

Psicosis

PARANOIDE

- Proyec Paranoides
- Actitud hostil
- Act grandiosa y expans

DESORGANIZADA

- Desorganiz conceptual
- Desorientación
- Desorientación/excitac

DEPRESIVA

- Retraso psicomotor
- Apatía
- Autocastigo/ans/culp

Psicosis: Vías de neurotransm

Teoría dopaminérgica

Hiperactividad en recep D2 vía mesolímbica
Hipoactividad en vía mesocortical

Teoría glutamatérgica

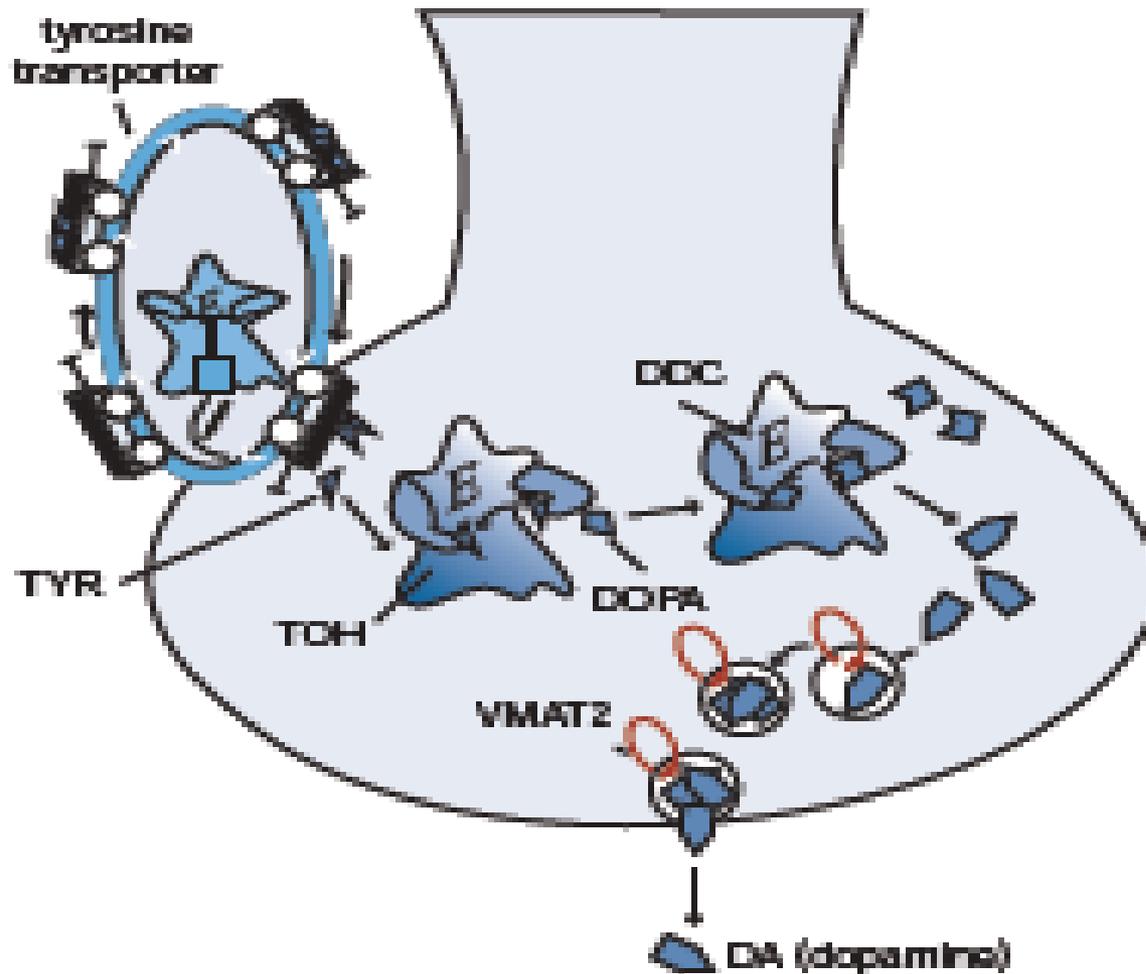
Hipofunción recep NMDA en neuronas GABA

Teoría serotoninérgica

Hiperfunción recep 5HT_{2A} en el córtex

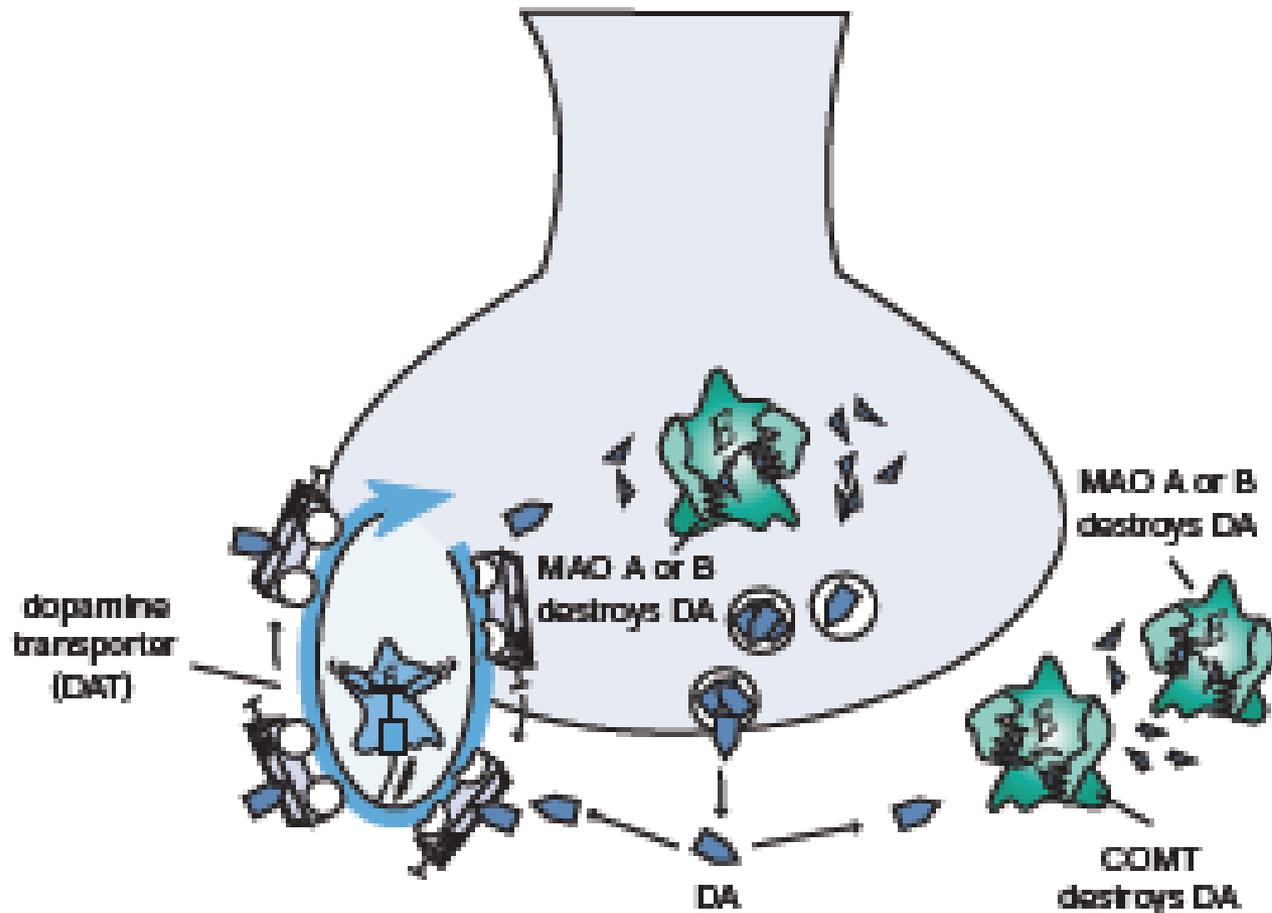
SÍNTESIS DE DOPAMINA

Dopamine is Produced

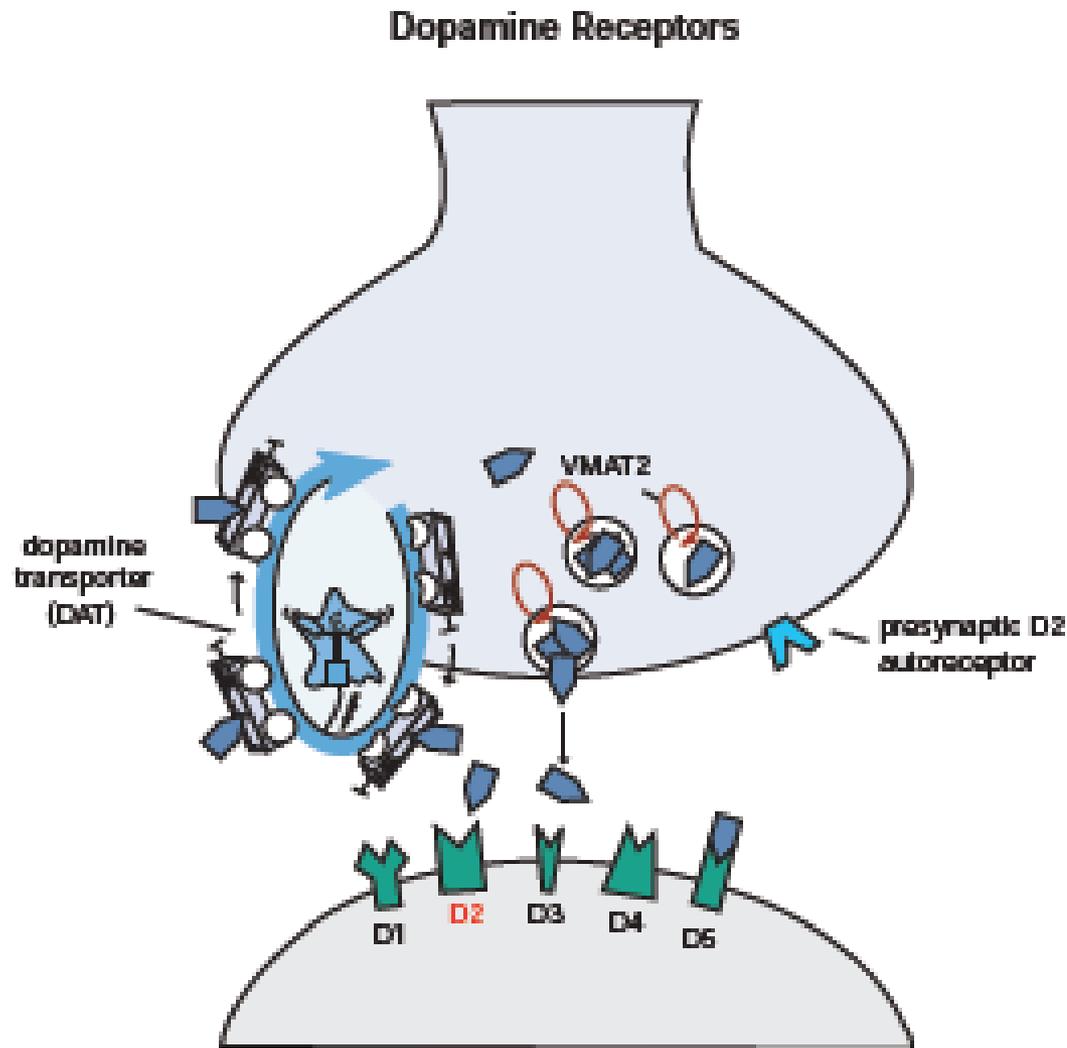


DEGRADACIÓN DE LA DOPAMINA

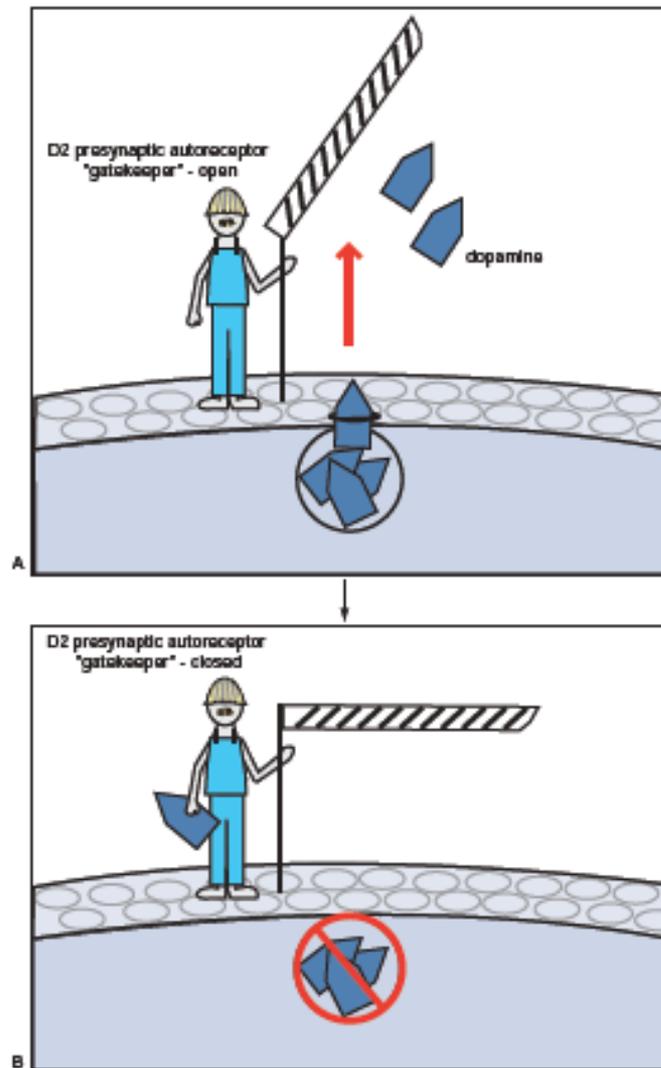
Dopamine's Action is Terminated



RECEPTORES DE DOPAMINA

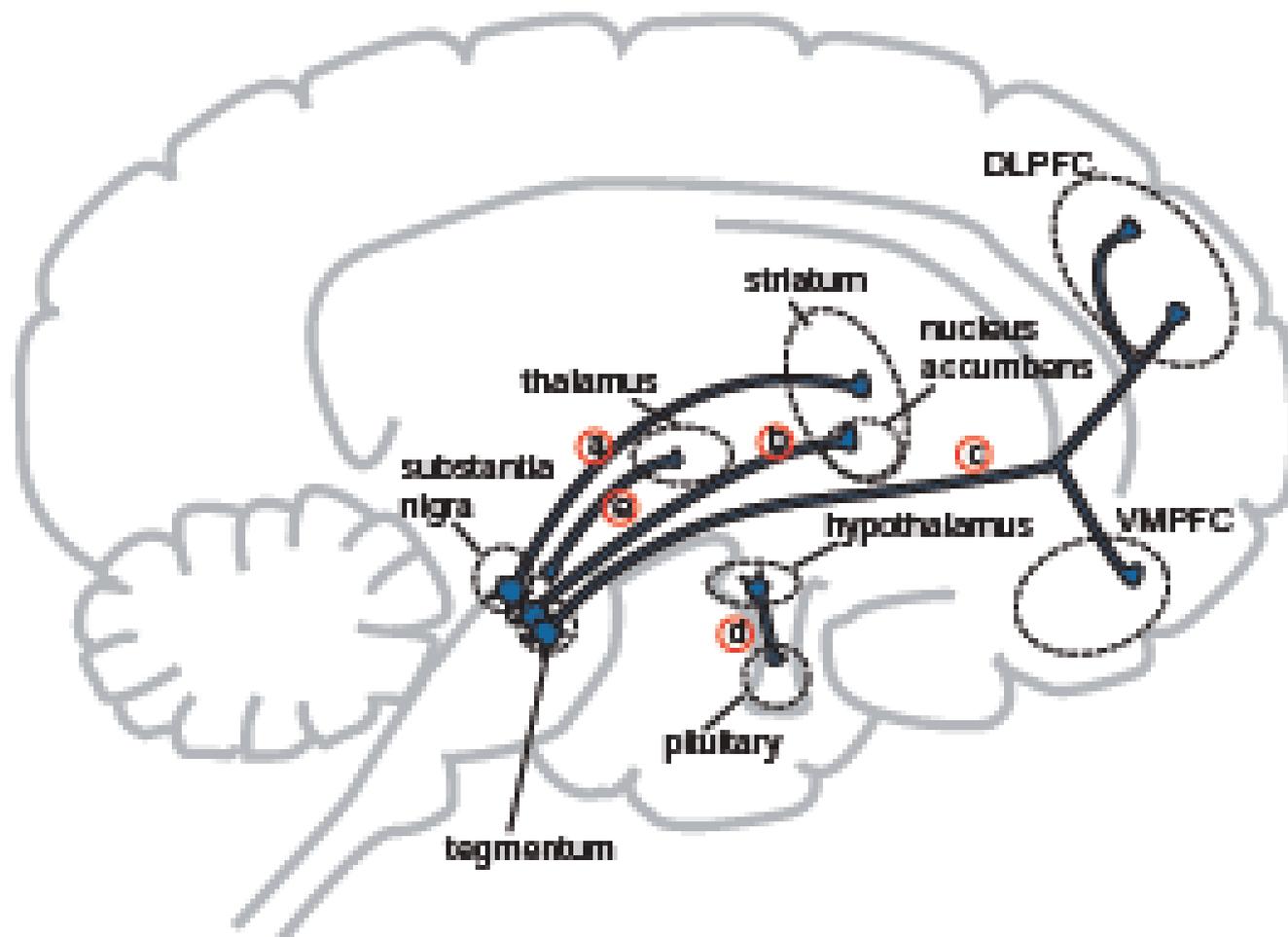


AUTORRECEPTOR D₂

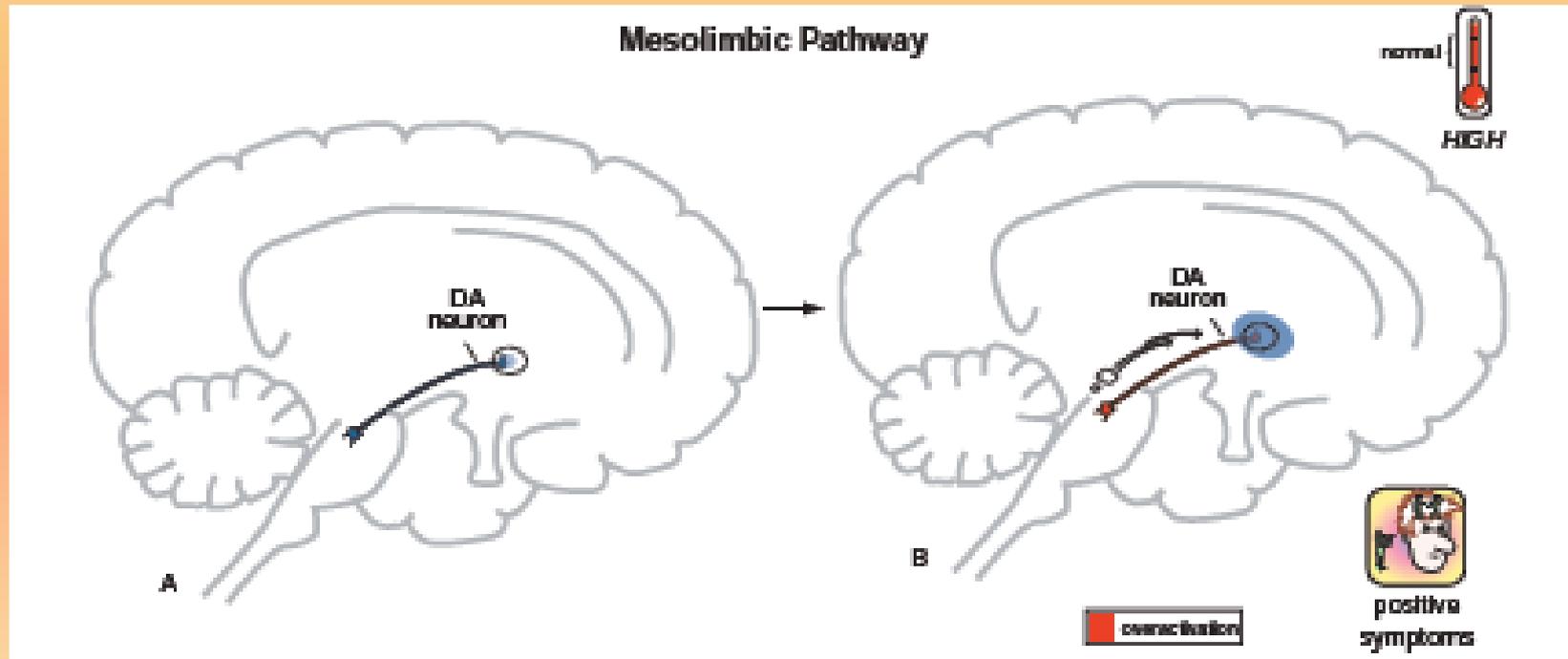


VÍAS DOPAMINÉRGICAS

Dopamine Pathways and Key Brain Regions

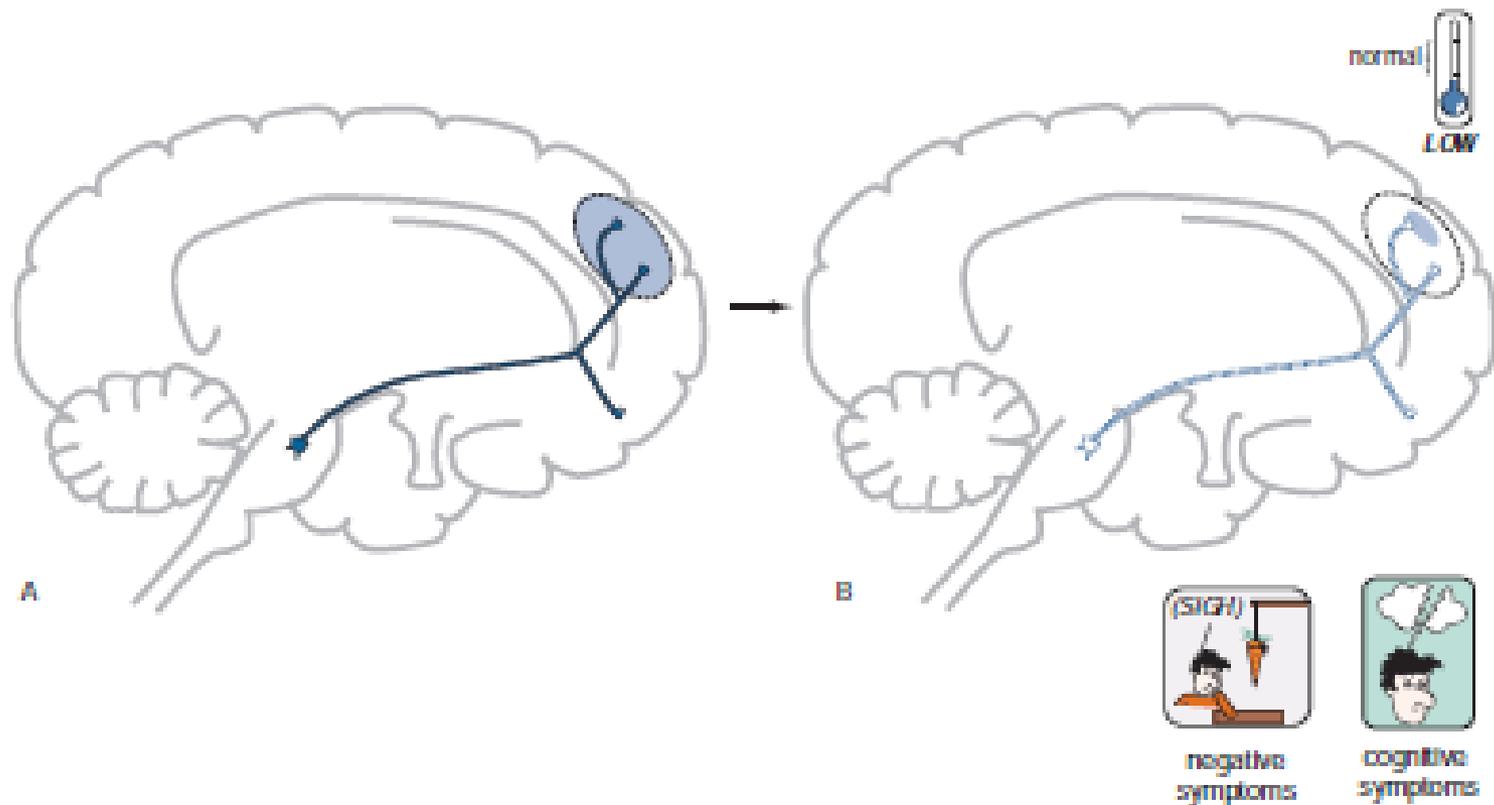


HIPERACTIVACIÓN VÍA M-L



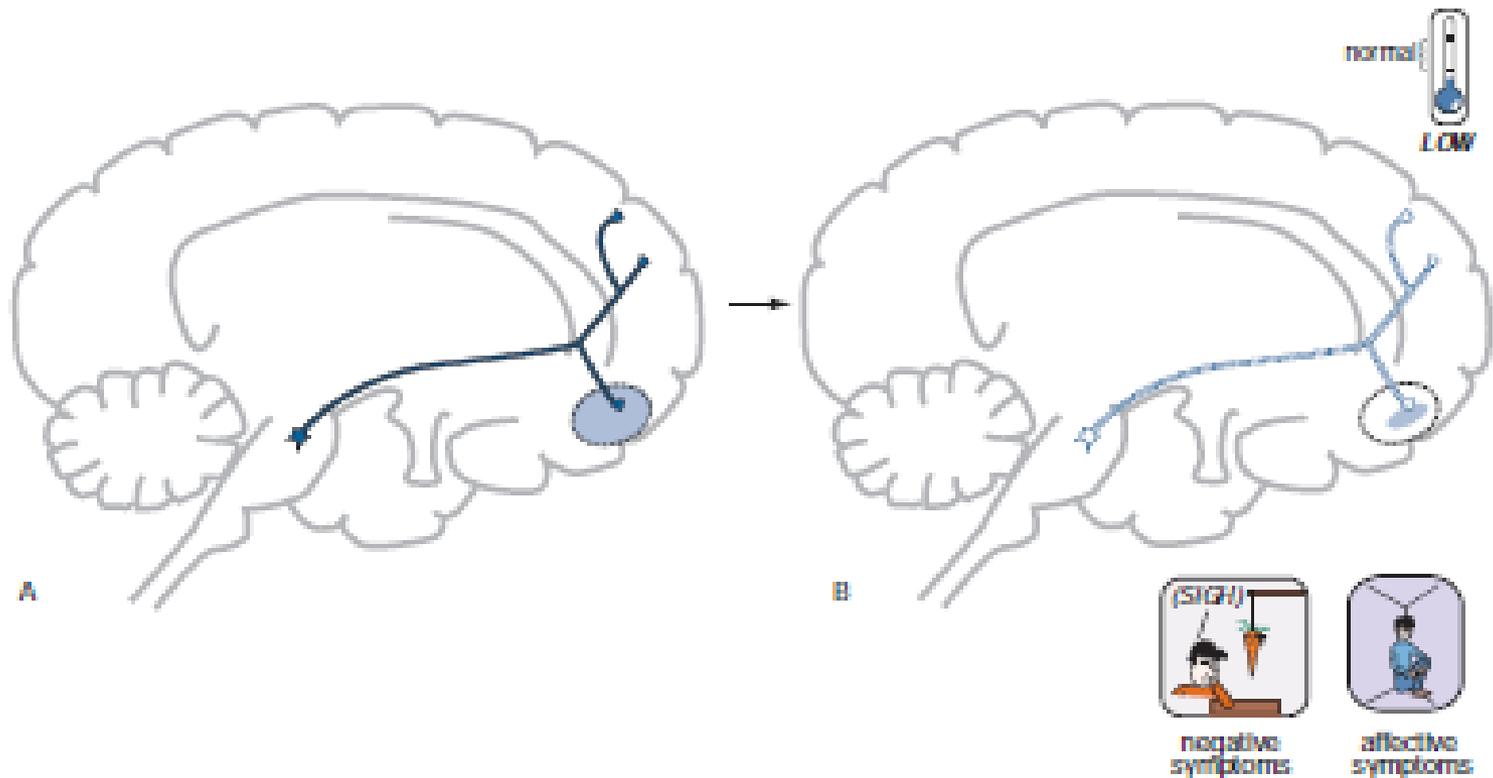
HIPOACTIVACIÓN VÍA M-C

Mesocortical Pathway to DLPFC



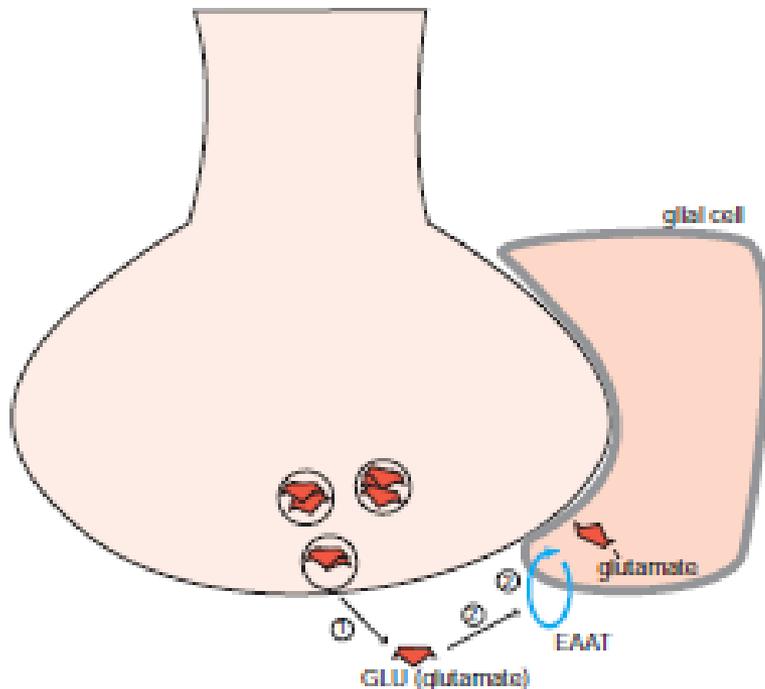
HIPOACTIVACIÓN VÍA M-C

Mesocortical Pathway to VMPFC

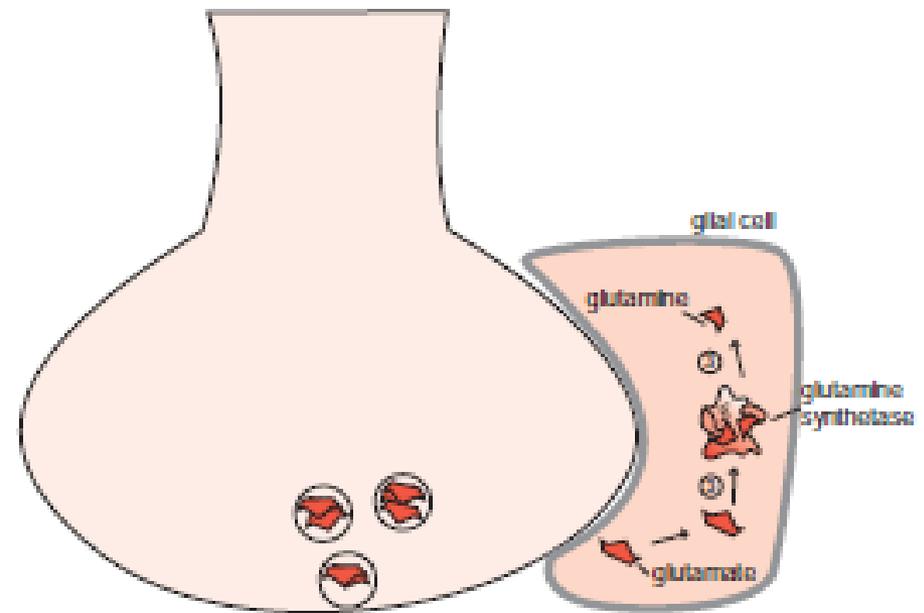


SÍNTESIS DE GLUTAMATO

Glutamate is Recycled and Regenerated: Part 1

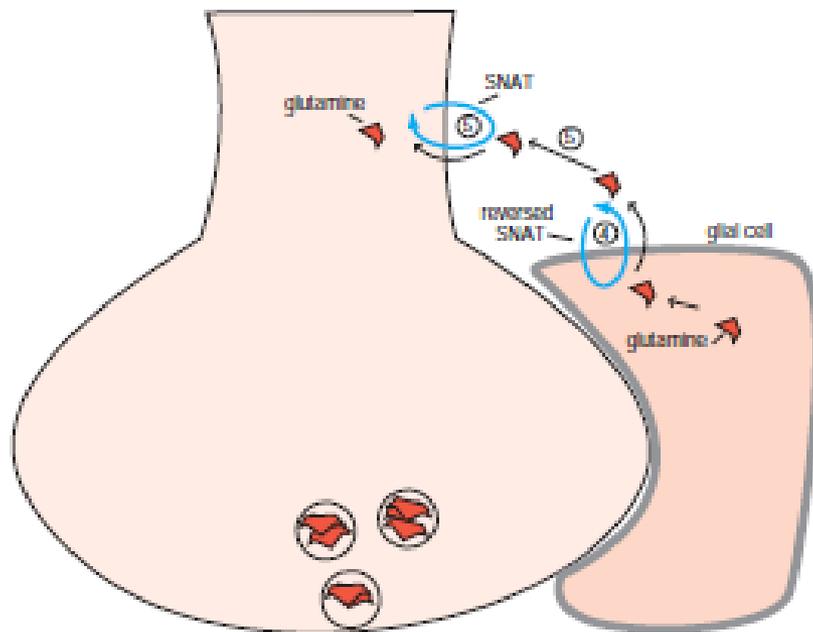


Glutamate is Recycled and Regenerated: Part 2

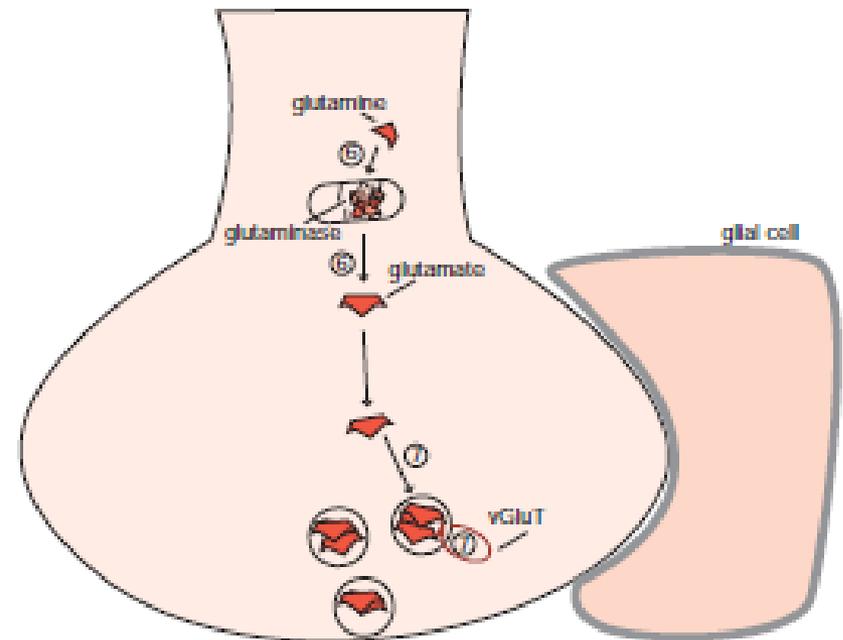


SÍNTESIS DE GLUTAMATO

Glutamate is Recycled and Regenerated: Part 3

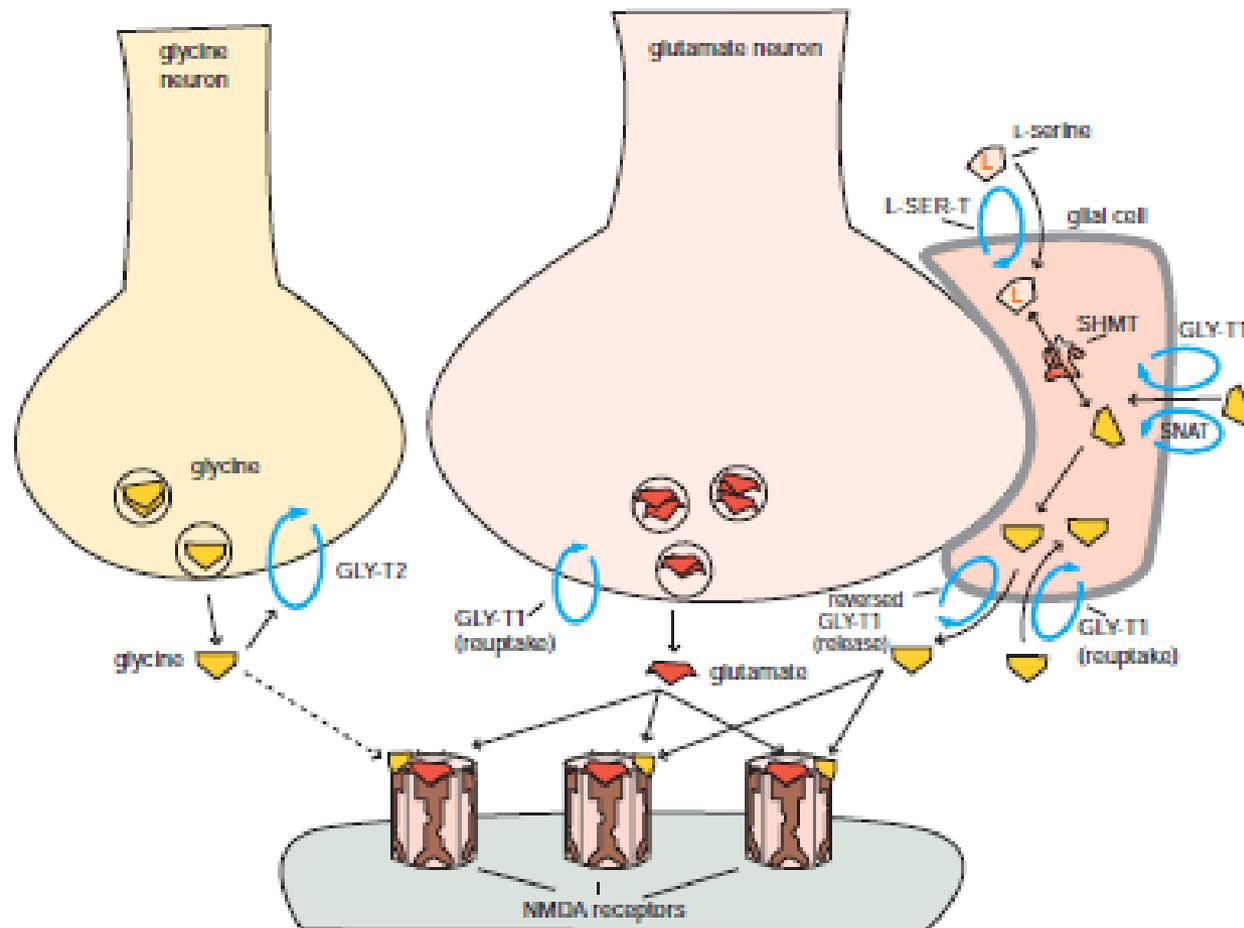


Glutamate is Recycled and Regenerated: Part 4



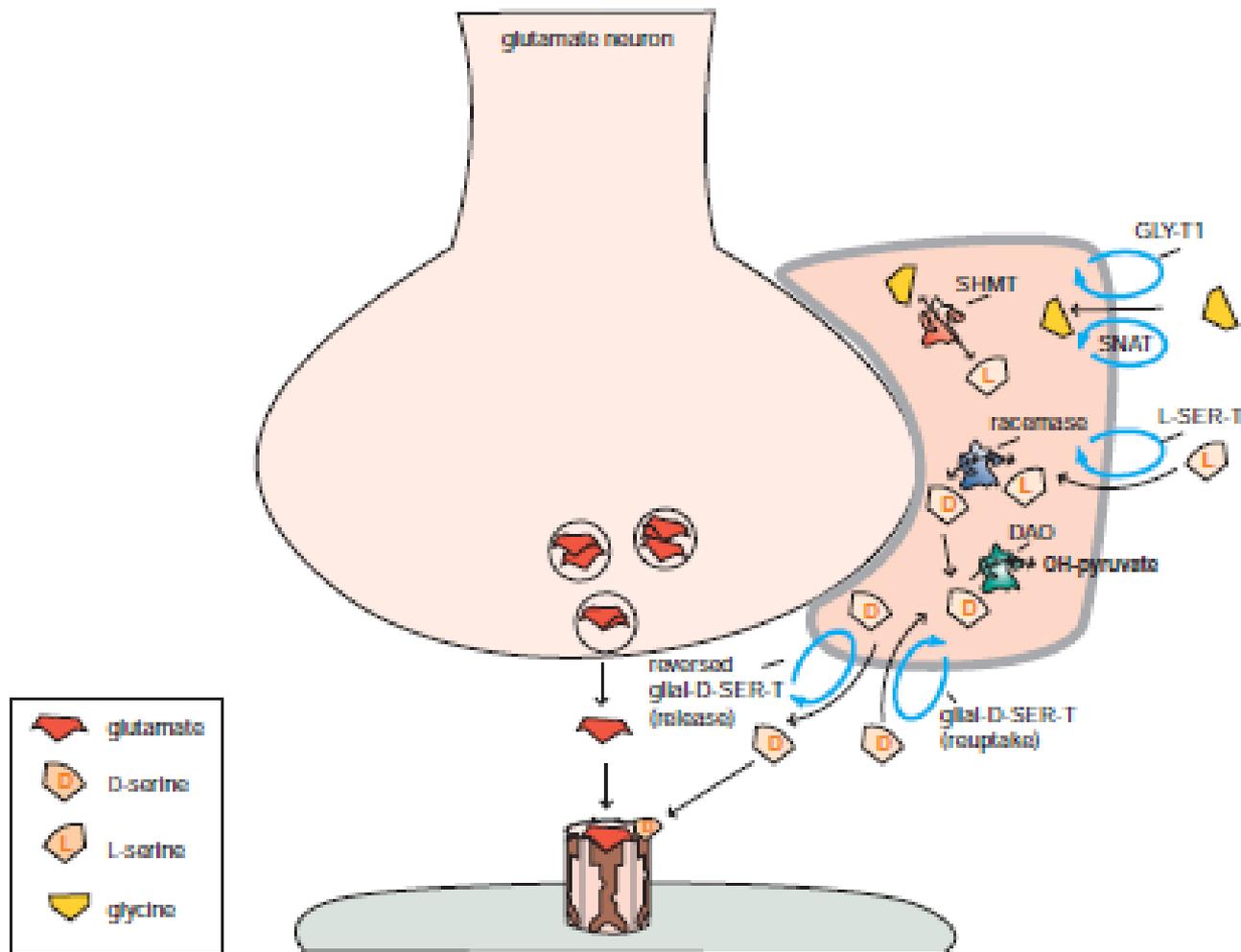
COTRANSMISIÓN RECEPTOR NMDA

NMDA Receptor Cotransmitter Glycine Is Produced

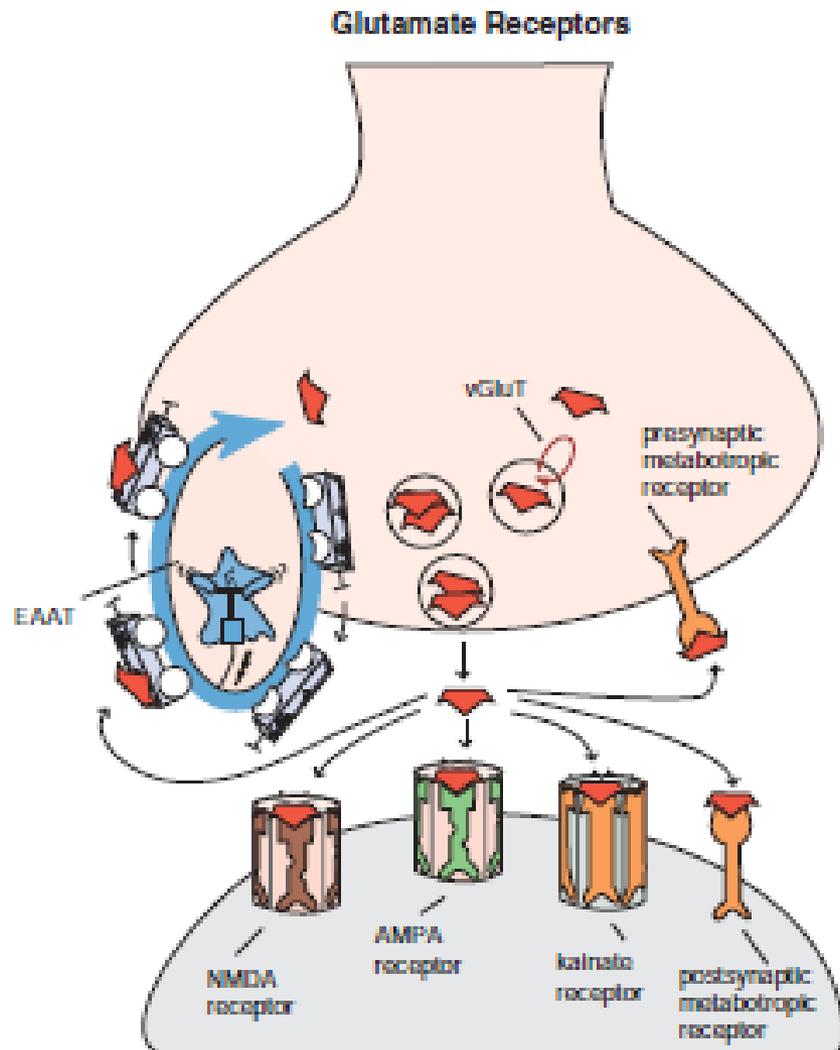


SÍNTESIS D-SERINA

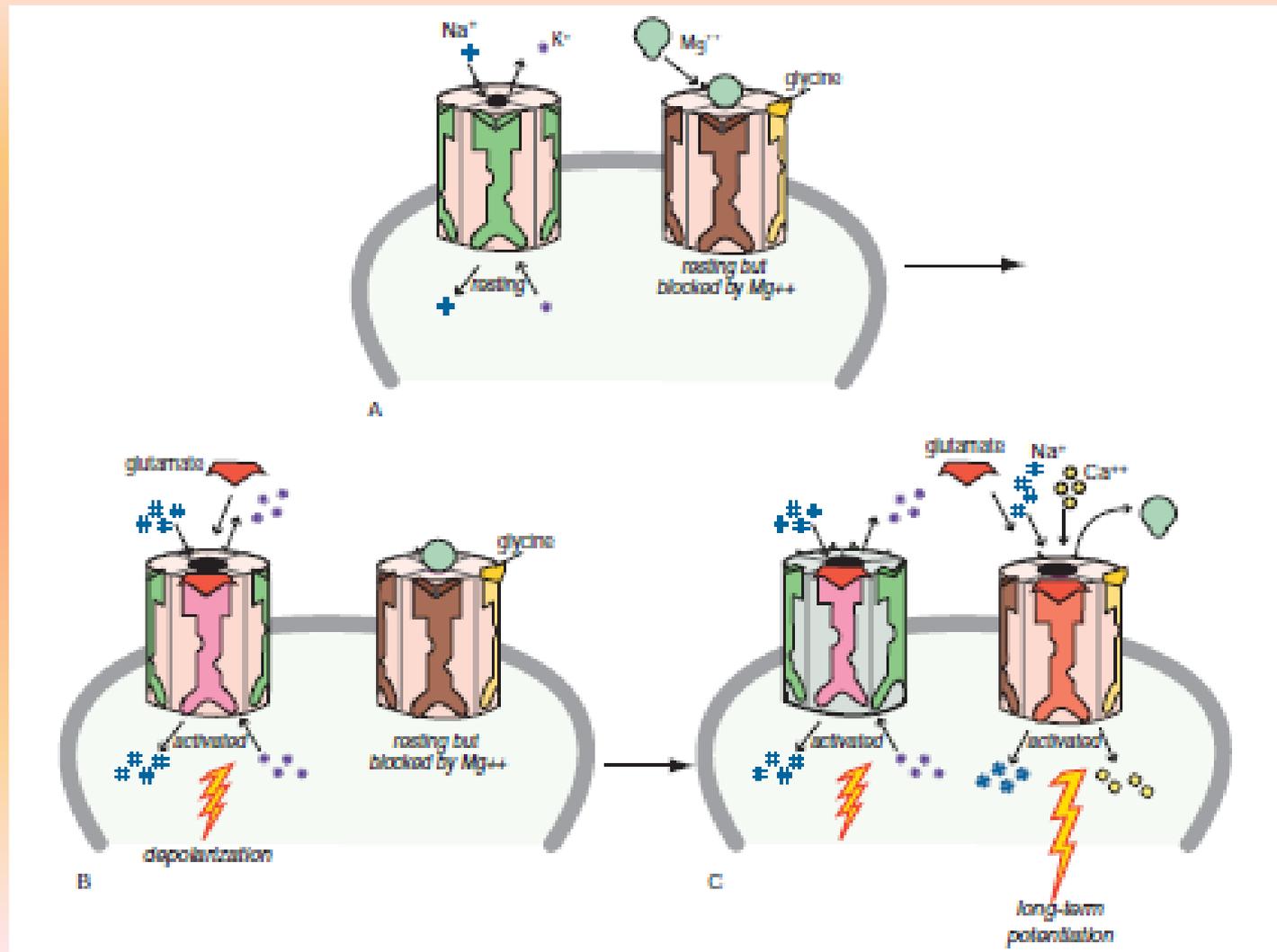
NMDA Receptor Cotransmitter D-Serine Is Produced



RECEPTORES DE GLUTAMATO

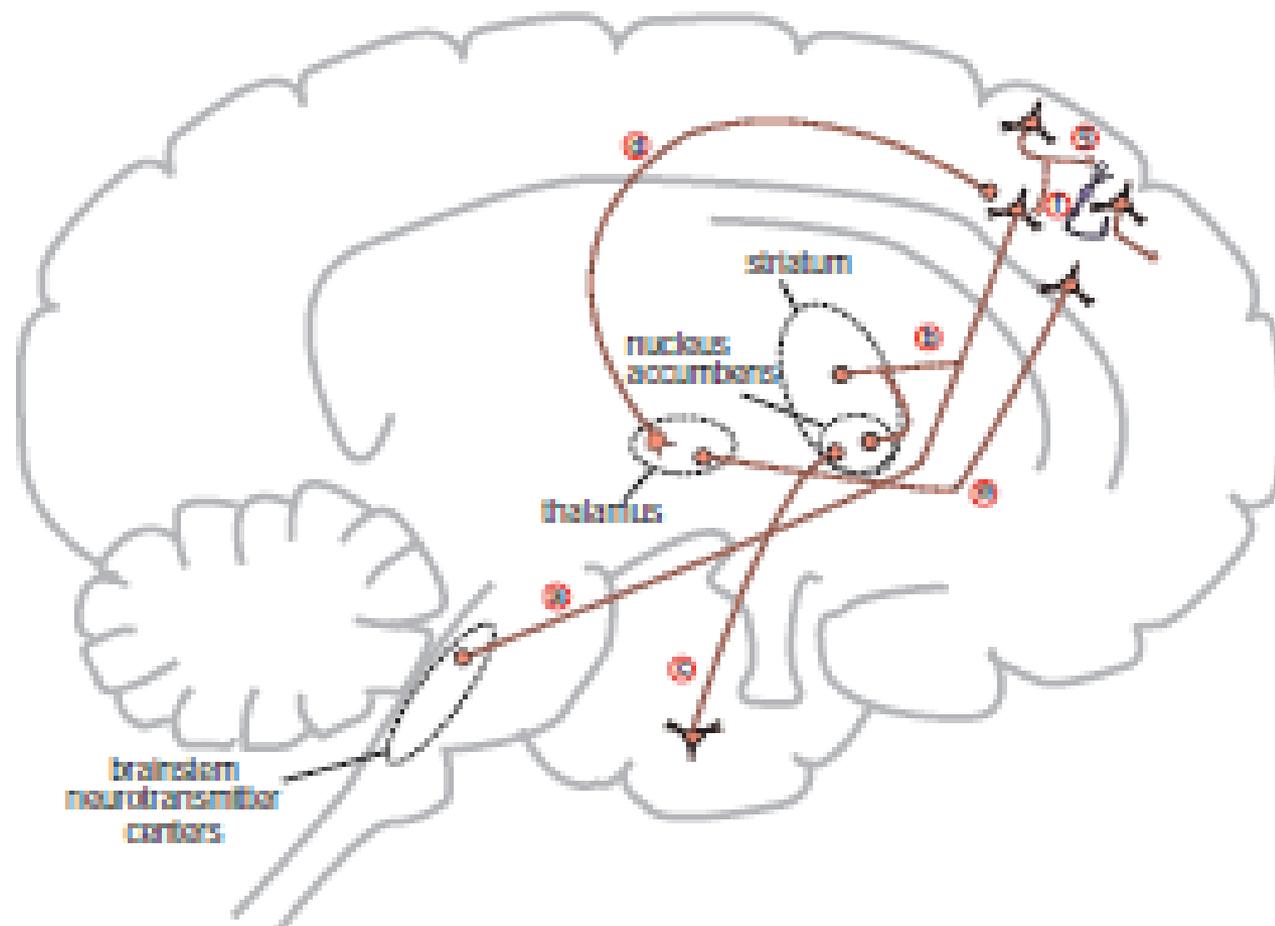


RECEPTORES AMPA Y NMDA



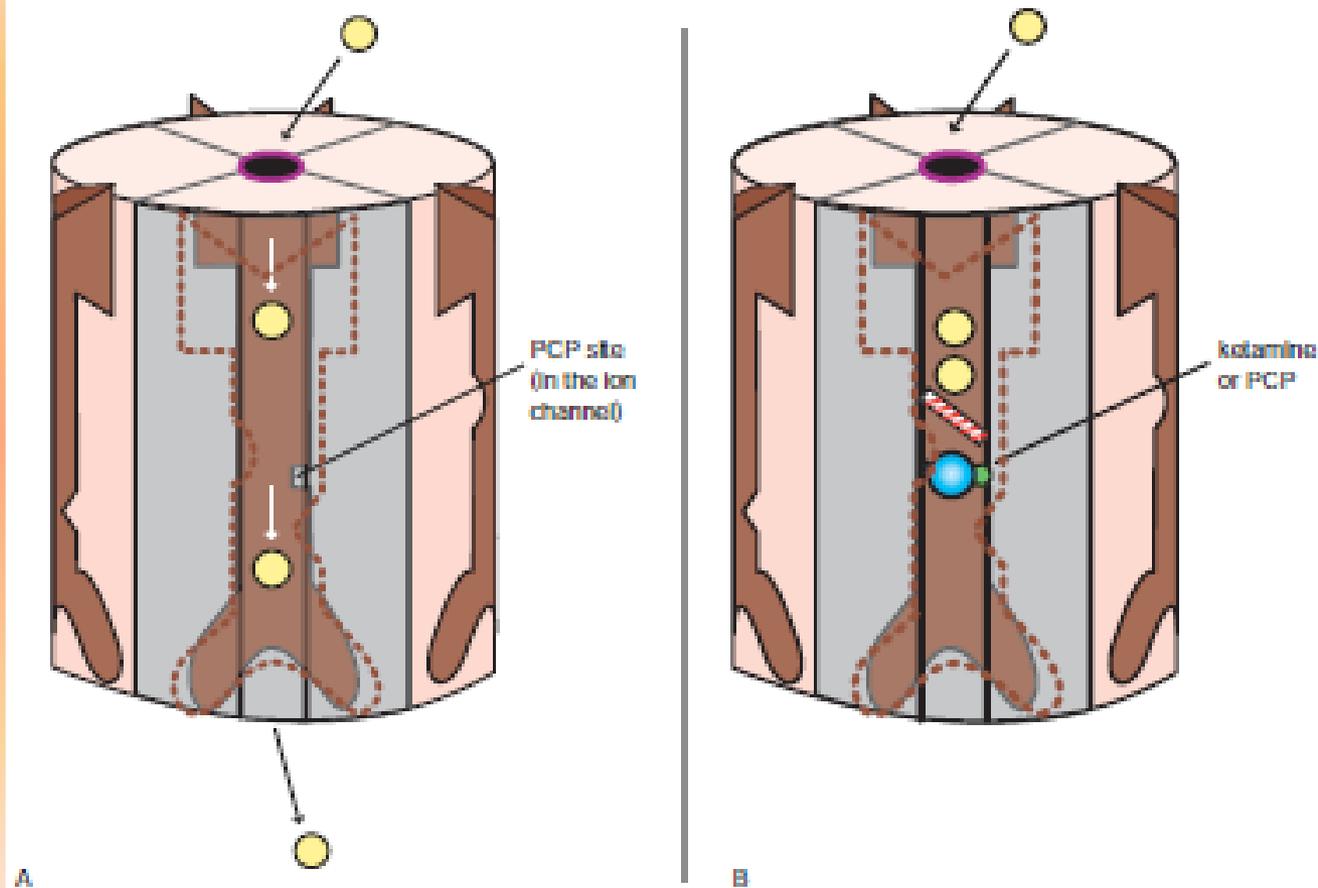
VÍAS GLUTAMATÉRGICAS

Key Glutamate Pathways

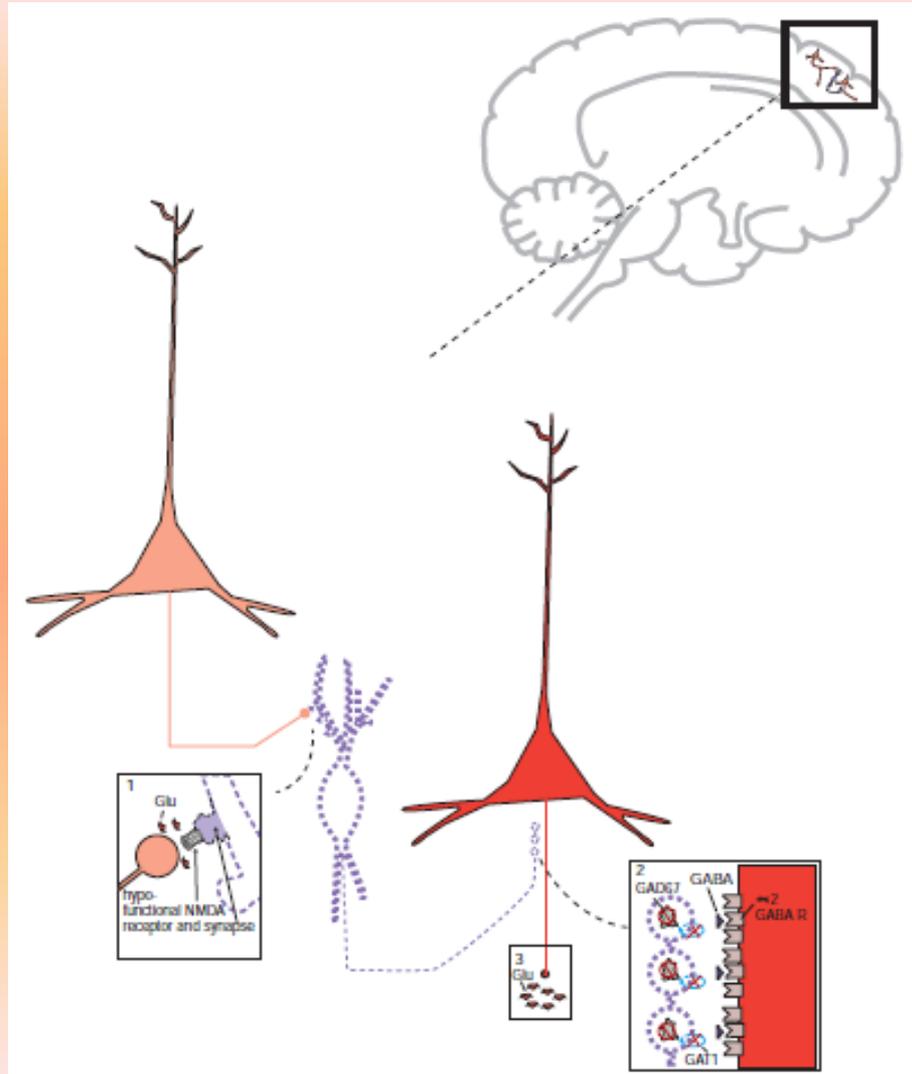


PCP Y SÍNTOMAS DE LA ESQUIZOFRENIA

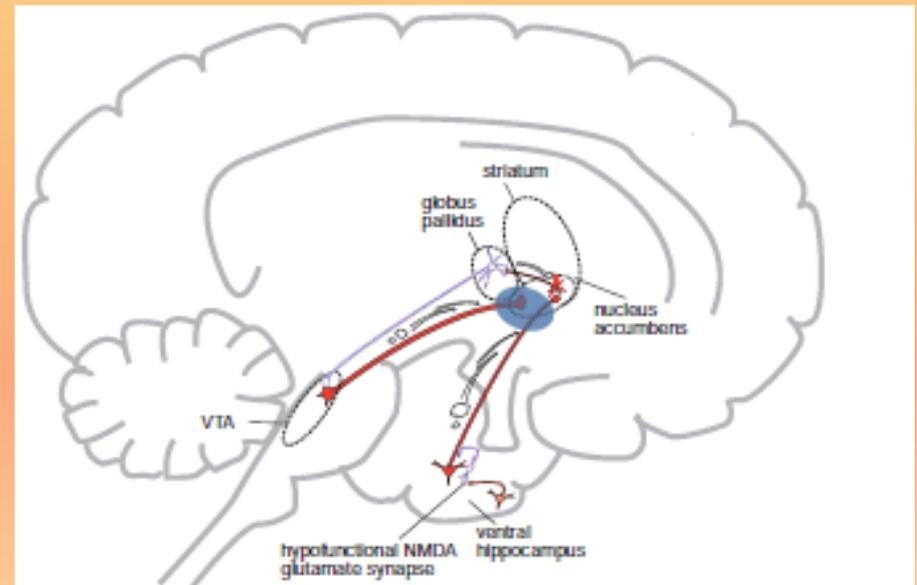
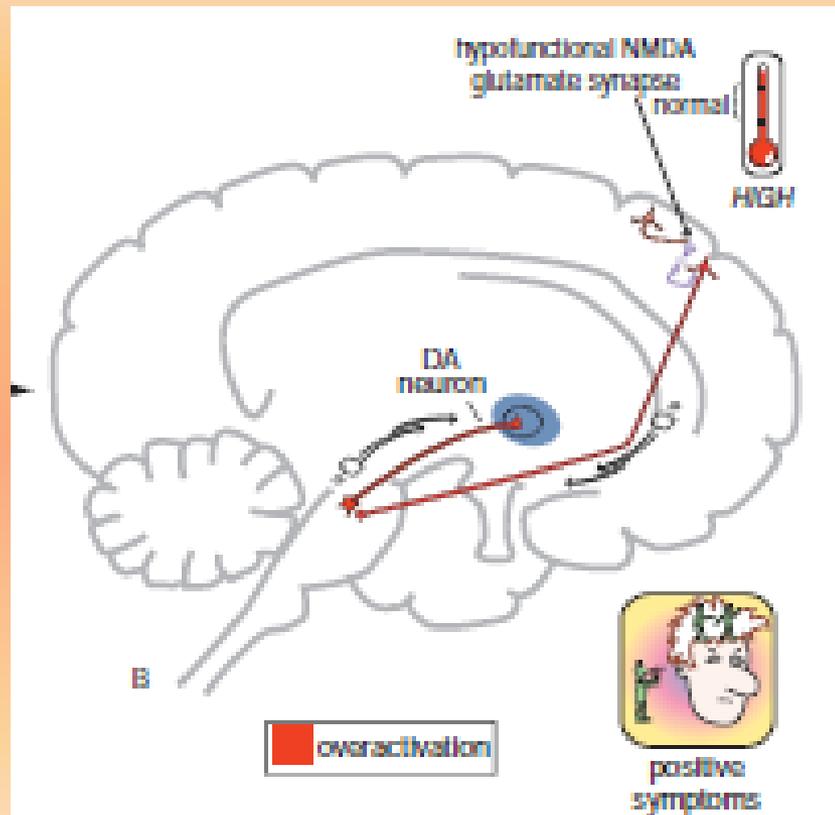
Site of Action of PCP and Ketamine: Bind to Open Channel at PCP Site to Block NMDA Receptor



HIPÓTESIS HIPOFUNCION NMDA

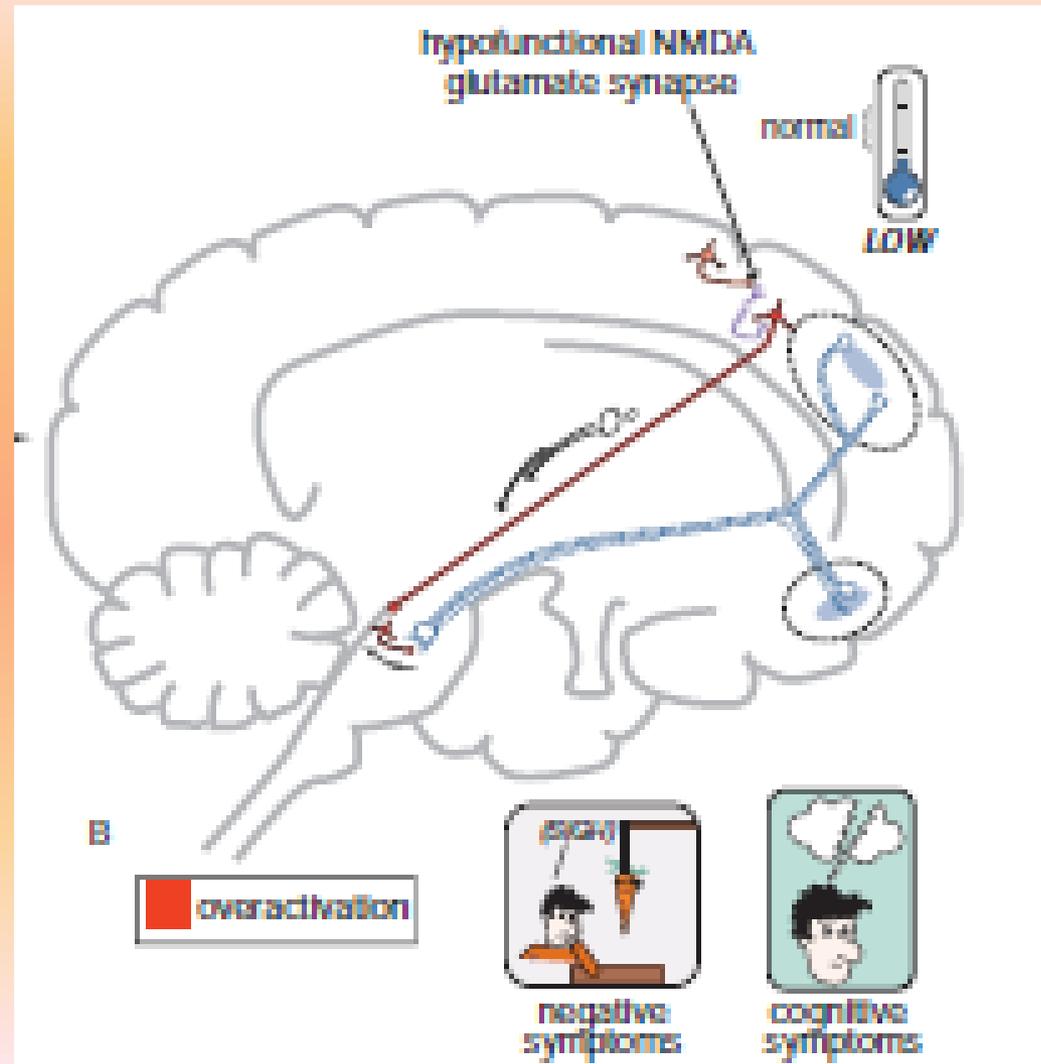


HIPÓTESIS HIPOFUNCIÓN NMDA SÍNTOMAS POSITIVOS



HIPÓTESIS HIPOFUNCIÓN NMDA

SÍNTOMAS NEGATIVOS



Equizofrenia

- Importancia síntomas negativos → Entre episodios y pródromo
- No deterioro memo corto plazo → Sí en demencia
- Sínt afectivos → Difícil distinguir de transt humor y ans
→ Importante tratarlos → 5% suicidio →
añadir fárm epec
- Agresividad → Psicótica // Impulsiva // Organizada (psicopática)
- La mayoría no son violentos
- Causa → Conspiración muchos genes y estrés ambiental
- Se hereda el riesgo de enfermedad, no la enfermedad

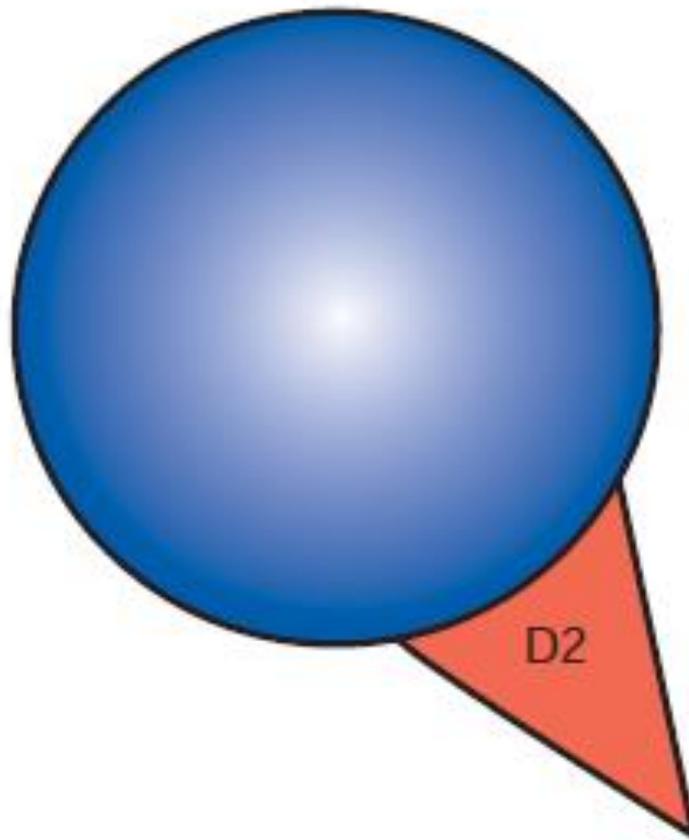
Fármacos para Psicosis

- Antagonistas D₂
- Antagonistas D₂ y 5HT_{2A}
- Antagonistas 5HT_{2A}
- Agonistas parciales D₂ y 5HT_{1A}

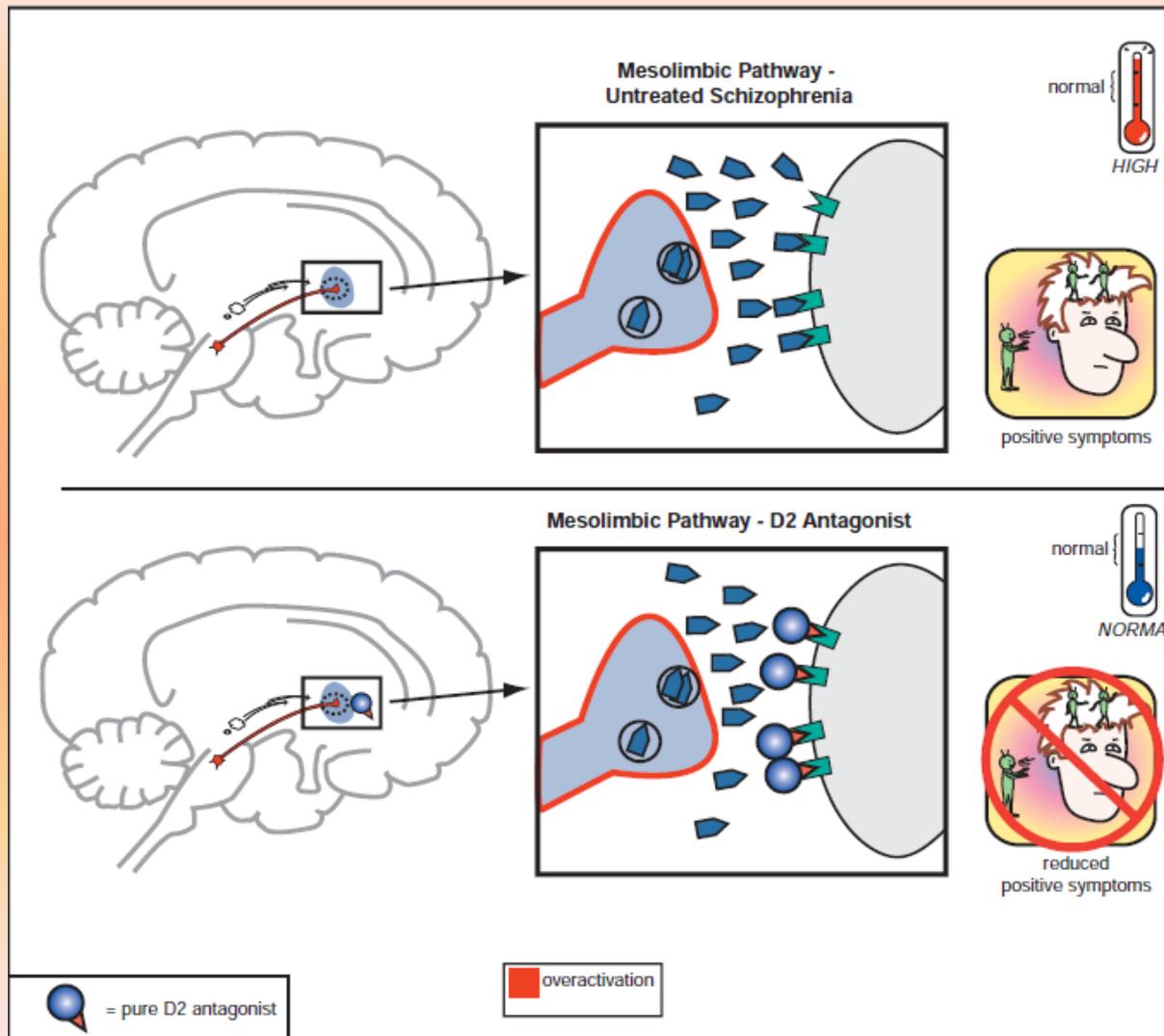
Antipsicóticos convencionales

What Makes an Antipsychotic Conventional?

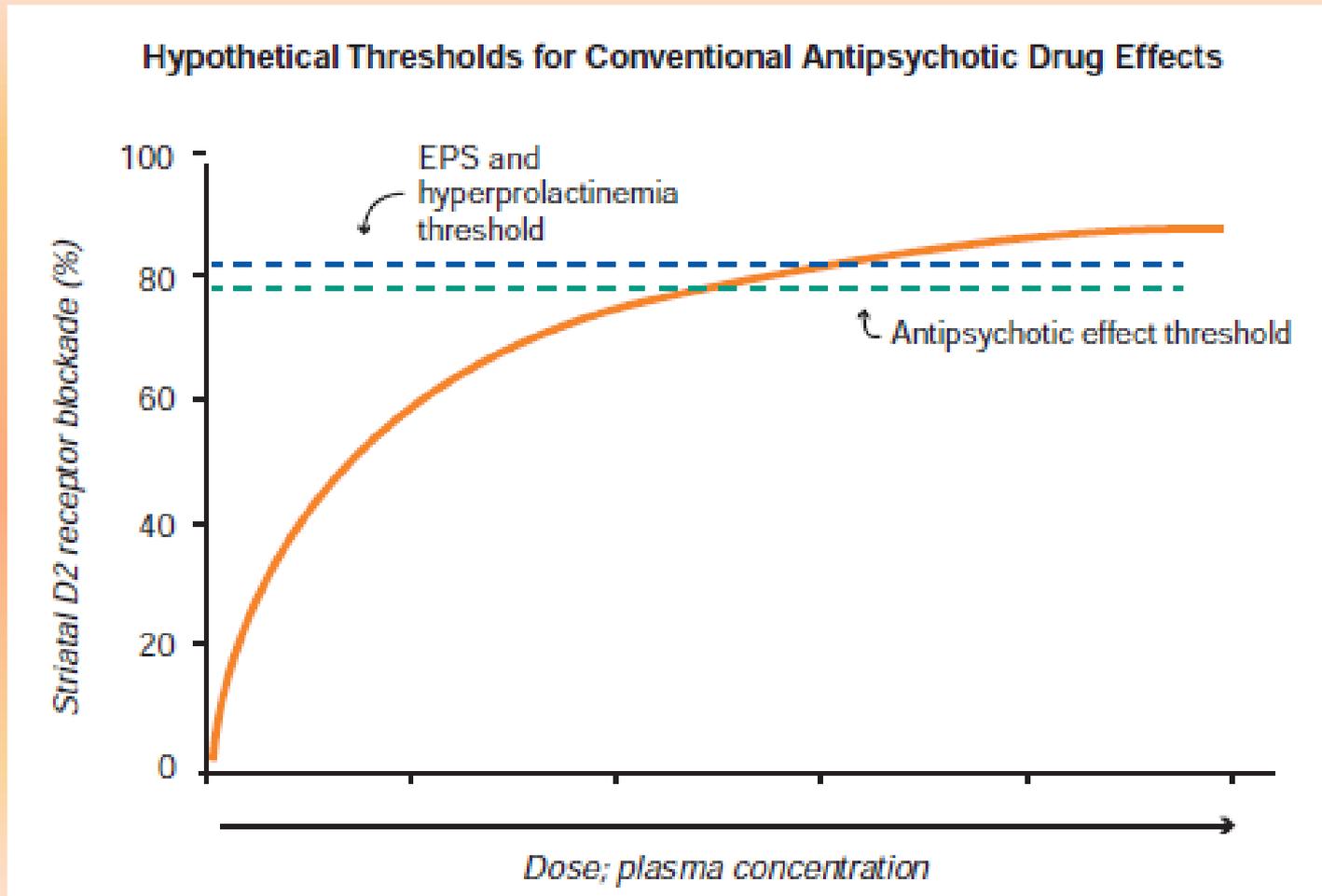
D2 Antagonist Actions



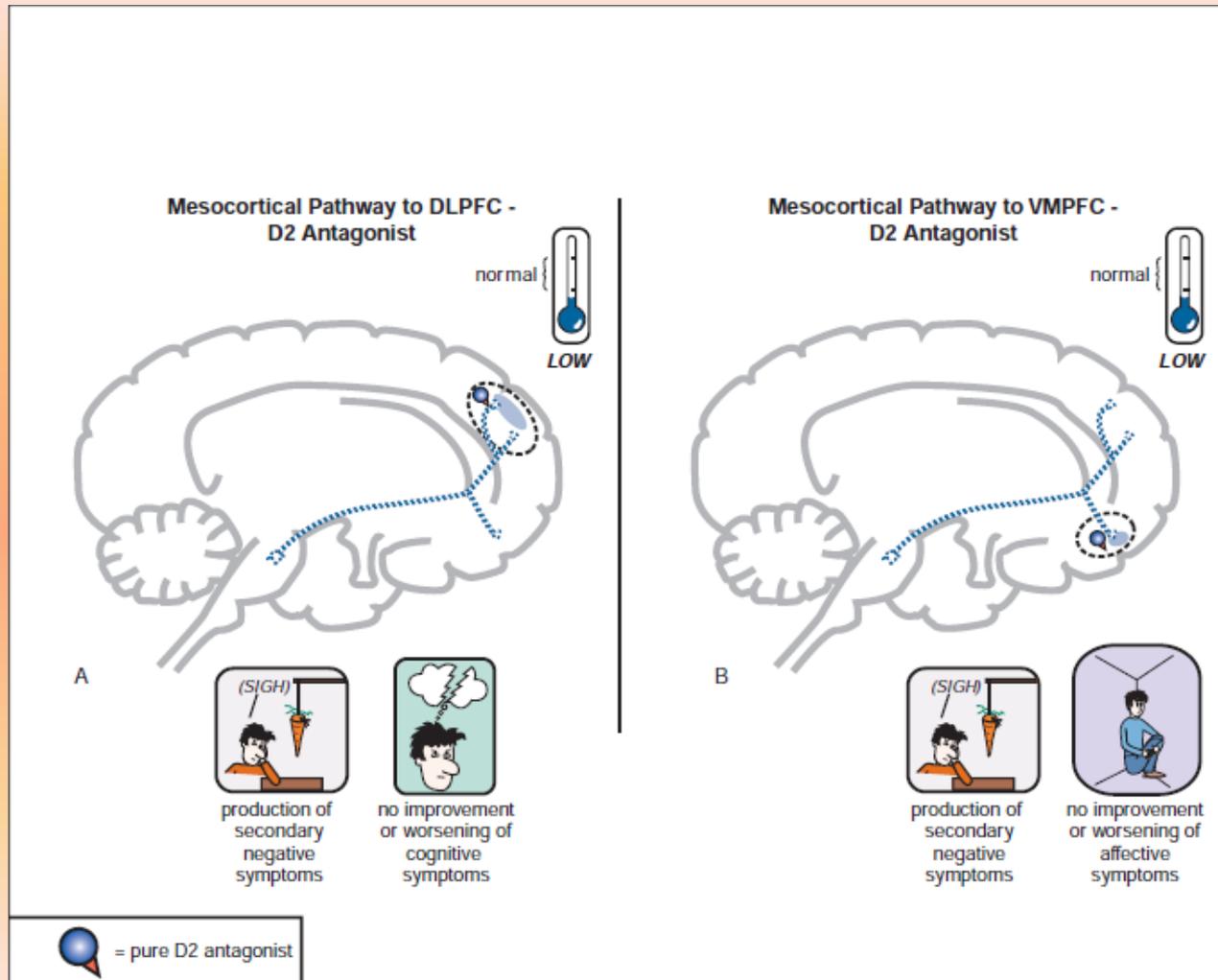
Antipsicóticos convencionales



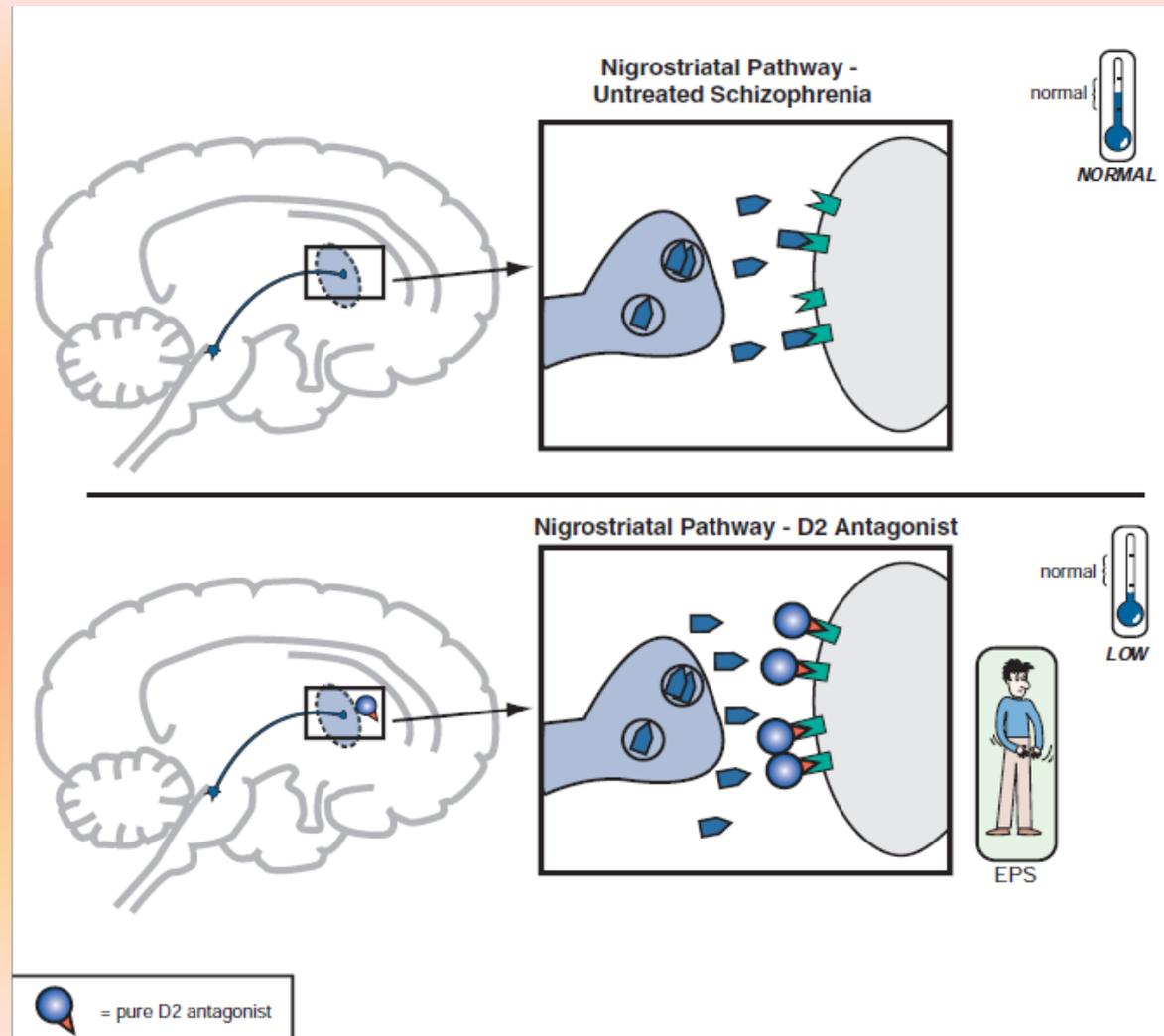
Antipsicóticos convencionales



Neuroleptosis

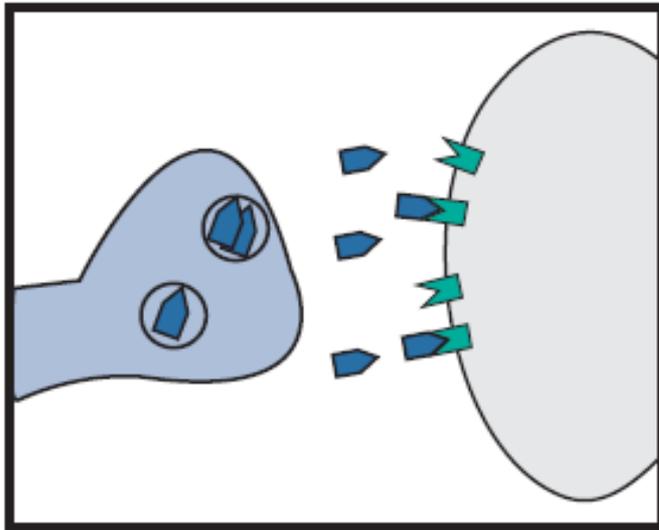


'Síntomas extrapiramidales



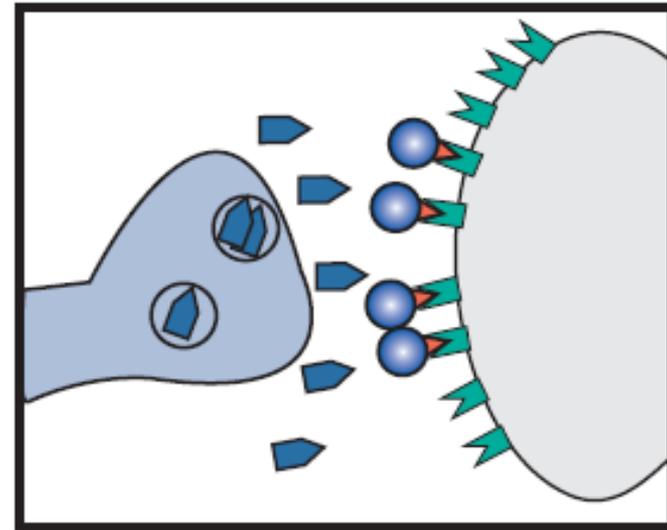
Disquinesia tardía

blockade of D2 receptors in the nigrostriatal dopamine pathway causes them to upregulate



A

this upregulation may lead to tardive dyskinesia

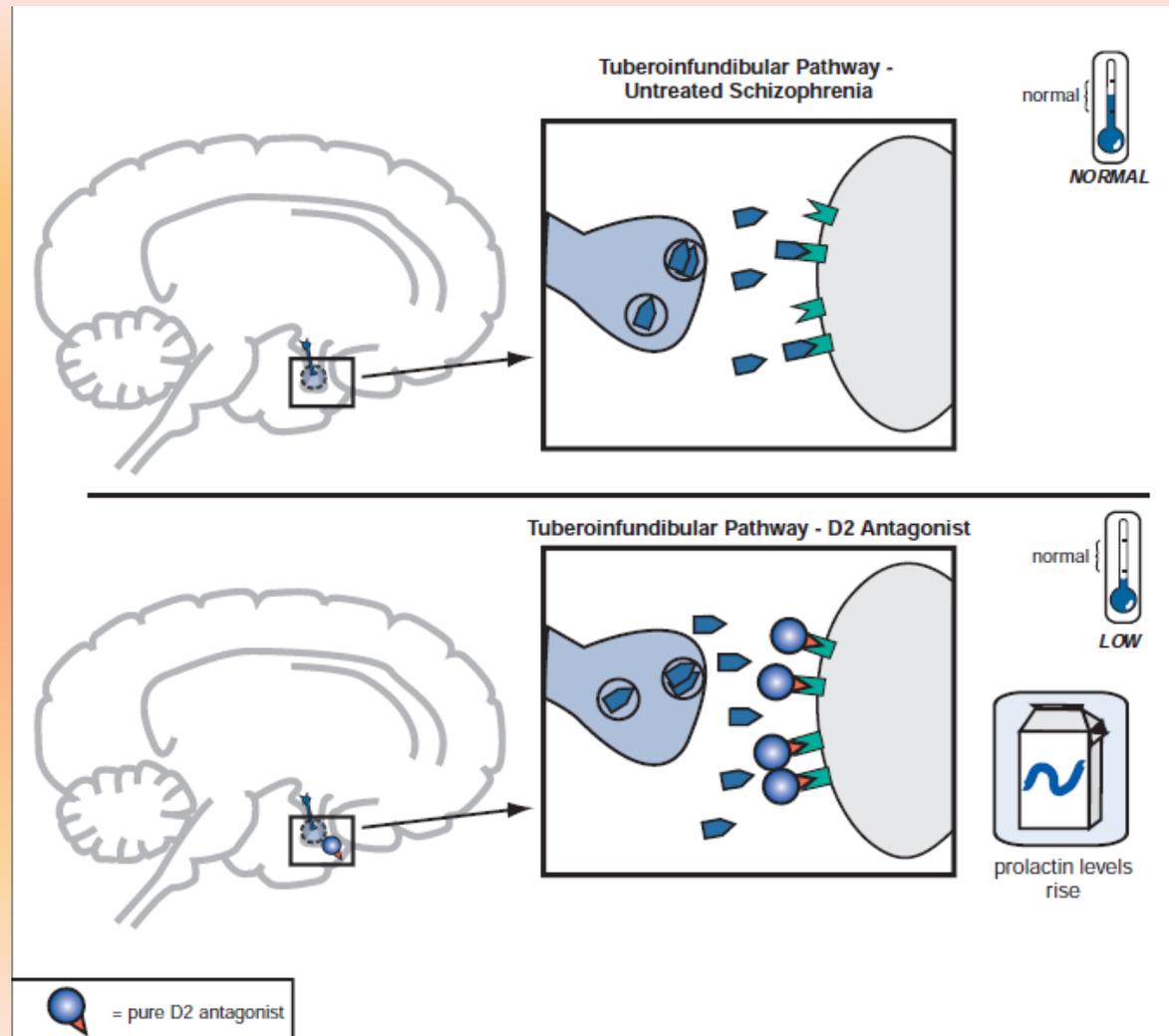


B



tardive dyskinesia

Hiperprolactinemia

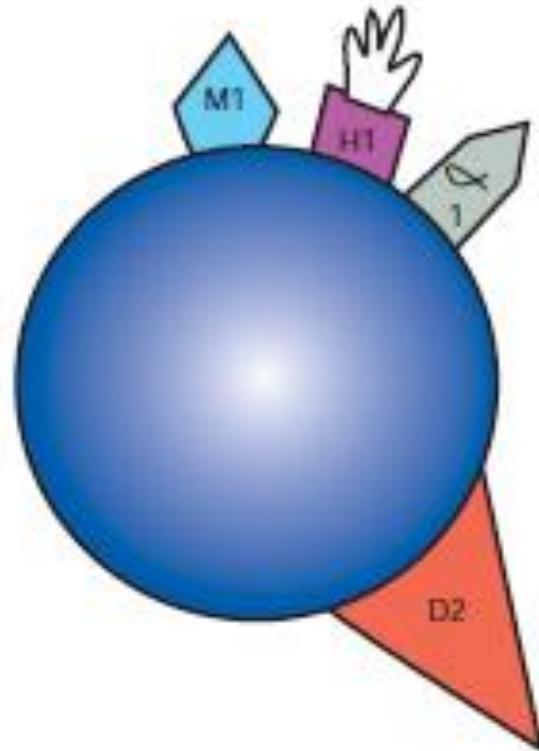


Otros efectos secundarios

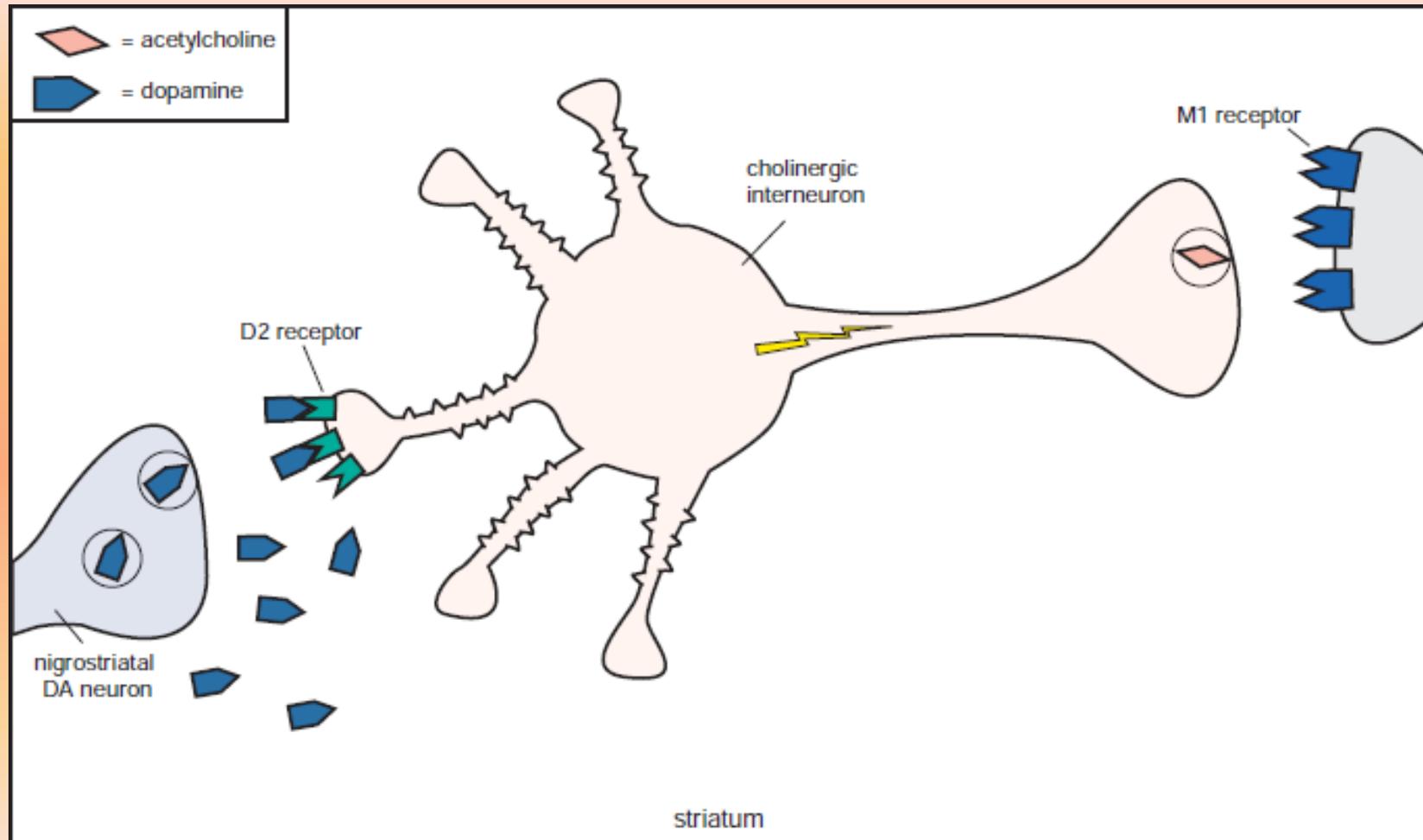
- Distonía aguda → Anticolinérg intramusc
- Acatisia → Adrenérg // Benzos // 5HT 2^a
- S Neuroléptico Maligno → Retirada // dantroleno // Agonistas DA

Antipsicóticos convencionales: propiedades adicionales

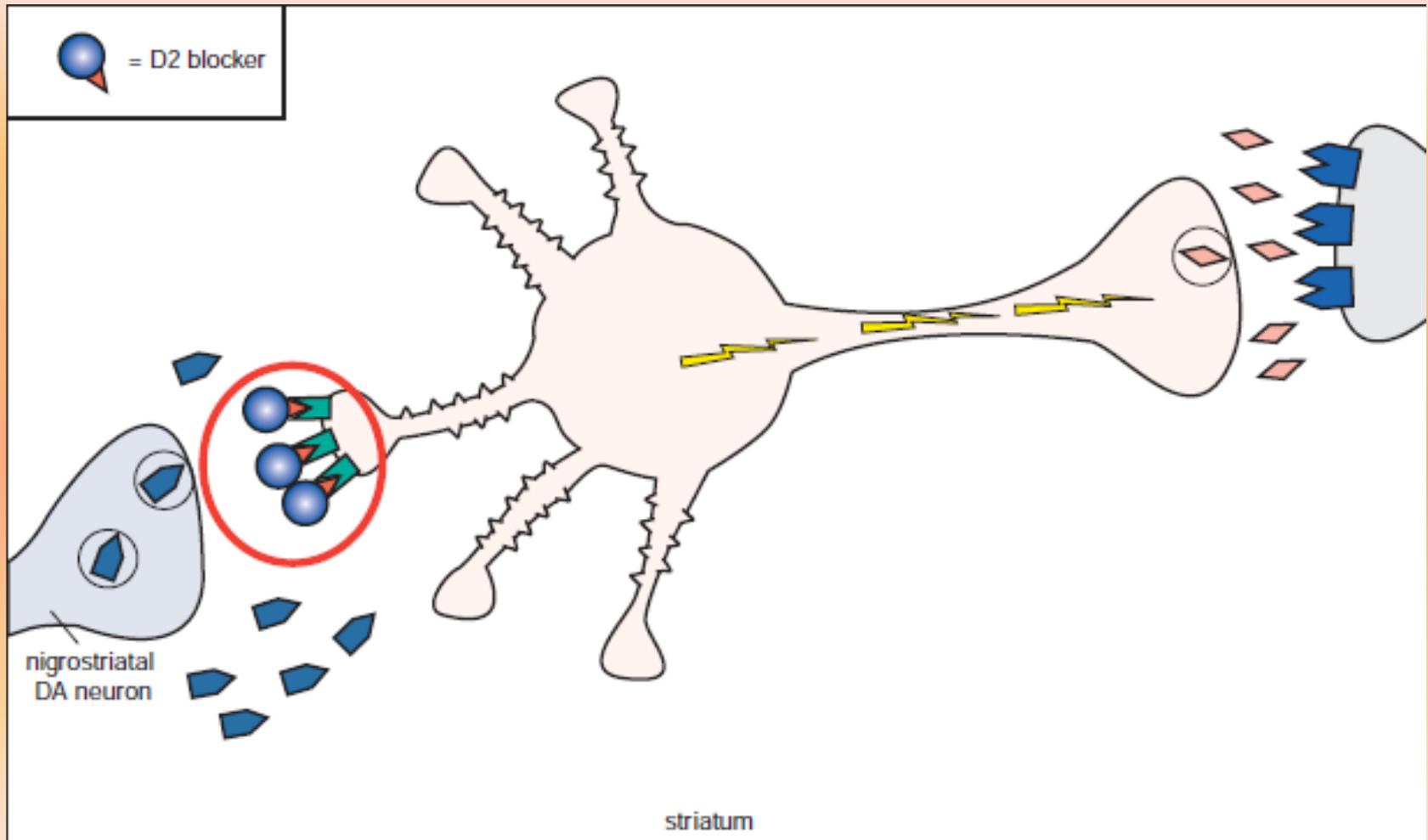
Various Binding Properties of Conventional Antipsychotics



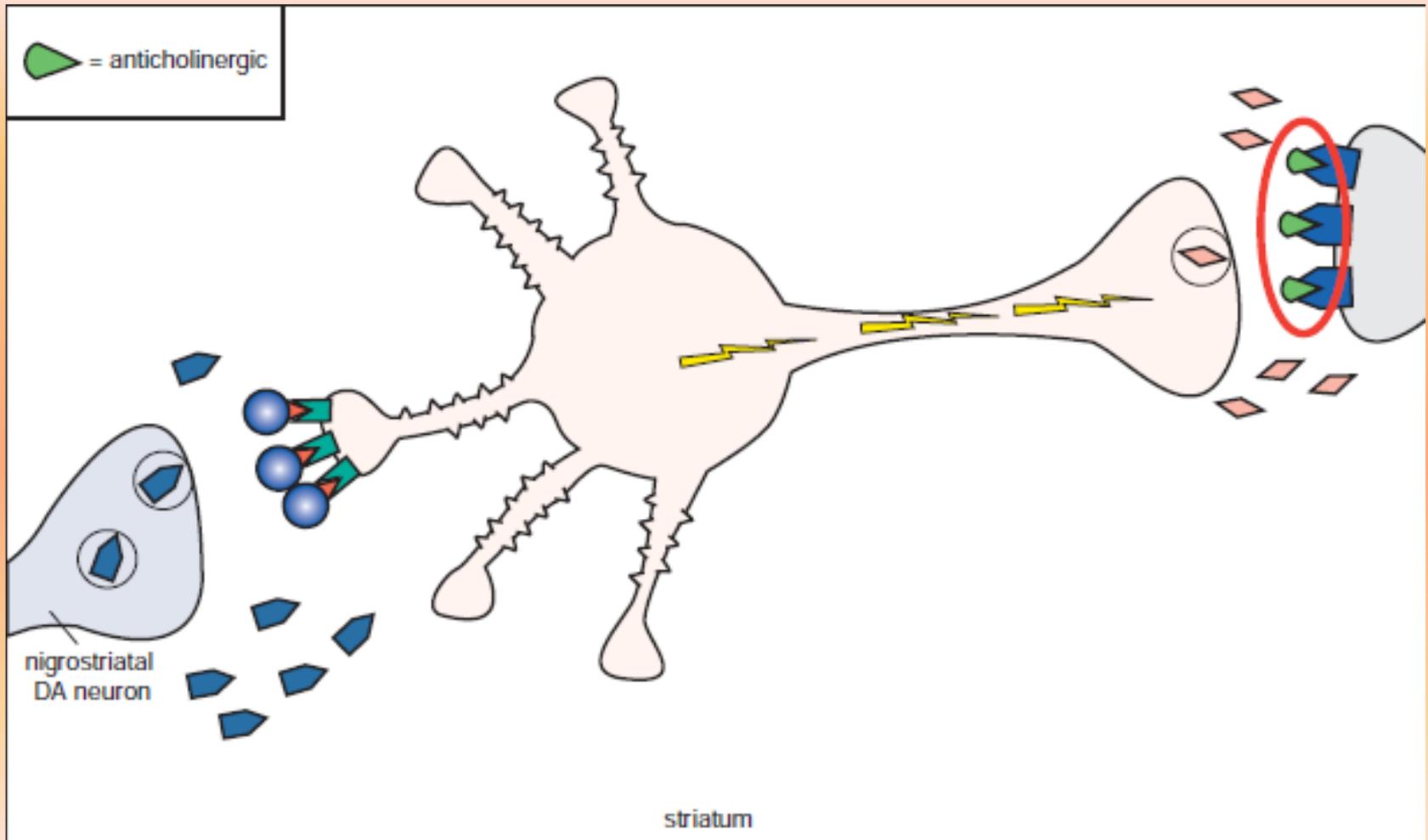
Interacción dopamina-acetilcolina (vía nigroestriada)



Hiperactividad colinérgica

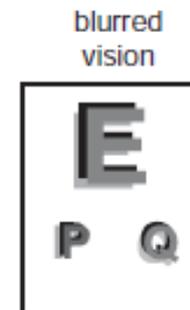
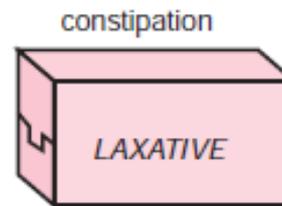
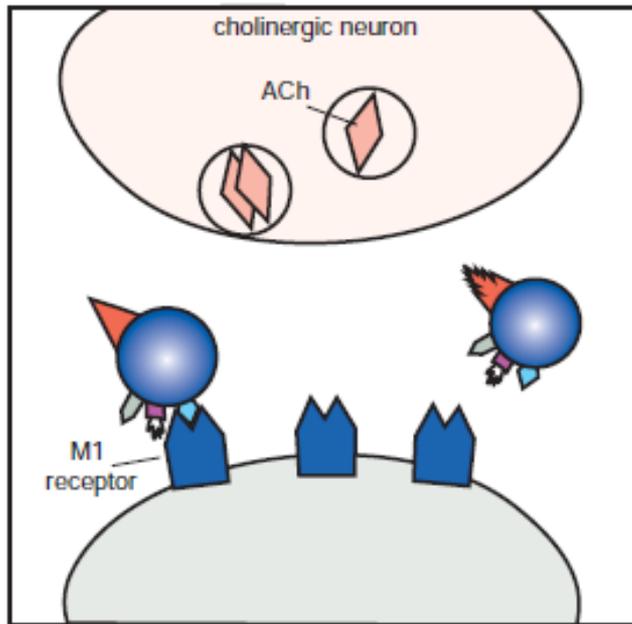


Antagonismo M₁ mejora SEP



Efectos secundarios

M1 Inserted

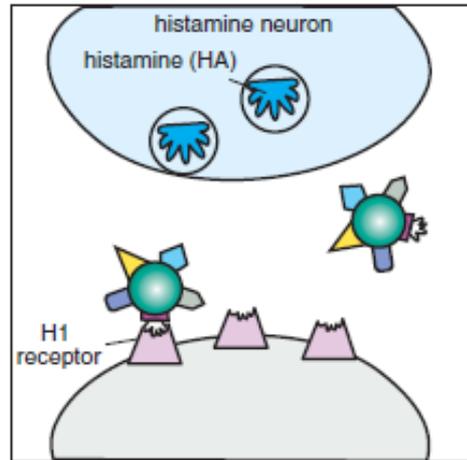


dry mouth

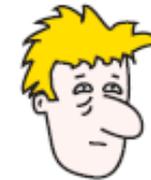
drowsiness

Efectos secundarios

H1 Inserted

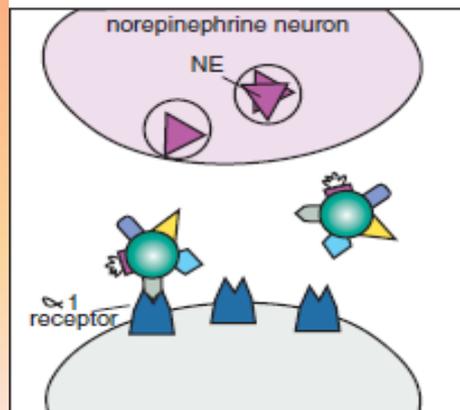


weight gain



drowsiness

α_1 Inserted



dizziness



decreased
blood pressure

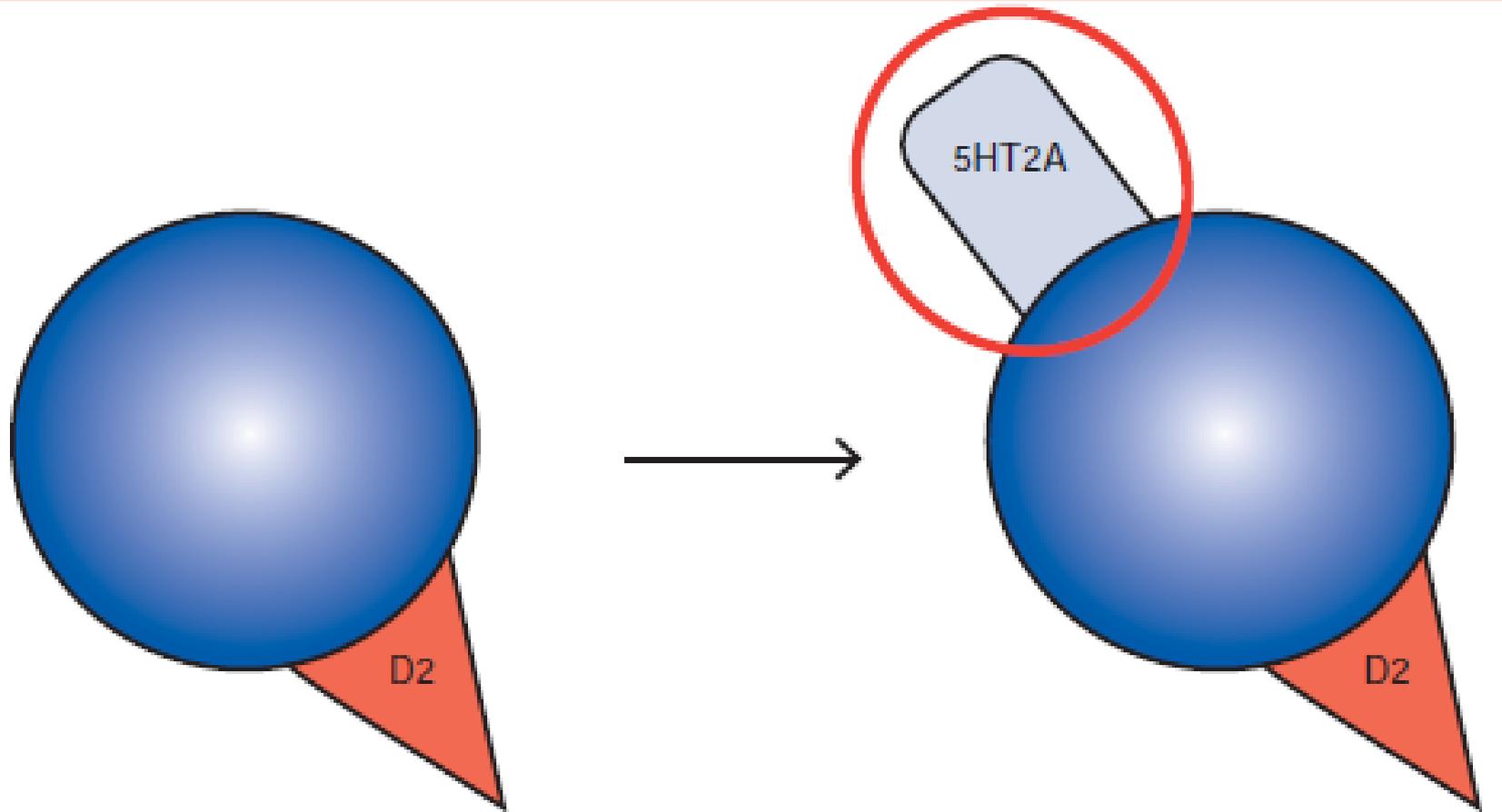


drowsiness

Antagonistas D₂

- Clorpromacina: Sedación. Trata agitación
- Flufenacina: Más potente y menos sedante
- Haloperidol: Potente y menos sedante
- Sulpirida: Mejor tolerada
- Amisulpirida: + selec D₂ mesolim q nigroest.
Débil 5HT₇ = antidep y ok sínt neg a dosis bajas

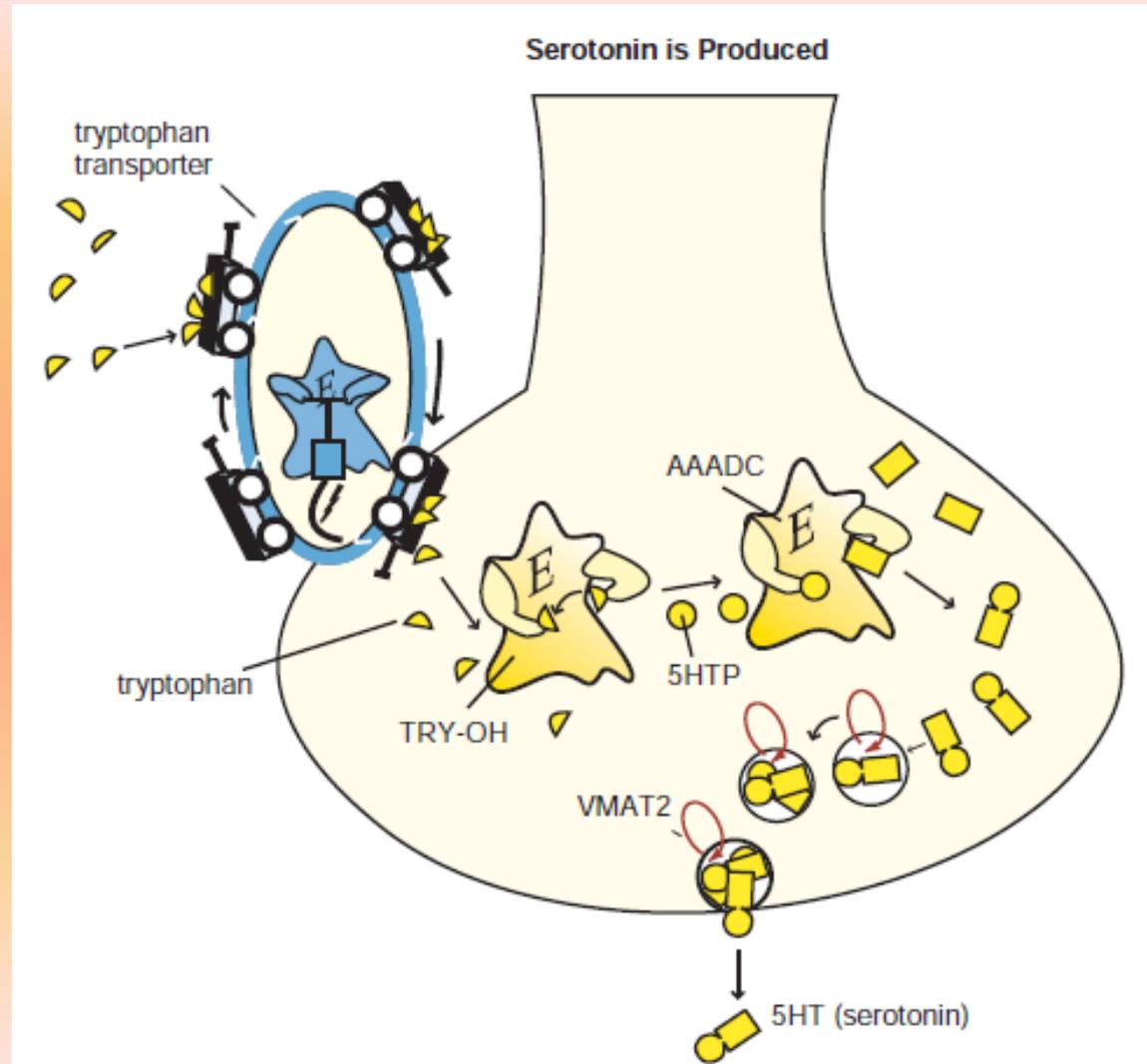
Antipsicóticos atípicos



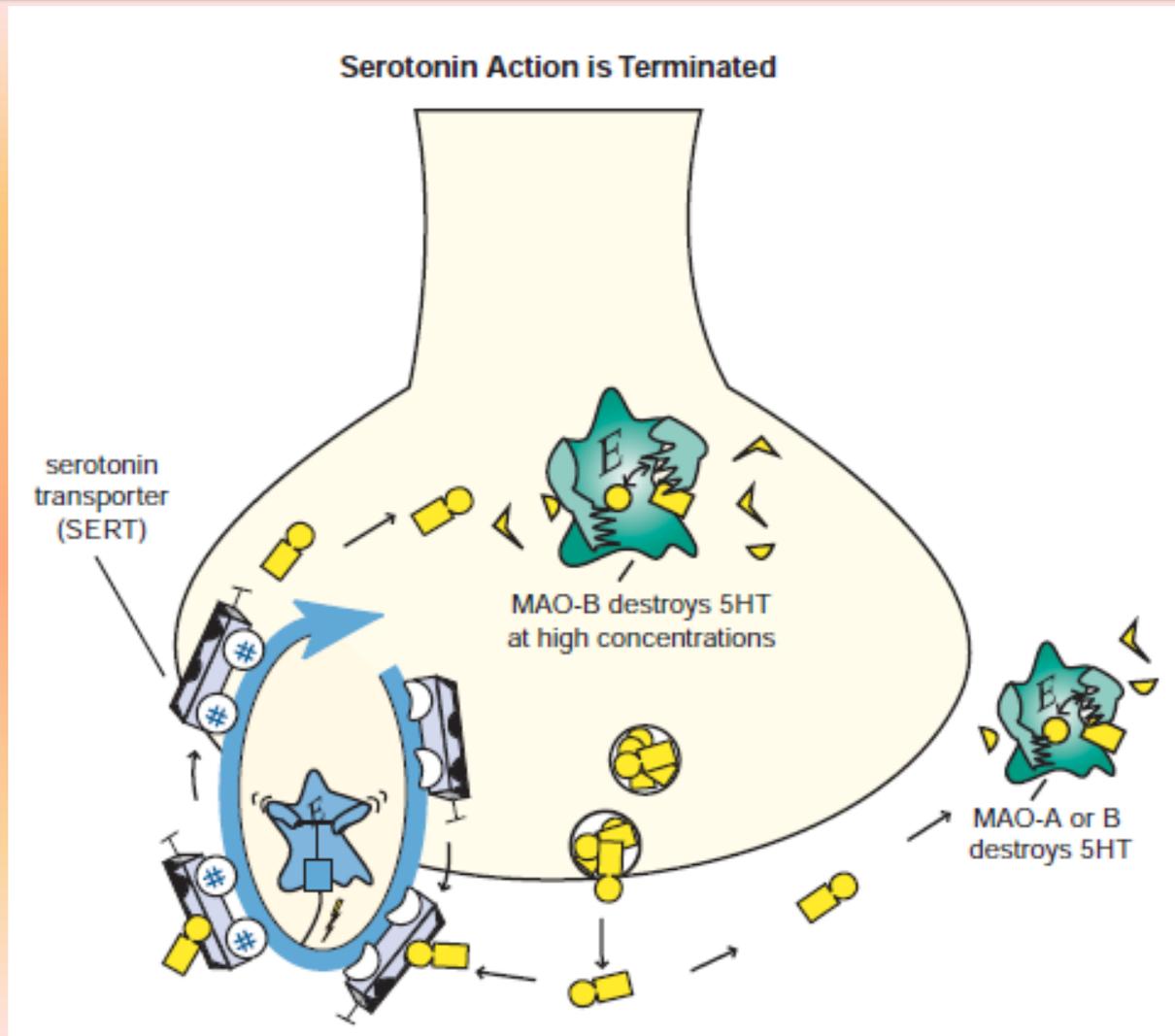
conventional antipsychotic

atypical antipsychotic

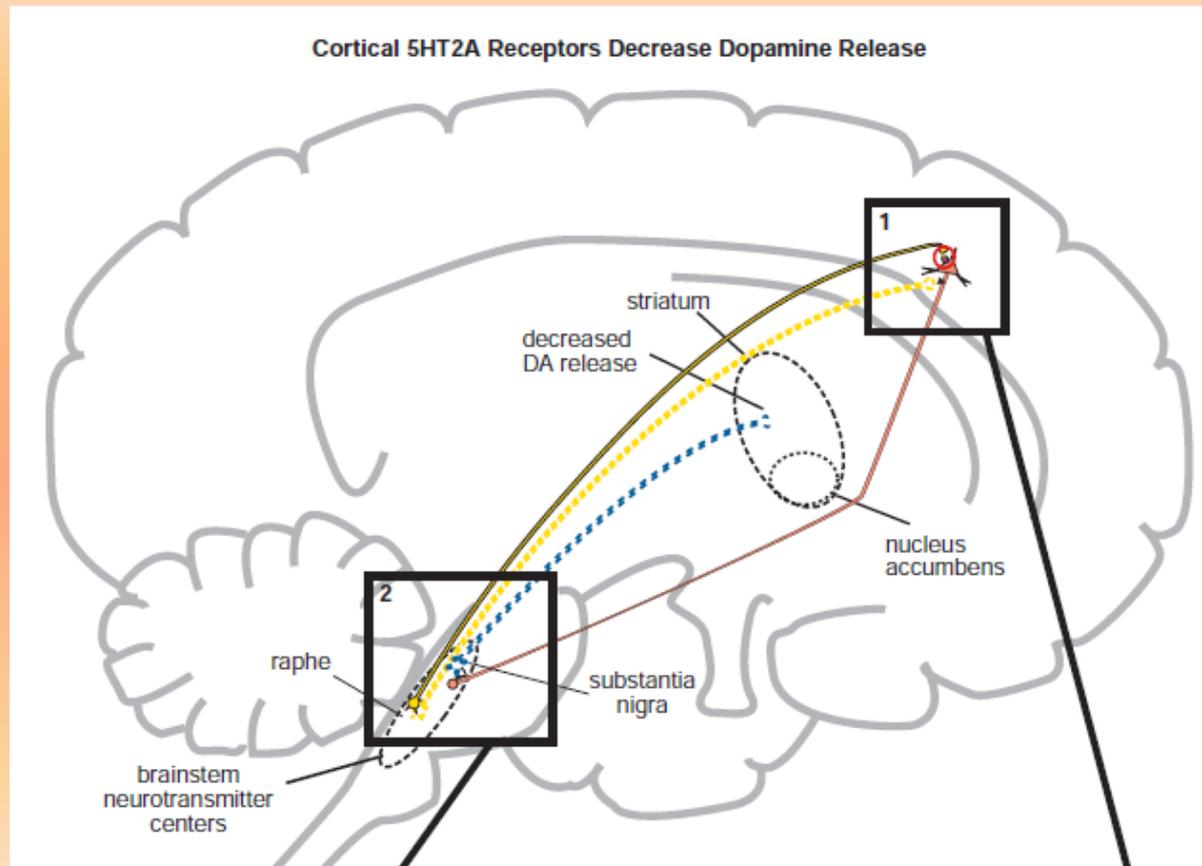
Síntesis de serotonina



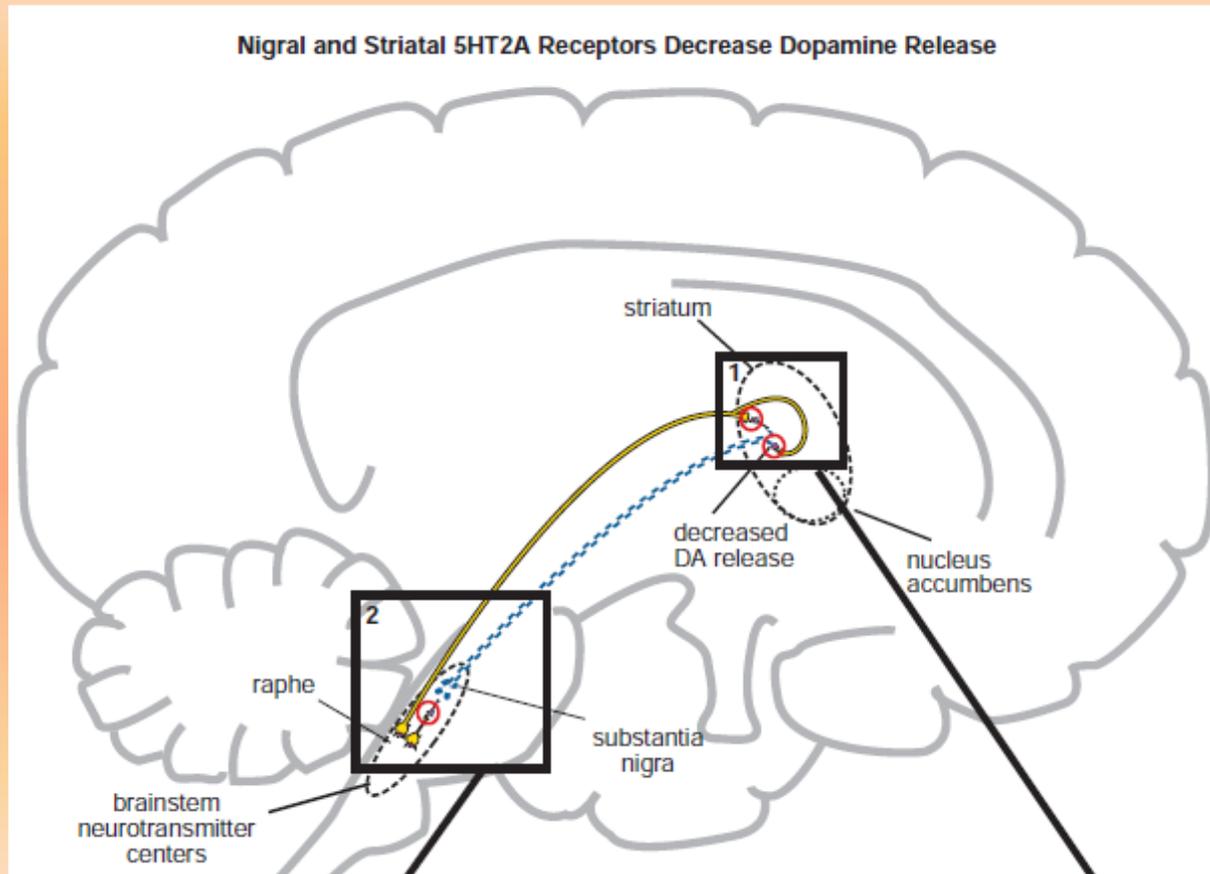
Degradación de serotonina



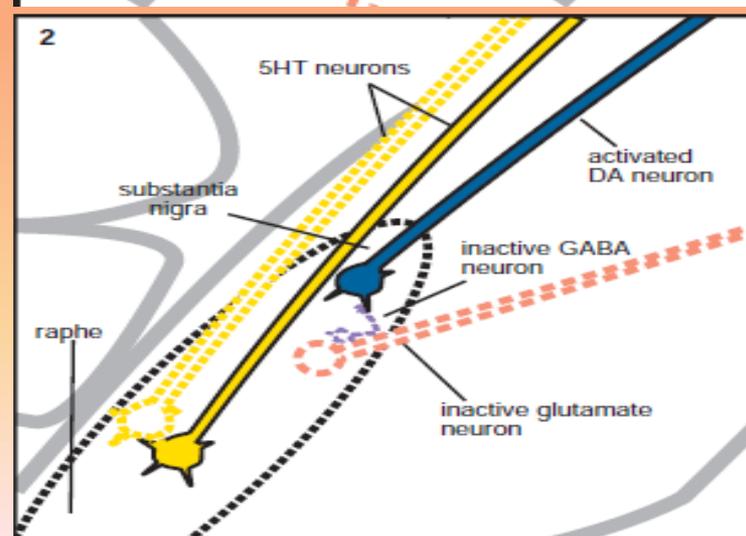
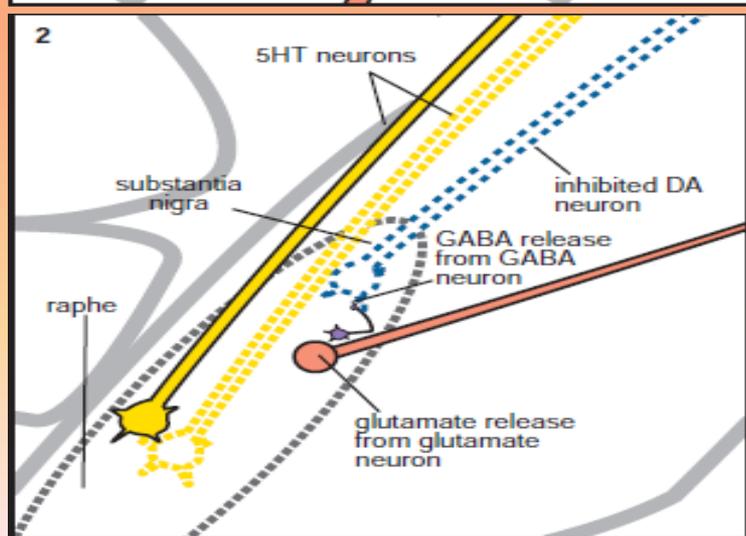
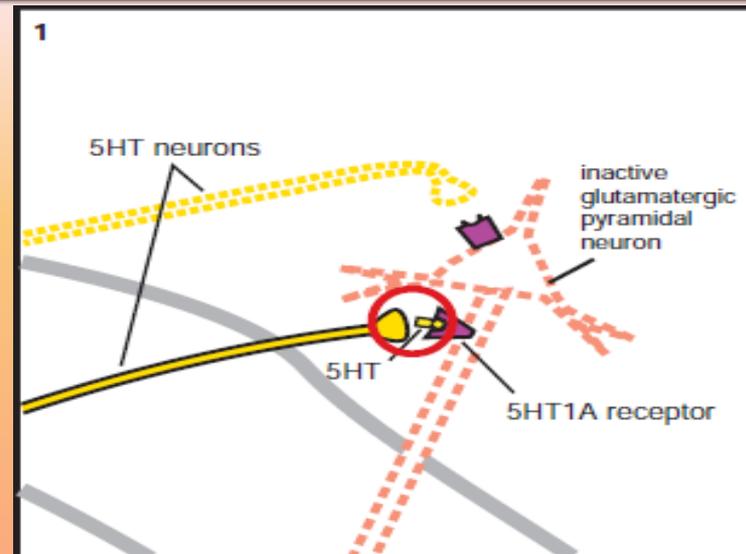
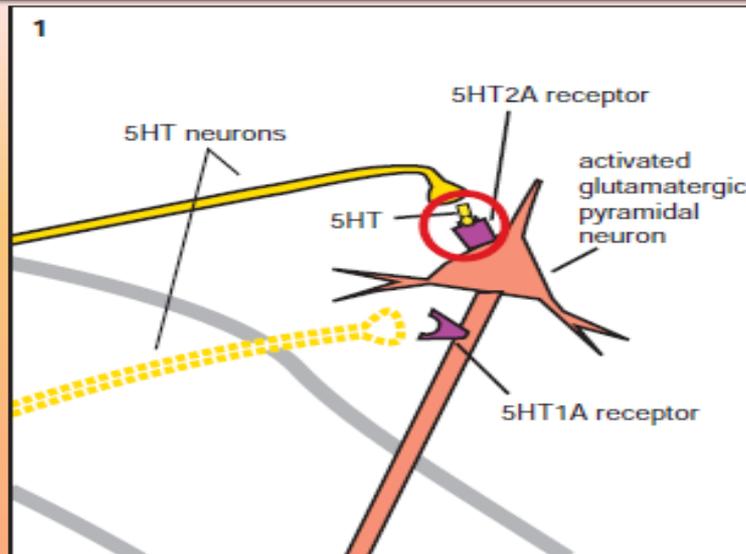
Influencia de la serotonina en la vía nigroestriada



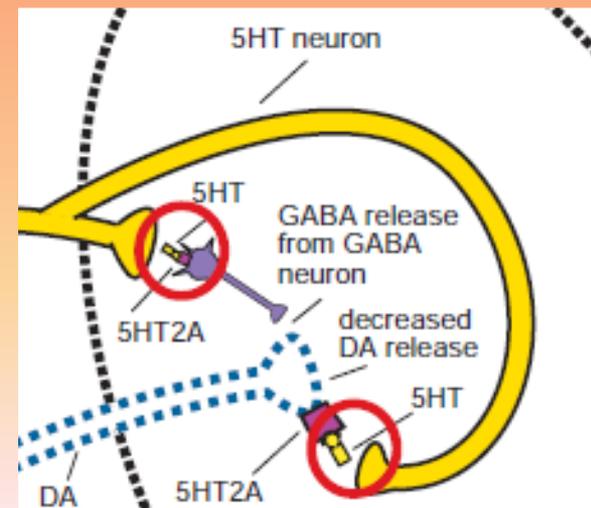
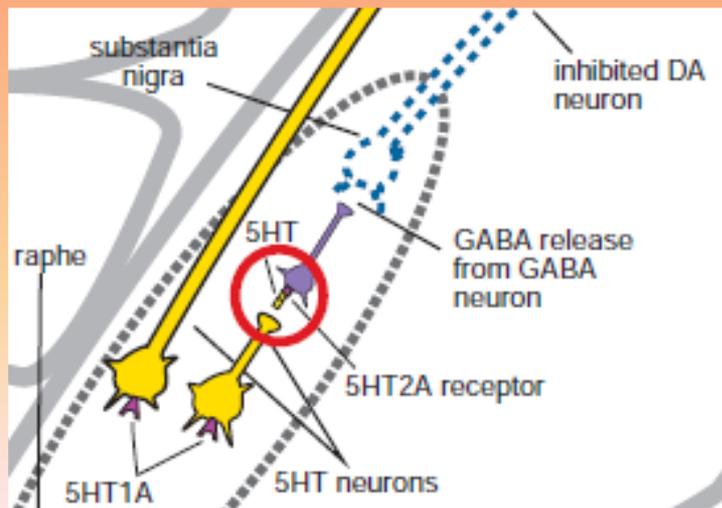
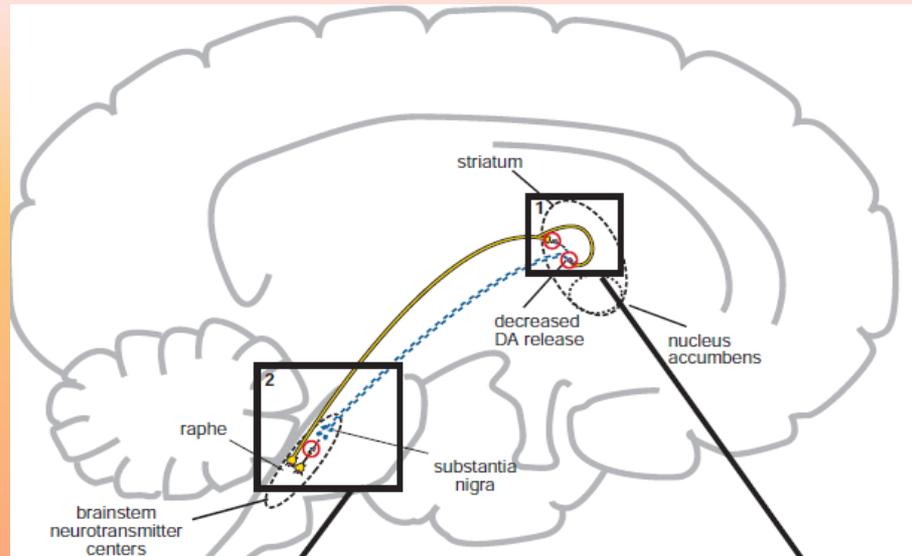
Influencia de la serotonina en la vía nigroestriada



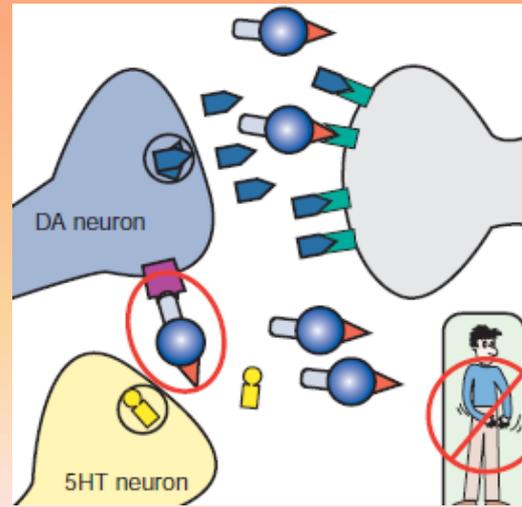
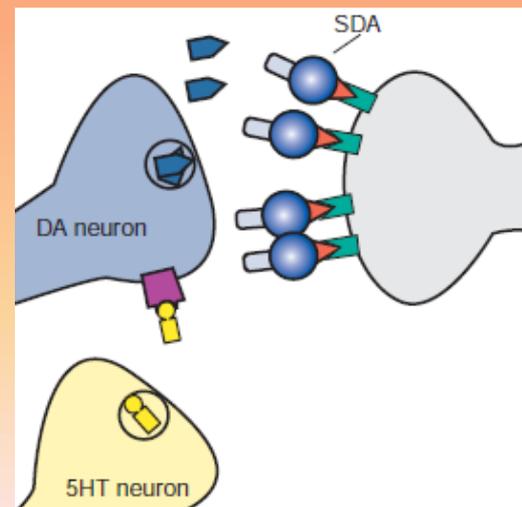
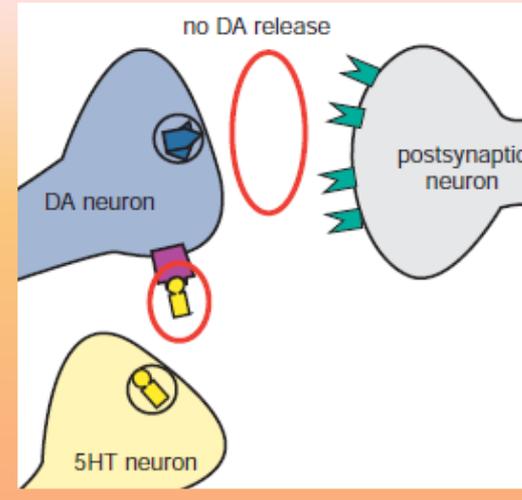
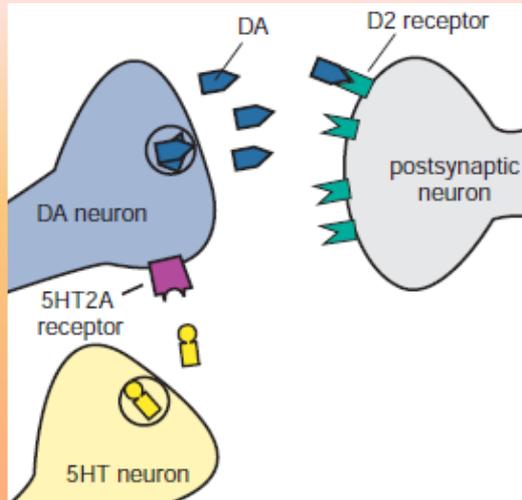
Receptores de serotonina en neuronas glutamatérgicas



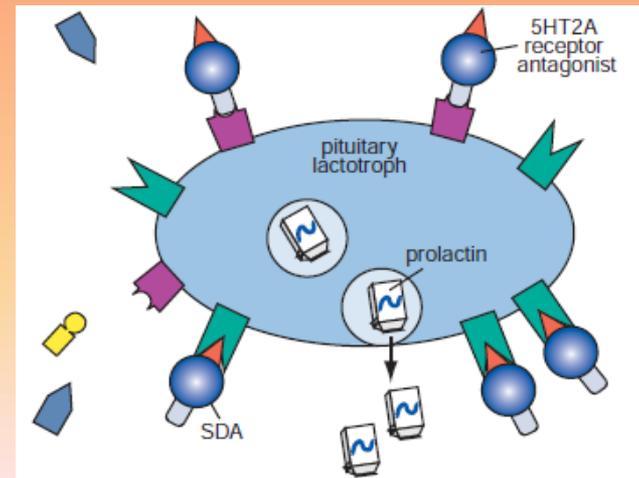
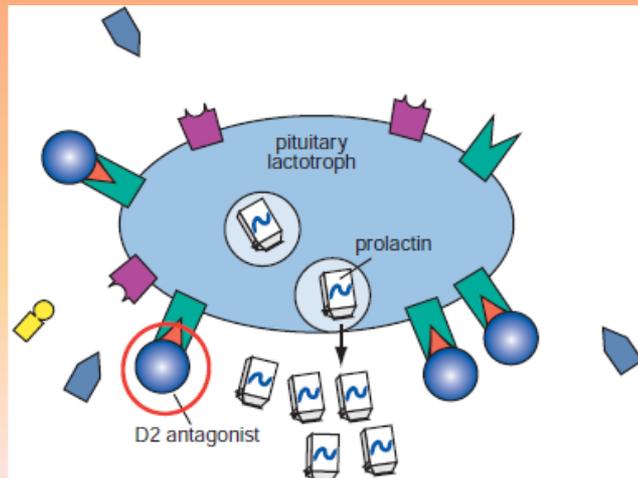
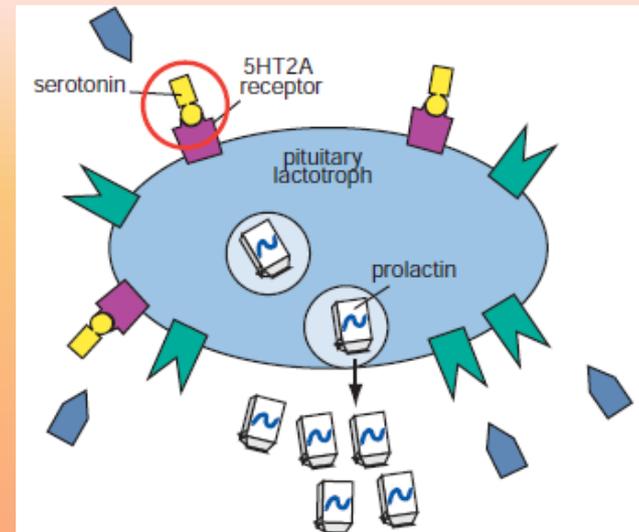
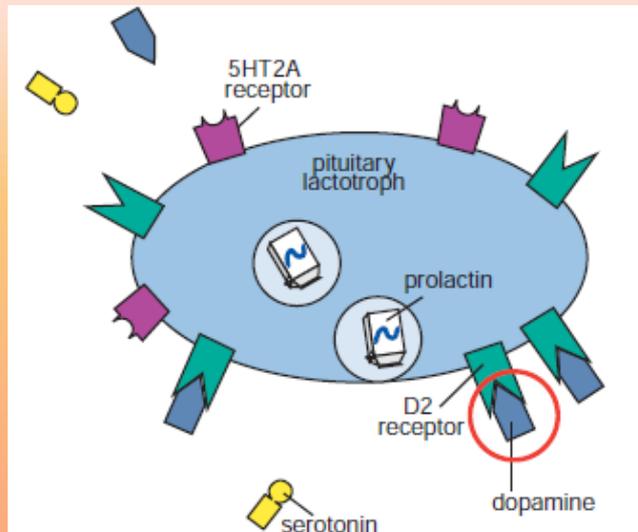
Receptores de serotonina en neuronas GABAérgicas, serotoninérgicas y dopaminérgicas



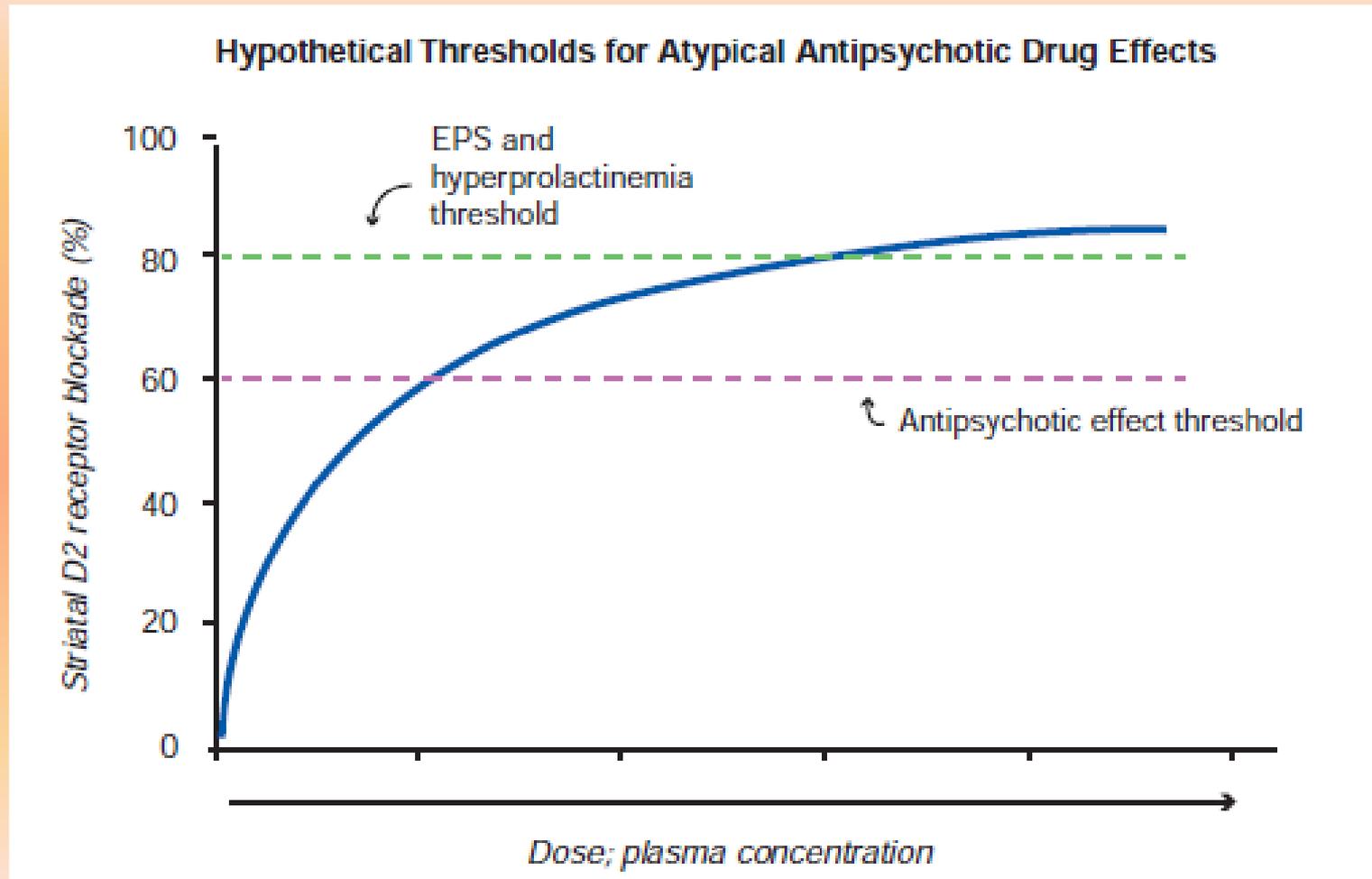
Efecto neto en la vía nigroestriada



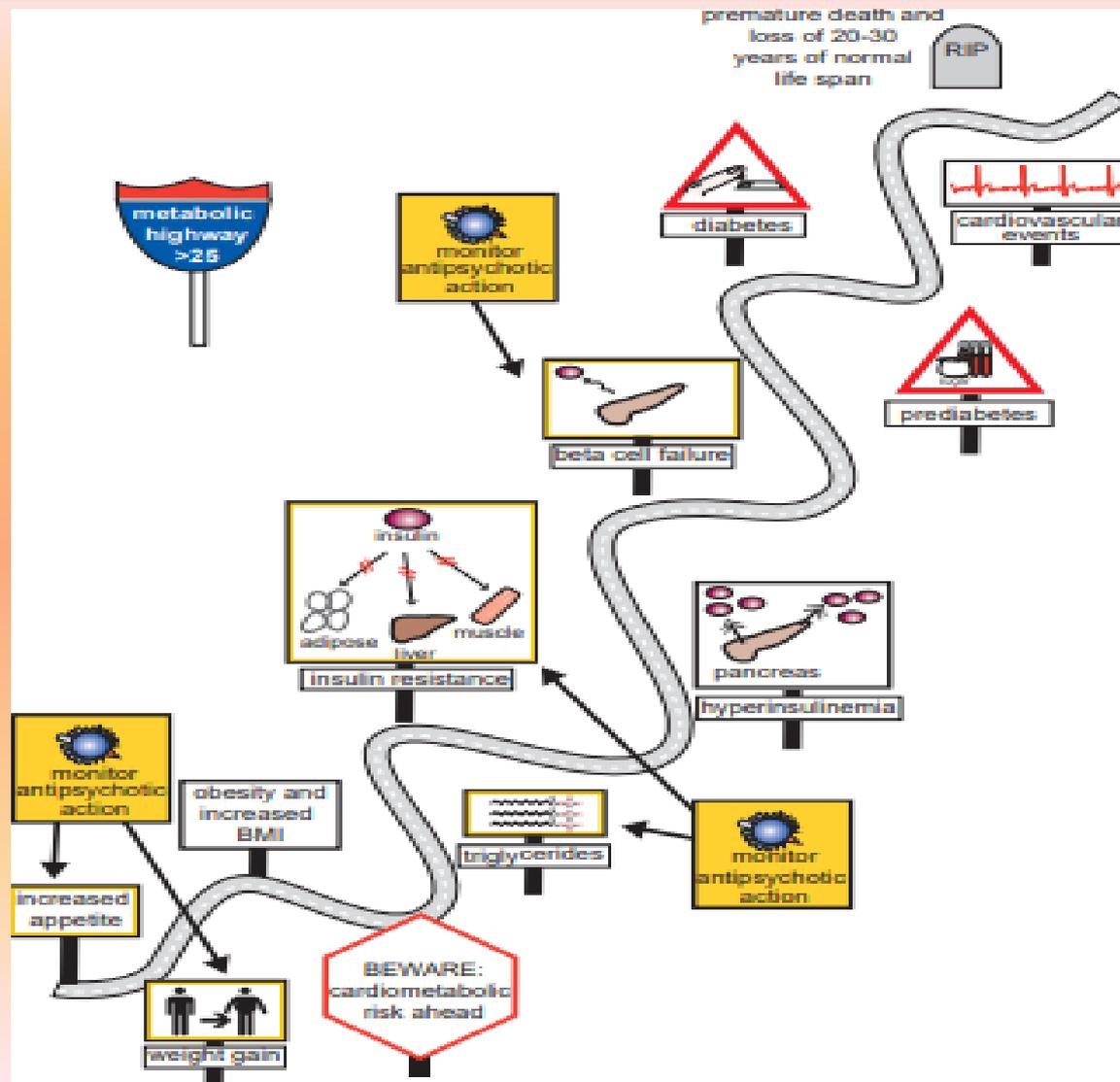
Efecto en células lactótropas



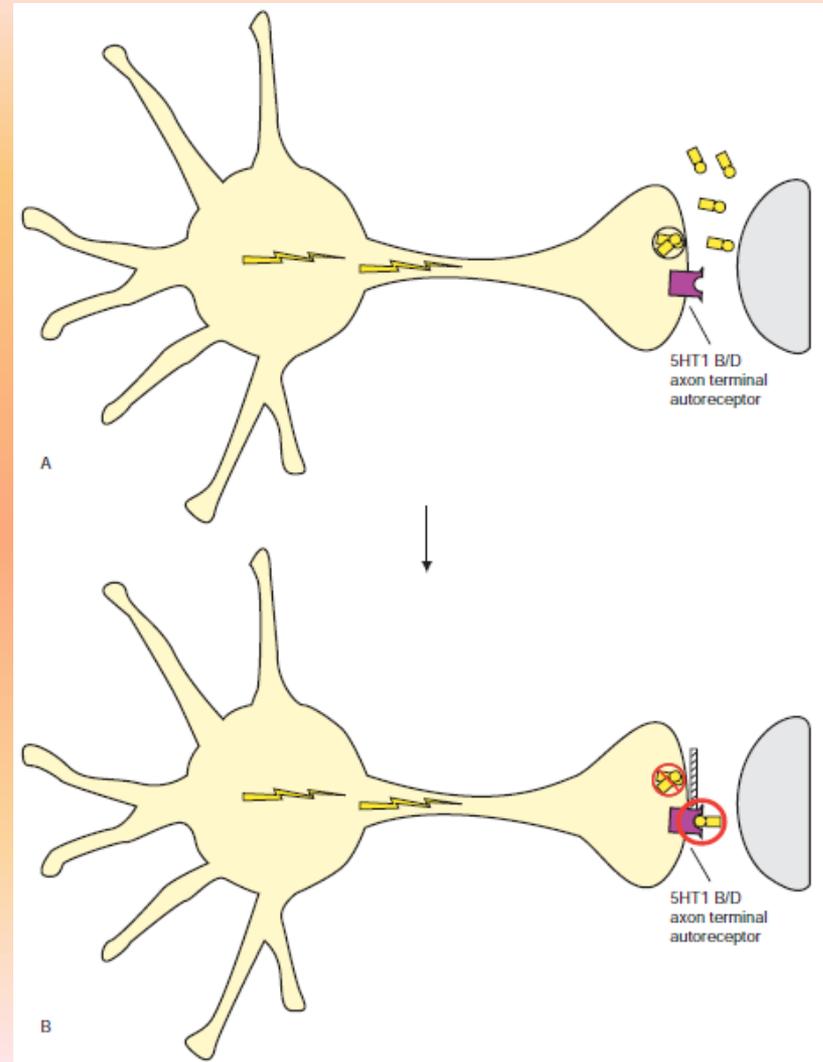
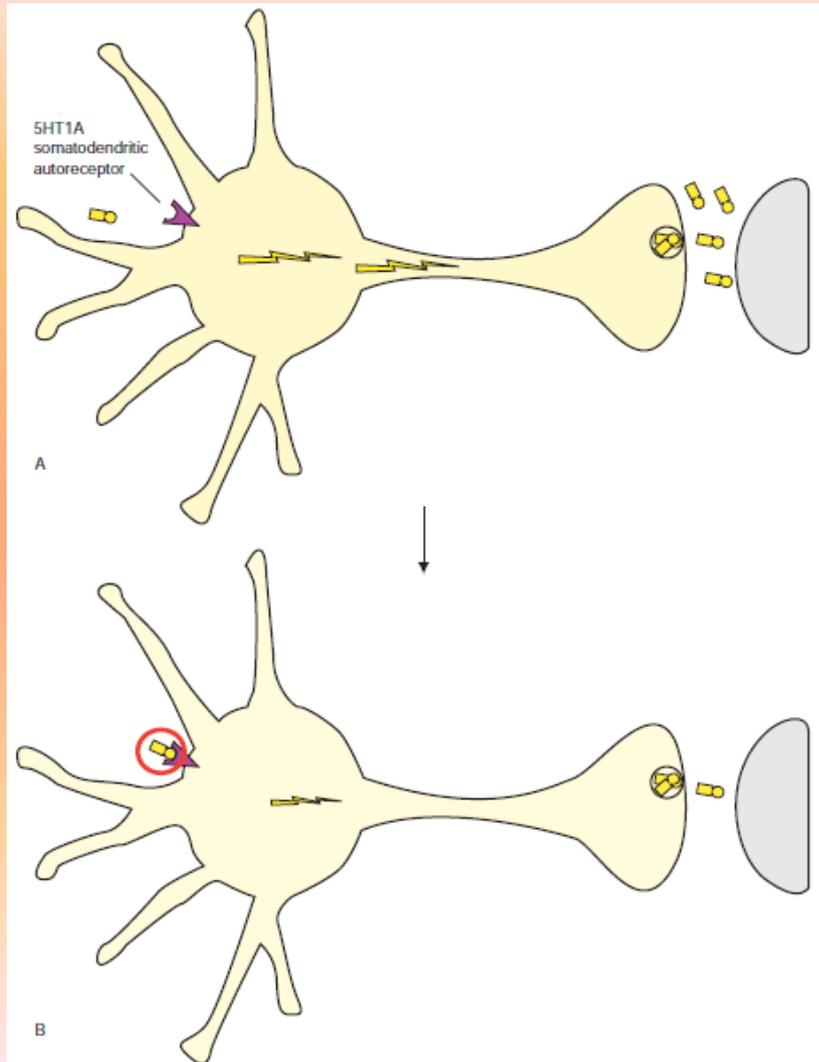
Ampliación de la ventana terapéutica



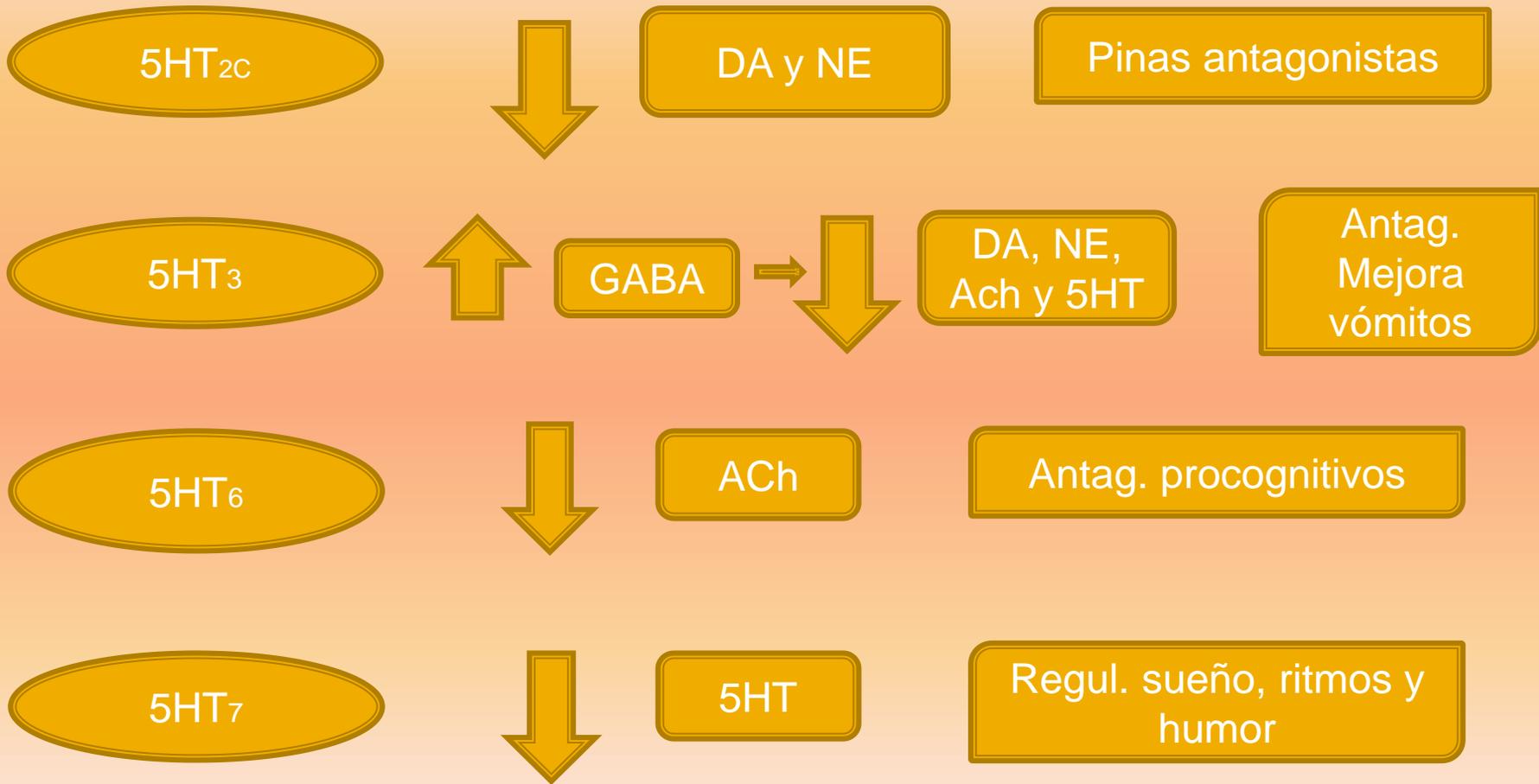
Autopista metabólica



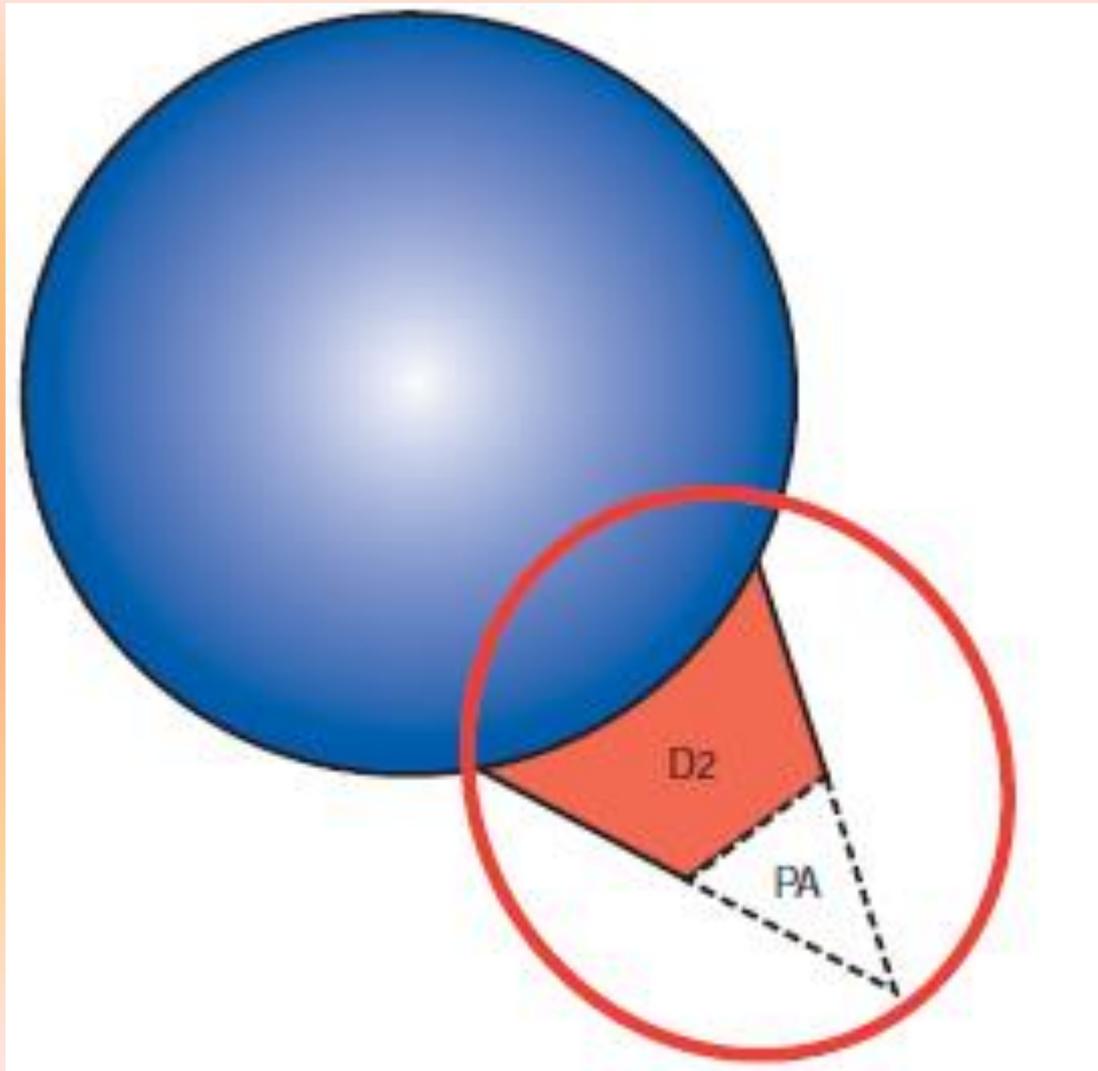
Autorreceptores serotoninérgicos



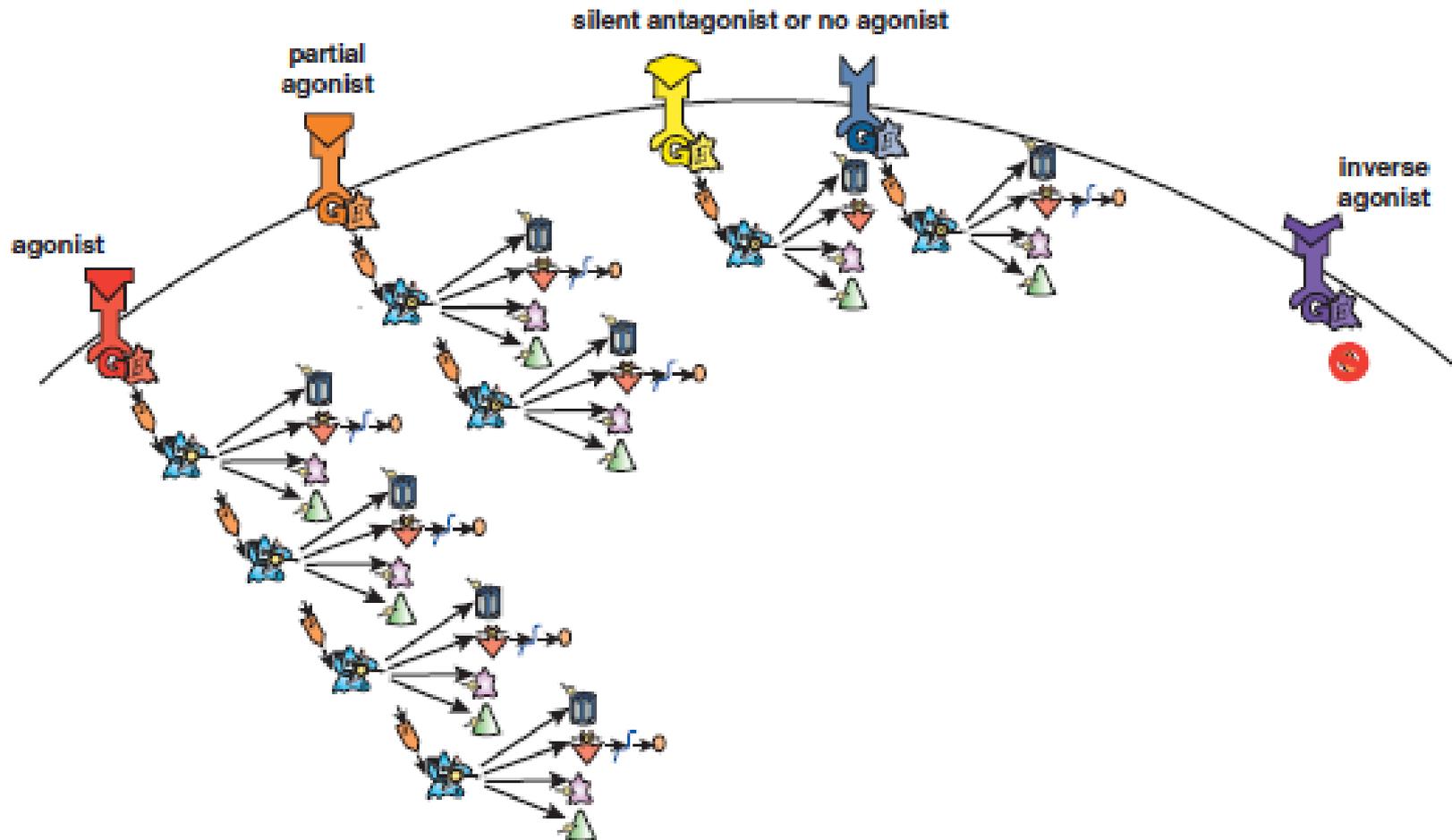
Otros receptores 5HT



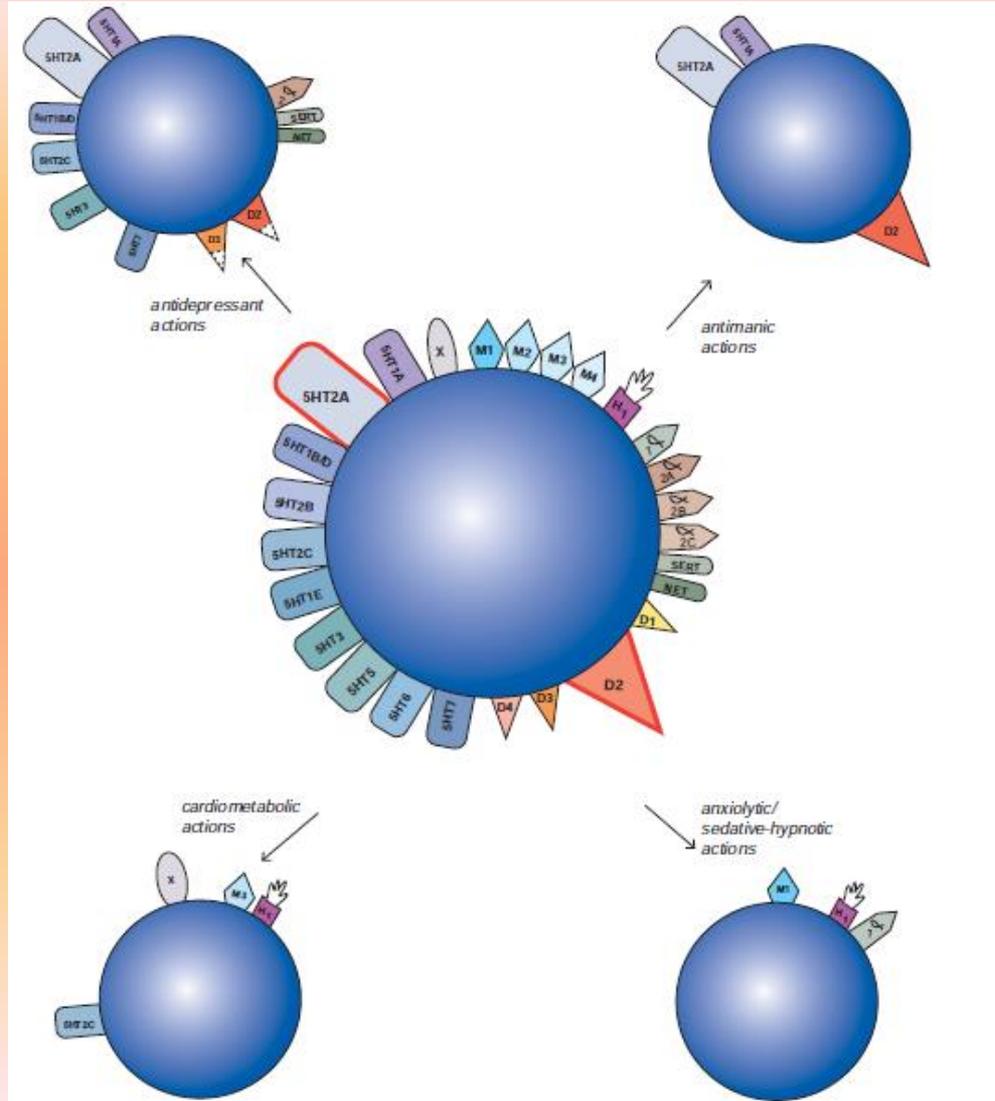
Otra posibilidad de antipsicótico atípico: agonista parcial D₂



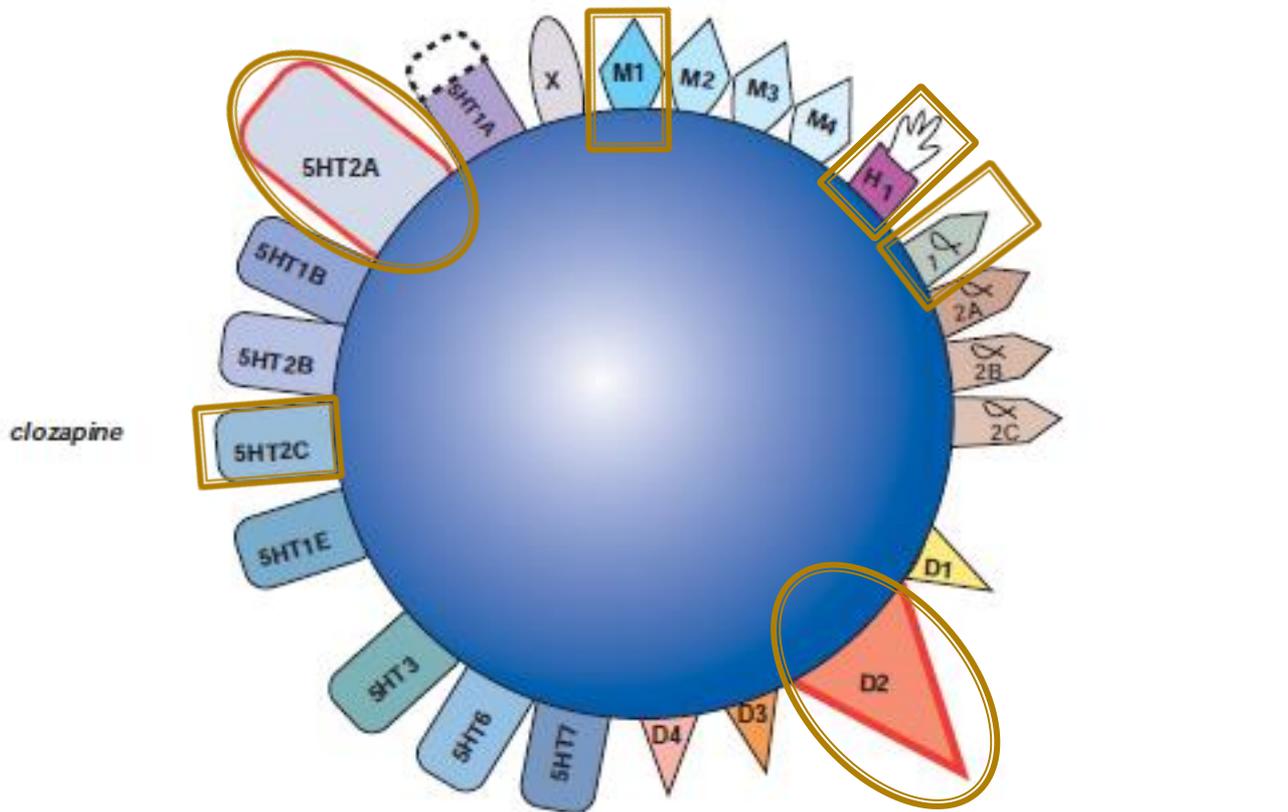
Espectro agonista



Acciones clínicas



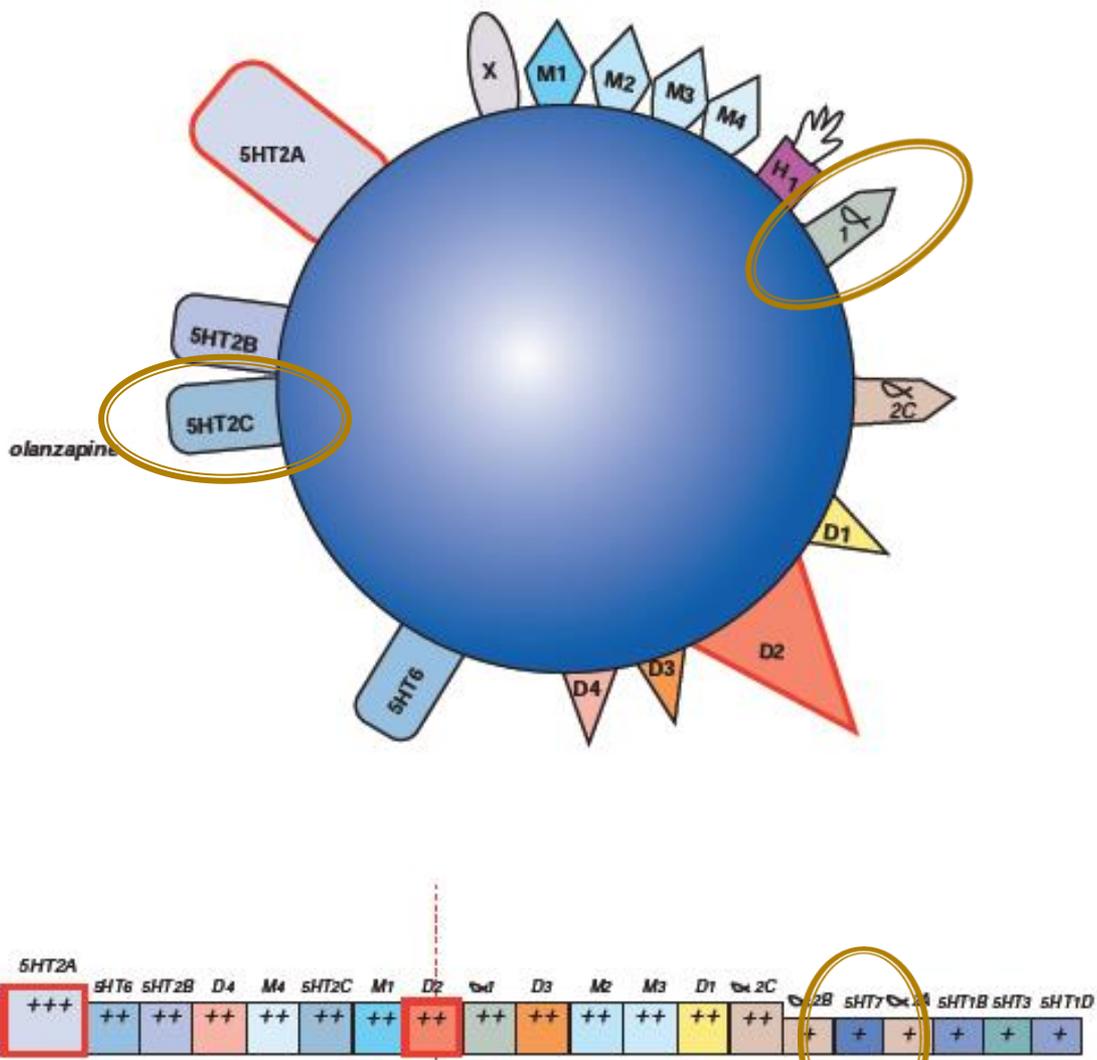
Antipsicóticos atípicos: las pinas



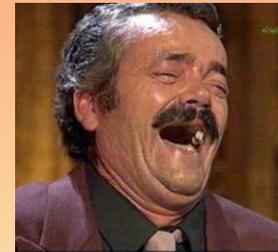
Agranulocitosis
convulsiones
exceso de saliva
miocarditis
ganancia peso
sedación

H1	α 1	5HT2B	M1	5HT2A	5HT6	5HT2C	α 2C	M4	α 2B	D4	5HT7	M3	α 2A	M2	5HT1A	5HT3	DP	D3	D1	5HT1B	5HT1E
+++	+++	+++	+++	++	++	++	++	++	++	++	++	++	++	++	+	+	+	+	+	+	+

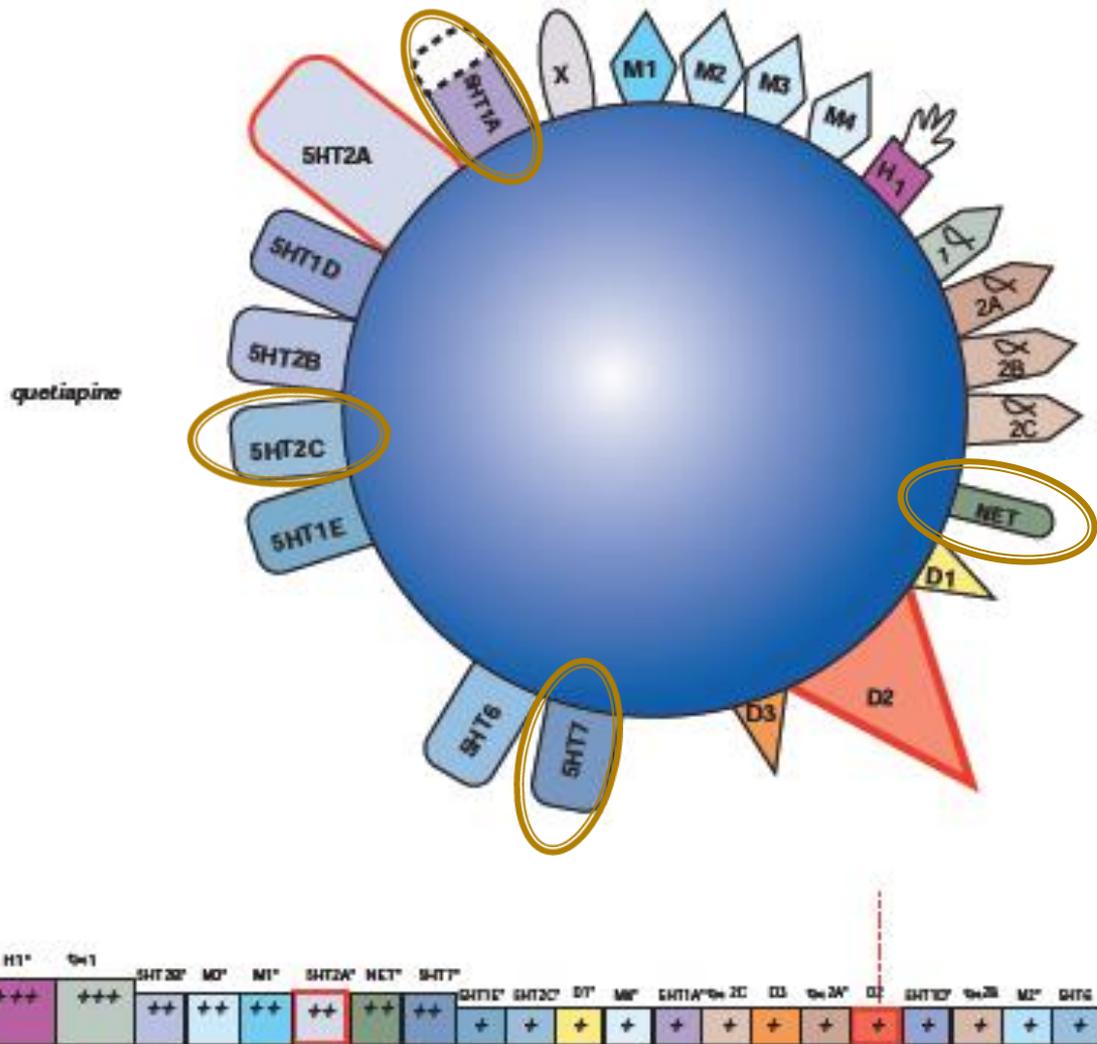
Antipsicóticos atípicos: las pinas



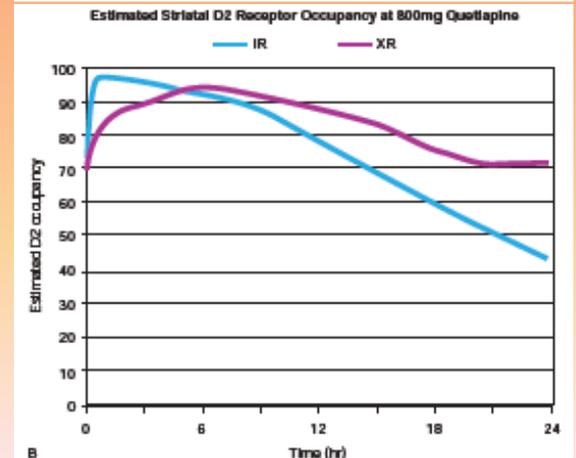
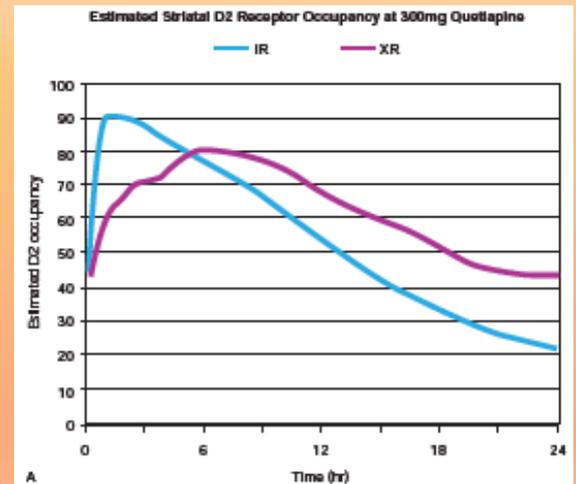
Sedación (- clo)
Ganancia de peso
Riesgo cardiometabólico



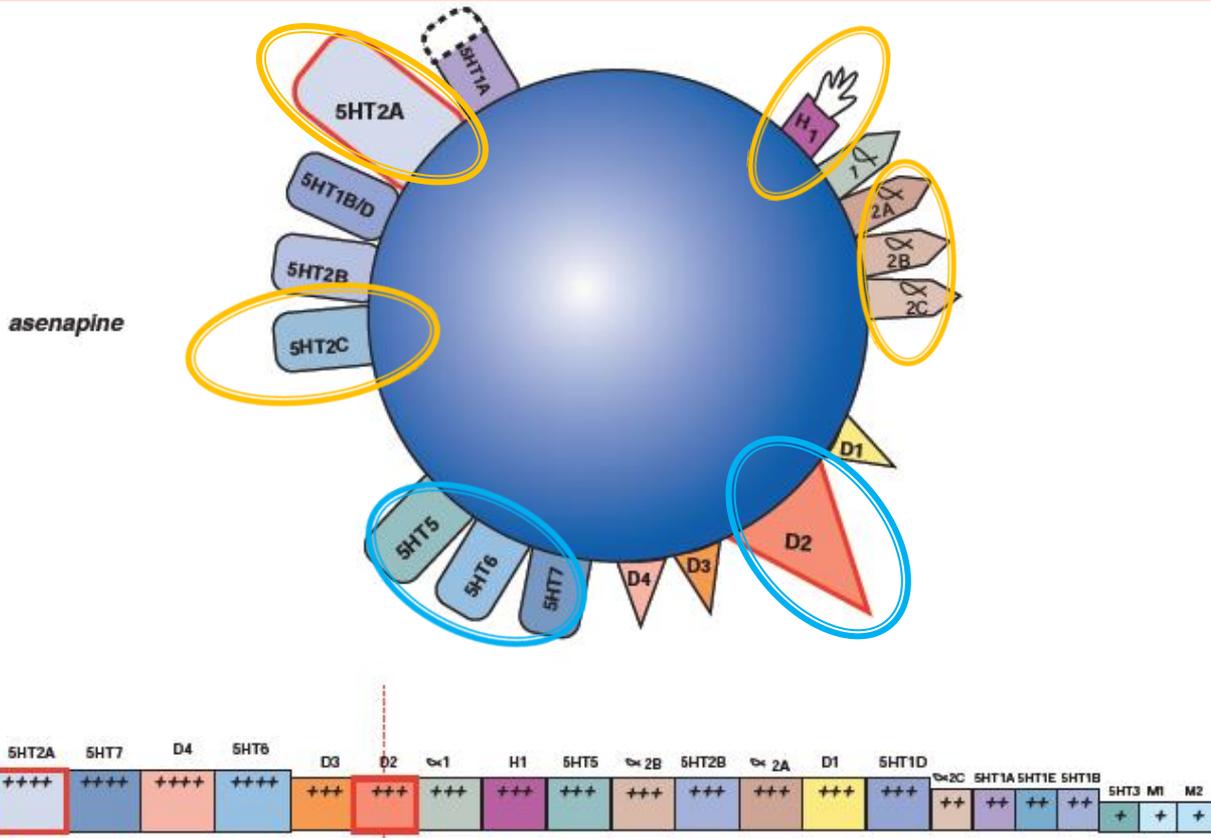
Antipsicóticos atípicos: las pinas



Metabolito norquetiapina



Antipsicóticos atípicos: las pinas

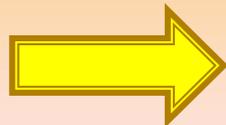


= Mirtazapina:

≠ Mirtazapina

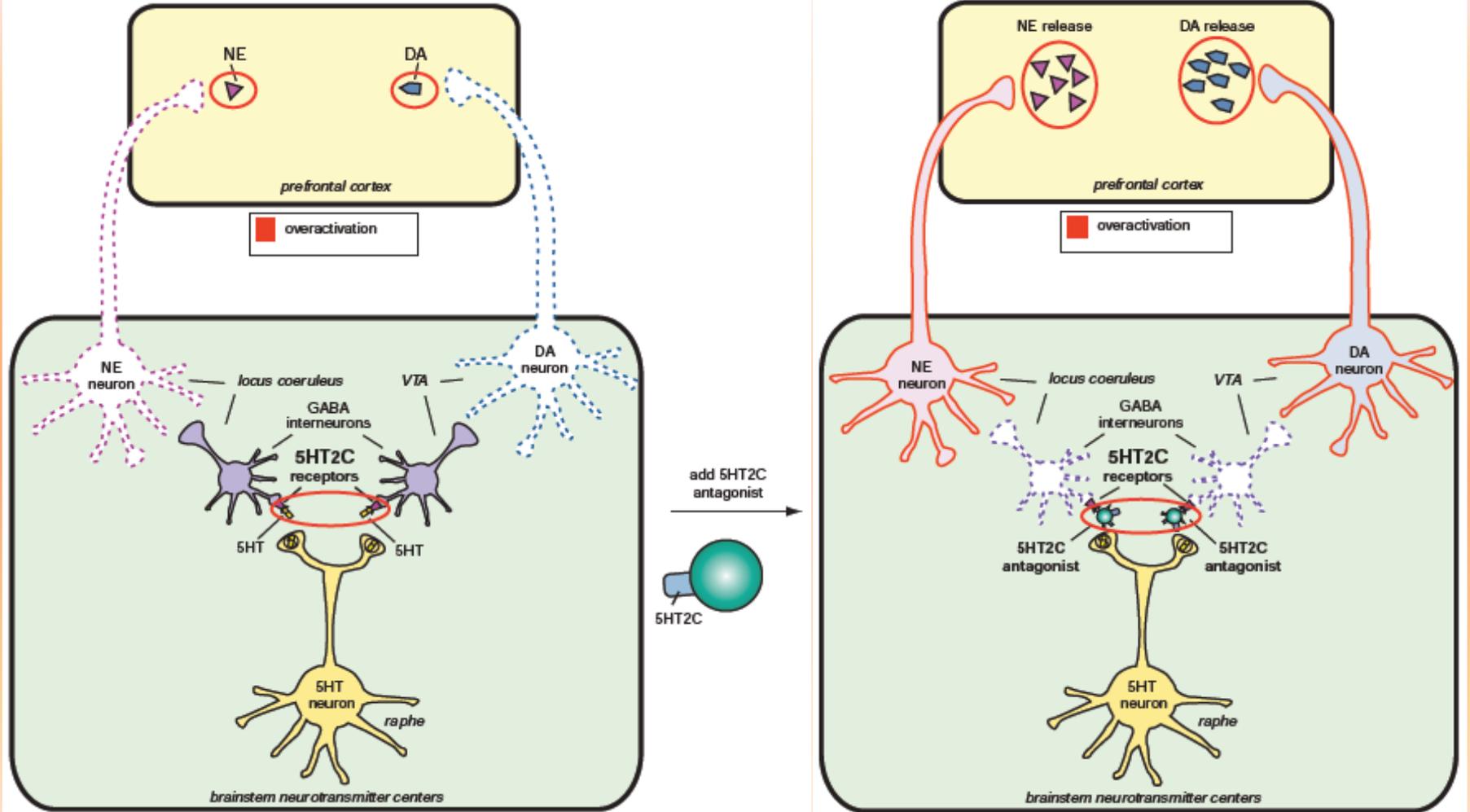


Teórico antipsicótico y antidepresivo

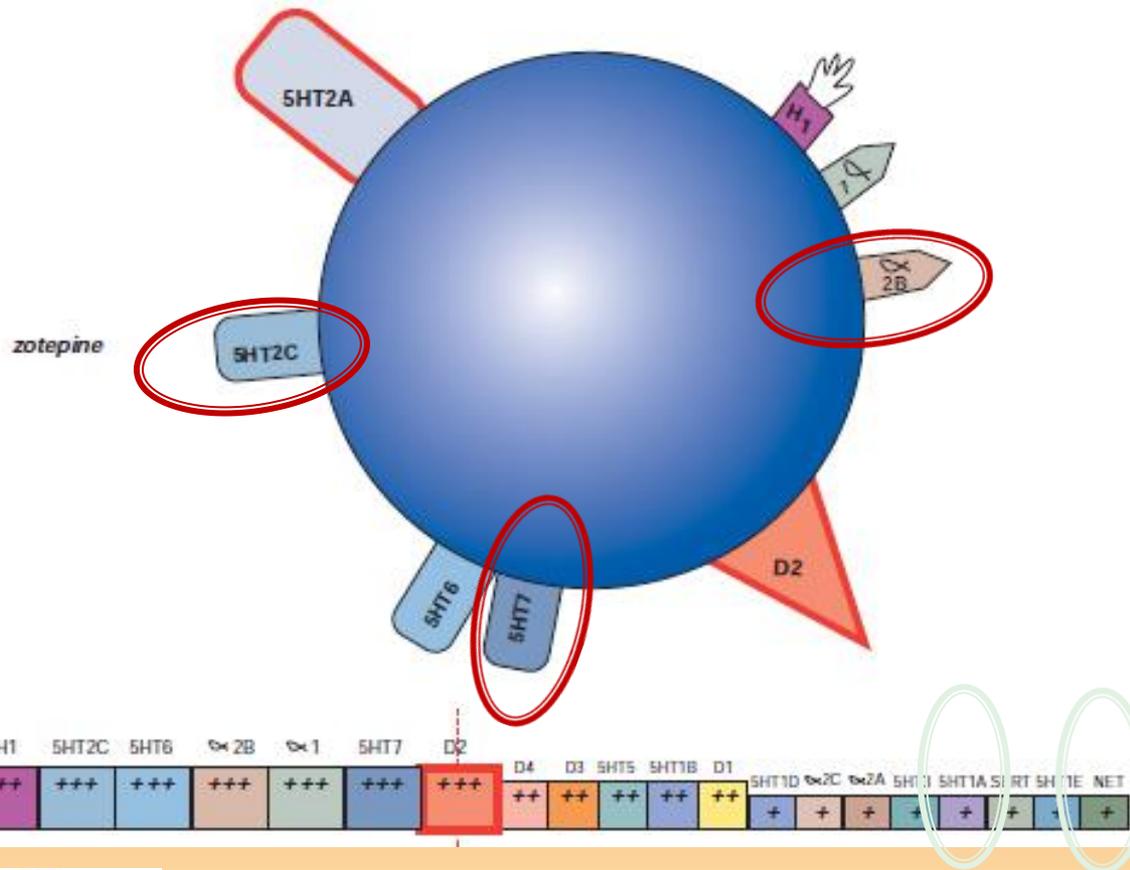


2 tomas diarias / uso antips. de acción rápida / hipoestesia oral / no comer ni beber hasta 10' después

Efectos del antagonismo 5HT2C



Antipsicóticos atípicos: las pinas



Fuerte

Débil

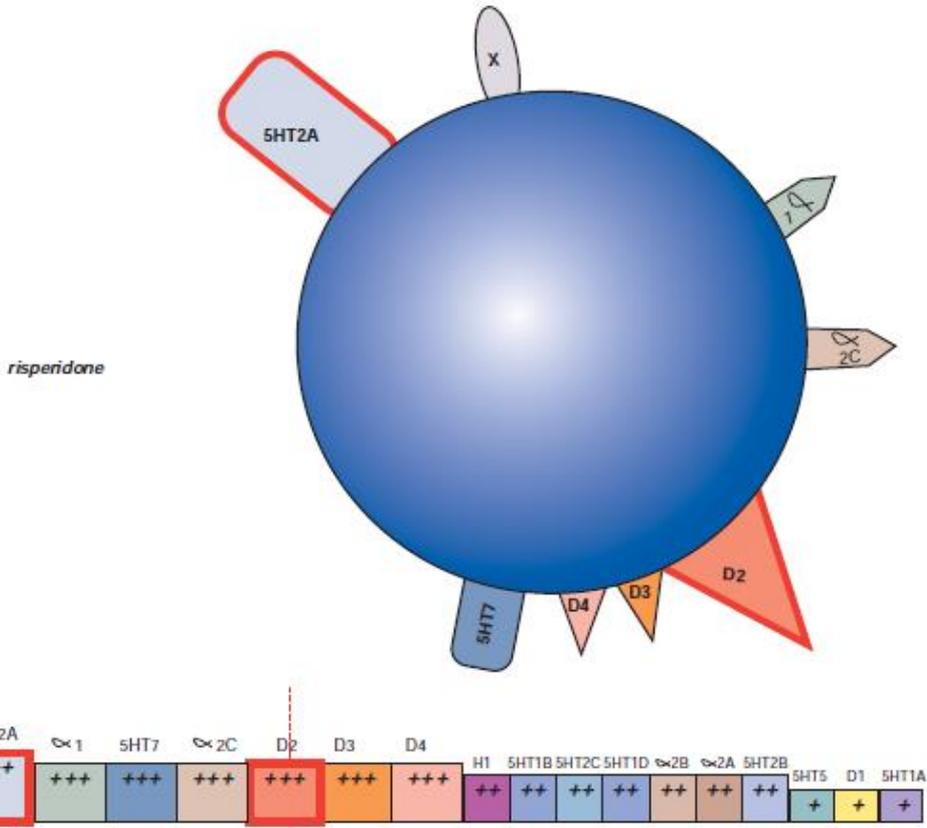
Sí en Japón y Europa

No en EE.UU.



Riesgo SEP / Elevación prolactina / Convulsiones / Aumento de peso y sedación

Antipsicóticos atípicos: las donas



Atípico a dosis bajas
Convencional a dosis altas



Niños y adolescentes.
Irritabilidad en autistas

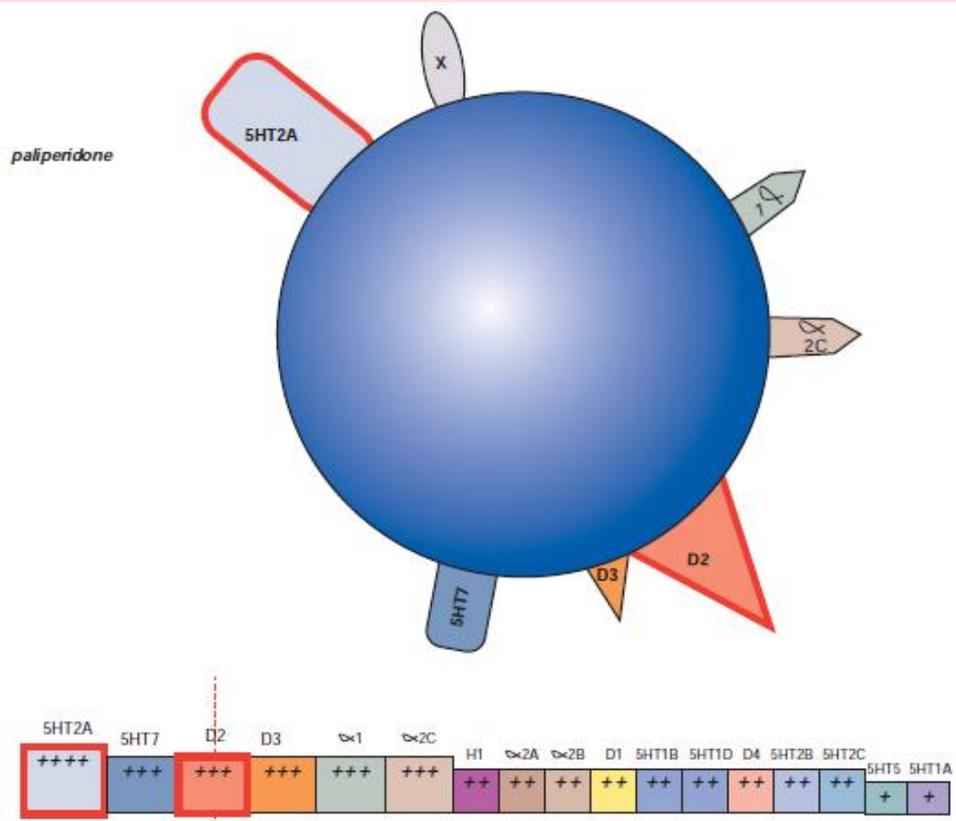


Depot 15 días
Comprimidos
líquido



Aumento peso
y prolac. Incluso
a dosis bajas

Antipsicóticos atípicos: las donas



Metabolito de Risperidona
Menos efectos secundarios
Mejor a dosis altas
Diferente farmacocinética
No metaboliza en el hígado



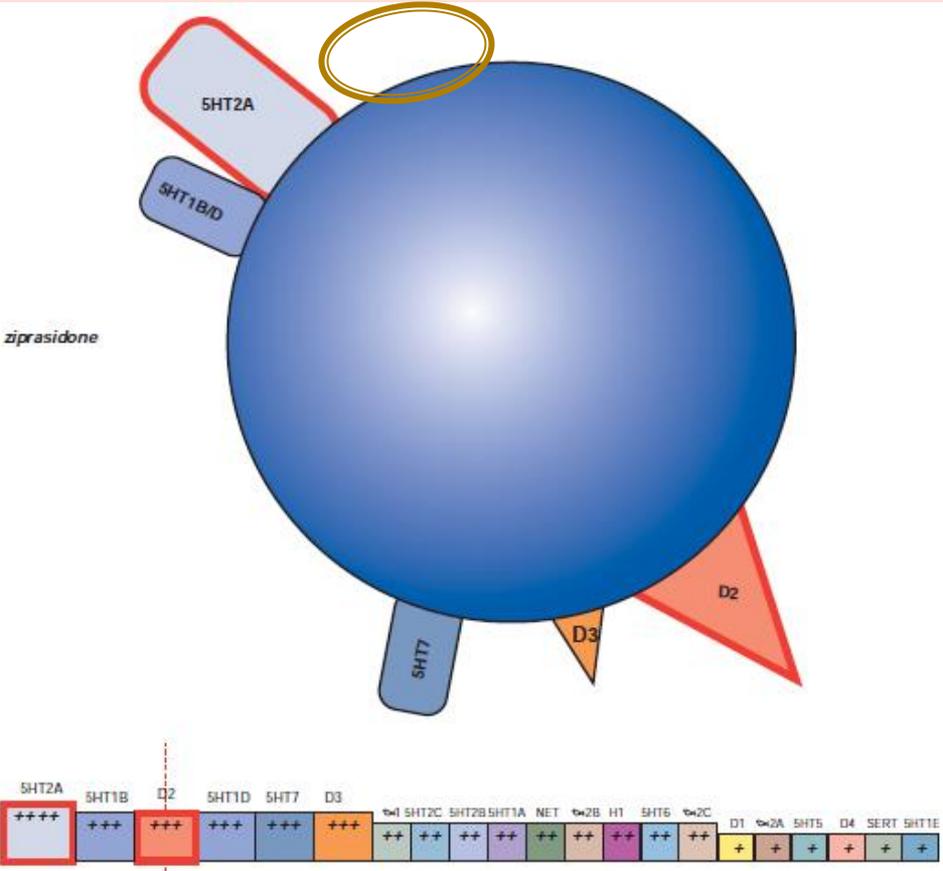
Oral de liberación prolongada ----- 1 dosis / día
Depot de 4 semanas ----- El depot preferido

Antipsicóticos atípicos: las donas

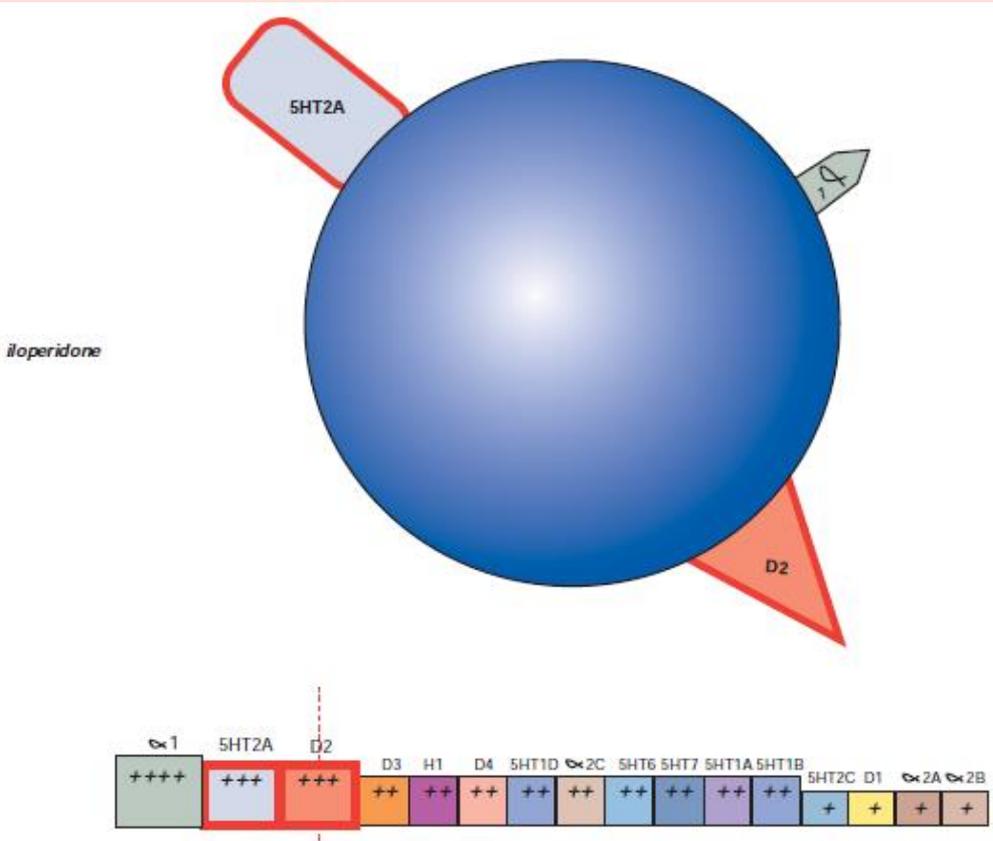
NO GANANCIA DE PESO
 No riesgo metabólico
 No aumento intervalo Q-Tc



2 veces al día con comida 500 cal. / intramuscular de urgencia

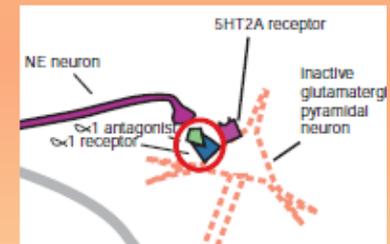
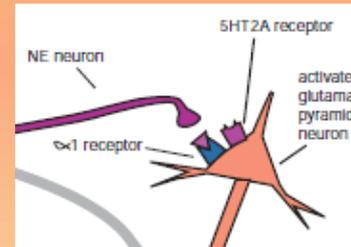


Antipsicóticos atípicos: las donas



Bajo SEP
Baja dislipidemia
Poco aumento de peso

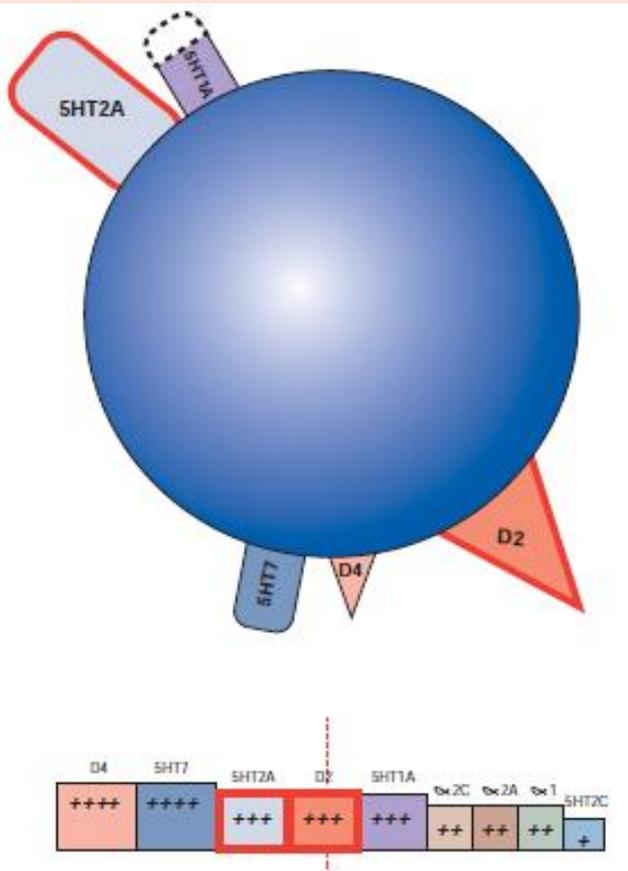
Antagonismo α como cloza y + que queti



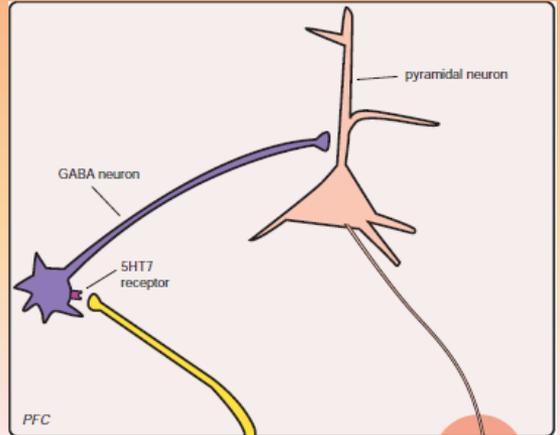
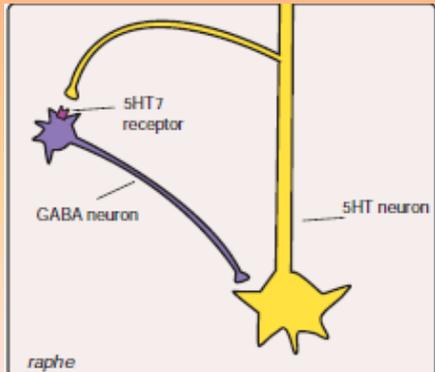
Desceso tensión \rightarrow 2 dosis / día e ir ajustando \rightarrow no sustituto rápido

Antipsicóticos atípicos: las donas

No sedación / No peso / No dislipidemia



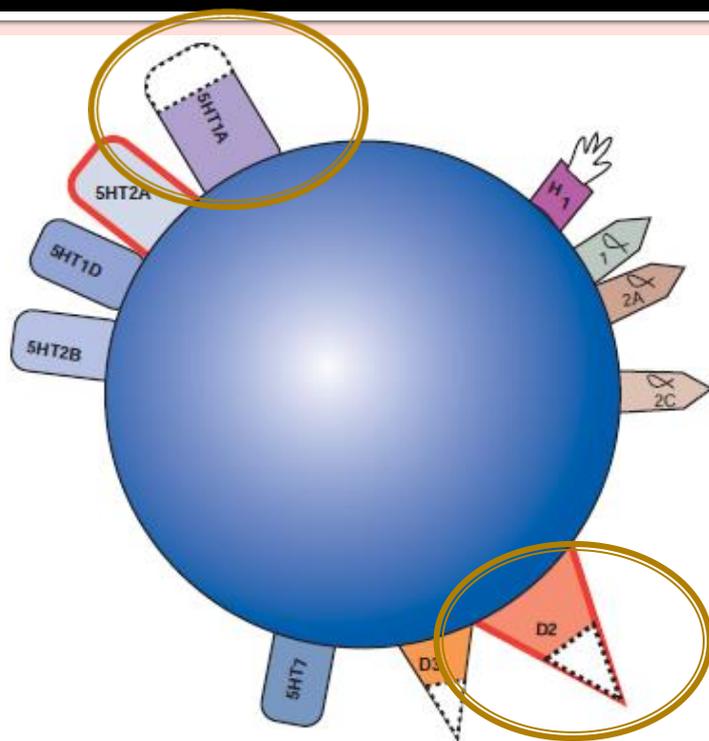
Mejor con comida 500 cal



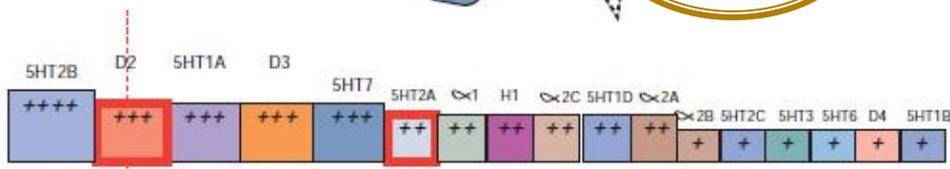
La rona

- Lumateperona
 - - A diferencia de donas, inhib recap 5HT
 - - Pruebas preclínicas indican que puede funcionar sobre D2 como agonista presináptico y como antagonista postsináptico

Antipsicóticos atípicos: 2 pips y 1 rip



aripiprazole



No aumento de peso ni dislipidemia



Antidepresivo a dosis bajas / más ago D2 a dosis bajas

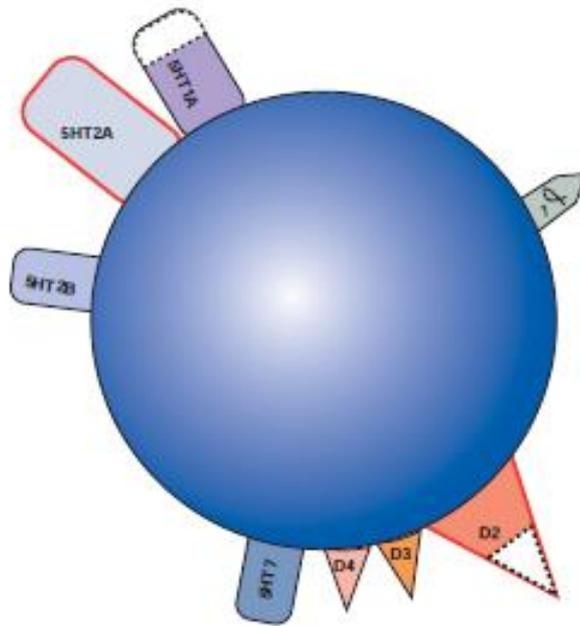
Eficaz en esquizofrenia y manía



Niños y adolescentes.
Agitación en autistas



Antipsicóticos atípicos: 2 pips y 1 rip



bripiprazole



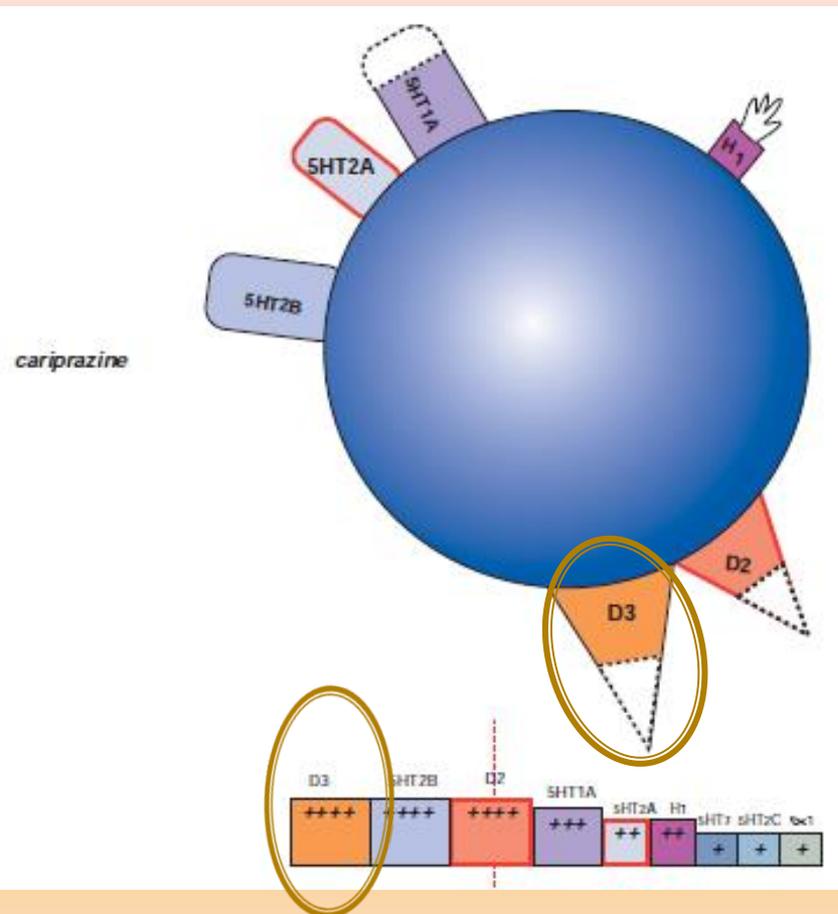
Respecto a Aripri:

- Más Ago Par 5HT_{1A}
- Más Anta 5HT_{2A} y α₁

Potencialmente:

Antipsicótico más tolerable
Antidepresivo
Tratamiento para agitación y
psicosis en demencia (Alfa 1)

Antipsicóticos atípicos: 2 pips y 1 rip



Potente ag/parc D₃ = mejora sínt neg

Dosis altas → Manía y esquizofrenia

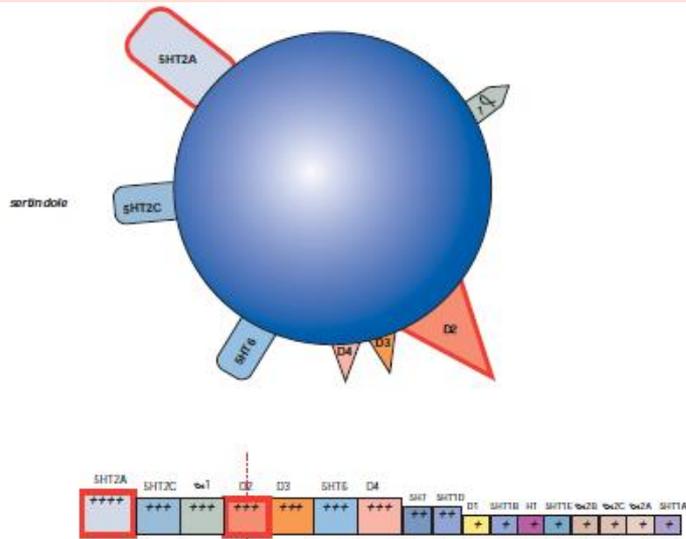
Dosis Bajas → Depresión

Dos metabolitos de muy alta duración → Posible depot oral hasta mensual

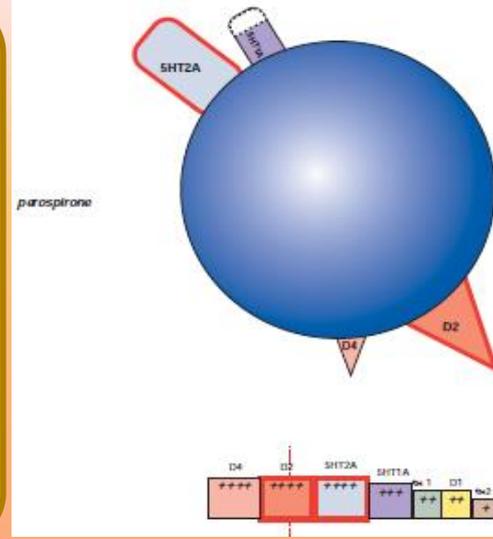
Antagonista selectivo 5HT_{2A}

- Pimavanserina
 - - Único antipsicótico sin acción sobre D₂
 - - Potente antag 5HT_{2A} + antag 5HT_{2C}
 - - Aprov para psicosis en Párkinson y última fase de ensayos para psicosis en demencia

Antipsicóticos atípicos: los otros



Anta
5HT_{2A}-D₂
Riesgo Q-Tc
Reintroduc.
2ª línea



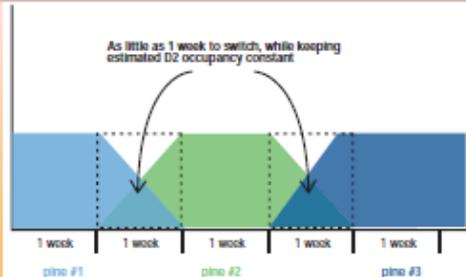
Anta
5HT_{2A}-D₂
Japón
Ago Par
5HT_{1A}

Blonanserina

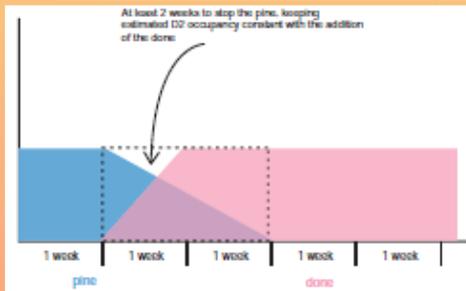
Anta 5HT_{2A}-D₂
Más afinidad x D₃ que la DA
Posible mejora sínt neg y depre bipolar

Práctica clínica: A cambiar

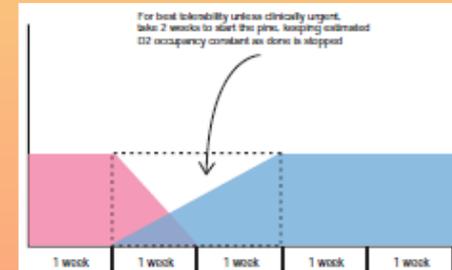
De = a =



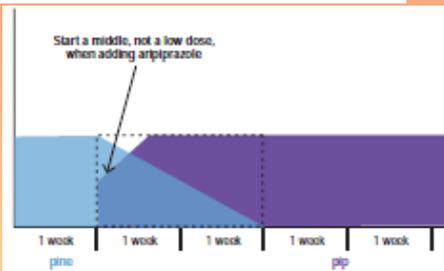
De P a D



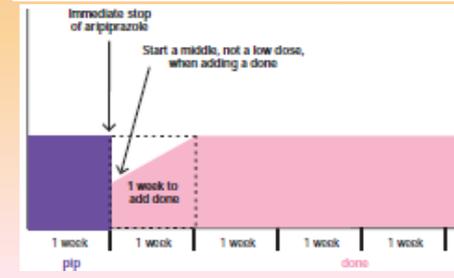
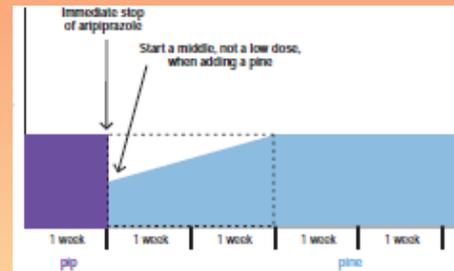
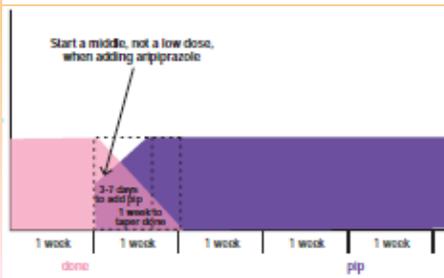
De D a P



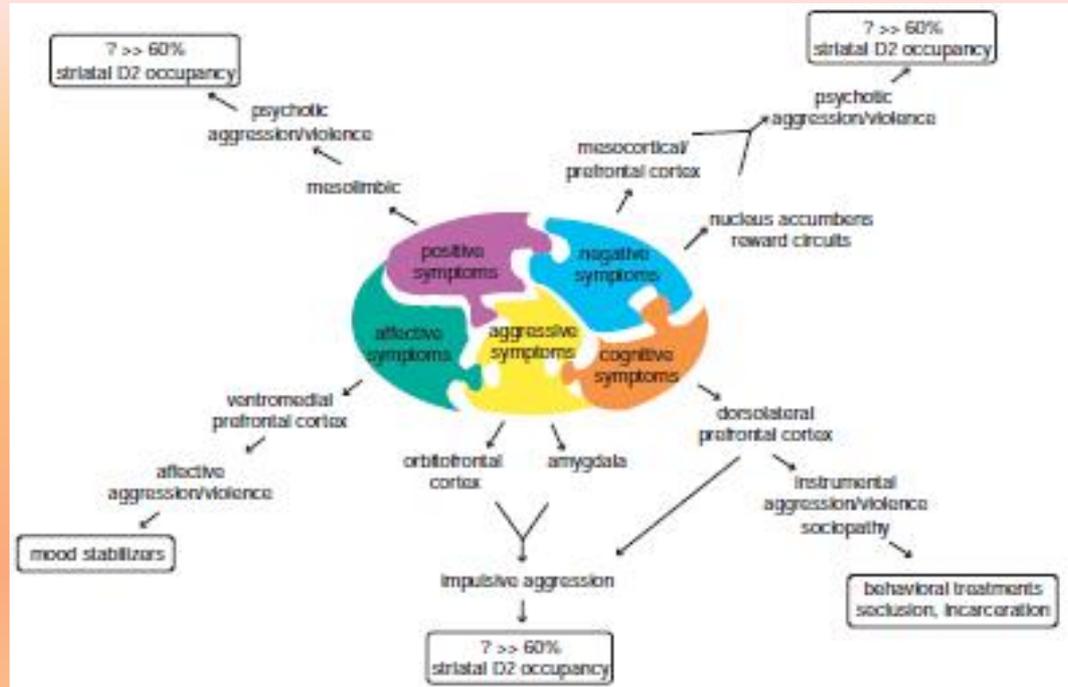
A Aripri



De Aripri



Práctica clínica: Violencia

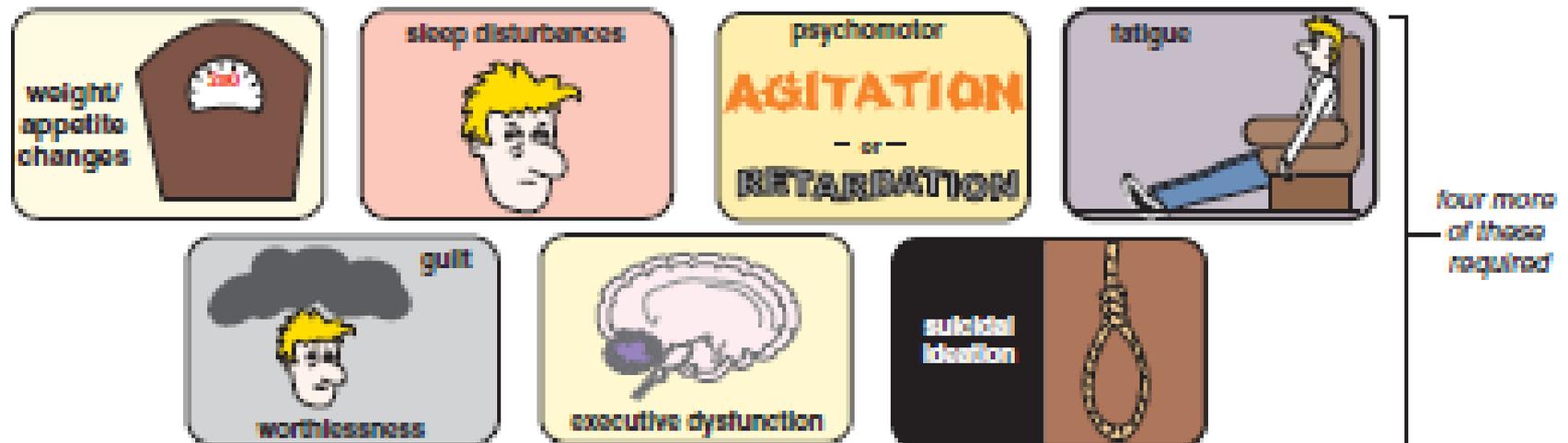


Fallo farmacoCINÉTICO

Fallo farmacoDINÁMICO

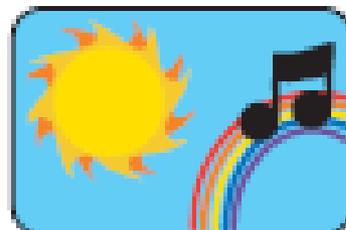
Trastornos del humor: Dimensiones sintomáticas

Symptom Dimensions of a Major Depressive Episode

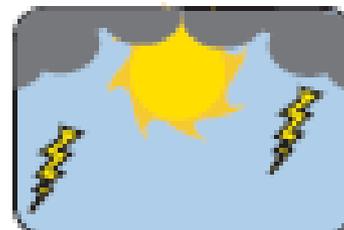


Trastornos del humor: Dimensiones sintomáticas

Symptom Dimensions of a Manic Episode



elevated/expansive mood



irritable mood

symptoms necessary for diagnosis



inflated self-esteem/grandiosity



increased goal-directed activity or agitation



risk taking



decreased need for sleep



distractible/concentration



more talkative/pressured speech

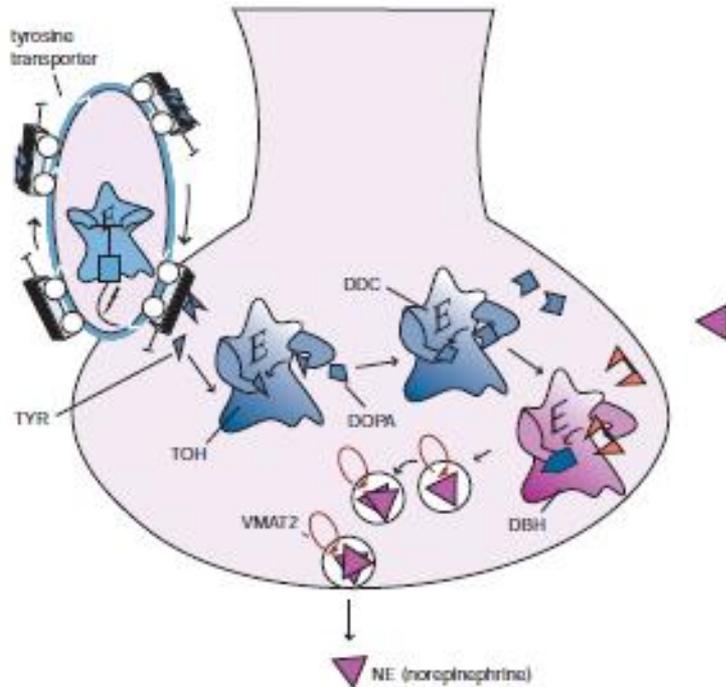


flight of ideas/racing thoughts

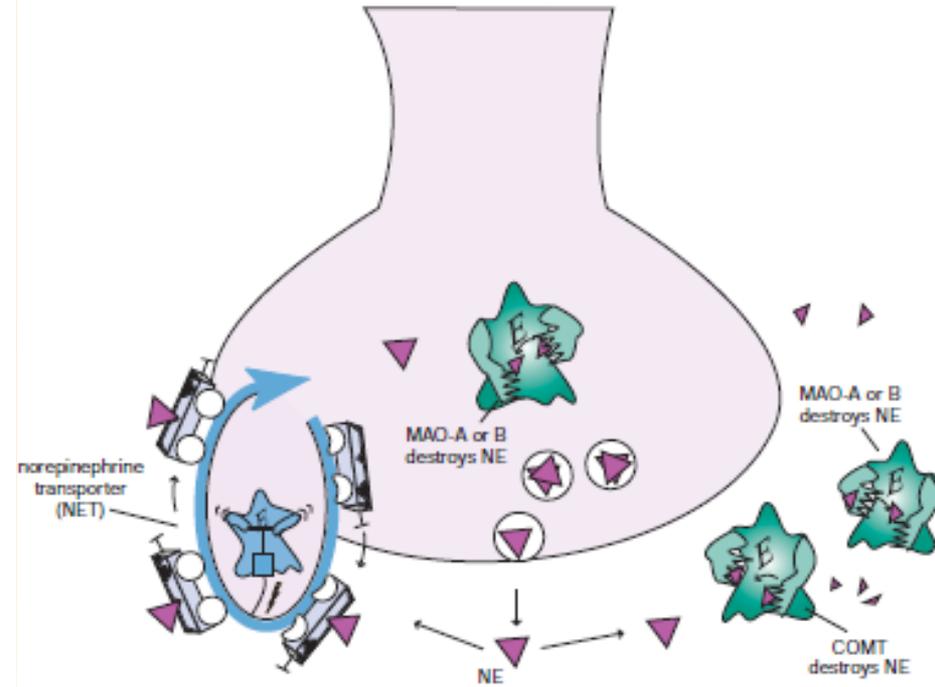
plus three or more of these (four if mood is only irritable)

Trastornos del humor: La tercera monoamina

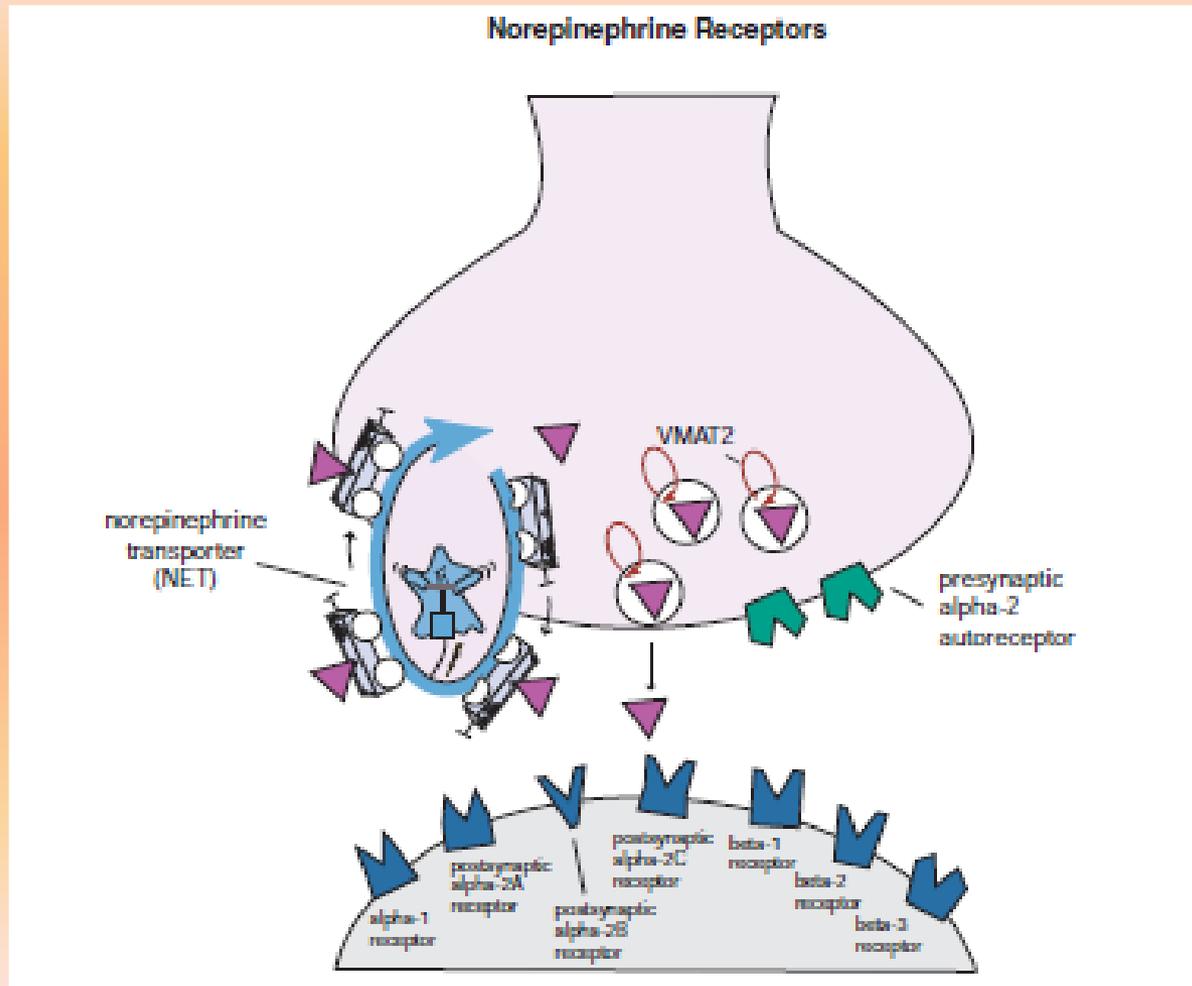
Norepinephrine Is Produced



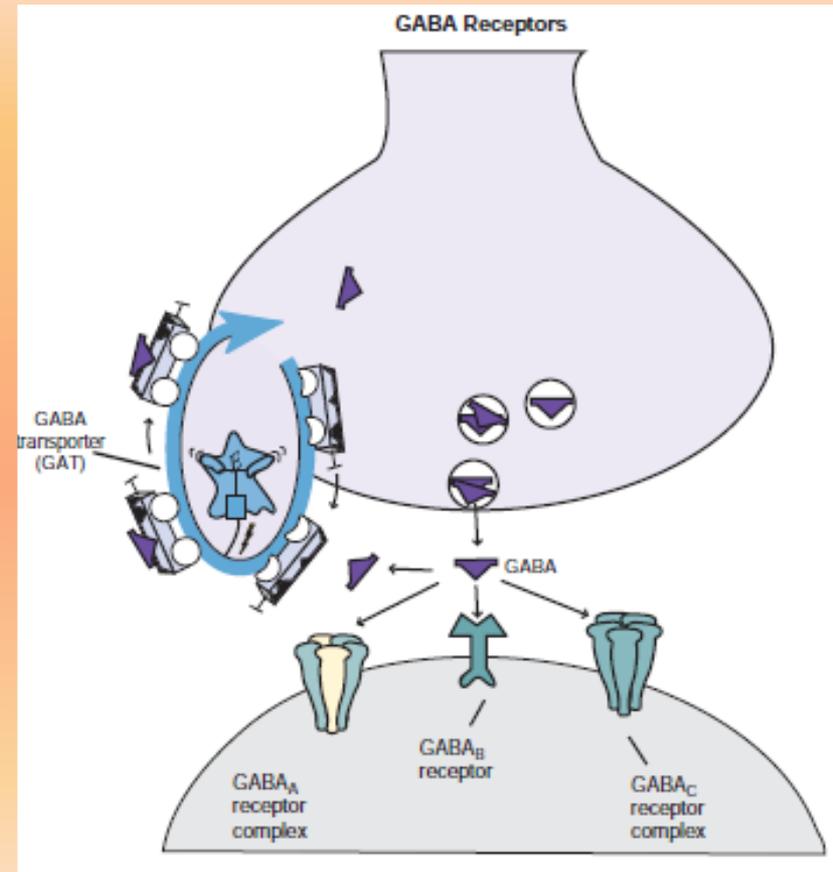
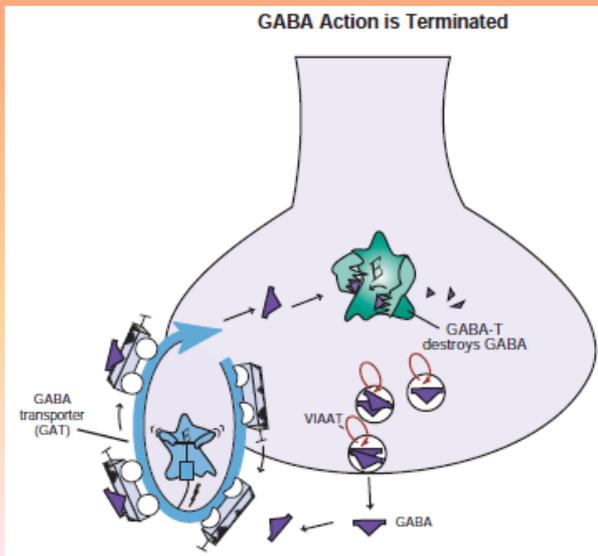
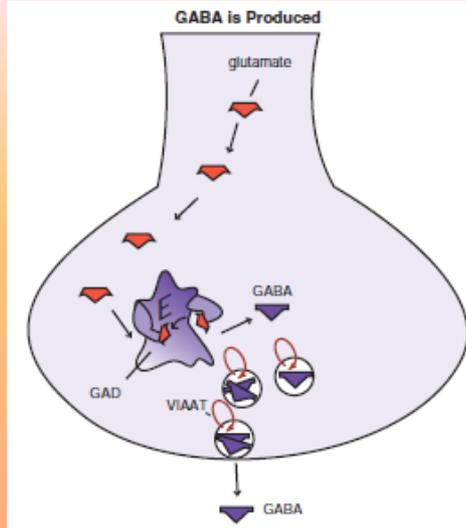
Norepinephrine Action Is Terminated



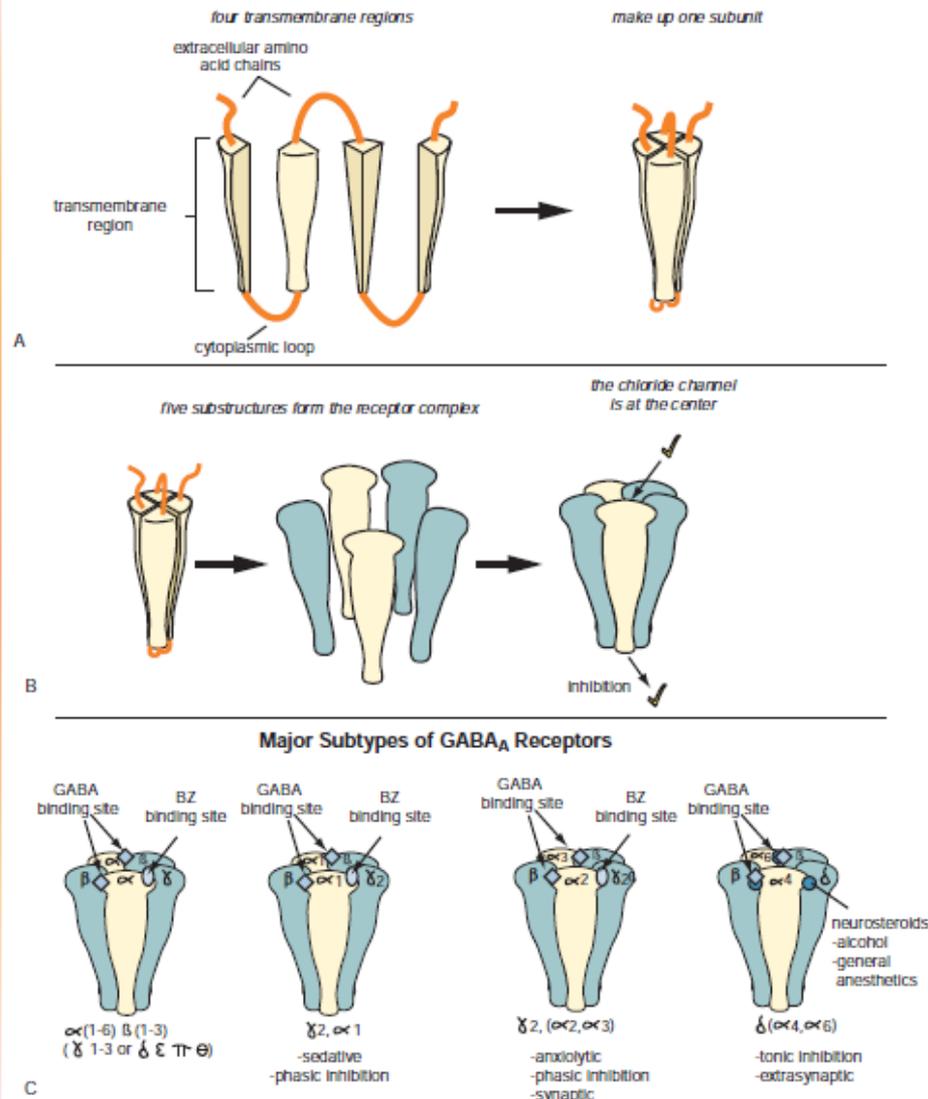
Trastornos del humor: La tercera monoamina



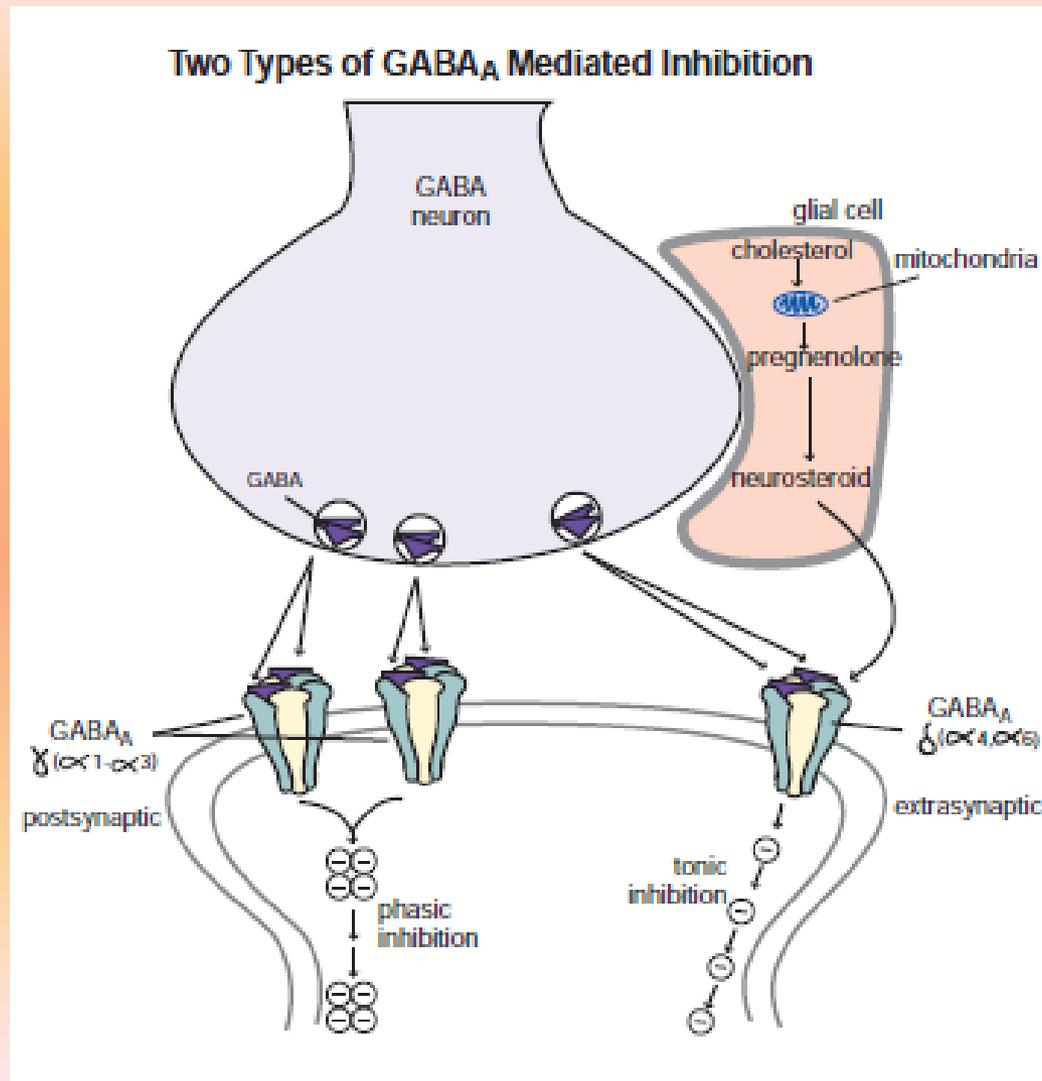
Neurotransmisión GABAérgica



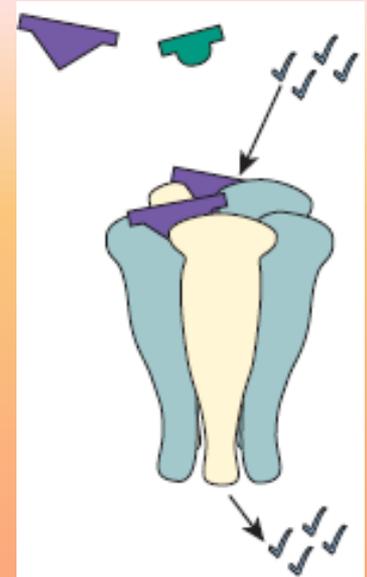
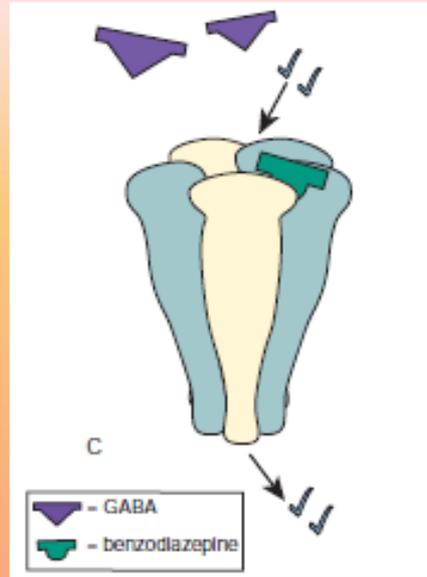
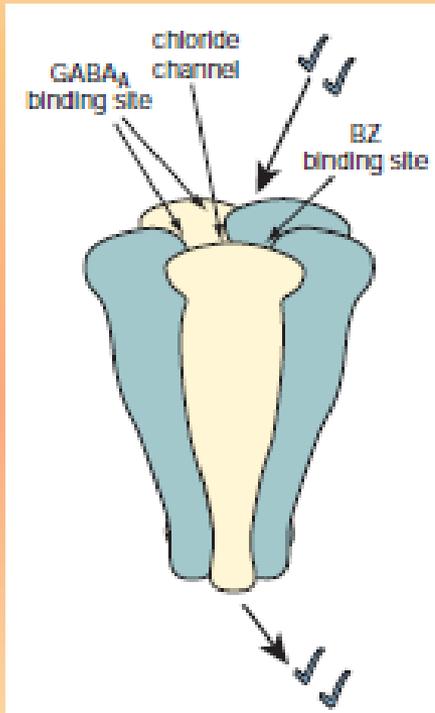
Estructura de receptores GABA_A



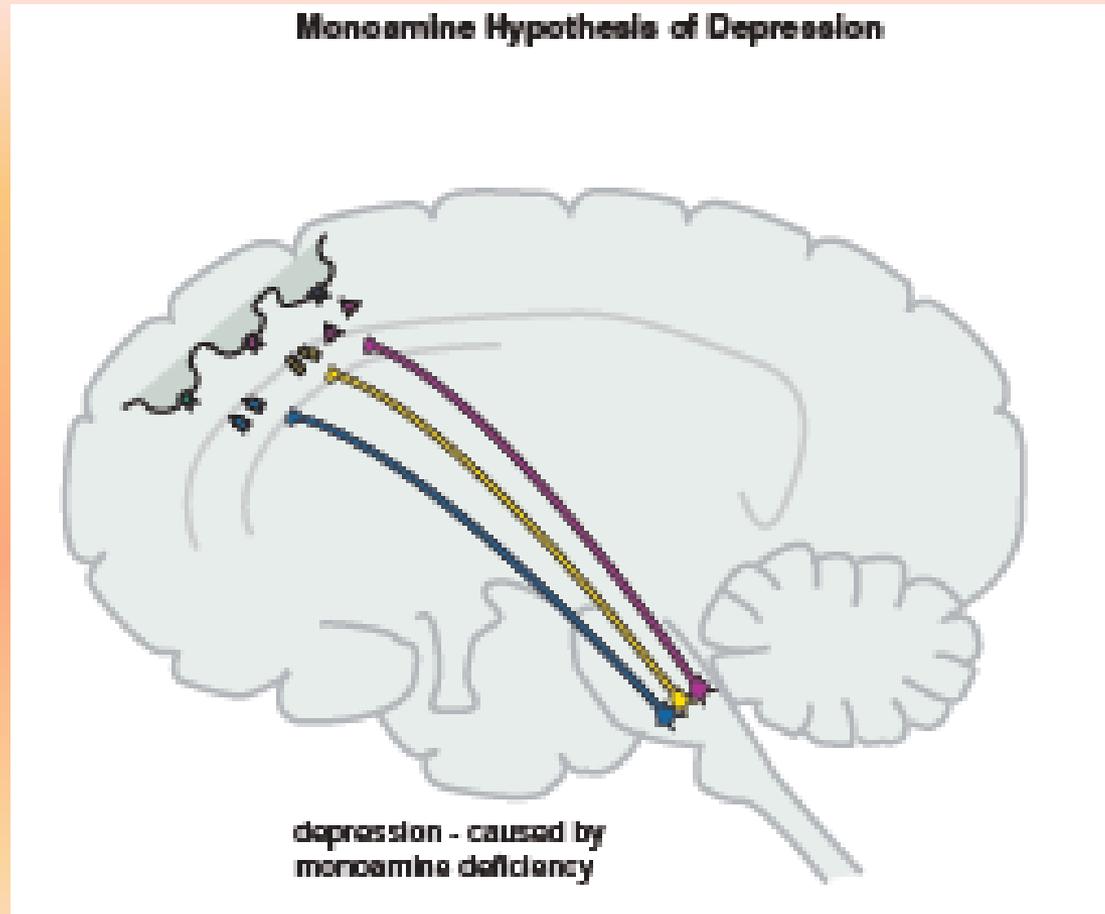
Inhibición GABAérgica



Inhibición GABAérgica



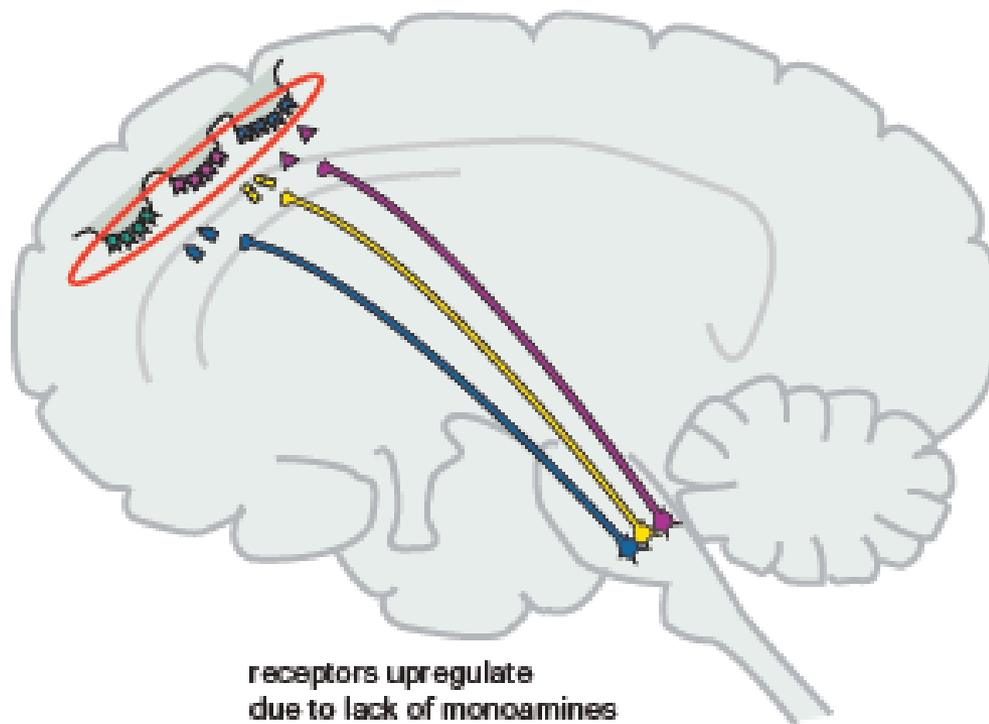
Trastornos del humor: Hipótesis monoaminérgica



No hay evidencia suficiente

Trastornos del humor: Hipótesis receptor monoaminérgico

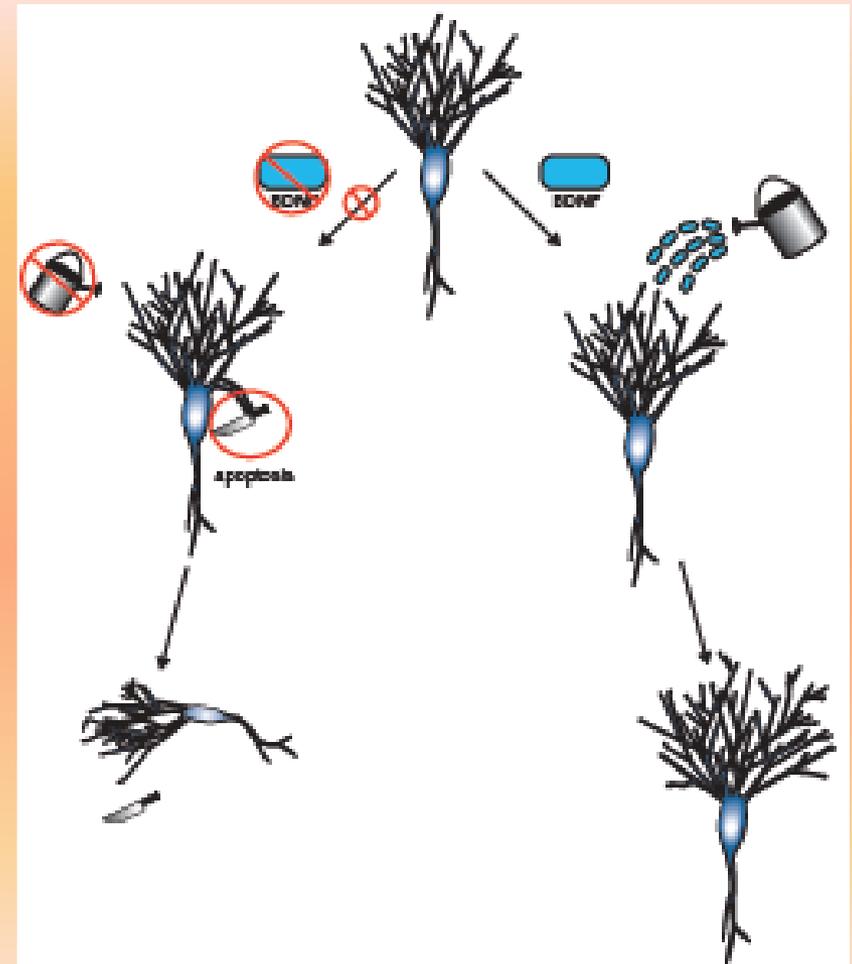
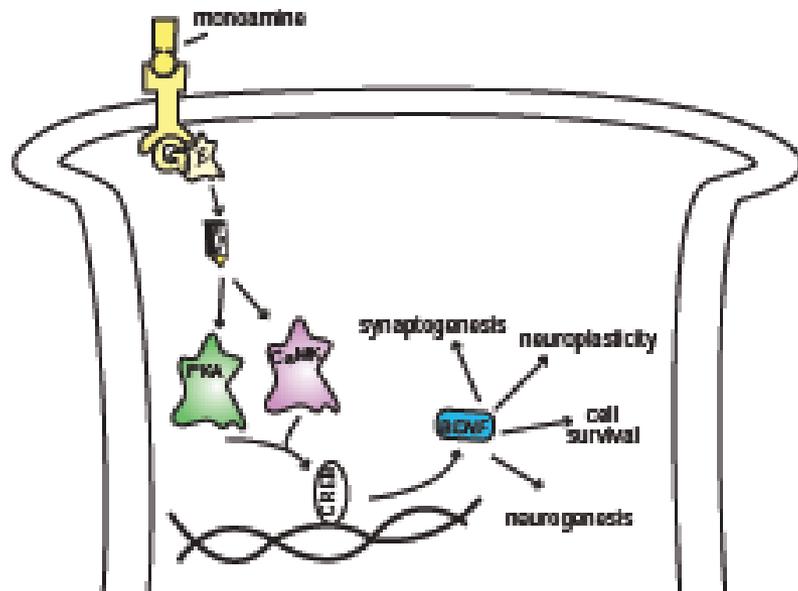
Monoamine Receptor Hypothesis of Depression



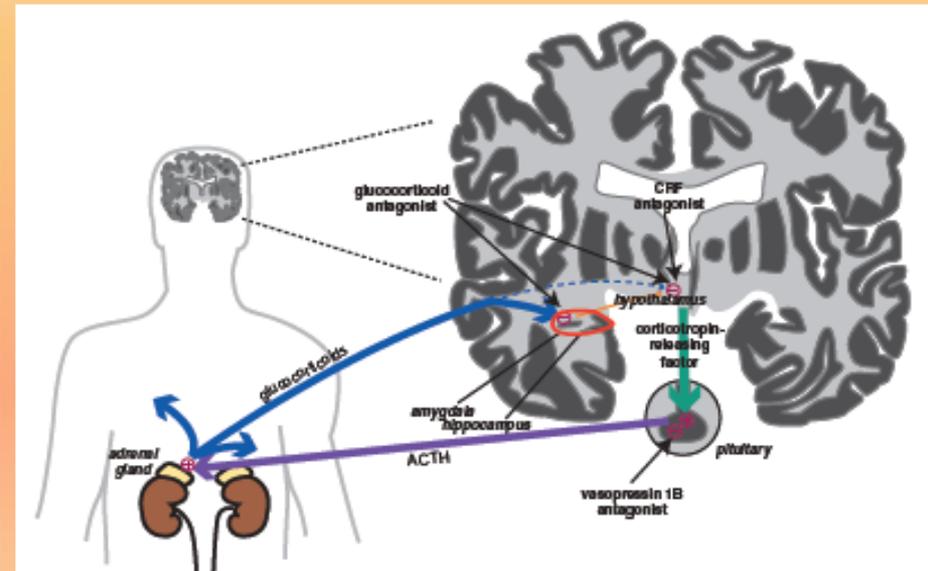
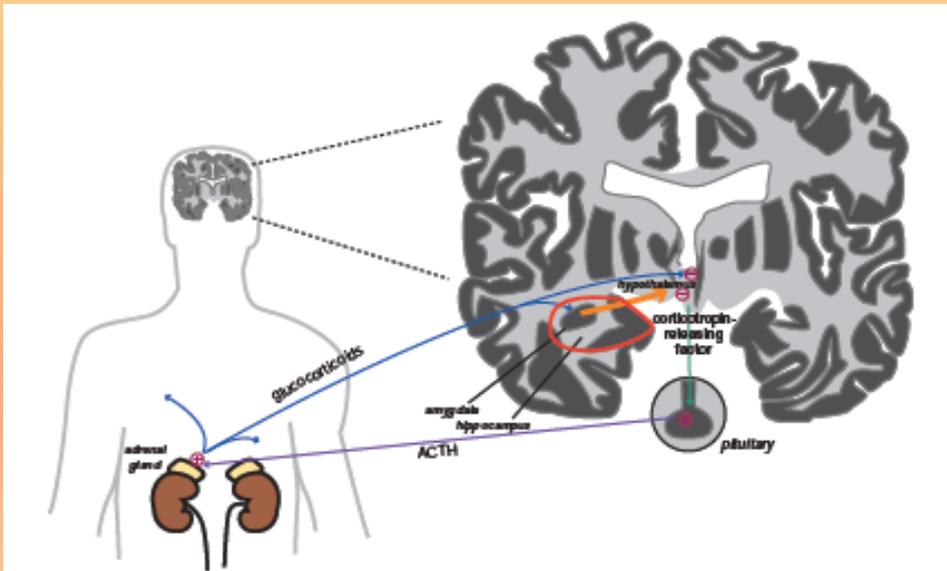
Tampoco suficiente evidencia

Trastornos del humor: Aguas abajo

Monoamine Signaling Increases BDNF Release which Modifies Monoamine Innervation

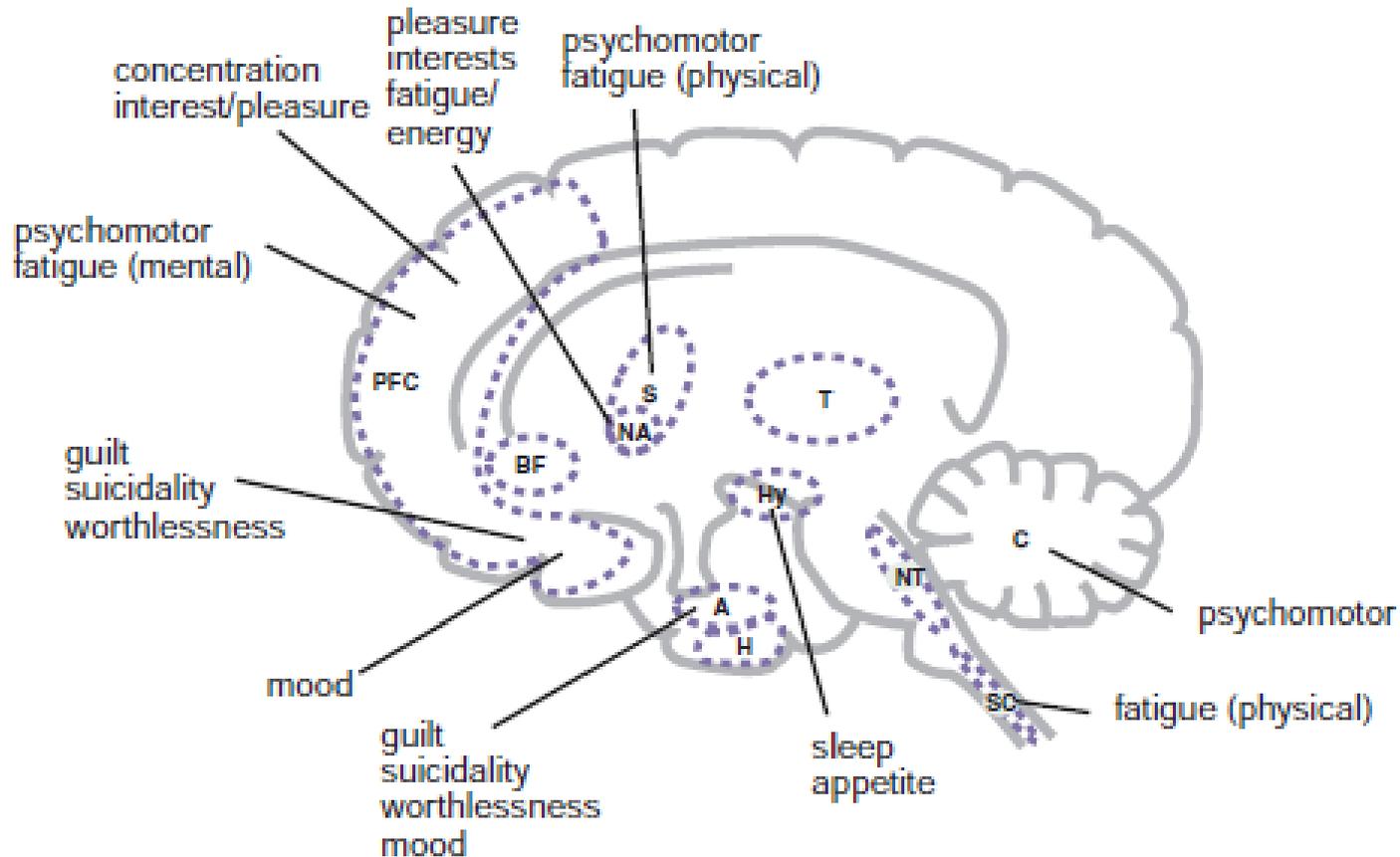


Trastornos del humor: Efectos del estrés crónico



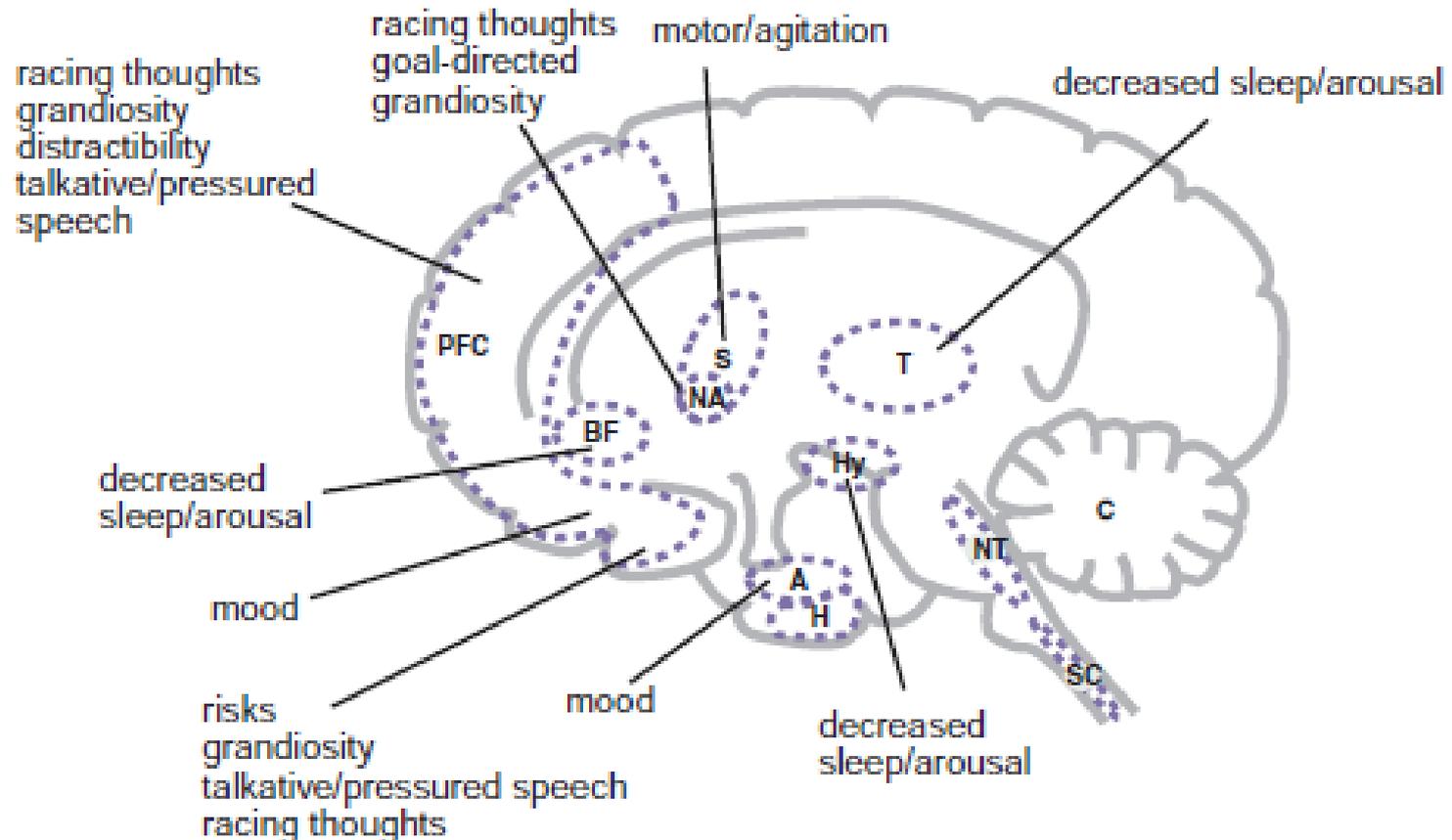
Trastornos del humor: Dimensiones sintomáticas

Match Each Diagnostic Symptom for a Major Depressive Episode to Hypothetically Malfunctioning Brain Circuits

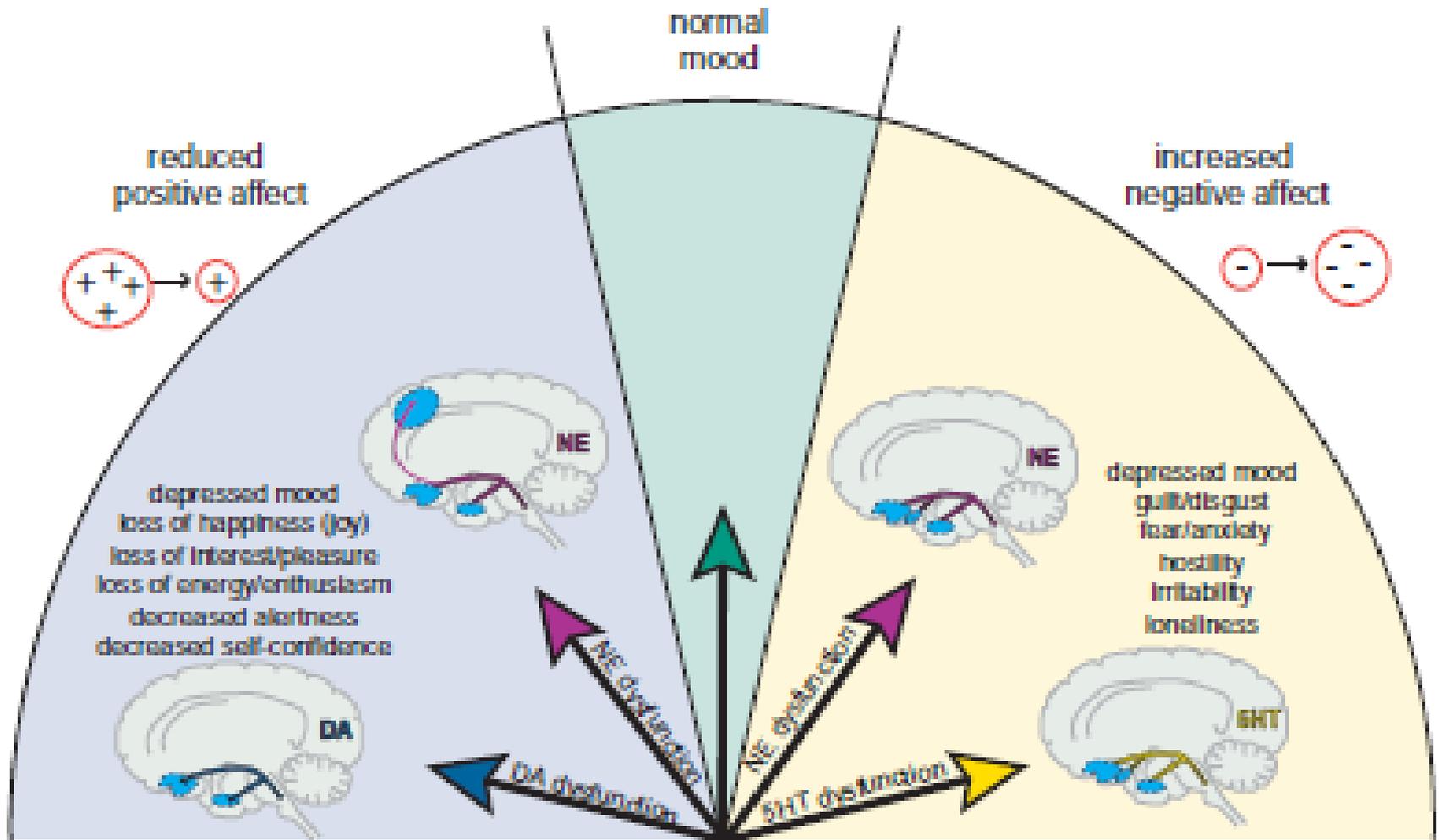


Trastornos del humor: Dimensiones sintomáticas

Match Each Diagnostic Symptom for a Manic Episode to Hypothetically Malfunctioning Brain Circuits



Trastornos del humor: Dimensiones sintomáticas



Antidepresivos

TSER

NAT

TDA

ISRS

Fluoxetina
Sertralina
Paroxetina
Fluvoxamina
Citalopram
Escitalopram

IRSN

Venlafaxina
Desvenlafaxina
Duloxetina
Milnacipran

IRND

Bupropion

APIRS

Vilazodona

AIRS

Trazodona
Vortioxetina

2ª Línea

Ag MT₁ y 2

Agomelatina

Anta α_2

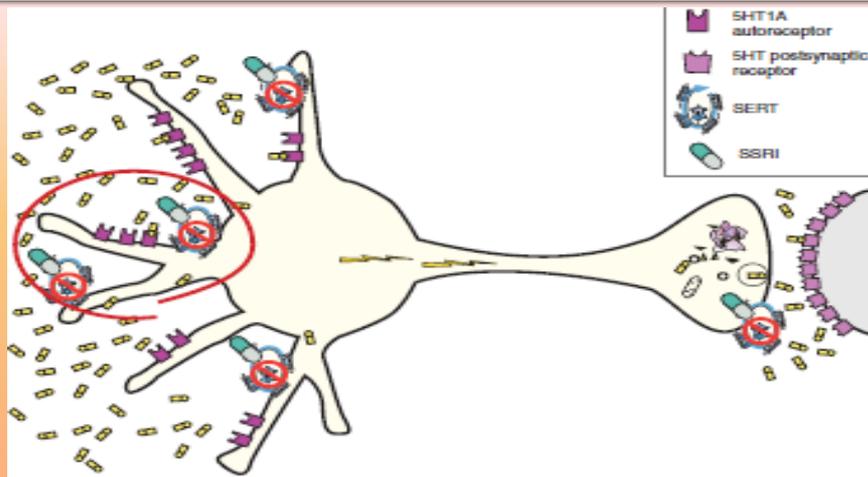
Mirtazapina

Esteroides
neuroactivos

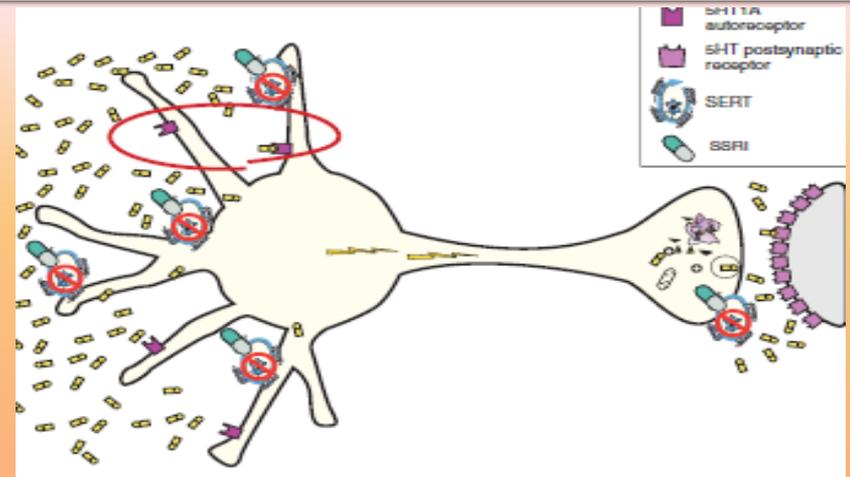
Tricíclicos

IMAOS

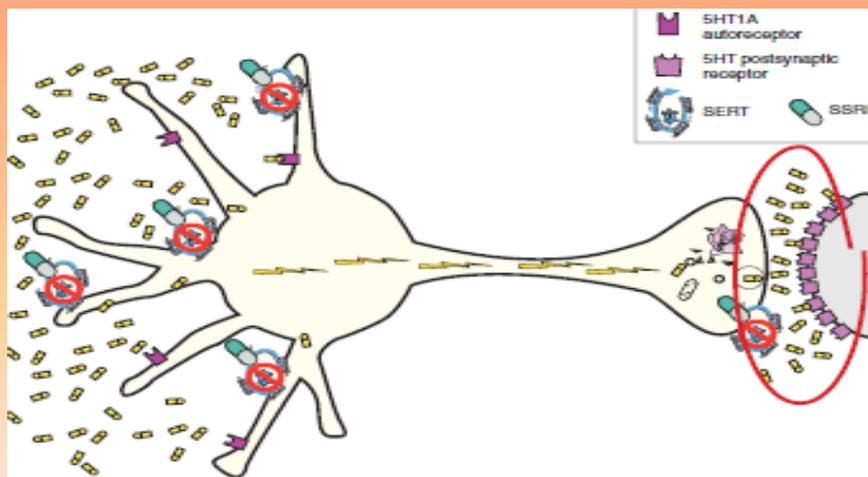
Antidepressivos: mecanismos



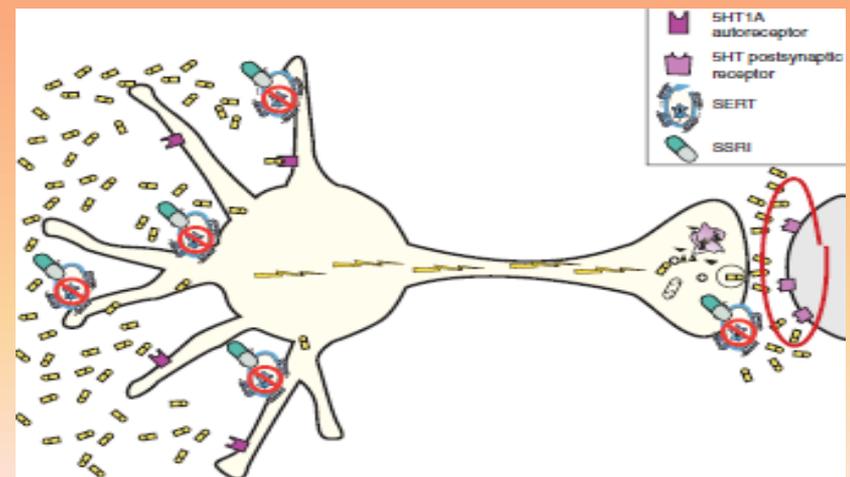
Antidepressant action: antidepressant blocks 5HT reuptake both at the dendrites and at the axon



The increase in 5HT causes the autoreceptors to desensitize / downregulate



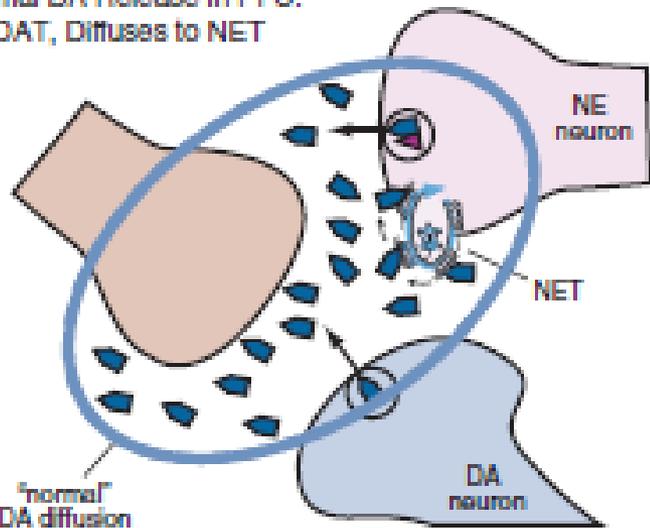
The downregulation of the autoreceptors causes the neuron to release more 5HT at the axon



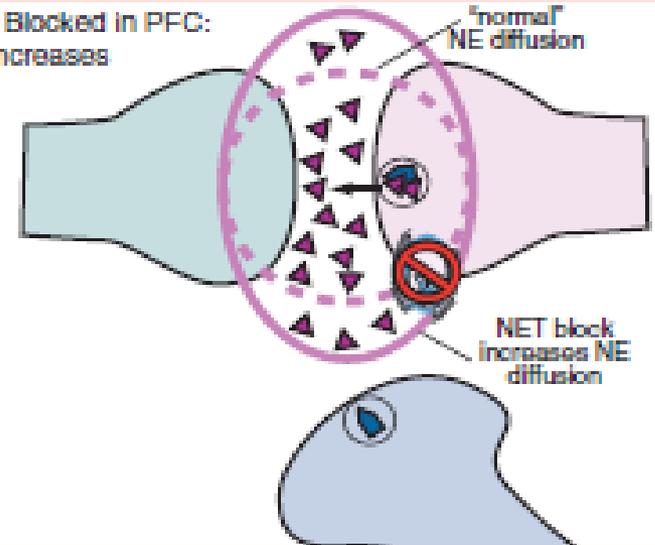
The increase of 5HT at the axon causes the postsynaptic receptors to desensitize / downregulate, reducing side effects

Antidepressivos: mecanismos

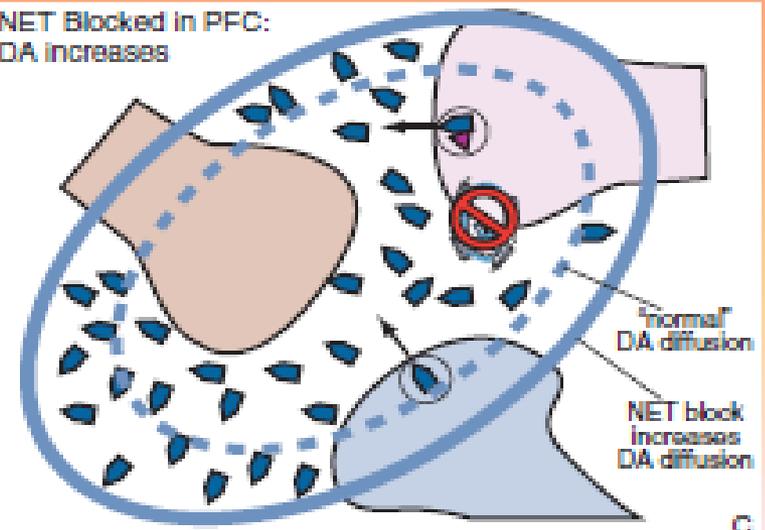
Normal DA Release in PFC:
No DAT, Diffuses to NET



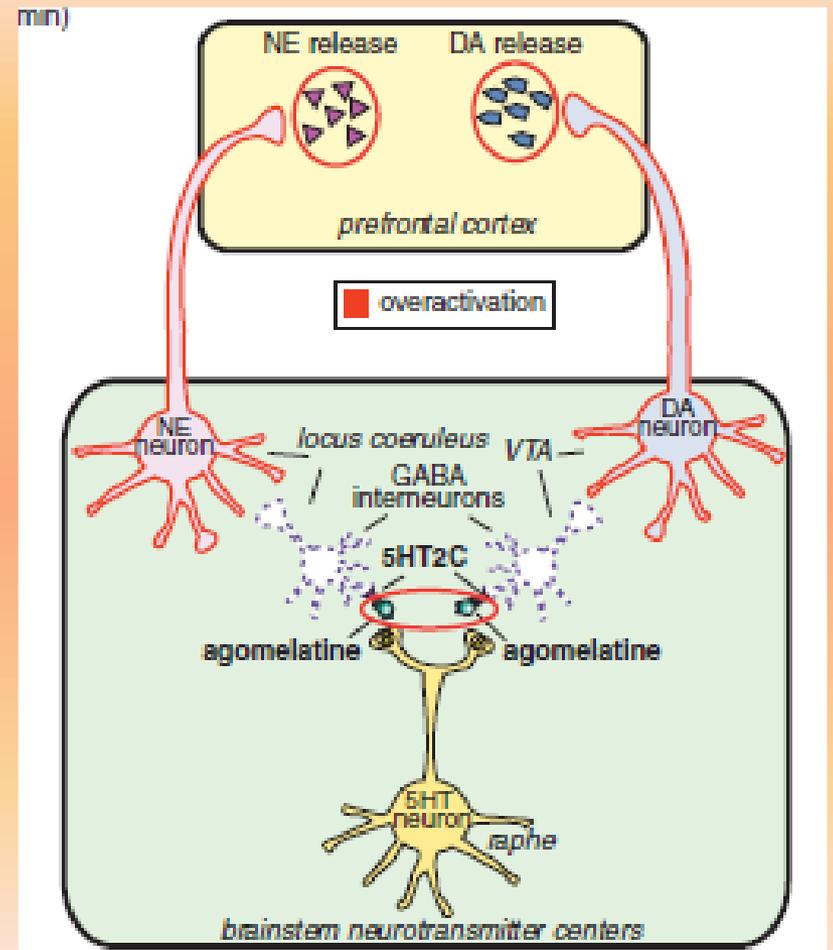
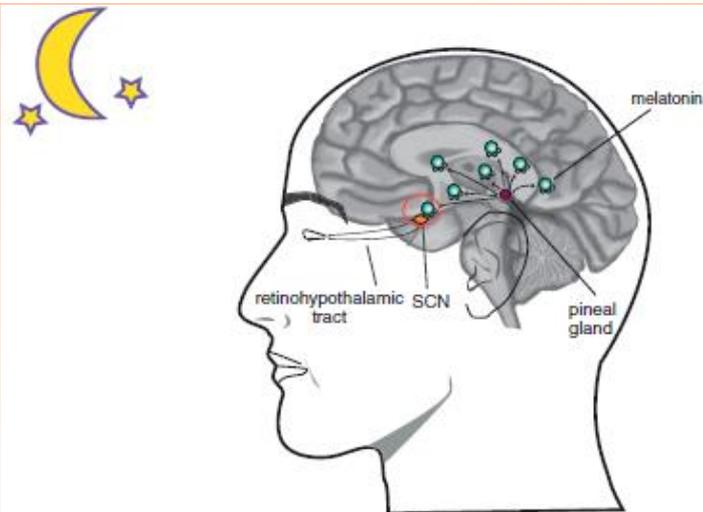
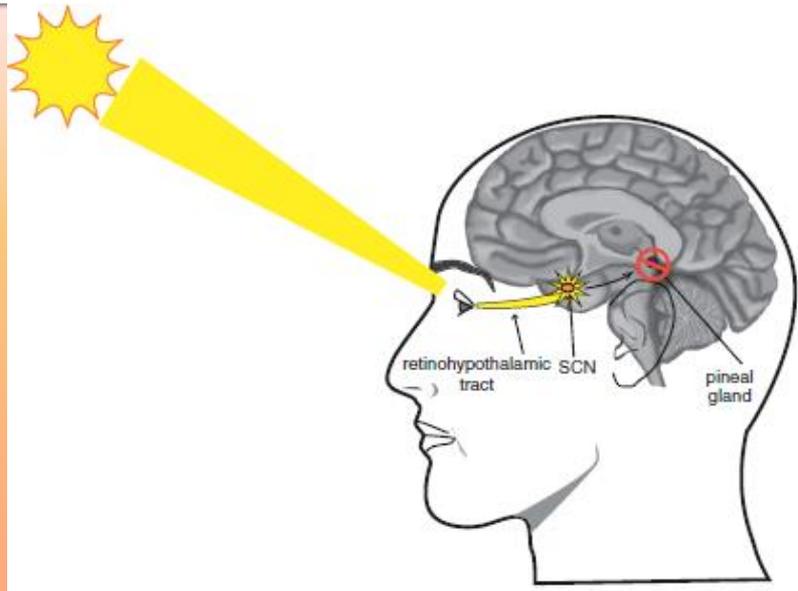
NET Blocked in PFC:
NE increases



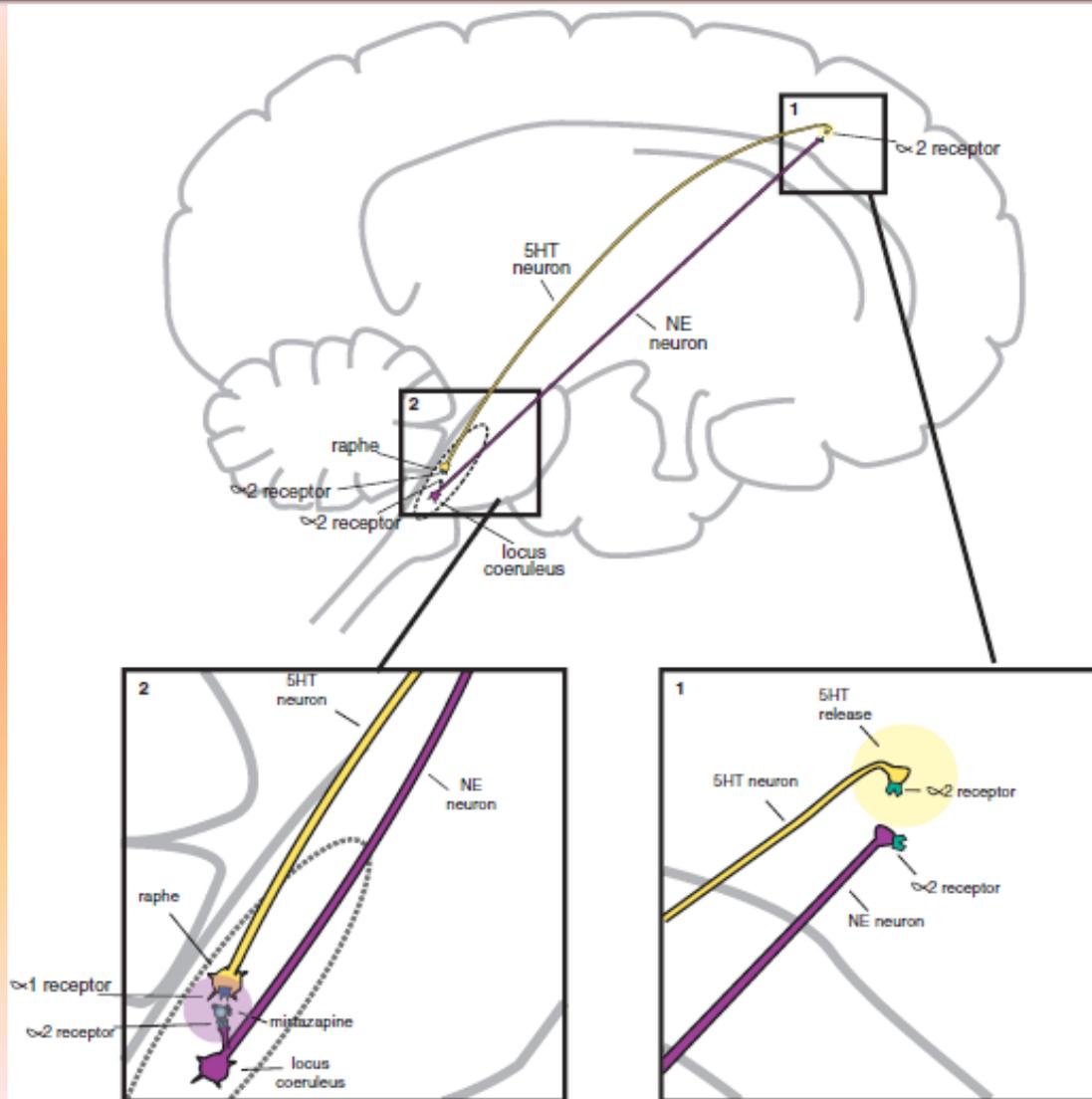
NET Blocked in PFC:
DA increases



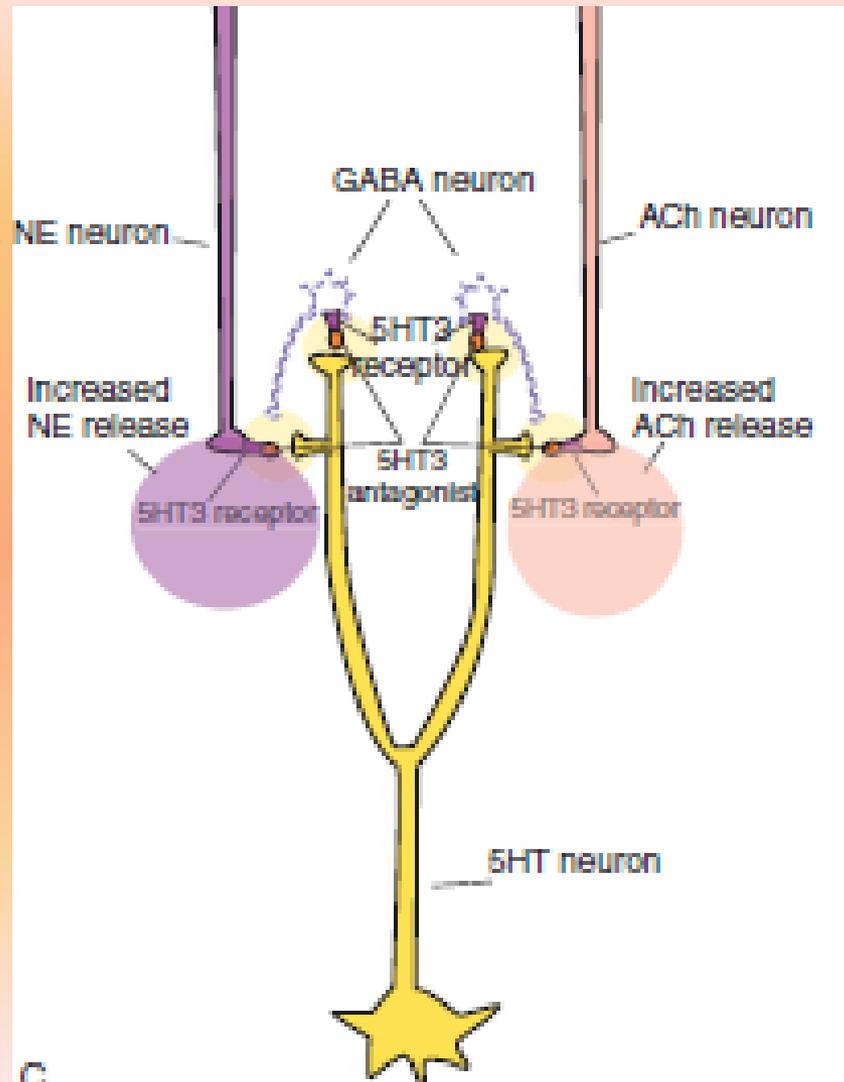
Antidepressivos: mecanismos



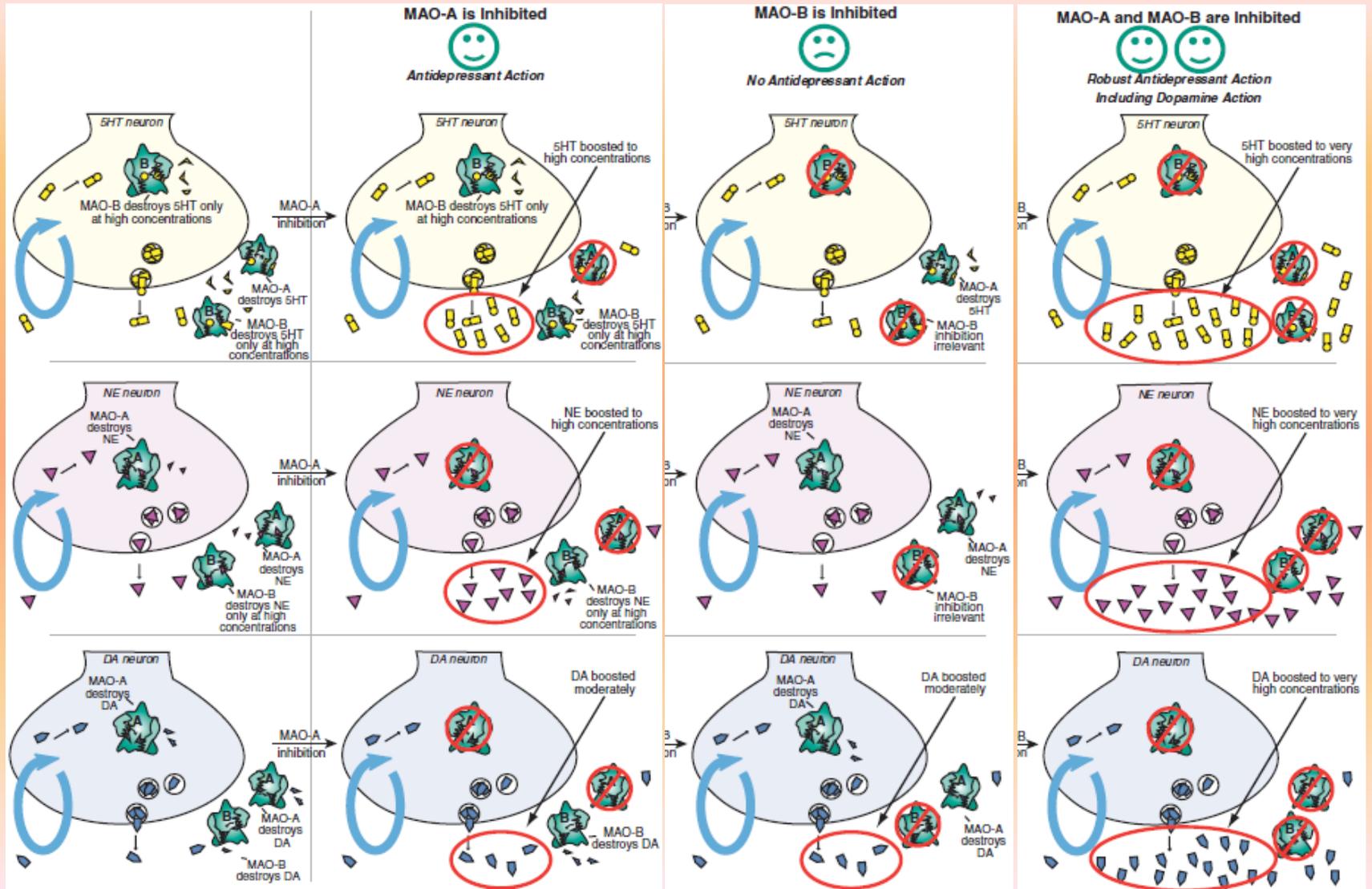
Antidepressivos: mecanismos



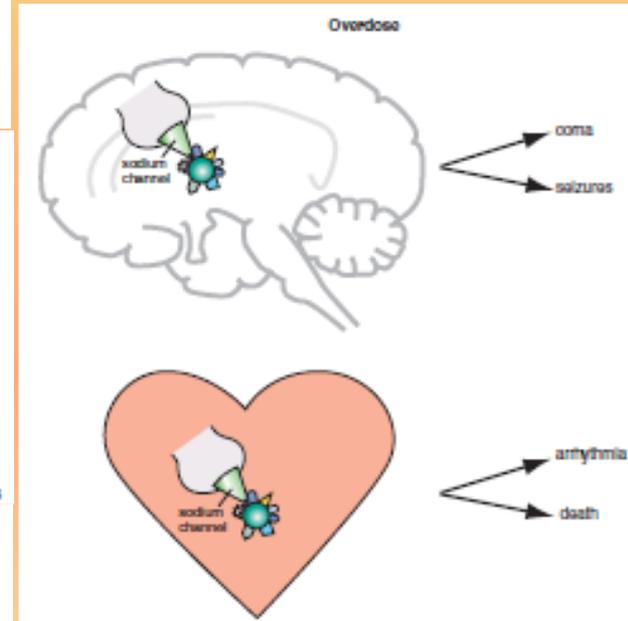
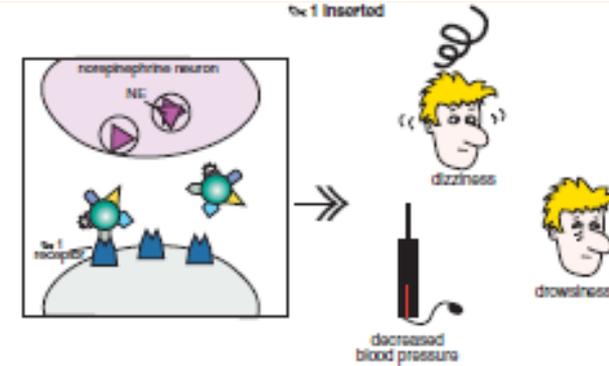
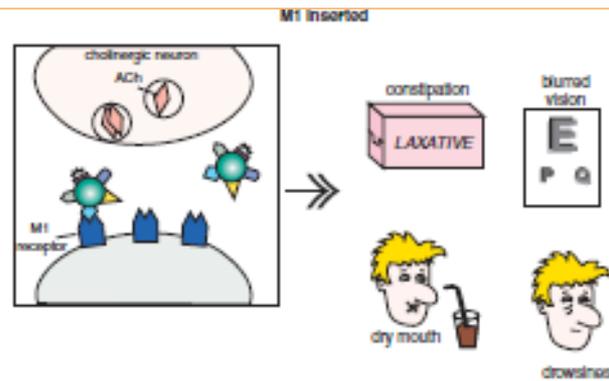
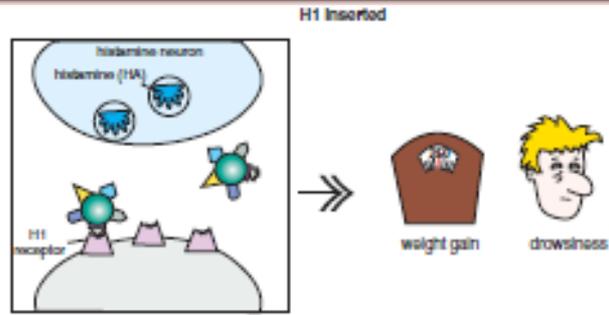
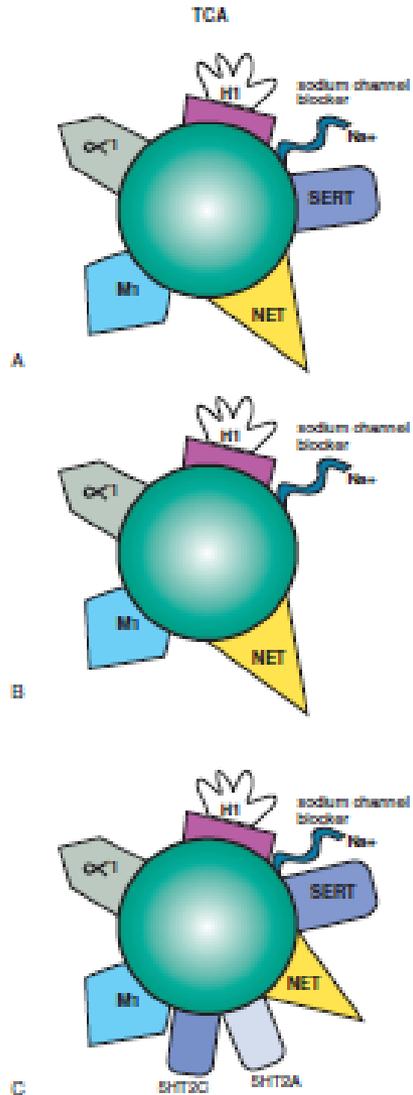
Antidepressivos: mecanismos



Antidepressivos: mecanismos



Antidepressivos: ATC



Resistencia al tratamiento

Antag/Agon 5HT/DA

Olanza + Fluoxet
Aripiprazol
Brexipiprazol
Caripracina

Ketamina y Esketamina

- Infusión intravenosa dosis subanestésica
- Mejoría casi inmediata
- Desaparece en pocos días

-Bloqueo NMDA → ↑ Glu → →
→ ↑ Sinaptog + Liberac BDNF y VEGF

En desuso

Litio
Bupiriona
Horm Tiroideas

Combos

Triple acción: ISRS/IRSN + IRND
Combos Cohet Calif: IRSN + Mirtaza
Combos activadores: IRSN + inh TDA

Trastorno bipolar

Antag/Agon 5HT/DA (1ª línea)

Olanza + Fluoxet
Quetiapina
Lurasidona
Caripracina

Litio

Anticonvulsivos

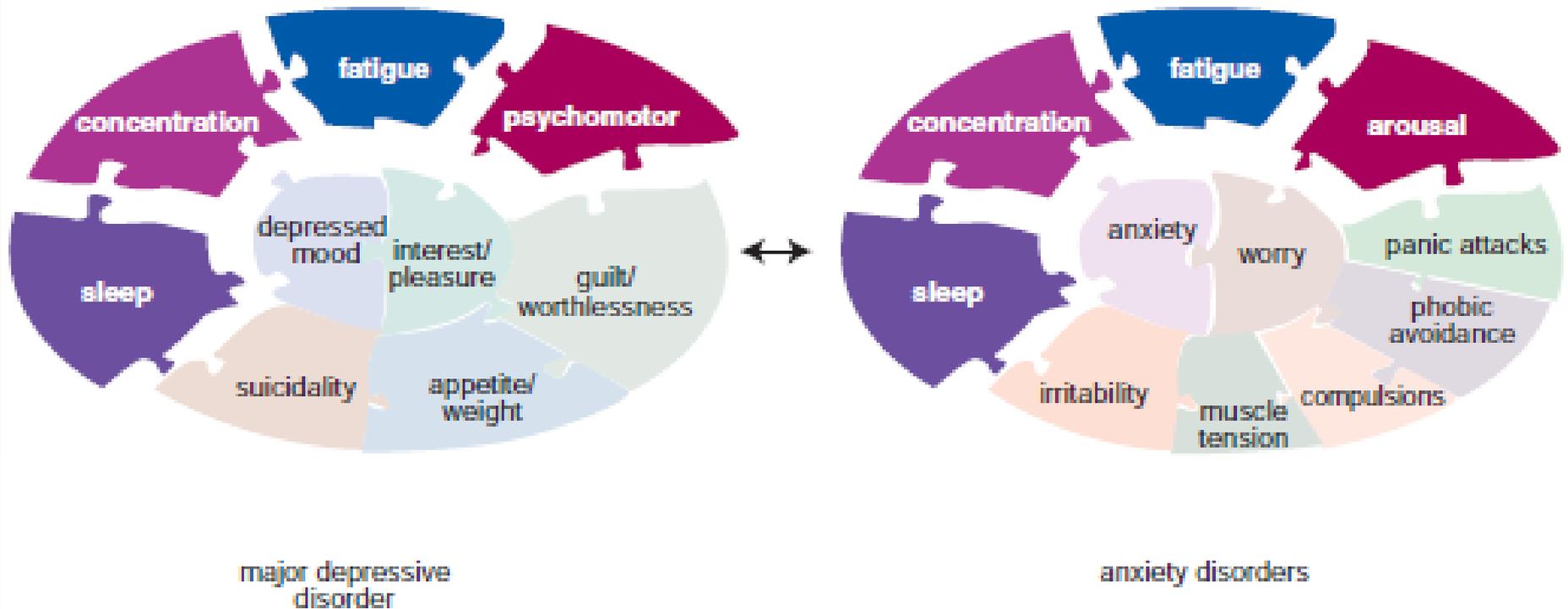
Ácido Valproico
Carbamazepina
Lamotrigina
(único desde abajo)

Anticonvulsivos de eficacia dudosa

Oxcarbazepina/ eslicarbazepina
Topiramato
Gabapentina y pregabalina
Bloqueadores canal Ca tipo L
Riluzol

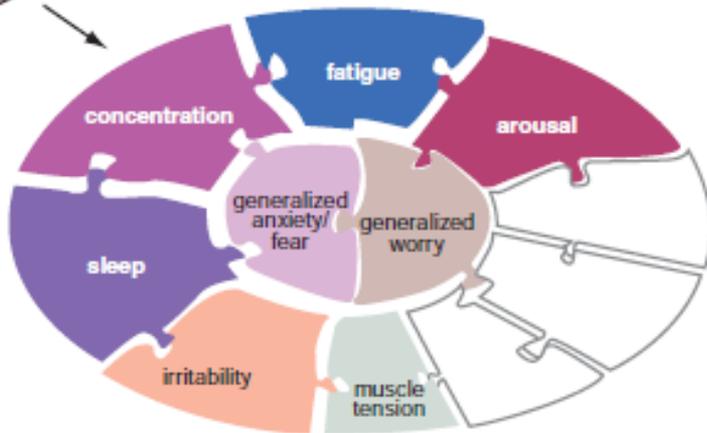
Trastornos de ansiedad

Overlap of MDD and Anxiety Disorders

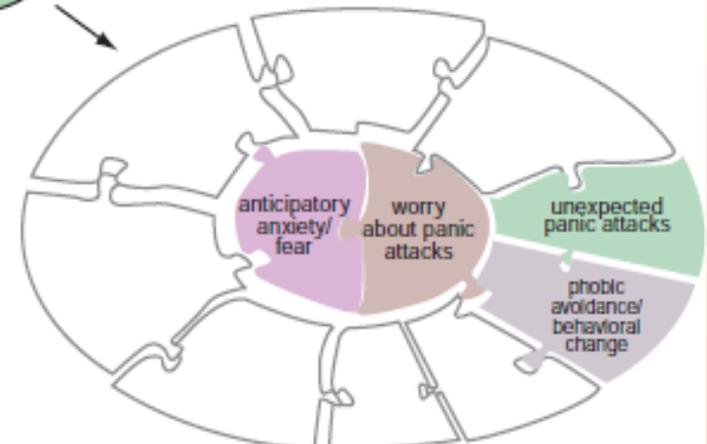


Trastornos de ansiedad

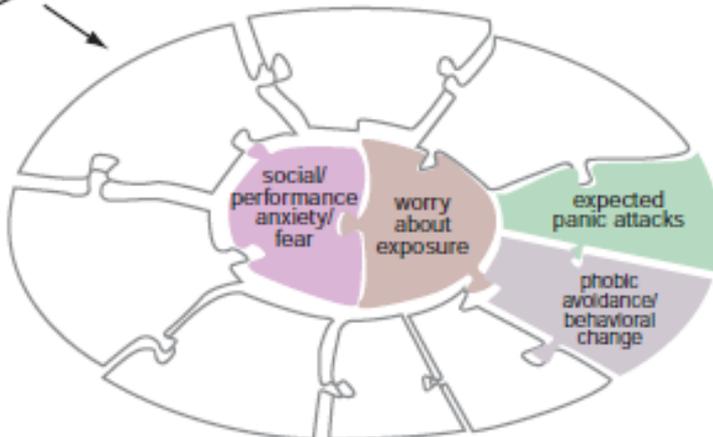
GAD



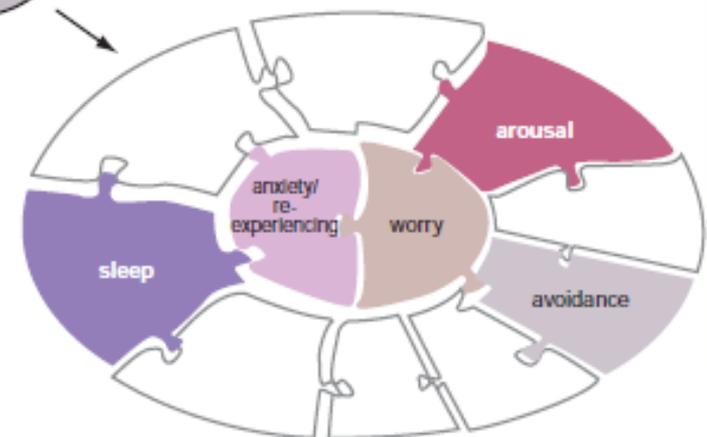
panic disorder



social anxiety disorder

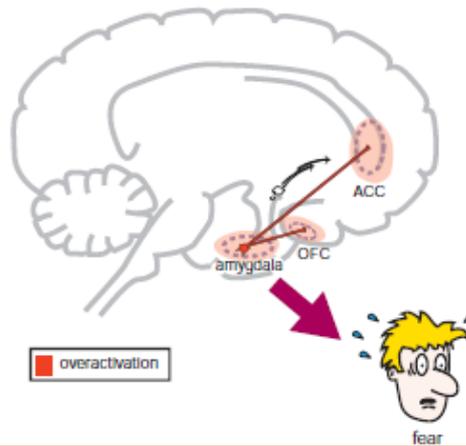


PTSD

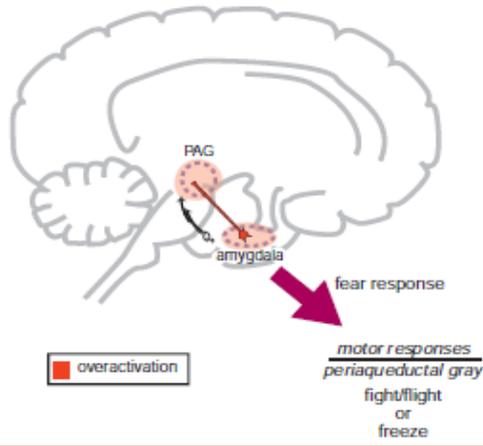


Amígdala y miedo

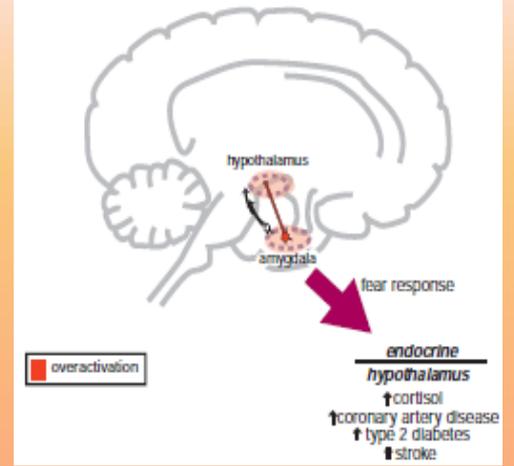
Affect of Fear



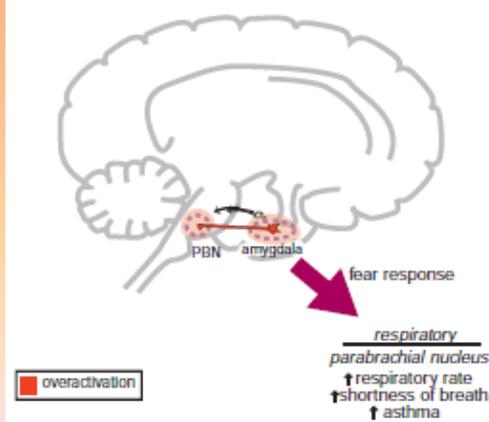
Avoidance



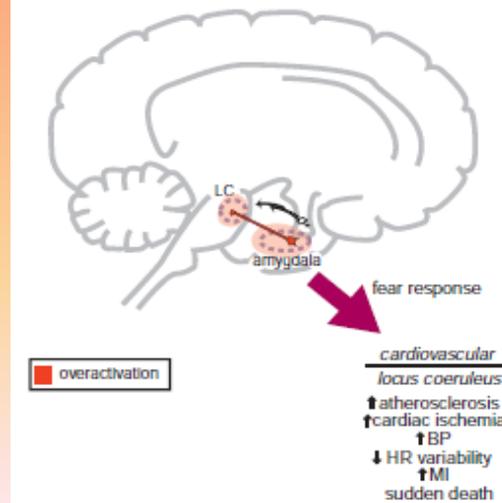
Endocrine Output of Fear



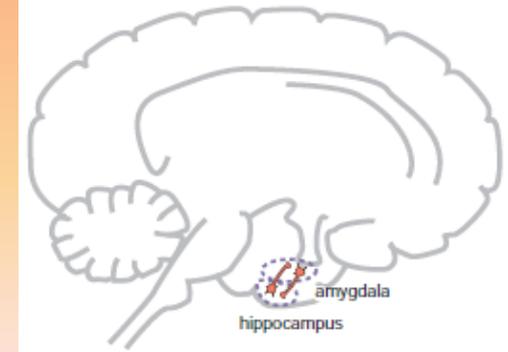
Breathing Output



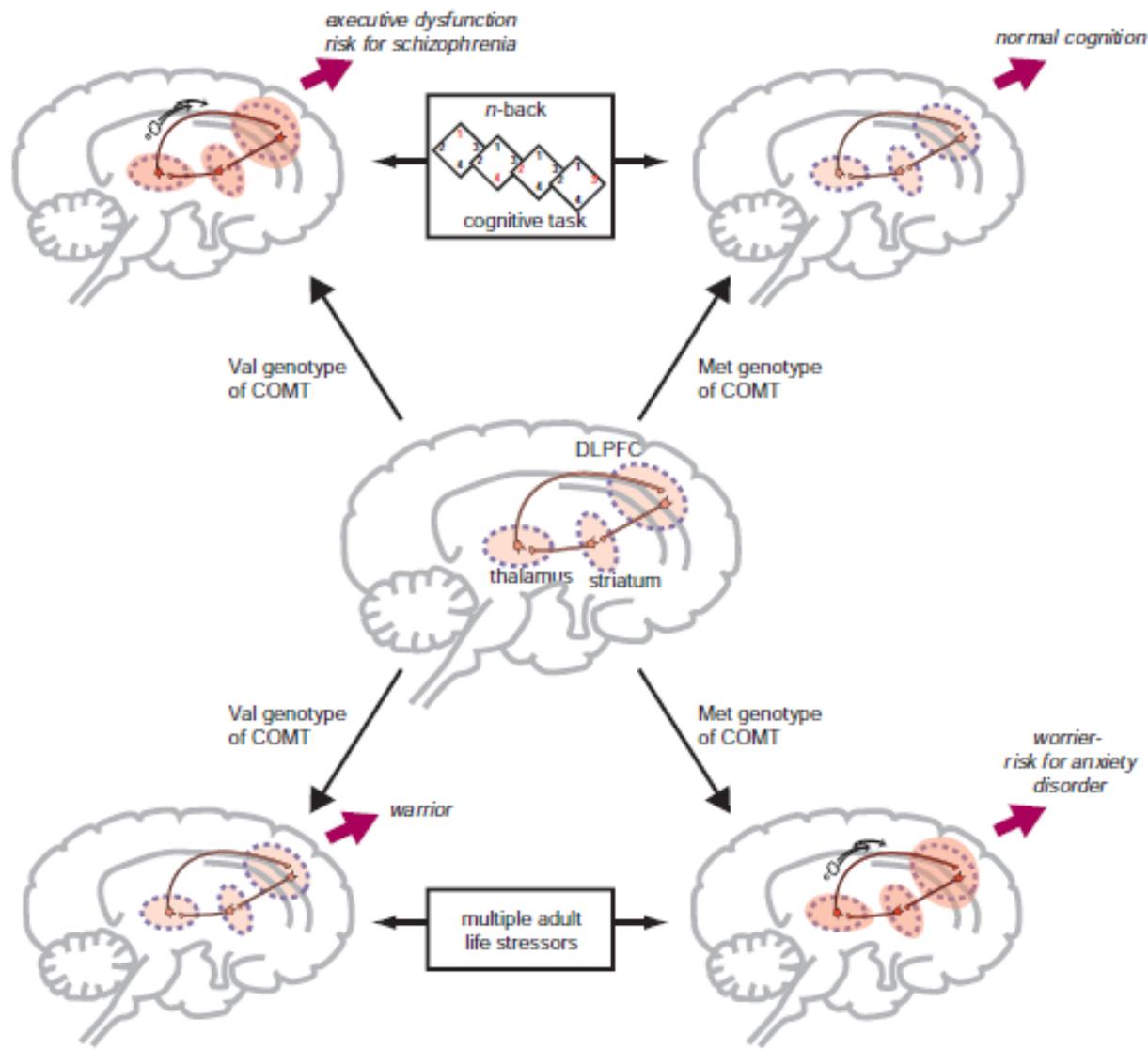
Autonomic Output of Fear



The Hippocampus:
An Internal Fearmonger

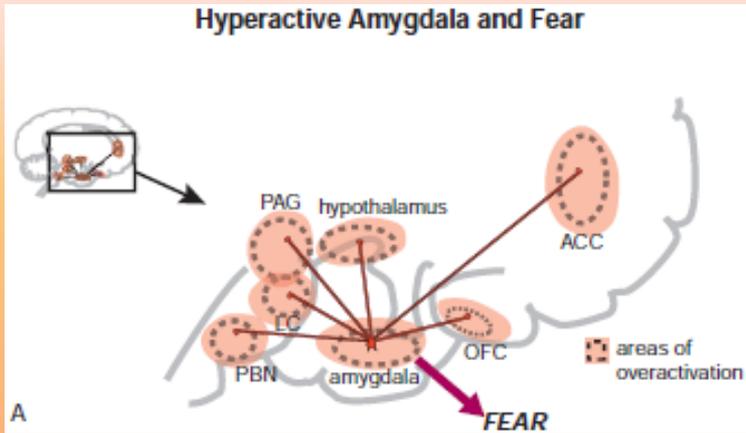


Circuito de preocupación

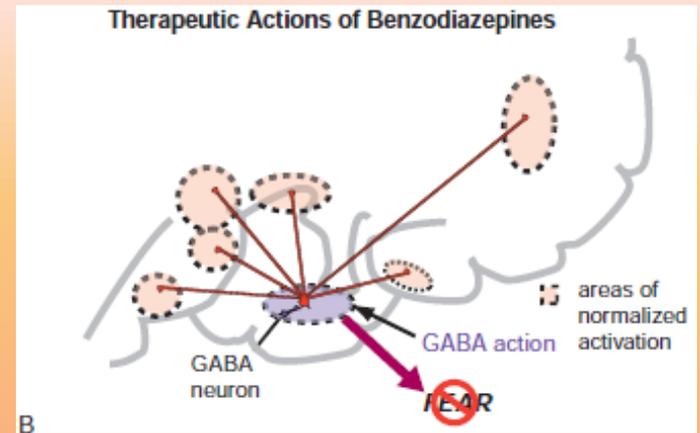


Miedo y ansiolisis

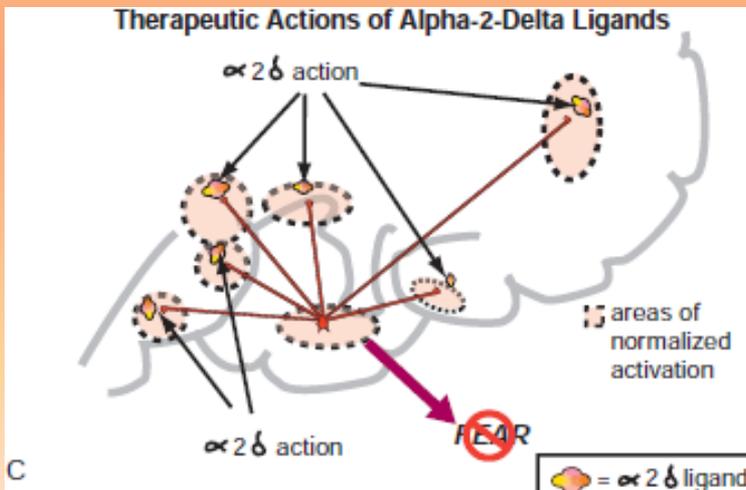
Hyperactive Amygdala and Fear



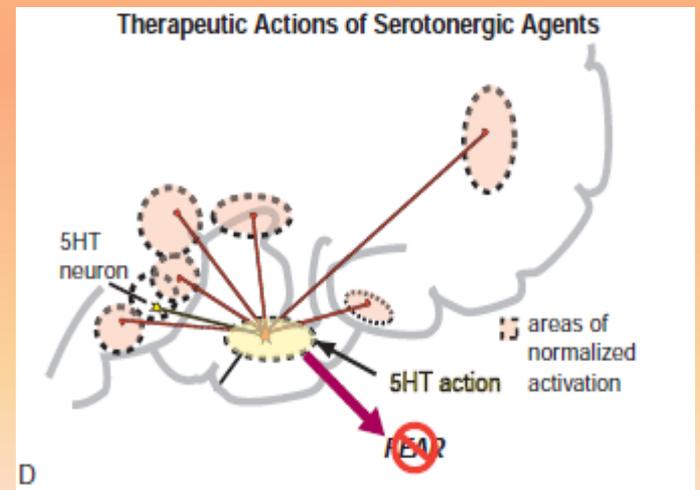
Therapeutic Actions of Benzodiazepines



Therapeutic Actions of Alpha-2-Delta Ligands



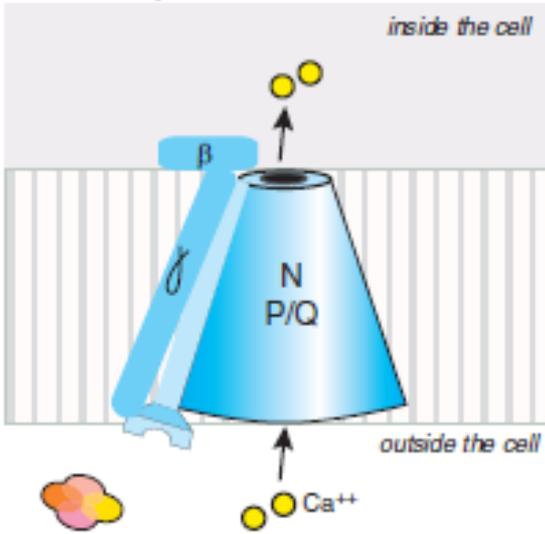
Therapeutic Actions of Serotonergic Agents



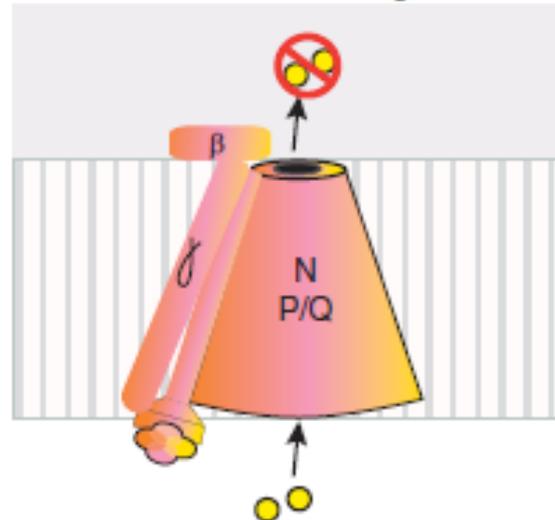
Miedo y ansiolisis

Funcionamiento de los ligandos Alfa-2-Delta

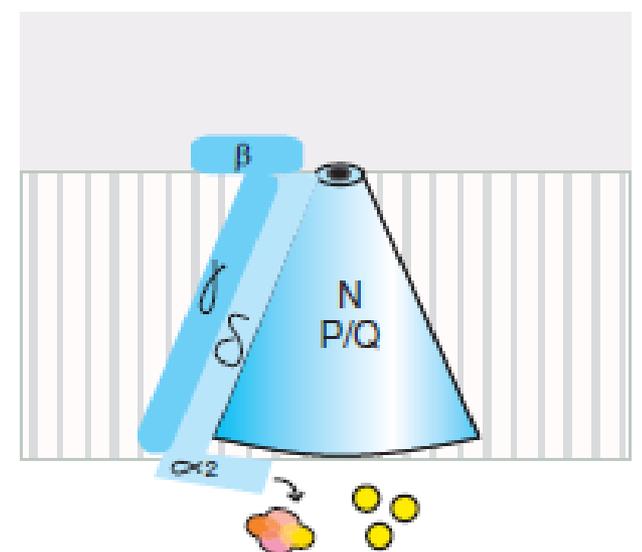
A. Open conformation of VSCC



B. Alpha-2-delta ligand binding to open conformation and inhibiting VSCC

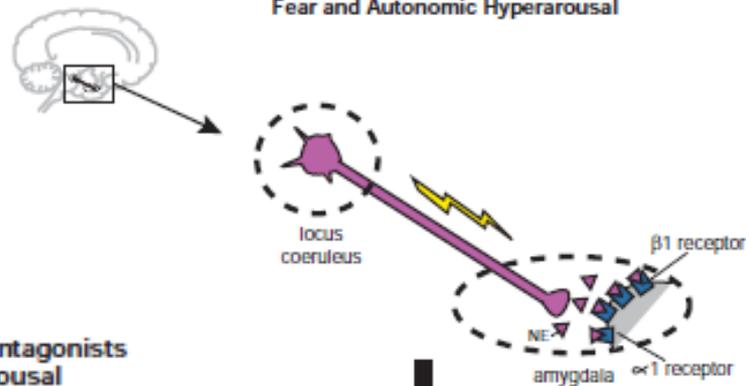


C. Closed conformation of VSCC



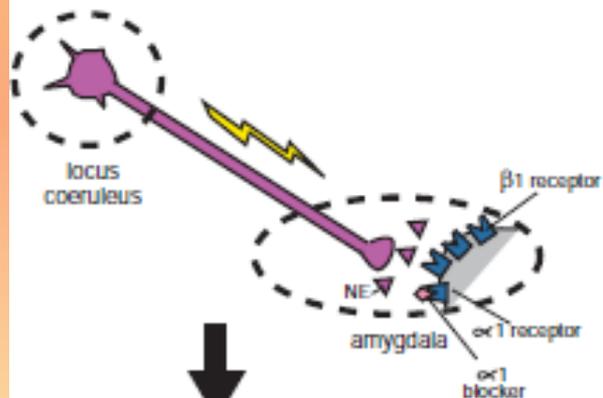
Miedo y ansiolisis

Noradrenergic Hyperactivity in Anxiety, Fear and Autonomic Hyperarousal



fear/panic attacks
tremor
sweating
tachycardia
hyperarousal
nightmares

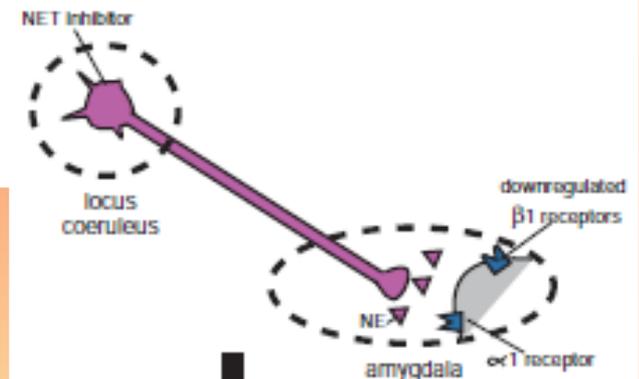
Therapeutic Actions of Alpha 1 Antagonists on Nightmares and Hyperarousal



~~fear/panic attack
tremor
sweating
tachycardia
hyperarousal
nightmares~~

B

Therapeutic Actions of NET Inhibitors on Anxiety, Fear and Hyperarousal

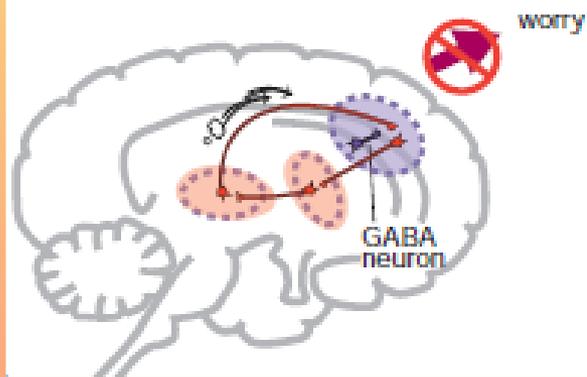


~~fear/panic attack
tremor
sweating
tachycardia
hyperarousal
nightmares~~

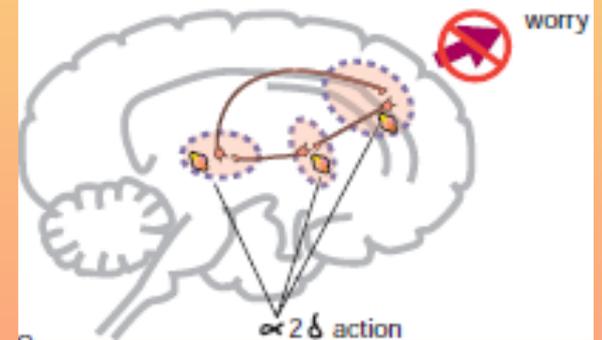
C

Preocupación y ansiolisis

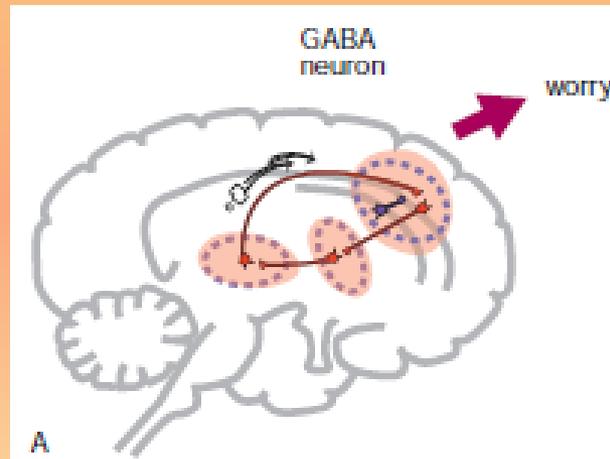
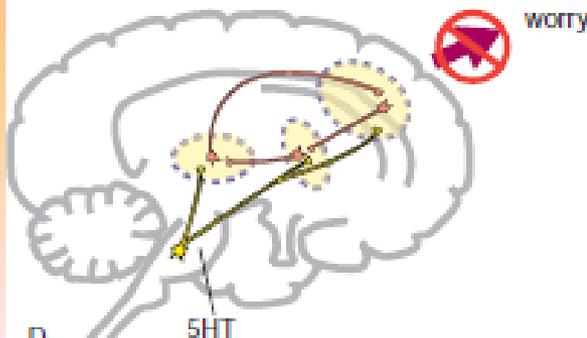
Therapeutic Actions of Benzodiazepines



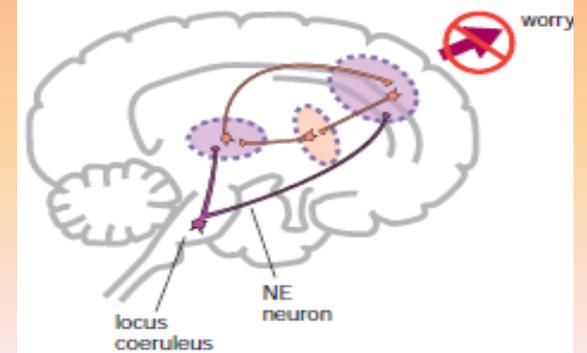
Therapeutic Actions of Alpha-2-Delta Ligands



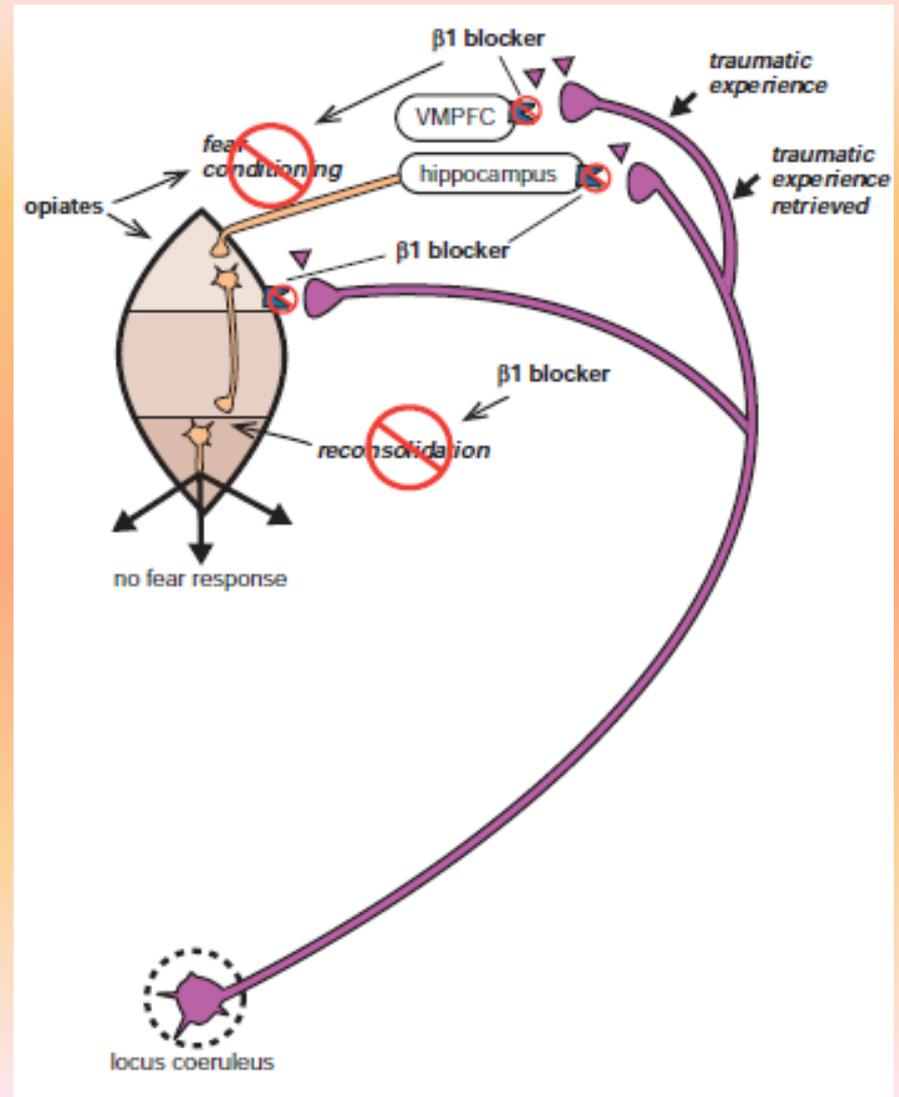
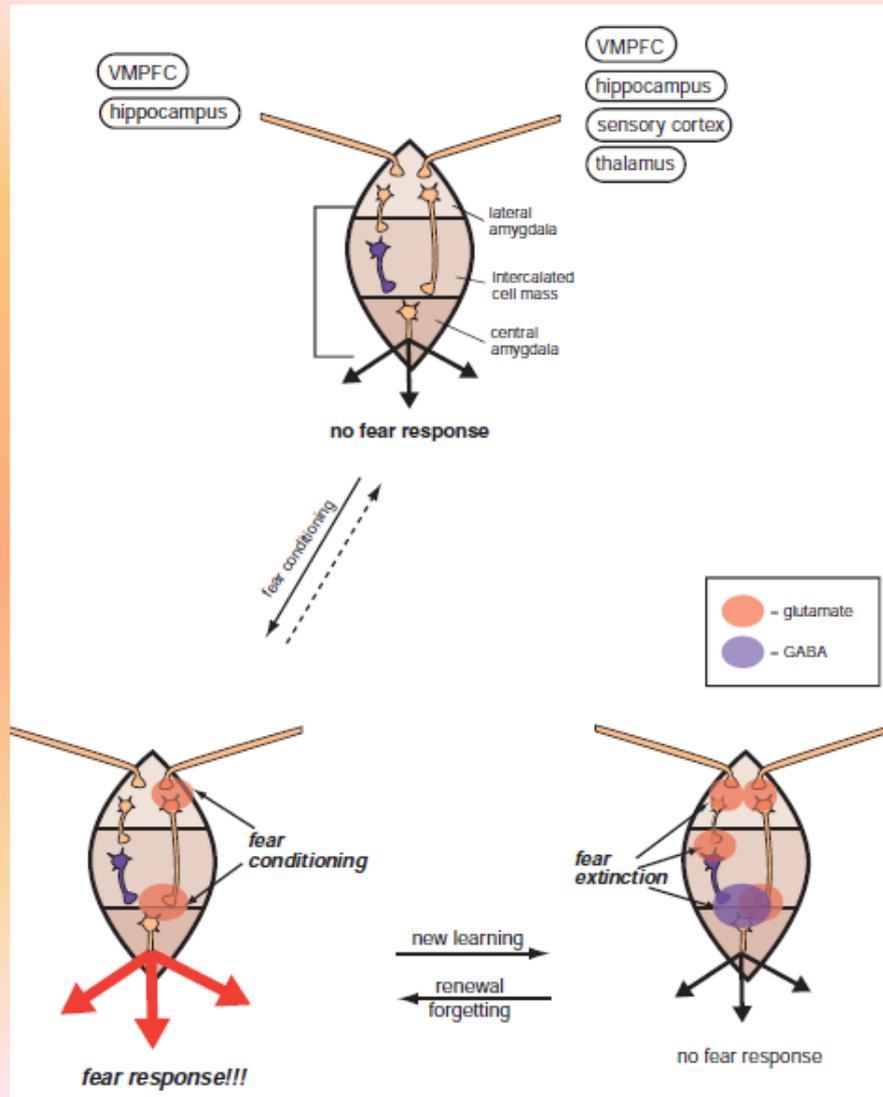
Therapeutic Actions of Serotonergic Agents



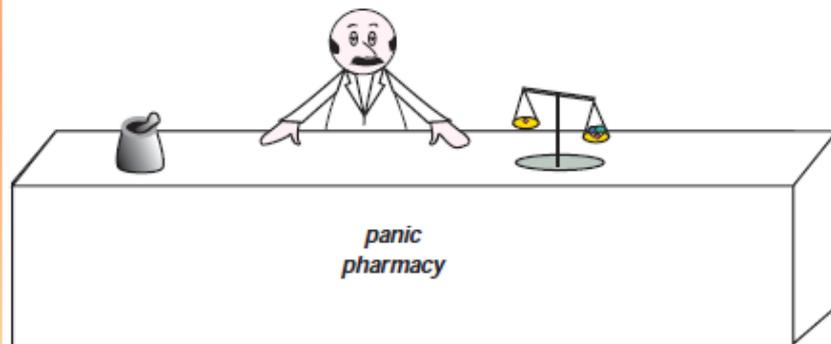
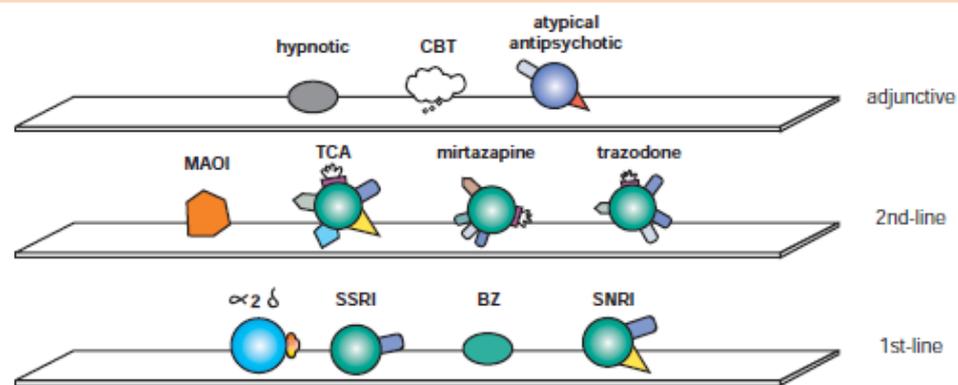
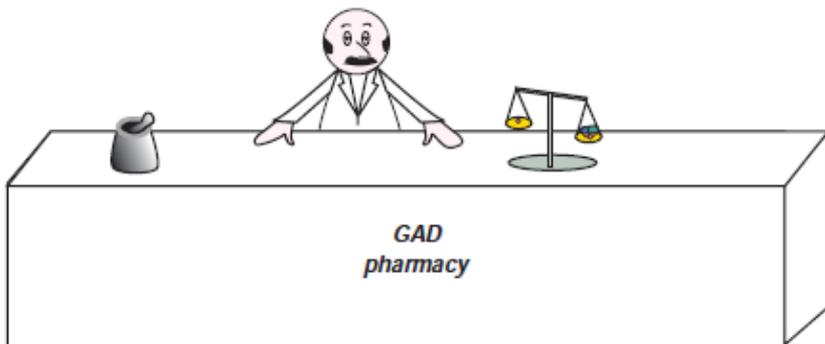
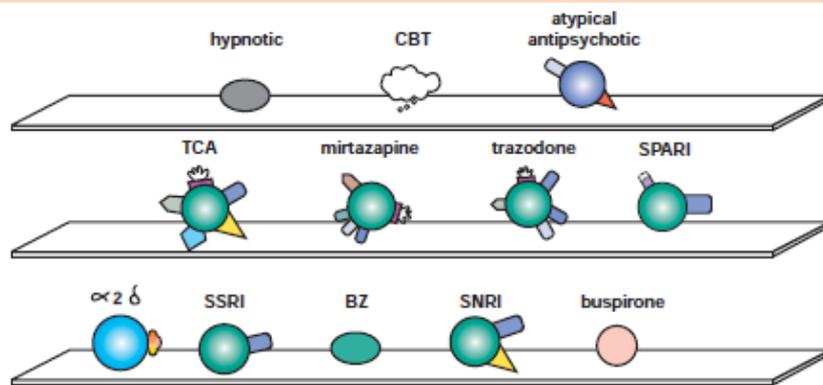
Delayed Therapeutic Actions of NET Inhibitors



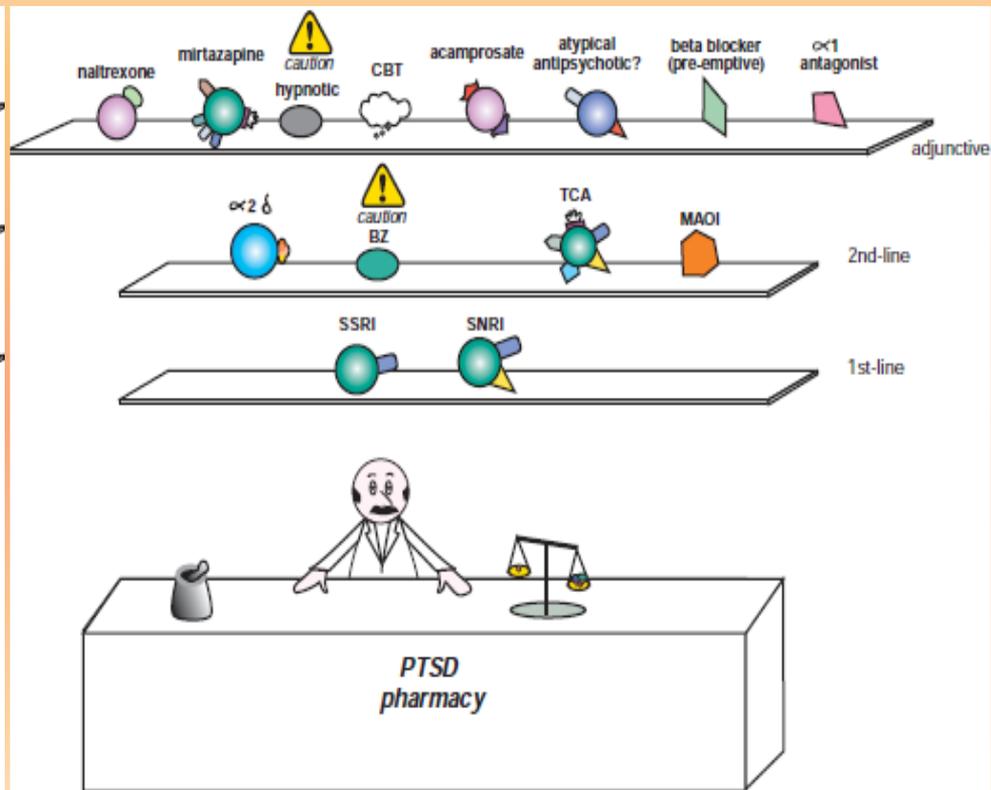
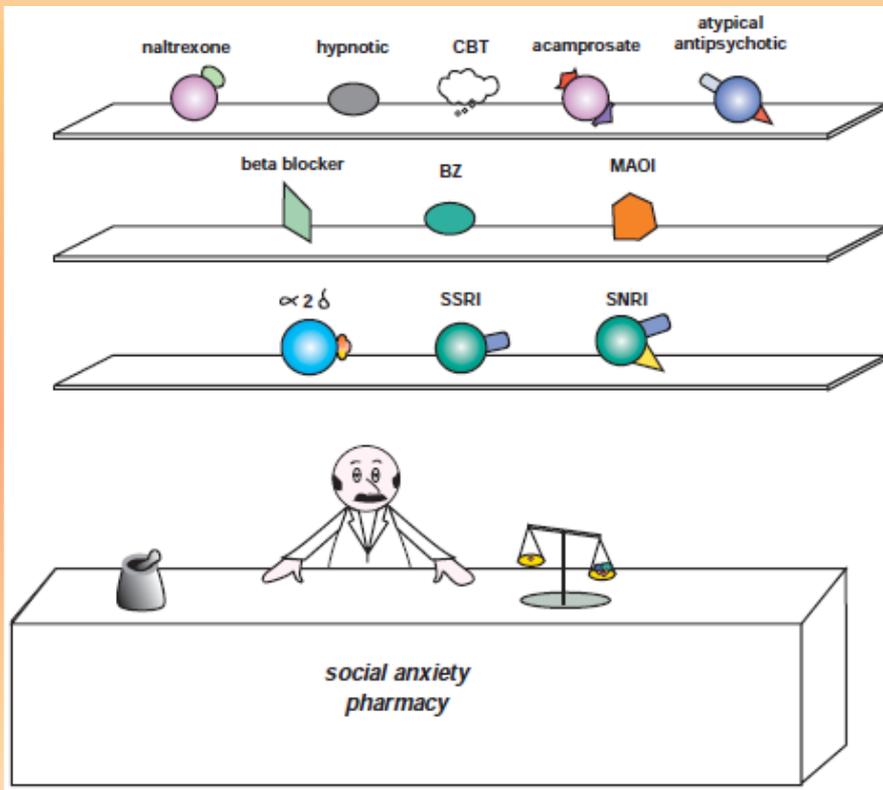
Condicionamiento, extinción y reconsolidación



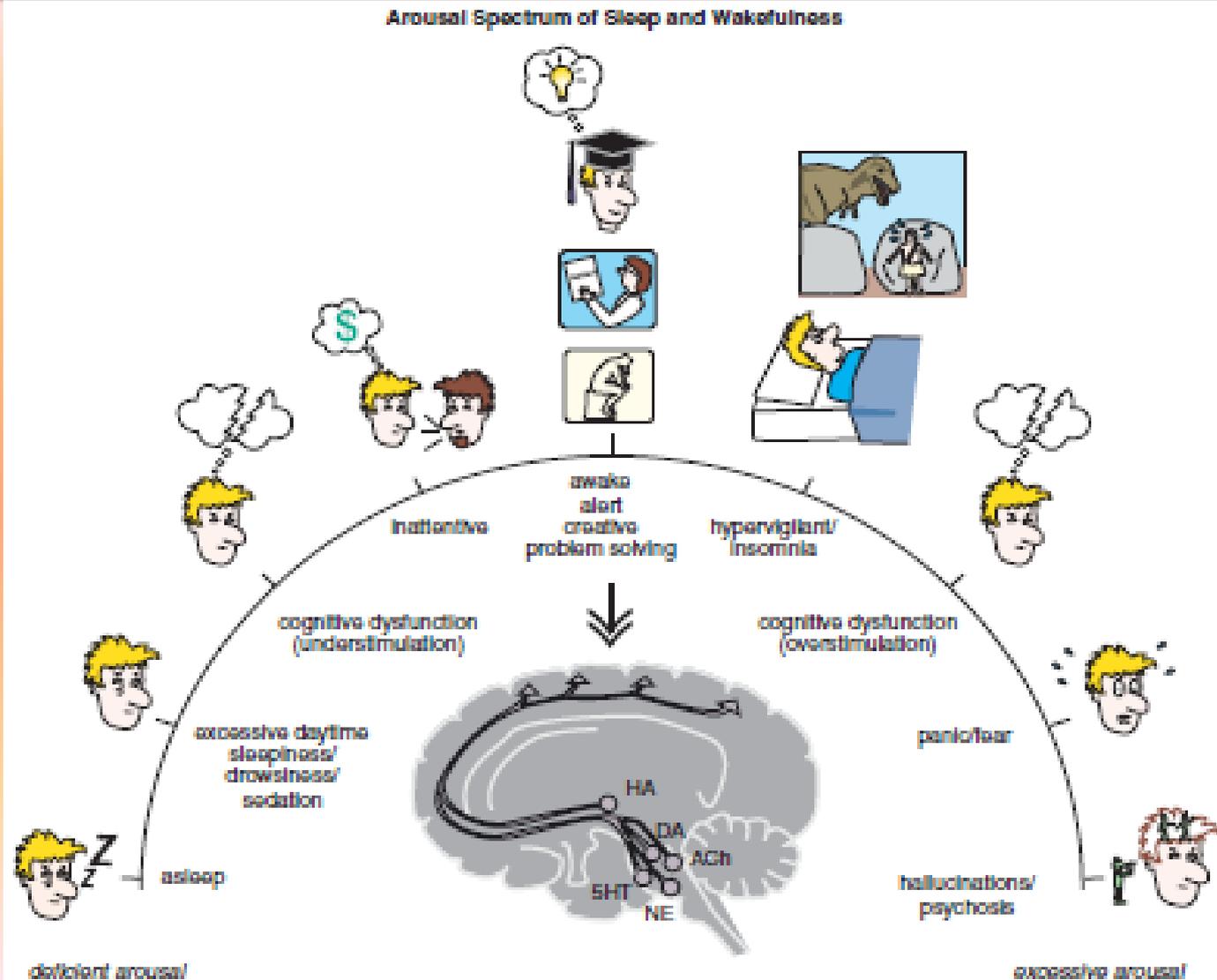
Farmacopea



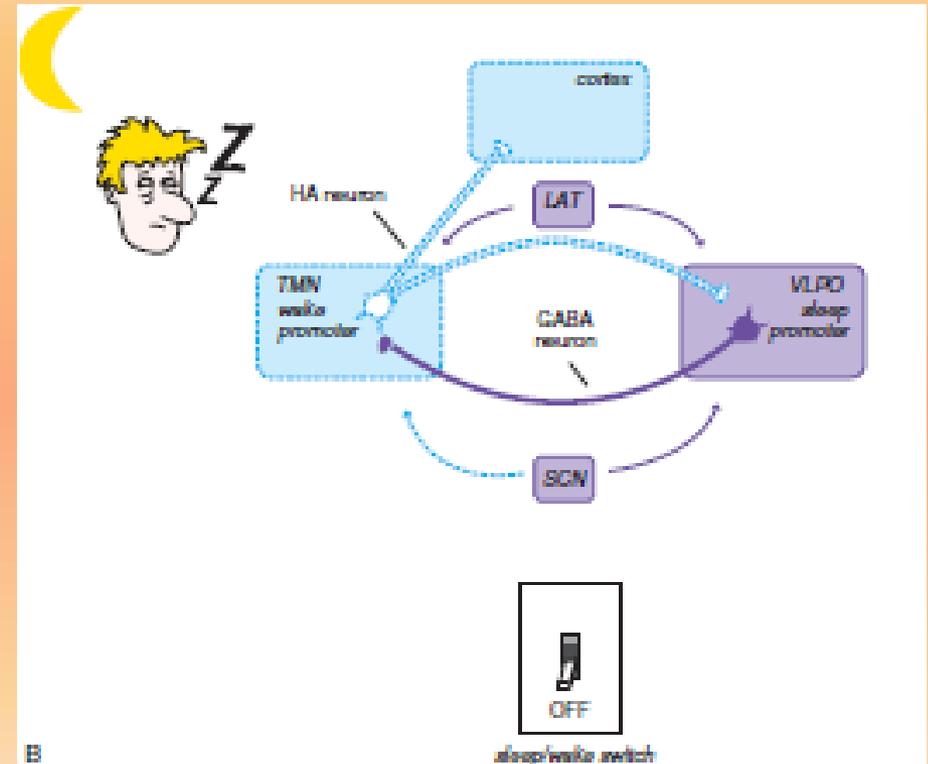
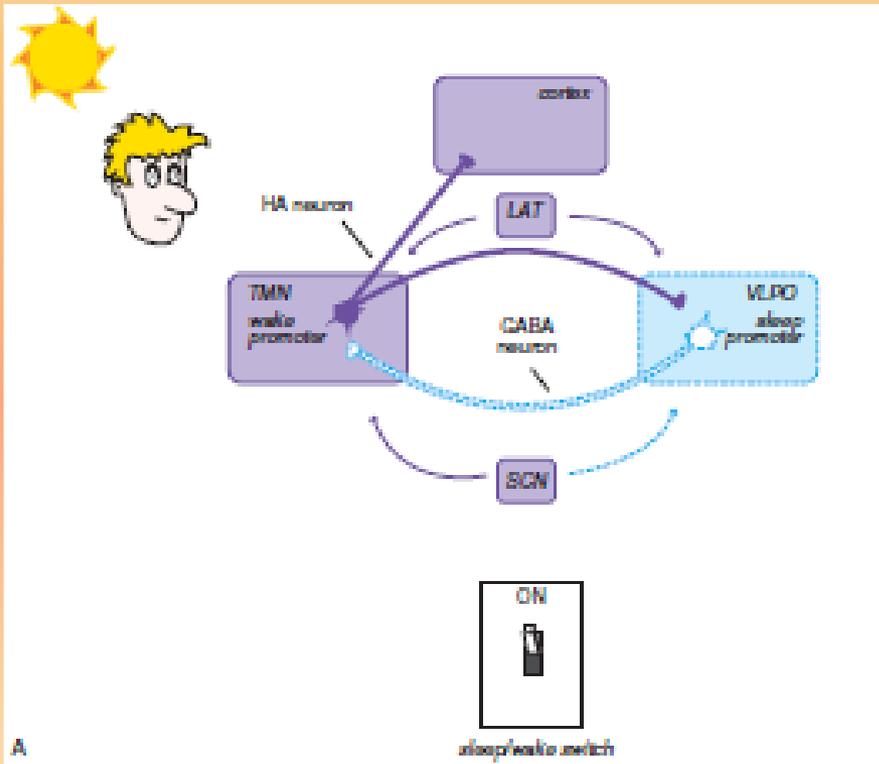
Farmacopea



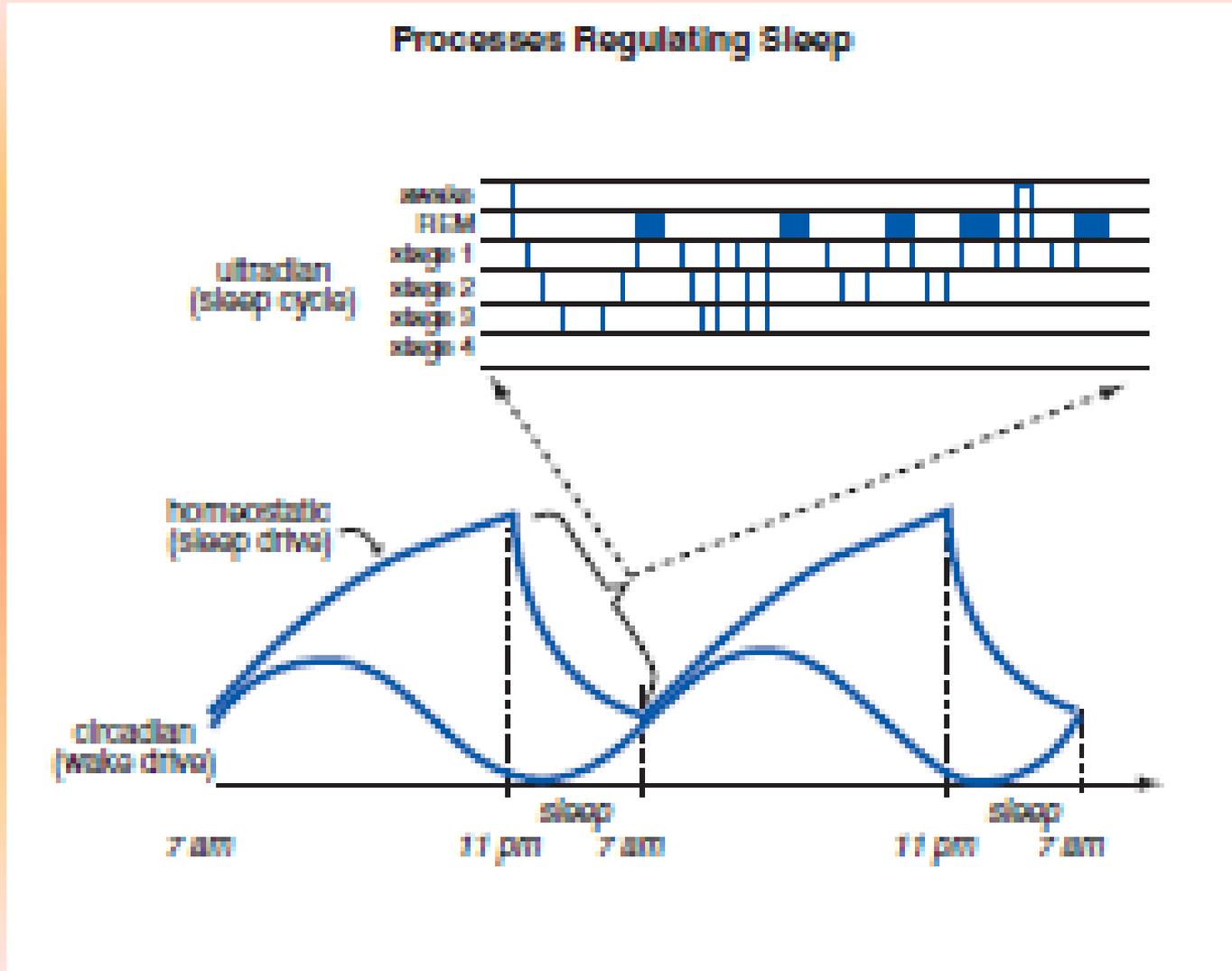
Trastornos del sueño



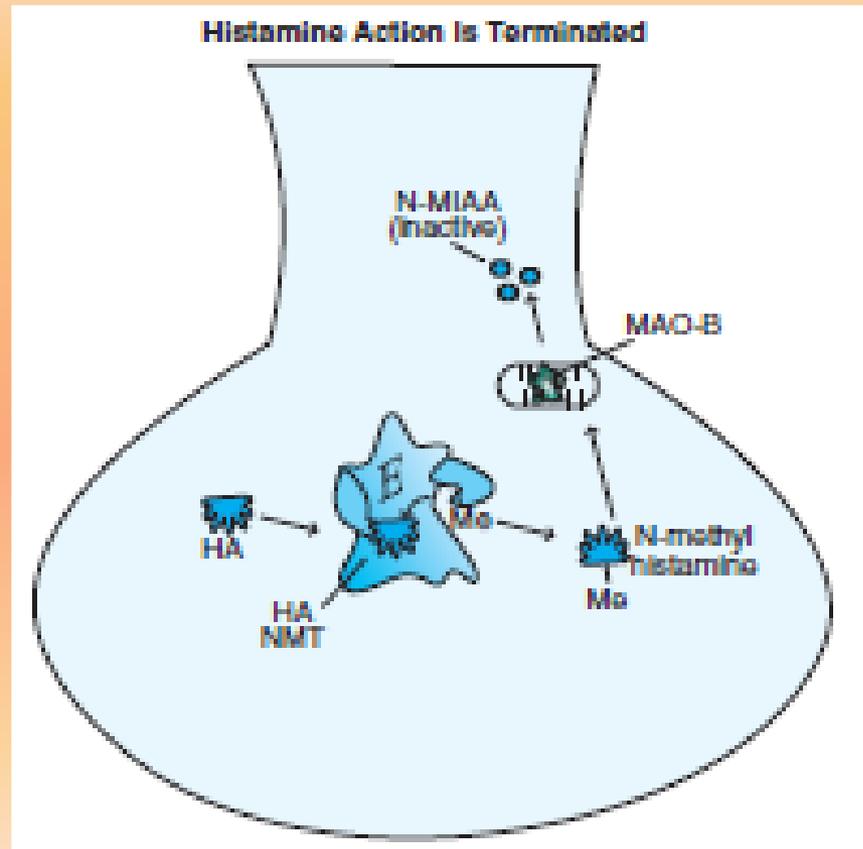
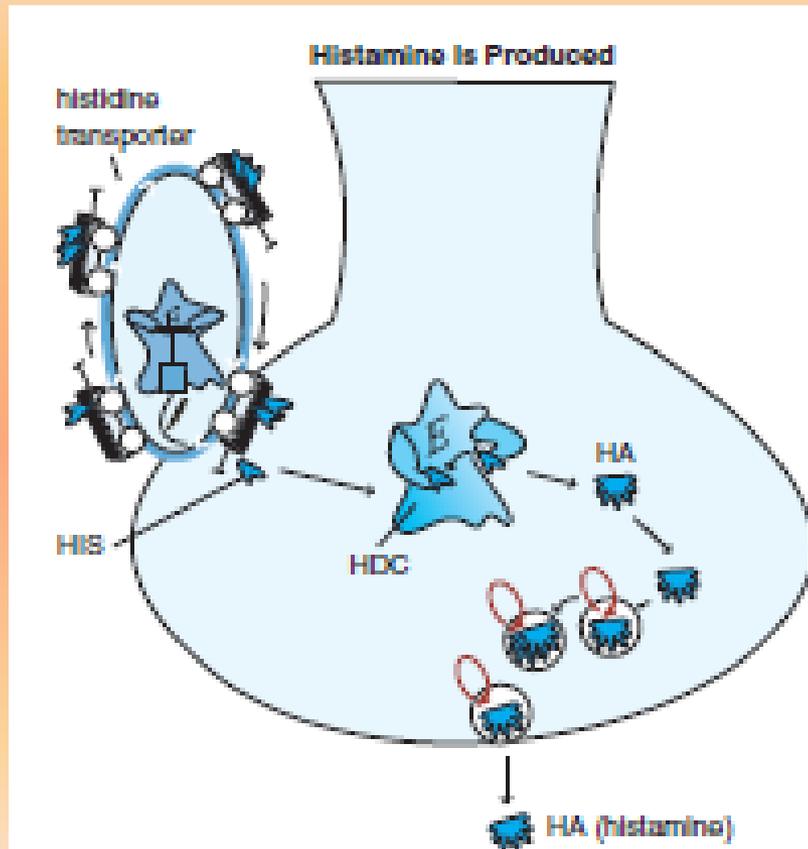
Trastornos del sueño



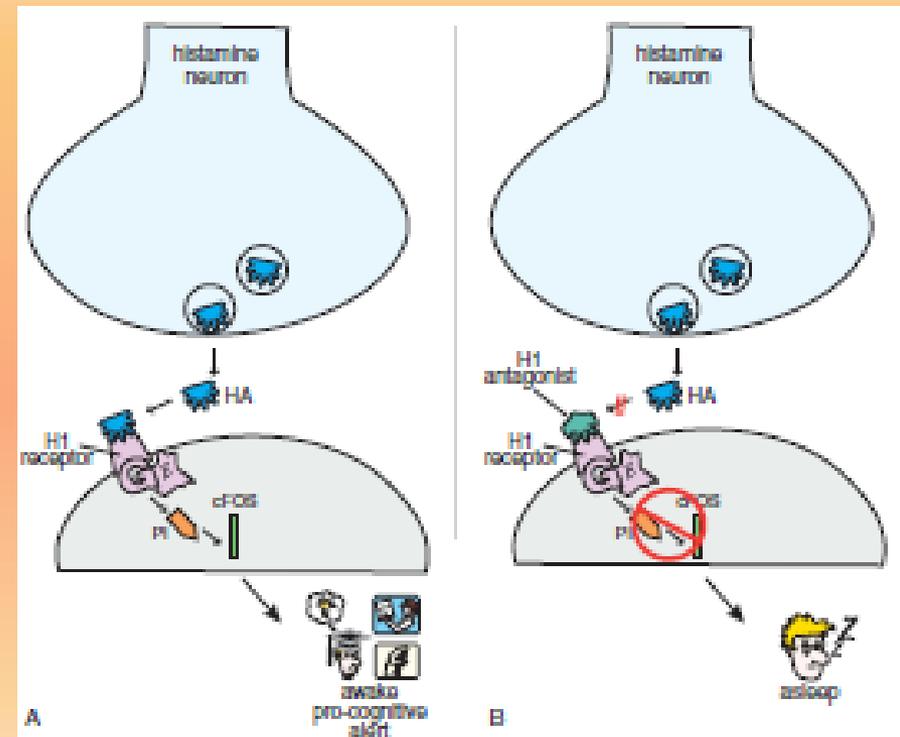
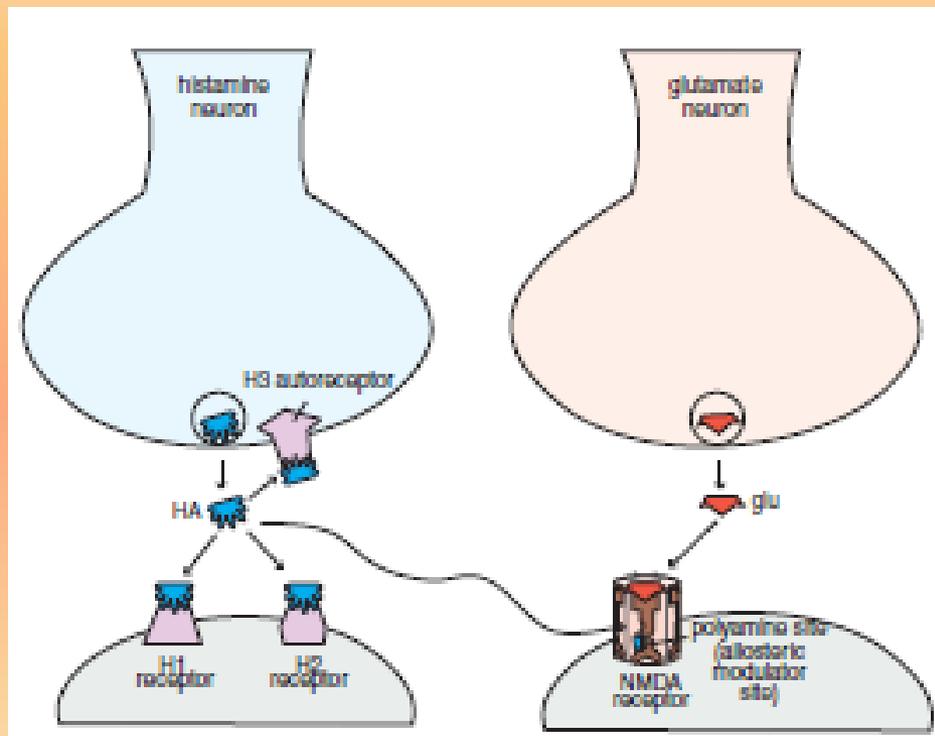
Sueño y ritmo circadiano



Histamina



Receptores de histamina

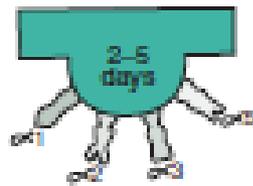


Moduladores alostéricos GABA_A

Benzo Hypnotics



flurazepam (Dalmane)



quazepam (Doral)



triazolam (Halcion)



estazolam (ProSom)



temazepam (Restoril)

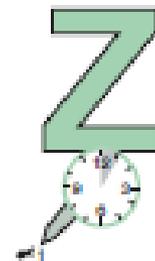
GABA_A PAMs - "Z Drugs"



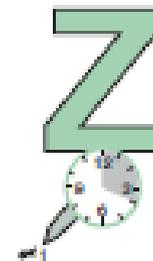
R,S-zopiclone
(Stilnox - not in U.S.)



eszopiclone
(Lunesta)



zolpidem
(Sonata)



zolpidem
(Ambien)



zolpidem CR
(Ambien CR)