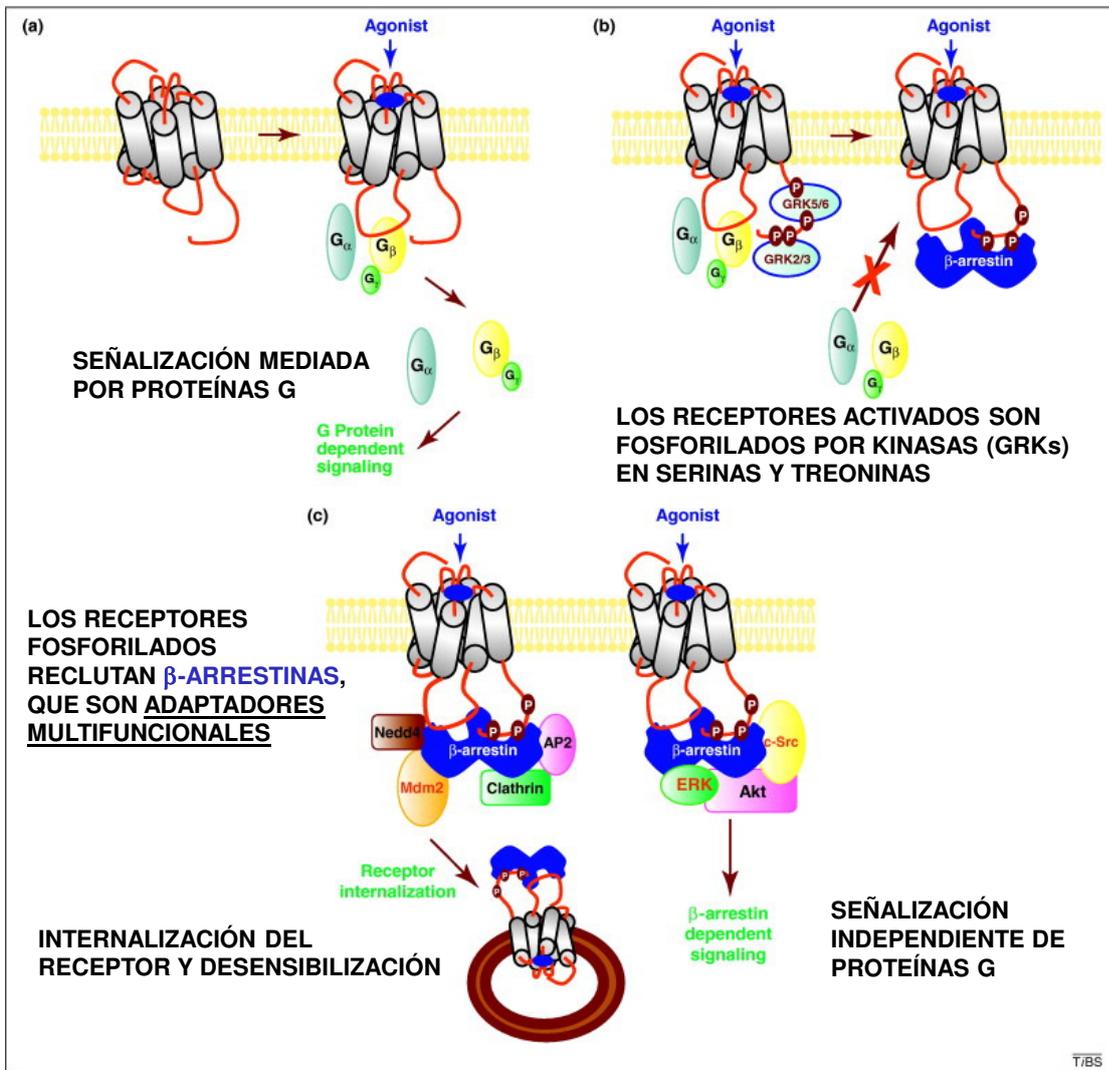
Clase	Función	Toxina
$\alpha_s$	Estimulación adenililciclasa: $\uparrow$ cAMP	CTX ( <i>Vibrio cholerae</i> ): <u>activa</u> irreversiblemente
$\alpha_{i/o}$	Inhibición adenililciclasa: $\downarrow$ cAMP	PTX ( <i>Bordetella pertussis</i> ): <u>inactiva</u> irreversiblemente
$\alpha_{q/11}$	Activación fosfolipasa C: $\uparrow$ IP <sub>3</sub> y DAG	
$\alpha_{12}$	Activ. canales K <sup>+</sup> / Inactiv. canales de Ca <sup>2+</sup>	PTX ( <i>Bordetella pertussis</i> ): <u>inactiva</u> irreversiblemente

**Modelo cúbico del complejo ternario**, construido para explicar la interacción de un ligando (L) con un receptor (R) acoplado a una proteína G (G) porque los nucleótidos de guanina afectan a la afinidad de los agonistas.

[Aplicación limitada en la práctica]



La capacidad del receptor de inducir la transducción de señales es función de  $R^* \cdot G$  para la actividad basal (con posible activación constitutiva) y  $R^* \cdot G + L \cdot R^* \cdot G$  para la actividad modulada por el ligando. Este modelo es una simplificación ya que pueden existir **múltiples estados activados del receptor**, cada uno acoplado a una proteína G diferente. Una serie de parámetros no mostrados ayudan a definir las propiedades de los ligandos (agonistas, antagonistas y agonistas inversos) y el **equilibrio de isomerización** entre los estados activado e inactivado del receptor.



Prof. Robert Lefkowitz (Duke University)

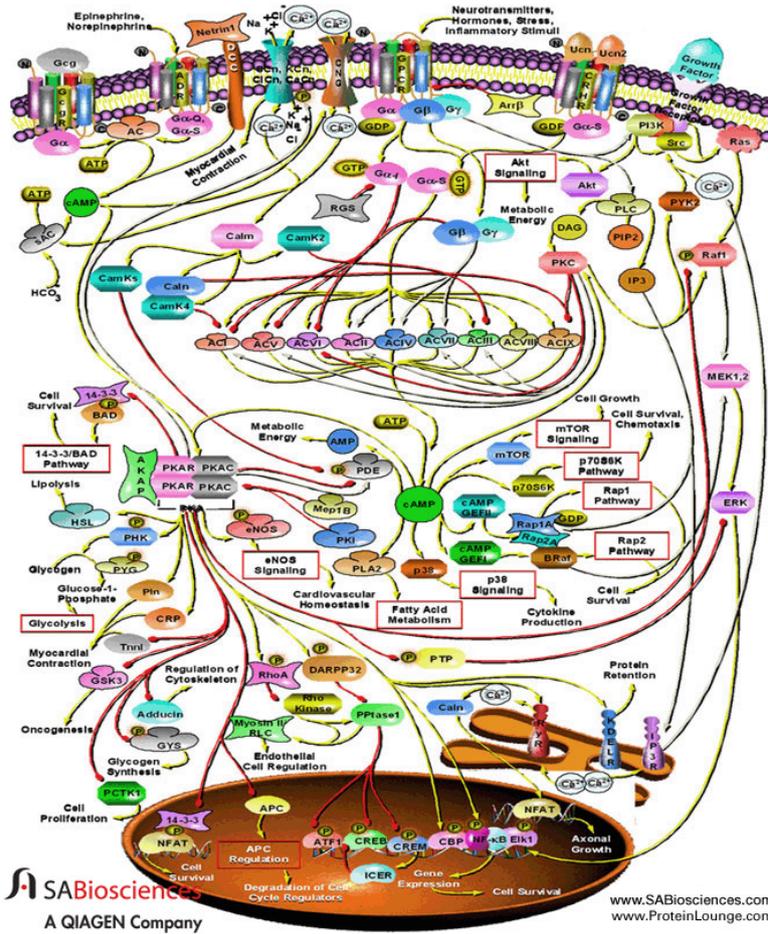
## New Signaling Paradigm

The diagram illustrates the 'New Signaling Paradigm' where  $\beta$ -arrestin acts as a central signaling hub. Agonist binding to a GPCR can activate G $\alpha$  proteins, leading to second messengers (cAMP, DAG, IP $_3$ ) and a cell response. Alternatively,  $\beta$ -arrestin is recruited to the receptor, leading to desensitization and independent signaling through MAP kinases, Src, Akt, and others, resulting in cell survival/anti-apoptosis, chemotaxis, and dopaminergic behavior. A Nobel Prize medal is shown in the top right corner.

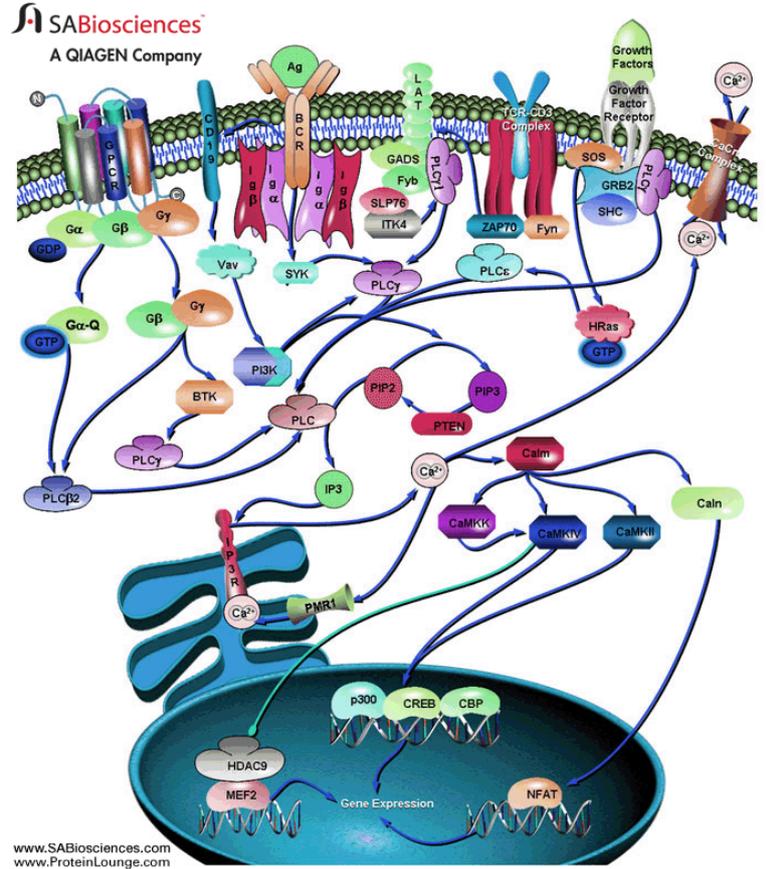
<https://www.youtube.com/watch?v=OPYqpYZ7xL4>

AMPc

IP<sub>3</sub>



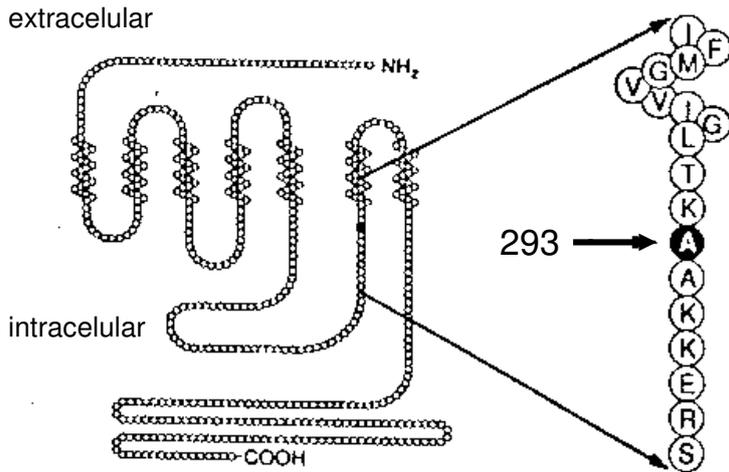
SABiosciences  
A QIAGEN Company



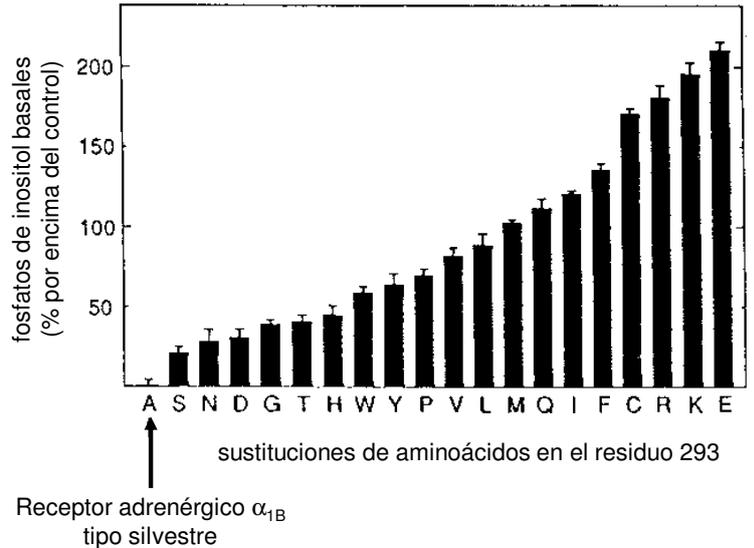
<http://www.sabiosciences.com/pathwaycentral.php>

# Farmacología Molecular

# ACTIVACIÓN CONSTITUTIVA DEL RECEPTOR $\alpha_{1B}$ -ADRENÉRGICO POR MUTACIÓN DE UN ÚNICO AMINOÁCIDO



The Nobel Prize in Chemistry  
2012

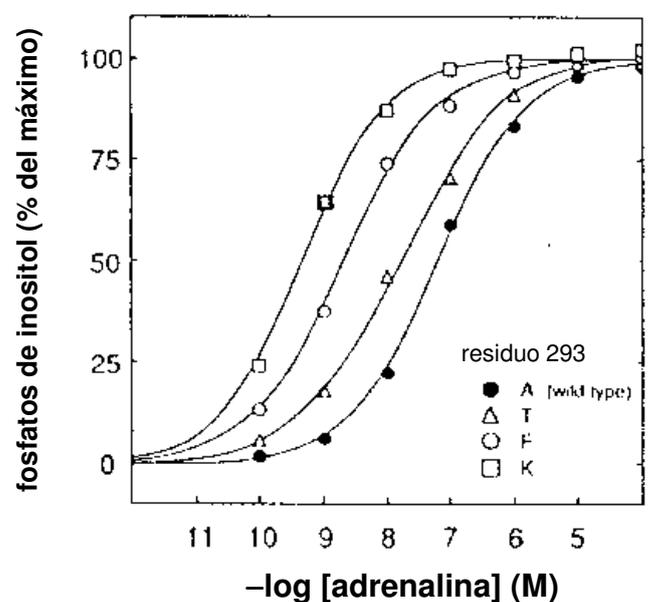
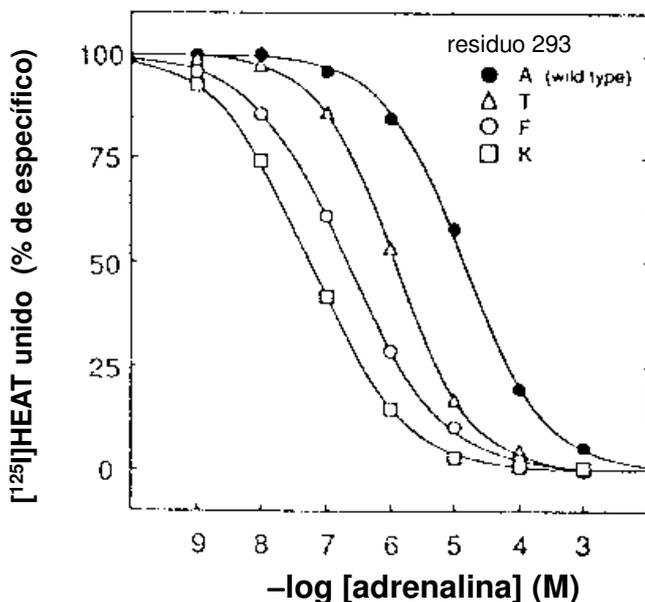


© The Nobel Foundation. Photo: U. Montan  
Robert J. Lefkowitz  
Prize share: 1/2

© The Nobel Foundation. Photo: U. Montan  
Brian K. Kobilka  
Prize share: 1/2

Kjelsberg MA, Cotecchia S, Ostrowski J, Caron MG, Lefkowitz RJ.  
Constitutive activation of the  $\alpha_{1B}$ -adrenergic receptor by all amino acid substitutions  
at a single site. Evidence for a region which constrains receptor activation.  
*J. Biol. Chem.* 267,1430-1433 (1992)

## LOS RECEPTORES $\alpha_{1B}$ -ADRENÉRGICOS CONSTITUTIVAMENTE ACTIVADOS TIENEN MAYOR AFINIDAD POR LA ADRENALINA (agonista endógeno) Y SON MÁS FÁCILMENTE ESTIMULADOS



Kjelsberg MA, Cotecchia S, Ostrowski J, Caron MG, Lefkowitz RJ.  
Constitutive activation of the  $\alpha_{1B}$ -adrenergic receptor by all amino acid substitutions  
at a single site. Evidence for a region which constrains receptor activation.  
*J. Biol. Chem.* 267,1430-1433 (1992)

## ENFERMEDADES CAUSADAS POR MUTACIONES “GANANCIA DE FUNCIÓN” EN RECEPTORES ACOPLADOS A PROTEÍNAS G (GPCR)

Receptor	Enfermedad	Tipo de herencia
Rodopsina	Ceguera nocturna para los colores	Autosómica dominante
LH	Pubertad precoz familiar	Autosómica dominante
LH	Tumores esporádicos de células de Leydig	Somática
TSH	Hipertiroidismo familiar no-autoinmune	Autosómica dominante
TSH	Adenomas tiroideos hiperfuncionantes esporádicos	Somática
Sensor de calcio	Hipocalcemia familiar	Autosómica dominante
PTH/PTHrP	Condrodisplasia metafisaria de Jansen	Autosómica dominante

Allen M. Spiegel and Lee S. Weinstein  
 Inherited diseases involving G proteins and G protein–coupled receptors.  
*Annu. Rev. Med.* **2004**, 55:27–39

**TINYGRAP MUTANT DATABASE**

<http://www.cmbi.ru.nl/tinygrap/search/>

## ENFERMEDADES CAUSADAS POR MUTACIONES “PÉRDIDA DE FUNCIÓN” EN RECEPTORES ACOPLADOS A PROTEÍNAS G (GPCR)

Receptor	Enfermedad	Tipo de herencia
Opsinas de los conos	Ceguera para los colores	Ligada a X; autosómica recesiva
Rodopsina	Retinitis pigmentosa	Autosómica dominante; recesiva
Vasopresina V2	Diabetes insípida nefrogénica	Ligada al cromosoma X
ACTH	Resistencia familiar a ACTH	Autosómica recesiva
LH	Pseudohermafroditismo en el varón	Autosómica recesiva
Sensor de calcio	Hipercalcemia hipocalciúrica familiar	Autosómica dominante
Endotelina B	Enfermedad de Hirschprung	Complejo
FSH	Trastorno ovárico hipergonadotrópico	Autosómica recesiva
TSH	Hipotiroidismo congénito	Autosómica recesiva
TRH	Hipotiroidismo central	Autosómica recesiva
GHRH	Deficiencia de hormona de crecimiento	Autosómica recesiva
GnRH	Hipogonadismo central	Autosómica recesiva
Melanocortina 4	Obesidad extrema	Codominante
PTH/PTHrP	Condrodisplasia de Blomstrand	Autosómica recesiva

Allen M. Spiegel and Lee S. Weinstein  
 Inherited diseases involving G proteins and G protein–coupled receptors.  
*Annu. Rev. Med.* **2004**, 55:27–39

# BASE DE DATOS DE RECEPTORES ACOPLADOS A PROTEÍNAS G (7TM)

 **GPCRDB**  
information system for G protein-coupled receptors

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Search Browse Tools Help

Welcome to the GPCRDB

The GPCRDB is a molecular-class information system that collects, combines, validates and stores large amounts of heterogenous data on G protein-coupled receptors (GPCRs). The GPCRDB contains data on sequences, ligand binding constants and mutations. In addition, many different types of computationally derived data are stored such as multiple sequence alignments and homology models. The GPCRDB is designed to be a data storage medium, as well as a tool to aid biomedical scientists with answering questions by offering a single point of access to many types of data that are integrated and visualized in a user-friendly way. Although most parts of the GPCRDB are self-explanatory, if you have not used this resource before we advice you to take a look at the [usage](#) page.

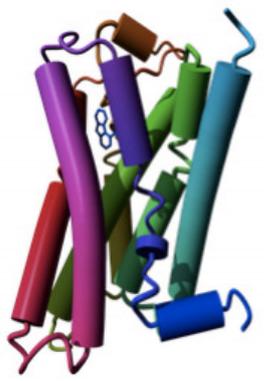
We advice you to take a look at the:

- [updates](#) page to see what has changed and what is new
- [usage](#) page to make sure you will quickly find your way

The informal collaboration of GPCR databases

These include GPCRDB at the CMBI, the Netherlands (formerly at the EMBL), [tinyGRAP Mutant Database](#) at the CMBI (formerly at Tromso, Norway), The [GPCR Oligomerization Knowledge Base](#) (GPCR-OKB) at the Weill Medical College of Cornell University, [Swiss-Prot](#) and the [GPCR Natural Variants Database \(NaVa\)](#).

Current version: 12.01.2011



<https://gpcrdb.org/>

## Familias de canales iónicos operados por neurotransmisores

### Receptores con asas de cisteínas (Cys-loop)

Receptor nicotínico de acetilcolina

- tipo muscular ( $\alpha$ ,  $\beta$ ,  $\delta$ ,  $\gamma/\epsilon$ )
- tipo "neuronal" ( $\alpha$ ,  $\beta$ ): nAChR

Receptor de GABA<sub>A</sub> ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\pi$ ,  $\theta$ ,  $\rho$ )

Receptor 5HT<sub>3</sub> (A – E)

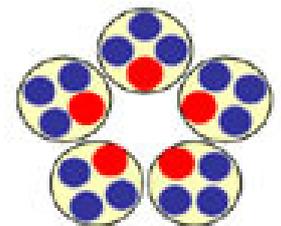
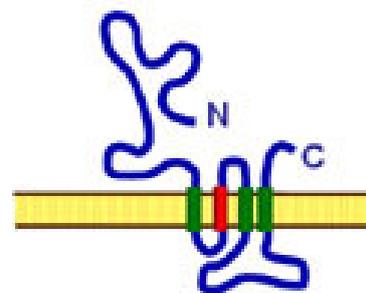
Receptor de glicina ( $\alpha$ ,  $\beta$ )

### Receptores ionotrópicos de glutamato (iGluR)

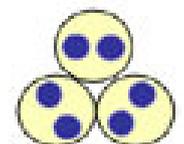
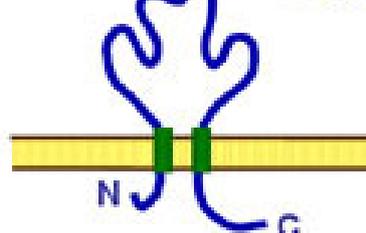
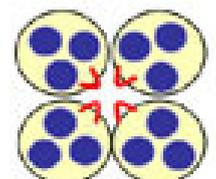
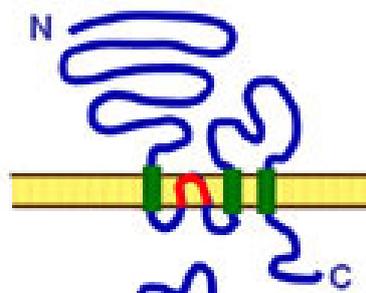
- NMDA (NMDAR1 – 3)
- AMPA (GluR1 – 4)
- kainato (GluR5 – 7, KA1 – 2)

### Receptores P2X para ATP

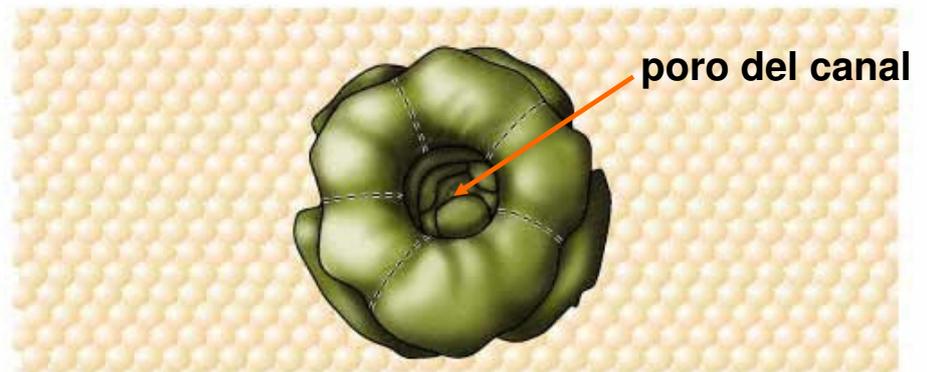
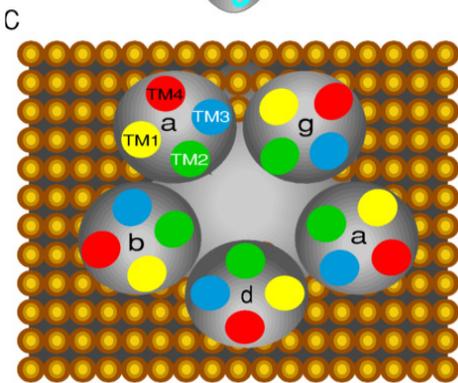
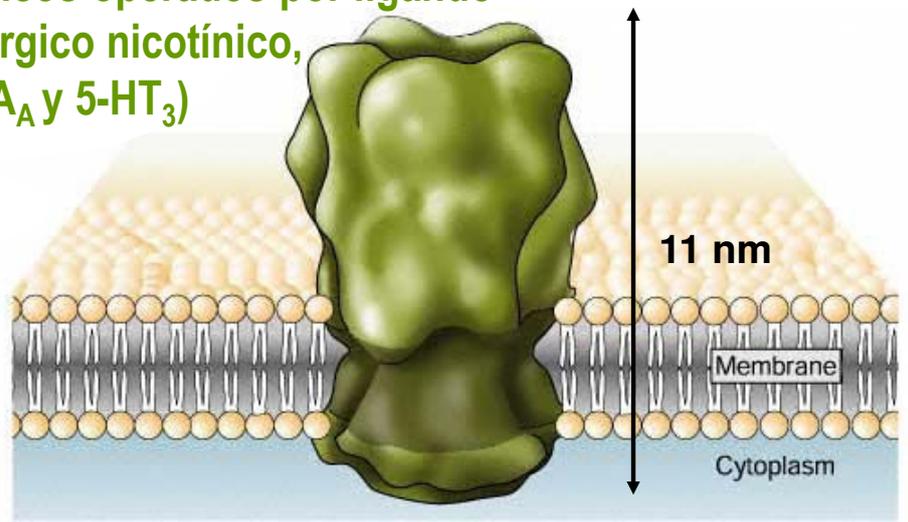
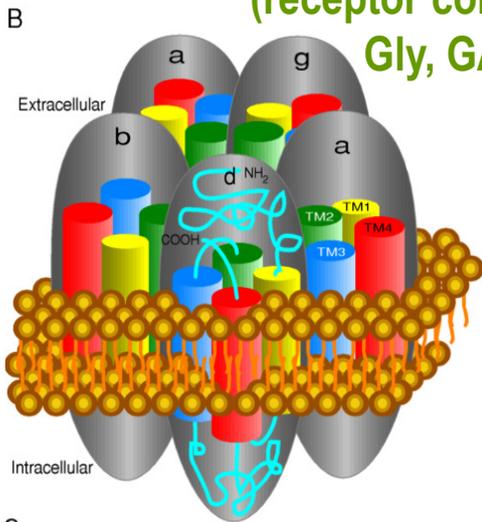
P2X<sub>1</sub>– P2X<sub>7</sub>



2 estequiometrías de subunidades  $\alpha$  y  $\beta$  ( $2\alpha:3\beta$  and  $3\alpha:2\beta$ )



# Canales iónicos pentaméricos operados por ligando (receptor colinérgico nicotínico, Gly, GABA<sub>A</sub> y 5-HT<sub>3</sub>)



Neuroscience – Exploring the Brain 2<sup>nd</sup> Edition 2001 by M.F. Bear, B.W. Connors & M.A. Paradiso. Lippincott, Williams & Wilkins, Baltimore MD, USA. ISBN: 0683-30596-4

doi:10.1016/j.jmb.2004.12.031

J. Mol. Biol. (2005) 346, 967–989

**JMB**

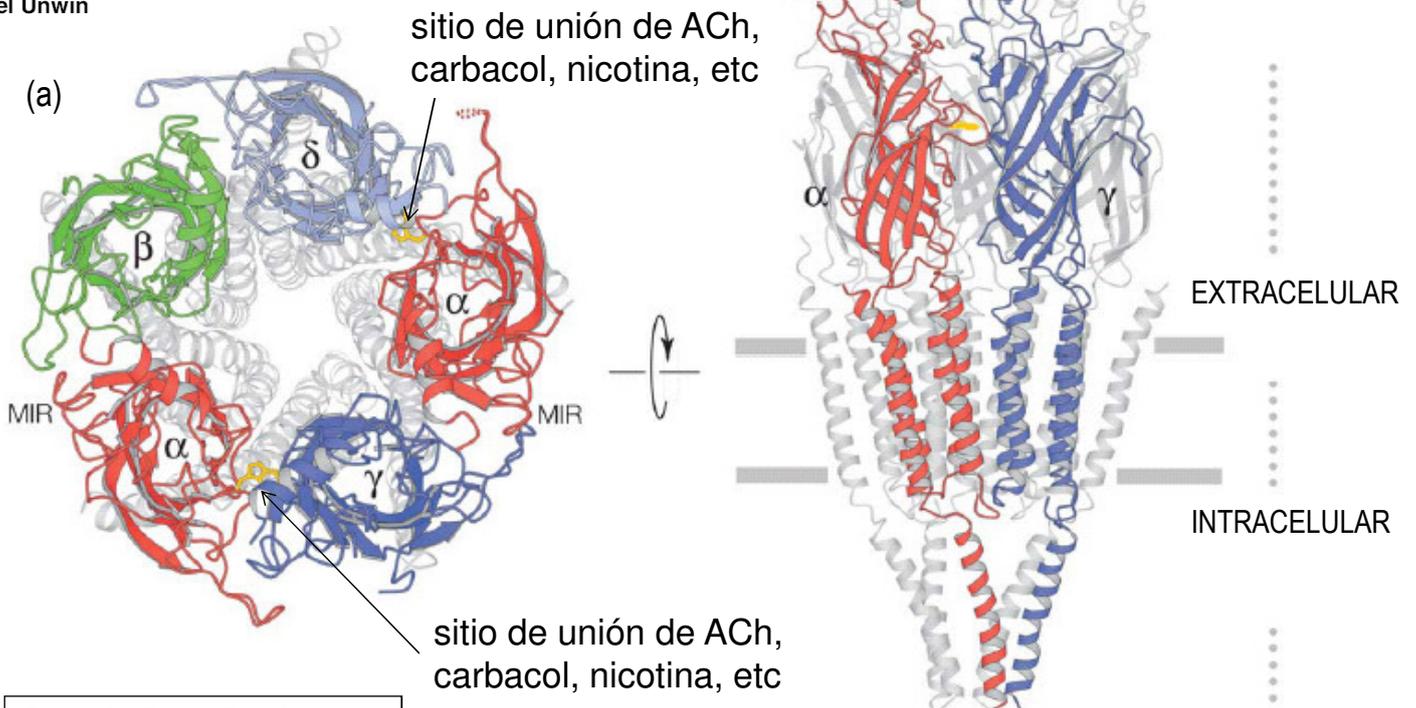
Available online at [www.sciencedirect.com](http://www.sciencedirect.com)  
SCIENCE @ DIRECT®



## RECEPTOR NICOTÍNICO DE ACETILCOLINA

### Refined Structure of the Nicotinic Acetylcholine Receptor at 4 Å Resolution

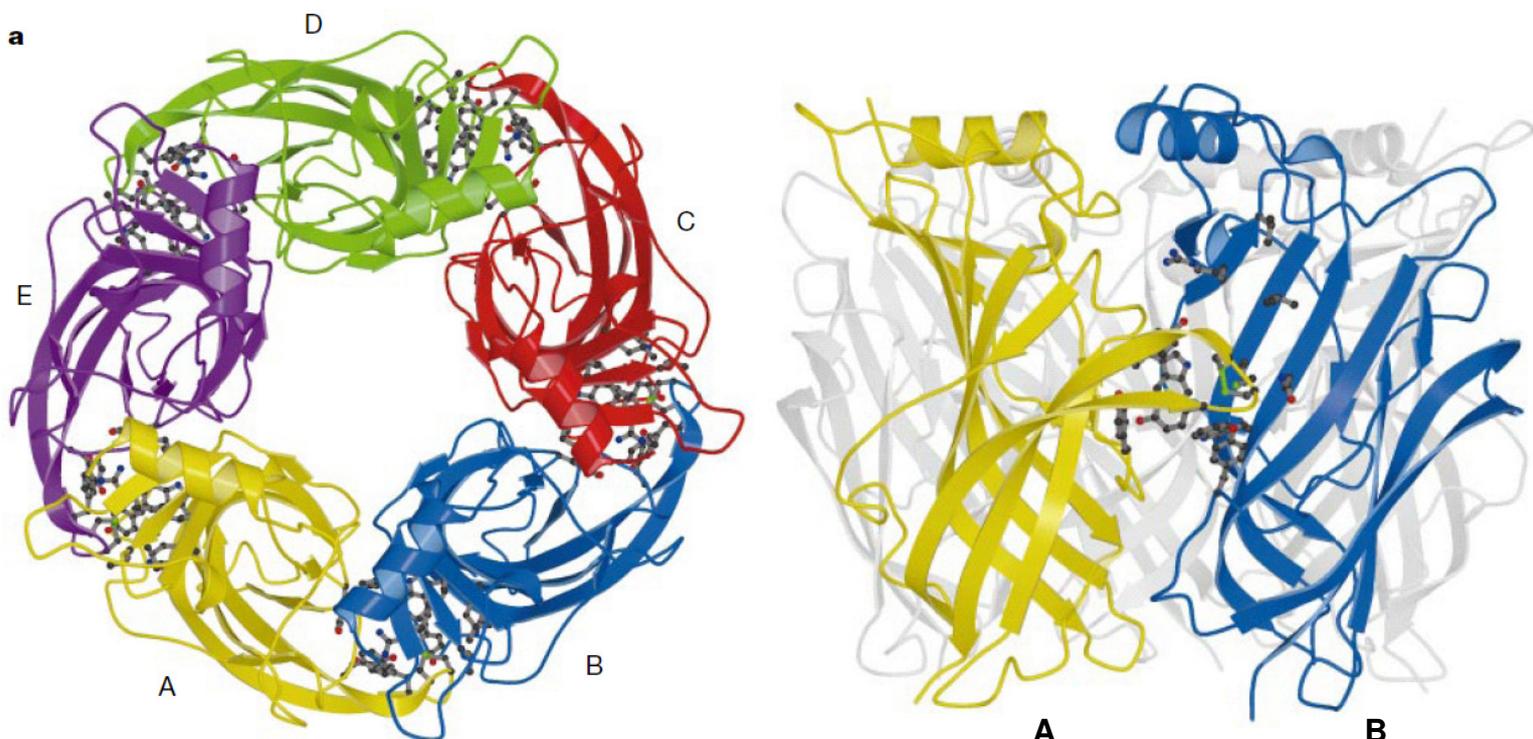
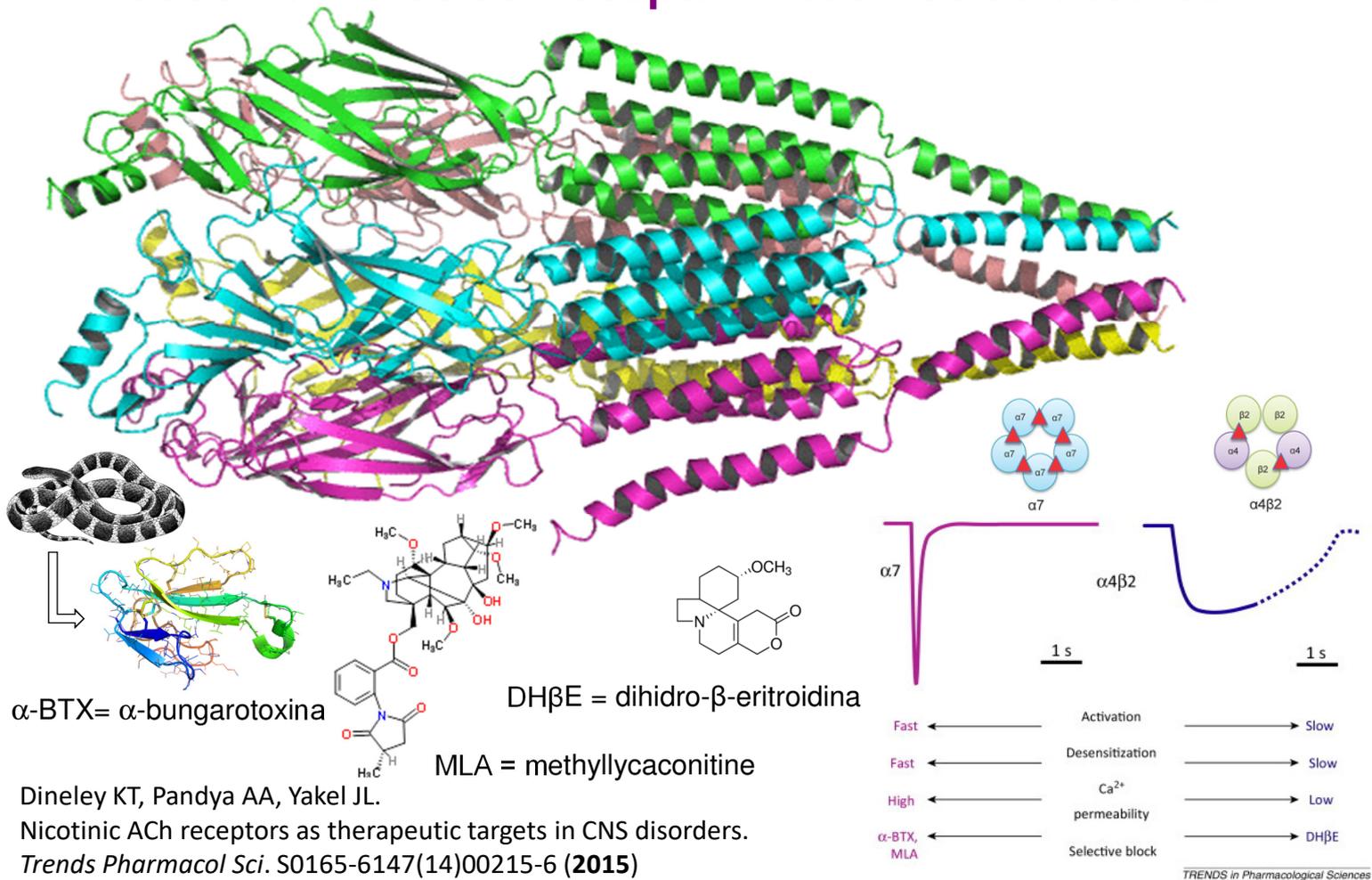
Nigel Unwin



**Protein Data Bank: 2BG9**

Diagramas de cinta del receptor completo, visto desde (a) la hendidura sináptica y (b) paralelo al plano de la membrana.

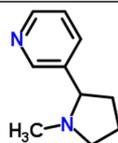
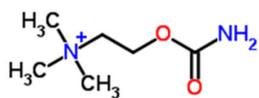
# Modos normales del receptor nicotínico de acetilcolina



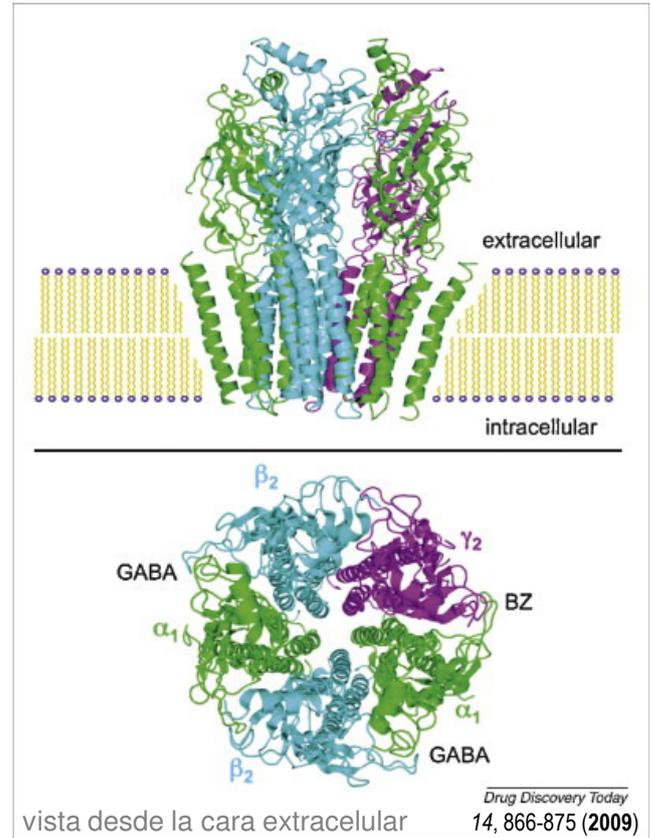
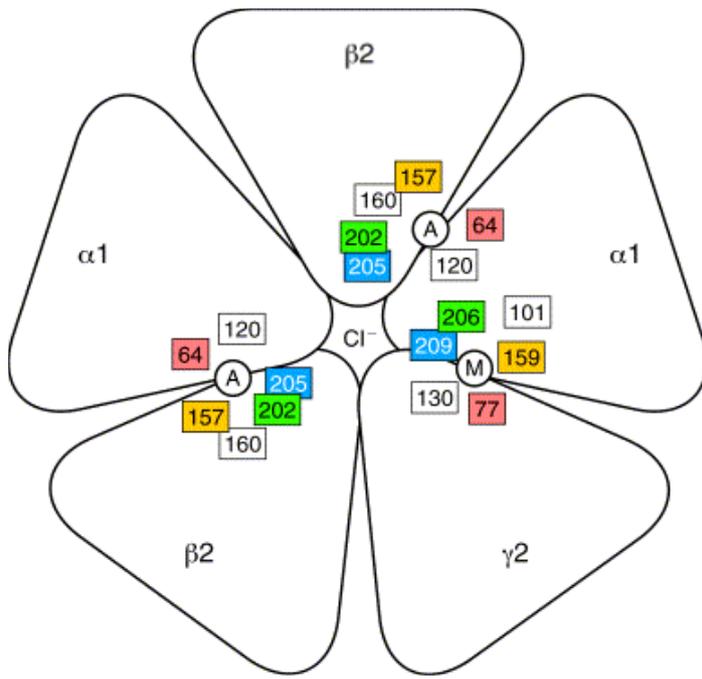
Proteína soluble de *Lymnaea stagnalis* que une acetilcolina (AChBP)

Protein Data Bank: 1UV6 (carbaco1), 1UW6 (nicotina)

**carbamoilcolina**



# Modelo hipotético del receptor de GABA tipo A

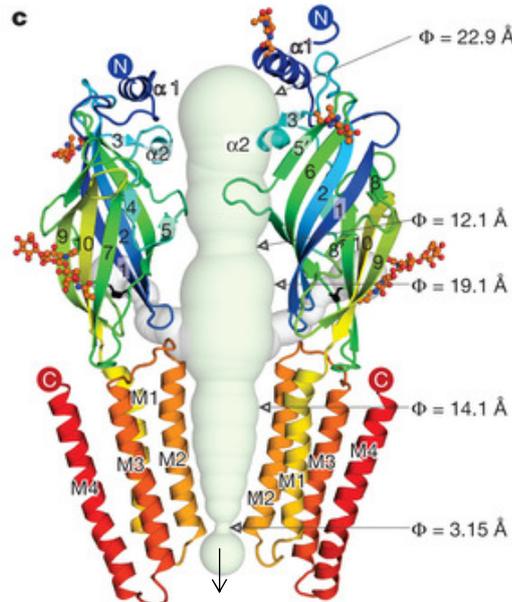
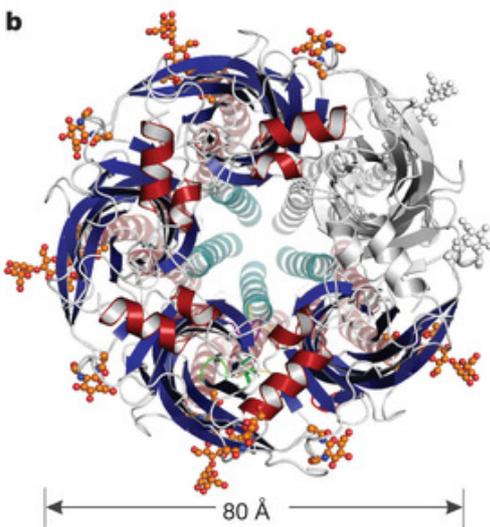


**A:** sitio de unión del agonista (GABA)

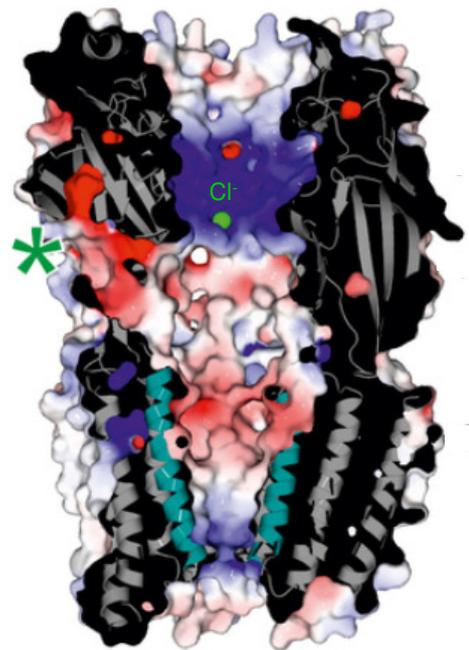
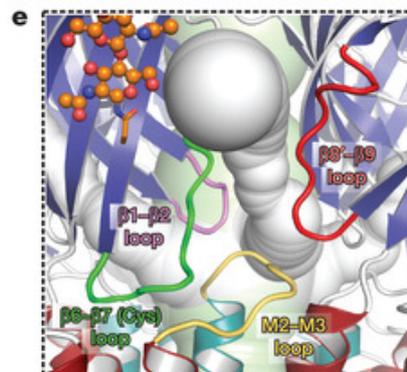
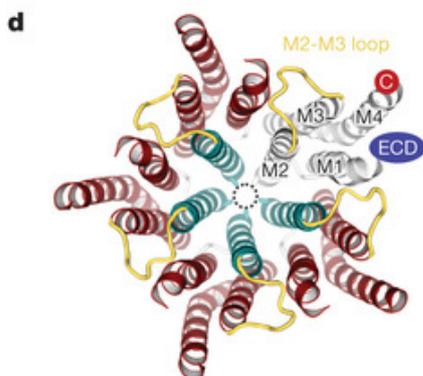
**M:** sitio modulador (alostérico) para ligandos tipo benzodiazepina (BZ)

El canal funciona como un transductor de señales, convirtiendo el mensaje químico (neurotransmisor) en señales eléctricas

# Estructura de rayos X del receptor humano de GABA tipo A



Protein Data Bank: 4COF

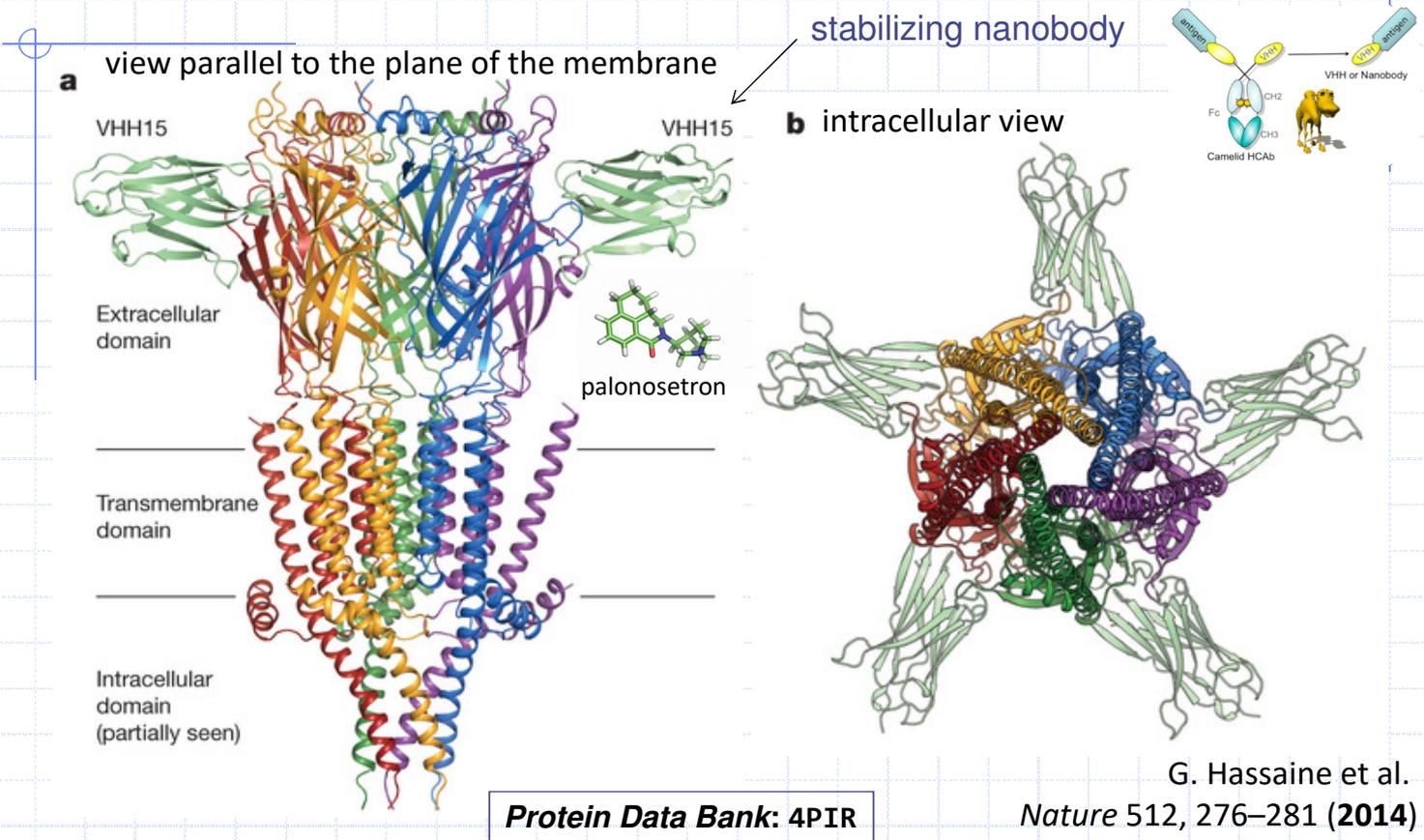


Potencial  
Electrostático  
Molecular

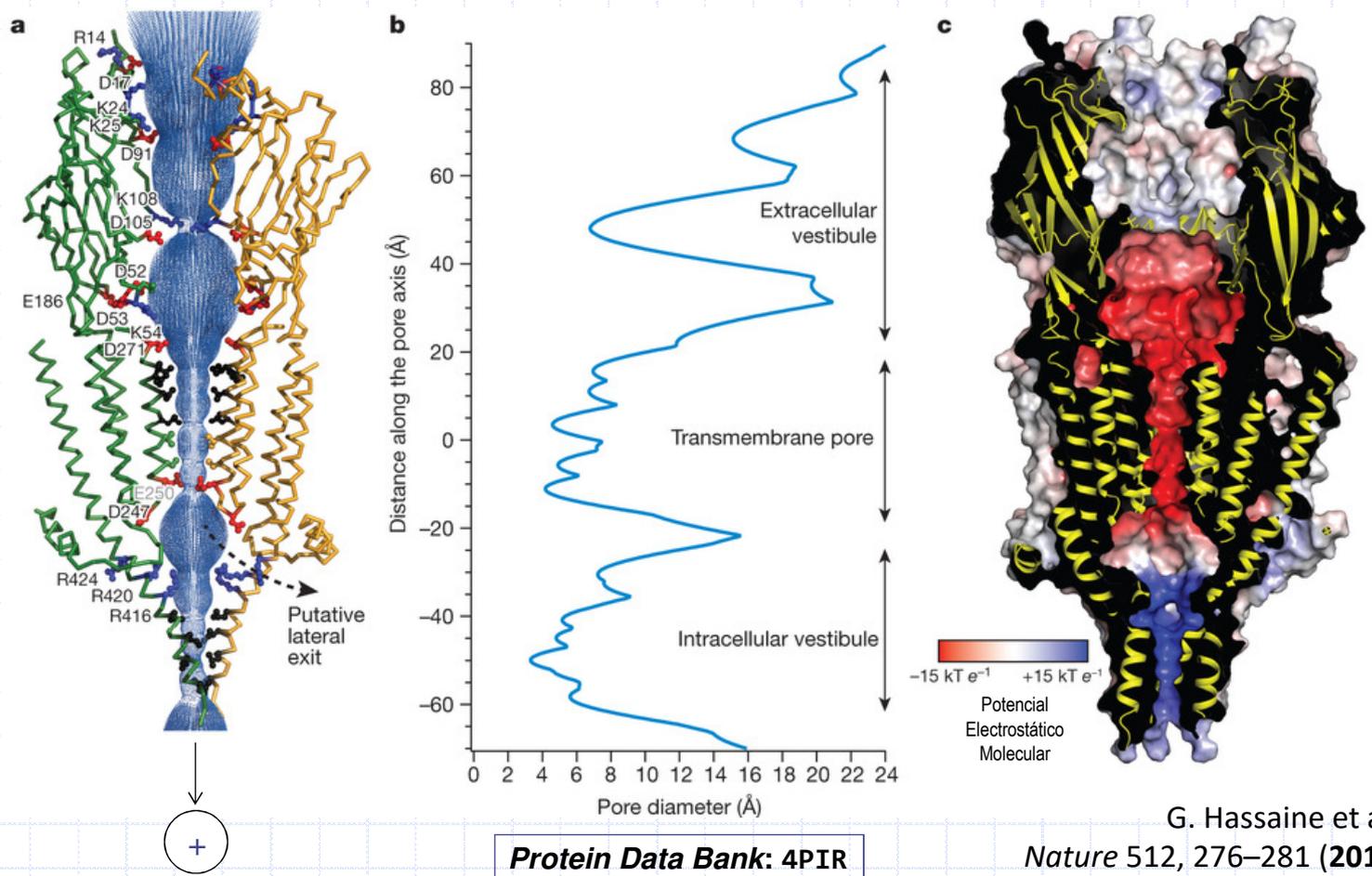
-10  $k_b T/e_c$  10  $k_b T/e_c$

Crystal structure of a human GABA<sub>A</sub> receptor  
P.S. Miller & A.R. Aricescu  
*Nature* 512, 270-275 (2014)

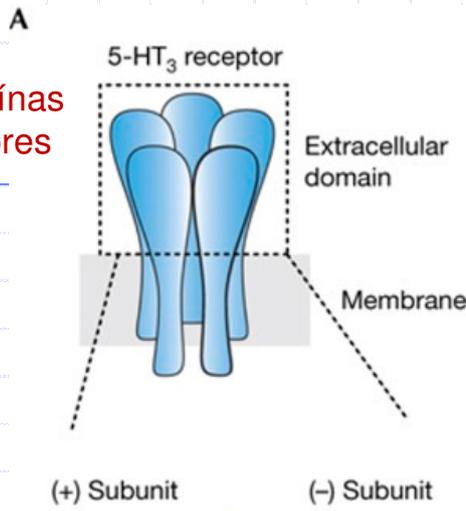
# Estructura de rayos X del receptor 5-HT<sub>3</sub> de ratón



# Estructura de rayos X del receptor 5-HT<sub>3</sub> de ratón



# Ingeniería de proteínas aplicada a receptores

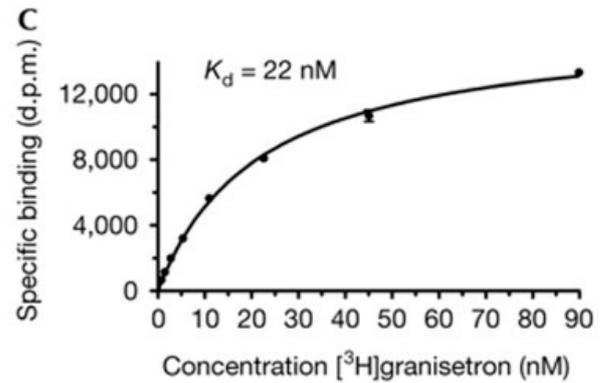
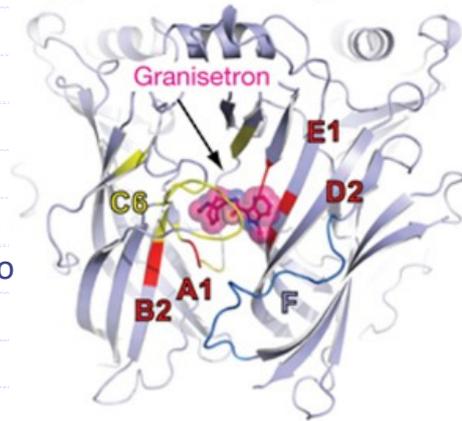


**B**

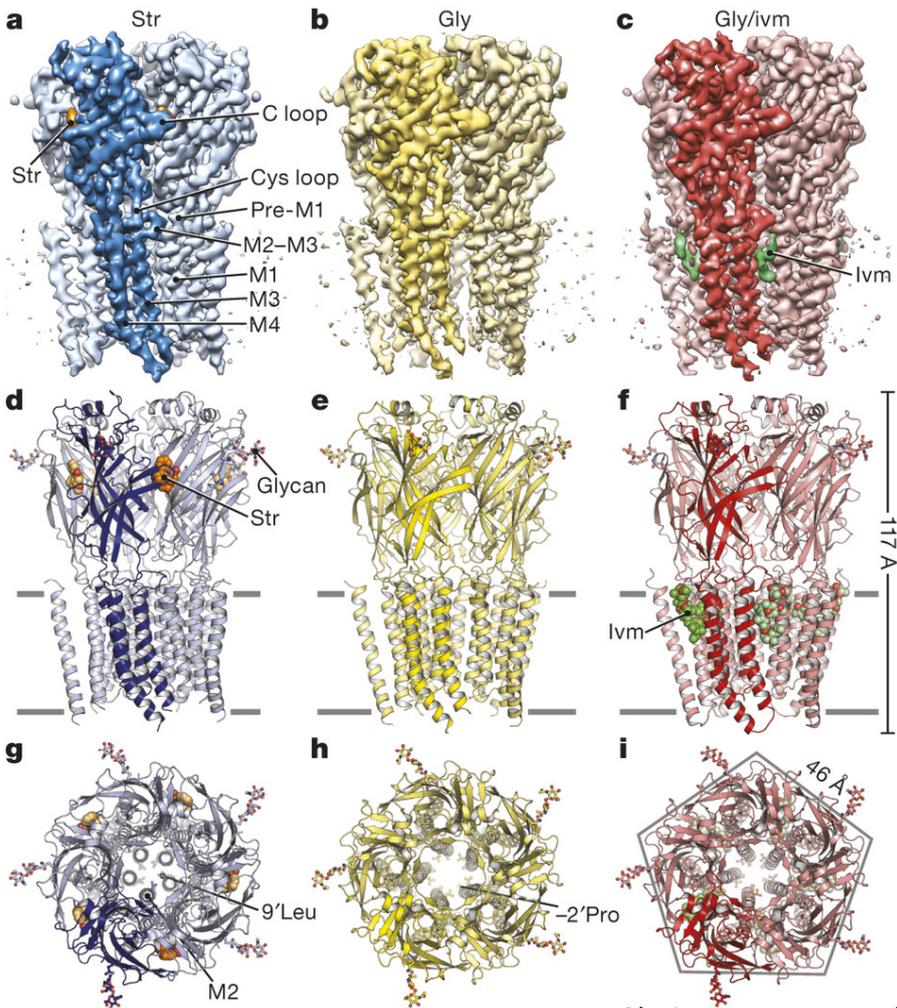
Protein	Residue	Sequence	Residue
Ac-AChBP	23	KDDP	56
Hs-SHT <sub>3R</sub>	60	WRKPTTVS	93
Mm-SHT <sub>3R</sub>	60	WRKPTTVS	93
Ac-AChBP	57	RWKLNS	90
Hs-SHT <sub>3R</sub>	94	YWTDFLQWN	127
Mm-SHT <sub>3R</sub>	94	YWTDFLQWT	127
Ac-AChBP	91	YSSTR	124
Hs-SHT <sub>3R</sub>	128	NEFVDVGKSPNI	161
Mm-SHT <sub>3R</sub>	128	NEFVDVGKSPNI	161
Ac-AChBP	125	CDPTGVDS	154
Hs-SHT <sub>3R</sub>	162	CSLDIYNFP	195
Mm-SHT <sub>3R</sub>	162	CSLDIYNFP	195
Ac-AChBP	155	KT-DTDQVD	187
Hs-SHT <sub>3R</sub>	196	RLPEKVKSR	227
Mm-SHT <sub>3R</sub>	196	RSPEKVKSR	227
Ac-AChBP	188	CCPEP	205
Hs-SHT <sub>3R</sub>	228	MESNNY	246
Mm-SHT <sub>3R</sub>	228	IDISNS	246

## SHTBP

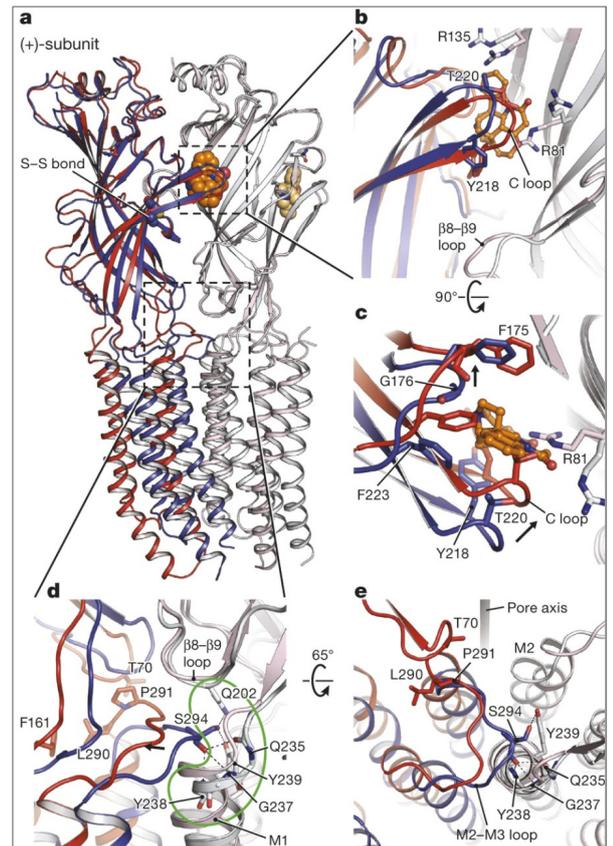
Proteína de unión a serotonina ~ dominio extracelular del receptor 5-HT<sub>3A</sub>



Kesters et al. *EMBO Rep.* 14(1): 49–56 (2013)



## Receptor de glicina (pez zebra)

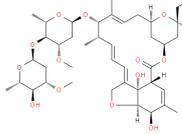


Du et al.

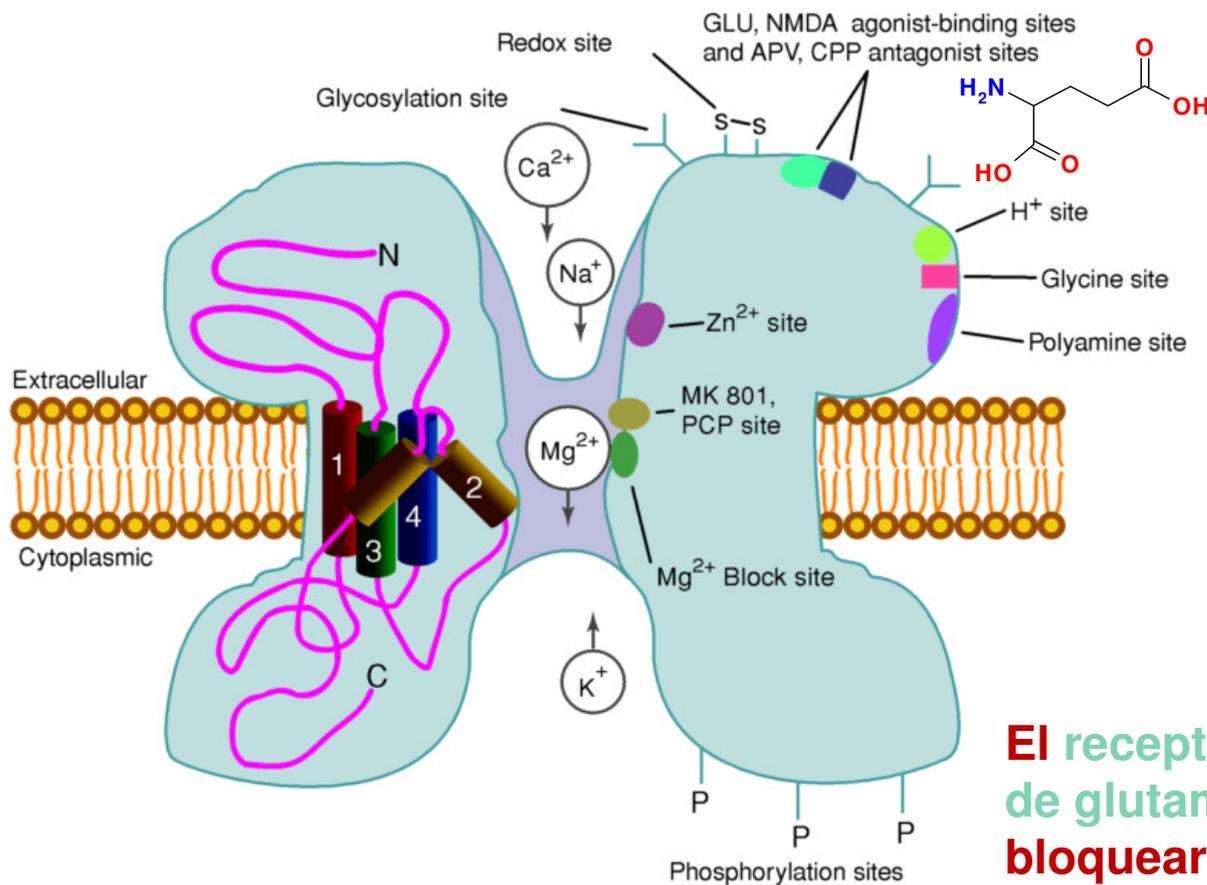
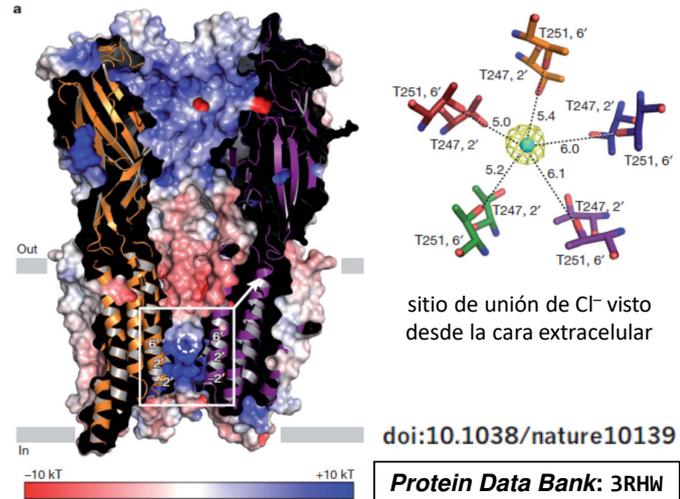
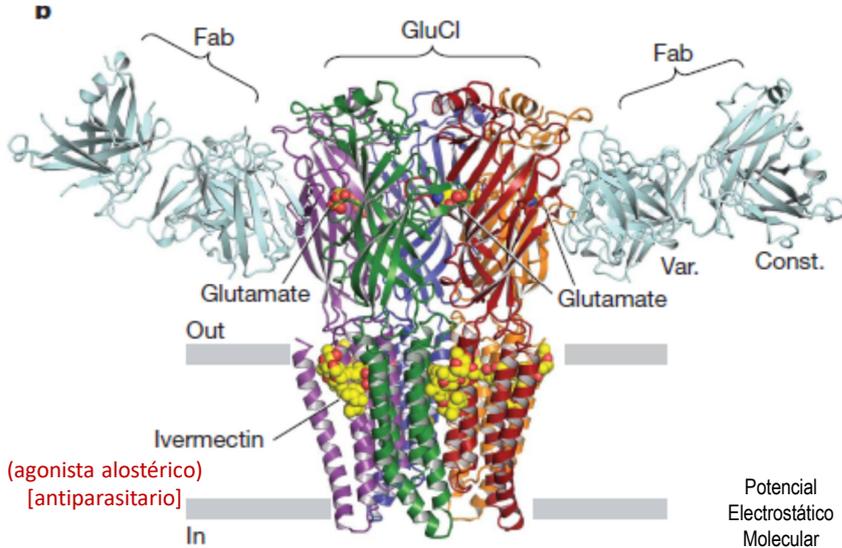
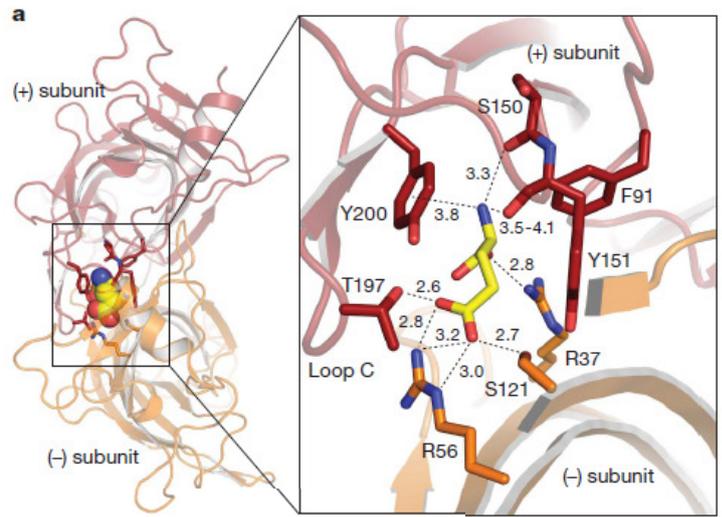
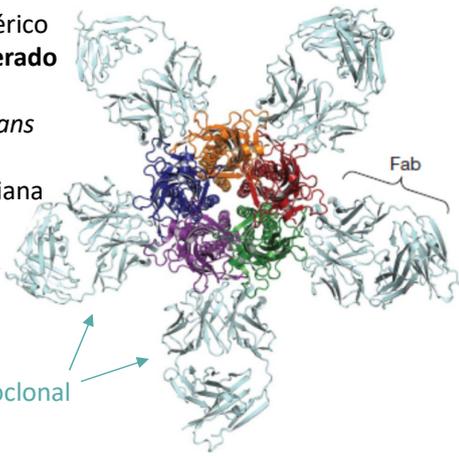
Glycine receptor mechanism elucidated by electron cryo-microscopy. *Nature* 526, 224–229 (2015)

PDB: 3JAD / 3JAE / 3JAF

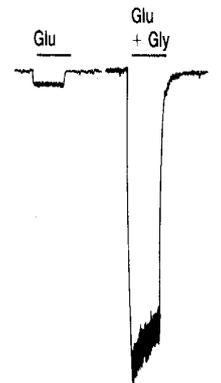
Canal homopentamérico de iones cloruro **operado por glutamato** de *Caenorhabditis elegans* (GluCl) a 3,3 Å de resolución (2011): diana para la **ivermectina**



Anticuerpo monoclonal

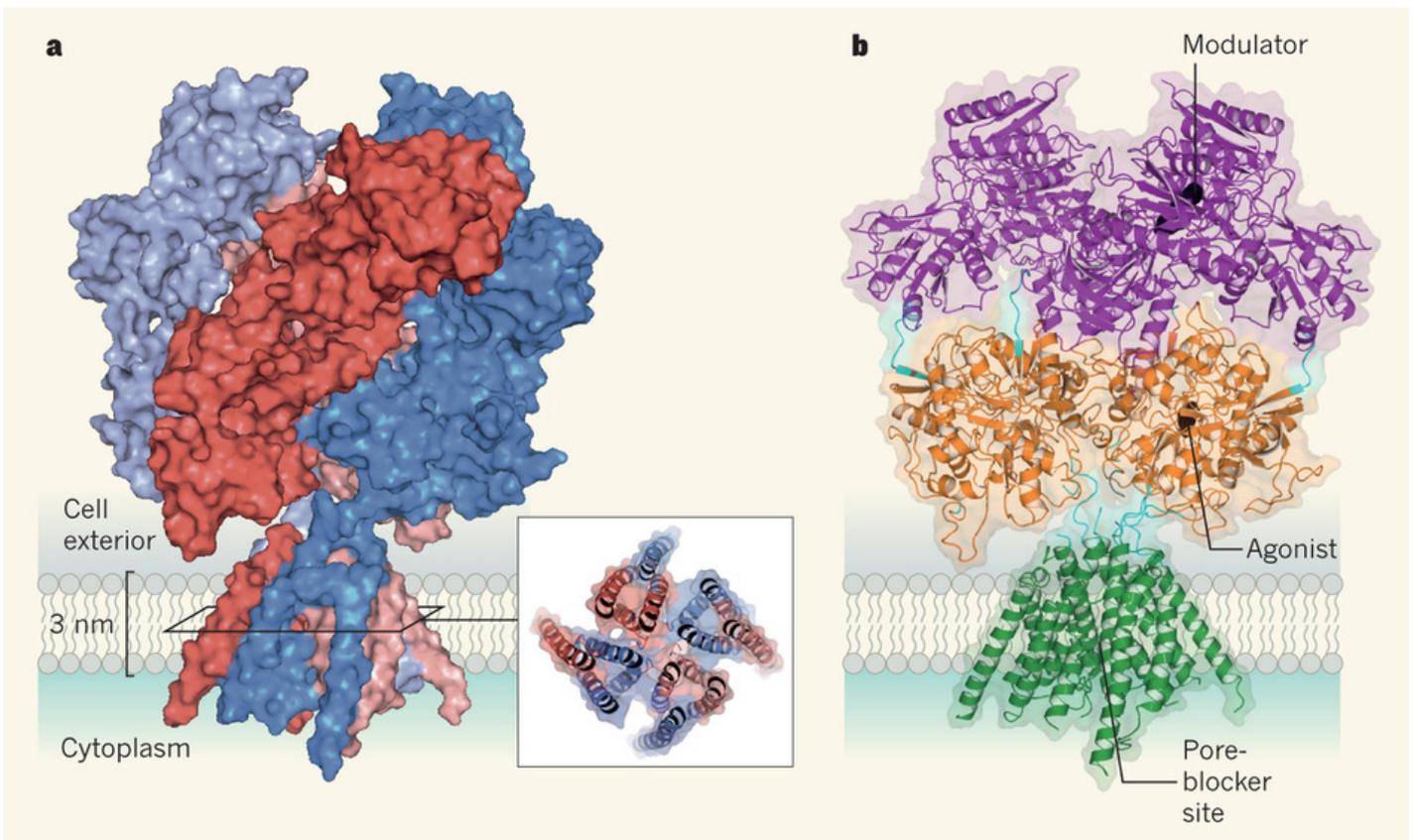


Co-activación por D-serina y glicina (Gly)



**El receptor NMDA de glutamato se puede bloquear/modular por una variedad de agentes**

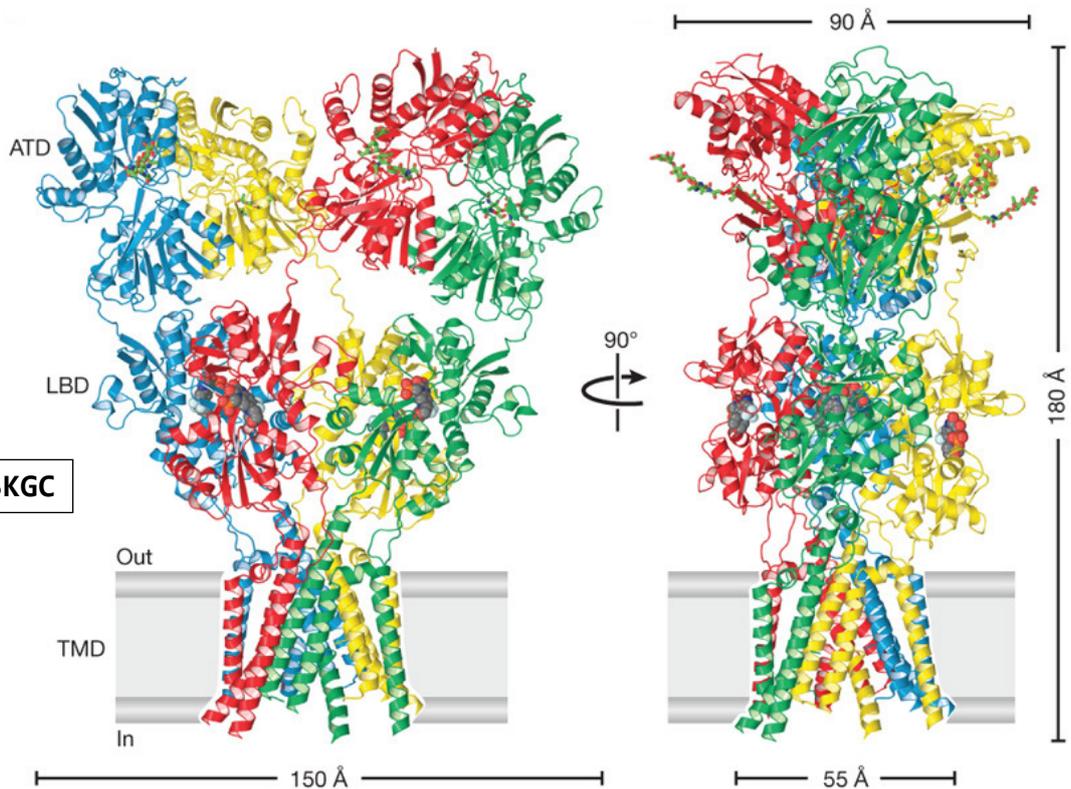
Primeras estructuras de rayos X de un **receptor NMDA**: el receptor GluN1–GluN2B



Rat: Karakas, E. & Furukawa, H. *Science* 344, 992–997 (2014)  
 Frog: Lee, C.-H. *et al. Nature* 511, 191–197 (2014)



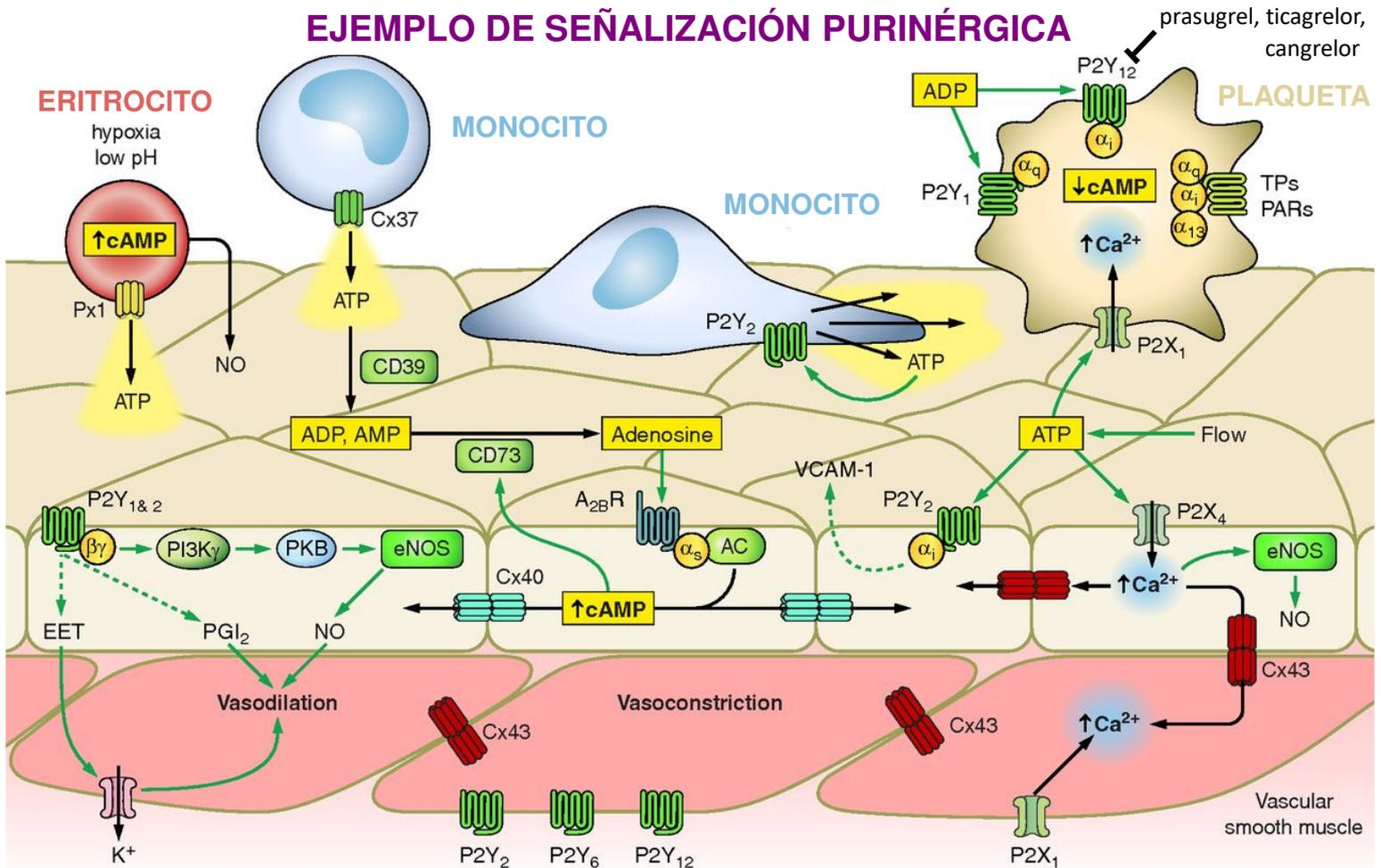
Estructura del **receptor de glutamato homotetramérico subtipo AMPA (GluA2)** unido a un antagonista competitivo



Protein Data Bank: 3KGC

X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor  
 A.I. Sobolevsky, M.P. Rosconi & E. Gouaux  
*Nature* 462, 745-756 (2009)

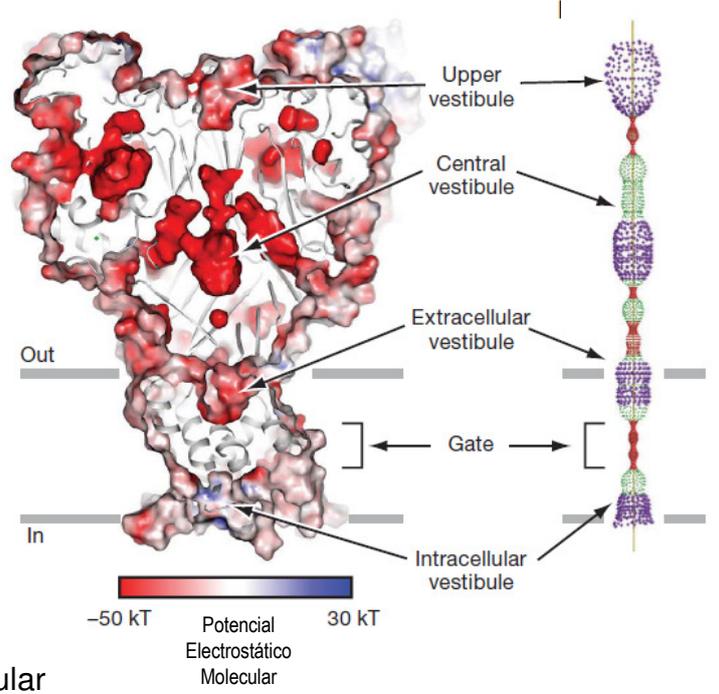
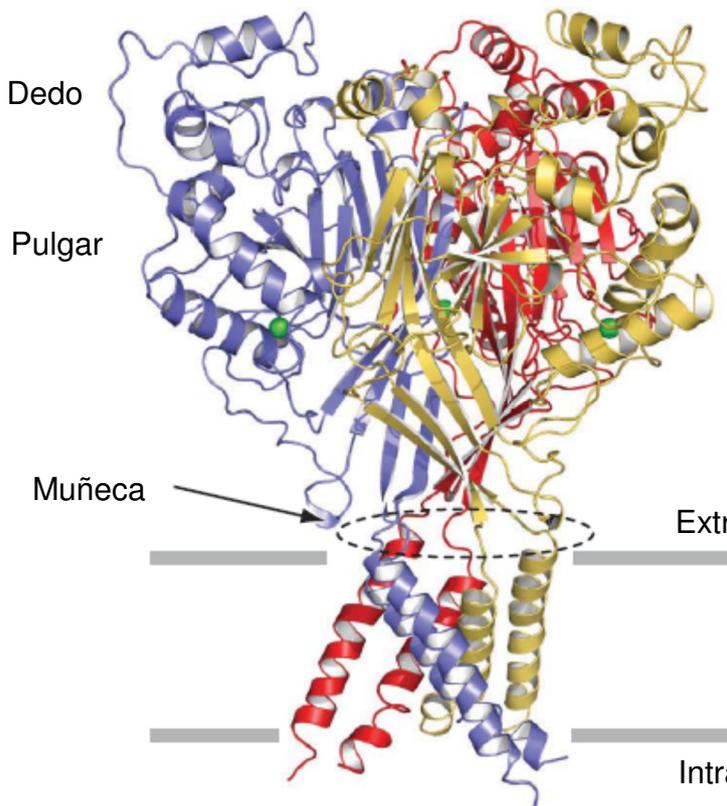
# EJEMPLO DE SEÑALIZACIÓN PURINÉRGICA



MUSCULATURA LISA VASCULAR

Paul N. Hopkins  
Molecular Biology of Atherosclerosis  
*Physiological Reviews* 93(3):1317-1542 (2013)

# Receptores ionotrópicos P2X

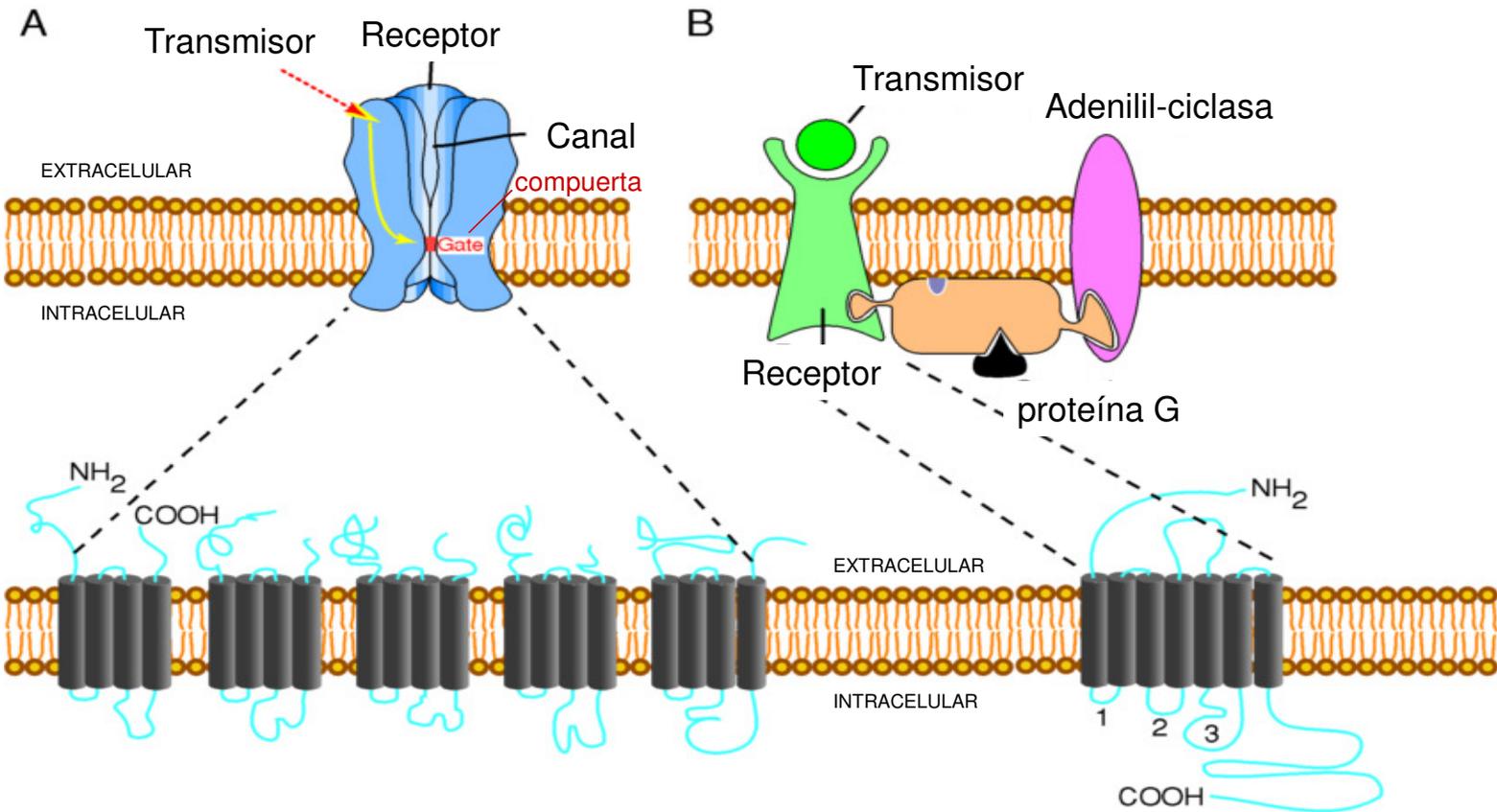


Selectivos para cationes y operados por **ATP** extracelular. Implicados en distintos procesos fisiológicos: transmisión sináptica, inflamación, percepción de sabores, sensación de dolor, etc

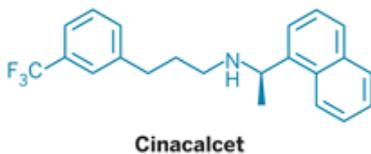
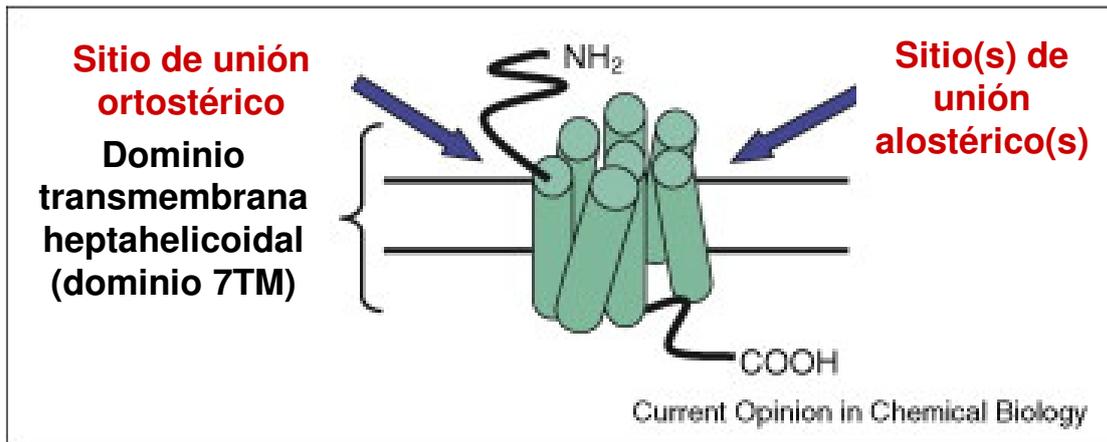
PDB ids.: 3I5D, 3H9V, 3HGC

Goaux y cols. *Nature* 460, 592-8; 599-605 (2009)

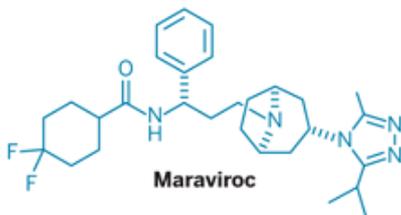
# COMPARACIÓN ENTRE CANALES OPERADOS POR LIGANDO (A) Y RECEPTORES ACOPLADOS A PROTEÍNAS G (B)



## Ejemplos de MODULADORES ALOSTÉRICOS de RECEPTORES ACOPLADOS A PROTEÍNAS G

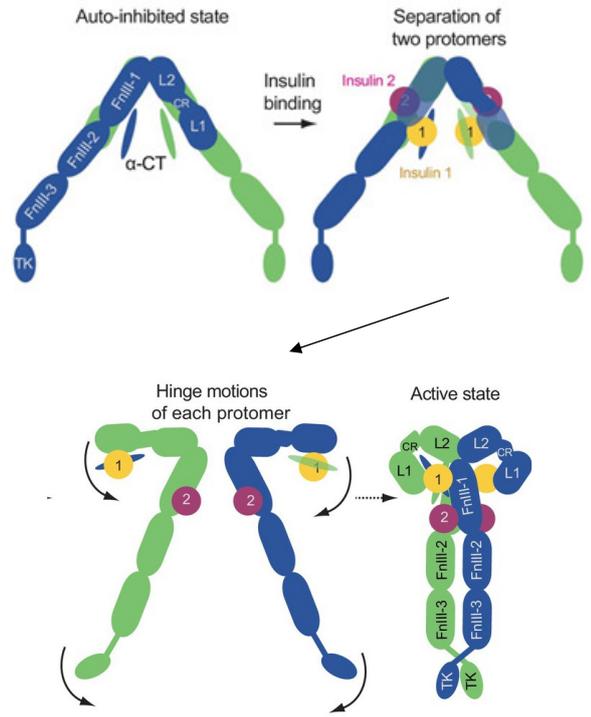
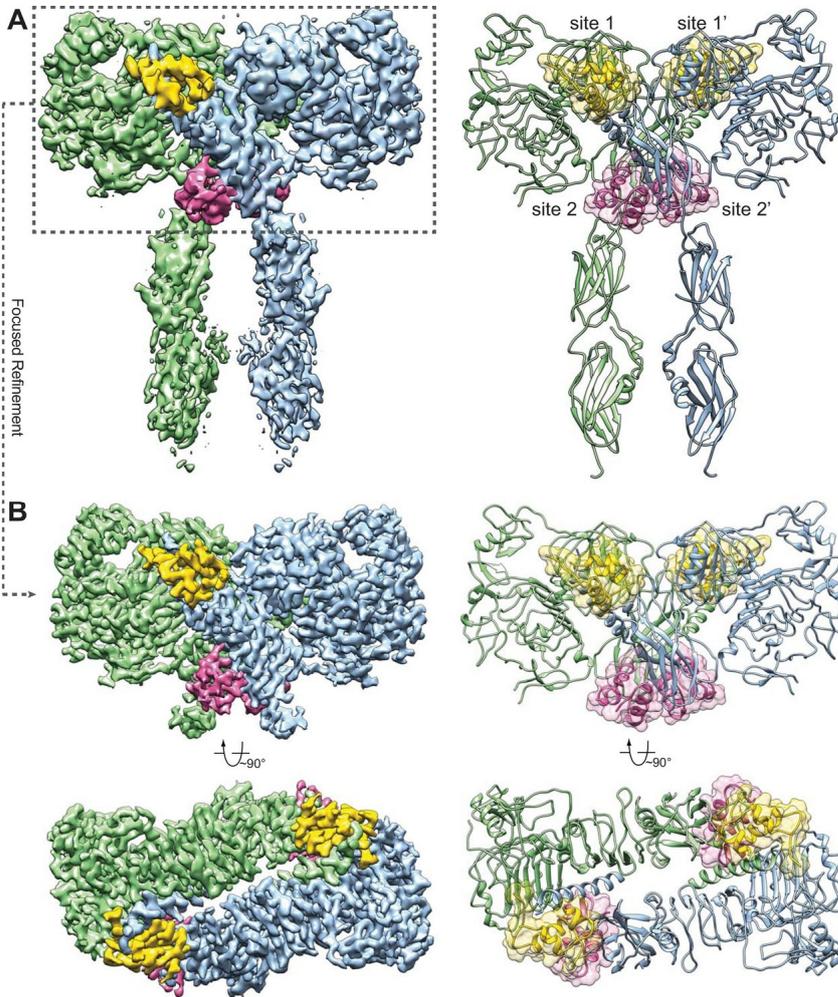


**Calcimimético tipo II:** potenciación afinidad por el ión calcio del receptor sensor de calcio (**CaSR**) en células del paratiroides. Utilidad en el tratamiento del hiperparatiroidismo.



**Inhibidor de la entrada del VIH:** bloquea el receptor de quimiocina **CCR5** que el virus utiliza como co-receptor en las células infectadas (vídeo en <http://www.youtube.com/watch?v=95J4dLHXEzM>).

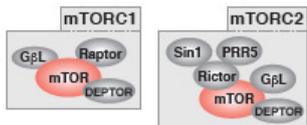
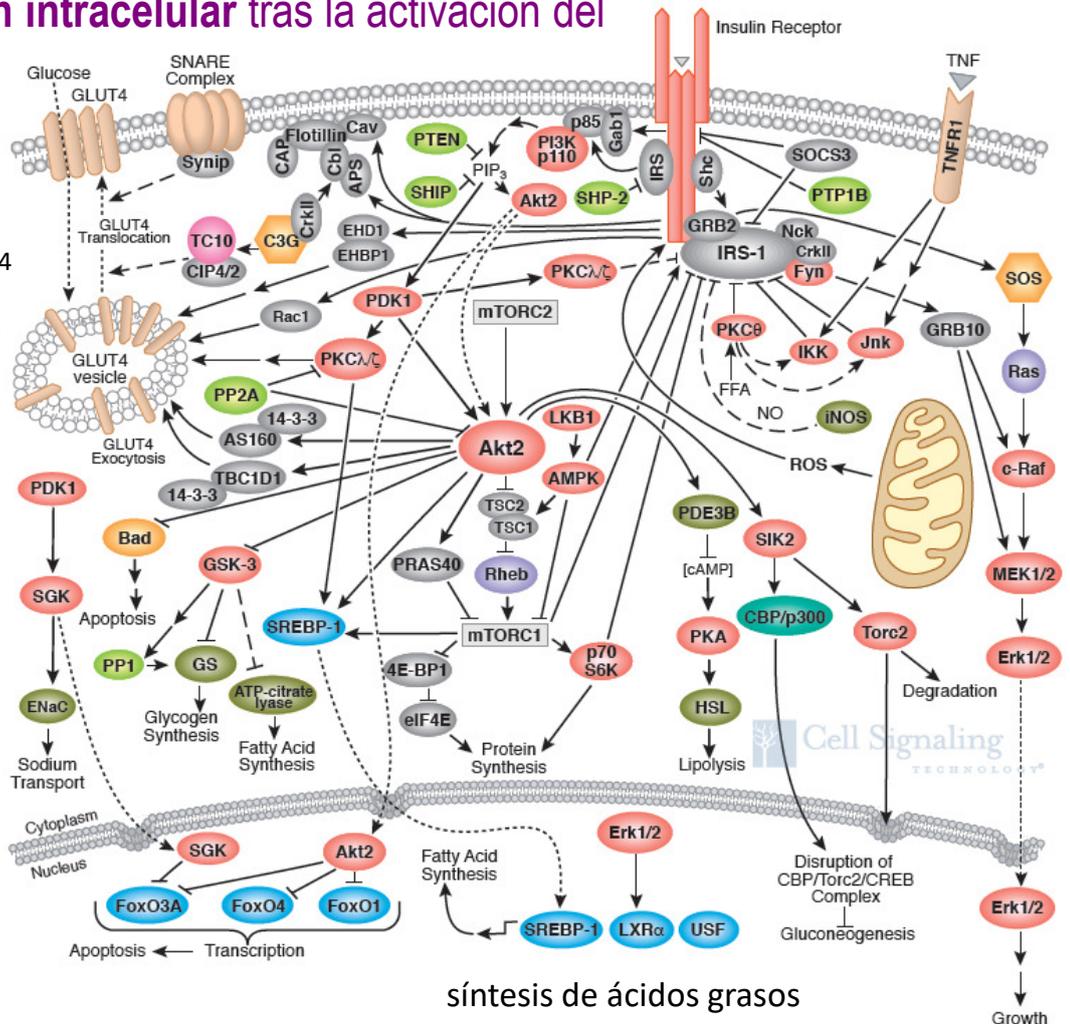
# ESTRUCTURA Y ACTIVACIÓN DEL RECEPTOR DE INSULINA



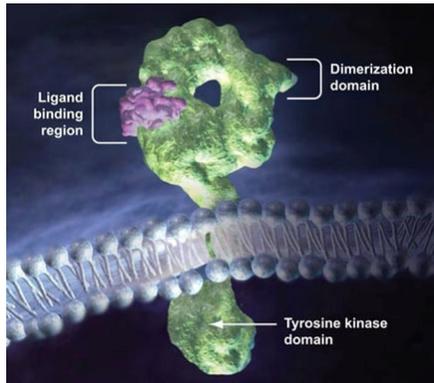
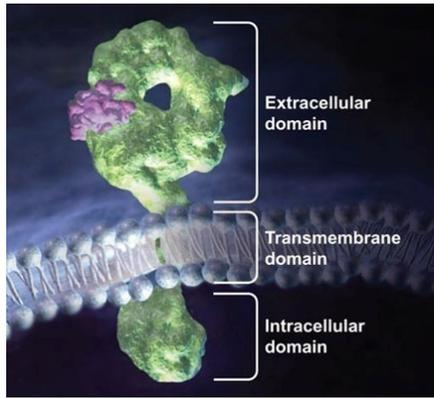
eLife 8:e48630 (2019)  
doi: 10.7554/eLife.48630

## Cascada de señalización intracelular tras la activación del receptor de insulina por la insulina

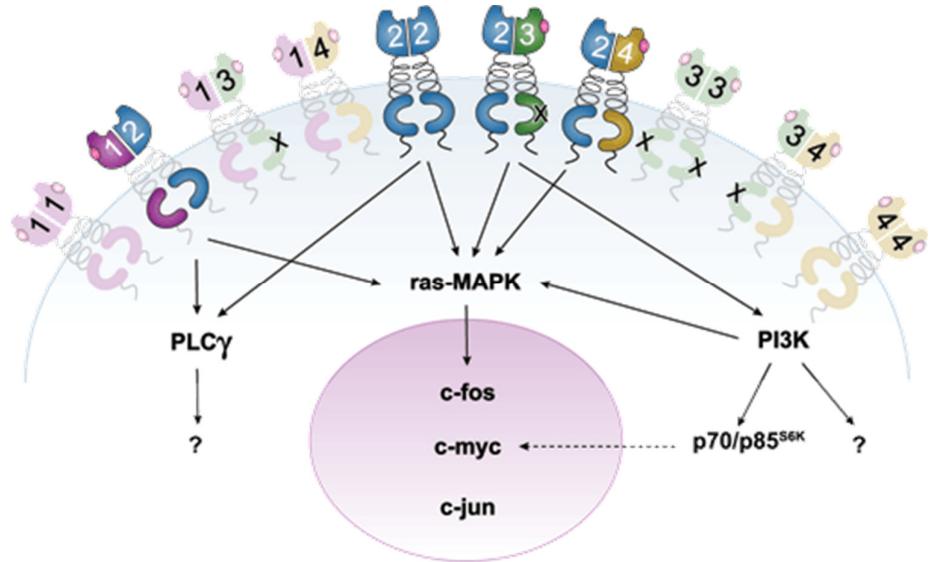
**GLUT4** = transportador de glucosa tipo 4 (tejido adiposo / músculo estriado): traslocación a la membrana plasmática



# Receptores HER: activados inadecuadamente en muchos tipos de cáncer

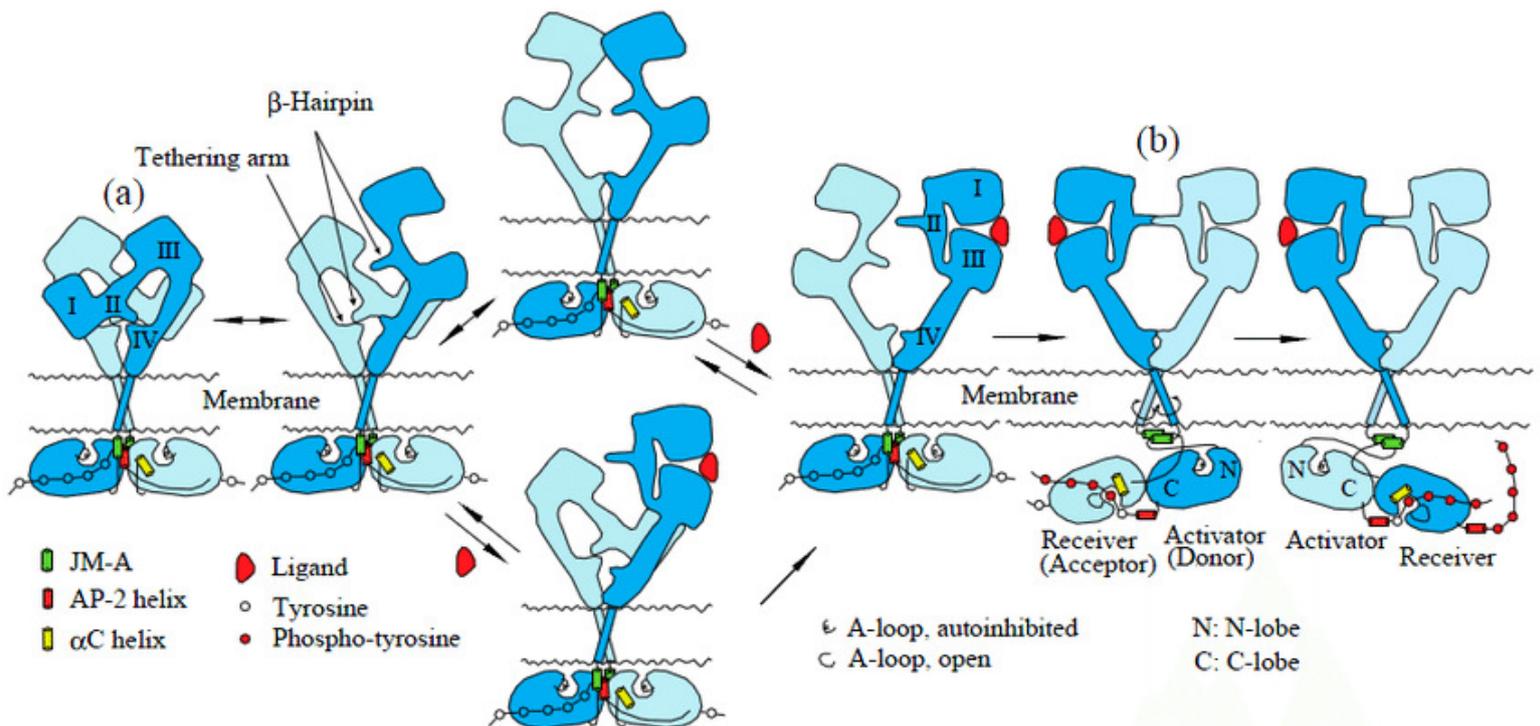


**HER1**, también conocido como receptor del factor de crecimiento epidérmico (EGFR) o ErbB1  
**HER2**, también conocido como ErbB2: bloqueado por **trastuzumab** (*Herceptin*)  
**HER3**, también conocido como ErbB3  
**HER4**



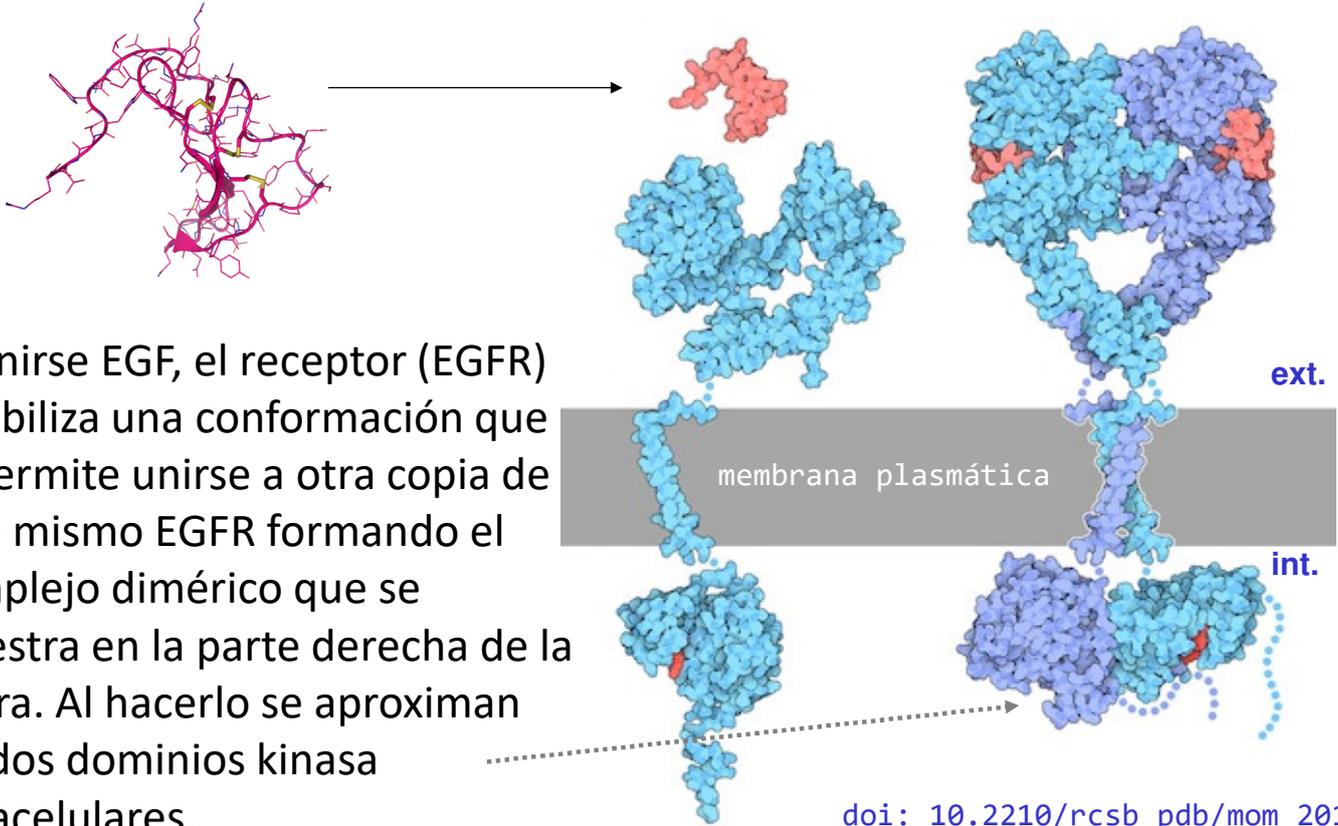
<http://www.researcherpathways.com/researcherpath/index.m>

## Modelo para explicar la activación del receptor del factor de crecimiento epidérmico (EGFR) por unión de su ligando EGF

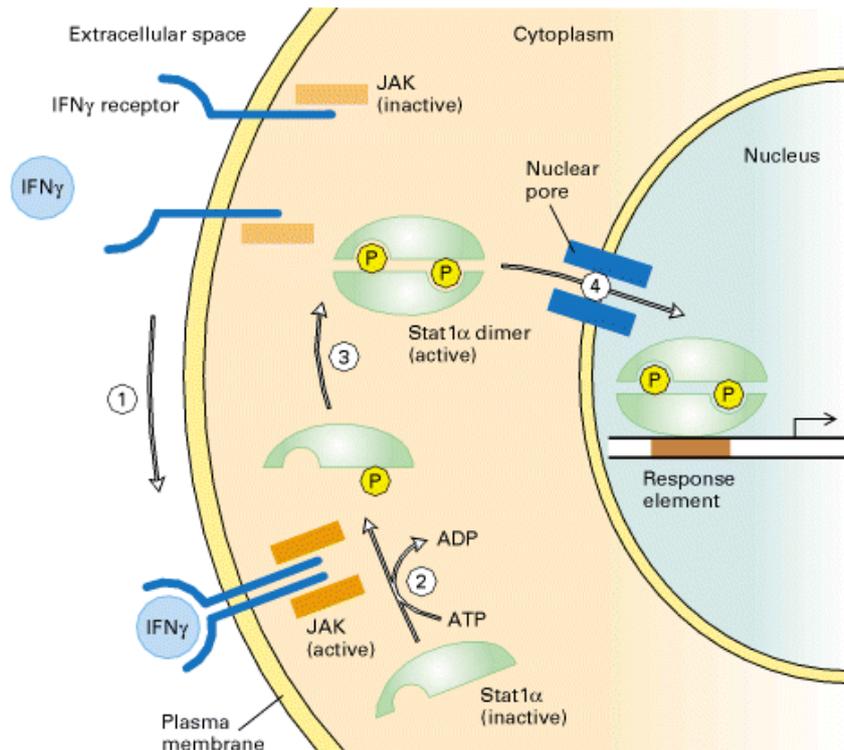


Purba ER, Saita EI, Maruyama IN.  
 Activation of the EGF Receptor by Ligand Binding and Oncogenic Mutations: The "Rotation Model".  
*Cells* 6(2):13 (2017)

**EGF** se une a cada lado del **receptor**, no en el medio como pasa en otros receptores semejantes (e.g. receptor de la hormona del crecimiento)



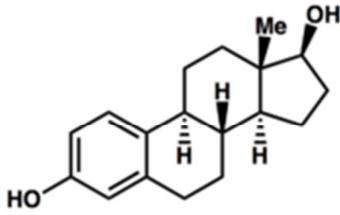
## Modelo de **activación génica** mediada por interferón gamma (IFN $\gamma$ ) a través de la fosforilación y dimerización de Stat1 $\alpha$



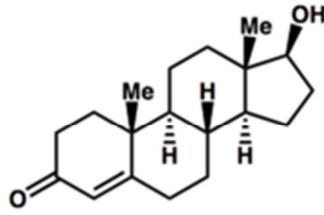
La kinasa JAK se activa cuando el receptor de IFN $\gamma$  dimeriza al unir IFN $\gamma$ . JAK activada fosforila un residuo específico de tirosina en los monómeros inactivos de Stat1 $\alpha$  en el citoplasma. La Stat1 $\alpha$  fosforilada dimeriza, y el dímero fosforilado se transloca entonces al núcleo donde se une a los elementos de respuesta correspondientes, promoviendo la transcripción de genes regulados por IFN $\gamma$  [véase K. Shuai et al., *Science* **1992**, 258, 1808].

# Ejemplos de ligandos endógenos que se unen a RECEPTORES NUCLEARES

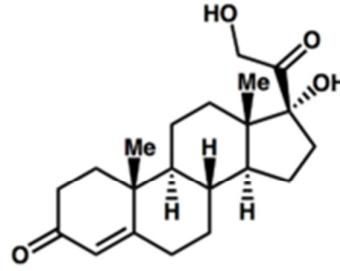
## esteroides



**17-β-estradiol**  
Receptor Estrogénico\*  
(ER)

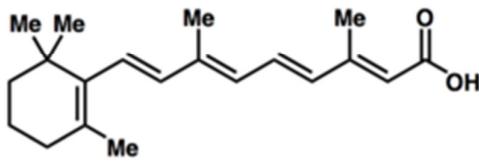


**Testosterona**  
Receptor Androgénico  
(AR)

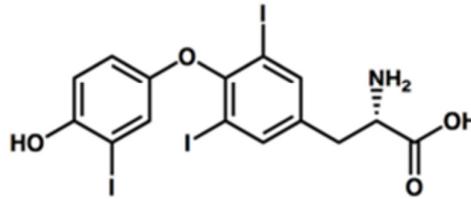


**Cortisol**  
Receptor Glucocorticoide  
(GR)

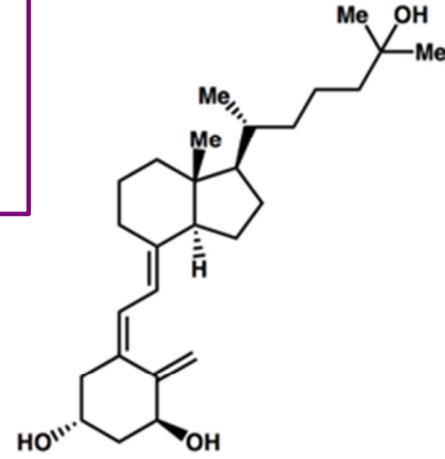
## no esteroides



**Vitamina A**  
Receptor de Acido Retinoico  
(RAR)



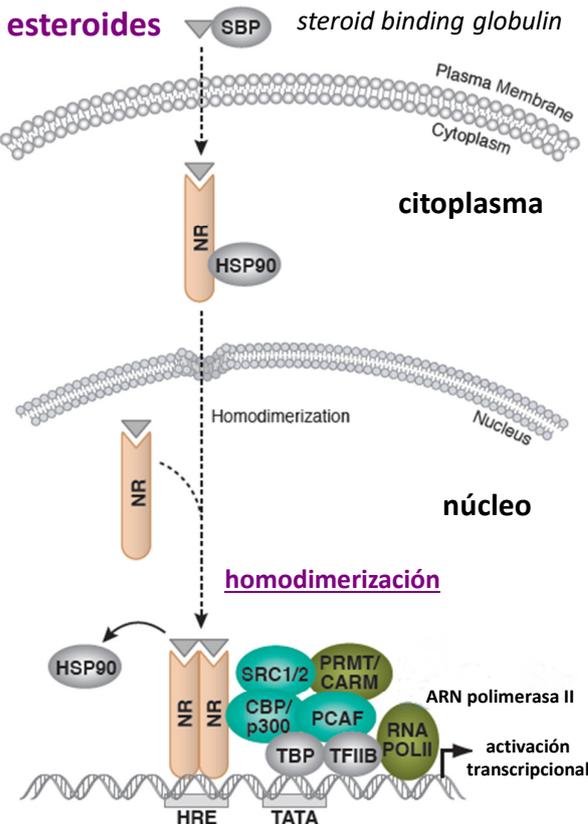
**Triyodotironina (T<sub>3</sub>)**  
Receptor de Hormona Tiroidea  
(TR)



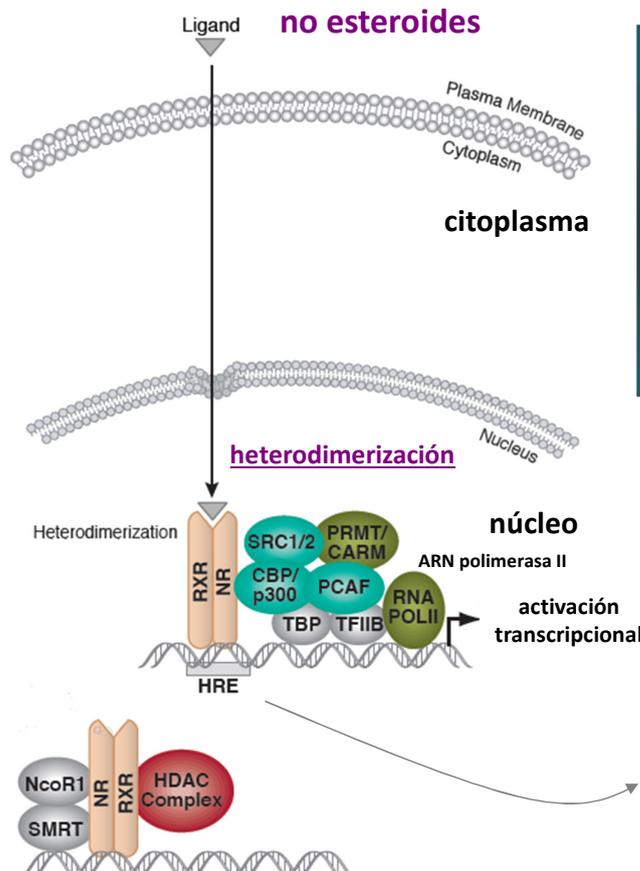
**Calcitriol**  
Receptor de Vitamina D  
(VDR)

\* También se han descrito rutas de señalización fuera del núcleo (e.g. membrana celular)

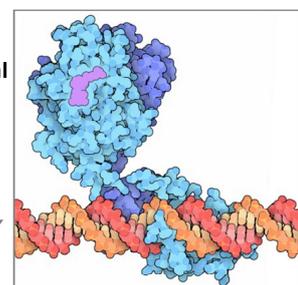
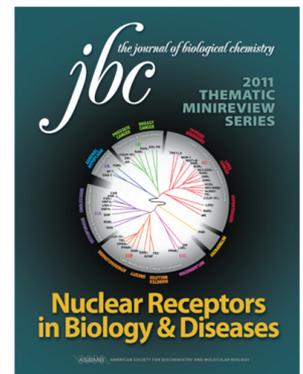
## MECANISMO DE ACCIÓN DE HORMONAS ESTEROIDES, TIROIDEAS, VITAMINA D, ÁCIDO RETINOICO, RETINOIDES Y ACTIVADORES DE LA PROLIFERACIÓN DE PEROXISOMAS



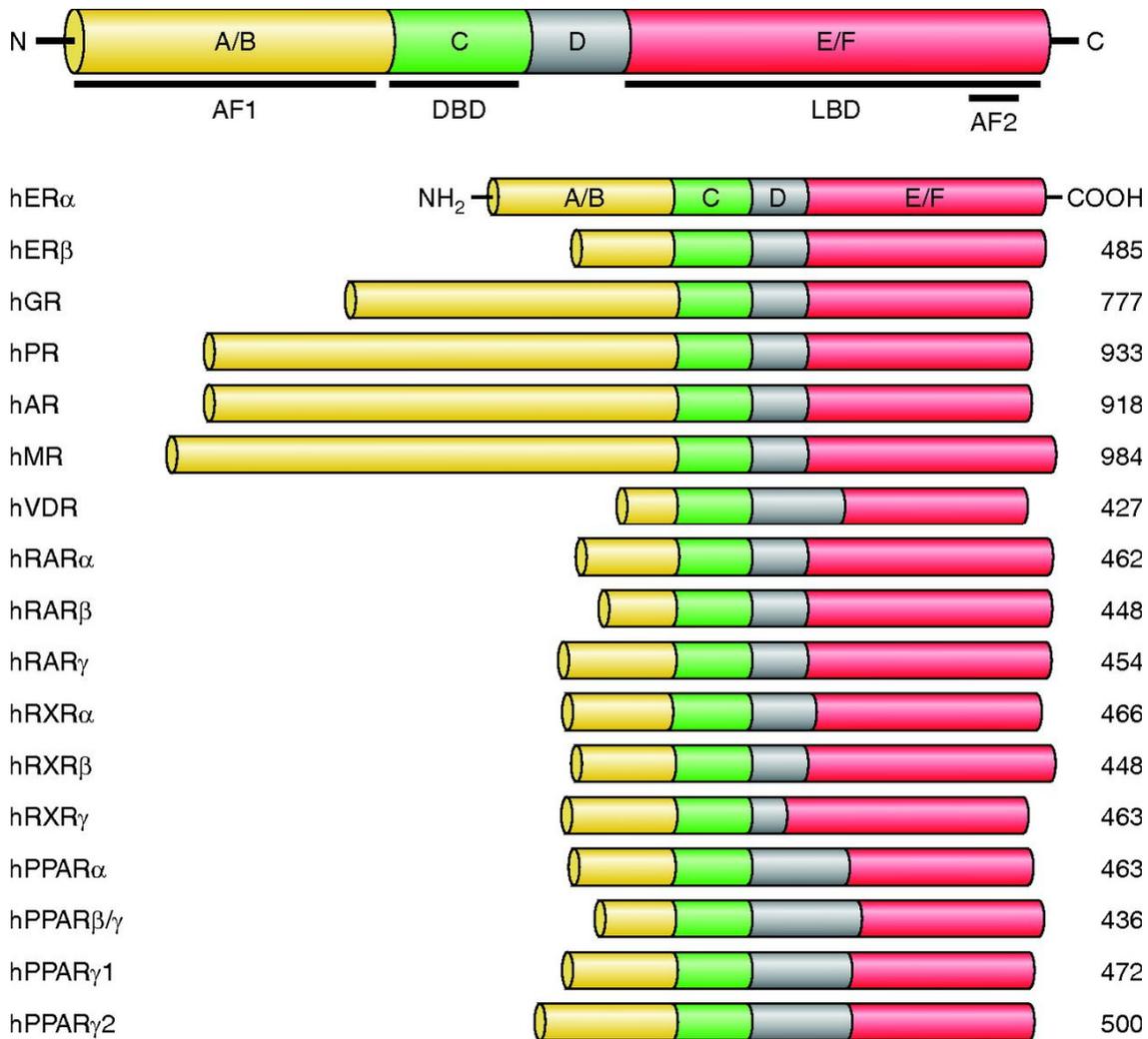
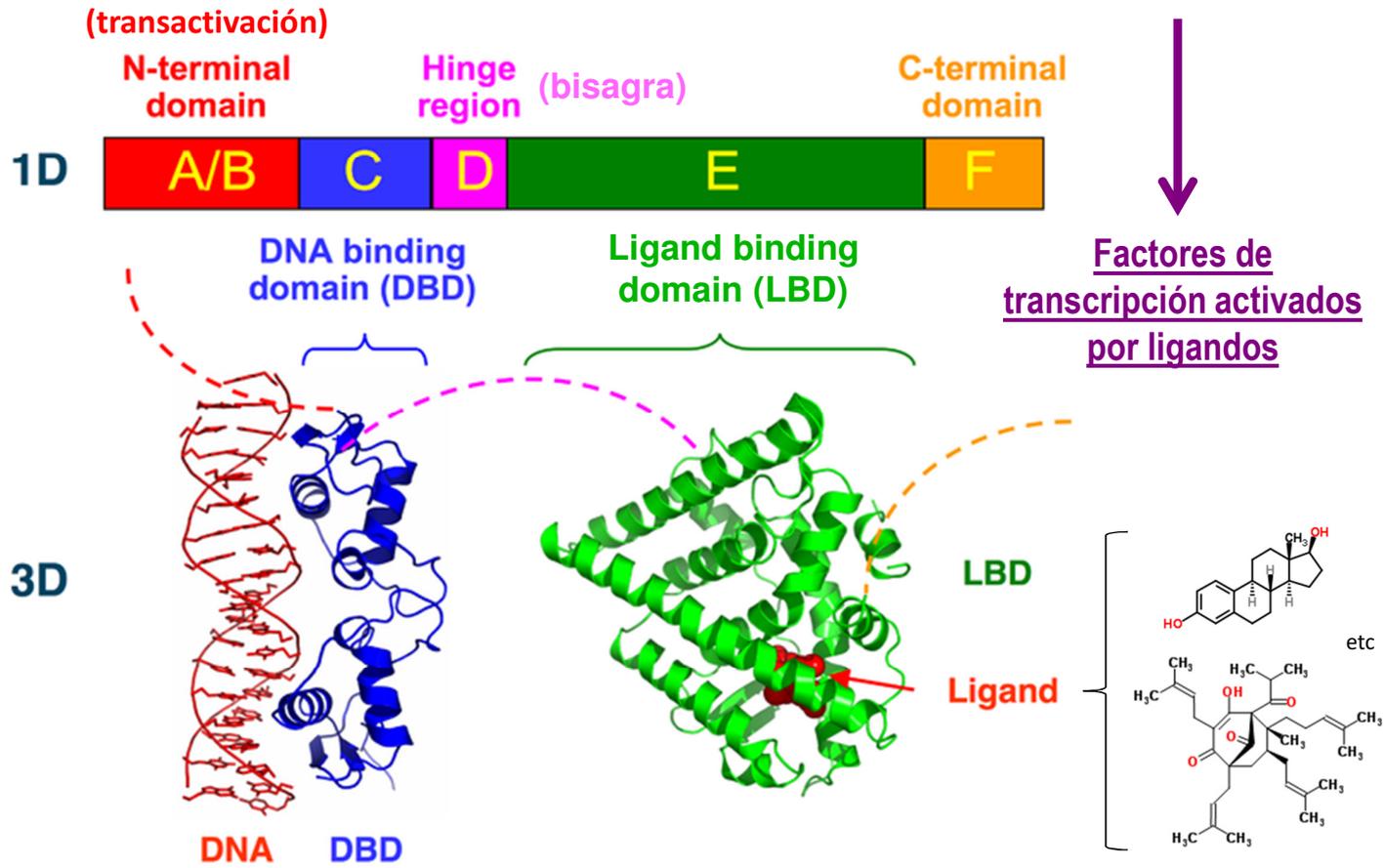
ELEMENTO DE RESPUESTA A HORMONAS



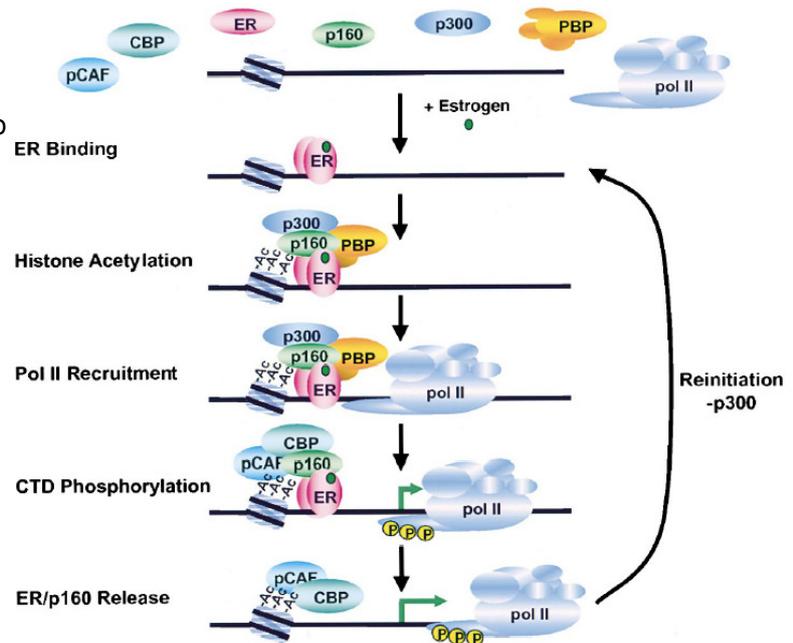
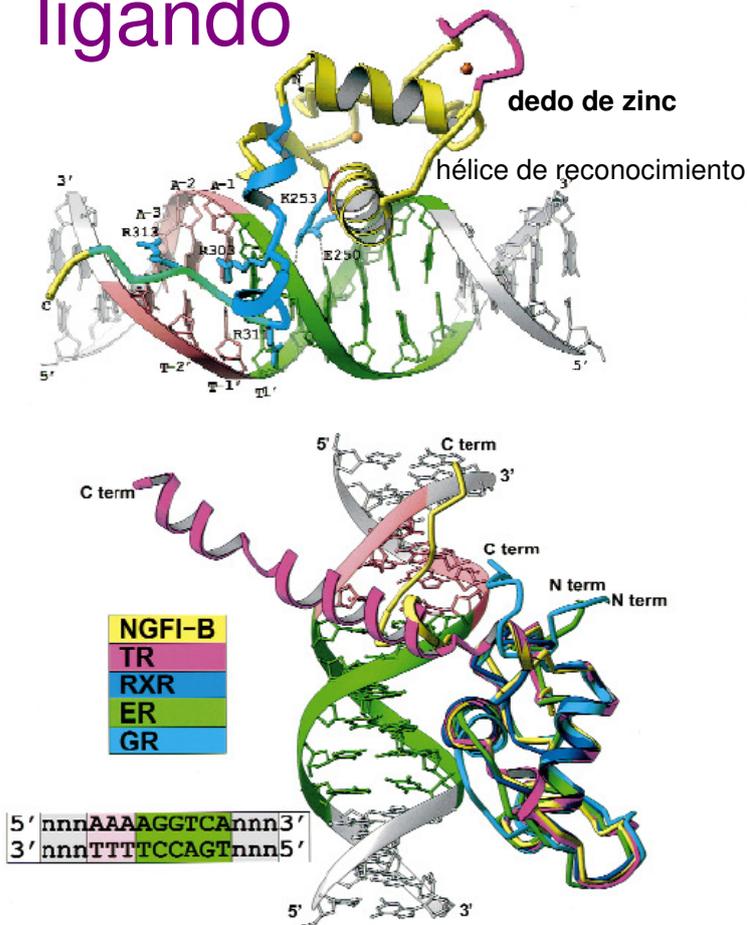
en ausencia de ligando: represión transcripcional



# ORGANIZACIÓN ESTRUCTURAL DE LOS RECEPTORES NUCLEARES

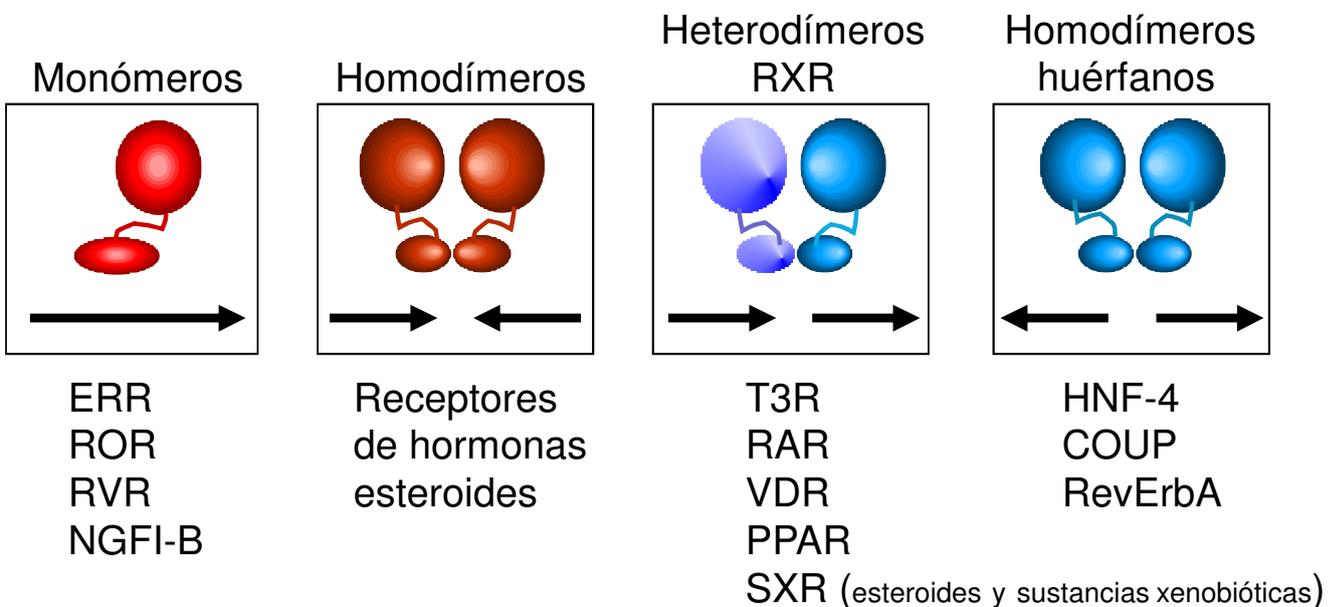
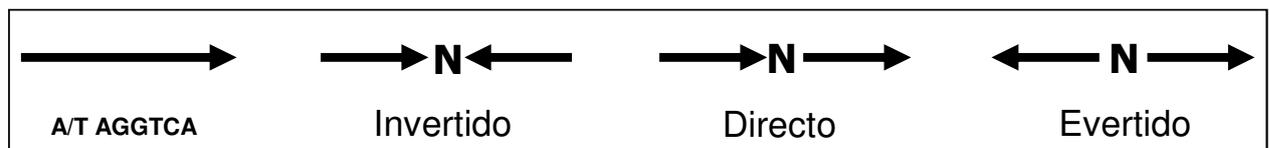


# Unión del receptor al ADN activada por ligando



... y reclutamiento de otros factores para activar la transcripción de genes por la ARN polimerasa II

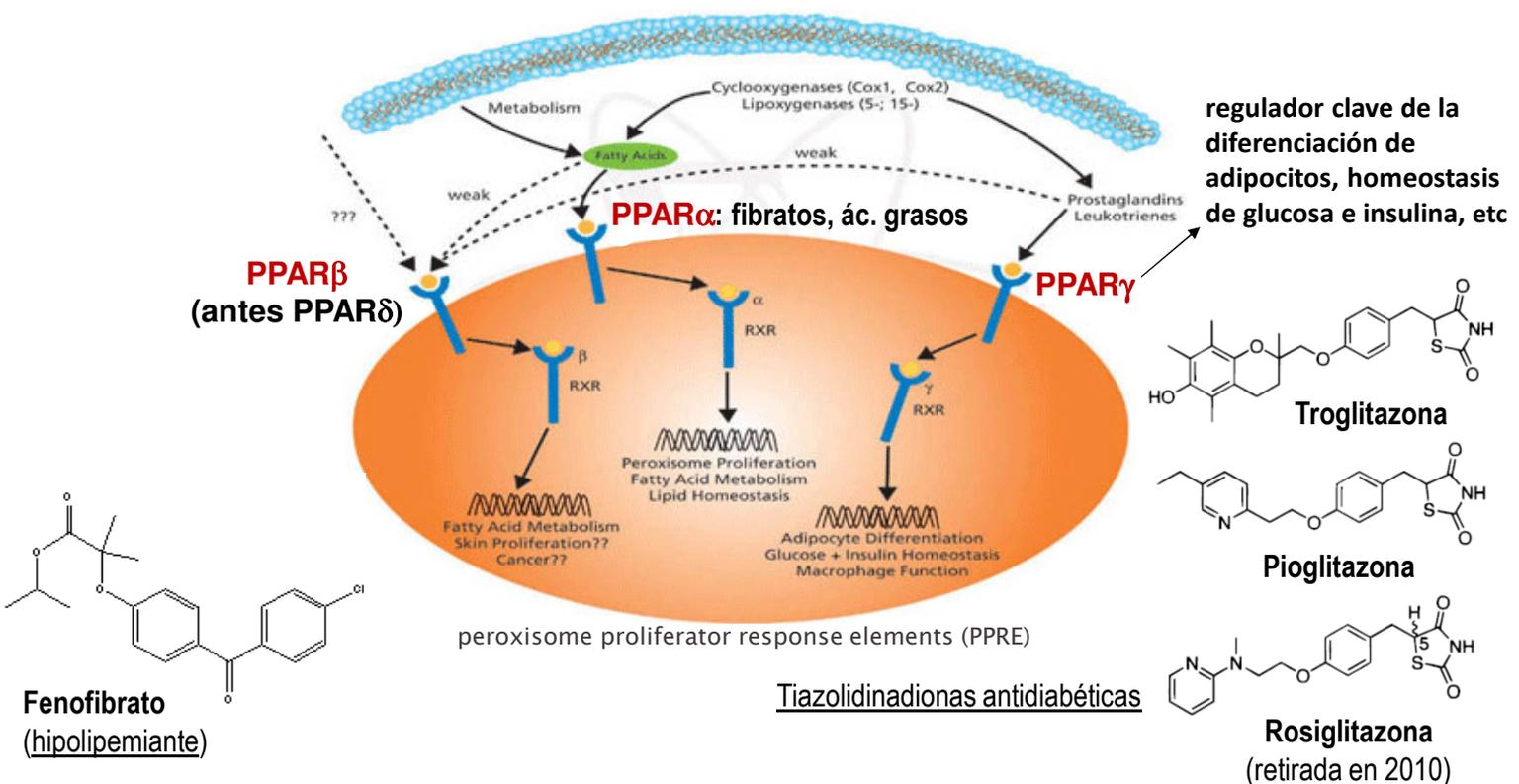
# Unión al ADN y especificidad de genes de los receptores nucleares



EJEMPLOS DE ELEMENTOS DE RESPUESTA A HORMONAS

RECEPTOR	(HRE)	SECUENCIA CONSENSO
Glucocorticoide Mineralcorticoide	GTTACA AAC TGTTCT	GGTACA <b>NNN</b> TGTTCT
Andrógeno	TGCACA GCG AGTTCT	""
Progesterona	TGTACA GGA TGTTCT	""
Estrógeno (ER)	GGTCA GCG TGACC TGTC A CTA TGTCC	GGTCA <b>NNN</b> TGA/TCC
Retinoide X / PPAR (proliferación peroxisomas)	AGGTCA C AGGTCA	AGGTCA <b>N</b> AGGTCA
Vitamina D (VDR)	GGGTGA ACG GGGGCA	AGGTCA <b>NNN</b> AGGTCA
Hormonas tiroideas	AGGTGA CAGG AGGACA	AGGTCA <b>NNNN</b> AGGTCA
Acido retinoico	GGTTCA CCGAA AGTTCA	AGGTCA <b>NNNNN</b> AGGTCA

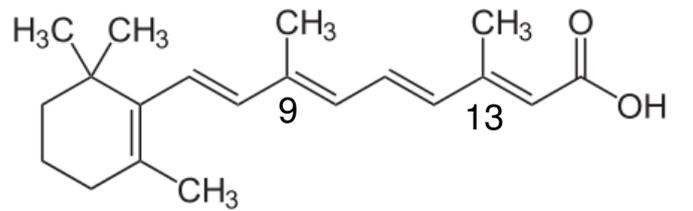
Receptores Activados por "Proliferadores de Peroxisomas":  
dianas terapéuticas en el tratamiento de enfermedades metabólicas



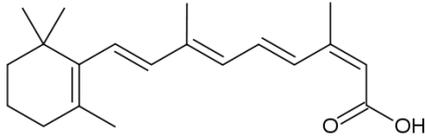
Sólo los receptores PPARα están implicados en la inducción de proliferación de peroxisomas en roedores

# Receptores de ácido retinoico: RAR $\alpha$ , RAR $\beta$ y RAR $\gamma$

- familia **NR1B**, activados por los agonistas derivados de la vitamina A: ATRA y ácido 9-*cis*-retinoico (alitretinoína)



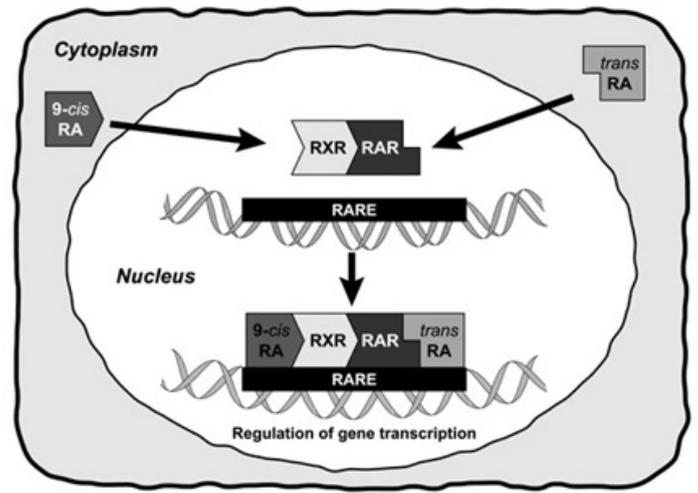
ácido all-*trans* retinoico (ATRA)



isotretinoína (ácido 13-*cis*-retinoico):  
**¡teratogénico!**

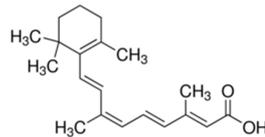


tto. acné quístico nodular severo recalcitrante



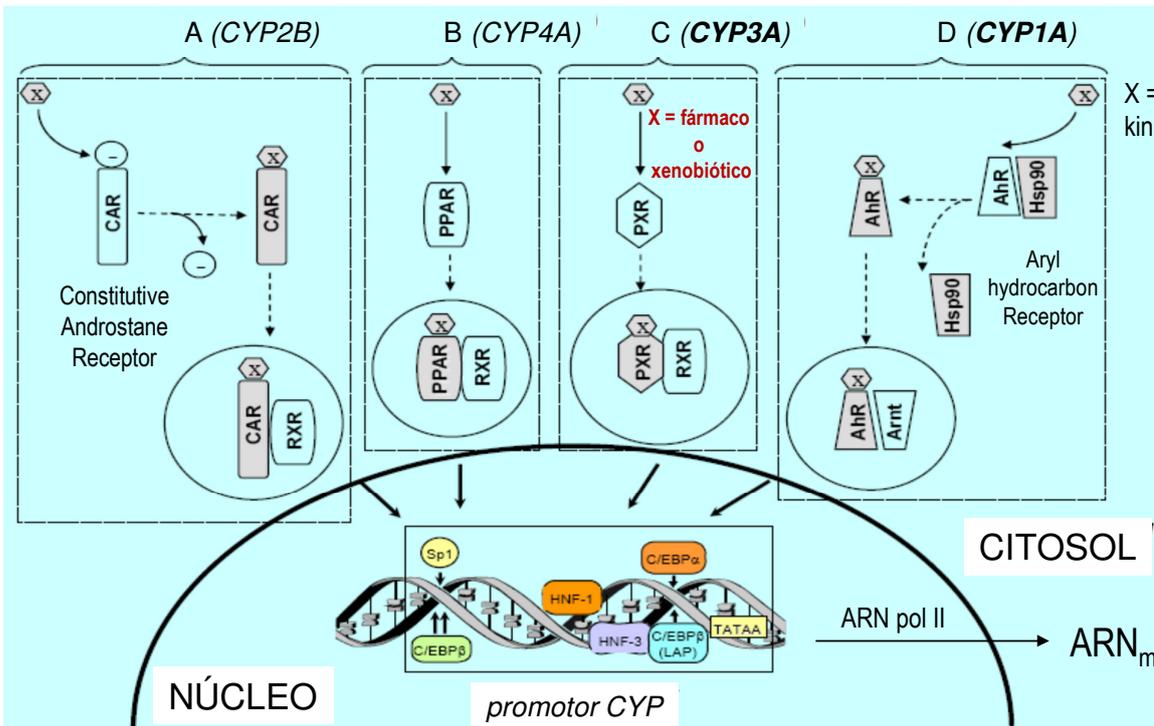
# Receptores de retinoides X: RXR $\alpha$ , RXR $\beta$ y RXR $\gamma$

- familia **NR2B**, activados por ácido 9-*cis*-retinoico (alitretinoína) y los agonistas selectivos bexaroteno y LG100268

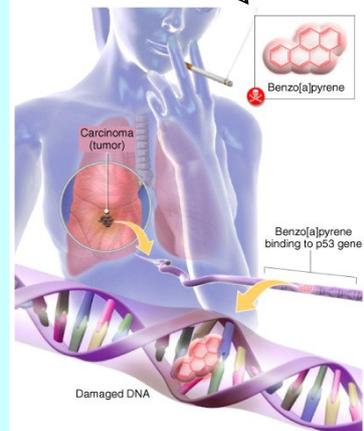


RAR y RXR forman heterodímeros RAR/RXR, los cuales se unen a regiones reguladoras de la expresión génica llamadas elementos de respuesta al ácido retinoico (RARE).

**Inducción enzimática:** la administración repetida del fármaco o la exposición al xenobiótico (X) conduce a un aumento de la expresión de ciertos genes que codifican enzimas implicadas en su biotransformación.



X = dioxina, benzo[a]pireno, kinurena, etc



# Nomenclatura de los citocromos P450

Familia CYP1:  
CYP1A1; **CYP1A2**; CYP1B1

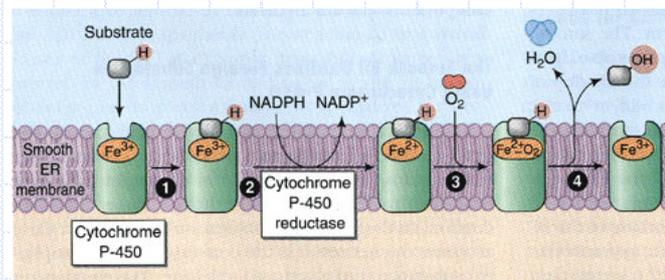
Familia CYP2:  
CYP2A6; CYP2A13; CYP2B6; CYP2C8; **CYP2C9**; **CYP2C19**;  
**CYP2D6**; **CYP2E1**; CYP2F1; CYP2J2; CYP2R1; CYP2S1

Familia CYP3:  
**CYP3A4**; CYP3A5; CYP3A7; CYP3A43

Familia CYP4:  
CYP4A11; CYP4A22; CYP4B1

Familias CYP>4: CYP5A1 - CYP8A1 -  
CYP19A1 - CYP21A2 - CYP26A1

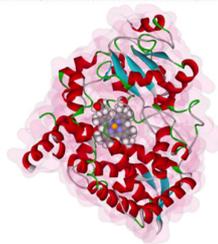
70-80%  
metabolismo  
fármacos  
utilizados en  
clínica



## Ejemplos de sustratos de citocromos P450 de la familia CYP3

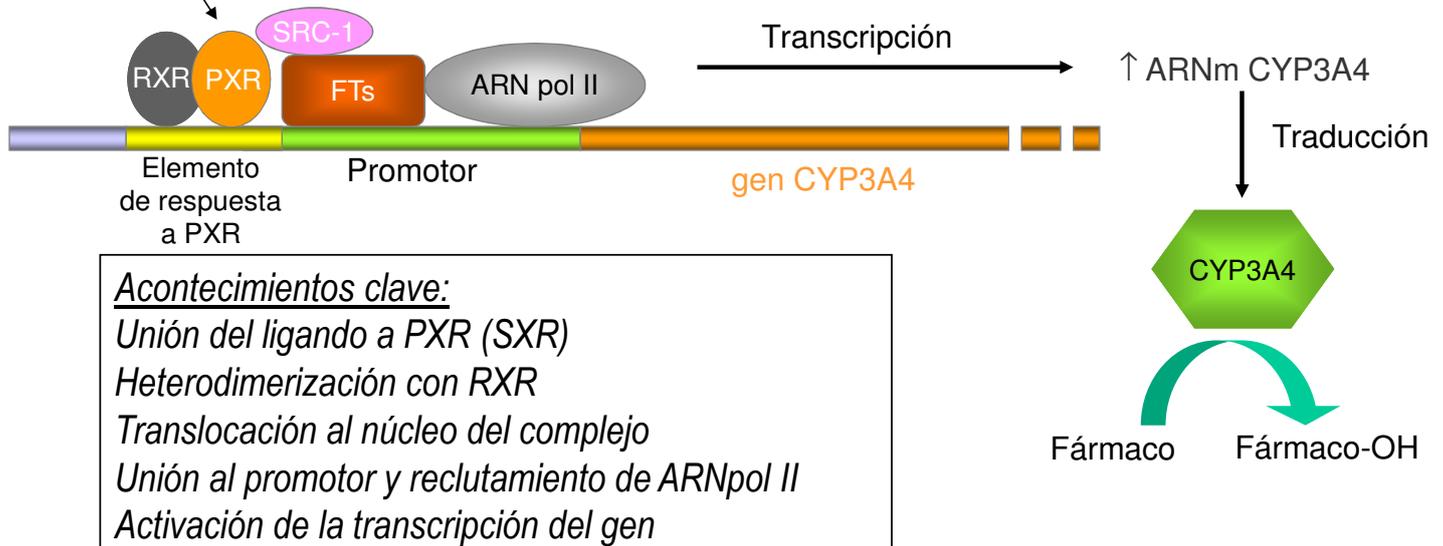
**CYP3A4**, CYP3A5, CYP3A7: antibióticos macrólidos (claritromicina, **eritromicina**, telitromicina, pero NO azitromicina), antifúngicos azólicos (**ketoconazol**, voriconazol, itraconazol), antiarrítmicos (quinidina), benzodiazepinas (alprazolam, diazepam, midazolam, triazolam), inmunosupresores (ciclosporina, tacrólimus), inhibidores de la proteasa del VIH (indinavir, **ritonavir**, saquinavir), antihistamínicos (astemizol, clorfeniramina), bloqueantes de canales de calcio (amlodipino, diltiazem, felodipino, nifedipino, nisoldipino, nitrendipino, verapamilo), inhibidores de la HMG CoA reductasa (**atorvastatina** pero NO rosuvastatina), aripiprazol, buspirona, imatinib, haloperidol (en parte), metadona, pimozida, quinina, sildenafilo, tamoxifeno, trazodona, vincristina, etc

Protein Data Bank: 1W0E  
(con metapirona y progesterona)



# Inducción de CYP3A4 mediada por PXR (=SXR, sensor de sustancias xenobióticas)

**L**  
**Rifampina/rifampicina, barbitúricos, sulfonpirazona, clotrimazol**  
**Hiperforina (hierba de San Juan, *Hypericum perforatum*)**



↑ traducción del ARNm → Mayor cantidad de enzima → **Actividad Enzimática Aumentada**



**NucleaRDB**

information system for Nuclear Receptors

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Go!

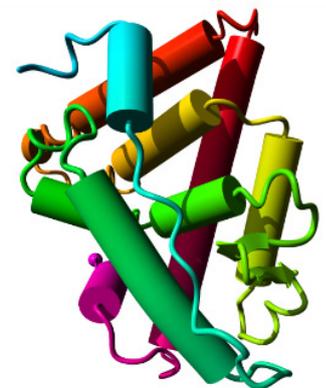
## Welcome to the NucleaRDB

The NucleaRDB is a molecular-class information system that collects, combines, validates and stores large amounts of heterogenous data on Nuclear Hormone Receptors (NHRs). The NucleaRDB contains data on sequences, ligand binding constants and mutations. In addition, many different types of computationally derived data are stored such as multiple sequence alignments and homology models. The NucleaRDB is designed to be a data storage medium, as well as a tool to aid biomedical scientists with answering questions by offering a single point of access to many types of data that are integrated and visualized in a user-friendly way. Although most parts of the NucleaRDB are self-explanatory, if you have not used this resource before we advice you to take a look at the [usage](#) page.

We advice you to take a look at the:

- [updates](#) page to see what has changed and what is new
- [usage](#) page to make sure you will quickly find your way

Current version: 11.7.1



Contact: [nucleardb@cmbi.ru.nl](mailto:nucleardb@cmbi.ru.nl)

<http://www.receptors.org/nucleardb/>

<http://www.guidetopharmacology.org/GRAC/NHRListForward>

# CANALES IÓNICOS Y EJEMPLOS DE FÁRMACOS QUE LOS AFECTAN

## Canales de calcio (operados por voltaje)

**Antianginosos** (nifedipino, amlodipino, felodipino, diltiazem, verapamilo)

**Antihipertensivos** (nifedipino, amlodipino, felodipino, diltiazem, verapamilo)

**Antiarrítmicos clase IV** (diltiazem, verapamilo)



## Canales de sodio (operados por voltaje)

**Anticonvulsivantes** (carbamazepina, fenitoína, valproato)

**Antiarrítmicos clase I**

IA (disopiramida, procainamida, quinidina)

IB (lidocaína, mexiletina, fenitoína, tocainida)

IC (encainida, flecainida, propafenona)

**Diuréticos** (amilorida)

**Anestésicos locales** (cocaína, lidocaína, tetracaína, bupivacaína, mepivacaína, ropivacaína)

## Canales de potasio (operados por voltaje)

**Antidiabéticos orales** (tolbutamida, glipizida, gliburida, tolazamida): KCNJ11

**Antihipertensivos** (diazóxido, minoxidilo)

**Antiarrítmicos clase III** (amiodarona, clofilium, dofetilida, *N*-acetilprocainamida, sotalol)

Fármacos que abren canales de potasio (adenosina, aprikalim, lev cromakalim, nicorandilo, pinacidilo)

## Canales TRP (Transient Receptor Potential)

Capsaicina, mentol, carvacrol, etc; *N*-acetil-*p*-benzoquinona imina (metabolito del paracetamol)

## Canales de cloruro (dep. voltaje y activados por Ca<sup>2+</sup> intracelular): CaCC

**Antialérgicos** (cromoglicato)

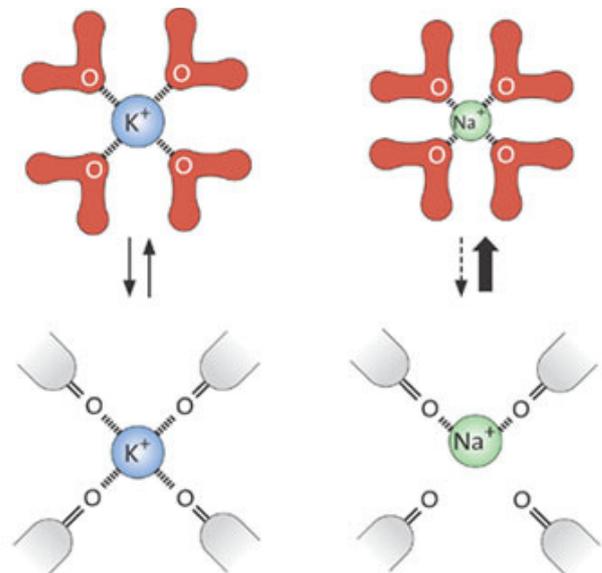
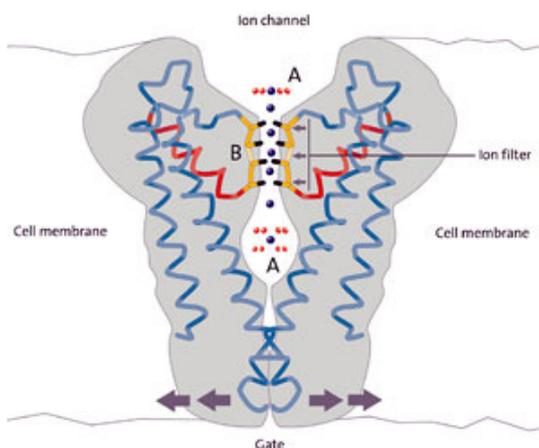
(Tomado de *New England Journal of Medicine* 336, 1575, 1997, y modificado por FGB).

## El primer canal iónico cartografiado átomo a átomo Roderick MacKinnon (1998)

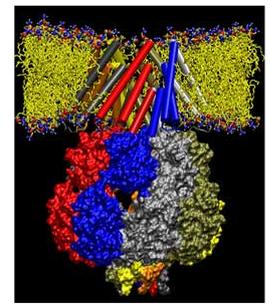
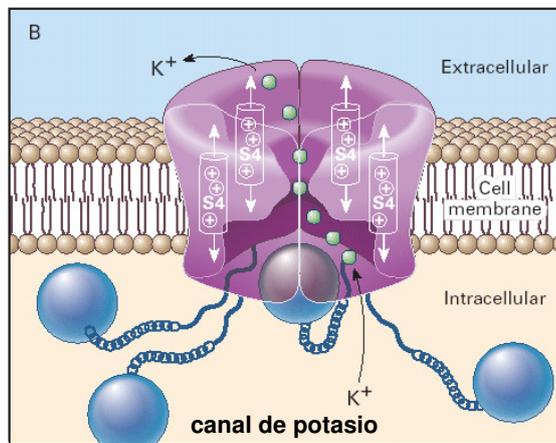
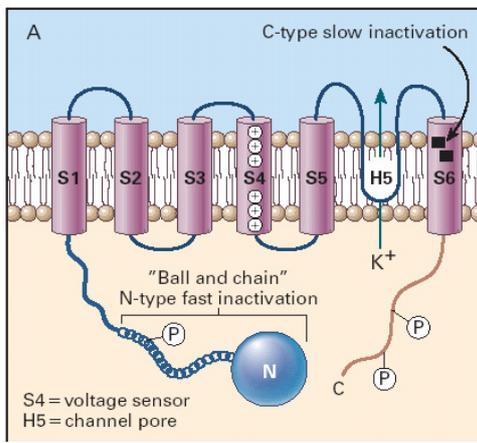
Premio Nobel de Química (2003)

KcsA de *Streptomyces lividans*

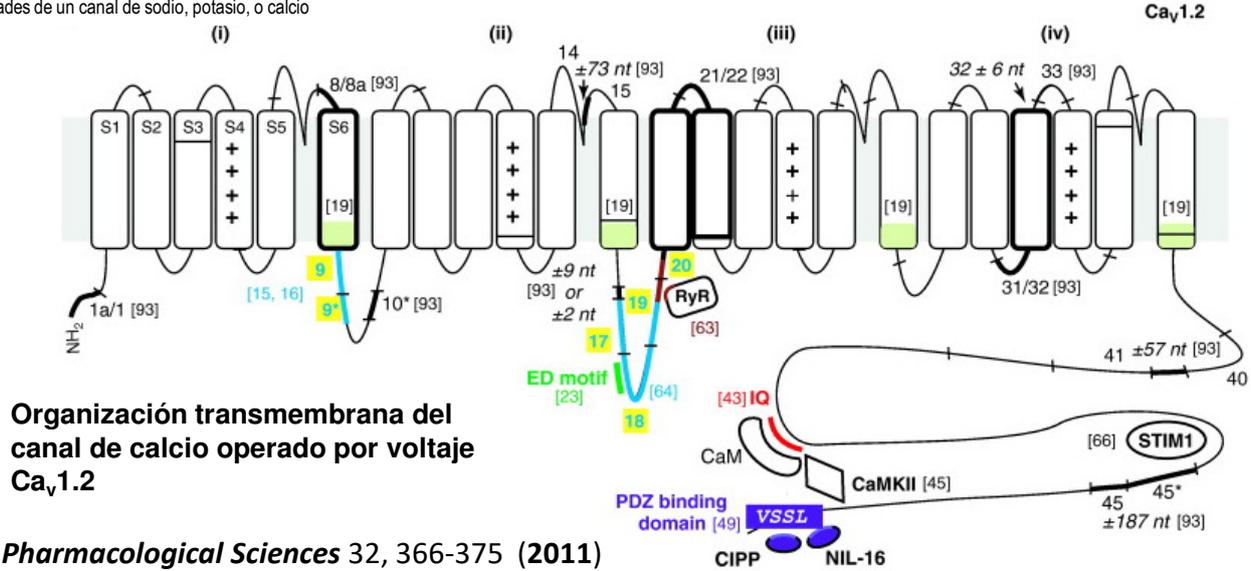
Protein Data Bank: 1BL8



[http://nobelprize.org/nobel\\_prizes/chemistry/laureates/2003/mackinnon-lecture.html](http://nobelprize.org/nobel_prizes/chemistry/laureates/2003/mackinnon-lecture.html)



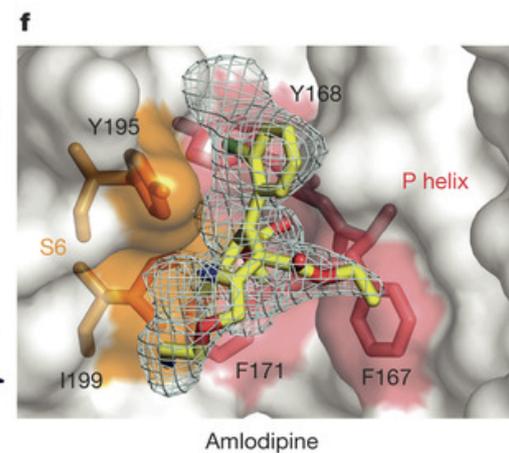
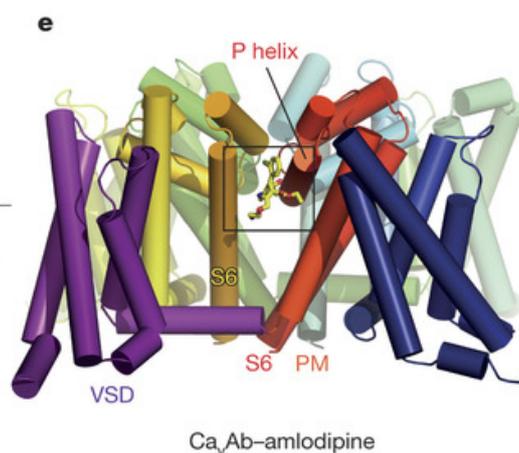
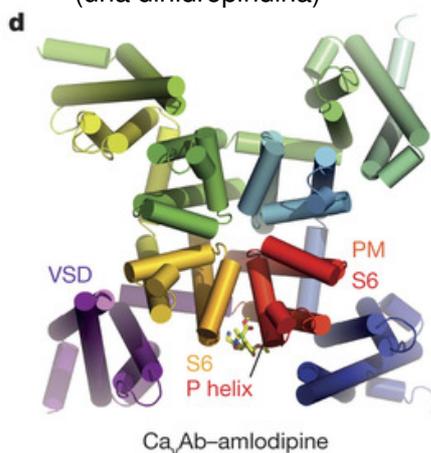
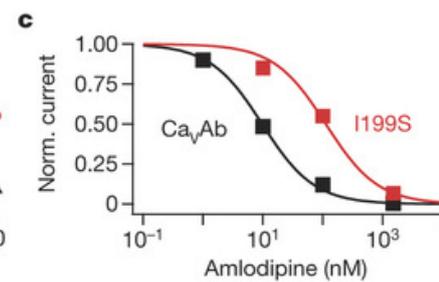
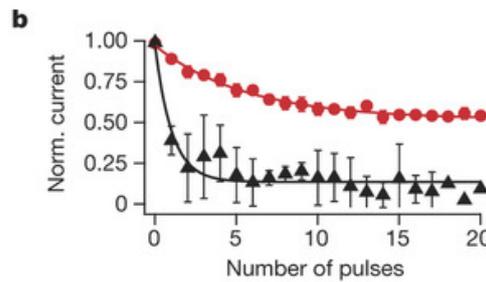
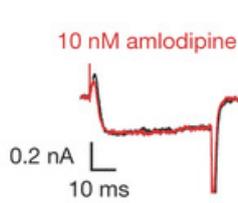
Esquema de los 6 dominios transmembrana que constituyen una de las subunidades de un canal de sodio, potasio, o calcio



Organización transmembrana del canal de calcio operado por voltaje Ca<sub>v</sub>1.2

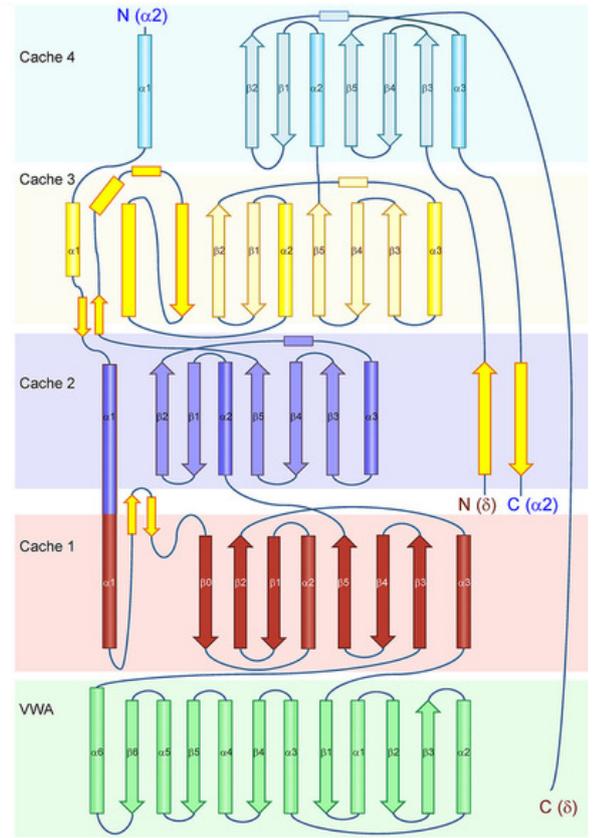
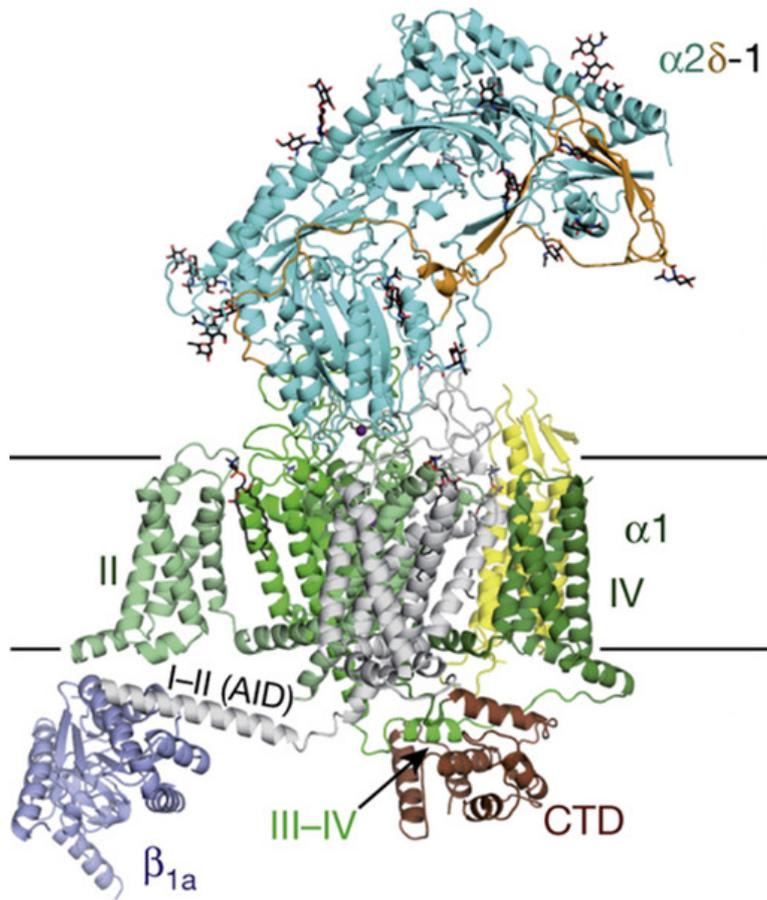
*Trends in Pharmacological Sciences* 32, 366-375 (2011)

## BASE ESTRUCTURAL PARA LA INHIBICIÓN DE UN CANAL DE CALCIO OPERADO POR VOLTAJE POR LOS “ANTAGONISTAS DEL CALCIO”



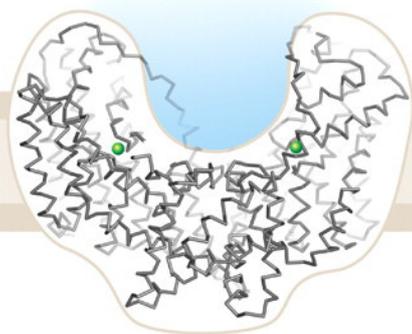
Tang et al.  
*Nature* 537, 117–121 (2016)

# Estructura del canal de calcio operado por voltaje Cav1.1 a 3,6 Å de resolución

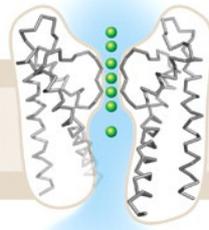


Wu et al.  
*Nature* 537, 191–196 (2016)

## Canales y Bombas: el transporte selectivo de iones depende de la arquitectura y conformación de la proteína



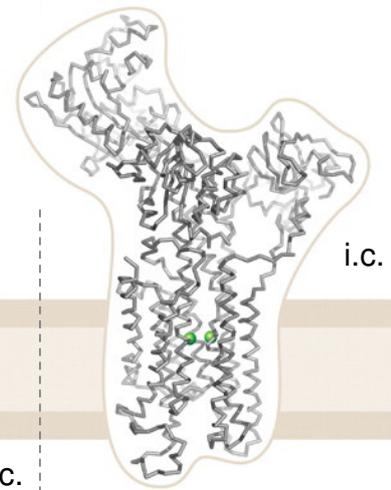
Glt<sub>Ph</sub>: homólogo procarionta de los transportadores de glutamato acoplados a sodio



KcsA: canal de potasio abierto



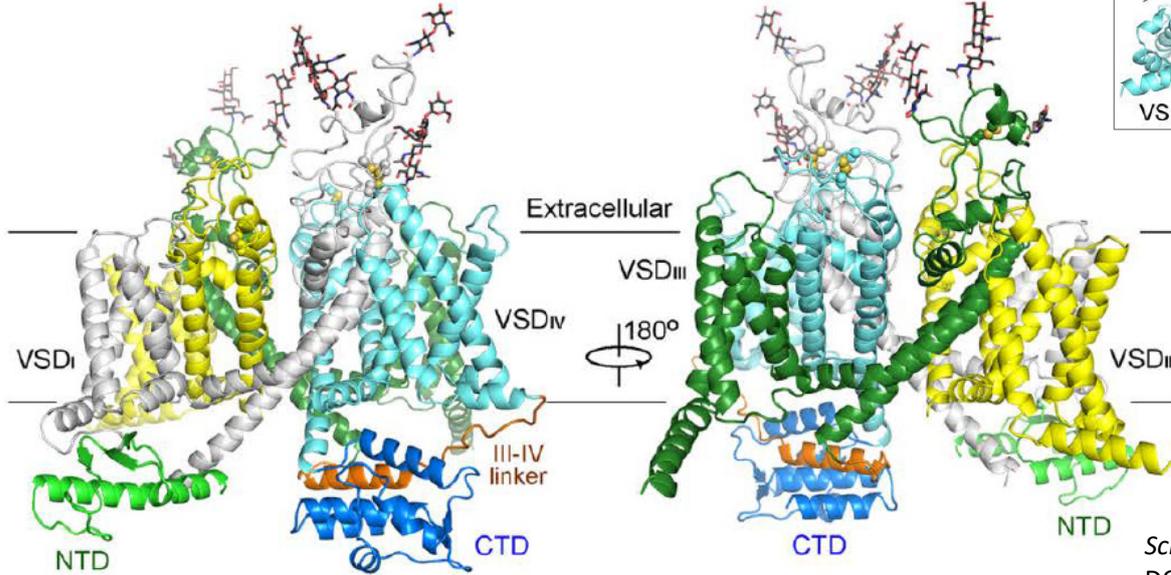
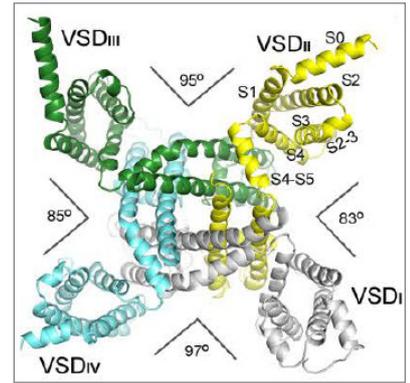
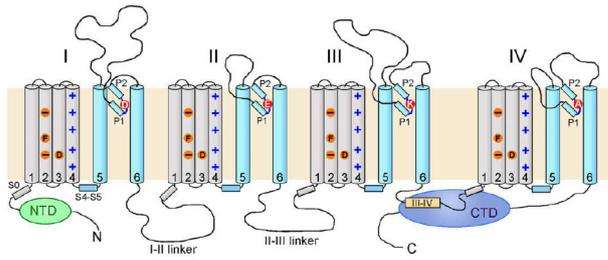
ClC: proteína transportadora de iones cloruro



ATPasa Ca<sup>2+</sup>

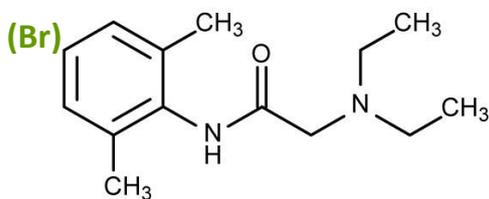
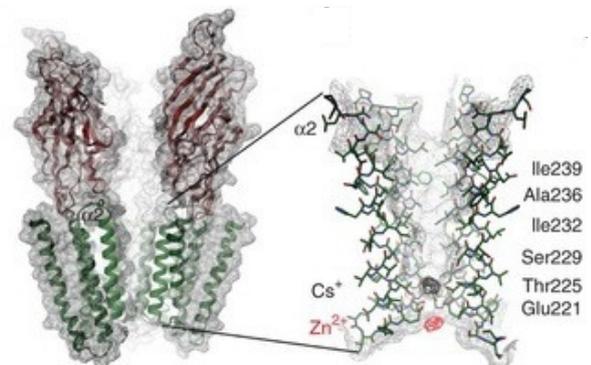
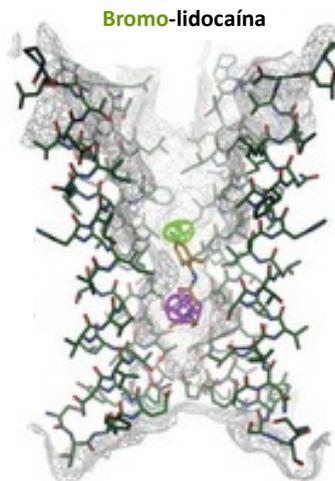
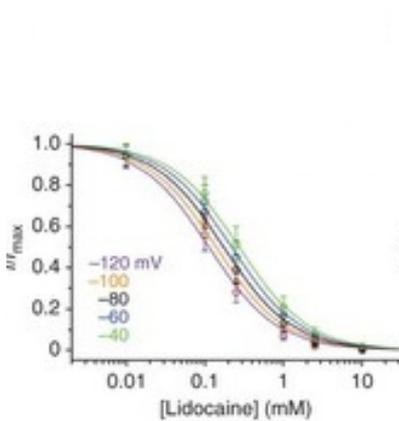
# Structure of a eukaryotic voltage-gated sodium channel at near-atomic resolution

Huaizong Shen,<sup>1,2\*</sup> Qiang Zhou,<sup>1,2,3\*</sup> Xiaojing Pan,<sup>1,2\*</sup> Zhangqiang Li,<sup>1,2,3\*</sup> Jianping Wu,<sup>1,2,3\*</sup> Nieng Yan<sup>1,2,3†</sup>



Science 355(6328) eaal43262017  
DOI: 10.1126/science.aal4326

## Base estructural del bloqueo de apertura de un canal iónico operado por ligando (procariota) por un anestésico local típico



**Lidocaína**

**Nota:** este es un canal pentamérico bacteriano, estructural y funcionalmente distinto del canal de sodio dependiente de voltaje "Na<sub>v</sub>" considerado como diana en mamíferos.

Nature Structural & Molecular Biology 17, 1330–1336 (2010)

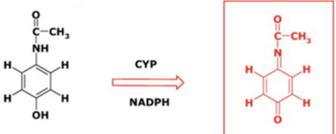
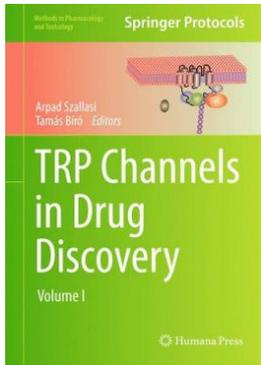
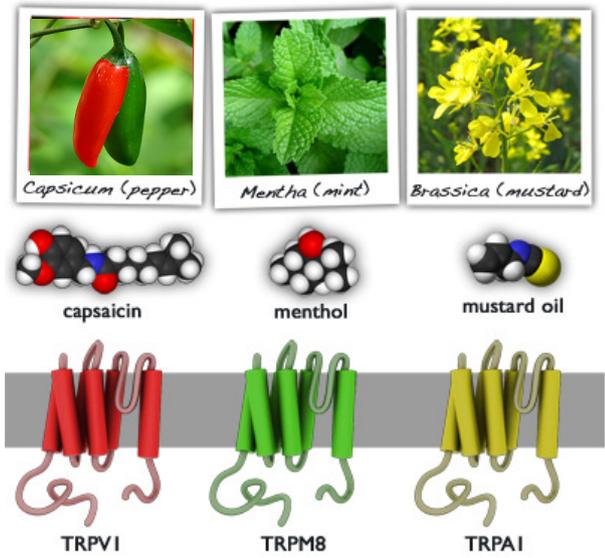
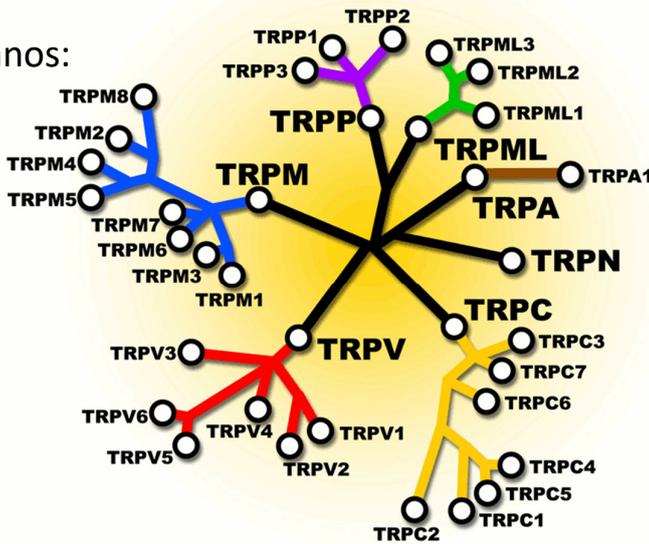
# Canales TRP sensoriales

(Transient Receptor Potential)

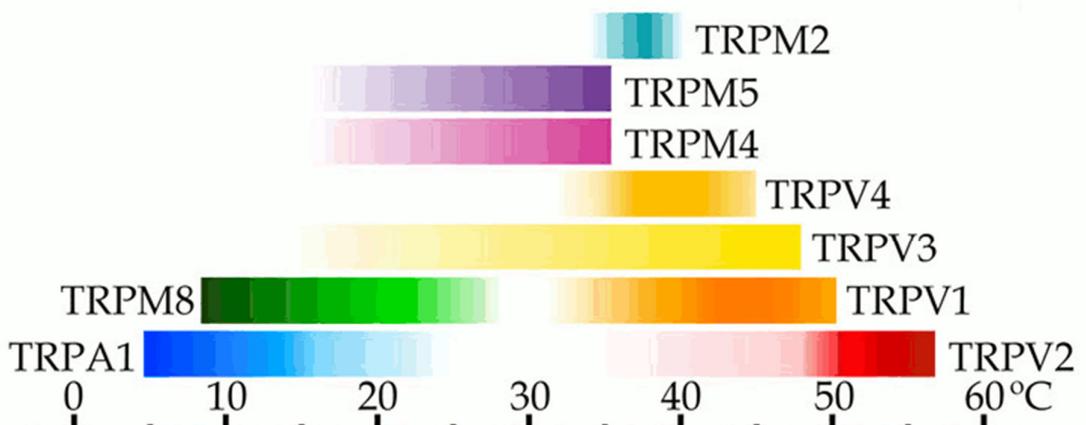
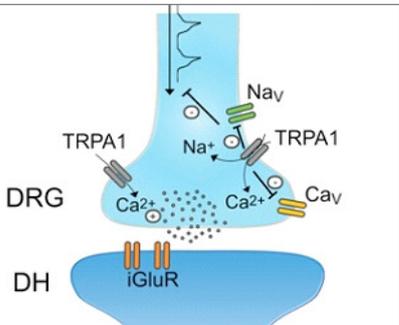
Las acciones de algunas sustancias vegetales mimetizan las de algunos estímulos físicos.

Ejs.: **capsaicina** (guindillas picantes), **mentol** (mentas) e **isotiocianato de alilo** (mostaza y wasabi) actúan como agonistas sobre TRPV1, TRPM8 y TRPA1, respectivamente.

En seres humanos:  
27 miembros  
6 familias



N-acetil-p-benzoquinona imina (metabolito del paracetamol) y Δ<sup>9</sup>-tetrahidrocannabinol

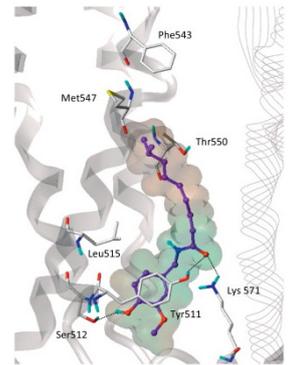
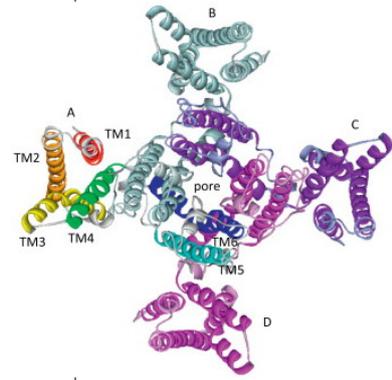
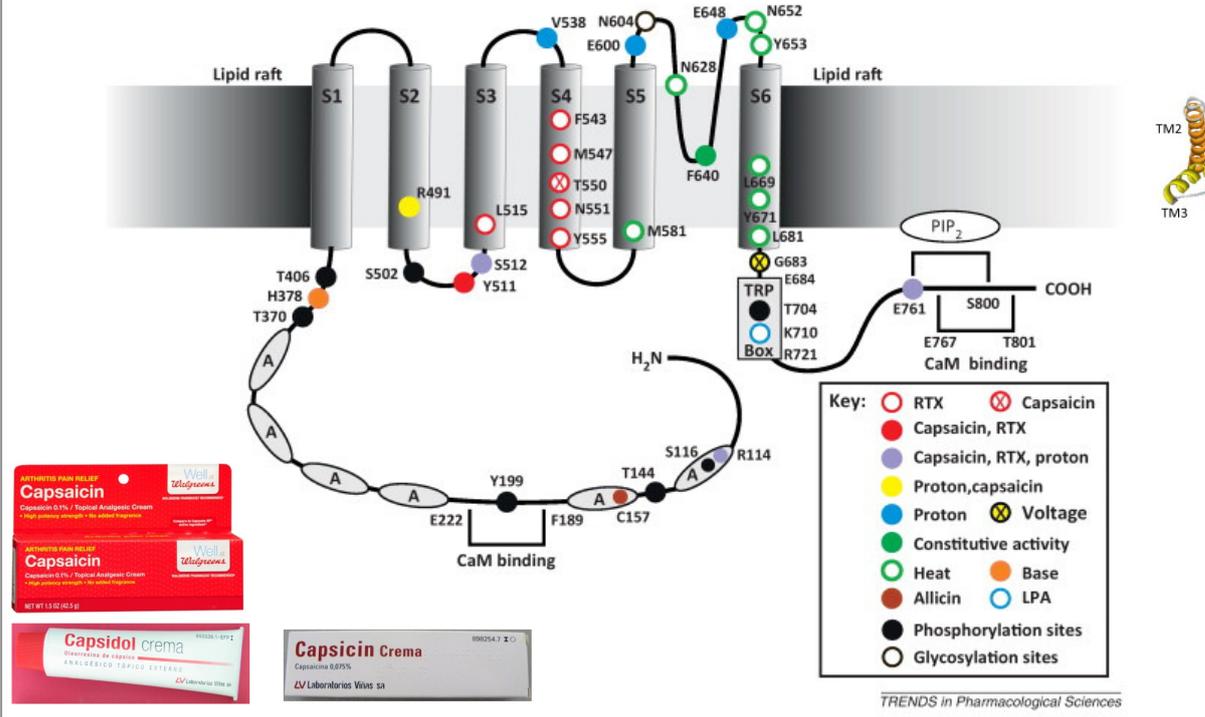


# Transient receptor potential vanilloid type 1 (TRPV1):

capsaicin



Regions and amino acids critical in activation, sensitization and desensitization of TRPV1



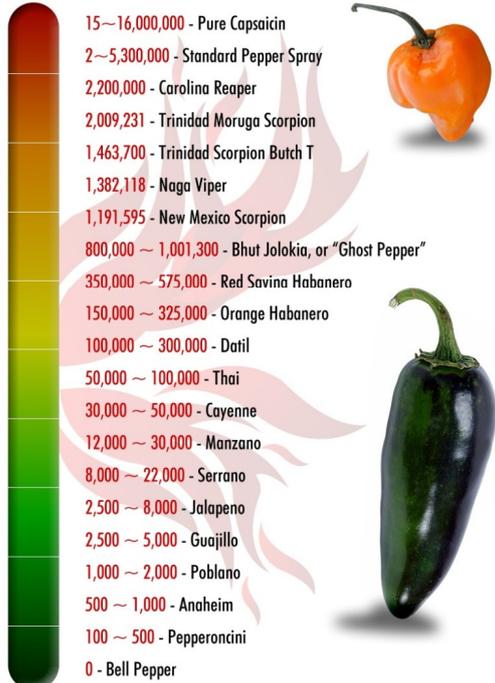
TRENDS in Pharmacological Sciences

# Escalas de sabor picante

## SCOVILLE HEAT SCALE for CHILI PEPPERS

When you Gotta Have it Hot!

Chili Peppers measured by Scoville Heat Units (SHU). How hot do you like it?



**Pick a Pepper!**

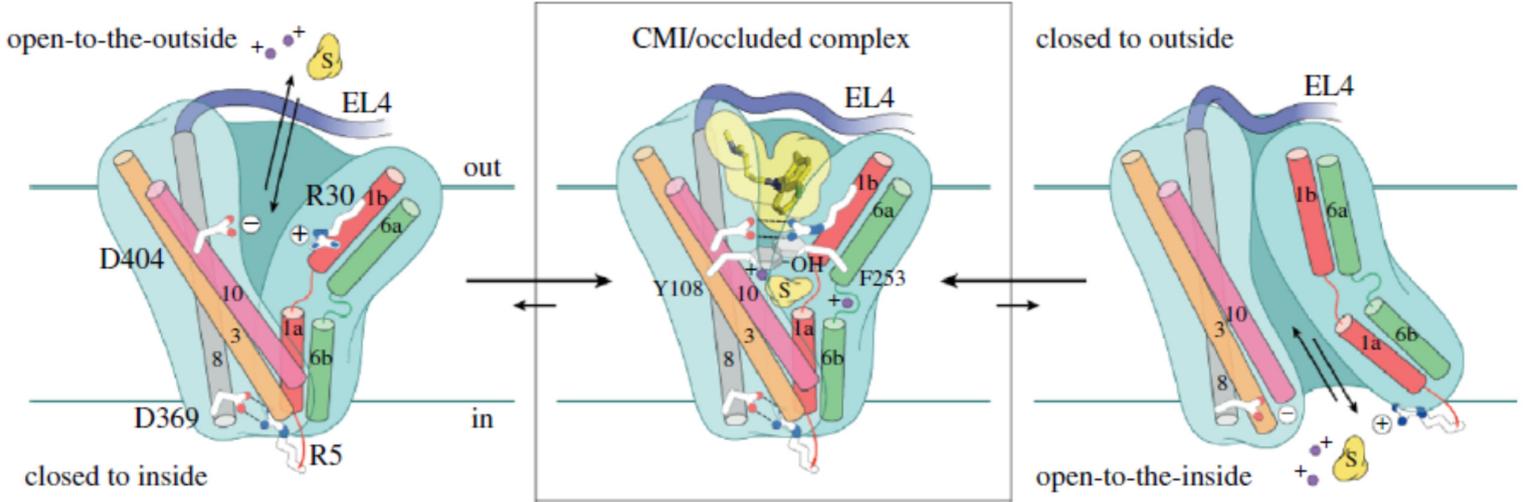
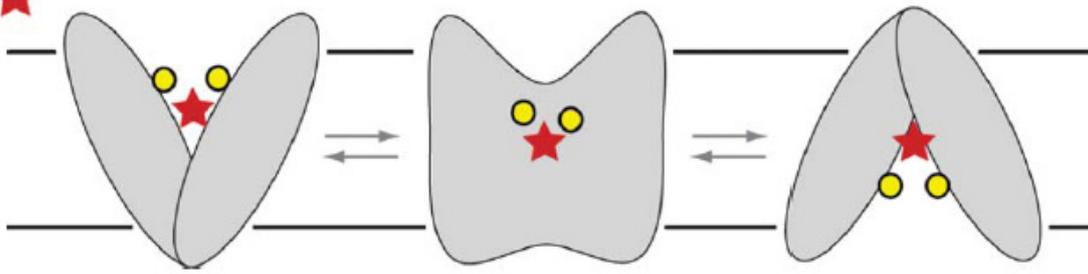
<b>Shishito, Italian Long Hots</b> 100 - 1,000	<b>Cubanelle</b> 1,000	<b>Jalapeno</b> 2,500 - 8,000	<b>Hungarian Wax</b> 5,000 - 10,000	<b>Thai Red/Green</b> 50,000-100,000
<b>Bell Peppers</b>	<b>Anaheim</b> 500 - 2,500	<b>Poblano</b> 1,000 - 1,500	<b>Fresno</b> 2,500 - 10,000	<b>Habanero</b> 100,000 - 350,000

\*Based on Scoville scale

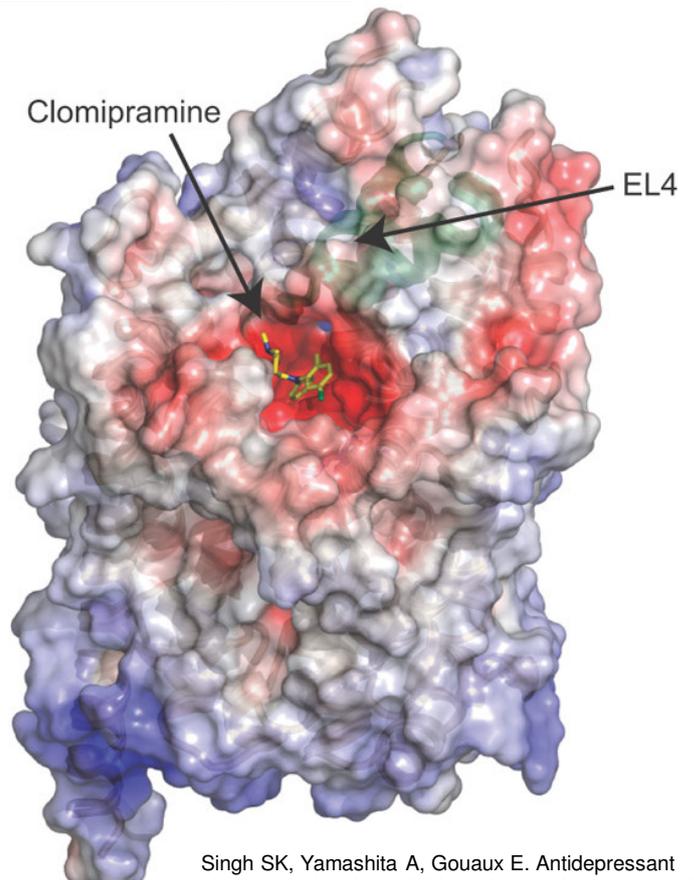
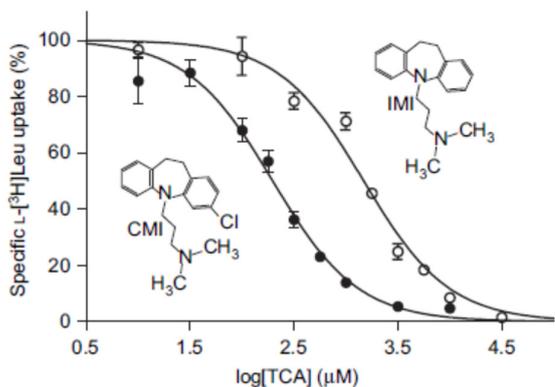
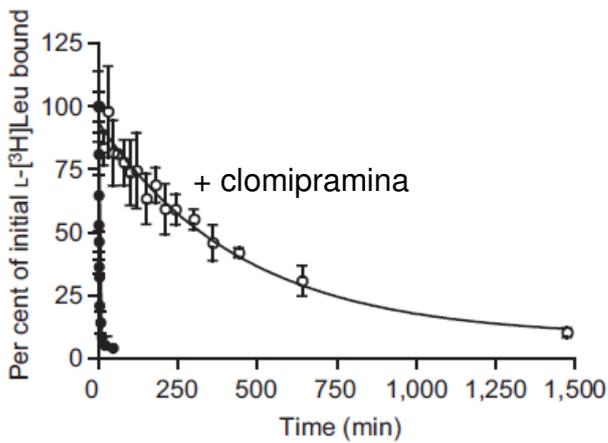
# Transportadores de neurotransmisores acoplados a iones sodio (homólogos procariotas)

high Na<sup>+</sup> ●

low substrate ★



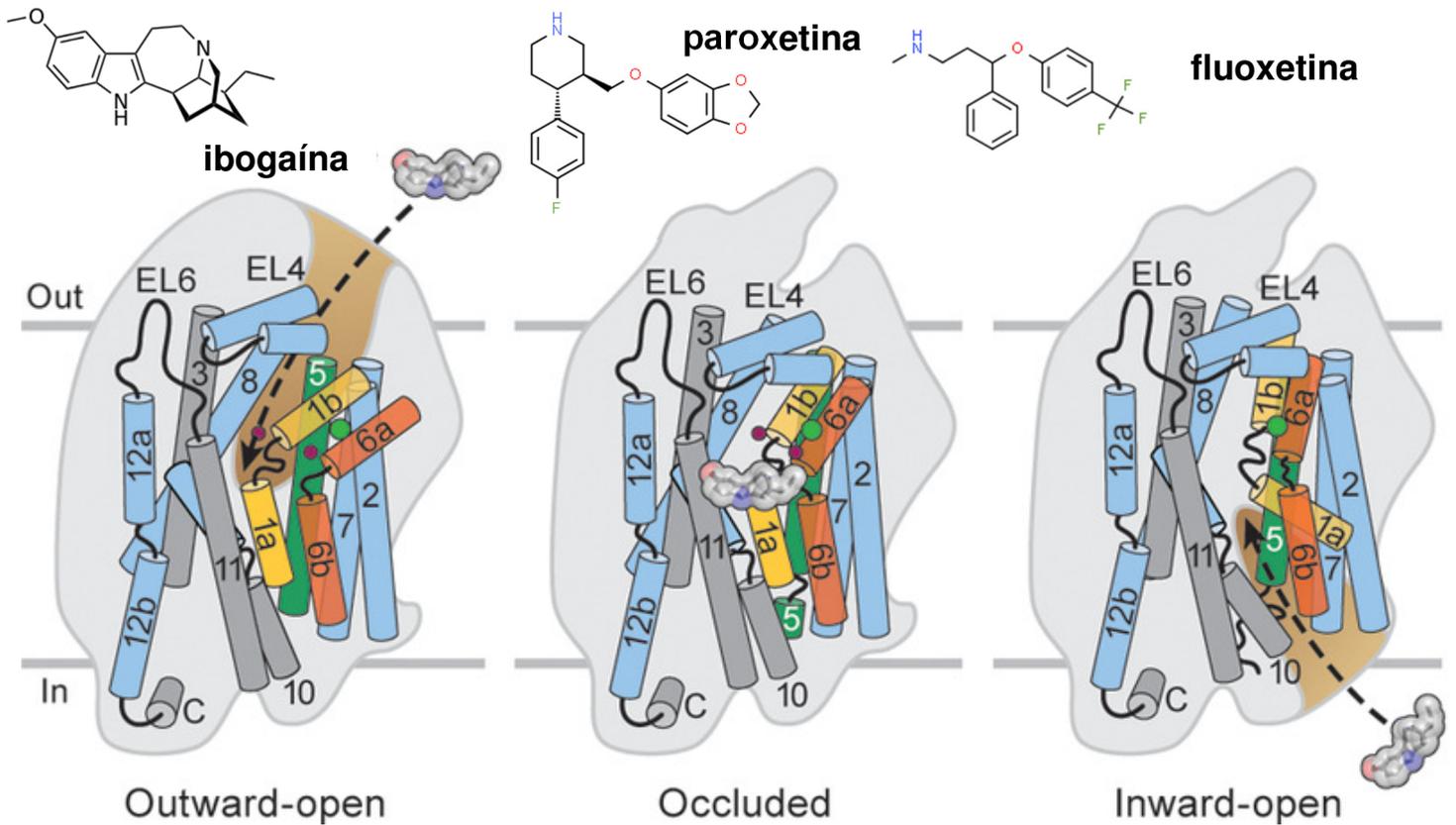
# Transportadores de neurotransmisores acoplados a iones sodio ("simportadores": inhibición por antidepresivos tricíclicos (ej. clomipramina))



Singh SK, Yamashita A, Gouaux E. Antidepressant binding site in a bacterial homologue of neurotransmitter transporters. *Nature* 448:952-62 (2007)

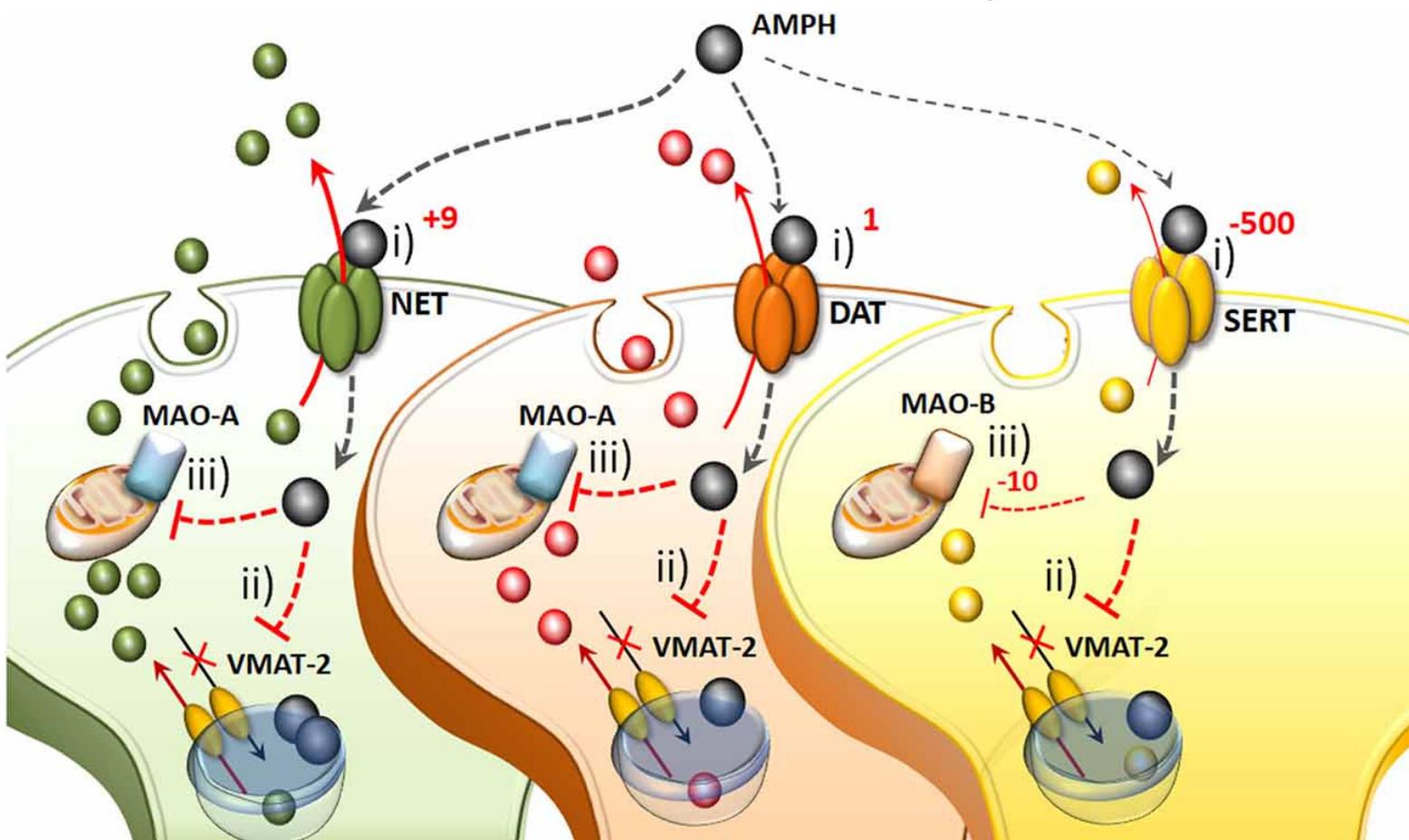
TM12

# TRANSPORTADOR DE SEROTONINA (SERT) como diana farmacológica:



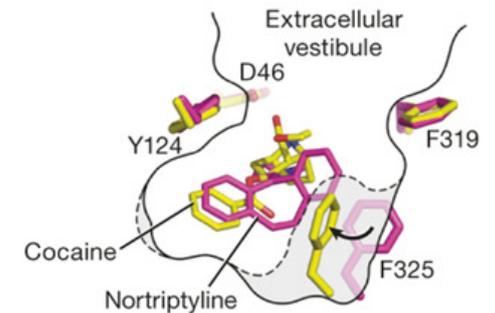
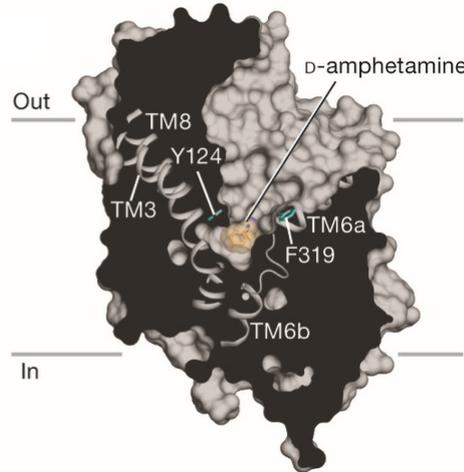
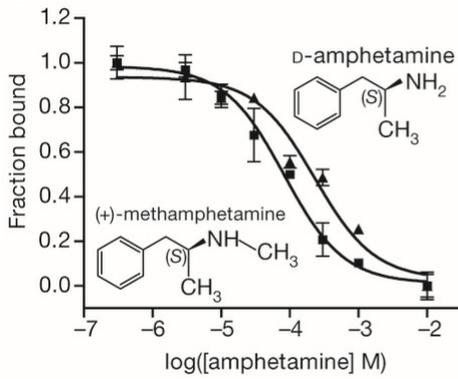
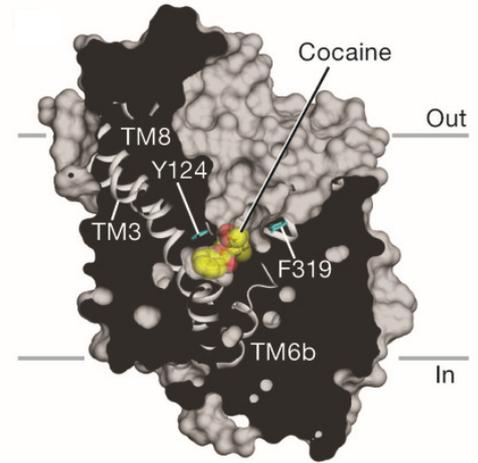
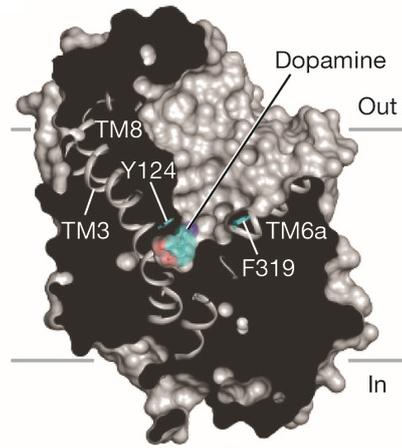
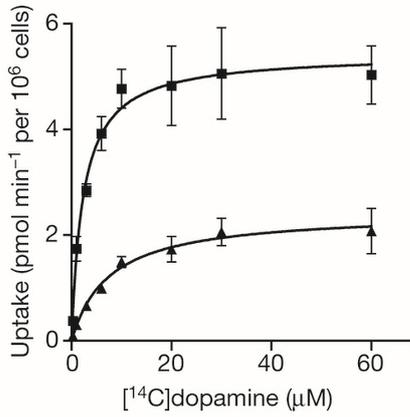
Coleman JA, Yang D, Zhao Z, Wen PC, Yoshioka C, Tajkhorshid E, Gouaux E. Serotonin transporter-ibogaine complexes illuminate mechanisms of inhibition and transport. *Nature* 569(7754):141-145 (2019)

## Mecanismos moleculares de la amfetamina (AMPH) en neuronas que contienen monoaminas



Ferrucci *et al.* The effects of amphetamine and methamphetamine on the release of norepinephrine, dopamine and acetylcholine from the brainstem reticular formation. *Front Neuroanat.* 13:48 (2019)

# Transportador vesicular de dopamina (*Drosophila melanogaster*)

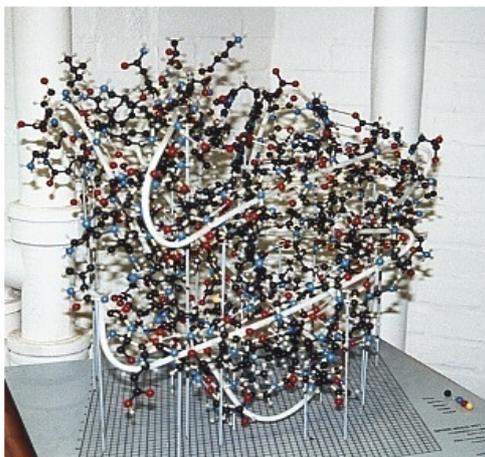


K. H. Wang, A. Penmatsa & Eric Gouaux  
Neurotransmitter and psychostimulant recognition by the dopamine transporter  
*Nature* 521, 322–327 (2015)

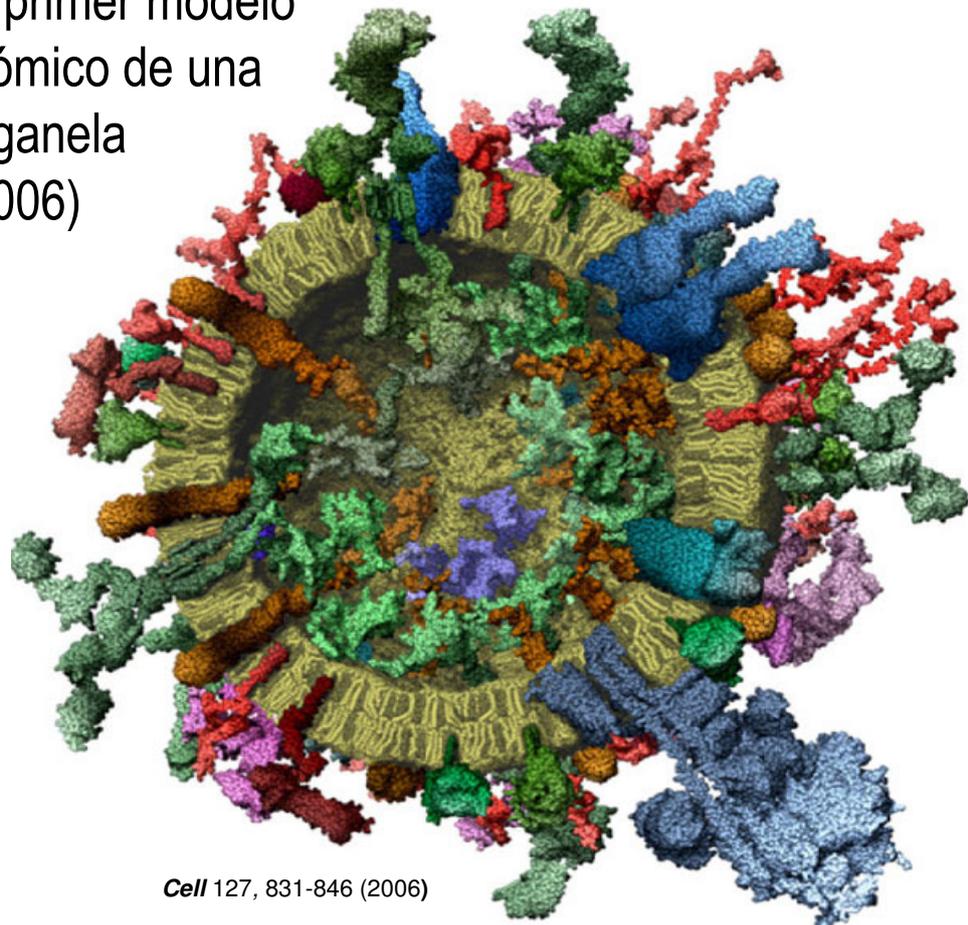
El primer modelo atómico de una macromolécula biológica (1960)



El primer modelo atómico de una organela (2006)



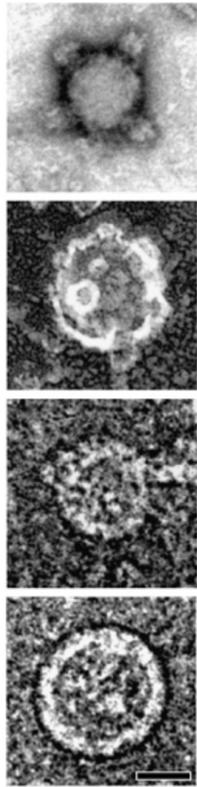
Mioglobina del cachalote  
*Nature* 185:422-27 (1960)



*Cell* 127, 831-846 (2006)

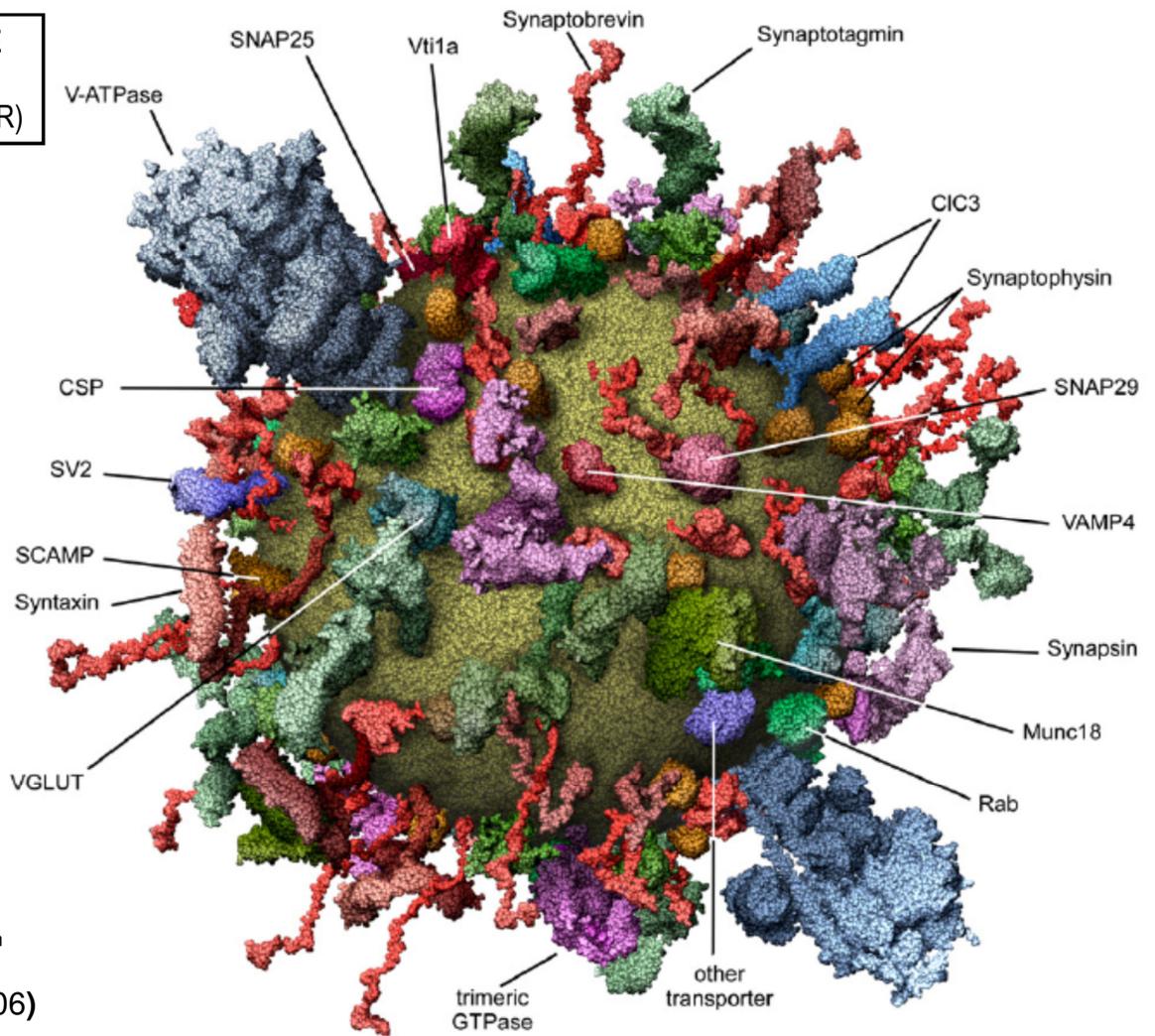
**ANATÓMICAMENTE CORRECTA** – Este modelo de una vesícula sináptica es la primera descripción con detalle atómico de una organela celular

**VESÍCULA SINÁPTICA DE CEREBRO DE RATA (VISTA DESDE EL EXTERIOR)**



20 nm

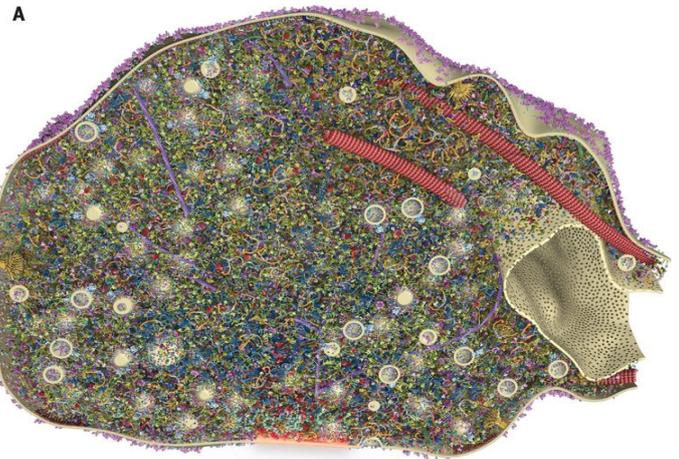
*Cell* 127, 831-846 (2006)



*Science* 344, 1023 (2014)

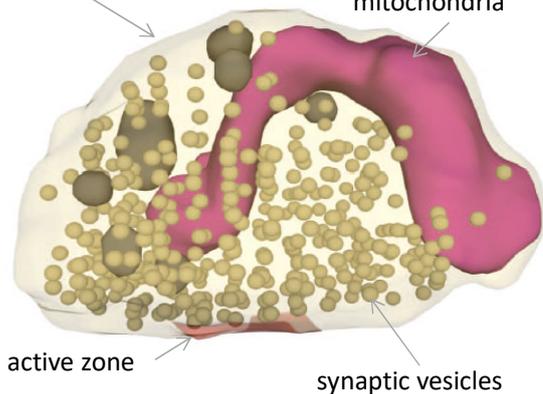
**Composition of isolated synaptic boutons reveals the amounts of vesicle trafficking proteins**

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plasma membrane

mitochondria



active zone

synaptic vesicles

