

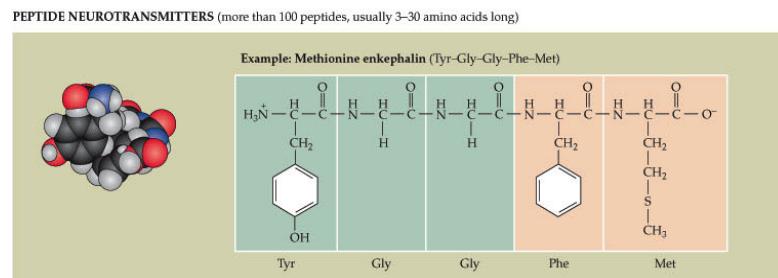
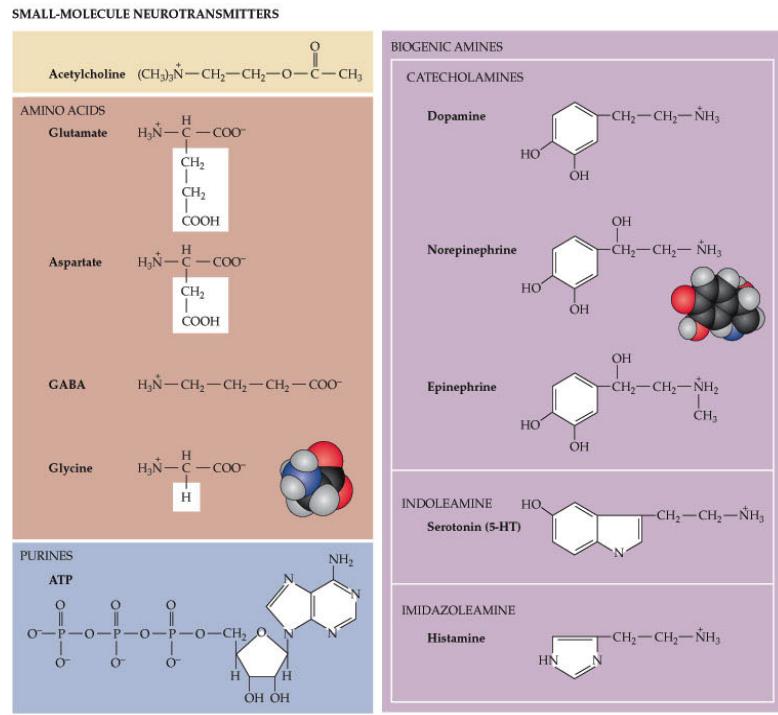
1.GABA Glutamaat, basics I

Richard

- -Receptoren (slow, fast, ion channel, G coupled, second messenger)
- -Agonisme, antagonisme, partieel agonisme, upregulatie, downregulatie, inverse agonist, -PAM en NAM (bv goed te illustreren aan benzo receptor (ik heb nog een aardig filmpje))
- -GABA, glutamaat, glutamine, netwerken (algemeen). Hoe te meten(spectraal fMRI), zie recent artikel uit Utrecht en artikel van Edith (bijna klaar).
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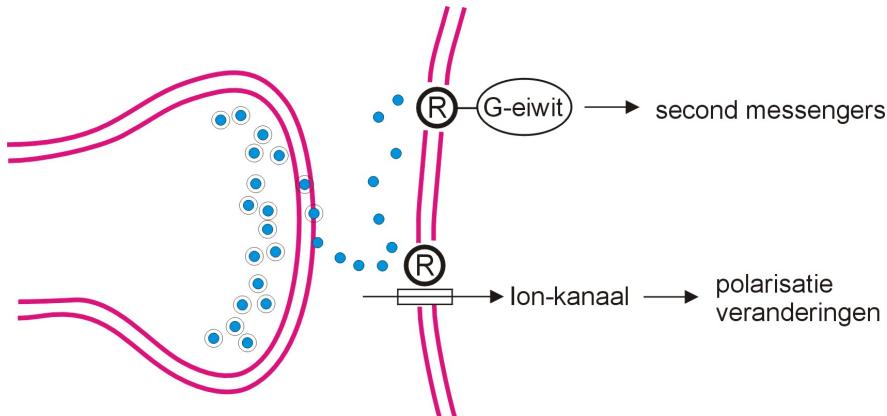
lange lijst van neurotransmitters

- acetylcholine (1926)
- monoamines:
 - dopamine,
 - serotonine,
 - noradrenaline
- aminozuren
 - (GABA,
 - glutamaat,
 - glycine)
- tientallen peptiden
- totaal > 300



Ionotrope receptoren:

(gekoppeld aan ionkanalen:
snelle werking)

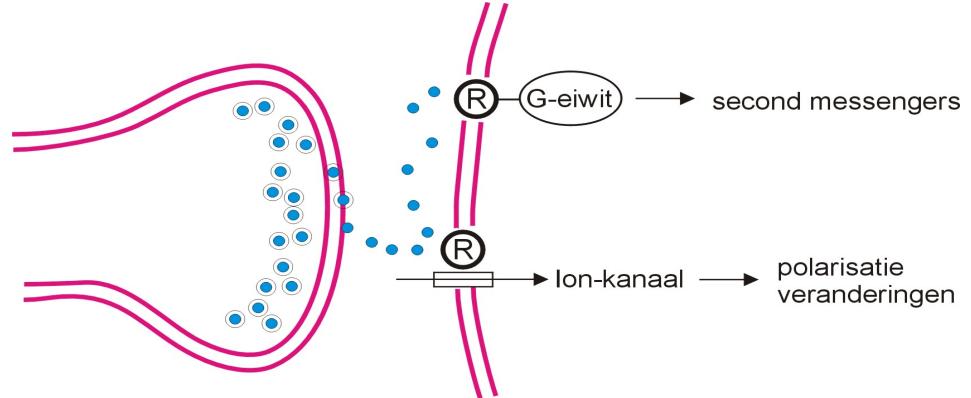


- glutamaat (NMDA, AMPA, Kainaat)
- glycine
- GABA-A
- acetylcholine (nicotine type)
- serotonine (5-hydroxytryptamine):
 - 5HT3



Metabotrope receptoren:

(gekoppeld aan G-eiwitten:
langzame werking)

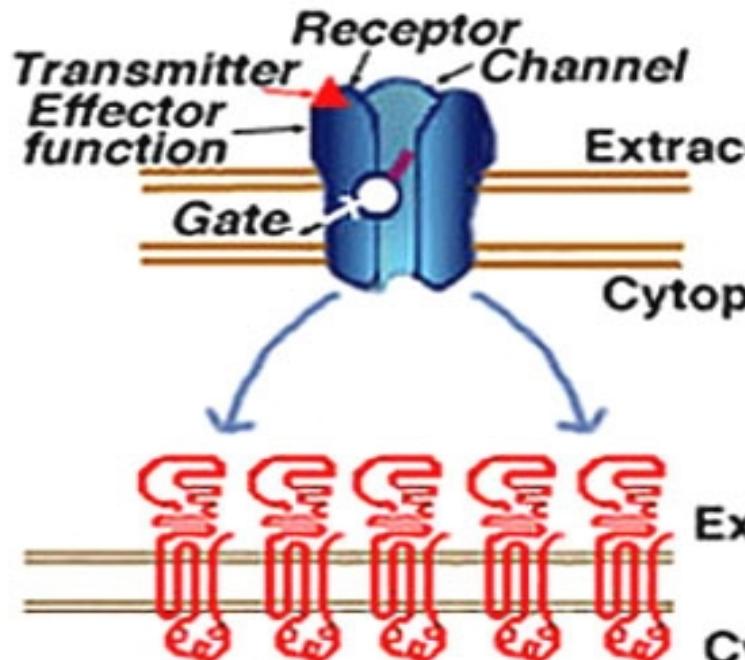


- Glutamaat (mGLU)
- GABA-B
- dopamine, serotonine, noradrenaline
- acetylcholine (muscarine-type)

Snel, directe activatie

Langzaam, modulatie

Ionotropic receptor



Metabotropic receptor

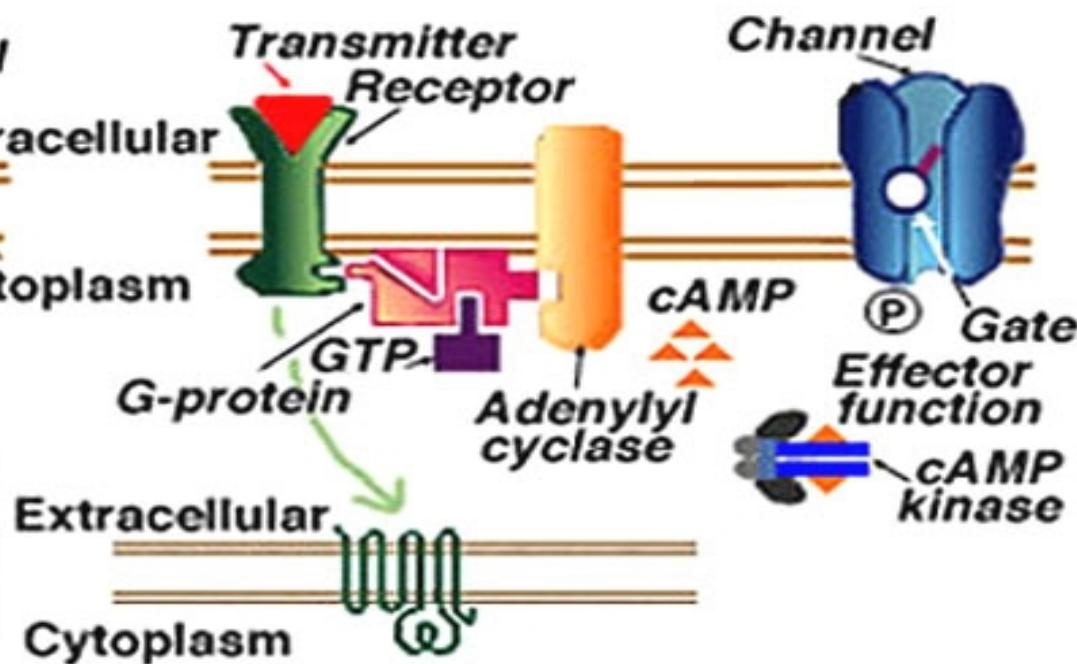
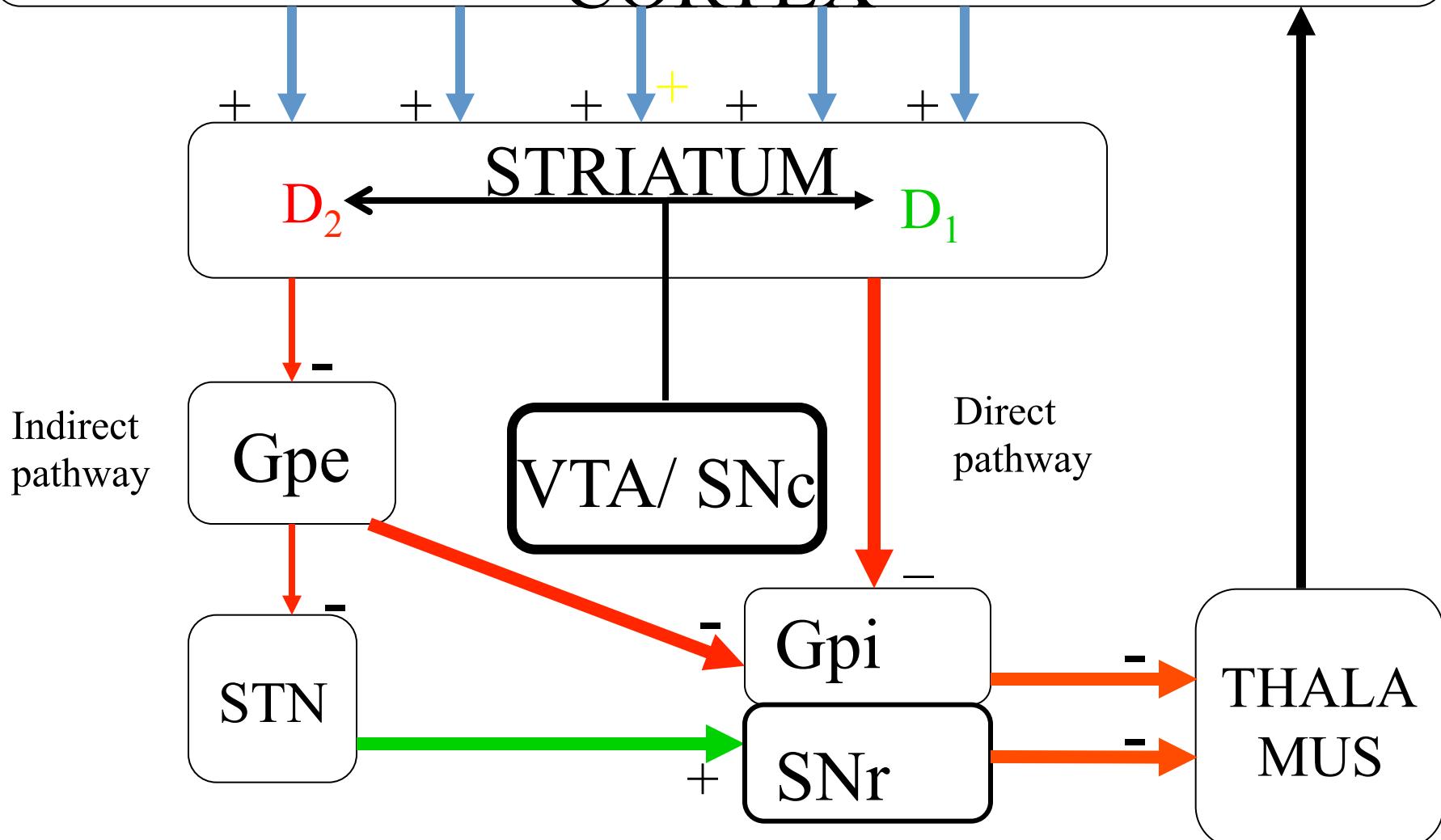


Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

Fig. 5b. Metabotropic receptors are coupled to their associated ion channels by a second messenger cascade (top). Each mGluR is composed of one polypeptide, which is coupled to a G-protein (from Kandel et al., 1991).

sensorimotor association limbic

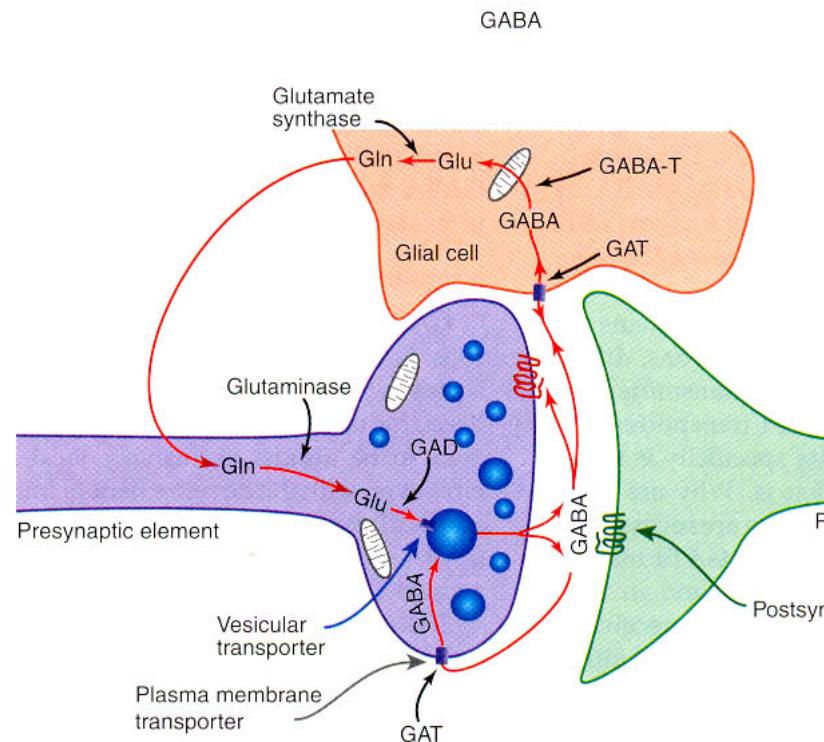
CORTEX



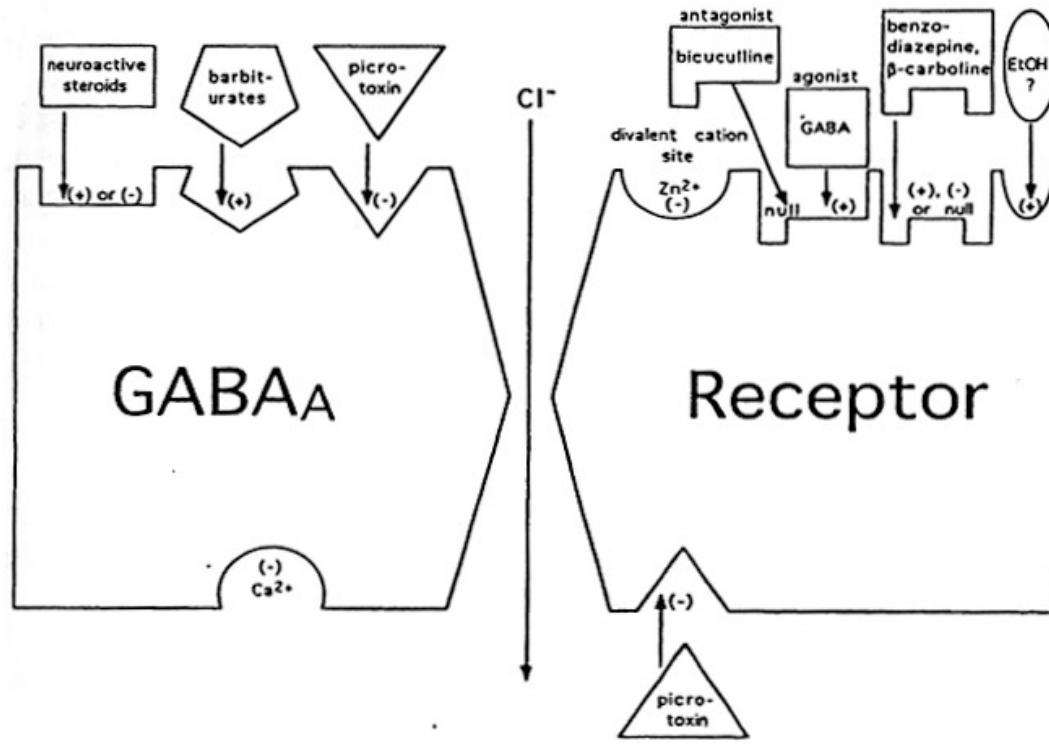
De GABA neuronen

GABA als neurotransmitter

- Bij ca 30% van alle synapsen is GABA betrokken
- uit glutaminezuur gevormd door glutamaat decarboxylase (GAD)
- gemetaboliseerd door GABA-transaminase
- na afgifte weer actief opgenomen in glia cellen

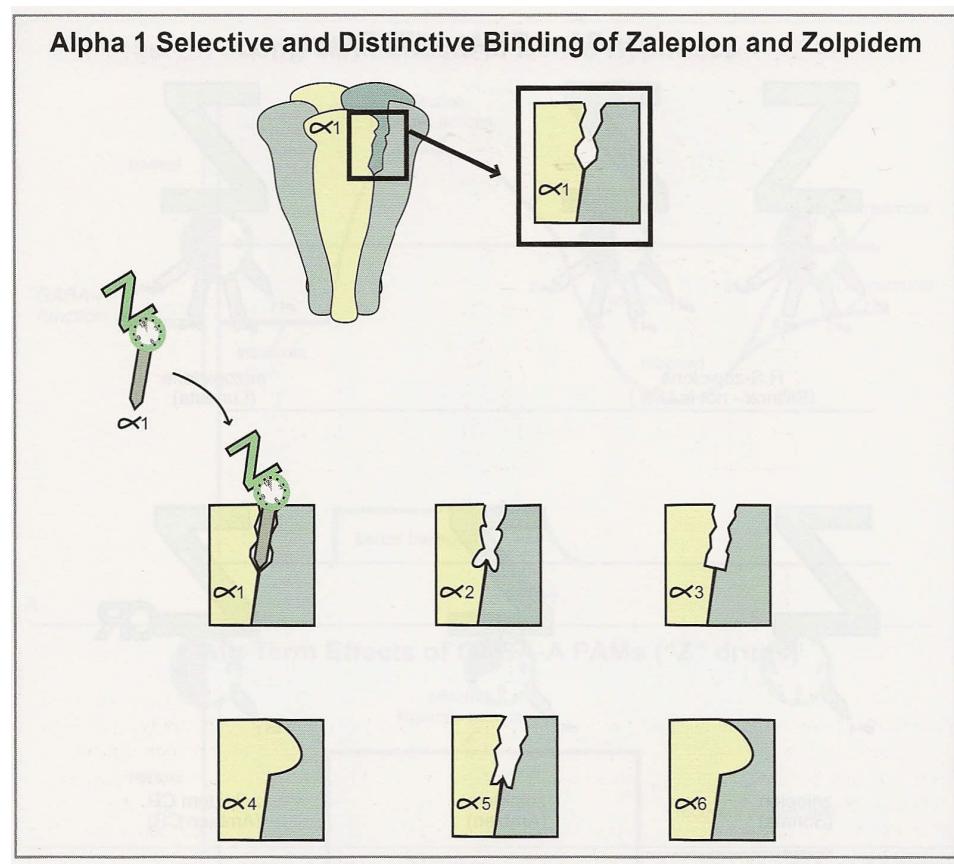


de GABA-A receptor

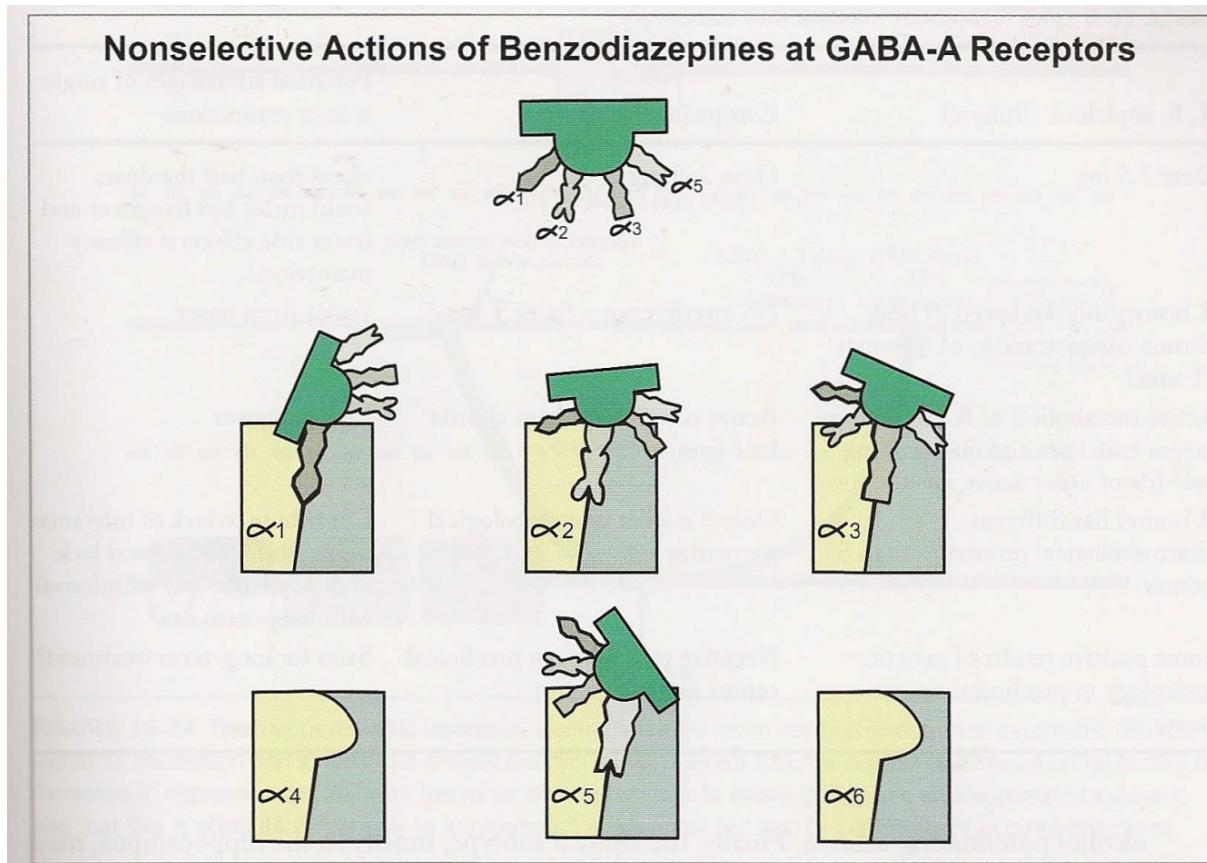


Opgebouwd uit pentameren dus **5 subunits**,
er zijn **5 typen subunits** (families)

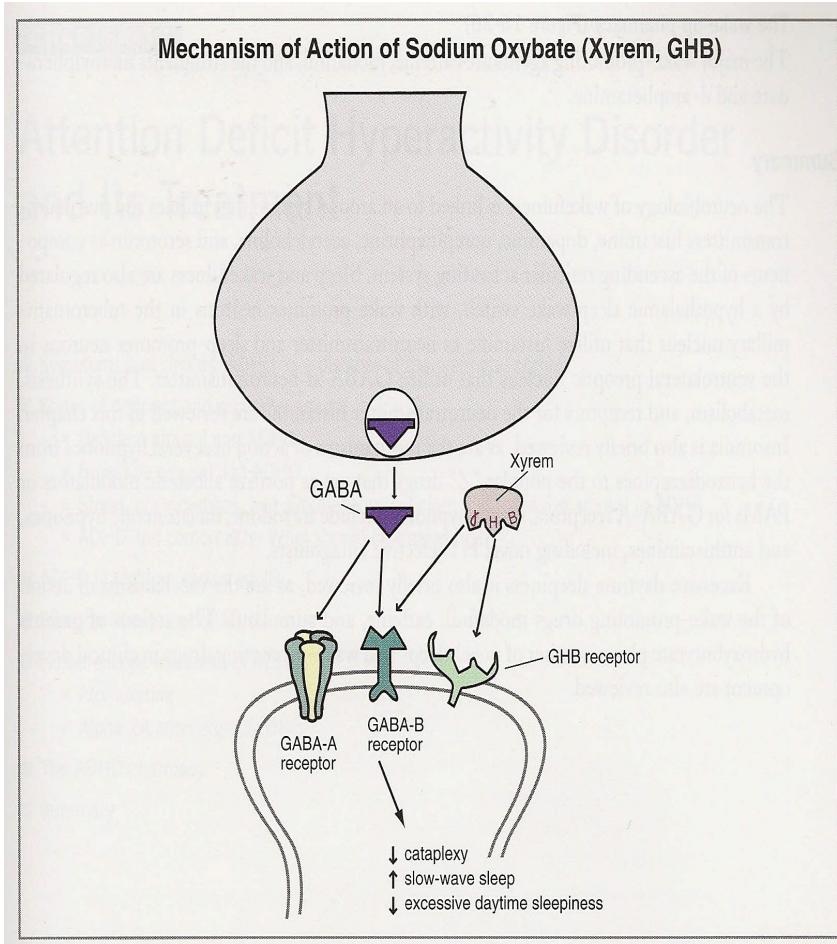
GABA modulatie via selectieve alfa-1receptor : zolpidem



Non selectieve werking van benzodiazepines op GABA-A receptors



Partiele GABA-B en GHB agonist

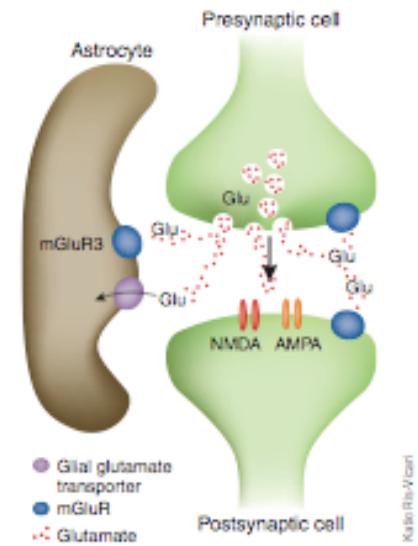


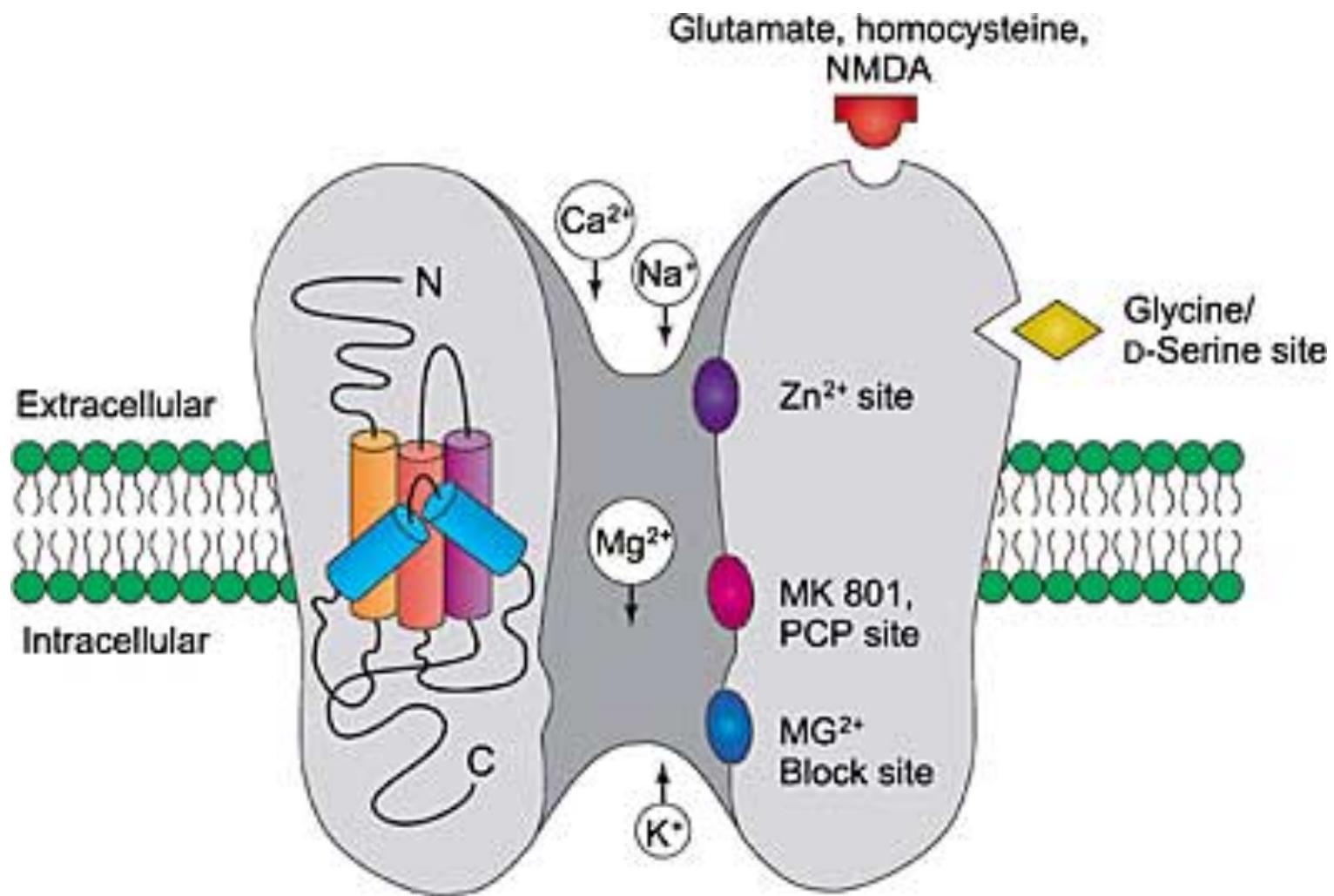
- Sodium oxybaat; gamma-hydroxyboterzuur.
- Gevormd uit GABA
- Partiele agonist voor GABA-B
- Agonist voor GHB-receptor
- Ind.: cataplexie en excessief slaapbehoefte

De glutamaat neuronen

Glutamaat als neurotransmitter

- Pas in de '70 erkend als neurotransmitter
- '70 Excitatory AminoAcid receptors
- '80 NMDA en non-NMDA receptor
- '90 NMDA, AMPA, kainaat en mGlu receptor
- Belangrijkste excitatoire transmitter
- Bij 90% van de synapsen betrokken
- Zeer sterke opname na afgifte (high affinity transporters)
- Zeer algemene functies (bv geheugen)





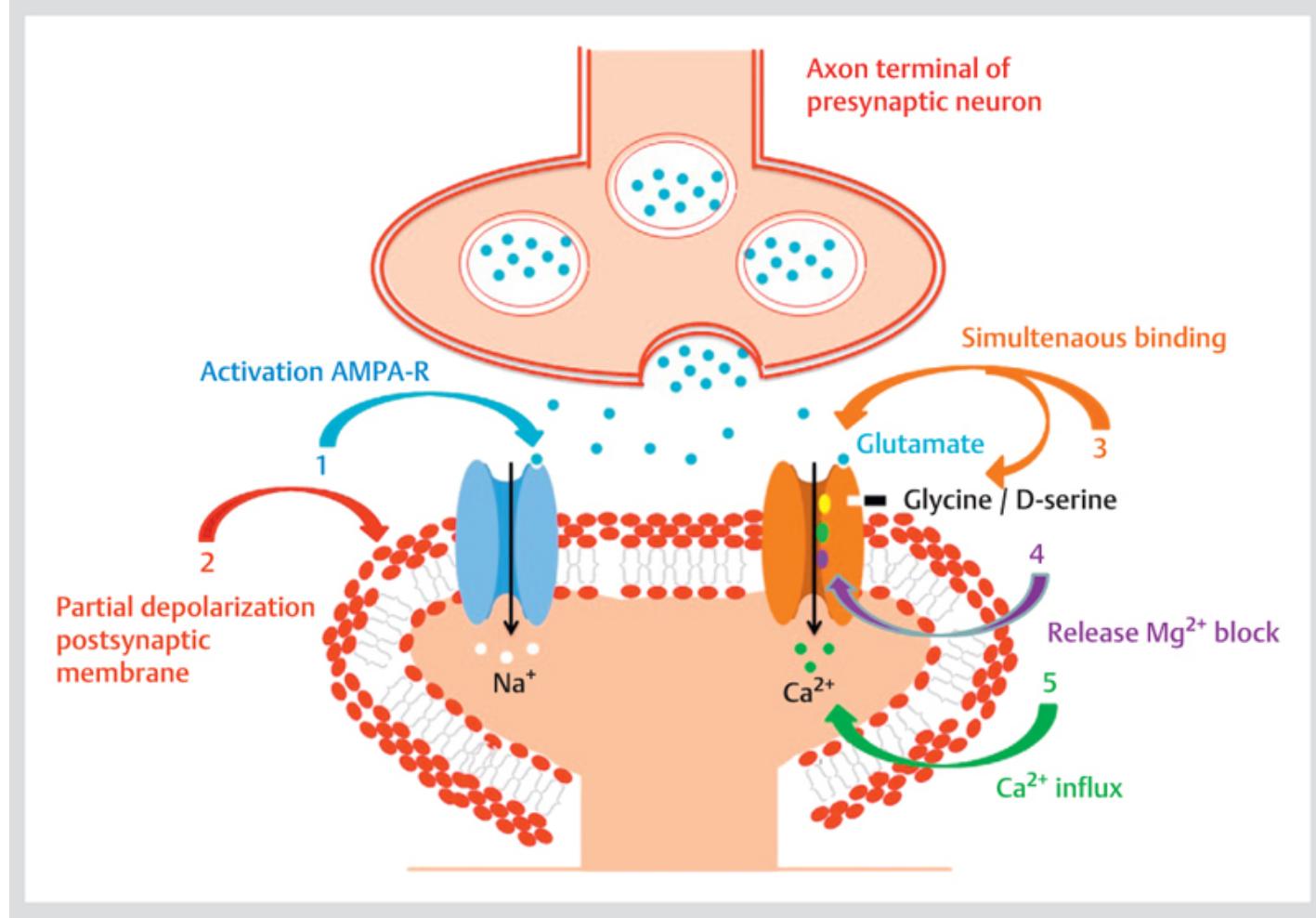


Fig. 1 Activation of NMDA receptors. Inotropic receptors gate cation channels, which are permeable to Na⁺, K⁺ and Ca²⁺.

Glutamate in the synaptic cleft activates the kainate and/or AMPA receptor on the postsynaptic membrane, resulting in substantial neuronal depolarization.

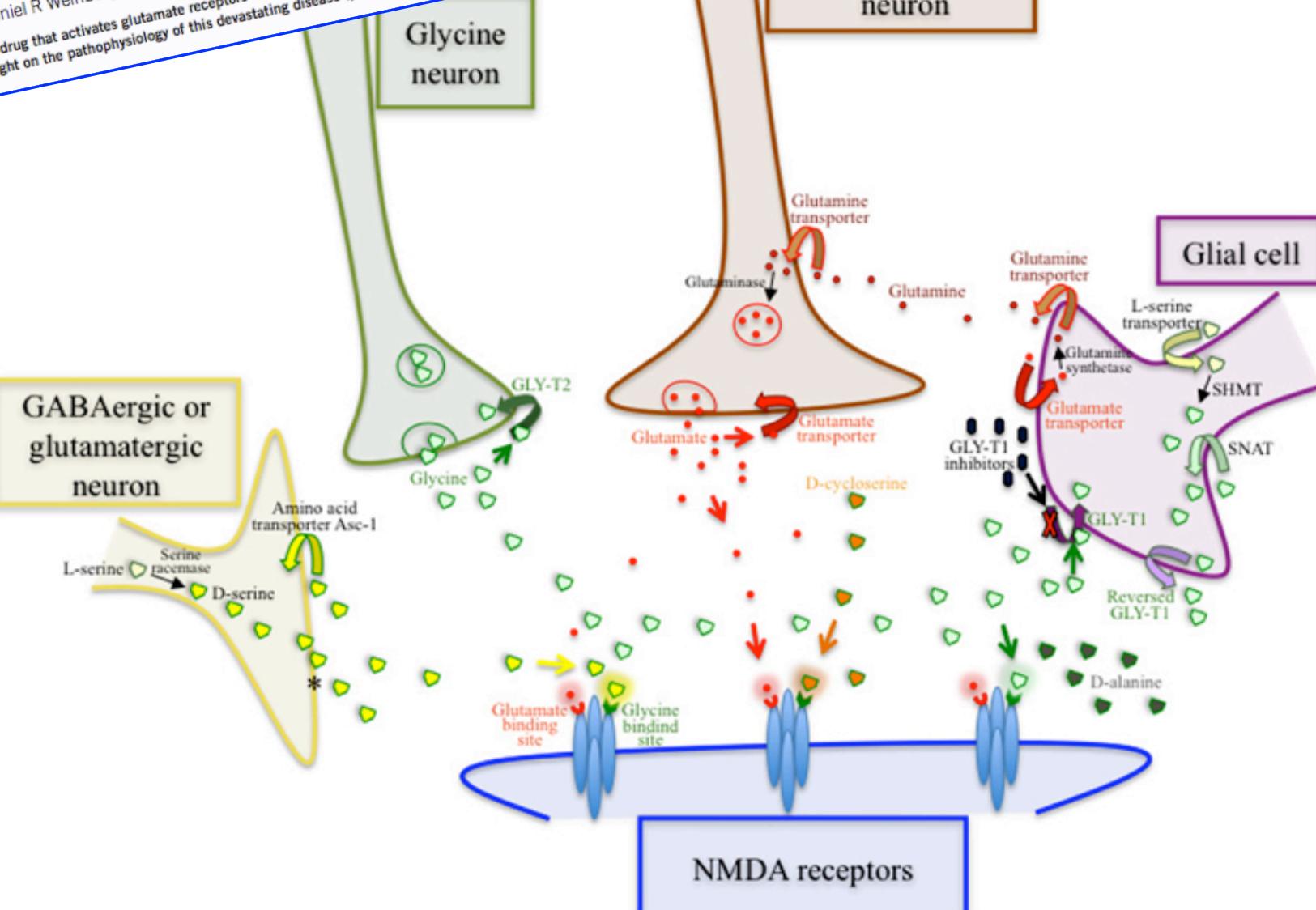
After partial depolarization of the postsynaptic membrane both glutamate and glycine or D-serine, which are endogenous co-agonists need to bind simultaneously to the tetrameric structure of the NMDA receptor.

The voltage-dependent Mg²⁺ block releases, the NMDA channel opens and Ca²⁺ flows into the postsynaptic neuronal cell.

Schizophrenia drug says goodbye to dopamine

Daniel R Weinberger

A drug that activates glutamate receptors offers promise for a new class of anti-psychotic therapeutics and sheds light on the pathophysiology of this devastating disease (pages 1102–1107).



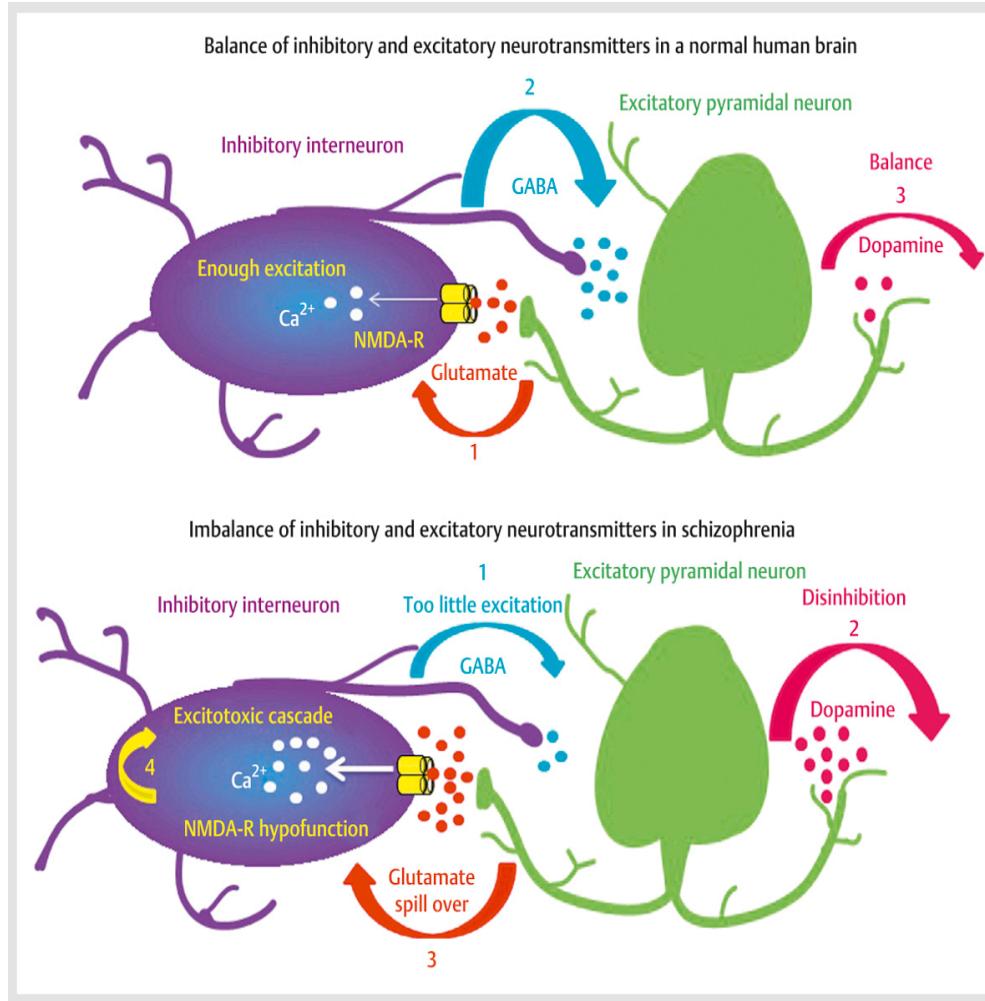


Fig. 2 Reciprocal relationship between glutamatergic synapses and dopaminergic axons.

Normally activation of NMDA receptors by glutamate stimulates cortical inhibitory interneurons, which release GABA to excitatory pyramidal neurons, resulting in inhibition of release of dopamine from the mesolimbic dopamine pathway.

In schizophrenia NMDA hypofunction results in decreased activity of cortical GABA-ergic interneurons.

Reduced release of GABA leads to diminished inhibitory control of pyramidal neurons, resulting in increased dopamine release.

Due to NMDA hypofunction glutamate accumulates in the synaptic space. Ca²⁺ influx increases, triggering an excitotoxic cascade.