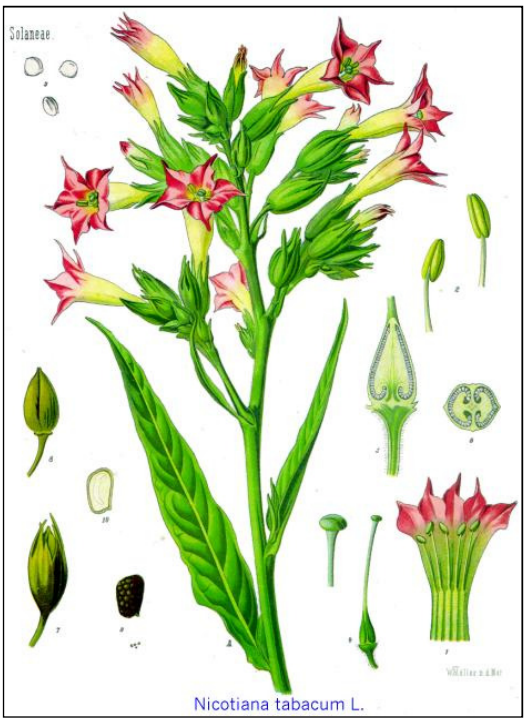
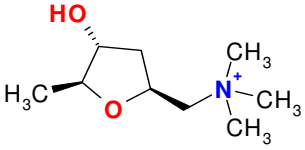
Farmacología y Farmacoterapia I
Grado en Farmacia - UAH

Tema 6 (curso 2021-2022)

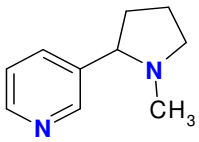
Concepto y ejemplos de agonista, antagonista, agonista parcial y agonista inverso.

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

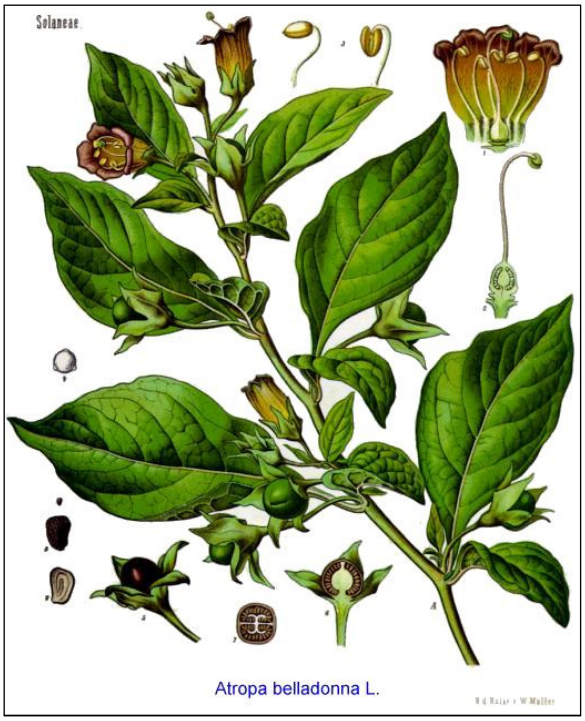


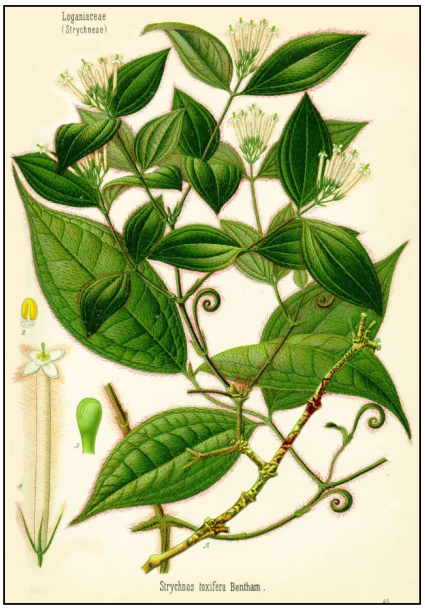


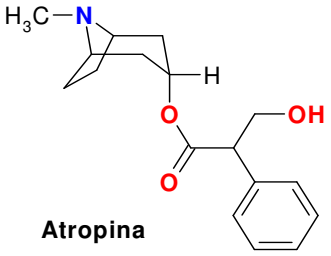
Muscarina



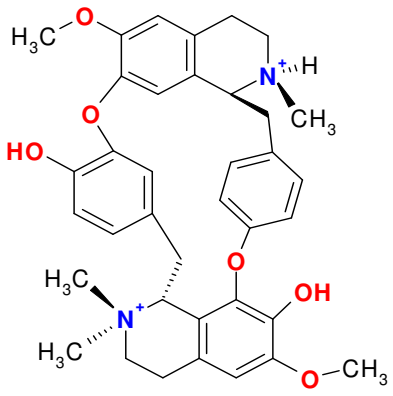
Nicotina



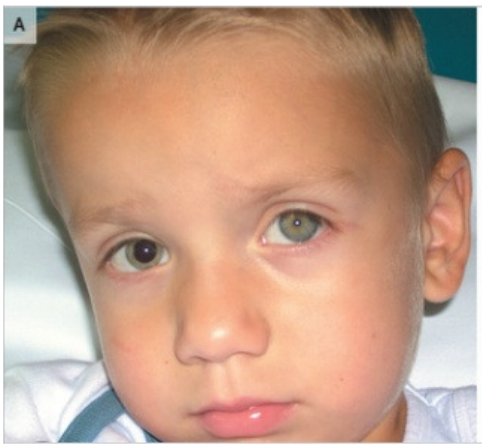




Atropina



d-tubocurarina



A healthy 3-year old boy was brought to our emergency department because of an acutely dilated right pupil (Panel A), which developed after he had played in the garden. Half an hour before presentation, his parents noticed he had been crying. They reported no fall and no ocular or head trauma. The right eye showed no pupillary light reflex and no accommodation. Physical examination was otherwise normal. A detailed history revealed that he had touched and held a flower from an angel's trumpet plant (Panel B) and then rubbed his right eye. Angel's trumpet, a member of the genus *Brugmansia*, is an ornamental plant from South America that is increasingly found worldwide and contains **parasympatholytic alkaloids** such as **scopolamine**, **hyoscyamine**, and **atropine**. In cases of sudden, unilateral, nonreactive mydriasis in healthy children, exposure to angel's trumpet should be suspected. Severe intoxication resulting from ingestion can lead to hallucinations, hyperthermia, convulsions, flaccid paralysis, and death. In the absence of any other sign of toxicity, we reassured the parents and discharged the child. The mydriasis disappeared spontaneously within 3 days.

Aaron Vunda, M.D. & Gabriel Alcoba, M.D.
University Hospitals of Geneva, Geneva, Switzerland

N Engl J Med. 367:1341 (**2012**)

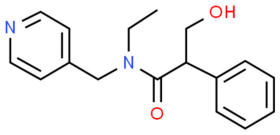
Contracción esfínter

Pupila

Contracción músculos radiales

Parasimpático
(par craneal III)

Simpático
(ganglio cervical superior)



MIOSIS **MIDRIASIS**

Mióticos

- agonistas muscarínicos:
carbacol, metacolina, pilocarpina
- inhibidores acetilcolinesterasa:
neostigmina, piridostigmina

Midriáticos

- antimuscarínicos:
atropina, ciclopentolato, tropicamida
- agonistas α_1:
fenilefrina

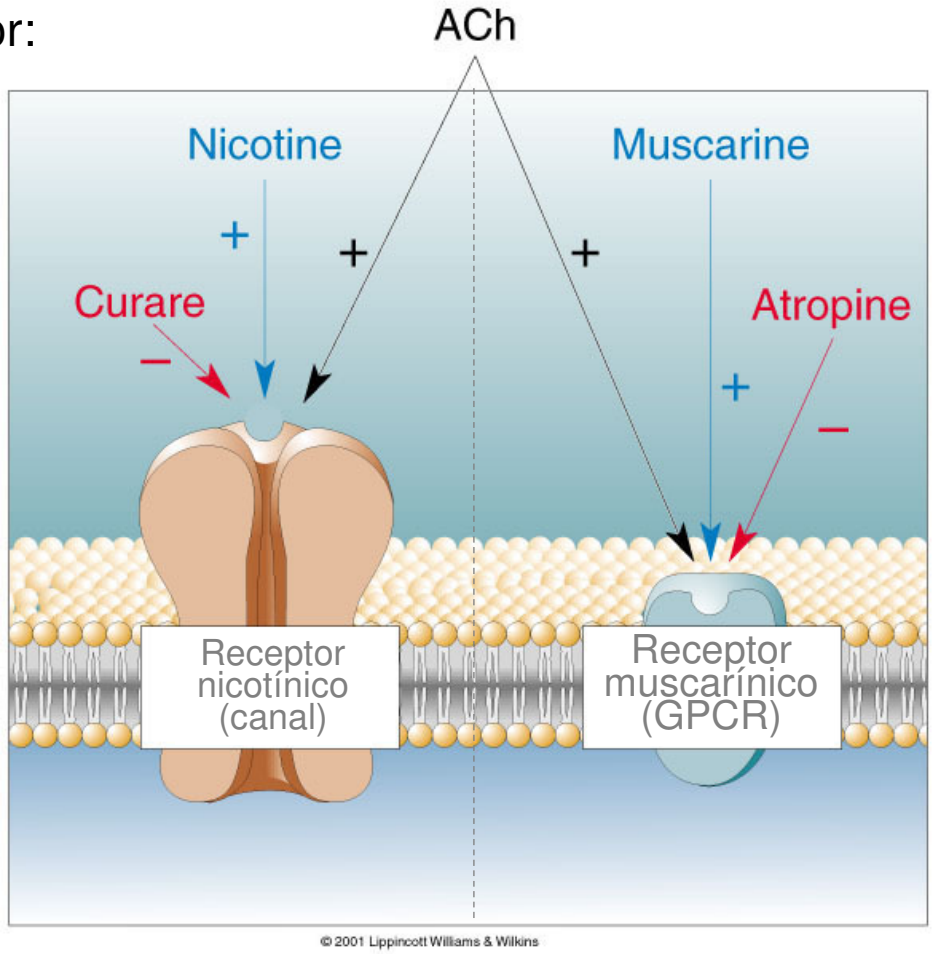
Neurofarmacología de la transmisión sináptica colinérgica. A los sitios de los receptores de neurotransmisores pueden unirse el propio neurotransmisor (acetilcolina, ACh), agonistas que lo mimetizan, o antagonistas que bloquean el efecto de los agonistas.

Neurotransmisor:

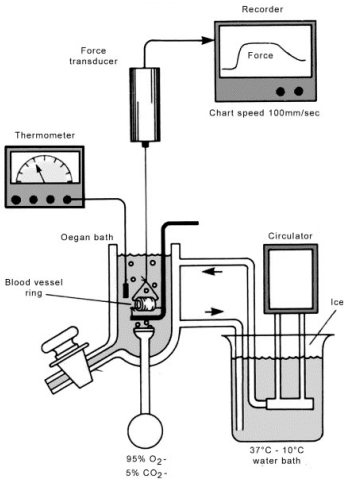
Agonistas:

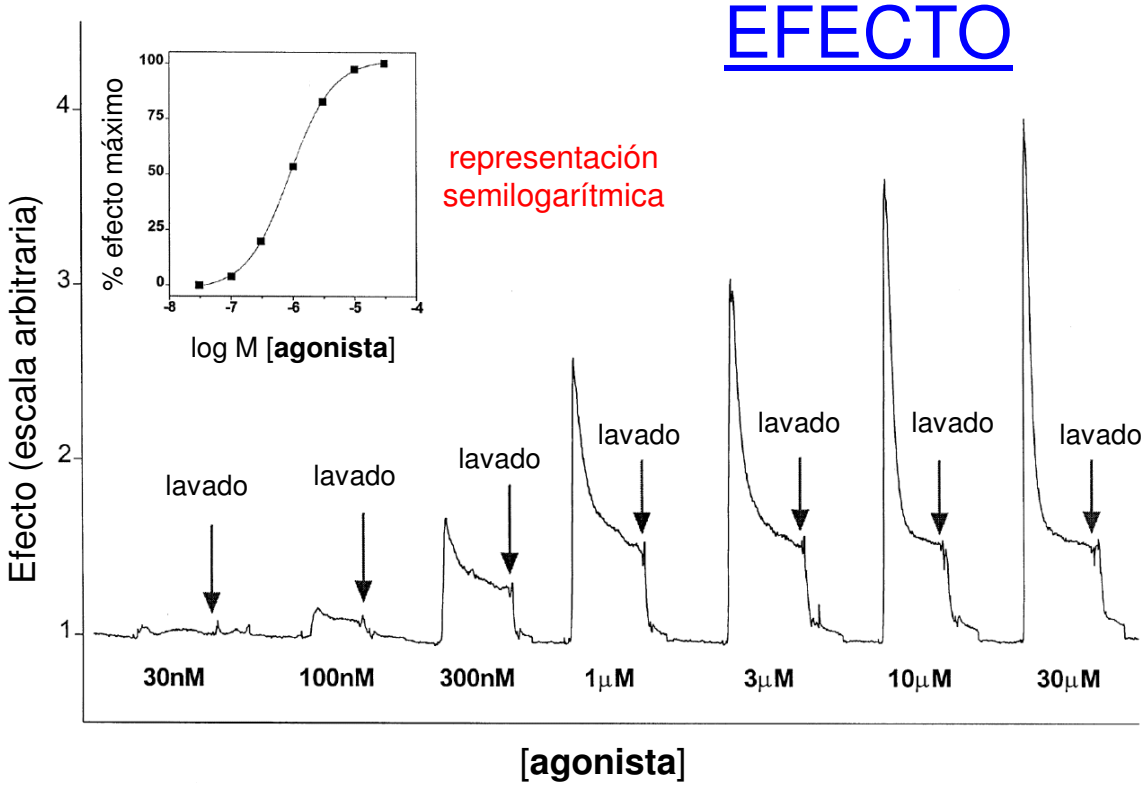
Antagonistas:

Receptores:



EFECTO



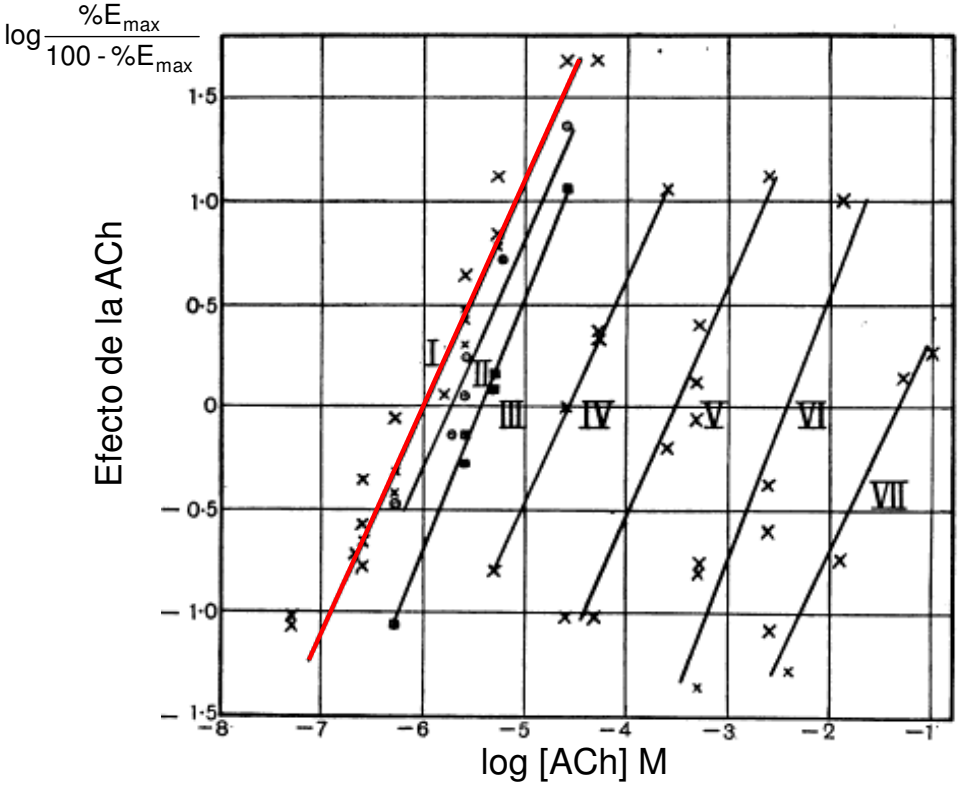


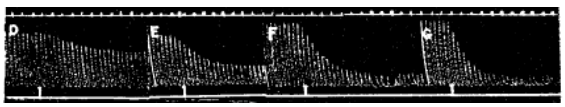
Resultados de un típico experimento farmacológico en el que se mide la dependencia de un efecto biológico (por ejemplo, contracción, secreción, cambios de conductancia a iones, o producción de un segundo mensajero) con la concentración de agonista añadida. Entre adiciones sucesivas de agonista existe un período de lavado de varios minutos. La **curva sigmoidea** de la gráfica representa cada respuesta individual como **porcentaje del efecto máximo** en función del logaritmo de cada concentración de agonista utilizada.

J Physiol. **1926** August 6; 61(4): 547–556.

THE ANTAGONISM OF ACETYL CHOLINE BY ATROPINE. By A. J. CLARK.

(From the Pharmacological Department, University College, London.)

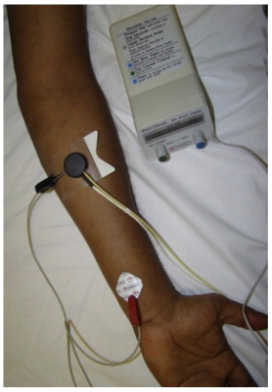


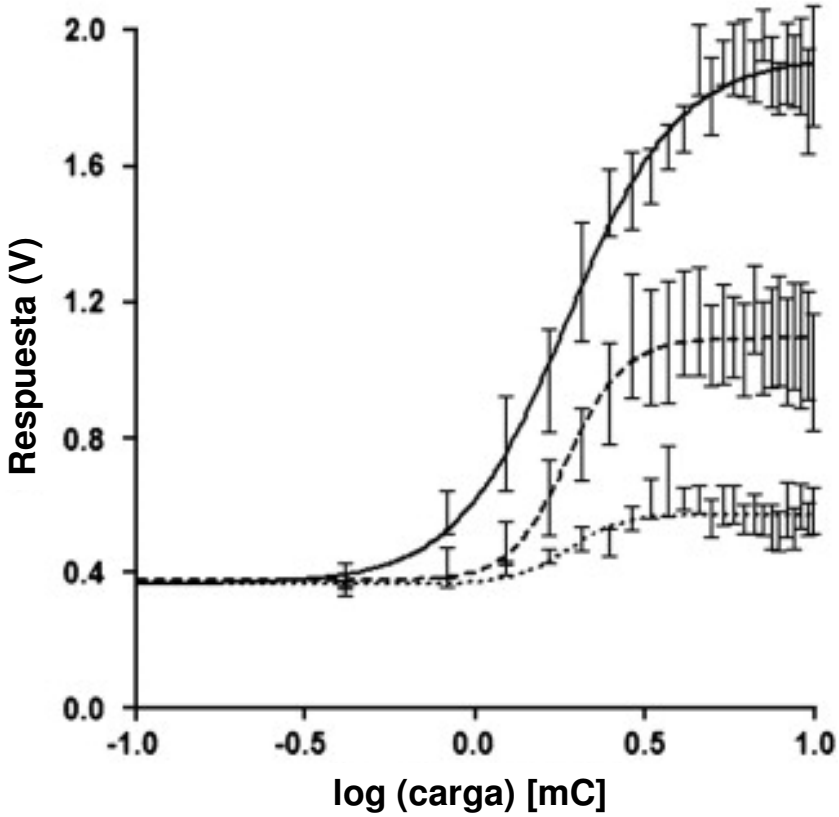


Efecto sobre corazón de rana

I	Sin atropina
II	10^{-8} M atropina
III	10^{-7} M atropina
IV	10^{-6} M atropina
V	10^{-5} M atropina
VI	10^{-4} M atropina
VII	10^{-3} M atropina

RESPUESTA DEL FLUJO SANGUÍNEO A LA APLICACIÓN TRANSDÉRMICA POR IONTOFORESIS DE 55 mmol/L DE ACh





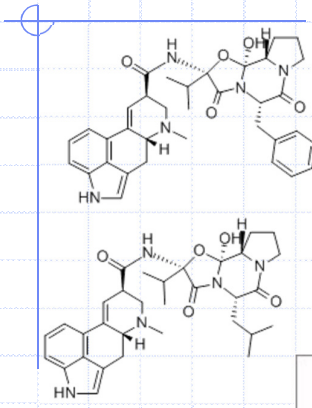
Sin pretratamiento

pretratado con 0,114 mmol/L de atropina

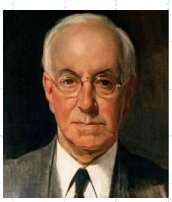
pretratado con 1,14 mmol/L de atropina

E. Tesselaar & F. Sjöberg
Microvascular Research, 81(1), 88–96 (**2011**)

Reversión del efecto de la adrenalina por el ergot (*Claviceps purpurea*)



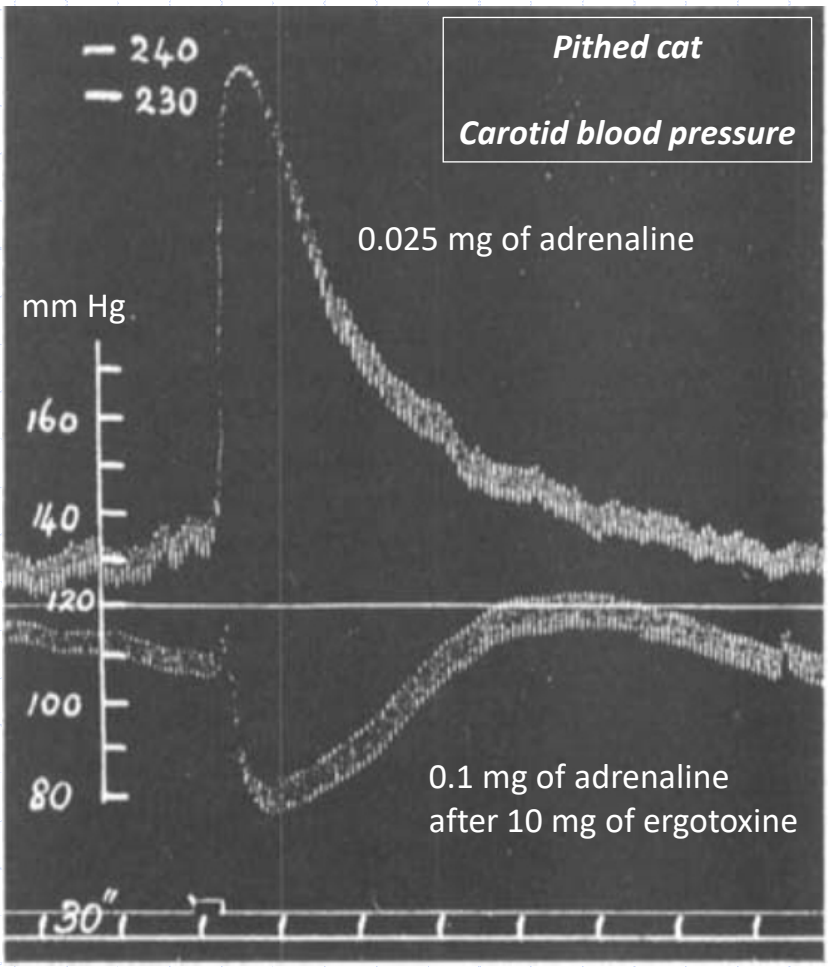
ergotoxina



1936

Claviceps purpurea

Dale, H.H. (**1913**) On the action of **ergotoxine**: with special reference to the existence of sympathetic vasodilators.
J. Physiol. Lond., **46**, 291–300

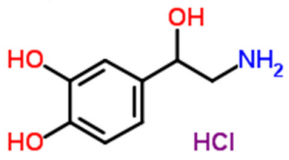


...pero no analizó el problema en términos de receptores. Hubo que esperar a Ahlquist...

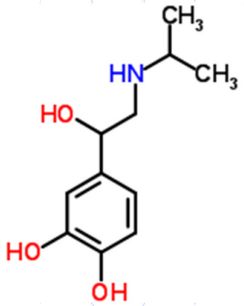
Receptores adrenérgicos (Ahlquist): α y β

Raymond Ahlquist
Department of Pharmacology
Medical College of Georgia

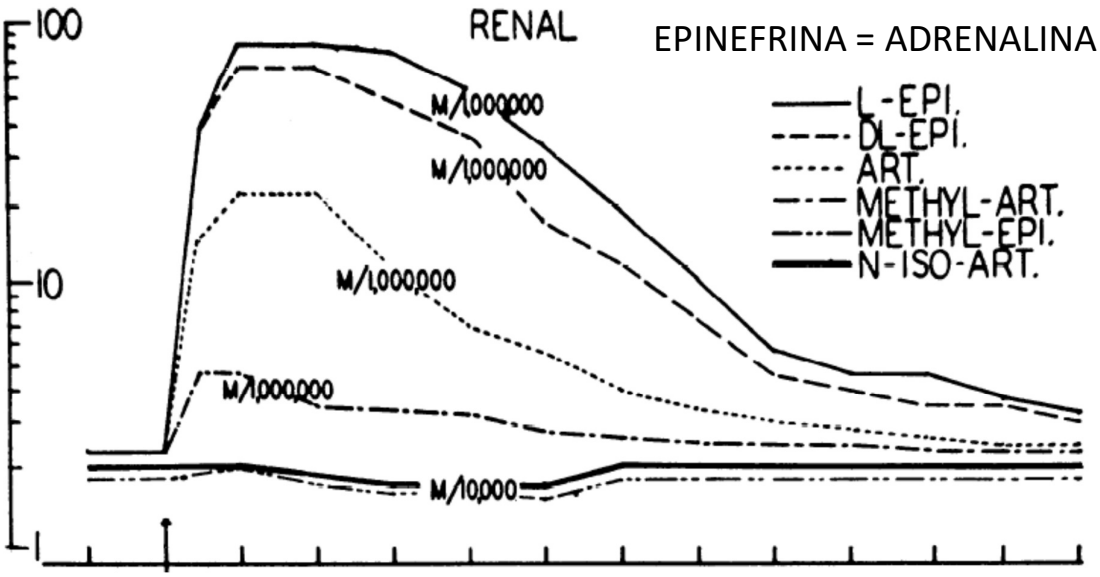
I. *dl*-(3,4-dihydroxyphenyl) ethanolamine. Arterenol, *art.*
II. *dl*-(3,4-dihydroxyphenyl) isopropanolamine. Cobefrine, *methyl-art.*
III. and IV. *dl*, and *l*-(3,4-dihydroxyphenyl) methyl ethanolamine. Racemic and levo epinephrine, *dl-epi.* and *l-epi.*
V. *dl*-(3,4-dihydroxyphenyl) methyl isopropanolamine. *Methyl-epi.*
VI. *dl*-(3,4-dihydroxyphenyl) isopropyl ethanolamine. N-isopropyl arterenol, *N-iso-art.*



arterenol = noradrenalina

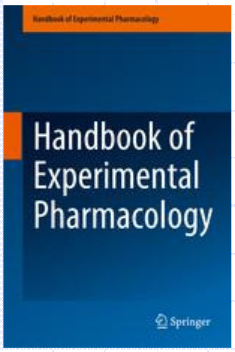


isopropilarterenol = isoprenalina = isoproterenol

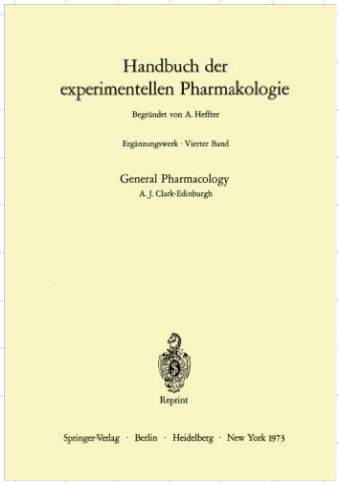


EPINEFRINA = ADRENALINA

Fig. 1. Comparative action of amines on vasomotor resistance in the renal, mesenteric and femoral vascular beds of dogs. *Ordinates:* VR plotted logarithmically for convenience only; *abscissae:* time marks at 10 sec. intervals. The amines were injected intra-arterially as 0.1 cc. of the concentration shown. In the case of the renal and mesenteric curves, lower concentrations of *methyl-epi.* and *N-iso-art.* had no appreciable effect on the VR.



Serie 1937-2017



by Walter Stoneman (1931)
©National Portrait Gallery (London)

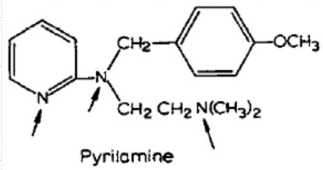
One of the features of this subject which hither to has been regarded as mysterious, is that in a homologous series of drugs some members may not only fail to produce the action typical of the series but may even antagonize the action of other members.

— Alfred Joseph Clark (1885–1941)

"Una de las características de esta materia, que hasta ahora ha sido considerada como misteriosa, es que en una serie congenérica de fármacos puede que algunos miembros no solo fallen en la producción de la acción típica de la serie sino que incluso antagonicen la acción de otros miembros"

Premio Nobel en Fisiología o Medicina (1957): Daniel Bovet

"por sus descubrimientos relacionados con compuestos sintéticos que inhiben la acción de ciertas sustancias corporales y especialmente su acción sobre el sistema vascular y los músculos esqueléticos".



Pyrilamine

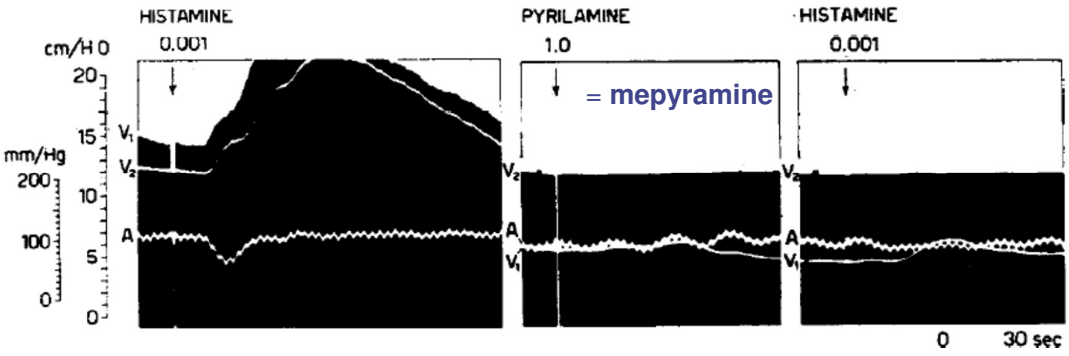


Fig. 7. Antagonistic action of pyrilamine with respect to the vasodilating effects of histamine in cerebral circulation.

Dog, under chloralose anaesthesia - A = femoral artery pressure (mmHg); V_1 = pressure measured in catheter introduced centrifugally in the external jugular vein (nun H_2O); V_2 = pressure in the internal jugular vein (mm H_2O). Injections in the saphenous vein, doses in mg/kg. (After Virno, Gertner, and Bovet, 1956.)

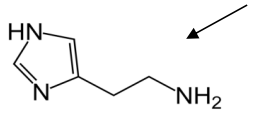
- Estudios en animales de la relaciones entre la estructura química y el efecto biológico.
- Variaciones sistemáticas y simplificaciones estructurales progresivas condujeron a moléculas que resultaron ser, desde el punto de vista de la especificidad y la ausencia de efectos secundarios indeseables, muchos **más útiles que los productos naturales**.

Sir James W. Black

The Nobel Prize in Physiology or Medicine 1988

Gran potencial farmacoterapéutico de fármacos que bloquean o estimulan receptores de aminas neurotransmisoras

Neuronas, glándulas — Mastocitos

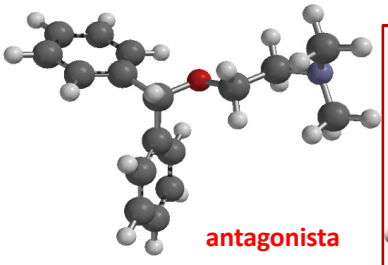


HISTAMINA

Receptor H_1 — **Receptor H_2**

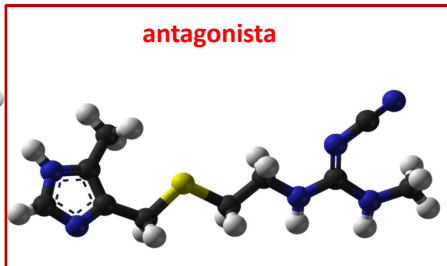
Dr. George Rieveschl (1943)

Alergia — Secreción gástrica



antagonista

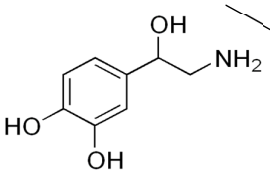
DIFENHIDRAMINA



antagonista — antagonista

CIMETIDINA — PROPRANOLOL

Nervios simpáticos — Glándula adrenal



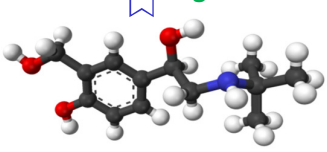
ADRENALINA
NORADRENALINA

Receptor α — **Receptor β**

Contracción m. liso
↓ flujo sanguíneo
↓ NA

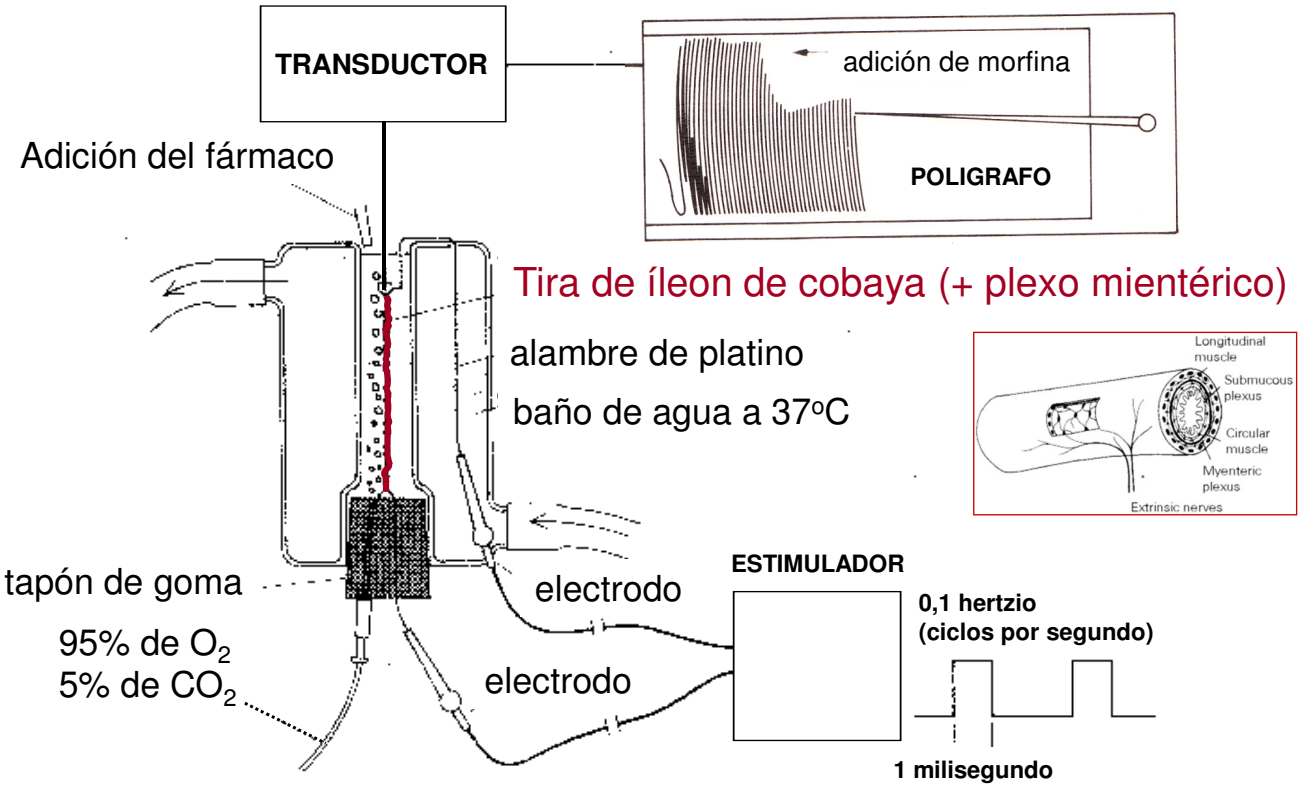
Relajación m. liso
Estimulación cardiaca
Dilatación alveolos
↑ metabolismo

agonista

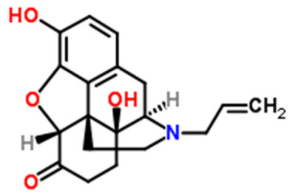


SALBUTAMOL

BIOENSAYO



"A pharmacologist is *a jack of all trades*, borrowing heavily from other disciplines, such as physiology, biochemistry, pathology, microbiology and statistics, but he has developed one technique of its own, and that is the method of bioassay." (J.H. Gaddum)



NALOXONA

…ciertos derivados de morfina son antagonistas frente a la acción depresora respiratoria de los alcaloides del opio…

United States Patent Office

3,254,088
Patented May 31, 1966

1

3,254,088
MORPHINE DERIVATIVE

Mozes Juda Lewenstein, 80—49 Park Lane, Kew Gardens, Long Island, N.Y., and Jack Fishman, Rego Park, N.Y.; said Fishman assignor to said Lewenstein

No Drawing. Filed Mar. 14, 1961, Ser. No. 95,506
4 Claims. (Cl. 260—285)

This invention relates to new morphine derivatives and has particular relation to N-allyl-14-hydroxydihydro-nor-morphinone and its salts and to a process for preparing the same. The invention also relates to 14-hydroxydihydro-nor-morphinone and its salts.

It has been known that certain morphine derivatives are antagonists against the respiratory depressive action of opium alkaloids, their derivatives and synthetic analgesies. Several such antidotes have been made in the past, such as N-allylnormorphine and levallorphan. We have now found that compounds of this invention, i.e. N-allyl-14-hydroxydihydro-nor-morphinone and its therapeutically applicable salts are more potent antagonists to the respiratory depressive effects of potent analgesics than the antagonists hitherto known. The 14-hydroxydihydro-nor-morphinone has been found to be a potent and effective analgesic.

The following examples describe some specific embodiments of and best modes for preparing the compounds of the invention, to which the invention is not limited.

Example 1

10 grams of 14-hydroxydihydromorphinone was converted into its diacetate by warming it on the steam bath with 80 ccm. of acetic anhydride for about 2 hours. The acetic anhydride was removed on the water bath under a vacuum of about 30 mm. absolute pressure. The melting point of the residue was 220° C. The residue was taken up in 100 ccm. of chloroform. An equal amount by weight of cyanogen bromide was added and the mixture was refluxed at about 60° C. for about 5 hours. After refluxing, the mixture was washed with 100 cc. of a 5% aqueous hydrochloric acid solution, dried over sodium sulfate and the chloroform removed by evaporation under a vacuum of about 30 mm. The residue had a melting point of 240° C.

2

The salts of the new compound can be prepared in conventional manner, e.g. by reacting the base with a substantially equivalent amount of an inorganic or organic acid in aqueous medium and recovering the salt thus formed by crystallization, or precipitation with a suitable water-miscible organic solvent. Or the base and acid are dissolved in a volatile organic solvent and the salt is recovered by evaporation of the solvent.

Example 2

One gram of N-allyl-14-hydroxydihydro-nor-morphinone was dissolved in 50 cc. of ethanol. An equivalent of 6 N hydrochloric acid was added. Addition of ether precipitated the hydrochloric salt which could be crystallized from ethanol-ether.

Example 3

One gram of N-allyl-14-hydroxydihydro-nor-morphinone was dissolved in 50 cc. of ethanol. An equivalent of tartaric acid was added and the solution was warmed. Evaporation of solvent yielded the bitartrate salt which could be crystallized from dilute ethanol.

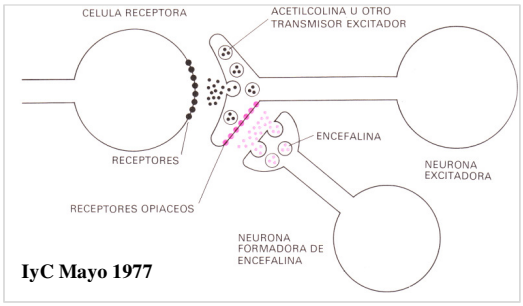
Salts of 14-hydroxydihydro-nor-morphinone can be prepared substantially in the same manner as described in the above Examples 2 and 3.

As further examples of acids which can be used for preparing salts of the new bases, the following are mentioned: sulfuric acid, phosphoric acid, nitric acid, hydrobromic acid, oxalic acid, maleic acid, succinic acid, benzoic acid, and lactic acid.

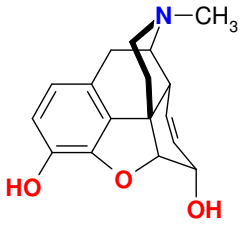
The compounds embodying this invention are of low toxicity so that they can be used without the danger of toxic effects when administered to human subjects.

In obtaining the desired antagonizing effects, the compounds of the present invention can be administered prior to or after administration of the analgesics, or in mixture with the analgesics, preferably by intravenous, subcutaneous, or intramuscular injection.

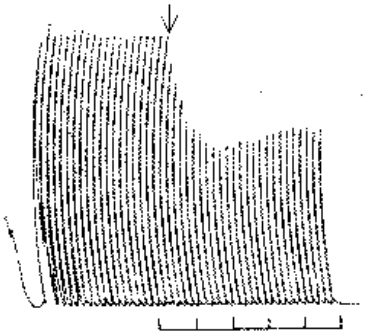
The N-allyl-14-hydroxydihydro-nor-morphinone and its salts are antagonists of unexpectedly high potency against the respiratory depressive action of potent analgesics. For example, the new compounds are about 10 times more potent in antagonistic action than N-allyl-nor-morphine. It has been found that in order to counteract the depression produced by morphine, the action



IyC Mayo 1977

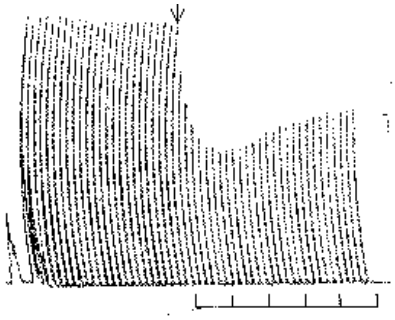


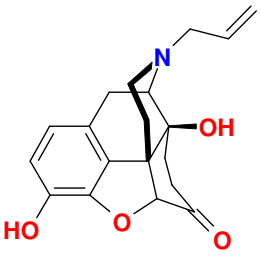
MORFINA



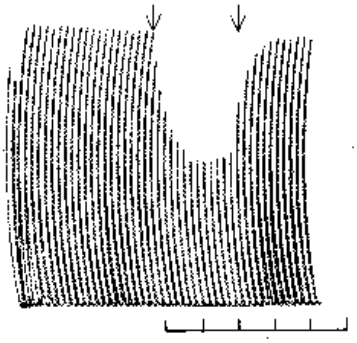
UN MINUTO CADA DIVISION

METIONINA-ENCEFALINA

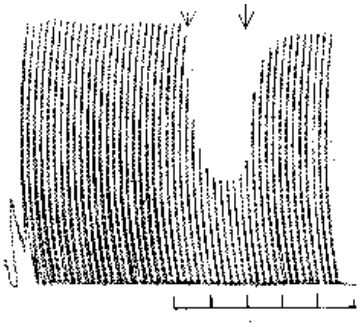




MORFINA NALOXONA



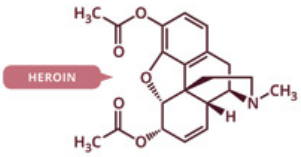
METIONINA-ENCEFALINA NALOXONA



THE OPIOID EPIDEMIC

Opioid overdoses killed more than 33,000 people in the U.S. in 2015. Here we take a look at the drugs behind the opioid epidemic and available treatments for opioid overdose and addiction.

HEROIN & OPIOIDS

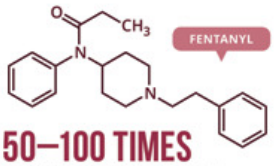


Like other opioids, heroin turns on opioid receptors to relieve pain and produce a feeling of euphoria. Opioids are highly addictive and at high doses can depress breathing, leading to death.

63.1% OF DRUG OVERDOSE DEATHS IN 2015 INVOLVED AN OPIOID DRUG

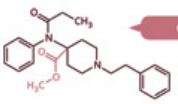
Street heroin is now being mixed with other opioids, making it more potent and dangerous. Users often do not know what the heroin they are using contains, increasing the risk of overdose.

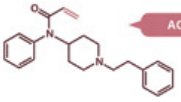
FENTANYL & ANALOGS

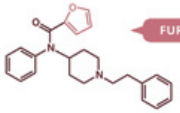


50–100 TIMES AS POTENT AS HEROIN

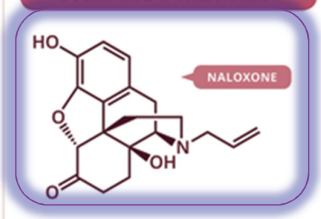
Fentanyl is a synthetic opioid that doctors prescribe to treat chronic pain. The fentanyl in street heroin is illicitly manufactured. Fentanyl analogs (selection shown below) are also increasingly common. Their higher potency increases the risk of overdose.



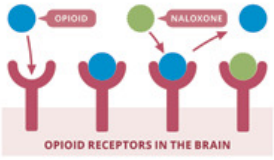




OVERDOSE & TREATMENT

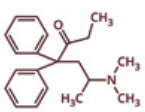


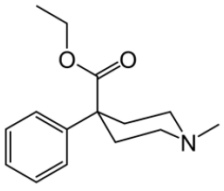
Naloxone reverses the effects of opioid overdoses. It has a stronger affinity for opioid receptors than opioids do and turns off the receptors. The antidote works within two minutes when injected.



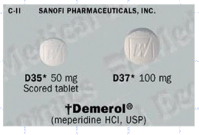
Methadone eases withdrawal symptoms for people with opioid addiction getting sober. Its effects are similar to heroin's but are less intense and longer lasting.

METHADONE





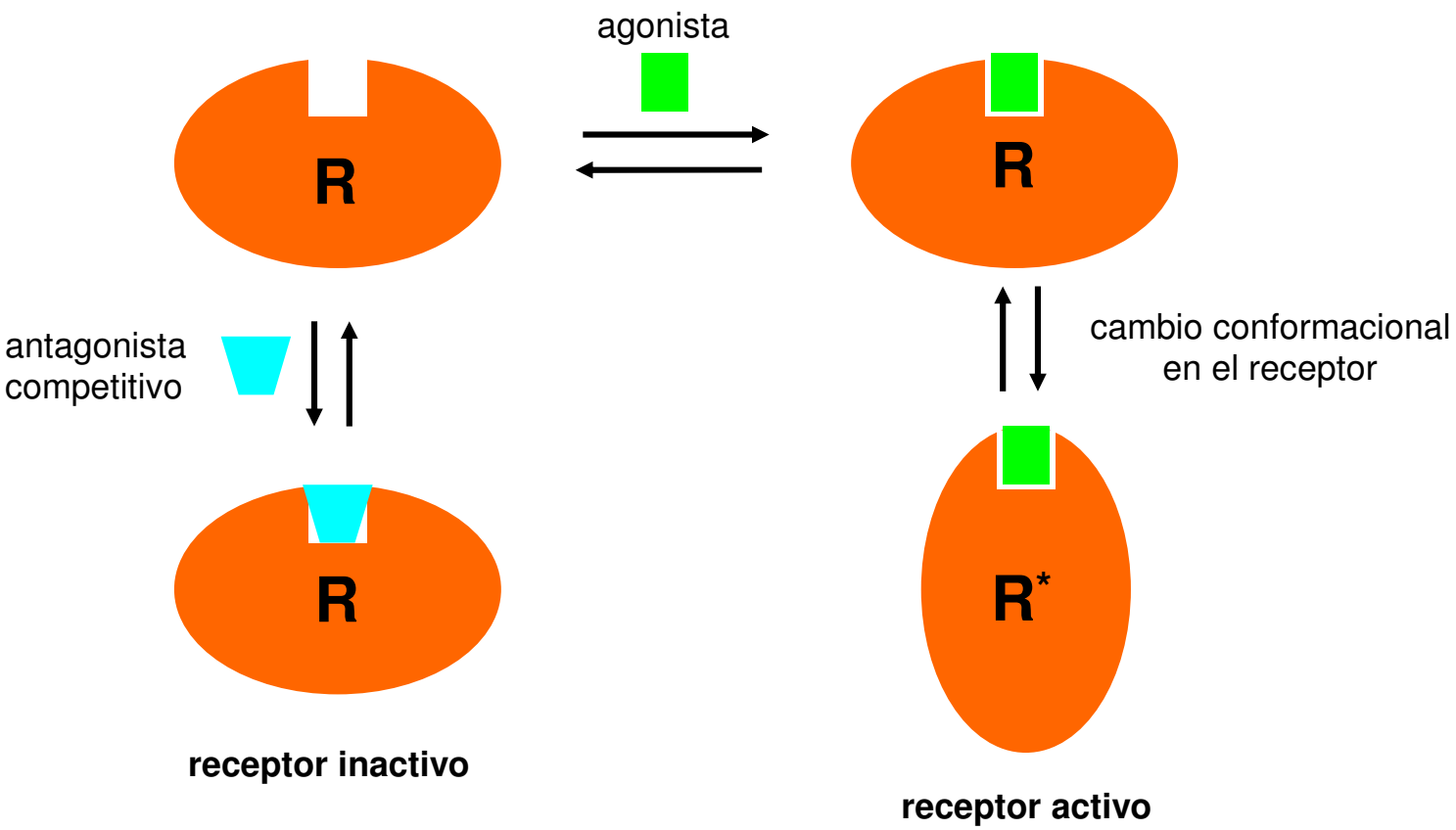
MEPERIDINE (PETHIDINE)



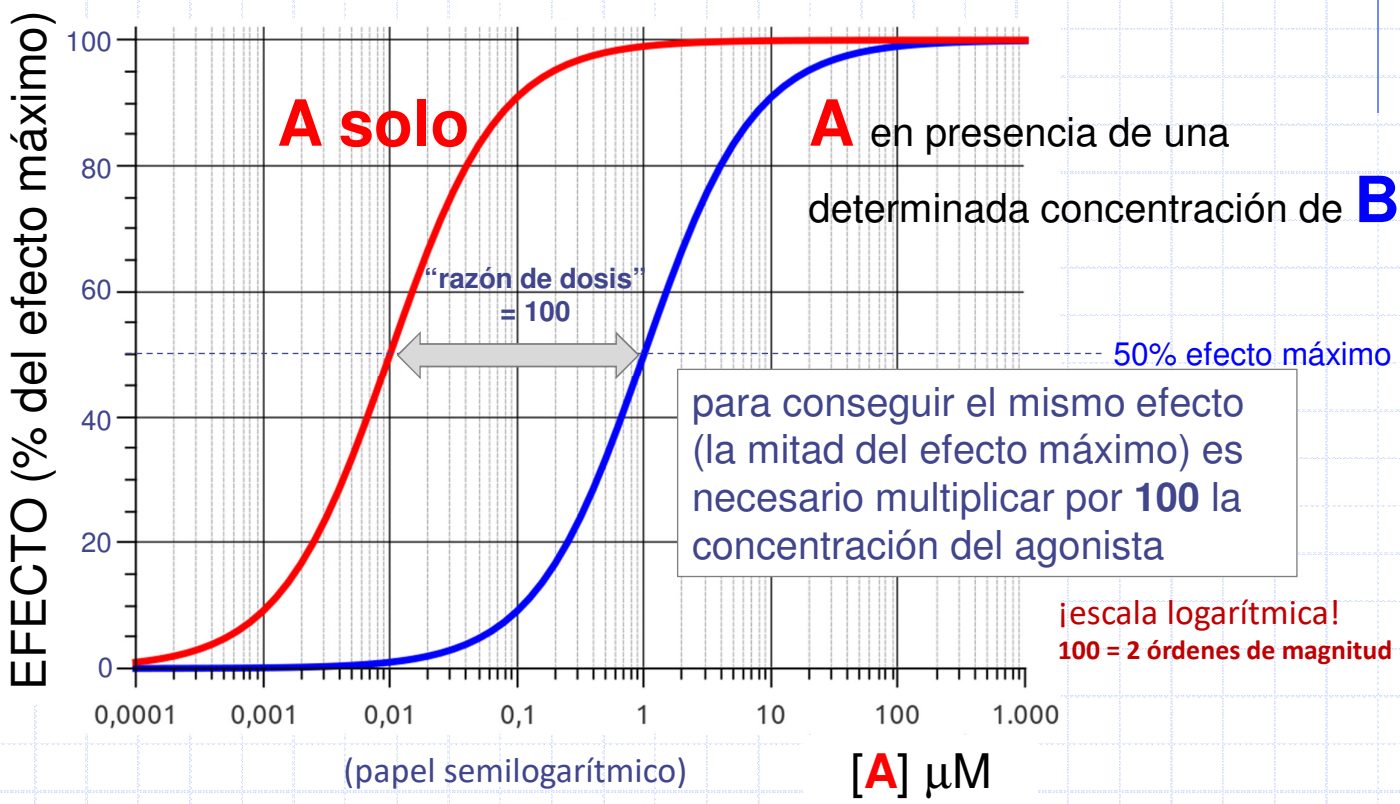
Los antagonistas:

- se unen al receptor en su estado basal y lo mantienen en su conformación inactiva
- cuando están unidos al receptor, impiden la unión de los agonistas, por lo que disminuyen o bloquean el efecto de los mismos
- pueden revertir el efecto de los agonistas al desplazarlos de su unión al receptor (dependiendo de sus afinidades relativas y las concentraciones utilizadas: *ley de acción de masas*)

Modelo Clásico de Activación de Receptores



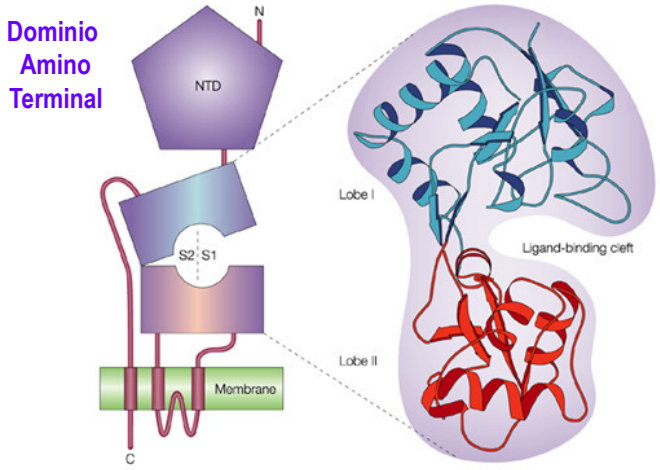
Desplazamiento a la derecha de la curva concentración-efecto de un agonista **A** por parte de un antagonista competitivo reversible **B** ("antagonismo superable")

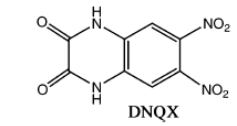


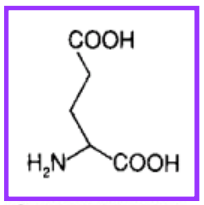
Agonistas y Antagonistas que actúan sobre Receptores Acoplados a Proteínas G (GPCRs)

GPCR	*Agonista*	*Antagonista*
muscarínico	acetilcolina, **muscarina** **pilocarpina**	**atropina**, ipratropio, tiotropio tropicamida
adrenoceptor α	noradrenalina adrenalina clonidina (α_2)	prazosina (α_1) yohimbina (α_2)
adrenoceptor β	noradrenalina adrenalina isoprenalina **salbutamol** (β_2)	**propranolol** atenolol (β_1) butoxamina (β_2)
H_1 H_2	histamina histamina, impromidina	**difenhidramina**, prometazina **cimetidina**, ranitidina
OP_3 (opioide µ)	**morfina**, fentanilo	**naloxona**
$GABA_B$	baclofeno	2-hidroxisaclofeno
$5\text{-}HT_2$	serotonina (5-HT)	ketanserina
D_2	dopamina	**clorpromazina**
LT1	leucotrieno LTE4	montelukast
AT1	angiotensina	losartán
ET_A, ET_B	endotelina	bosentán

Receptor ionotrópico de glutamato

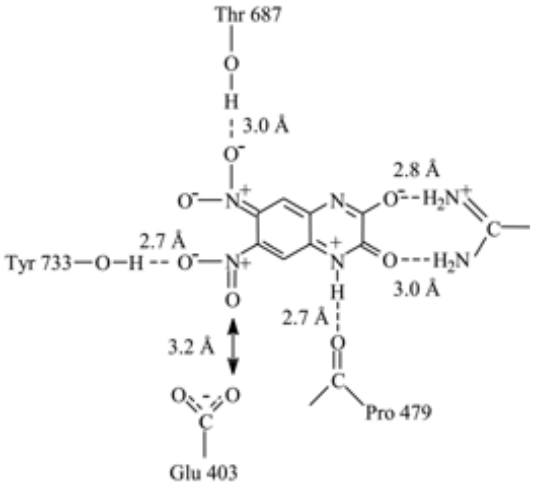


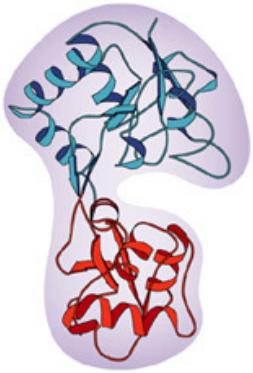




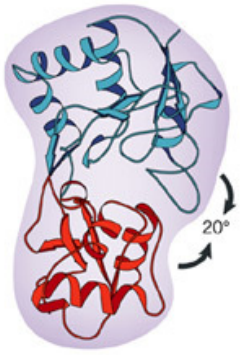
DNQX antagonist

Glutamate full agonist





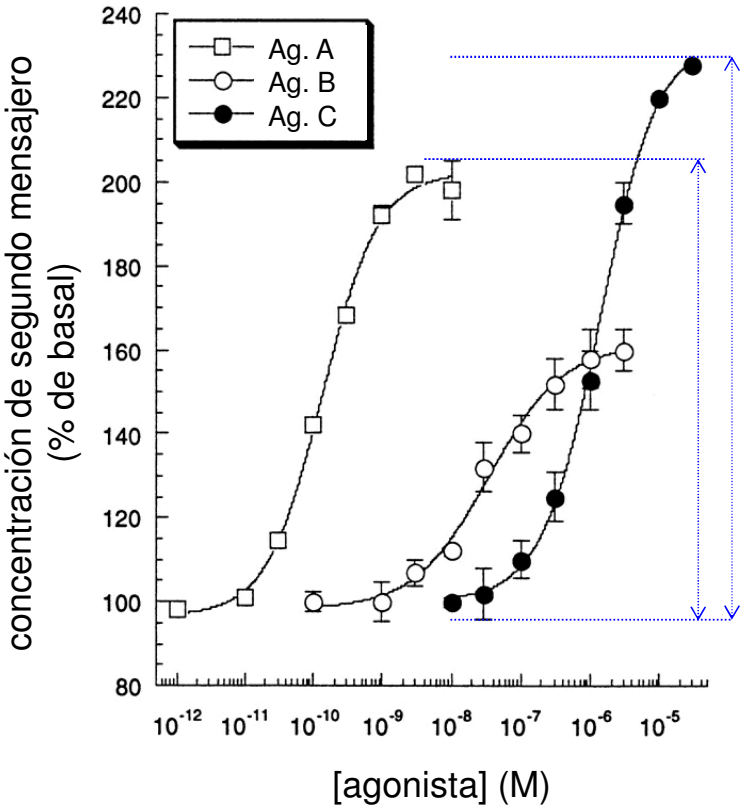
1FTL



1TXF [PDB]

Nature Reviews | Neuroscience

Agonismo parcial: reflejo de eficacias menores de la unidad



100% efecto máximo

Para conseguir un efecto dado, se requiere una mayor ocupación fraccional de receptores para los agonistas parciales que para los agonistas completos

Efecto de incrementar las concentraciones de distintos agonistas sobre un mismo sistema receptor-efector. La producción de segundo mensajero se expresa en este caso como porcentaje de su concentración en condiciones basales, es decir en ausencia de agonista. Nótese la escala logarítmica del eje de abscisas y cómo puede haber **agonistas completos** (C) con baja afinidad (CE_{50} del orden de micromolar) y **agonistas parciales** (A) con alta afinidad (CE_{50} del orden de nanomolar). El agonista de menor **eficacia** sería B, y C el de menor afinidad.

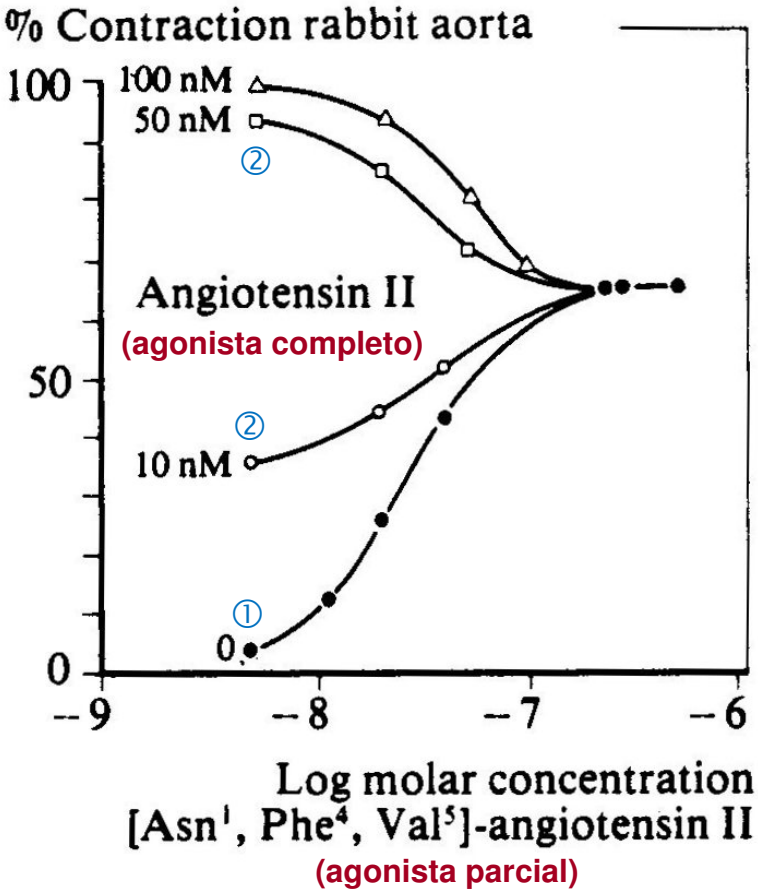
Carácter "dualista" de los agonistas parciales

✓ ① agonista (en ausencia de agonista completo)

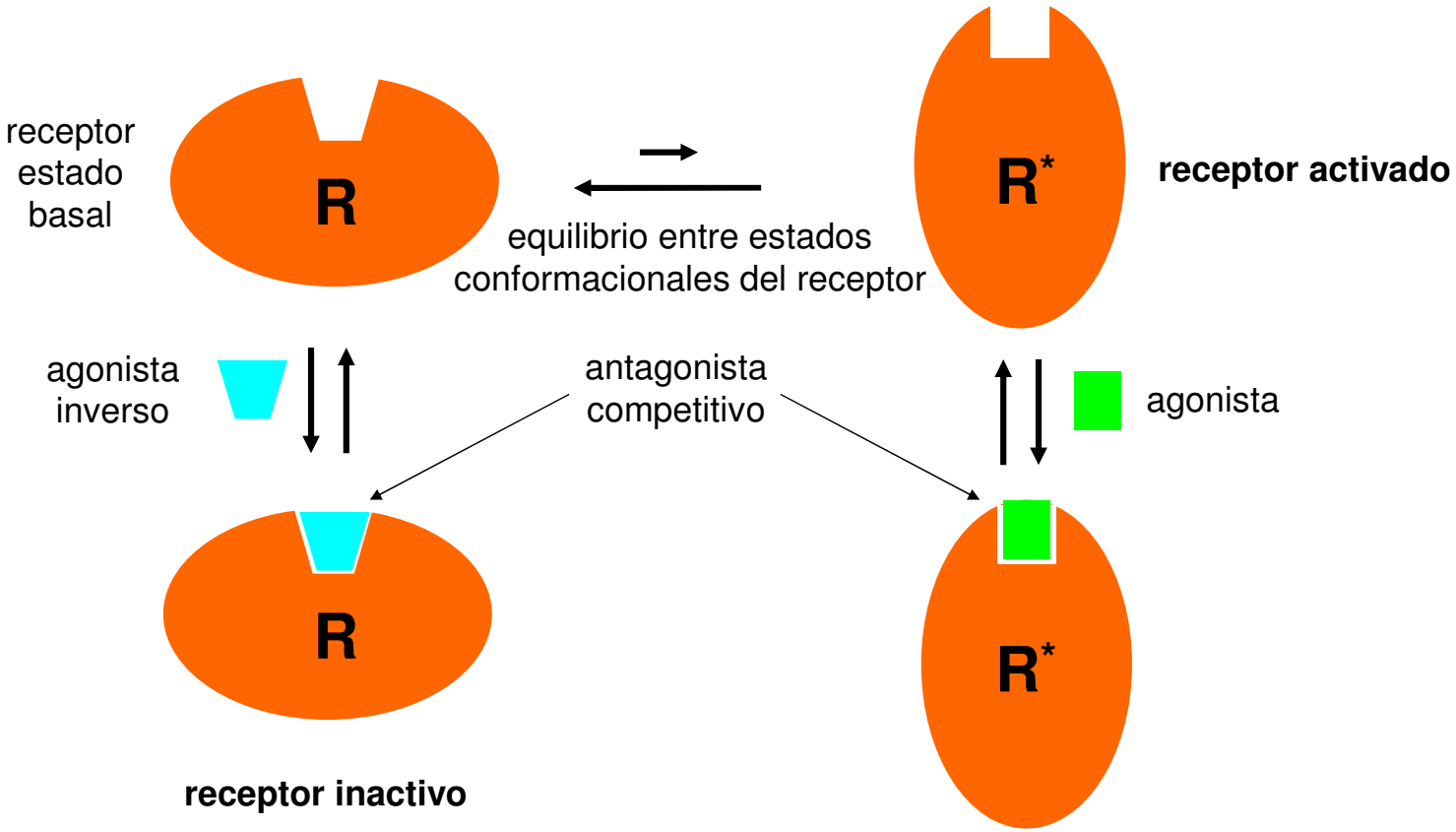
✓ ② antagonista (en presencia de un agonista completo)

Otros ejemplos:

- pentazocina y buprenorfina sobre receptores opioides μ (OP_3)
- pindolol sobre adrenoceptores β
- vareniclina sobre receptores nicotínicos cerebrales
- aripiprazol sobre receptores D_2
- salmeterol sobre adrenoceptores β_2

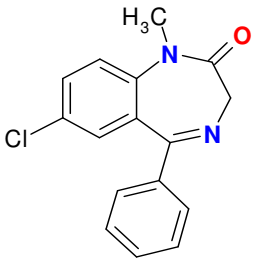


Modelo de los Dos Estados

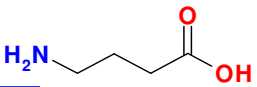


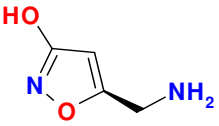
Receptor de $GABA_A$: modulación farmacológica de la respuesta

modulador alostérico positivo (agonista)

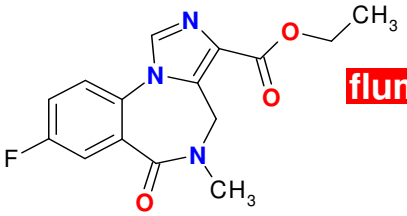


Diazepán (Valium®)

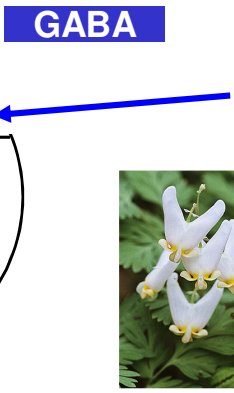


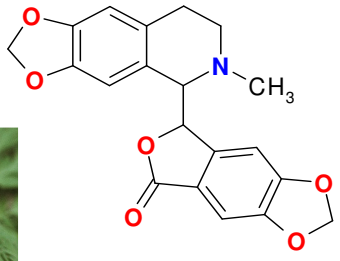


Muscimol *(agonista)*



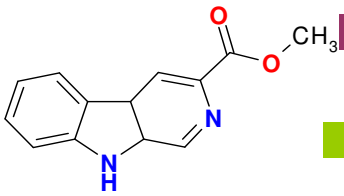
Flumazenilo (Anexate®) *(antagonista)*





Bicuculina *(antagonista)*

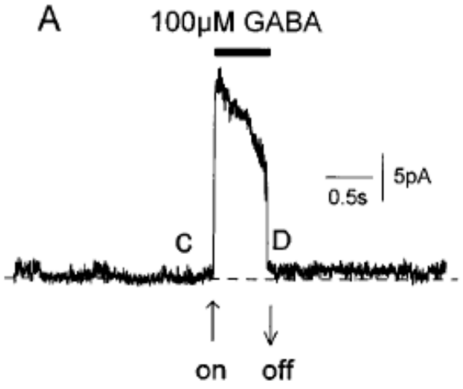
modulador alostérico negativo (agonista inverso)



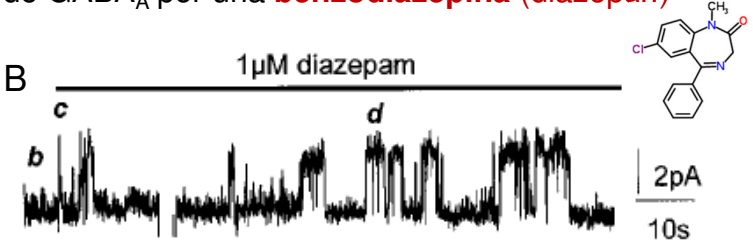
β-carbolina-3-carboxilato de metilo

Science (**1982**) 216, 1241-1243 / *TiPS* (**1986**) 7, 28-32

Activación rápida de canales por **GABA**

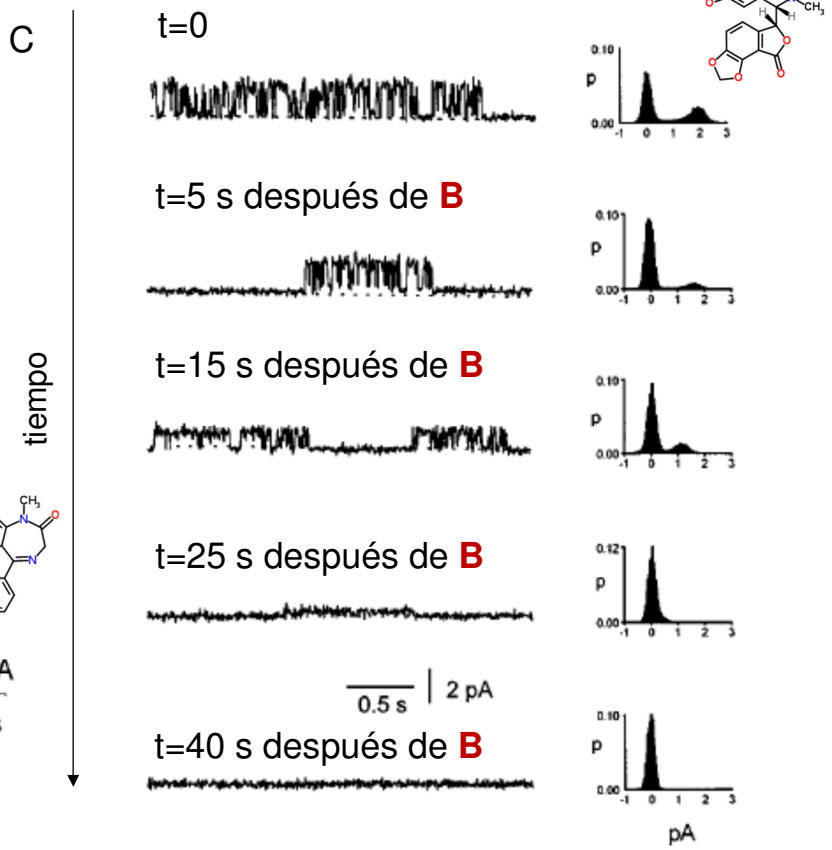


Incremento (modulación +) de las corrientes espontáneas mediadas por canales/receptores de $GABA_A$ por una **benzodiazepina** (diazepán)

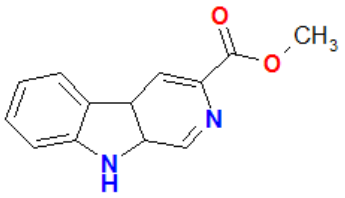


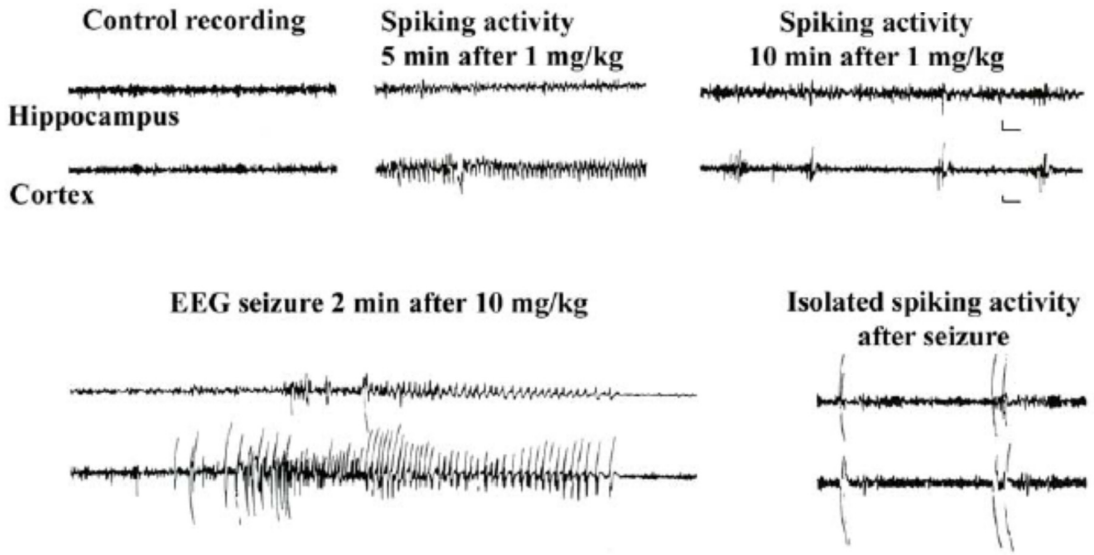
British Journal of Pharmacology (2000) 131, 695–704

Efecto de **bicuculina (B)** 100 μM sobre la conductancia de canales de apertura espontánea en neuronas piramidales CA1 del hipocampo de rata



Convulsiones inducidas por β-carbolina 3-carboxilato de metilo: datos electroencefalográficos





Prado de Carvalho, L., Grecksch, G., Cavalheiro, E.A., Dodd, R.H., Chapouthier, G., and Rossier, J. (1984) Characterization of convulsions induced by methyl beta-carboline-3-carboxylate in mice. *Eur. J. Pharmacol.* **103(3–4)**, 287–293.

Descubrimiento de antagonistas con eficacia negativa en receptores opioides δ acoplados a proteínas G

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 7321–7325, October 1989
Biochemistry

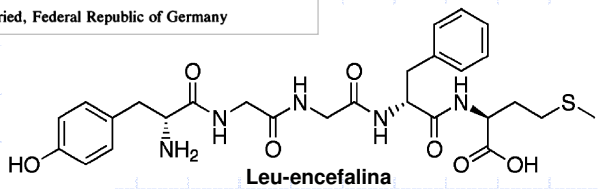
Antagonists with negative intrinsic activity at δ opioid receptors coupled to GTP-binding proteins

(guanine nucleotide-binding regulatory proteins/GTPase/ternary complex)

TOMMASO COSTA* AND ALBERT HERZ

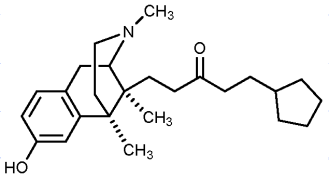
Department of Neuropharmacology, Max-Planck-Institut fuer Psychiatrie, Am Klopferspitz 18a, Martinsried, Federal Republic of Germany

ABSTRACT According to classical models of drug–receptor interactions, competitive antagonists share with agonists the ability to bind to a common site on the receptor molecule. However, they are different from agonists, as they cannot trigger the "stimulus" that leads to biological responses—i.e., they lack intrinsic activity. For those receptors whose signals are transduced to effector systems by GTP-binding regulatory proteins (G proteins), a mechanistic equivalent of such a stimulus is an increased ability of agonist-bound receptor to accelerate nucleotide exchange and thus GTPase activity on the G-protein molecule. Here we show that for a member of this family of receptors (δ opioid receptors in membranes of NG108-15 neuroblastoma–glioma cells), two types of competitive antagonists can be distinguished. One type has no intrinsic activity, since it neither stimulates nor inhibits the GTPase activity of G proteins and its apparent affinity for the receptor is not altered by pertussis toxin-mediated uncoupling of receptor and G protein. The second type, however, can inhibit GTPase and thus exhibits negative intrinsic activity; its affinity for receptors is increased following uncoupling from G proteins. The existence of antagonists with negative intrinsic activity may be a general feature of several classes of neurotransmitters or hormone receptors and calls for a reevaluation of biological effects produced by competitive antagonists.

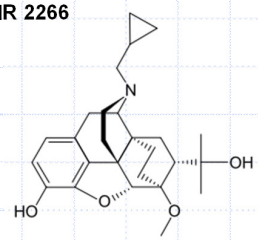


Leu-encefalina

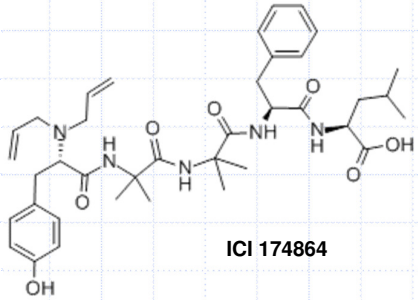
DADLE = [D-Ala², D-Leu⁵]-encefalina



MR 2266



diprenorfina



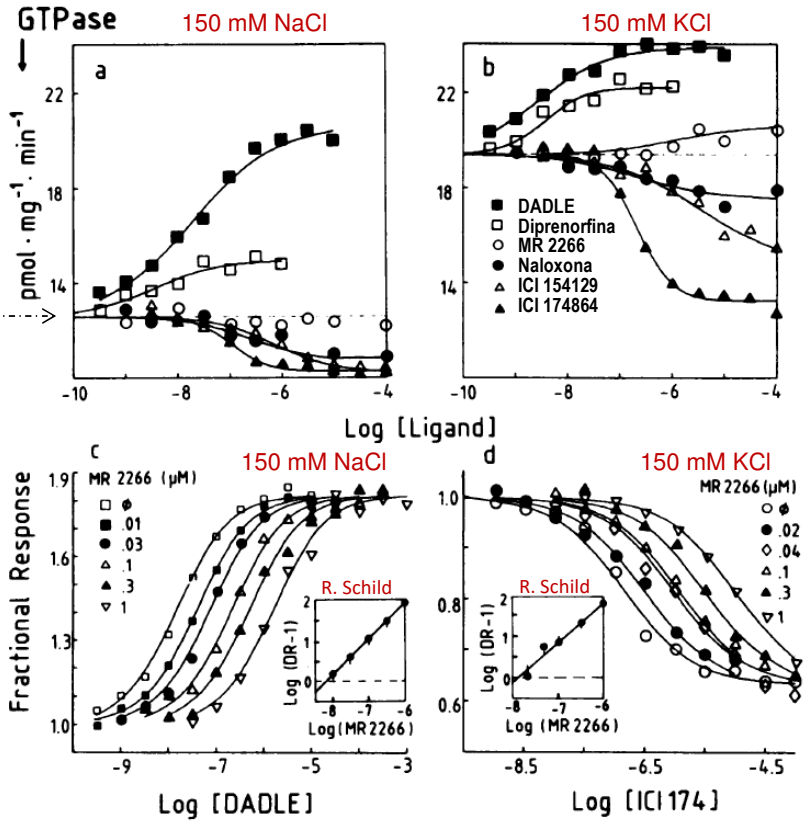
ICI 174864

Descubrimiento de antagonistas con eficacia negativa en receptores opioides δ acoplados a proteínas G

(**a**) (**b**) Efecto de distintos ligandos opioides sobre la actividad GTPasa en membranas de células NG108-15

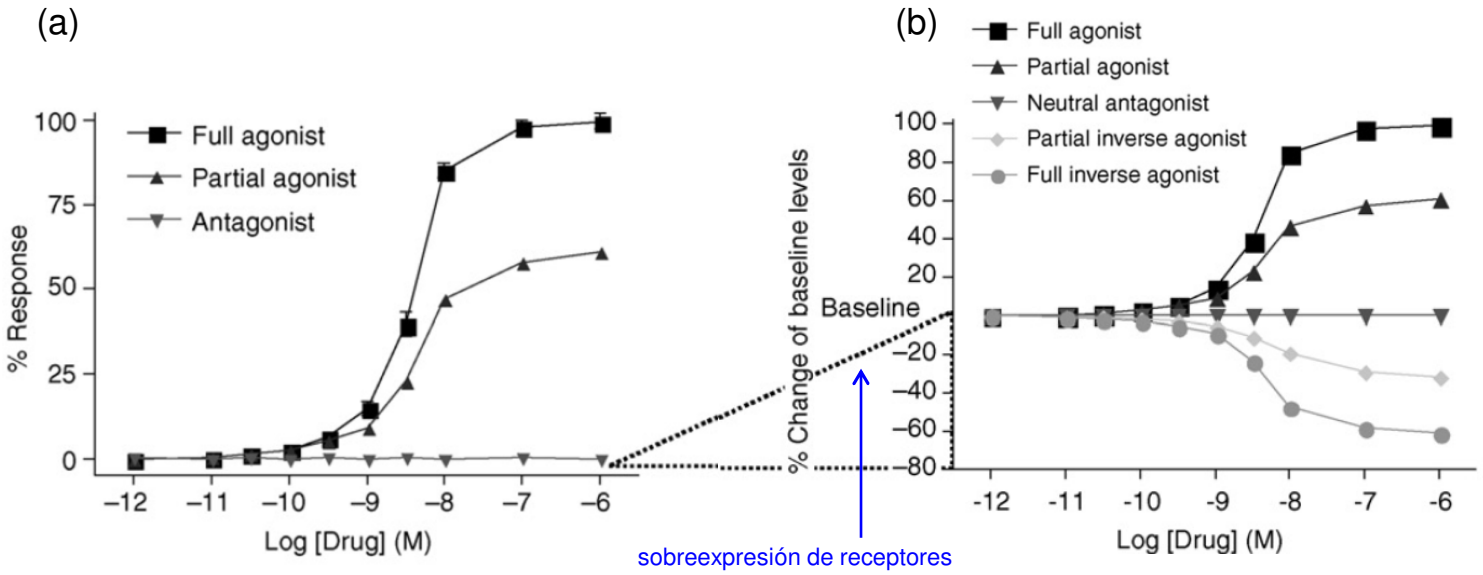
(**c**) (**d**) Curvas concentración-respuesta para el efecto estimulatorio del agonista DADLE y el efecto inhibitorio de ICI 174864 en presencia de MR 2266 (0–1 µM)

Respuesta fraccional = razón (cociente) entre la actividad GTPasa en presencia de ligando y en su ausencia



Curvas dosis-respuesta teóricas de fármacos con eficacias diferentes.

(a) Posible comportamiento de ligandos observado en un sistema sin actividad constitutiva.
(b) Efectos de fármacos en un sistema constitutivamente activado, en el que la línea punteada que sale de la línea base en el panel (a) se ha expandido para revelar el **agonismo inverso**.



S. Parra & R.A. Bond
Current Opinion in Pharmacology 7:146–150 (2007)

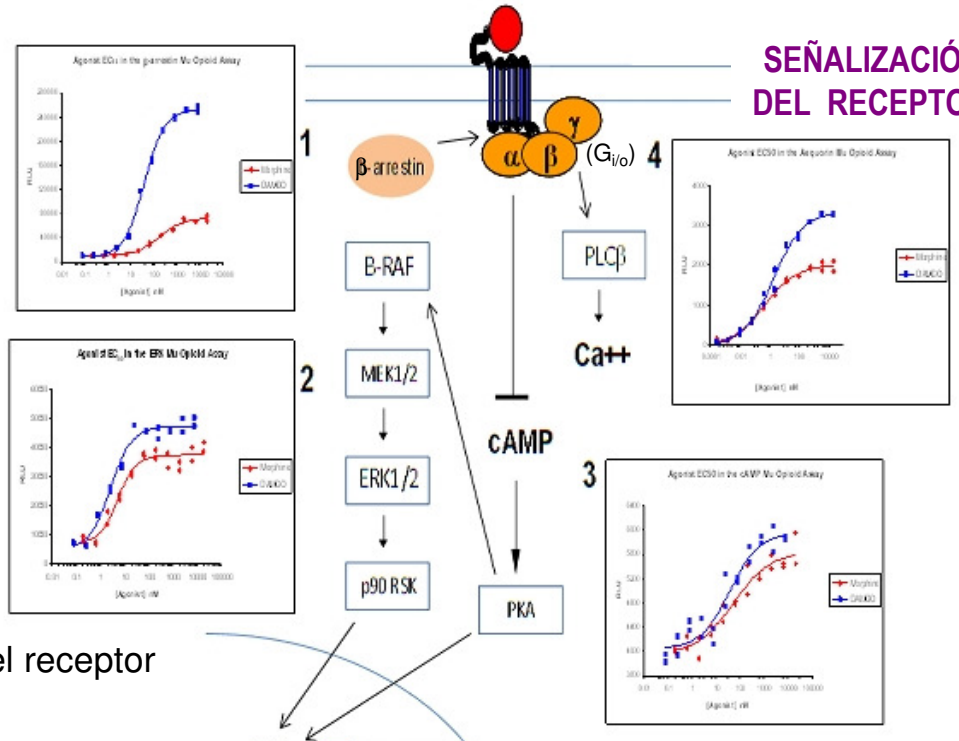
¿Hay fármacos eficaces en clínica que sean agonistas inversos?

Nombre genérico	Área terapéutica	Receptor diana	¿Agonista inverso?	Referencia
Olanzapina	Antipsicótico	5-$HT_{2C/5}$-HT_{2A}/otros	**Sí**	Herrick-Davis et al., 2000
Losartán	Cardiovascular	AT1	**Sí**	Groblewski et al., 1997; Miserey-Lenkei et al., 2002
Risperidona	Antipsicótico	5-HT_2/dopamina D_2,D_3	**Sí**	Vanhauwe et al., 1999; Herrick-Davis et al., 2000
Fexofenadina	Respiratorio	histamina H_1	Probablemente	Leurs et al., 2002
Clopidogrel	Trombosis	P2Y12	sin establecer	Conley and Delaney, 2003
Valsartán	Hipertensión	AT1	sin establecer	
Montelukast	Respiratorio	$CysLT_1$	sin establecer	
Loratadina	Respiratorio	histamina H_1	Probablemente	Leurs et al., 2002
Quetiapina	Antipsicótico	dopamina $D_{2/5}$-HT_{2C}/$5HT_{2A}$	sin establecer	Rauser et al., 2001
Cetirizina	Respiratorio	histamina H_1	Probablemente	Leurs et al., 2002
Metoprolol	Cardiovascular	adrenoceptor β_1	**Sí**	Engelhardt et al., 2001; Levin et al., 2002
Tolterodina	Genitourinario	muscarínico M_3/M_2	sin establecer	
Famotidina	Gastrointestinal	histamina H_2	**Sí**	Alewijnse et al., 1998

G. Milligan, *Mol. Pharmacol.* (**2003**) 64:1271-1276

SELECTIVIDAD FUNCIONAL: CONCEPTO DE AGONISMO SESGADO

Dos agonistas:
Morfina
DAMGO (encefalina)

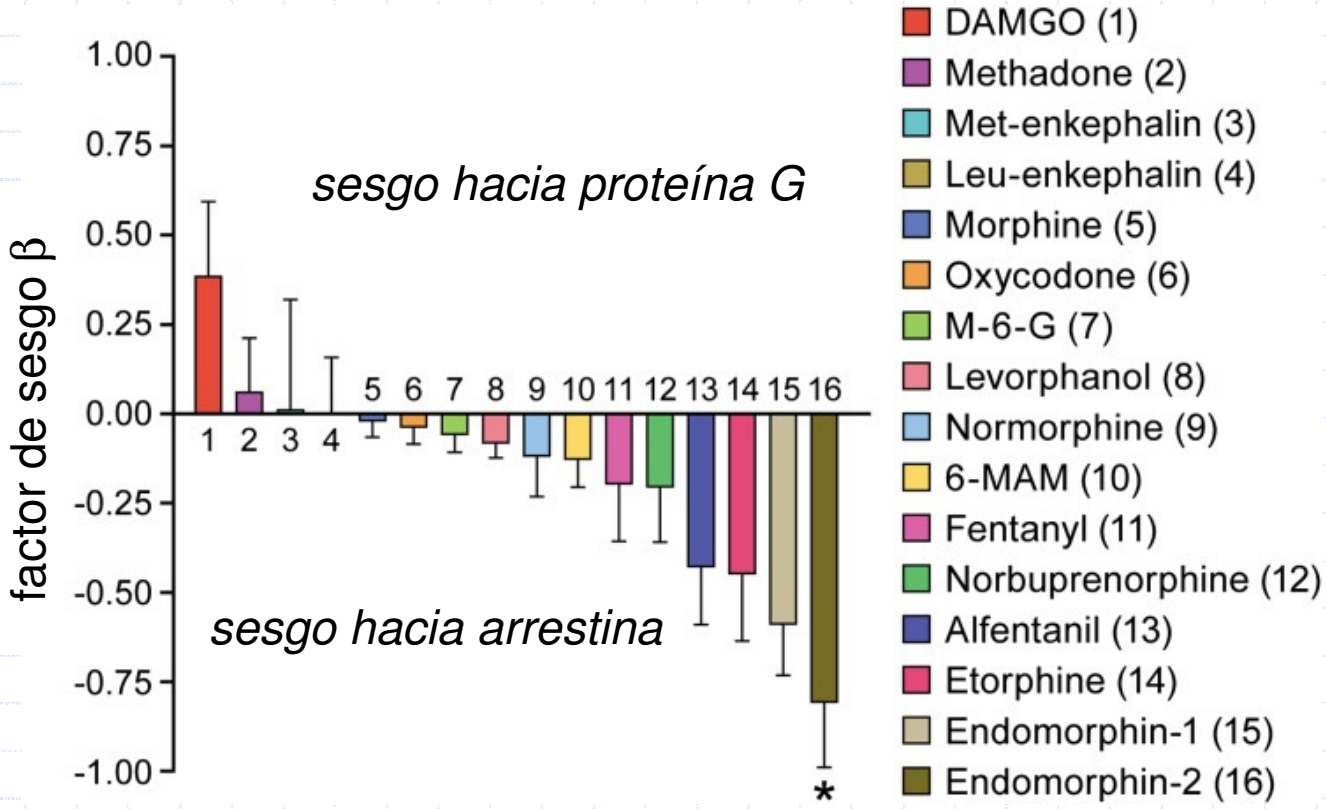


El estímulo inicial del receptor da lugar a:

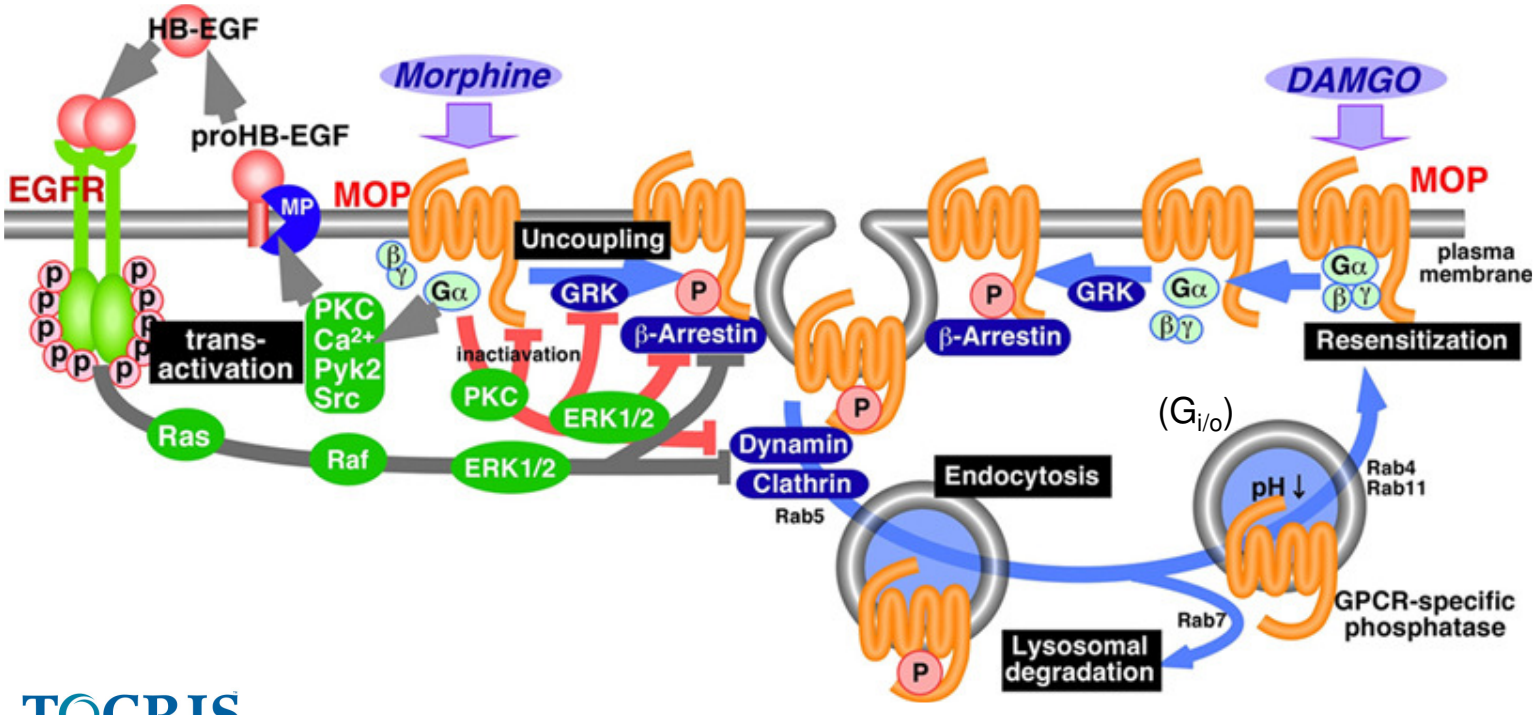
1 reclutamiento de β-arrestina
2 fosforilación de ERK1/2
3 ↓ niveles de AMPc
4 liberación de calcio

*¡Curvas concentración-respuesta **diferentes** para los dos agonistas dependiendo del punto de la cascada de señalización monitorizado en el ensayo!*

Agonismo "sesgado" en el receptor opioide de morfina (ROM) = selectividad funcional



Tráfico diferencial de señales tras la activación del receptor opioide μ por diferentes agonistas

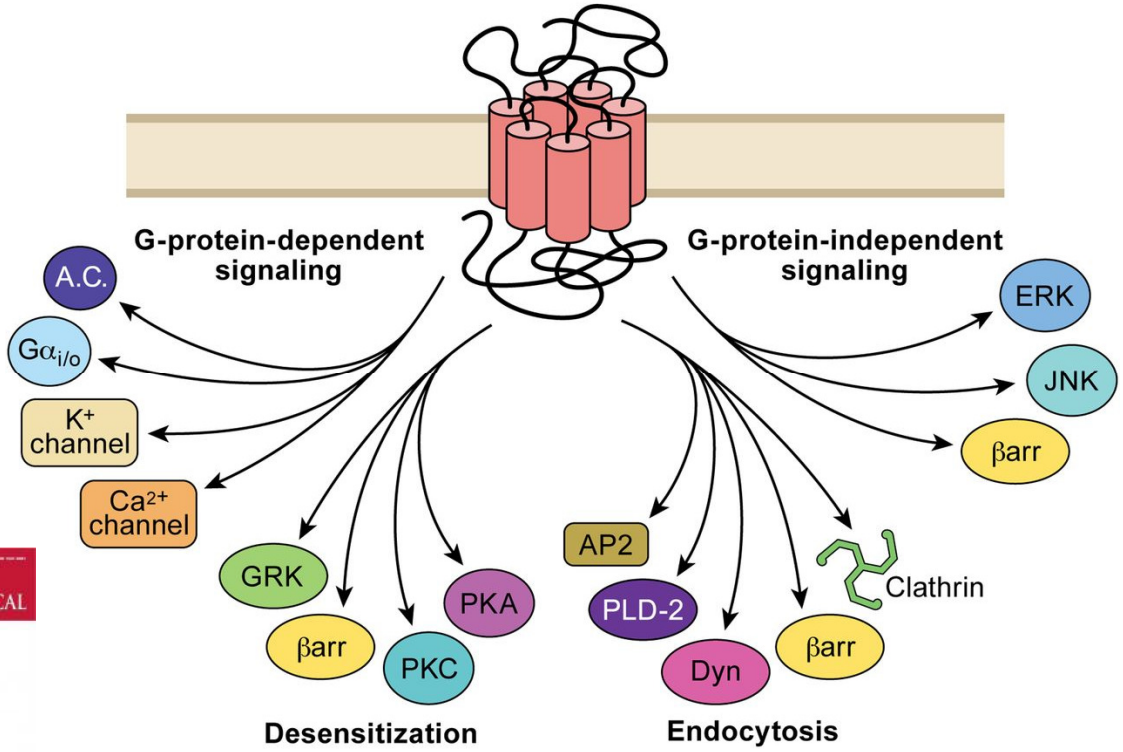


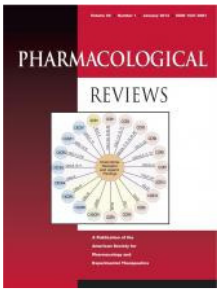
TOCRIS a bio-techne brand

Frontiers in Bioscience 14, 5260-5272 (**2009**)

Poster sobre agonismo sesgado:
https://resources.tocris.com/pdfs/literature/posters/gpcr-efficacy-biased-agonism-poster-v1-2019.pdf

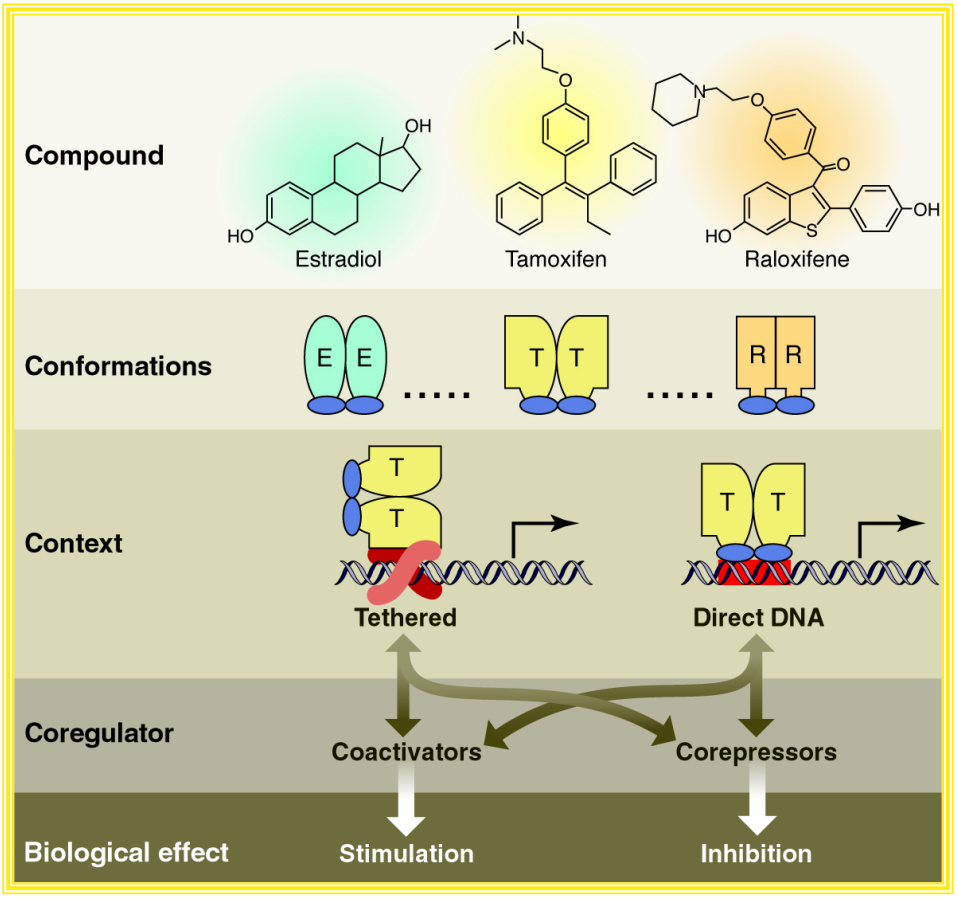
Señalización intracelular tras activación del receptor opioide μ (OP_3, MOR)

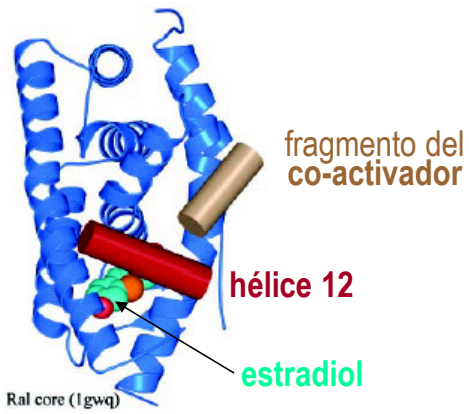


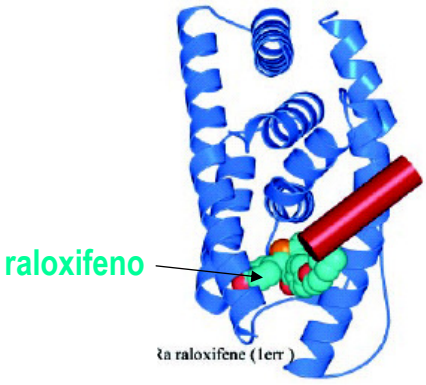


Pharmacological Reviews 65 (1) 223-254 (**2013**)

Moduladores Selectivos de los Receptores Estrogénicos

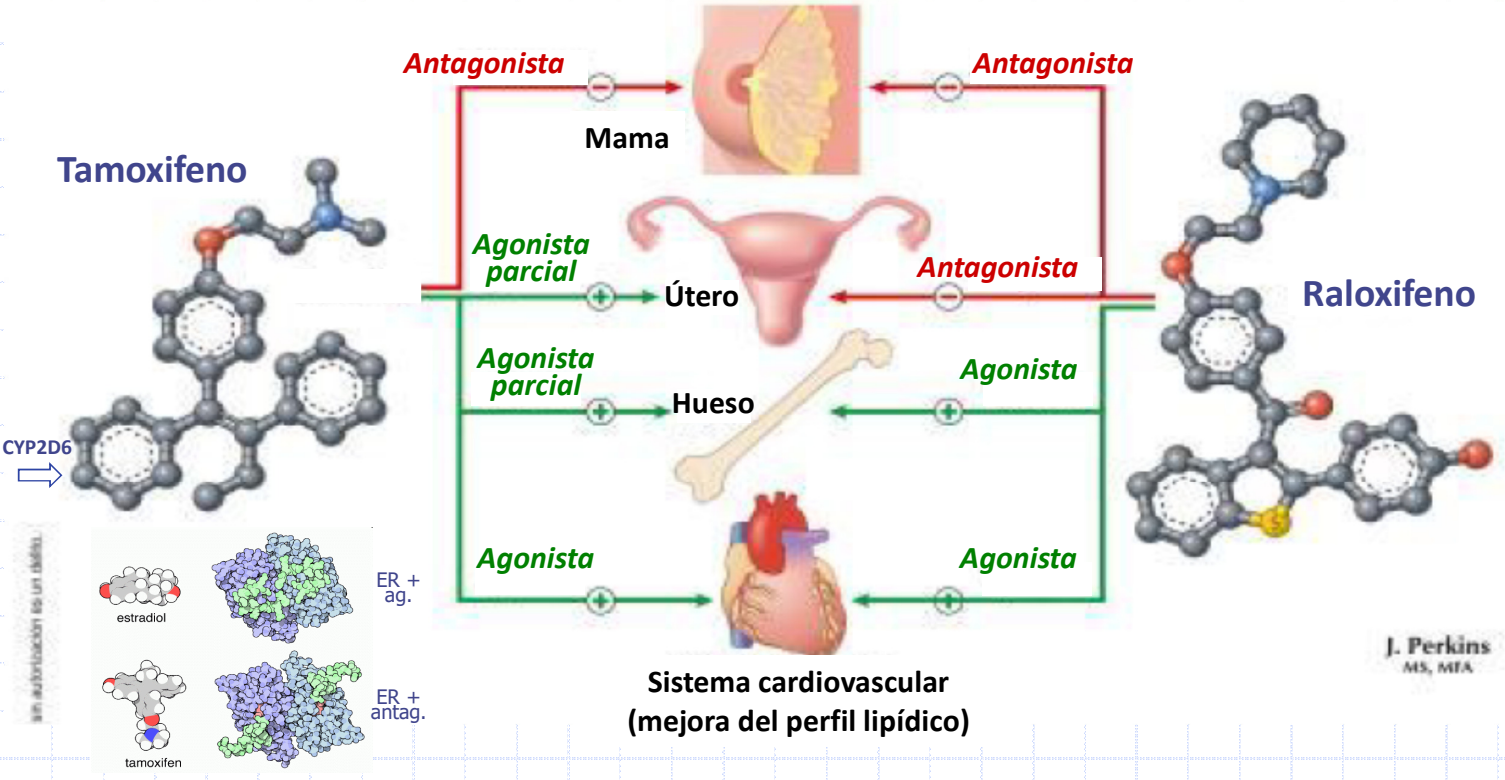






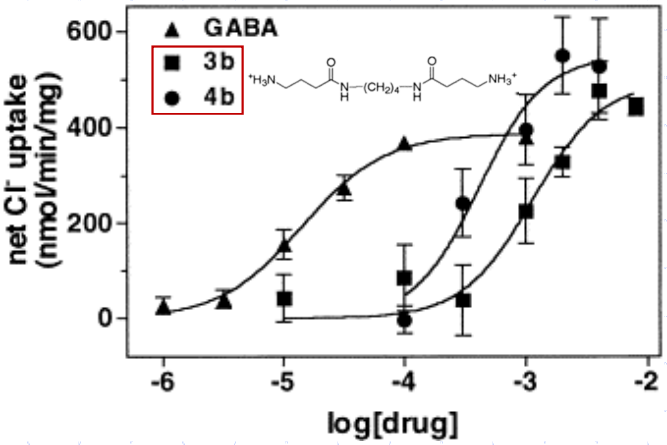
B. & J. Katzenellenbogen
Science 295: 2380 (**2002**)

Moduladores selectivos de los receptores estrogénicos (SERM)

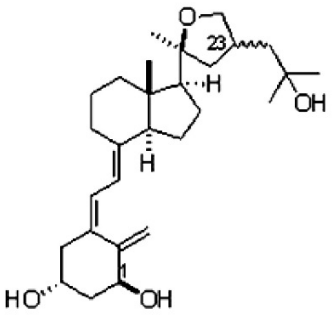


Sistema cardiovascular (mejora del perfil lipídico)

Concepto de "superagonista"

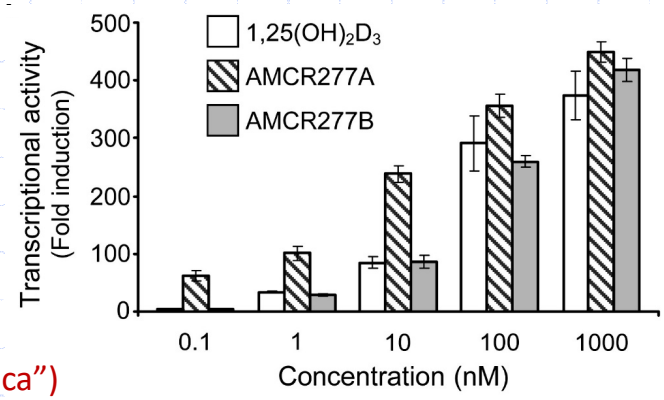


Bioorg. Med. Chem. Lett. **12** (15): 1985–8 (**2002**)

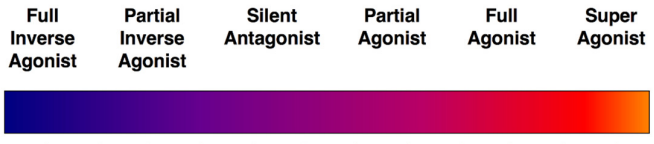


AMCR277A (C23S)

AMCR277B (C23R)



- Tipo de agonista capaz de producir una **respuesta máxima mayor que la producida por el agonista endógeno sobre el mismo receptor.**
- Agonista con **eficacia mayor del 100%** ("suprafisiológica")



Chem. Biol. **15** (4): 383–392 (**2008**)