Psychiatry, Medications and the Brain: Past, Present and Future

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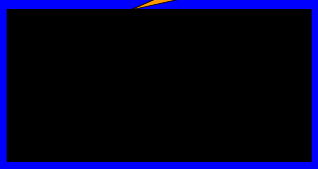
Barre, MA

OBJECTIVES

- Briefly review the history of psychiatric medication discovery and our earliest psychiatric medications.
- Review and appreciate the impressive tool box of psychiatric medications that are currently FDA approved, with a focus on antipsychotics, mood stabilizers and antidepressants.
- Understand the basic mechanism of action of some of our current commonly prescribed psychiatric medications.
- Discuss some of the possible future psychiatric drugs currently in development by the pharmaceutical industry.

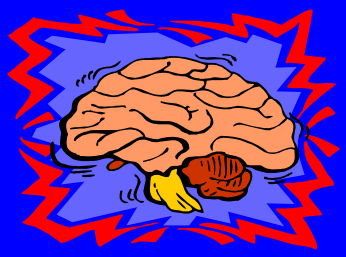
The "Black Box"

Hi!! I'm your brain. I'm a black box and nobody understands me.



Circa 1980s

The Wiring of the Brain



- There are approximately 100 billion neurons in the human brain
- There are on average 1,000 synapses/neuron
- Hence, there are approximately 100 trillion synapses in the human brain

The history of psychiatric drug discovery and our earliest psychiatric medications:

a case of serendipity

Antipsychotics - Thorazine

- Chlorpromazine (Thorazine) – FDA approved 1954
- Antipsychotic efficacy discovered by a French physician in 1952 who observed that agitated psychotic patients with nausea, had their nausea, agitation *and psychosis* improve with chlorpromazine.
- Shifted the focus of treatment to the "positive symptoms" of schizophrenia.

Introduction of Chlorpromazine (Thorazine) to the United States

Significantly decreased use of:

- ECT (electroconvulsive therapy)
- Psychosurgery
- Insulin shock therapy
- Provided a treatment which facilitated the deinstitutionalization movement

Consequence of the introduction of Chlorpromazine to the US Market

Year	# of in-patients in state and county psychiatric hospitals in the USA
1955	558,922
1970	337,619
1980	150,000
1990	115,000

McKenzie, James F.; Pinger, R. R.; Kotecki, Jerome Edward (2008). *An introduction to community health*. Boston: Jones and Bartlett Publishers

October 31, 1963 President John F. Kennedy signed the Community Mental Health Act into law.

"The time has come for a bold new approach, … If we apply our medical knowledge and social insights fully, all but a small portion of the mentally ill can eventually achieve a wholesome and constructive social adjustment."

Year	# of in-patients institutionalized in NH State Hospital
1963	2,700
2013	120

Mood Stabilizer - Lithium: our oldest psychiatric medication

- Reportedly used in spring water to treat mania in the Roman and Greek eras.
- 19th century used to treat gout.
- 1870s used to treat mania in USA and Denmark.
- 1900 lithium abandoned as a medication because pharmaceutical companies could not patent it.

Mood Stabilizer - Lithium:
our oldest psychiatric medication

- 1949 Australian psychiatrist John Cade rediscovered the effectiveness of Li salts in the treatment of mania.
- 1970 FDA approved for mania.
- 1974 FDA approved for the prevention of manic-depressive disorder.

Clue about depression - Reserpine:
an antihypertensive that lowers blood pressure by depleting norepinephrine

- **1952 Indian snakeroot (Rauwolfia serpentina) was found to contain reserpine.**
- **1954 reserpine was introduced in the USA.**
- **Norepinephrine depletion was associated with increased depression.**
- **Contributed significantly to the "monoamine depletion hypothesis of depression" (norepinephrine, dopamine and serotonin).**

First Antidepressant - Iproniazid

- 1952 researchers observed that patients treated with isoniazid for tuberculosis became “inappropriately happy”.
- Structure was modified, and in 1958 iproniazid was FDA approved as the first antidepressant.
- 1961 withdrawn from the US market due to liver toxicity.
- Mechanism of action is that of a monoamine oxidase inhibitor (MAOI). Raises levels of norepinephrine, dopamine and serotonin.
- Followed by the MAOIs Nardil and Parnate.

Psychiatric Medications Today

From Serendipity:
To Molecular “fingerprinting”

Antipsychotics

"Typical" versus "Atypical"

Medications from Thorazine to pre-Clozaril (1989) are all classified as "Typical".

These medications block the Dopamine-2 receptor tighter than the Serotonin 5HT-2A receptor.

Antipsychotics

"Typical" versus "Atypical"

Medications from Clozapine (1989) to Latuda (2011) are all classified as "Atypical".

These medications block the Serotonin 5HT-2A receptor tighter than the Dopamine-2 receptor, with the exception of Abilify which has an entirely different mechanism of action (antagonist-partial agonist at Dopamine D-2).

Antipsychotics - Typical

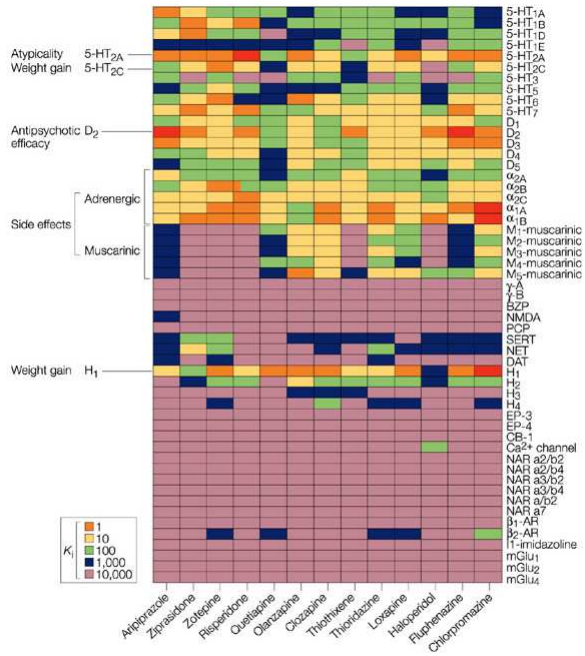
(Incomplete list)

- Thorazine
- Serentil
- Mellaril
- Loxitane
- Moban
- Orap
- Trilafon
- Stelazine
- Navane
- Haldol
- Prolixin

Antipsychotics – Atypical

(in the order of market entry)

- Clozaril
- Risperdal
- Zyprexa
- Seroquel
- Geodon
- Abilify
- Invega
- Fanapt
- Saphris
- Latuda



53 receptors

***Roth BL, Sheffler DJ and Kroeze WK. Nat Rev Drug Discov. 2004 Apr;3(4):353-9**

Nature Reviews | Drug Discovery

Medications for Bipolar Disorder

Simple salt	Anticonvulsants	Antipsychotics
Lithium	Depakote	Typical
	Tegretol (Equetro)	Atypical
	Lamictal	

Agents Approved for Bipolar Disorder in the U.S.

Acute Mania		Acute Depression	
Year	Drug	Year	Drug
1970	Lithium	2003	Olanzapine-fluoxetine combination
1973	Chlorpromazine	2006	Quetiapine
1994	Divalproex	2013	Lurasidone
2000	Olanzapine*		
2003	Risperidone*		
2004	Quetiapine*		
2004	Ziprasidone		
2004	Aripiprazole		
2004	Carbamazepine		
2009	Asenapine		

FDA-Approved Medication for treating Bipolar I Mania

- Lithium (Eskalith, Lithobid)
- Divalproex (Depakote)
- Carbamazepine (Equetro)
- Chlorpromazine (Thorazine)
- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)
- Asenapine (Saphris)

Antidepressants

- Classes:
  - Monoamine oxidase inhibitors (3)
  - Tricyclic Antidepressants (10)
  - Selective Serotonin Reuptake Inhibitors (6)
  - Serotonin Norepinephrine Reuptake Inhibitors (4)
  - Other (6)

Antidepressants

- Classes:
  - Monoamine oxidase inhibitors
    - Nardil
    - Parnate
    - Emsam (transdermal patch)

Antidepressants

- Classes:
  - Tricyclic Antidepressants
    - Amitriptyline
    - Imipramine
    - Nortriptyline
    - Desipramine
    - Clomipramine
    - Doxepin
    - Amoxapine
    - Trimipramine
    - Protriptyline
    - Maprotiline
      - *tetracyclic*

Antidepressants

- Classes:
  - Selective Serotonin Reuptake Inhibitors
    - Prozac
    - Zoloft
    - Paxil
    - Luvox
    - Celexa
    - Lexapro

Antidepressants

- Classes:
  - Serotonin Norepinephrine Reuptake Inhibitors
    - Effexor
    - Cymbalta
    - Pristiq
    - Fetzima

Antidepressants

- Classes:
  - Other
    - Trazodone
    - Serzone
    - Remeron
    - Wellbutrin
    - Viibryd
    - Brintellix

Our evolving understanding of how psychiatric medications work:

mechanism of action at the cellular level

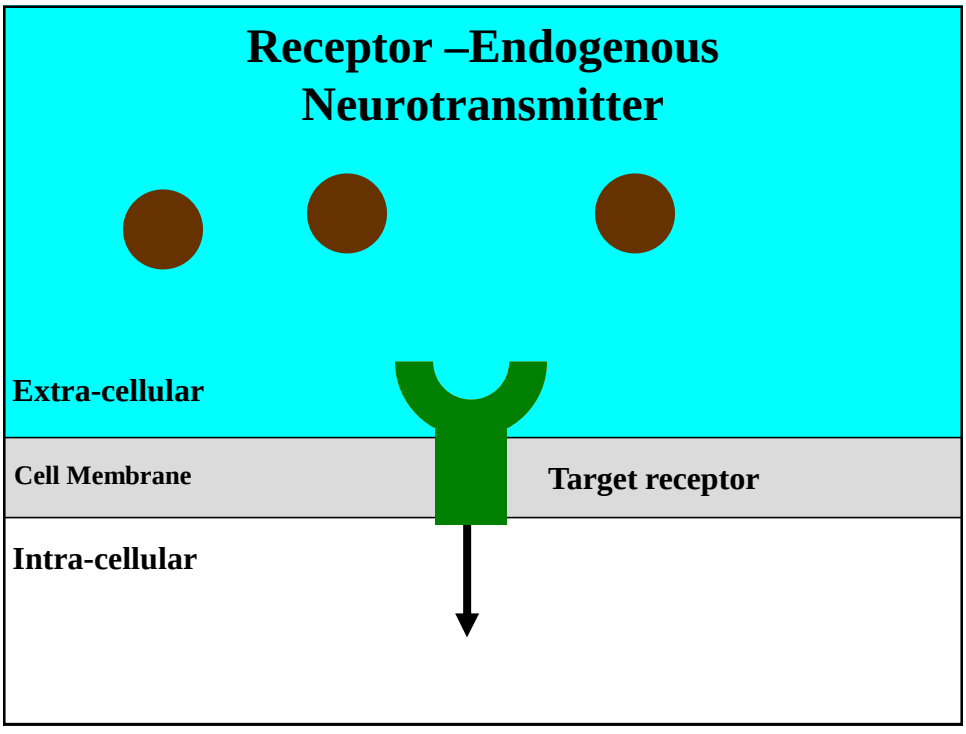
Affective and Psychotic Disorders: Three important monoamine neurotramsmitters

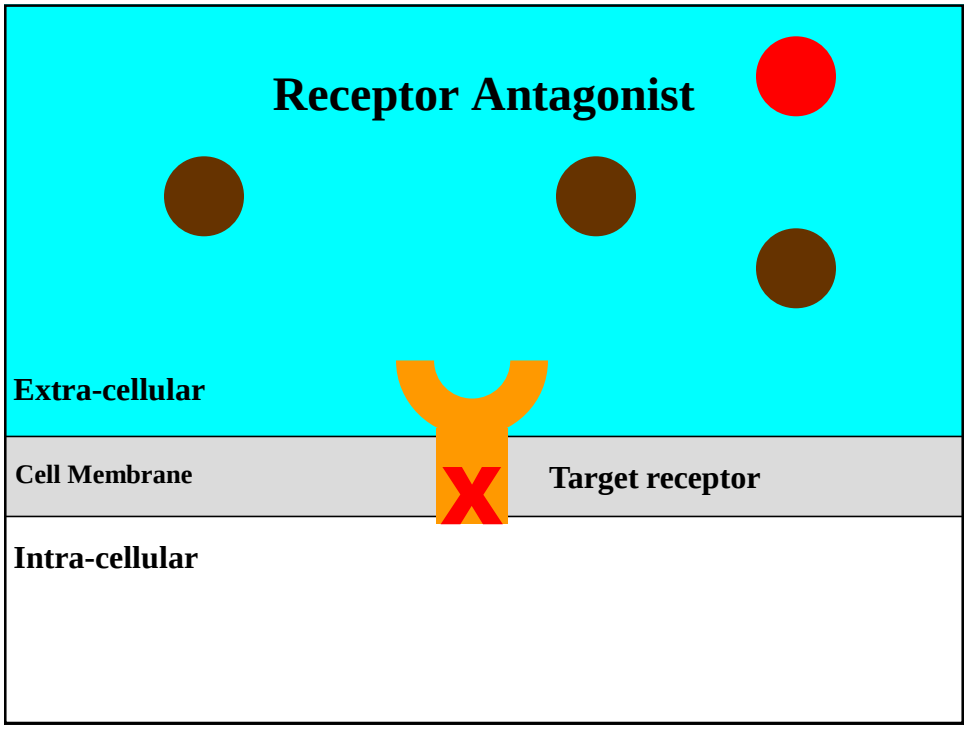
- Serotonin
- Dopamine
- Norepinephrine

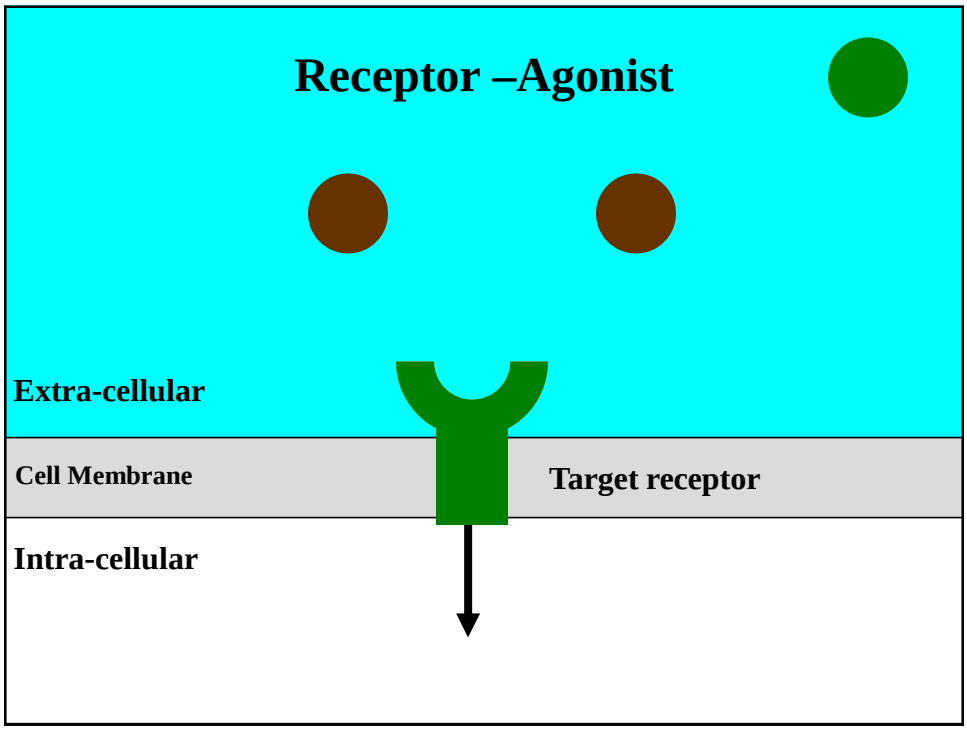
Current pharmacological agents for the treatment of schizophrenia

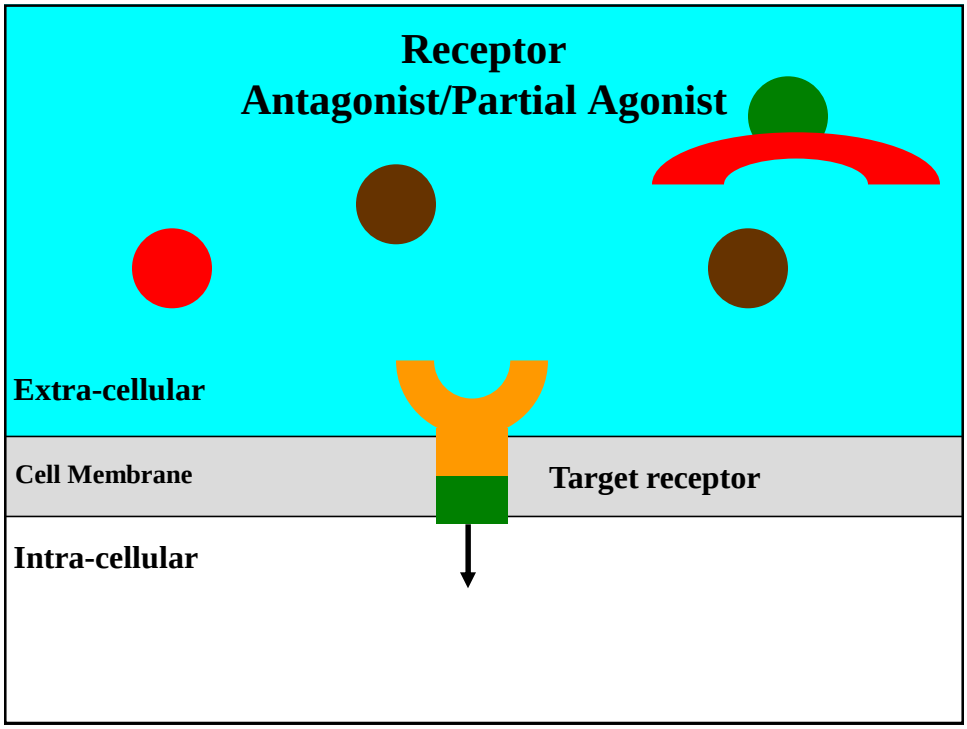
- All FDA approved medications that treat the postitive symptoms of schizophrenia share the property of blocking the dopamine D-2 receptor.

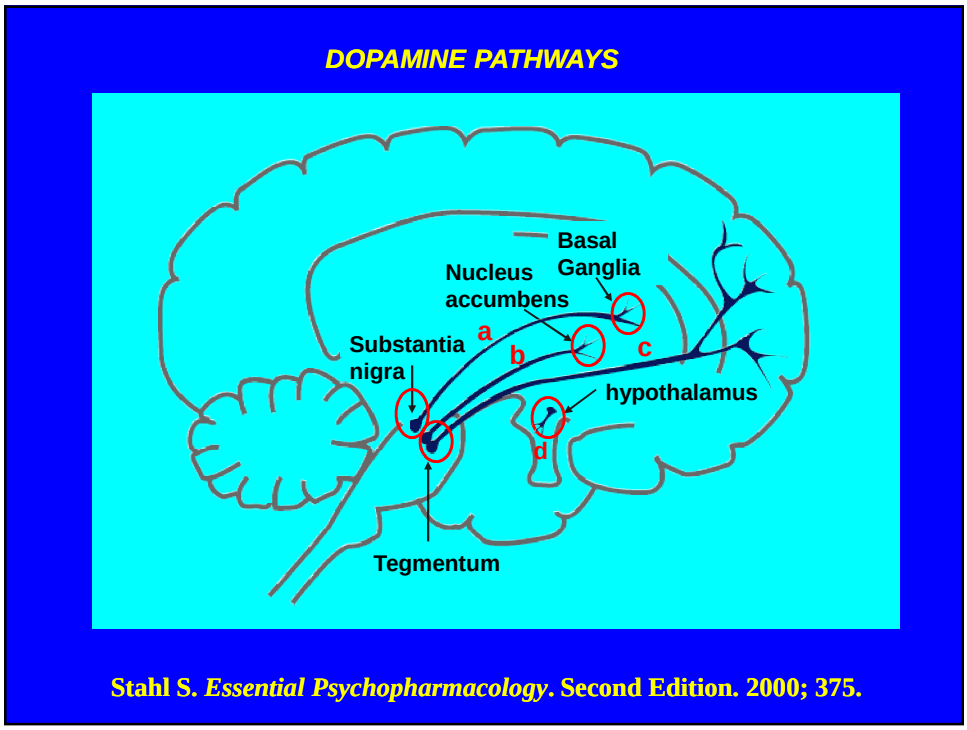
Receptor –Endogenous Neurotransmitter



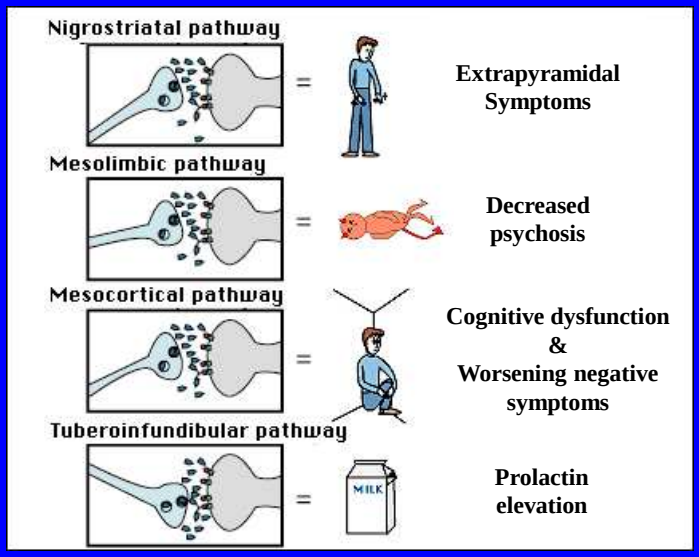

Receptor Antagonist
Extra-cellular
Cell Membrane
Target receptor
Intra-cellular


Receptor –Agonist
Extra-cellular
Cell Membrane
Target receptor
Intra-cellular


Receptor
Antagonist/Partial Agonist
Extra-cellular
Cell Membrane
Target receptor
Intra-cellular


DOPAMINE PATHWAYS
Basal Ganglia
Nucleus accumbens
Substantia nigra
a
b
c
d
hypothalamus
Tegmentum
Stahl S. Essential Psychopharmacology. Second Edition. 2000; 375.

Consequences of D-2 antagonism at the 4 dopamine circuits



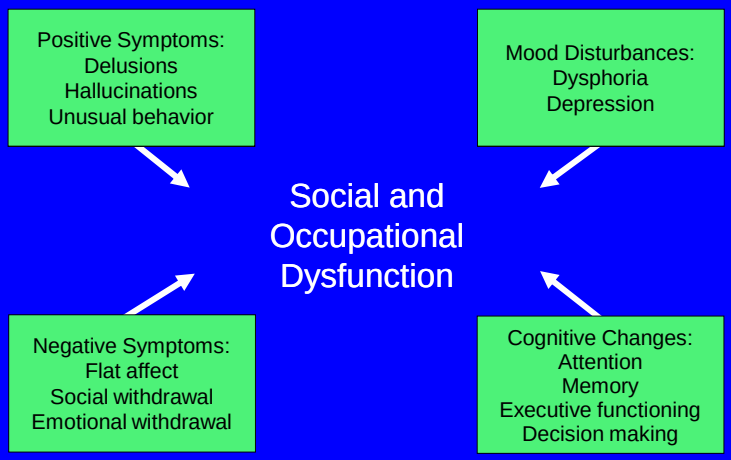
Adapted from: Stahl S. *Essential Psychopharmacology*. Second Edition. 2000; 403-407.

Consequences of increasing occupancy of D-2 receptors

% Occupancy of D-2 receptors	Clinical Consequences
< 60%	minimal
60 – 80%	Antipsychotic/antimanic
> 70%	Elevation of prolactin
> 80%	Increasing EPS

Kapur S. Mol Psychiatry. 1998 Mar; 3(2):135-40.
Tauscher J, et al. Psychopharmacology. 2002 Jun; 162(1):42-9.
Grunder G, et al. Arch Gen Psychiatry. 2003 Oct; 60(10):974-7.
Seeman P. Can J Psychiatry. 2002 Feb; 47(1):27-38.

Symptoms of schizophrenia

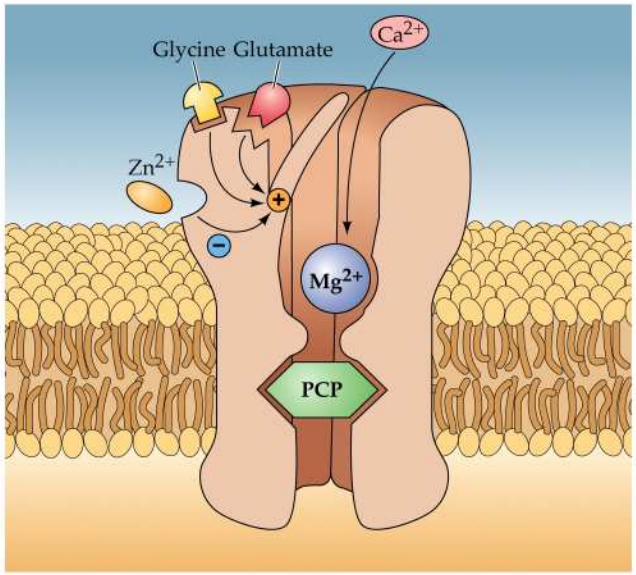


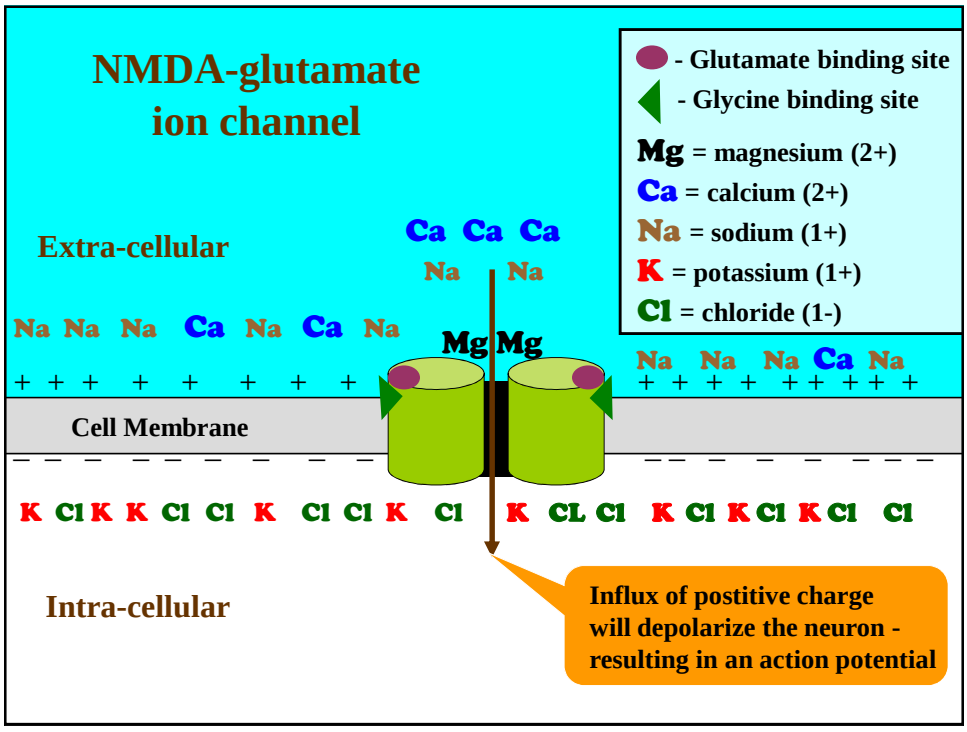
Black DW et al. *Introductory Textbook of Psychiatry.* 2001;204-228.
Siris SG. *Schizophrenia.* 1995;128-145.
Harvey PD et al. *Am J Psych*. 2001;158:176-184.
Stahl SM. *Essential Psychopharmacology*. 2nd ed. 2000;385-386.

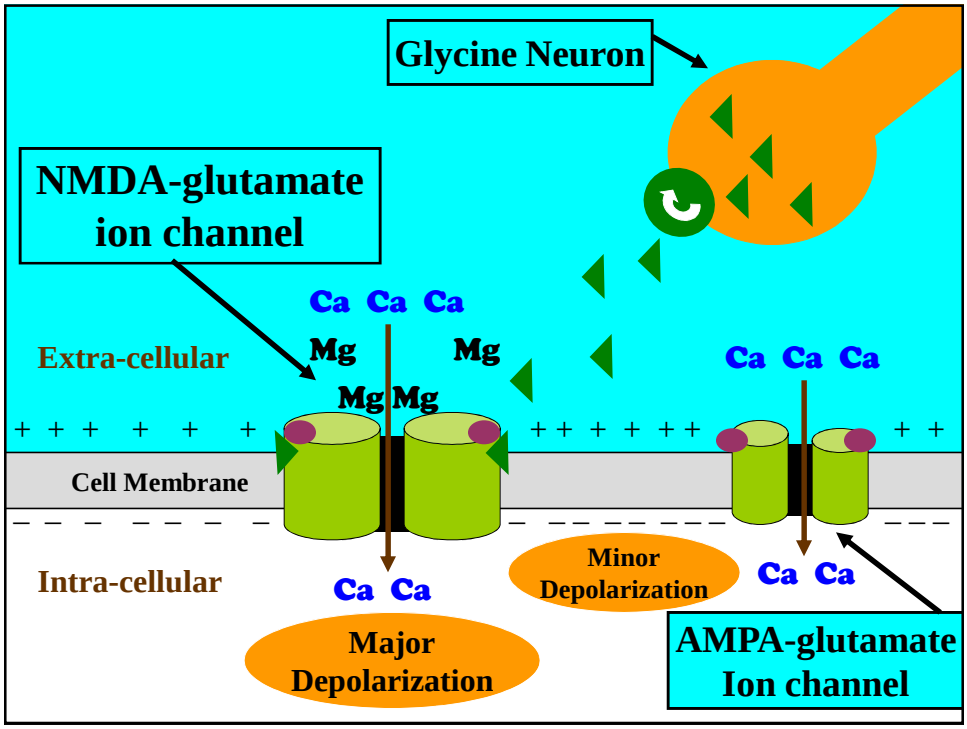
Animal models of schizophrenia

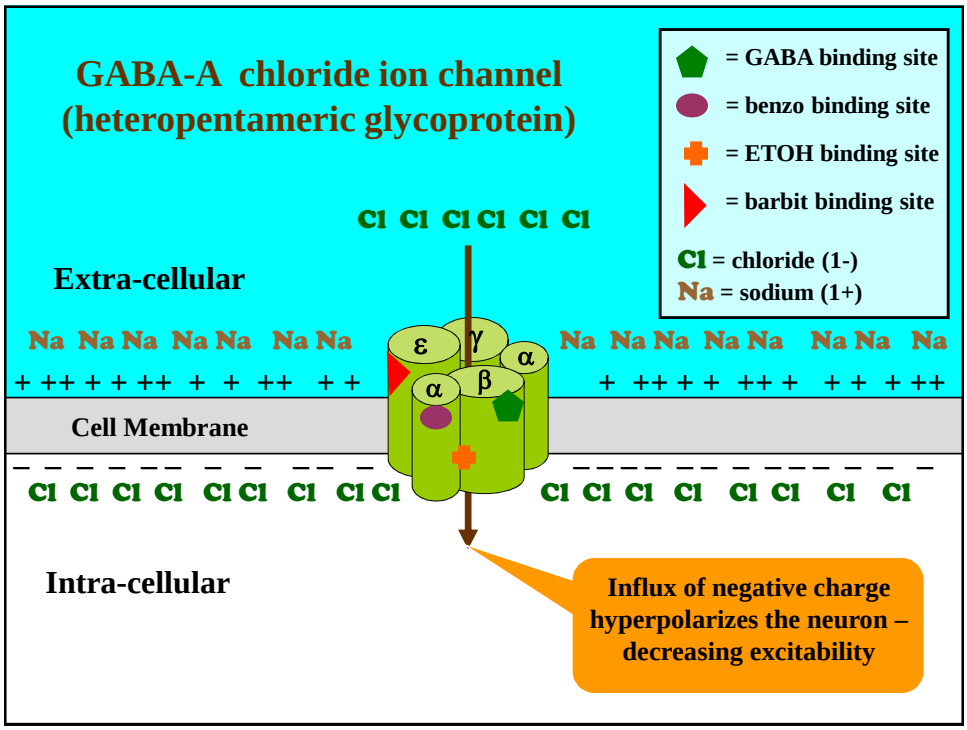
- **NMDA-glutamate antagonists induce both positive and negative schizophrenia-like symptoms in animal models:**
  - **Ketamine**
  - **Phencyclidine (PCP)**

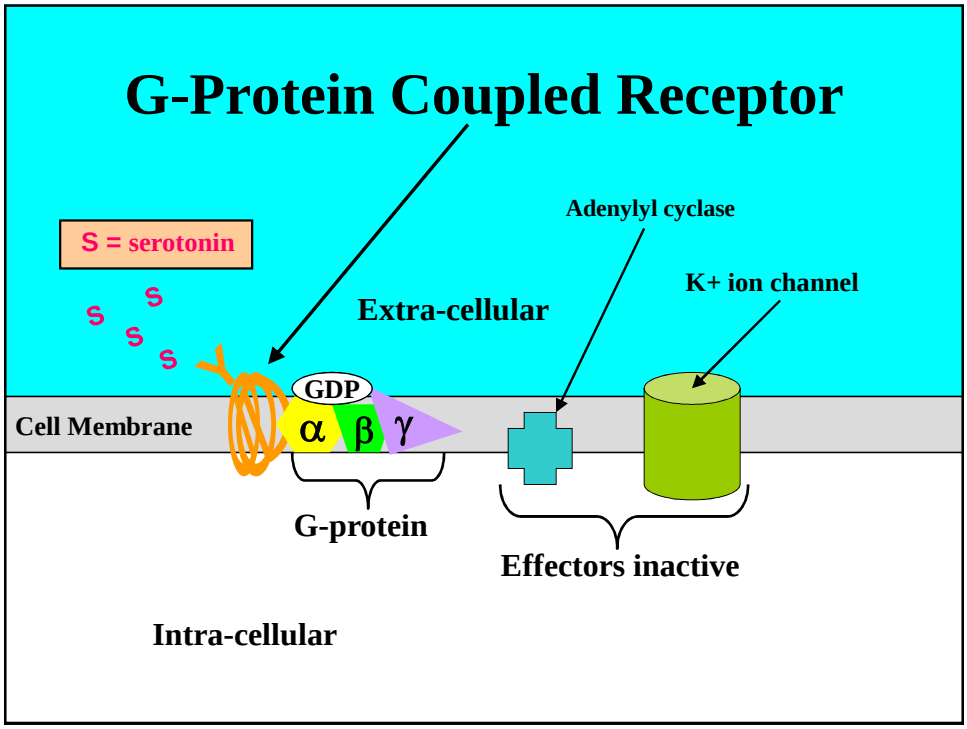
(*b*) A model of PCP action on the NMDA receptor

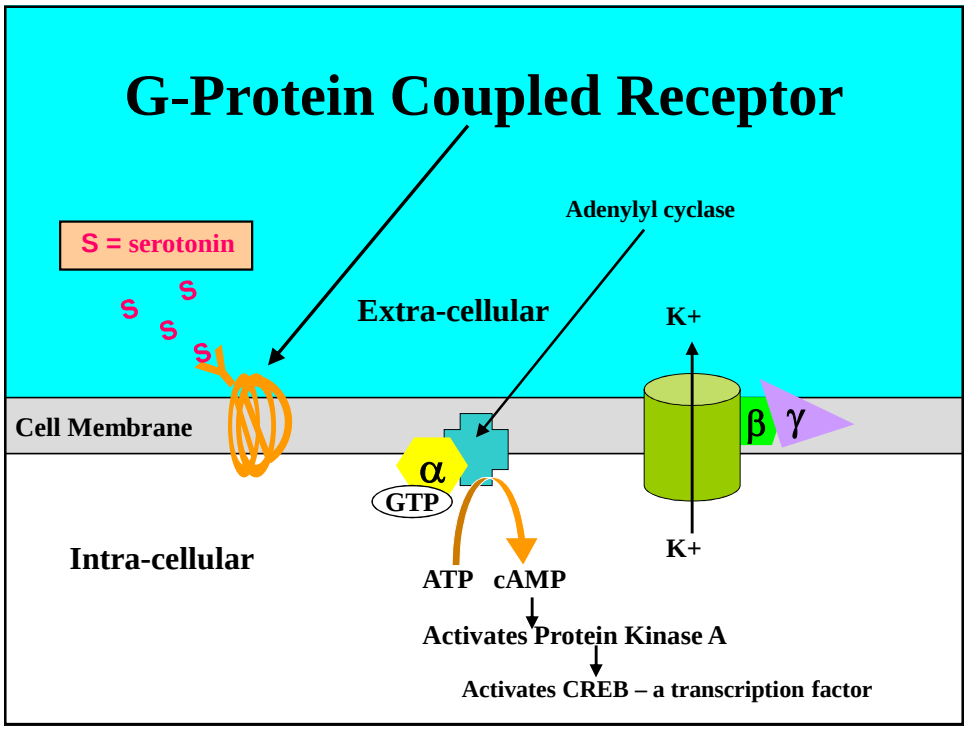


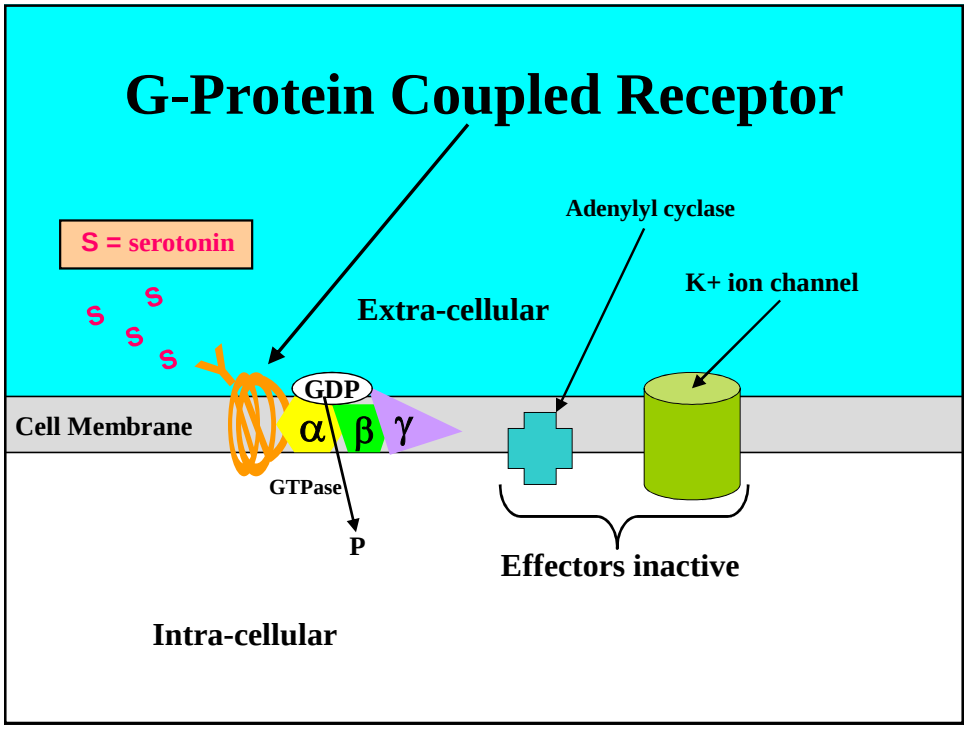



Glycine Neuron
NMDA-glutamate ion channel
Ca Ca Ca
Mg
Mg
Mg Mg
Extra-cellular
Ca Ca Ca
Cell Membrane
Intra-cellular
Ca Ca
Minor Depolarization
Ca Ca
Major Depolarization
AMPA-glutamate Ion channel


GABA-A chloride ion channel
(heteropentameric glycoprotein)
= GABA binding site
= benzo binding site
= ETOH binding site
= barbit binding site
Cl = chloride (1-)
Na = sodium (1+)
Cl Cl Cl Cl Cl Cl
Extra-cellular
Na Na Na Na Na Na Na
Na Na Na Na Na Na Na Na
ε
γ
α
α
β
Cell Membrane
Cl Cl Cl Cl Cl Cl Cl Cl Cl
Cl Cl Cl Cl Cl Cl Cl Cl
Intra-cellular
Influx of negative charge hyperpolarizes the neuron – decreasing excitability


G-Protein Coupled Receptor
S = serotonin
S
S
S
S
Extra-cellular
Adenylyl cyclase
K+ ion channel
GDP
Cell Membrane
α
β
γ
G-protein
Effectors inactive
Intra-cellular

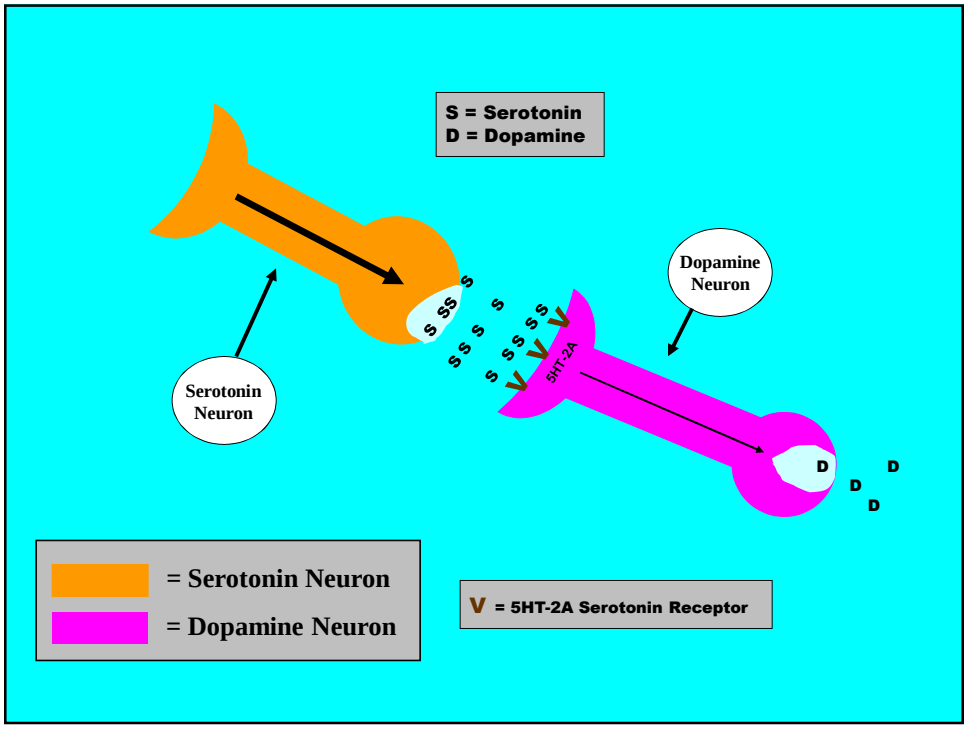

G-Protein Coupled Receptor
S = serotonin
S
S
S
S
Extra-cellular
Adenylyl cyclase
K+
Cell Membrane
β
γ
α
GTP
K+
Intra-cellular
ATP
cAMP
Activates Protein Kinase A
Activates CREB – a transcription factor

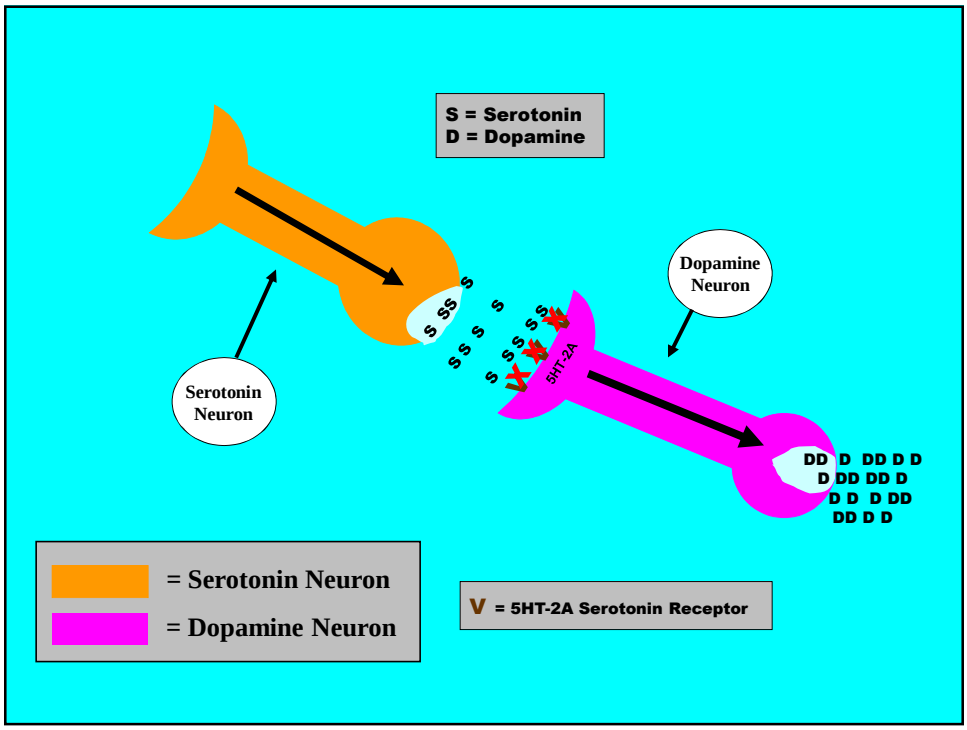


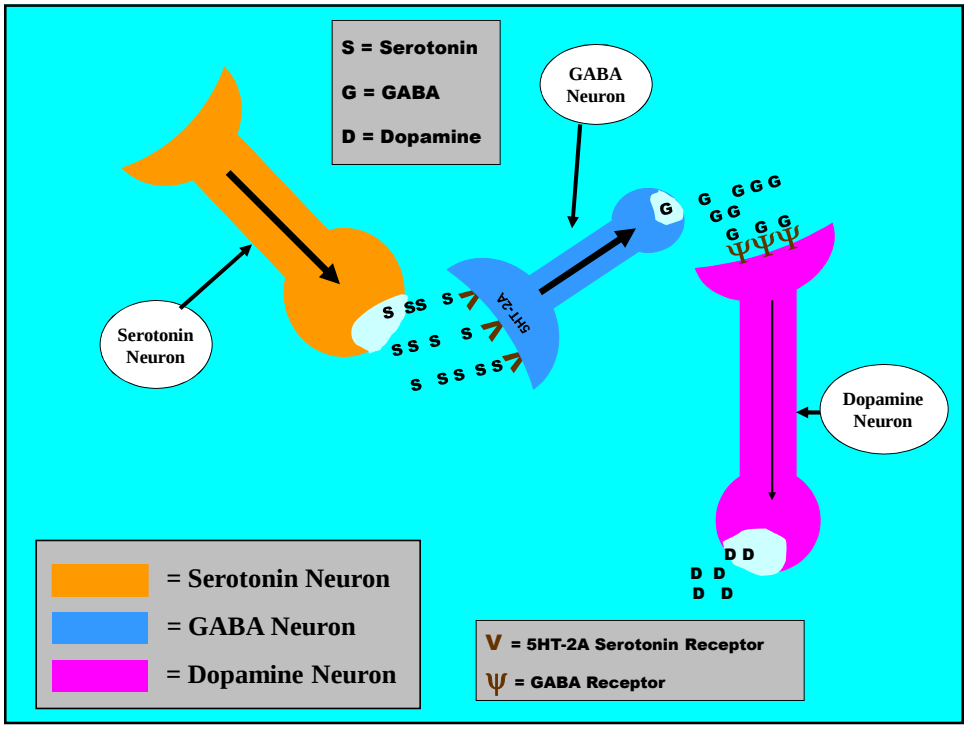
From receptors . . .

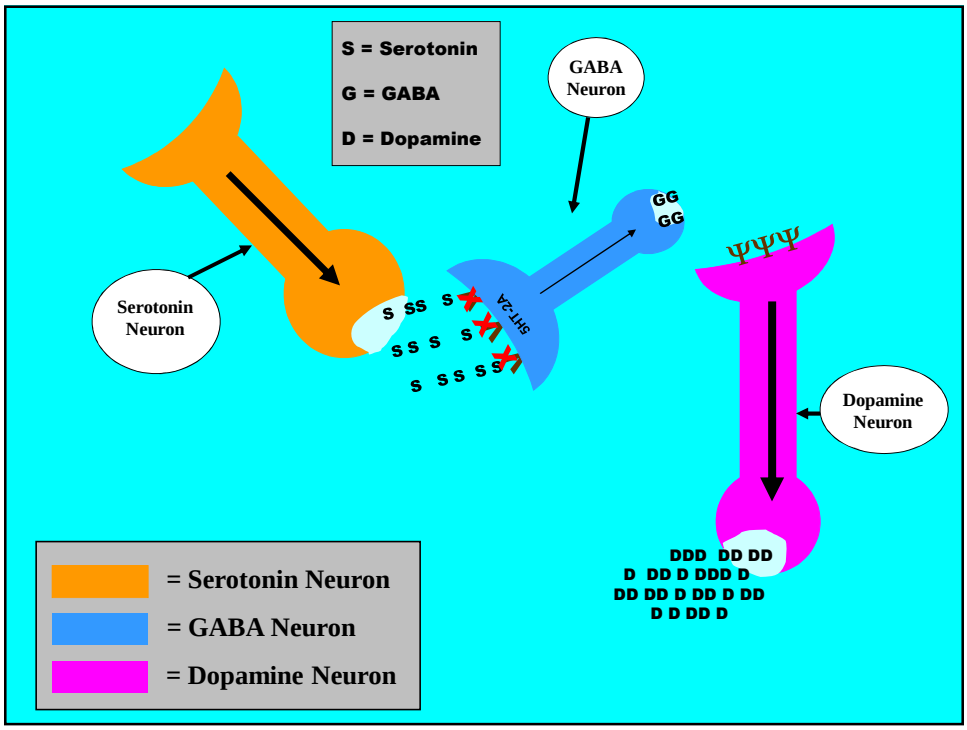
To . . .

Circuits


S = Serotonin
D = Dopamine
Dopamine Neuron
Serotonin Neuron
5HT-2A
D
= Serotonin Neuron
= Dopamine Neuron
V = 5HT-2A Serotonin Receptor

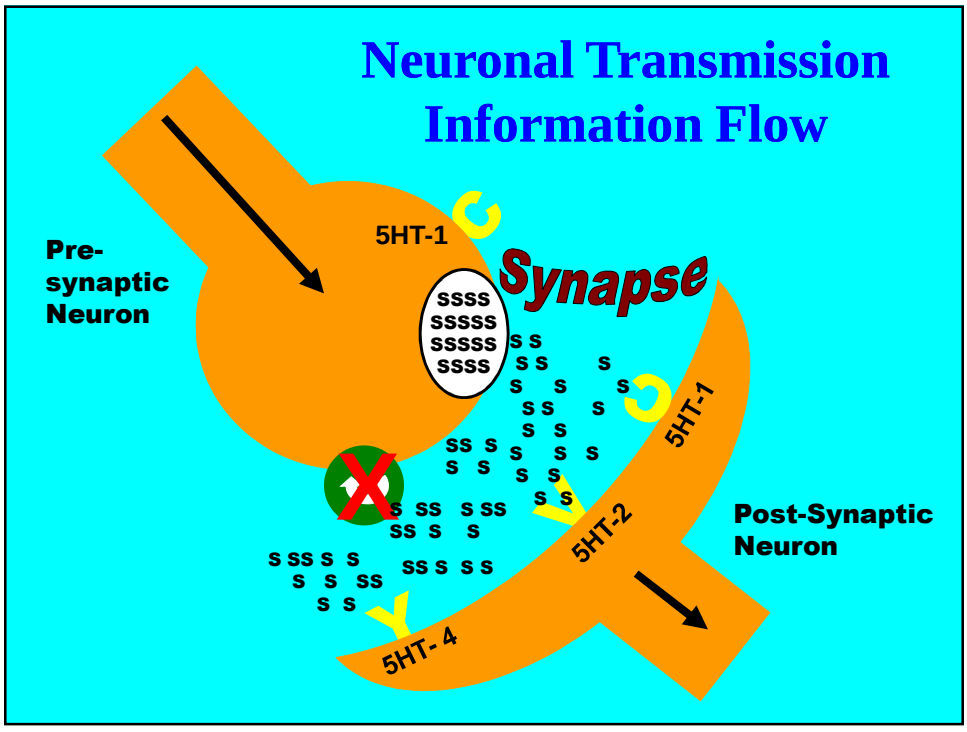

S = Serotonin
D = Dopamine
Dopamine Neuron
Serotonin Neuron
5HT-2A
= Serotonin Neuron
= Dopamine Neuron
V = 5HT-2A Serotonin Receptor

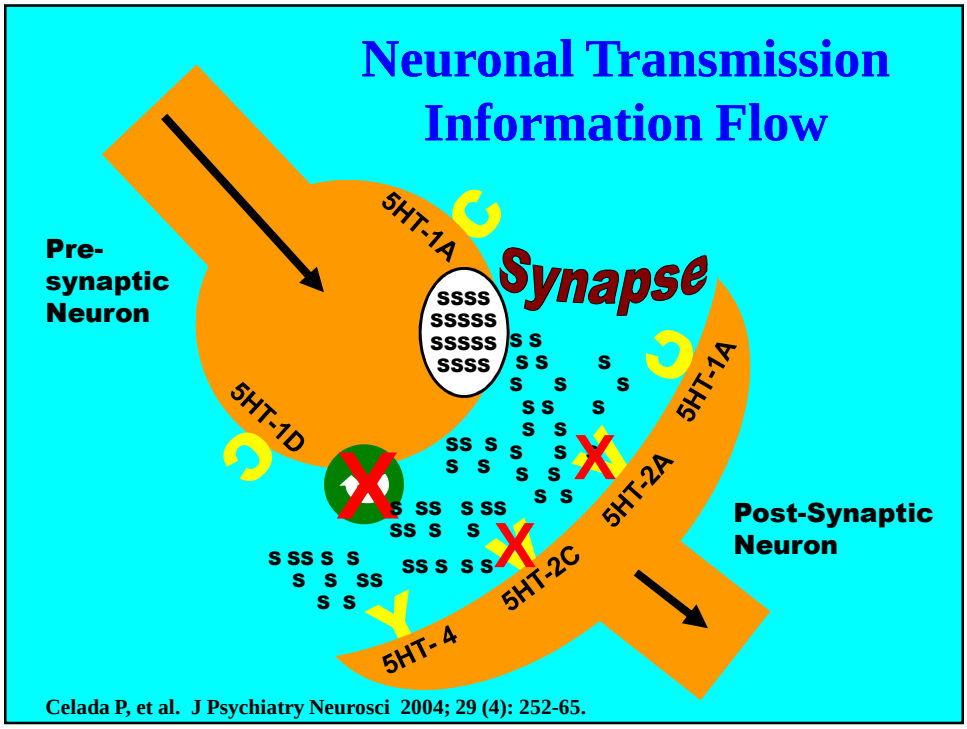

S = Serotonin
G = GABA
D = Dopamine
GABA Neuron
Serotonin Neuron
Dopamine Neuron
5HT-2A
= Serotonin Neuron
= GABA Neuron
= Dopamine Neuron
V = 5HT-2A Serotonin Receptor
Ψ = GABA Receptor

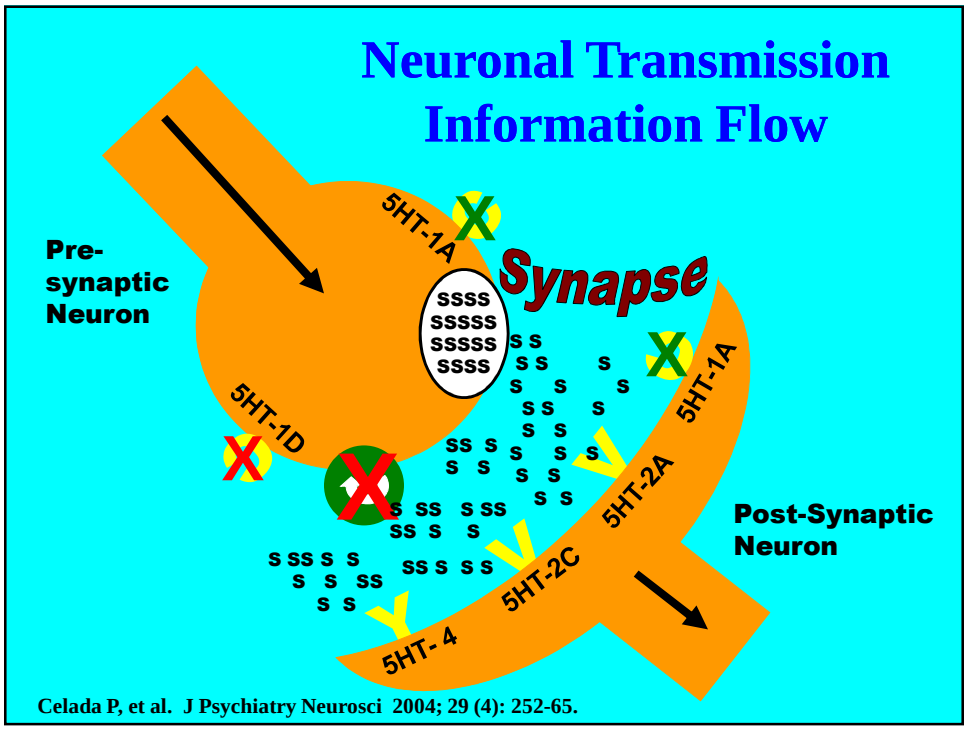

S = Serotonin
G = GABA
D = Dopamine
GABA Neuron
Serotonin Neuron
Dopamine Neuron
5HT-2A
= Serotonin Neuron
= GABA Neuron
= Dopamine Neuron

A close up view of a

synapse




Neuronal Transmission
Information Flow
Pre-
synaptic
Neuron
5HT-1A
Synapse
5HT-1D
5HT-1A
5HT-2A
Post-Synaptic
Neuron
5HT-2C
5HT- 4
Celada P, et al. J Psychiatry Neurosci 2004; 29 (4): 252-65.


Neuronal Transmission
Information Flow
Pre-
synaptic
Neuron
5HT-1A
Synapse
5HT-1D
5HT-1A
5HT-2A
Post-Synaptic
Neuron
5HT-2C
5HT- 4
Celada P, et al. J Psychiatry Neurosci 2004; 29 (4): 252-65.

Where do we go from here?

The evolving drug pipeline with new mechanisms of action

Glutamate modulators

- Drugs that fine tune the glutamate system show effectiveness in treating the psychotic symptoms of schizophrenia as well as our current dopamine receptor blockers, but without the dopamine side effects on the muscles, cognition and prolactin.
- Ketamine and ketamine analogues seem highly effective in treating refractory depression.

Cholinergic nicotinic agonists

- Cognitive enhancers for conditions like Alzheimers.
- Treat adult attention deficit hyperactivity disorder.
- Add on drug for antidepressant improvement.
- Improve the negative and positive symptoms of schizophrenia.

Serotonin receptor modulators

- There are at least 20 different types of serotonin receptors, all with very different functions.
- Develop drugs that stimulate some serotonin receptors and block others, to more finely tune a healthy serotonin balance.

The histamine H_3 receptor: from gene cloning to H_3 receptor drugs

Rob Leurs, Remko A. Bakker, Henk Timmerman & Iwan J. P. de Esch

Abstract

Since the cloning of the histamine H_3 receptor cDNA in 1999 by Lovenberg and co-workers, this histamine receptor has gained the interest of many pharmaceutical companies as a *potential drug target for the treatment of various important disorders, including obesity, attention-deficit hyperactivity disorder, Alzheimer's disease, schizophrenia,* as well as for myocardial ischaemia, migraine and inflammatory diseases. Here, we discuss relevant information on this target protein and describe the development of various H_3 receptor agonists and antagonists, and their effects in preclinical animal models.

Nature Reviews Drug Discovery 4, 107-120 (February 2005)

Questions??