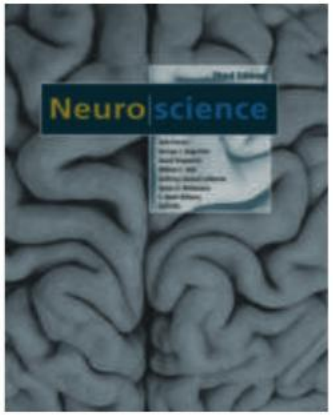
Ligand-Gated Ion Channels

The Other Machines That Make It Possible...

Topics I	Topics II
Introduction & Electrochemical Gradients	Synaptic Transmission
Passive Membrane Properties	Electrophysiology Techniques
Action Potentials	Basic Circuits (Spinal Cord)
Voltage-Gated Ion Channels	Sensory Systems Overview
Ligand-Gated Ion Channels	Synaptic Plasticity

Study Material

- NEUROSCIENCE Third Edition
  - Dale Purves
- Chapter 4 page 78
- Chapter 5 pages 117-127
- Chapter 6



THE COVER
Dorsal view of the human brain.
(Courtesy of S. Mark Williams.)

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Aims for this Lecture

- Know the most important classes of ligand-gated ion channels.
- Know the basic pharmacological tools to study them.
- Understand the concept of current-voltage relationship and its importance.
- Understand dose-response curves and the terms agonist and antagonist.

Recapitulation L4

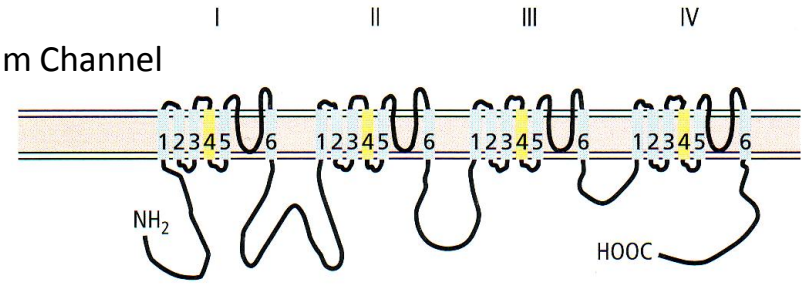
- Voltage-gated ion channels are crucial for generating electrical signals in neurons, in particular action potentials.
- They form families of related channels with the potassium channels having by far the most members.
- The simplest motif contains two transmembrane segments and a pore loop.

Recapitulation L4

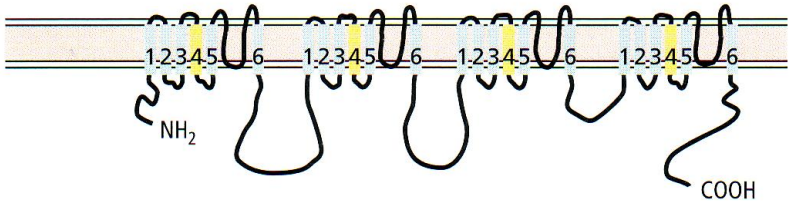
- Ion channels are either open or closed, with a very rapid transition between the two states.
- Ion channels behave stochastically – we can determine their open probaility, but we cannot predict their exact opening pattern.
- Ion selectivity requires precisely arranged amino acids – in the case of potassium their negatively charged residues allow the ion to shed its hydration shell.

Recapitulation L4

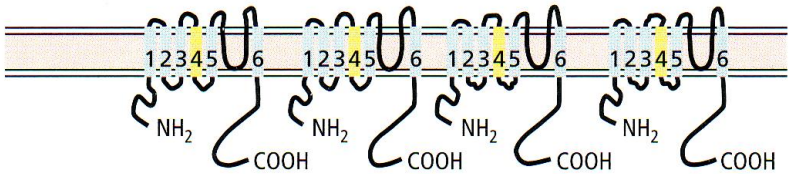
Sodium Channel



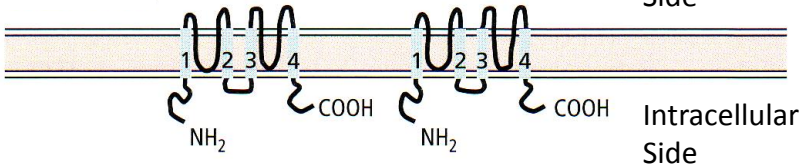
Calcium Channel



Potassium Channel

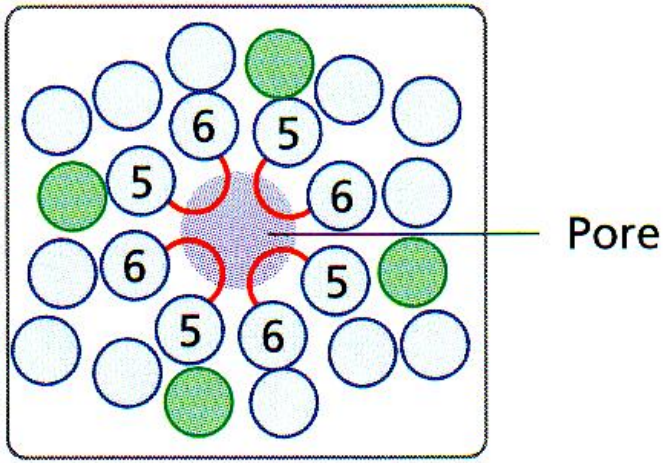


Leak K Channel



Extracellular Side

Intracellular Side



Ligand-Gated Ion Channels

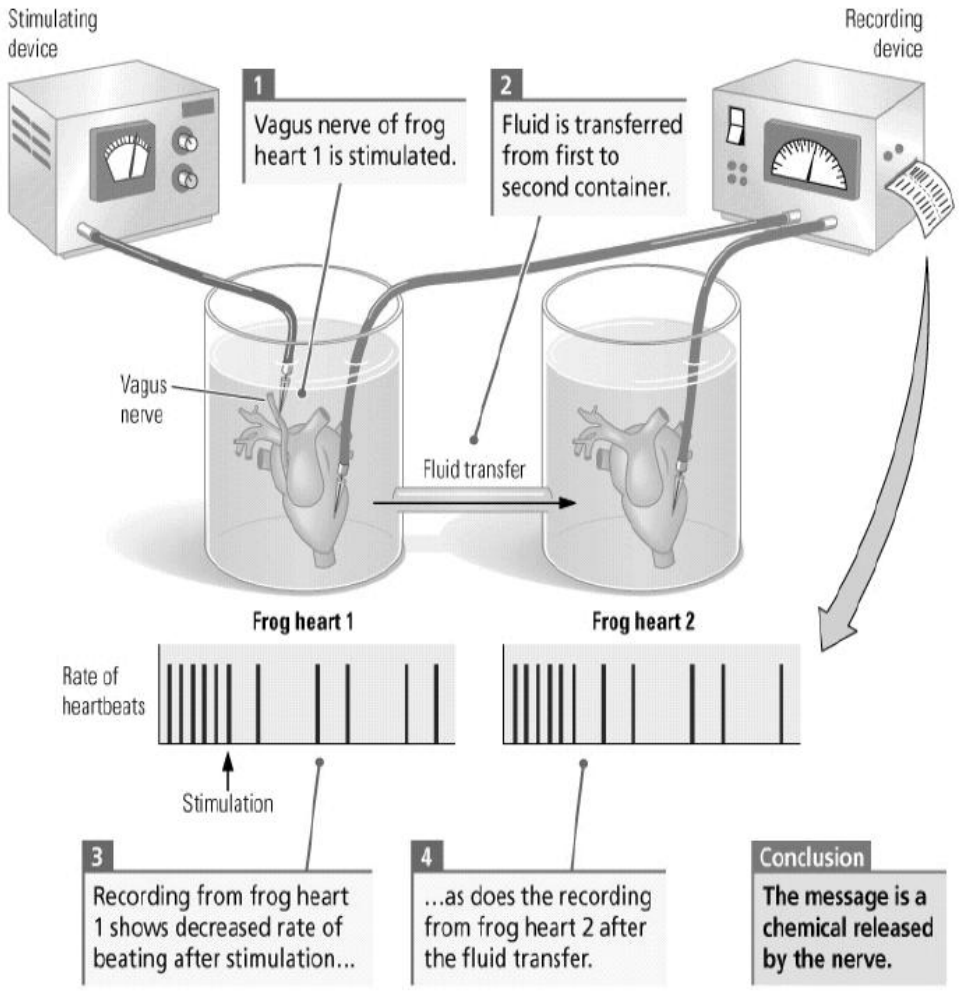
- Mediate between the chemical ‚domain' and the electrical ‚domain'.
- Whenever you have to quickly translate a chemical signal into an electrical response these ion channels are useful.
- Again we have many types, which form often families of related receptors.

Otto Loewi I

- 1873-1961
- Nobel Price 1936
- Escape to the USA 1940
- Position at the NYU

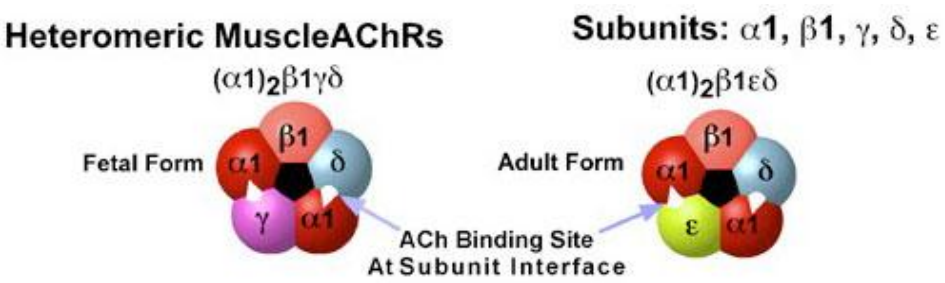
- ‘Dreams‘ of the decisive experiment

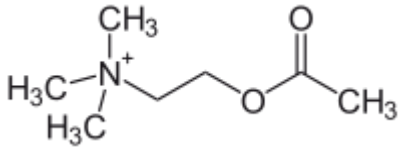
Otto Loewi II



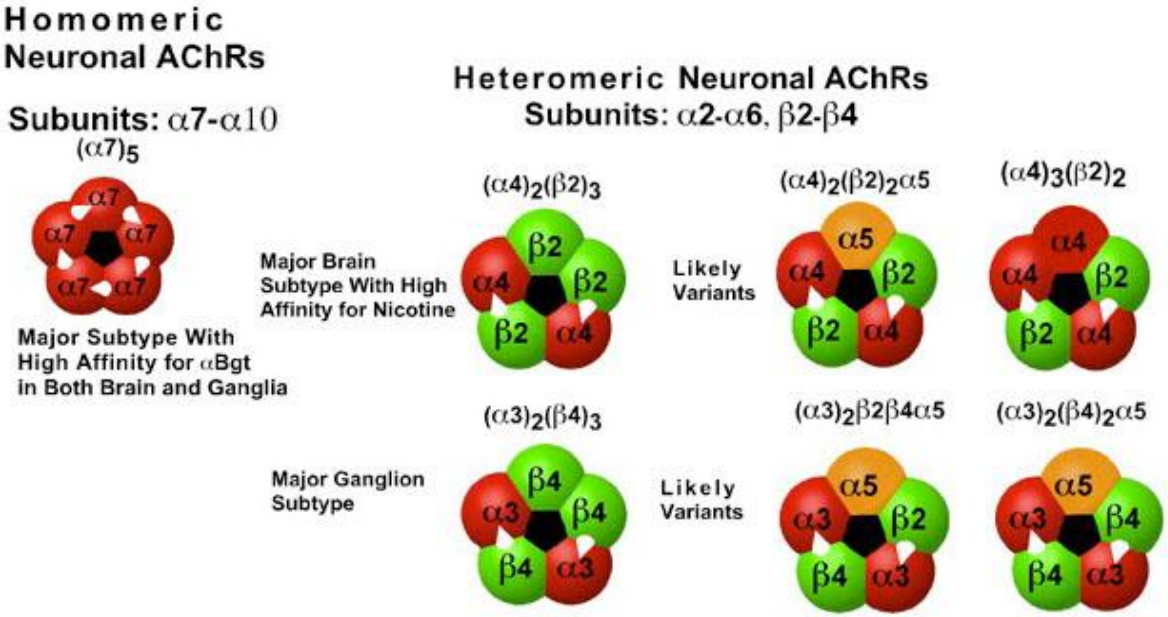
Otto Loewi did not discover ligand-gated ion channels.
The effect that he discovered is mediated by metabotropic (G-protein coupled) receptors.
However, he discovered

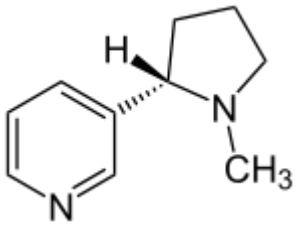
Nicotinic ACh Receptors





Acetylcholine



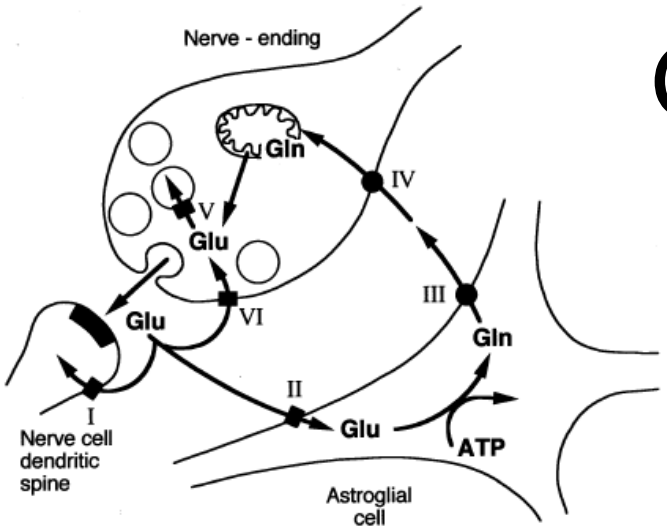


Nicotine

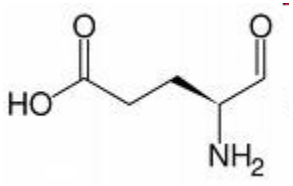
Nicotinic ACh Receptors

- Endogeneous Agonist
- Defining Agonist
- Antagonists

- Acetylcholine
- Nicotine
- Curare, Bungarotoxin

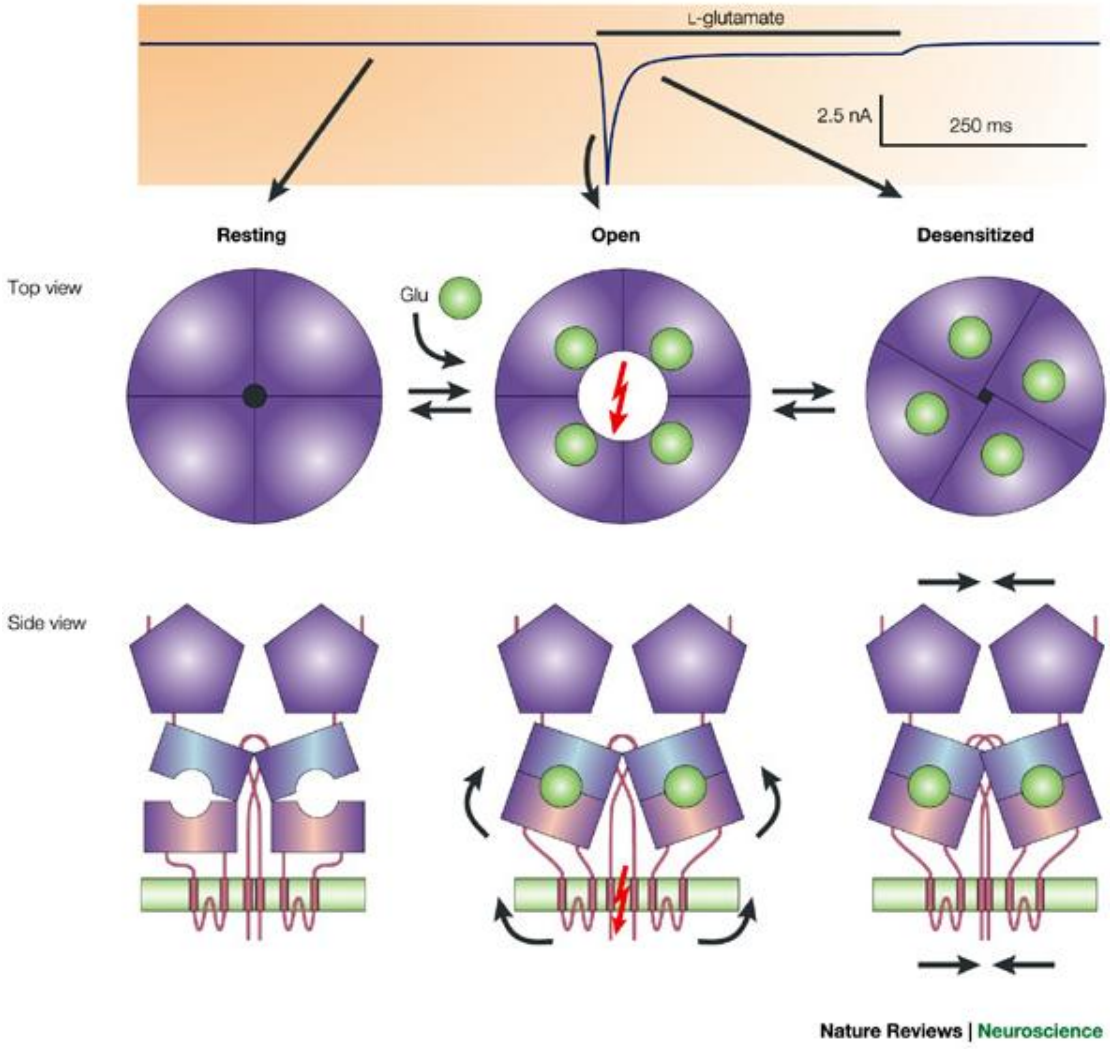


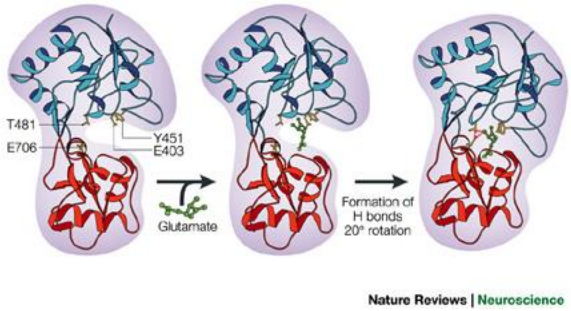
Glutamate



- Most important excitatory CNS transmitter
- Amino acid made from glutamine in the synaptic terminal.
- Transport into vesicles via VGLUT
- Uptake into glia via EAAT (excitatory amino acid transporter) Na dependent.
- Glutamate-glutamine-glutamate cycle.

AMPA Receptors





AMPA/Kainate type gluatmate receptors are equally permeable for Na and K ions. Their reversal potential is therefore around 0 mV. That is sufficient to depolarize a neuron above threshold. GluR2 subunit containing receptors are not calcium ion permeable. GluR1,3 and 4 containing ones are.

AMPA Receptors

- Endogeneous Agonist
- Defining Agonist
  - Glutamate
  - AMPA
  - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
- Antagonists
  - NBQX
  - (2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo[*f*]chinoxalin-2,3-dion)

NMDA Receptors

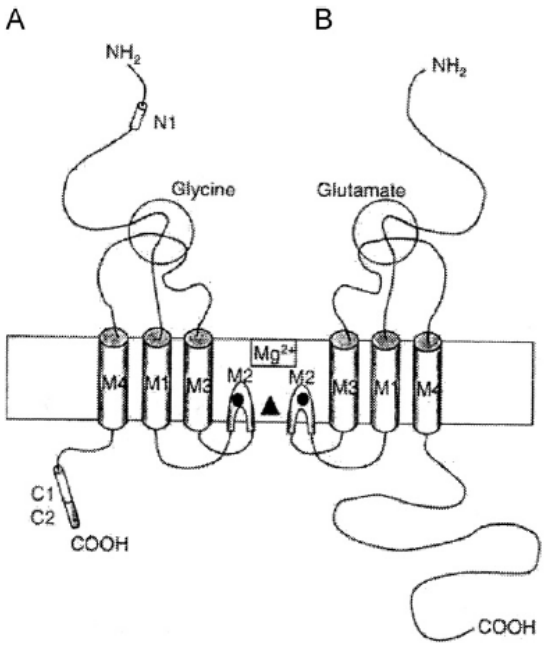
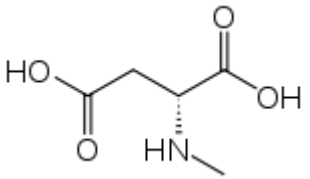


Figure 2 Schematic diagram showing the predicted transmembrane topology of an NR1 (A) and an NR2 (B) subunit showing the extracellular amino terminals, the intracellular carboxyl terminals, the membrane domains (M1-4) and the agonist binding sites.[3]

- NMDA receptors have a tetrameric arrangement.
- Their permeability depends on ligand binding and on membrane voltage.
- Mg Block.

NMDA Receptors

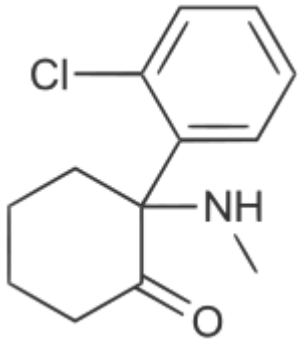


NMDA

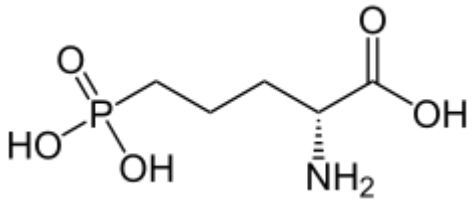
- Endogeneous Agonist
- Defining Agonist

- Antagonists

- Glutamate
- NMDA, *N*-Methyl-D-aspartate
- APV, (2*R*)-amino-5-phosphonovaleric acid
- Ketamine

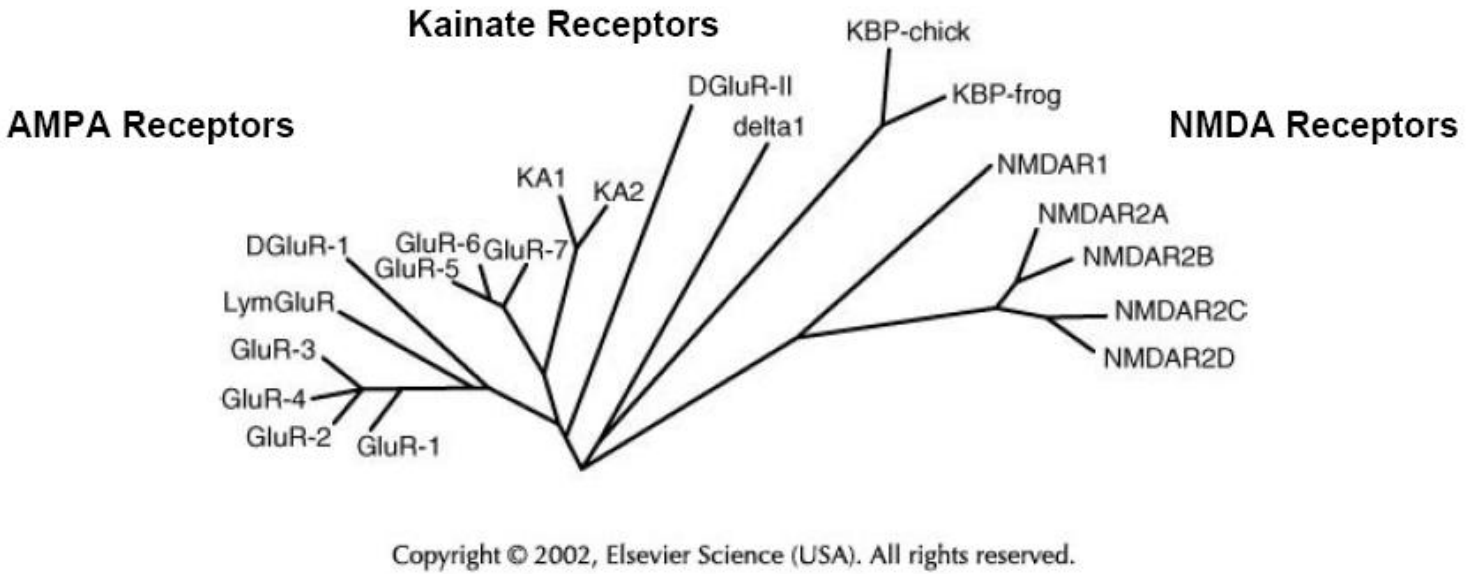


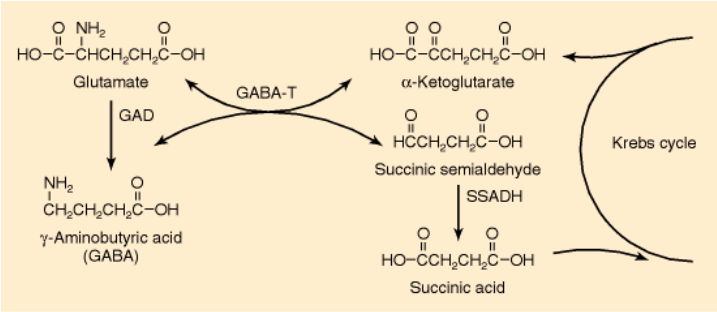
Ketamine



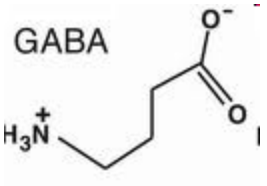
AP5, APV

The Whole GluR Family





GABA

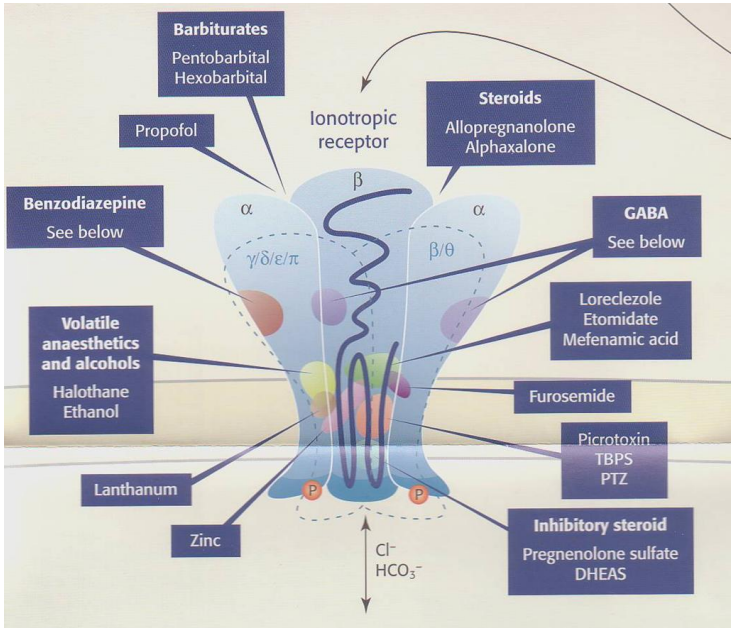


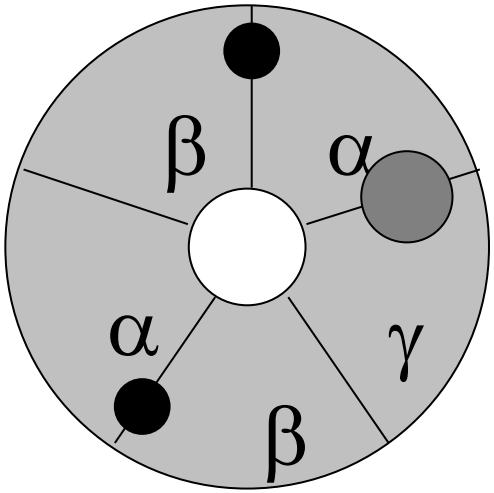
gamma-Aminobutyric acid

- Most important inhibitory neurotansmitter in the CNS (in brainstem and spinal cord also glycine)
- Metabolized from glutamate in the presynaptic terminal by decarboxylation (GAD65 und GAD67).
- Removed by glial uptake .

$GABA_A$ Receptors

- Most important recepors for fast synaptic inhibition.
- Related to NACh receptors – heteropentameric structure.





$GABA_A$ Receptors

- The pore is chloride ion permeant.
- The typical chloride ion reversal potential is close to the resting membrane potential.
- Activation of these receptors usually makes it harder to reach action potential threshold.

$GABA_A$ Receptors

- Endogeneous Agonist — GABA
- Defining Agonist — GABA
- Antagonists — Bicuculline, Picrotoxin
- Allosteric Agonist — Diazepam

Anamirta cocculus

Dose-Response Curve

- The effect of a pharmacological agent (often normalized to maximum) plotted against the concentration of that substance.
- For the concentration usually a logarithmic scale is used.