

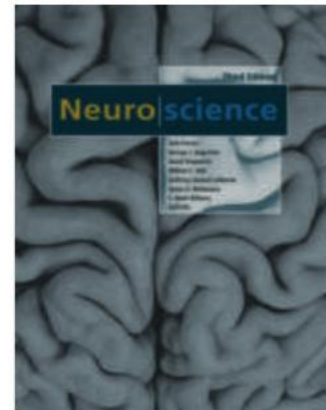
# Ligand-Gated Ion Channels

The **Other**  
Machines That  
Make It Possible...

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

# 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.)

NEUROSCIENCE: Third Edition  
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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.

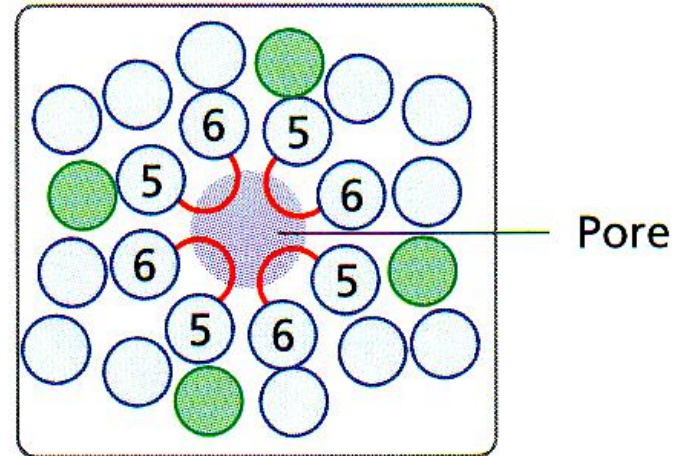
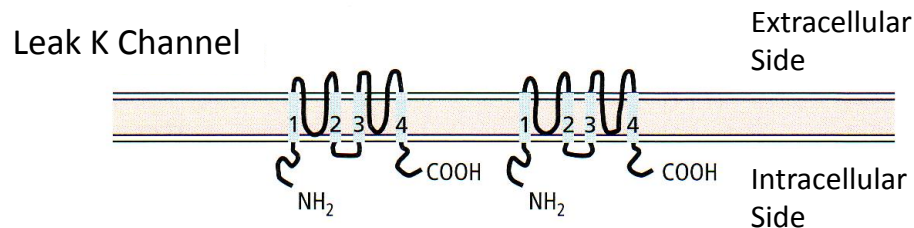
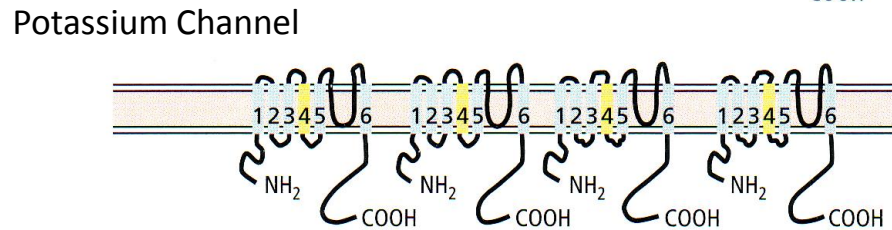
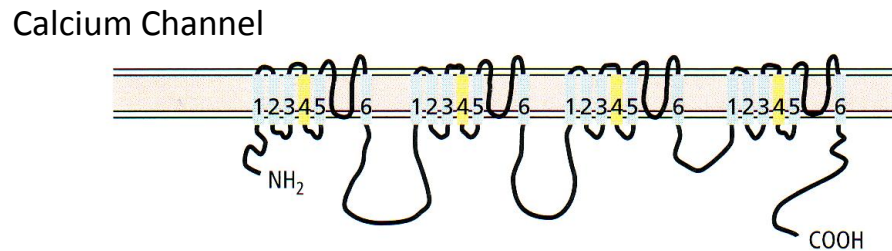
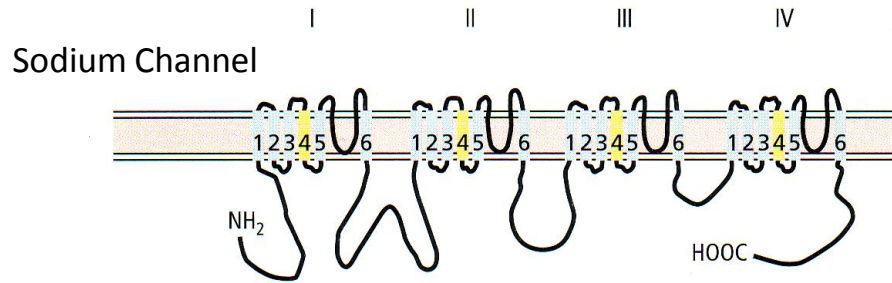
# Recapitulation L5

- 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 L5

- 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 probability, 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 L5



# 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

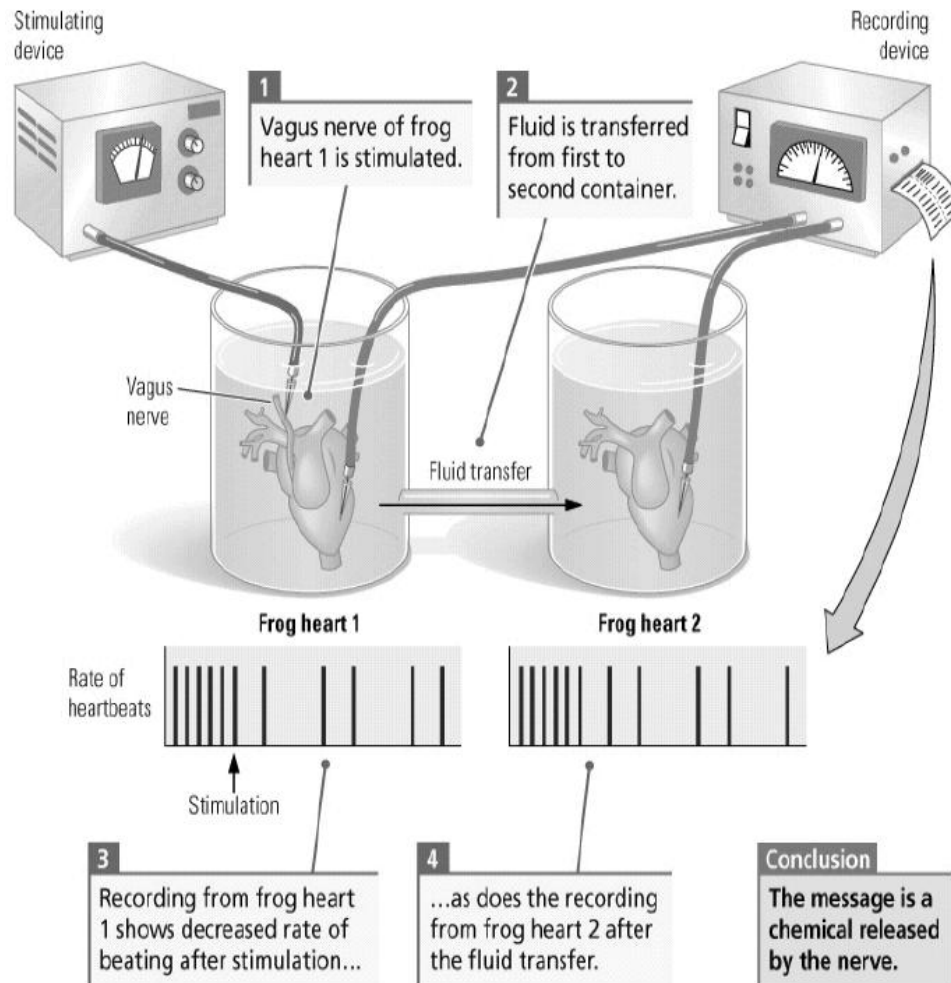


Dr. Otto Loewi 1955

- 1873-1961
- Nobel Prize 1936
- Escape to the USA 1940
- Position at the NYU
- 'Dreams' of the decisive experiment



# Otto Loewi II

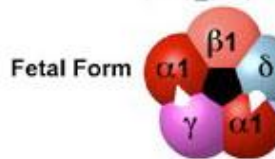


Otto Loewi did not discover ligand-gated ion channels. The effect that he discovered is mediated by metabotropic (G-protein coupled) receptors. However, he discovered

# Nicotinic ACh Receptors

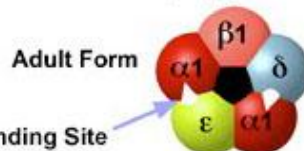
## Heteromeric Muscle AChRs

$(\alpha 1)_2 \beta 1 \gamma \delta$

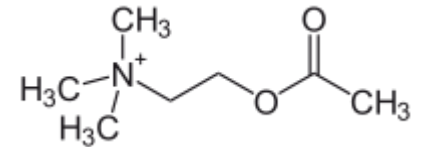


Subunits:  $\alpha 1, \beta 1, \gamma, \delta, \epsilon$

$(\alpha 1)_2 \beta 1 \epsilon \delta$



ACh Binding Site  
At Subunit Interface



Acetylcholine

## Homomeric Neuronal AChRs

Subunits:  $\alpha 7$ - $\alpha 10$   
 $(\alpha 7)_5$



Major Subtype With  
High Affinity for  $\alpha$ Bgt  
in Both Brain and Ganglia

Major Brain  
Subtype With High  
Affinity for Nicotine

## Heteromeric Neuronal AChRs

Subunits:  $\alpha 2$ - $\alpha 6, \beta 2$ - $\beta 4$

$(\alpha 4)_2(\beta 2)_3$



Likely  
Variants

$(\alpha 4)_2(\beta 2)_2 \alpha 5$



$(\alpha 4)_3(\beta 2)_2$



$(\alpha 3)_2(\beta 4)_3$

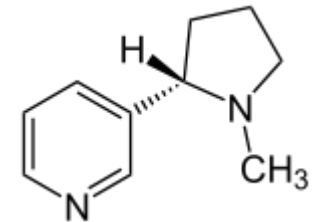


Likely  
Variants

$(\alpha 3)_2 \beta 2 \beta 4 \alpha 5$



$(\alpha 3)_2(\beta 4)_2 \alpha 5$



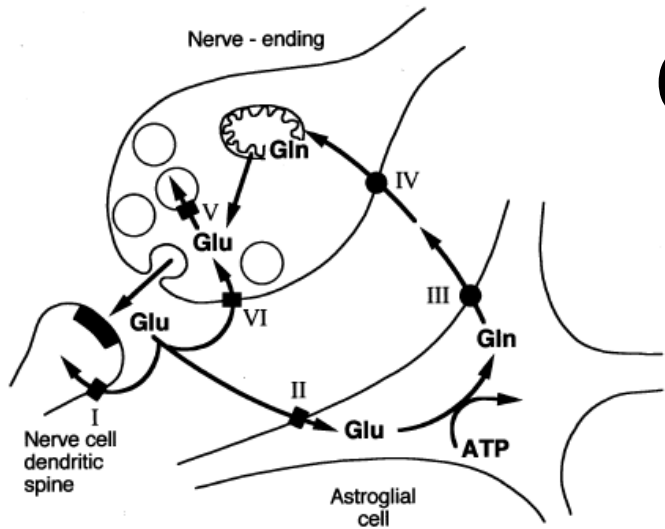
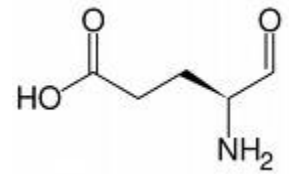
Nicotine

# Nicotinic ACh Receptors

- Endogeneous Agonist
- Defining Agonist
- Antagonists
- Acetylcholine
- Nicotine
- Curare, Bungarotoxin

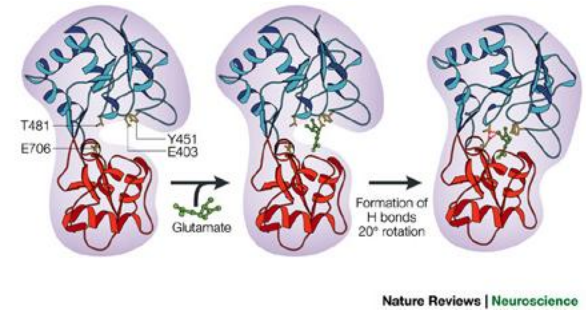
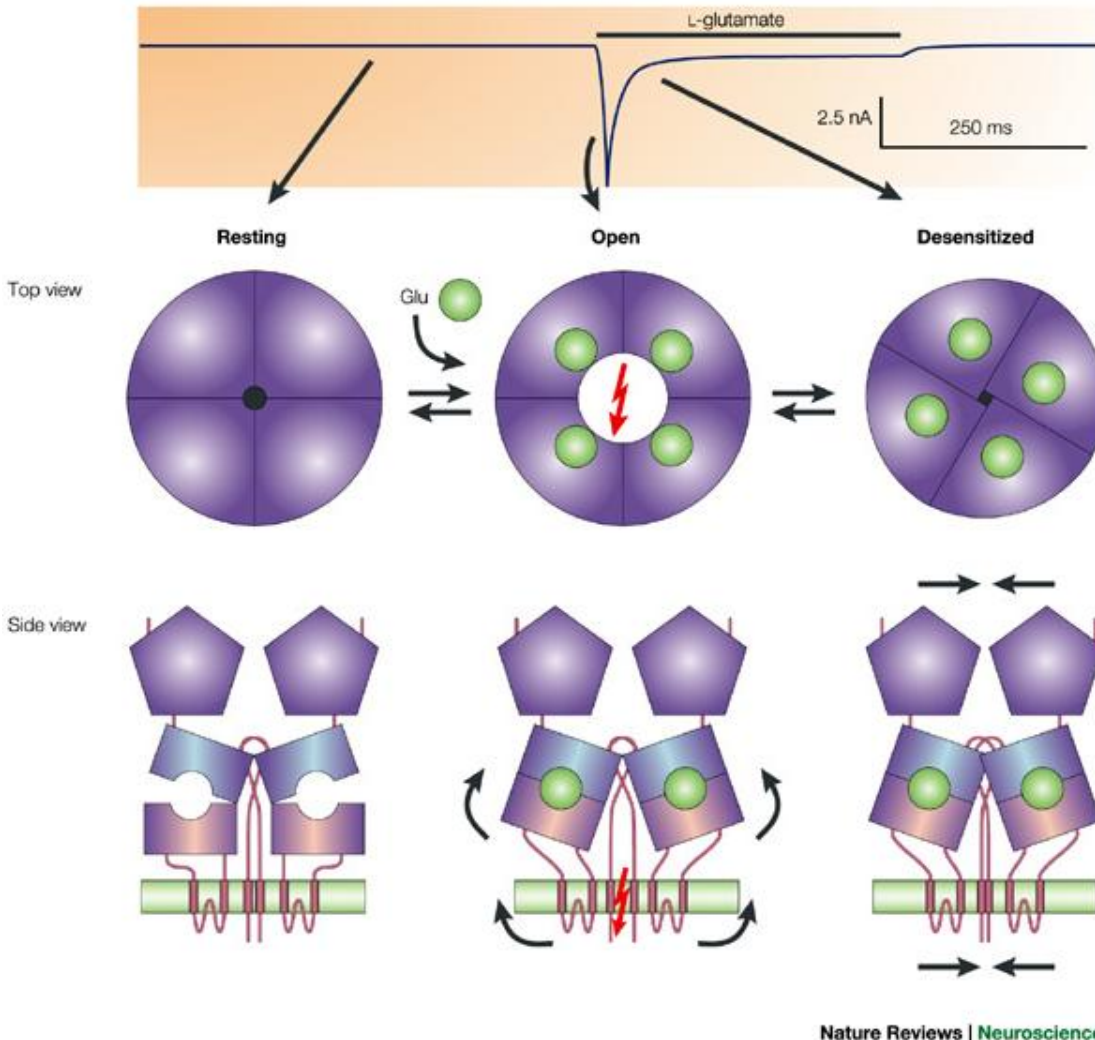


# Glutamate



- 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 glutamate 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
- Antagonists
  - Glutamate
  - AMPA
  - $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
  - NBQX
  - (2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo[f]chinoxalin-2,3-dion)

# NMDA Receptors

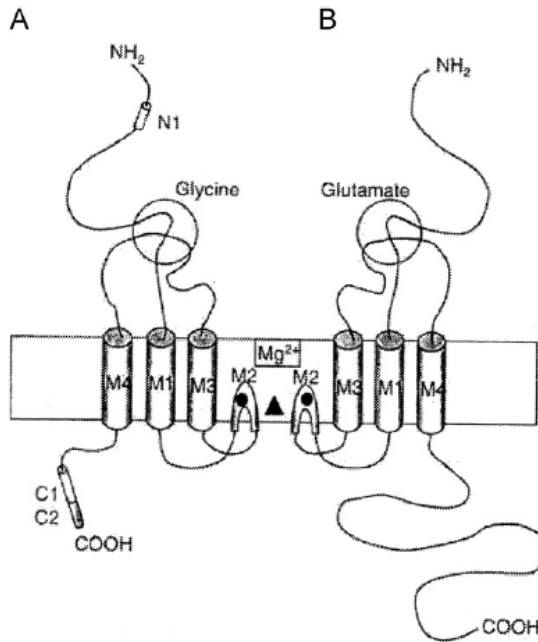
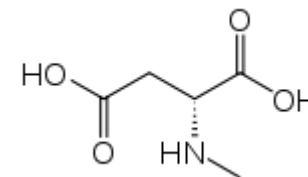


Figure 2 Schematic diagram showing the predicted transmembrane topology of an NR1 (A) and an NR2 (B) subunit showing the extracellular amino terminals, the intracellular carboxyl terminals, the membrane domains (M1-4) and the agonist binding sites.<sup>3</sup>

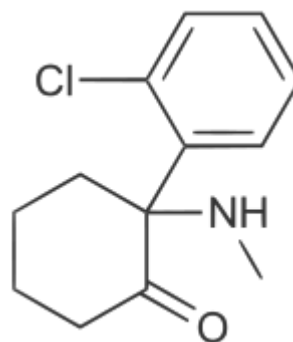
- NMDA receptors have a tetrameric arrangement.
- Their permeability depends on ligand binding and on membrane voltage.
- Mg Block.

# NMDA Receptors

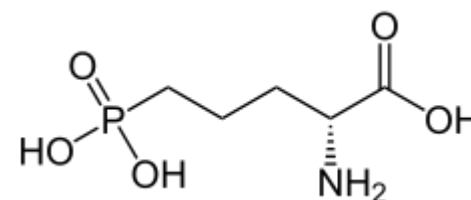


NMDA

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



Ketamine

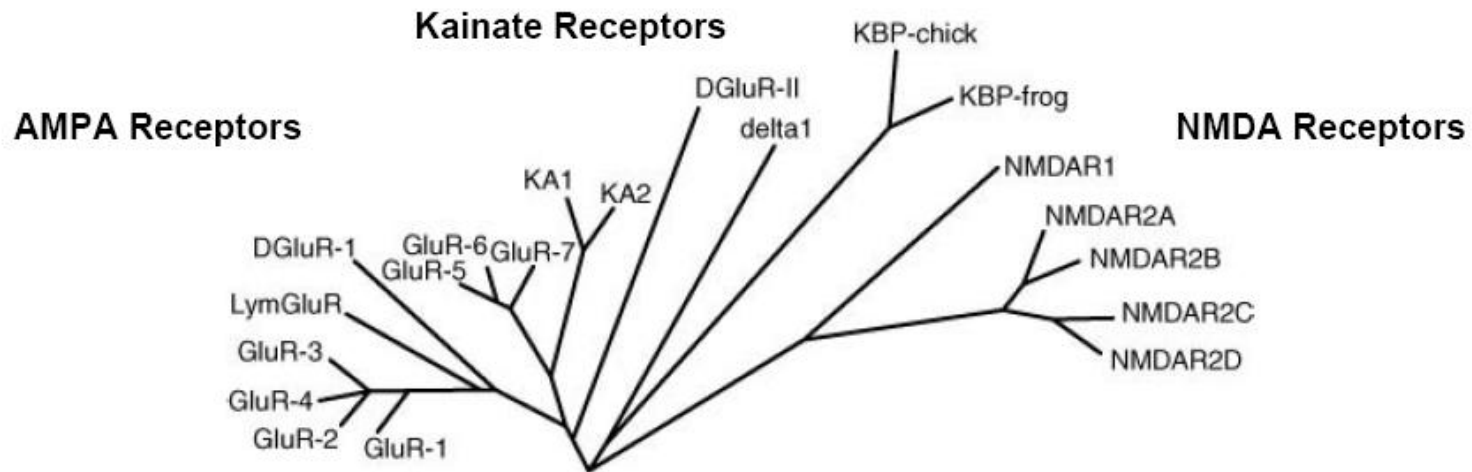


AP5, APV

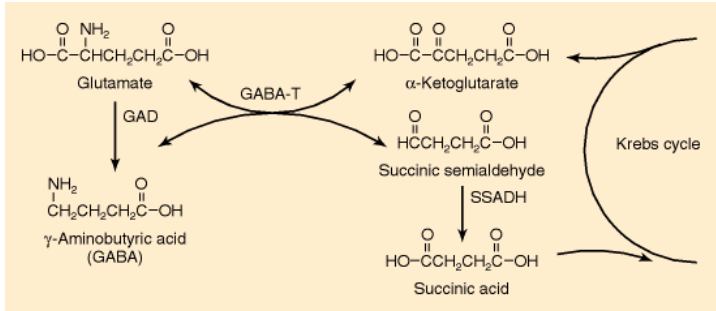


# The Whole GluR Family

## The Ionotropic Glutamate Receptor Family

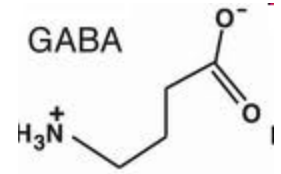


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# GABA

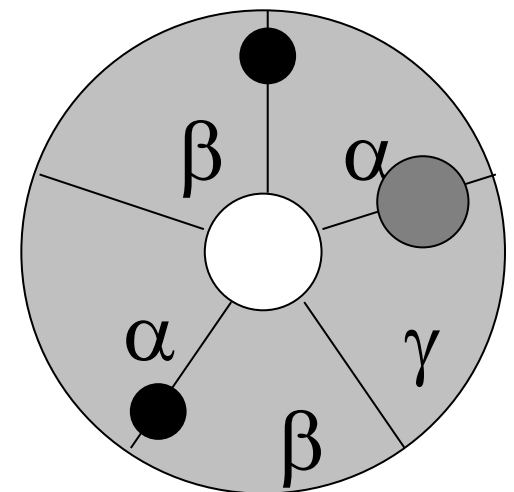
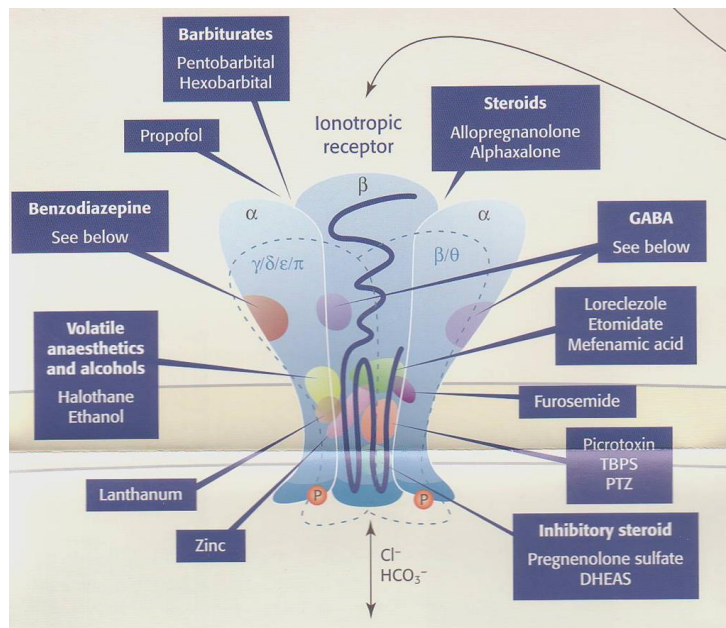
gamma-Aminobutyric acid



- Most important inhibitory neurotransmitter 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<sub>A</sub> Receptors

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



# GABA<sub>A</sub> 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<sub>A</sub> Receptors

- Endogeneous Agonist
- Defining Agonist
- Antagonists
- Allosteric Agonist
- GABA
- GABA
- Bicuculline, Picrotoxin
- 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.

