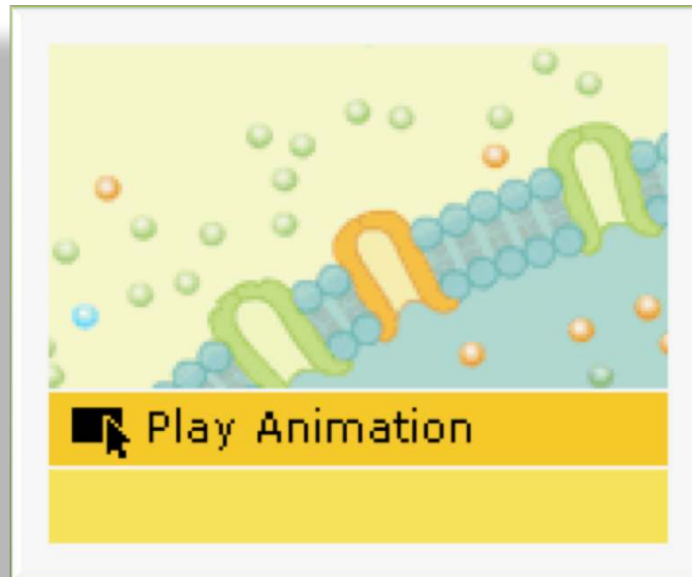


# **BASICS OF NEUROBIOLOGY**

## **IONOTROPIC RECEPTORS**

**ZSOLT LIPOSITS**

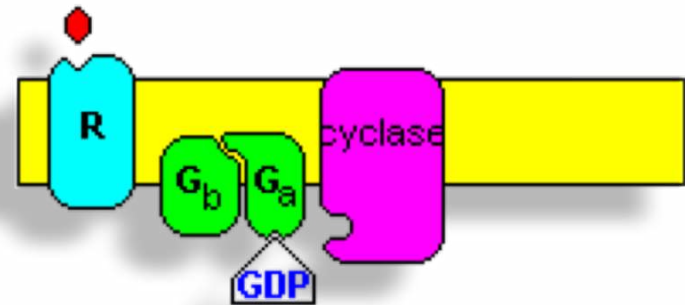
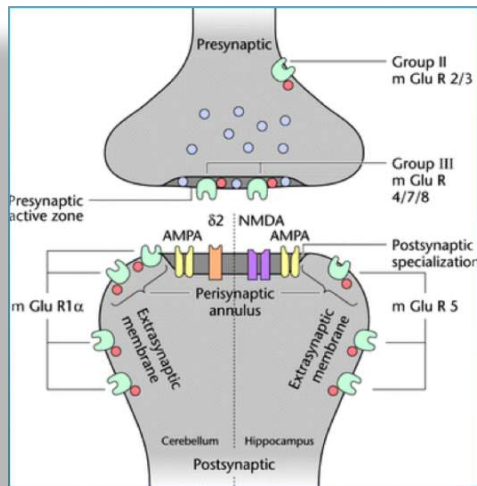
## NEURAL COMMUNICATION



<http://sciencecore.columbia.edu/s4.html>

# Post-synaptic mechanisms

## *Receptors-signal transduction-messengers*



# Basics of Neurobiology: Ionotropic receptors

## TRANSMITTER RECEPTORS

WITH THE EXCEPTION OF STEROID SIGNALS AND UNCONVENTIONAL GAS TRANSMITTERS (NO, CO), REGULAR NEUROMESSENGERS CAN NOT DIFFUSE THROUGH THE CELL MEMBRANE

THEIR EFFECTS ARE MEDIATED BY RECEPTORS THAT ARE EMBEDDED INTO THE POST-SYNAPTIC MEMBRANE

RECEPTORS ARE COMPLEX PROTEINS THAT SHOW HIGH-AFFINITY BINDING FOR TRANSMITTER LIGANDS

LIGAND BINDING ALTERS THE CONFORMATION OF THE RECEPTOR THAT EVOKES POSTSYNAPTIC RESPONSES

THE RESPONSE DEPENDS ON THE AMOUNT OF THE TRANSMITTER, THE NUMBER AND STATE OF THE RECEPTORS

TRANSMITTER RECEPTORS BELONG TO TWO CATEGORIES:

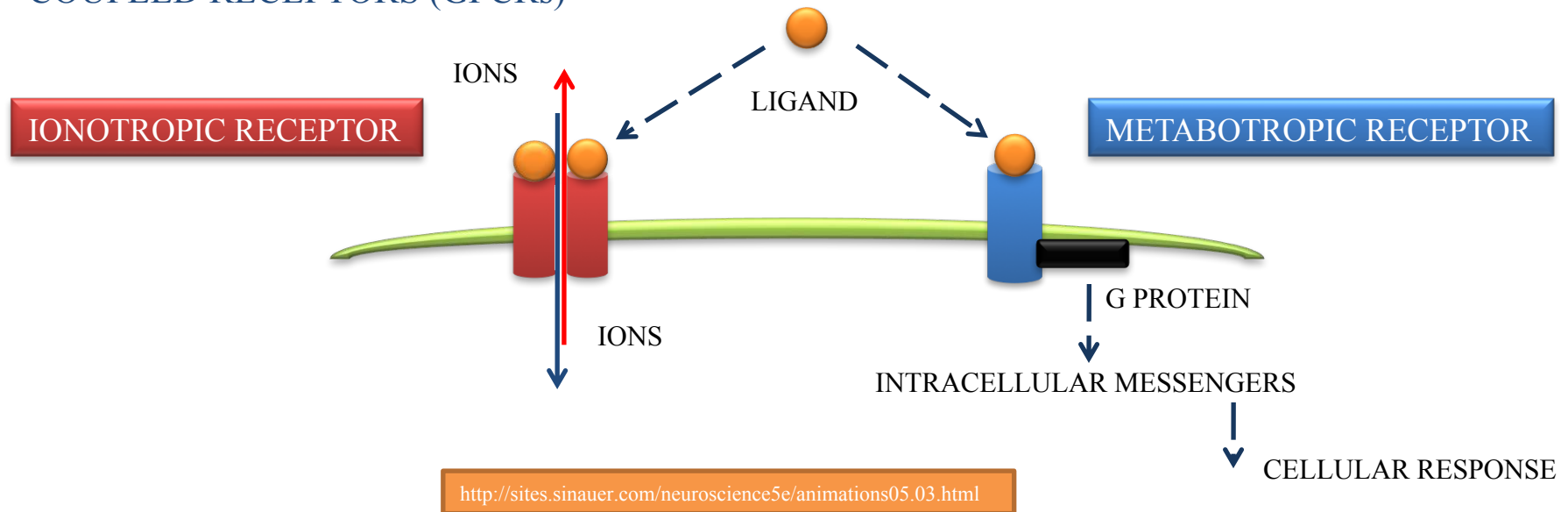
- IONOTROPIC RECEPTORS
- METABOTROPIC RECEPTORS

# Basics of Neurobiology: Ionotropic receptors

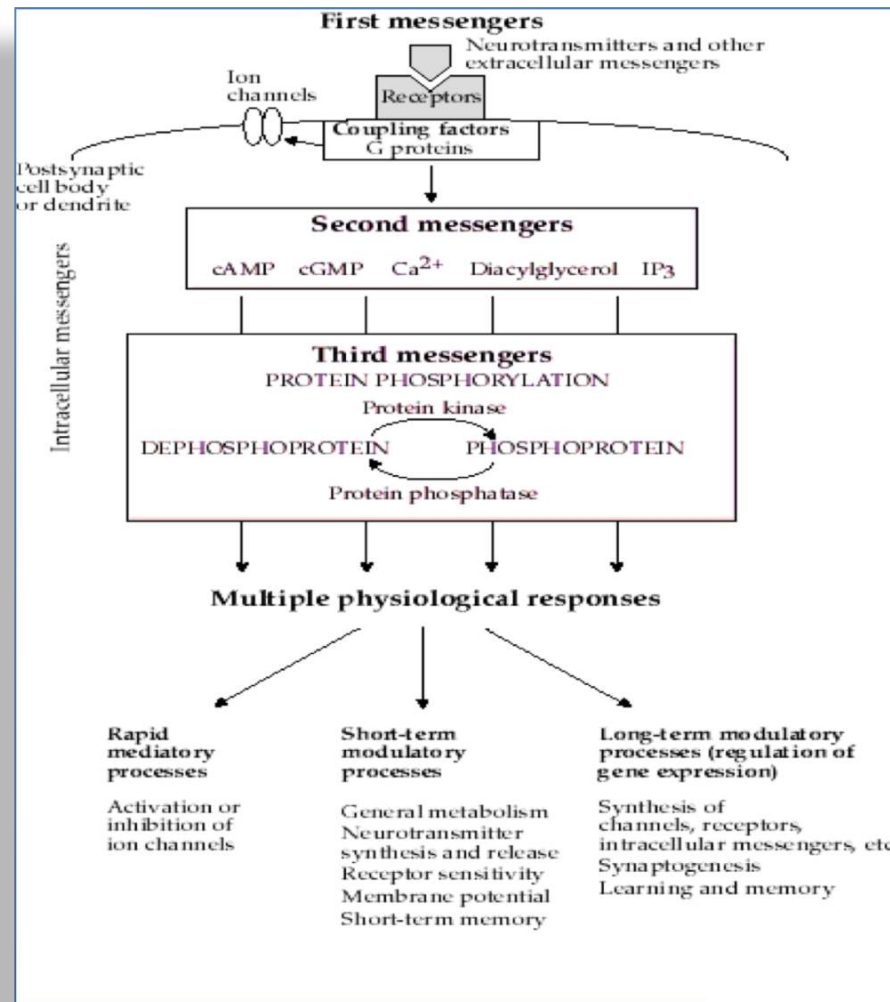
## TRANSMITTER RECEPTORS

IONOTROPIC RECEPTORS FORM PORES, SPECIFIC ION CHANNELS IN THE MEMBRANE THAT ALLOW THE PASSAGE OF IONS UPON ACTIVATION. THEY PERFORM AS LIGAND-GATED ION CHANNELS

METABOTROPIC RECEPTORS ARE COUPLED TO GTP-BINDING PROTEINS (G PROTEINS) VIA THEIR INTRACELLULAR DOMAINS. G PROTEIN ACTIVATION EVOKES SECONDARY RESPONSES IN THE CELL THAT ALTER THEIR METABOLISM. SYNONYM: G PROTEIN-COUPLED RECEPTORS (GPCRs)



# Basics of Neurobiology: Ionotropic receptors



# Basics of Neurobiology: Ionotropic receptors

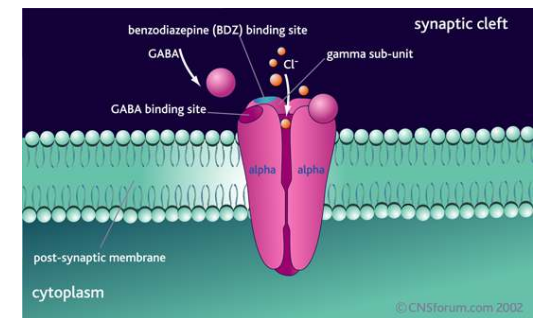
## IONOTROPIC RECEPTORS

IONOTROPIC RECEPTORS BY GATING ION CHANNELS CONTRIBUTE TO FAST POST-SYNAPTIC RESPONSES

WITH REGARDS TO THE POSTSYNAPTIC EFFECT, THEY ARE EXCITATORY OR INHIBITORY IN NATURE

IONOTROPIC RECEPTOR FAMILIES COMPRISE THE FOLLOWING RECEPTORS:

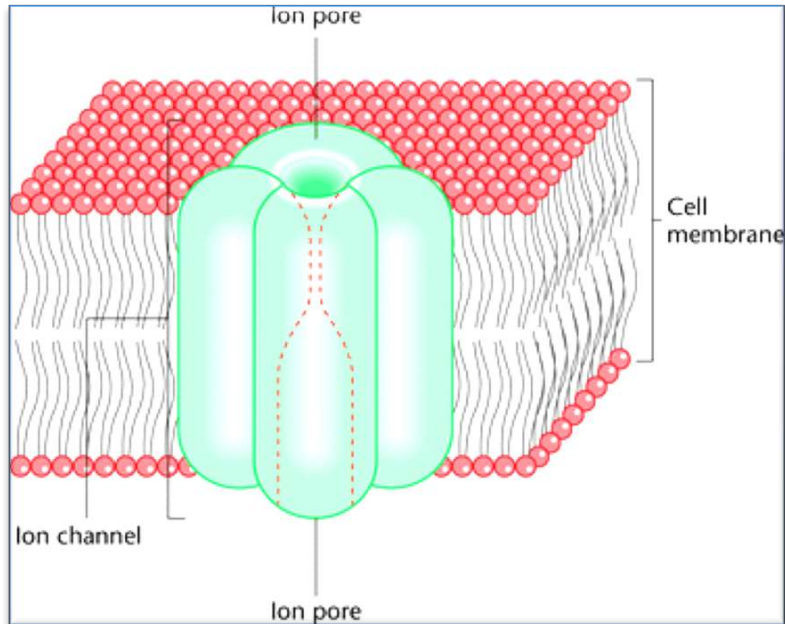
- ❑ NICOTINIC ACETYLCHOLINE RECEPTOR (nAChR)
- ❑ GAMMA-AMINOBUTYRIC ACID A RECEPTOR (GABA-A)
- ❑ GLYCINE RECEPTOR
- ❑ SEROTONIN RECEPTOR (5-HT<sub>3</sub> SUBCLASS)
- ❑ GLUTAMATE RECEPTORS
  - NMDA RECEPTOR
  - AMPA RECEPTOR
  - KAINATE RECEPTOR



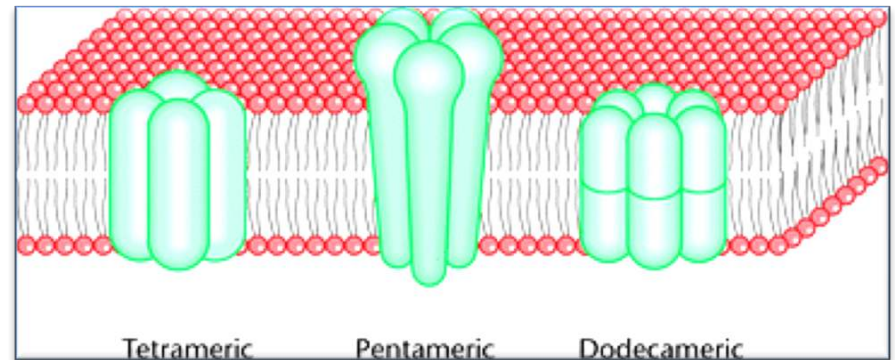
**GABA A RECEPTOR**

*COURTESY OF LUNDBECK INSTITUTE, DENMARK*

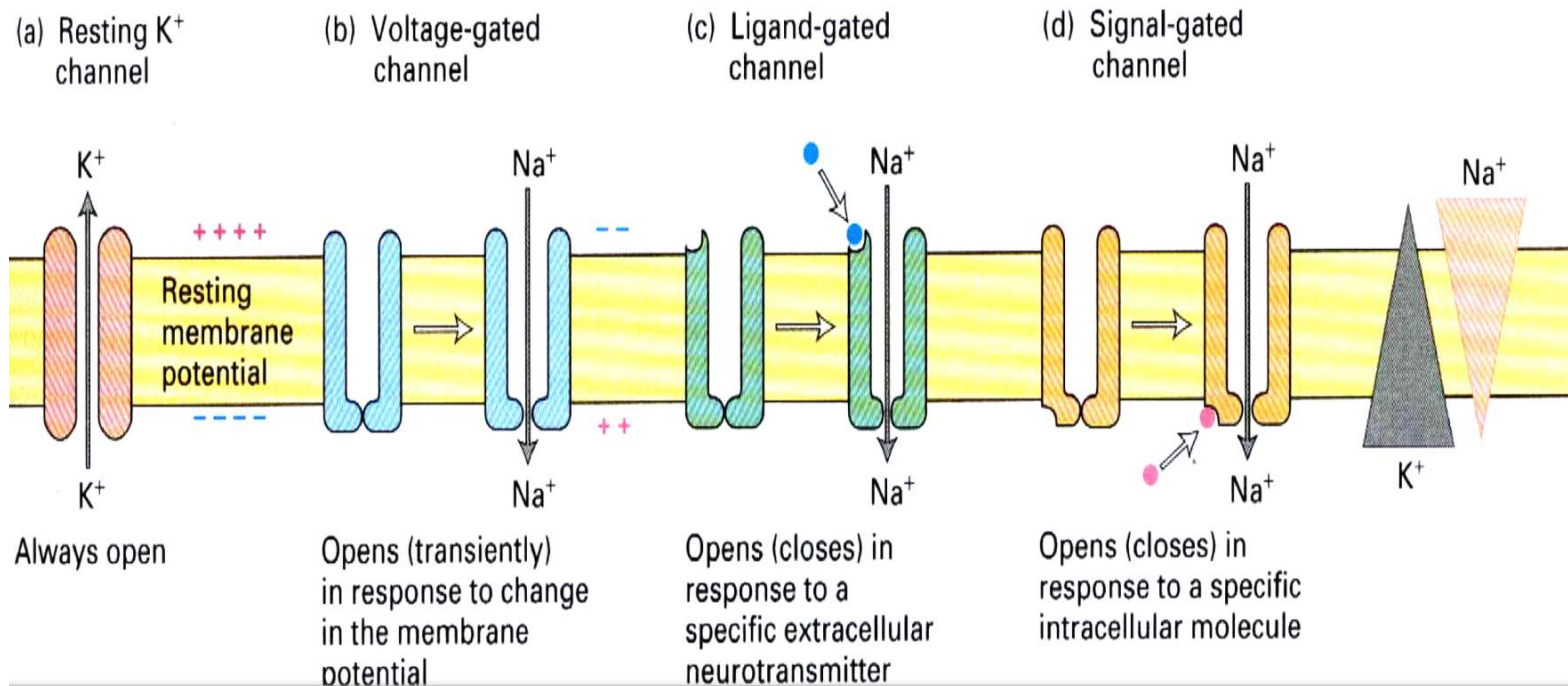
# Basics of Neurobiology: Ionotropic receptors



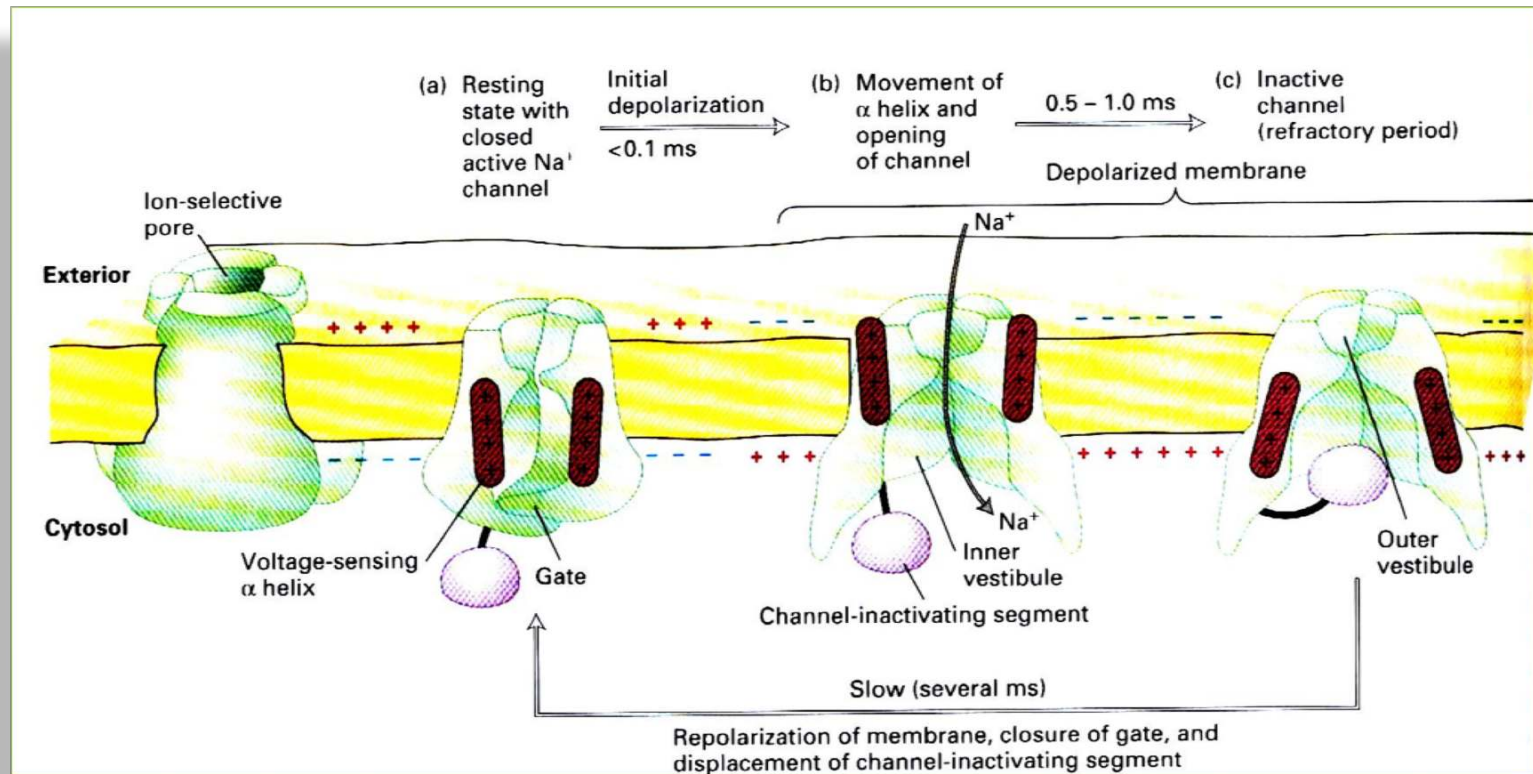
## ION CHANNELS



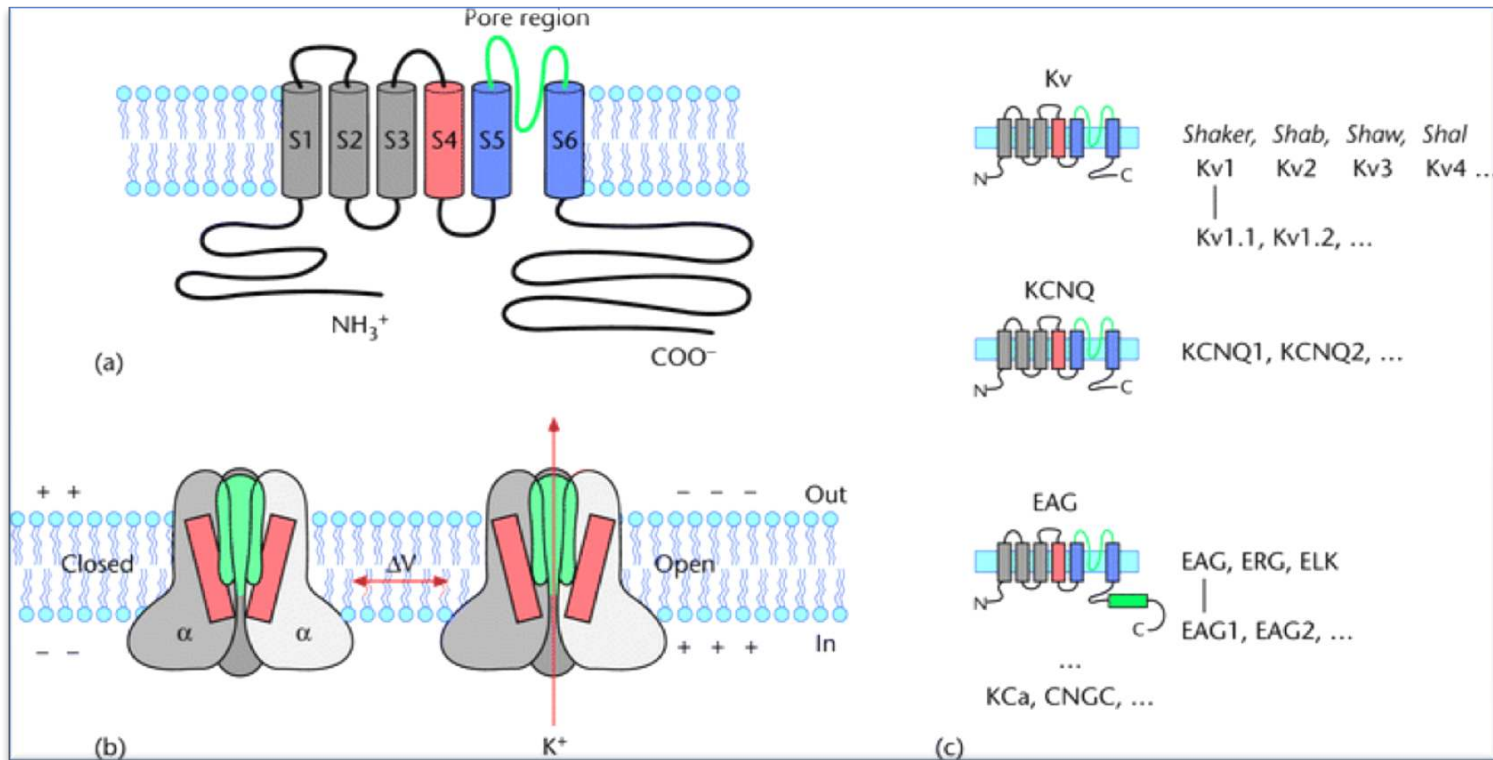
## Types of ion channels



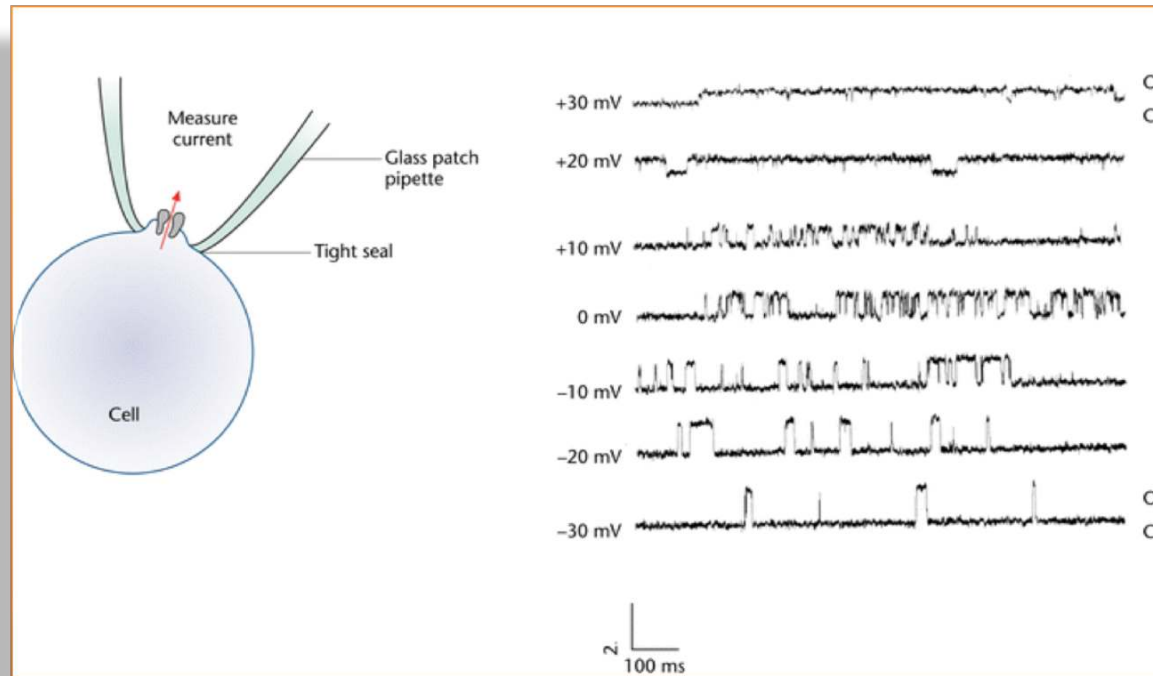
## Voltage-gated Na channel



## Voltage-gated K channel

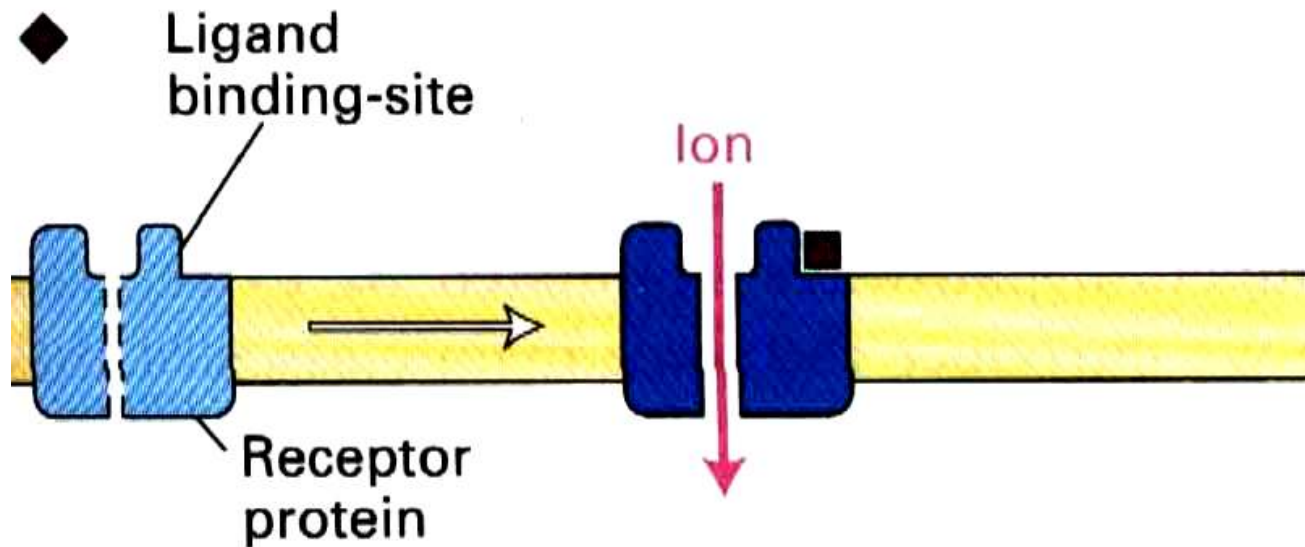


## Patch-clamp method



<http://sites.sinauer.com/neuroscience5e/animations04.01.html>

## Ligand-gated channel



# Basics of Neurobiology: Ionotropic receptors

## Ligand-gated ion channels

**TABLE 21-1** Neurotransmitter Receptors That Are Ligand-Gated Ion Channels

| Functional Type      | Ligand*                                               | Ion Channel                                   |
|----------------------|-------------------------------------------------------|-----------------------------------------------|
| Excitatory Receptors | Acetylcholine (nicotinic receptor)                    | $\text{Na}^+/\text{K}^+$                      |
|                      | Glutamate (NMDA class receptors) <sup>†</sup>         | $\text{Na}^+/\text{K}^+$ and $\text{Ca}^{2+}$ |
|                      | Glutamate (non-NMDA class receptors) <sup>‡</sup>     | $\text{Na}^+/\text{K}^+$                      |
|                      | Serotonin (5HT <sub>3</sub> class receptors)          | $\text{Na}^+/\text{K}^+$                      |
| Inhibitory Receptors | $\gamma$ -Aminobutyric acid, GABA (A-class receptors) | $\text{Cl}^-$                                 |
|                      | Glycine                                               | $\text{Cl}^-$                                 |

\*Most of these ligands also bind to receptors that are coupled to G proteins (see Table 21-2).

Their receptors that are ion channels are indicated in parentheses.

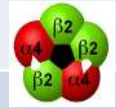
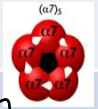
<sup>†</sup>Opening of the cation channel in these receptors requires a slightly depolarized membrane and binding of glutamate (or N-methyl-D aspartate, NMDA).

<sup>‡</sup>Opening of the cation channel in these receptors only requires binding of glutamate.

SOURCE: H. Lester, 1988, *Science* 241:1057; E. Barnard, 1988, *Nature* 335:301; N. Unwin, 1993, *Cell* vol. 72/*Neuron* vol. 10 (suppl.), pp. 31-41; A. Maricq et al., 1991, *Science* 254:432.

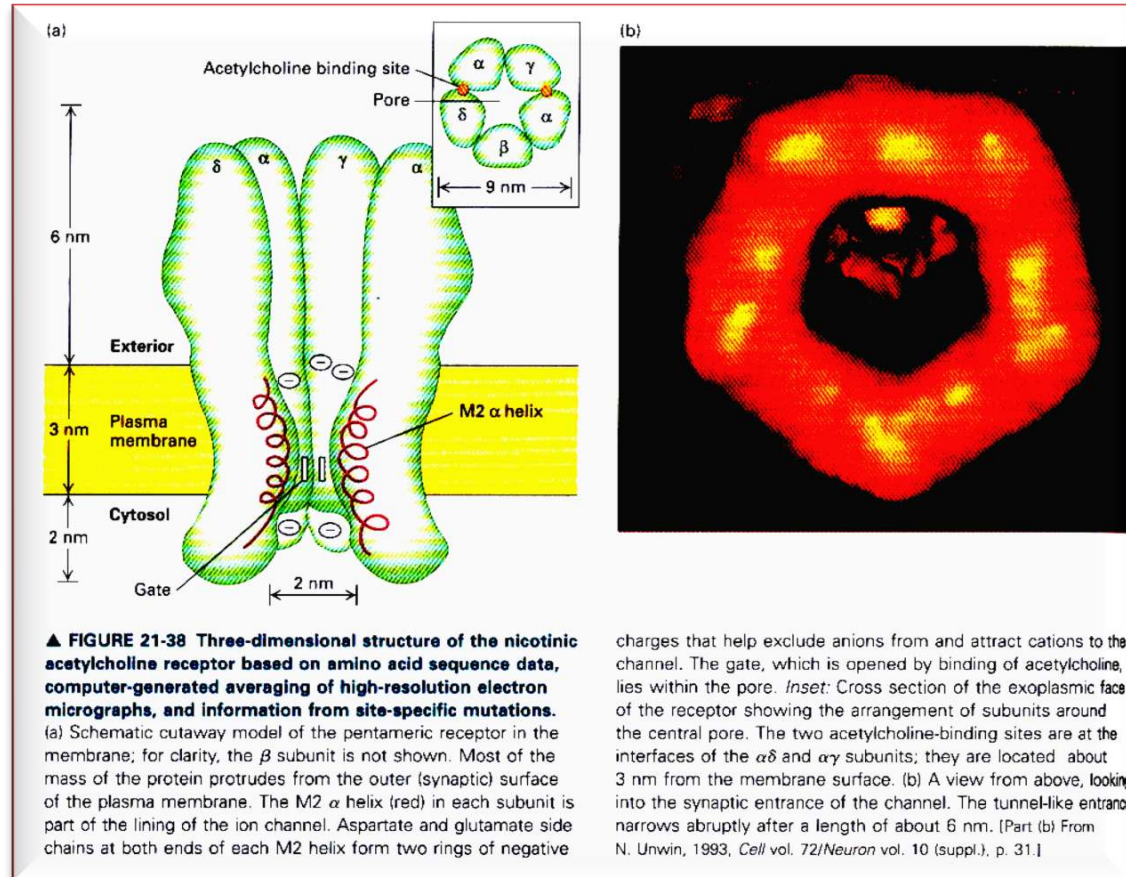
# Basics of Neurobiology: Ionotropic receptors

## NICOTINIC ACETYLCHOLINE RECEPTOR

| ATTRIBUTE        | DESCRIPTION                                                                                                                                                                                                                                                                             |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NAME             | NICOTINIC ACETYLCHOLINE RECEPTOR                                                                                                                                                                                                                                                        |
| SUPERFAMILY      | NICOTINIC ACETYLCHOLINE RECEPTOR                                                                                                                                                                                                                                                        |
| STRUCTURE        | <p>5 subunit</p> <p>PENTAMERIC, HOMO- OR HETEROMERIC VARIANTS</p> <p>different subunits</p>                                                                                                          |
| SUBUNITS         | <p><math>\alpha 1</math>-10, <math>\beta 1</math>-4, <math>\gamma</math>, <math>\delta</math>, <math>\epsilon</math></p> <p>subunits are the same</p>                                                |
| EXPRESSION TYPES | MUSCLE HETEROMERIC ( $\alpha 1$ ) <sub>2</sub> $\beta 1\delta\epsilon$ , BRAIN HETEROMERIC ( $\alpha 4$ ) <sub>2</sub> ( $\beta 2$ ) <sub>3</sub> , BRAIN, GANGLION HOMOMERIC ( $\alpha 7$ ) <sub>5</sub> , GANGLION HETEROMERIC ( $\alpha 3$ ) <sub>2</sub> ( $\beta 4$ ) <sub>3</sub> |
| LIGAND BINDING   | EXTRACELLULAR DOMAIN NEAR TO N TERMINUS, AT SUBUNIT INTERFACES                                                                                                                                                                                                                          |
| BASIC ROLE(S)    | OPENS PORES <u>FOR SODIUM ION INFLOW</u> AND <u>POTASSIUM ION OUTFLOW</u> , MUSCLE CONTRACTION, EPSP                                                                                                                                                                                    |
| AGONISTS         | NICOTINE, CHOLINE, EPIBATIDINE                                                                                                                                                                                                                                                          |
| ANTAGONISTS      | GANGLIONIC: HEXAMETHONIUM, MUSCLE: ATRACURIUM, SUCCINYLCHOLINE, BRAIN; 18-METHOXYCORONARIDINE                                                                                                                                                                                           |
| FUNCTIONAL ROLES | EXECUTION OF <u>MOVEMENT</u> AND <u>AUTONOMIC FUNCTIONS</u> , MODULATION OF CNS NETWORKS VIA <u>PRE- AND POSTSYNAPTIC REGULATION</u>                                                                                                                                                    |
| DISEASES         | MYASTHENIA GRAVIS, CONGENITAL MYASTHENIC DISEASES, TOBACCO ADDICTION                                                                                                                                                                                                                    |

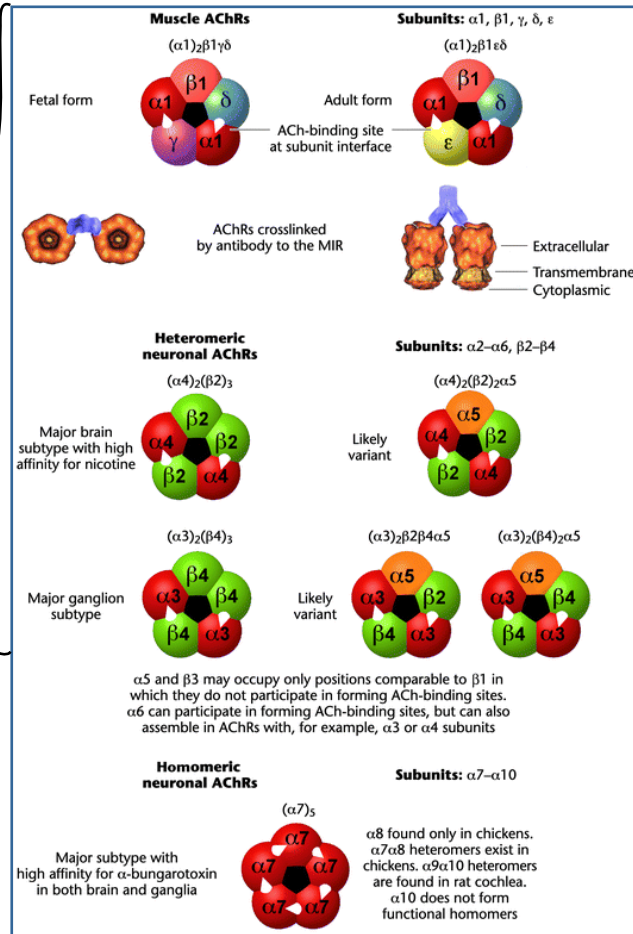
# Basics of Neurobiology: Ionotropic receptors

## Nicotinic acetylcholine receptor

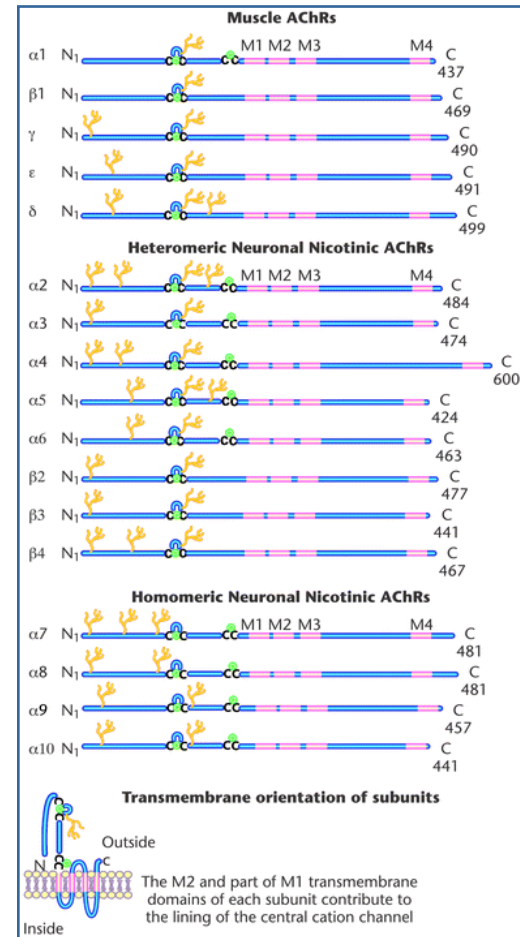


# Basics of Neurobiology: Ionotropic receptors

heteromeric



homomeric



# Basics of Neurobiology: Ionotropic receptors

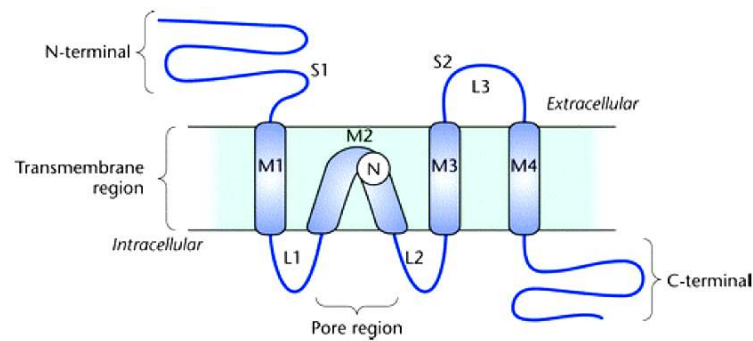
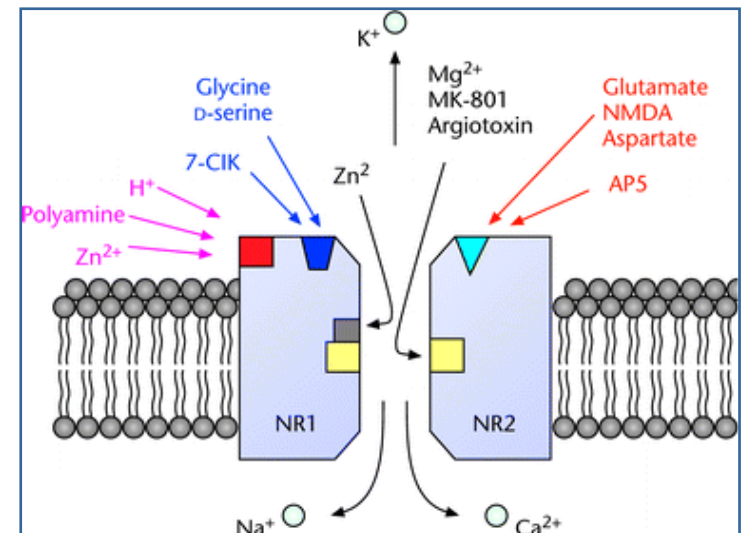
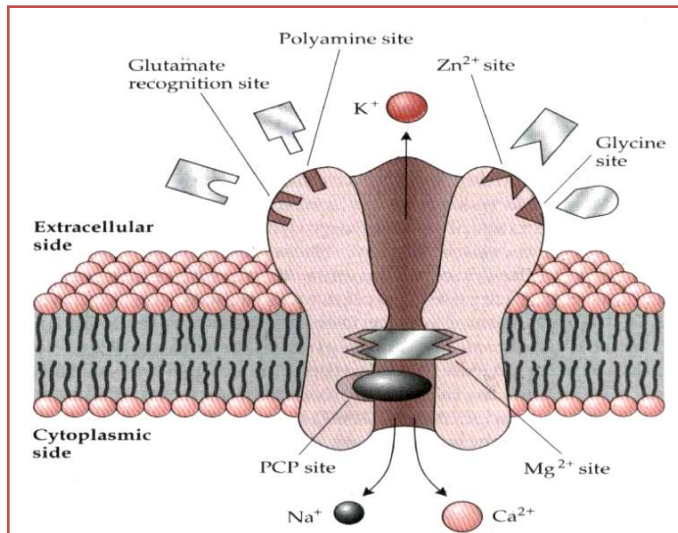
| SEROTONIN RECEPTOR (5-HT <sub>3</sub> SUBCLASS) |                                                                   |
|-------------------------------------------------|-------------------------------------------------------------------|
| ATTRIBUTE                                       | DESCRIPTION                                                       |
| NAME                                            | SEROTONIN RECEPTOR (5-HT <sub>3</sub> SUBCLASS)                   |
| SUPERFAMILY                                     | NICOTINIC ACETYLCHOLINE RECEPTOR                                  |
| STRUCTURE                                       | PENTAMERIC, HOMOMERIC OR HETEROMERIC FORMATIONS                   |
| SUBUNITS                                        | A-E                                                               |
| EXPRESSION TYPES                                | 5-HT <sub>3A</sub> AND 5-HT <sub>3B</sub> SUBUNITS IN CNS         |
| LIGAND BINDING                                  | AT THE INTERFACE OF TWO ADJACENT SUBUNITS                         |
| BASIC ROLE(S)                                   | OPENS PORES FOR SODIUM ION INFLOW AND POTASSIUM ION OUTFLOW, EPSP |
| AGONISTS                                        | BENZYLPIPERAZINE, QUIPAZINE                                       |
| ANTAGONISTS                                     | CARBAZOLE, INDAZOLES, INDOLES                                     |
| FUNCTIONAL ROLES                                | ROLE IN ADDICTION, ANXIETY, EMESIS, GI MOTILITY, NAUSEA           |
| DISEASES                                        | -----                                                             |

# Basics of Neurobiology: Ionotropic receptors

| GLUTAMATE RECEPTOR-NMDA TYPE |                                                                                                                                                                                                                                          |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATTRIBUTE                    | DESCRIPTION                                                                                                                                                                                                                              |
| NAME                         | NMDA (N-methyl-D-aspartic acid) RECEPTOR                                                                                                                                                                                                 |
| SUPERFAMILY                  | GLUTAMATE RECEPTOR                                                                                                                                                                                                                       |
| STRUCTURE                    | <u>HETEROMERIC ASSEMBLIES</u> MADE UP FROM NR1 SUBUNITS TOGETHER WITH AT LEAST ONE TYPE OF NR2 SUBUNIT                                                                                                                                   |
| SUBUNITS                     | NR1, NR2, NR3 SUBFAMILIES                                                                                                                                                                                                                |
| EXPRESSION TYPES             | NR1: 8 ISOFORMS, NR2A-2D, NR3A-B (FOR SPLICE VARIANTS SEE TEXTBOOKS)                                                                                                                                                                     |
| LIGANDS                      | IMPORTANT BINDING SITES FOR: NMDA, ASPARTATE, GLUTAMATE, GLYCINE, D-SERINE, POLYAMINE, $Zn^{2+}$ , $Mg^{2+}$ , $H^{+}$                                                                                                                   |
| BASIC ROLE(S)                | NON SPECIFIC CATION CHANNEL ALLOWING CALCIUM, SODIUM AND POTASSIUM PASSAGE. FEATURES: LOW KINETICS, HIGH $Ca^{2+}$ PERMEABILITY, VOLTAGE-DEPENDENT BLOCK BY $Mg^{2+}$ , GLYCINE CO-ACTIVATOR, POLYAMINE ACTIVATION, $Zn^{2+}$ INHIBITION |
| AGONISTS                     | GLUTAMATE, ASPARTATE, GLYCINE, D-SERINE                                                                                                                                                                                                  |
| ANTAGONISTS                  | AMANTADINE, KETAMINE, PHENCYCLIDINE                                                                                                                                                                                                      |
| FUNCTIONAL ROLES             | LONG TERM POTENTIATION, SYNAPTIC PLASTICITY                                                                                                                                                                                              |
| DISEASES                     | EXCITOTOXICITY                                                                                                                                                                                                                           |

# Basics of Neurobiology: Ionotropic receptors

## NMDA receptor

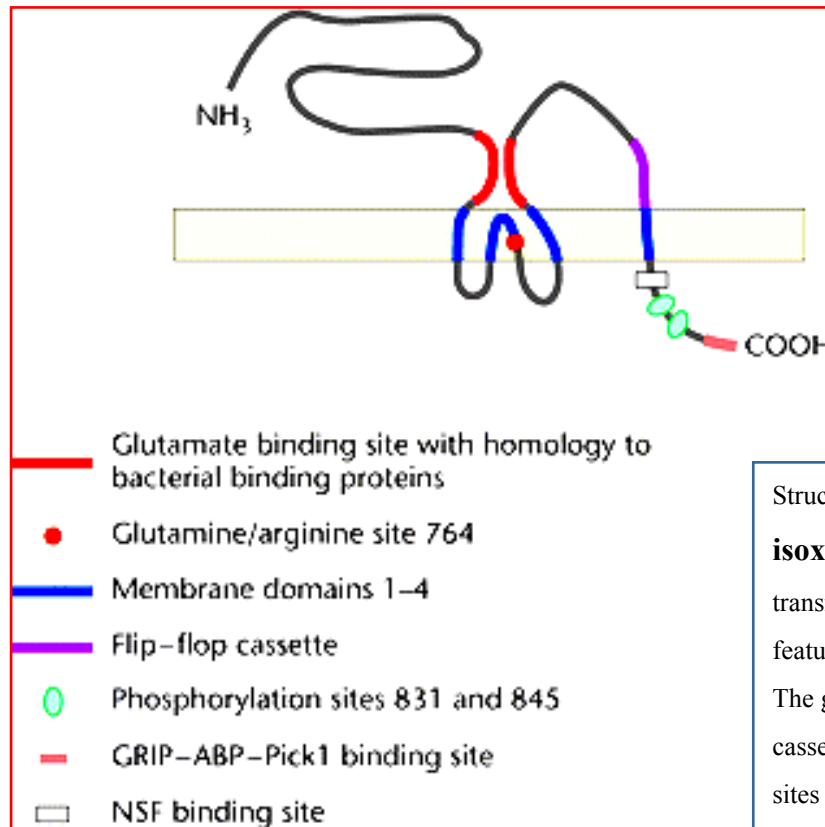


## Basics of Neurobiology: Ionotropic receptors

| AMPA RECEPTOR    |                                                                                               |
|------------------|-----------------------------------------------------------------------------------------------|
| ATTRIBUTE        | DESCRIPTION                                                                                   |
| NAME             | AMPA ( $\alpha$ -AMINO-3-HYDROXY-5-METHYLISOXAZOLE-4-PROPIONIC ACID ) RECEPTOR                |
| SUPERFAMILY      | GLUTAMATE RECEPTOR                                                                            |
| STRUCTURE        | HETEROTETRAMERIC                                                                              |
| SUBUNITS         | GluR1-GluR4                                                                                   |
| EXPRESSION TYPES | (GluR1) <sub>2</sub> (GluR2) <sub>2</sub>                                                     |
| LIGAND BINDING   | EACH SUBUNIT HAS AN AGONIST BINDING SITE. THE RECEPTOR OPENS AND CLOSES FAST, GATED BY SODIUM |
| BASIC ROLE(S)    | MEDIATE MOST EXCITATORY ACTIONS IN THE CNS, FAST KINETICS, LOW CALCIUM PERMEABILITY. EPSP     |
| AGONISTS         | AMPA, DOMOIC ACID                                                                             |
| ANTAGONISTS      | GYKI53655, KYNURENIC ACID                                                                     |
| FUNCTIONAL ROLES | SYNAPTIC TRANSMISSION, SYNAPTIC PLASTICITY                                                    |
| DISEASES         | MOTOR NEURON DISEASE (AMYOTROPHIC LATERAL SCLEROSIS; ALS                                      |

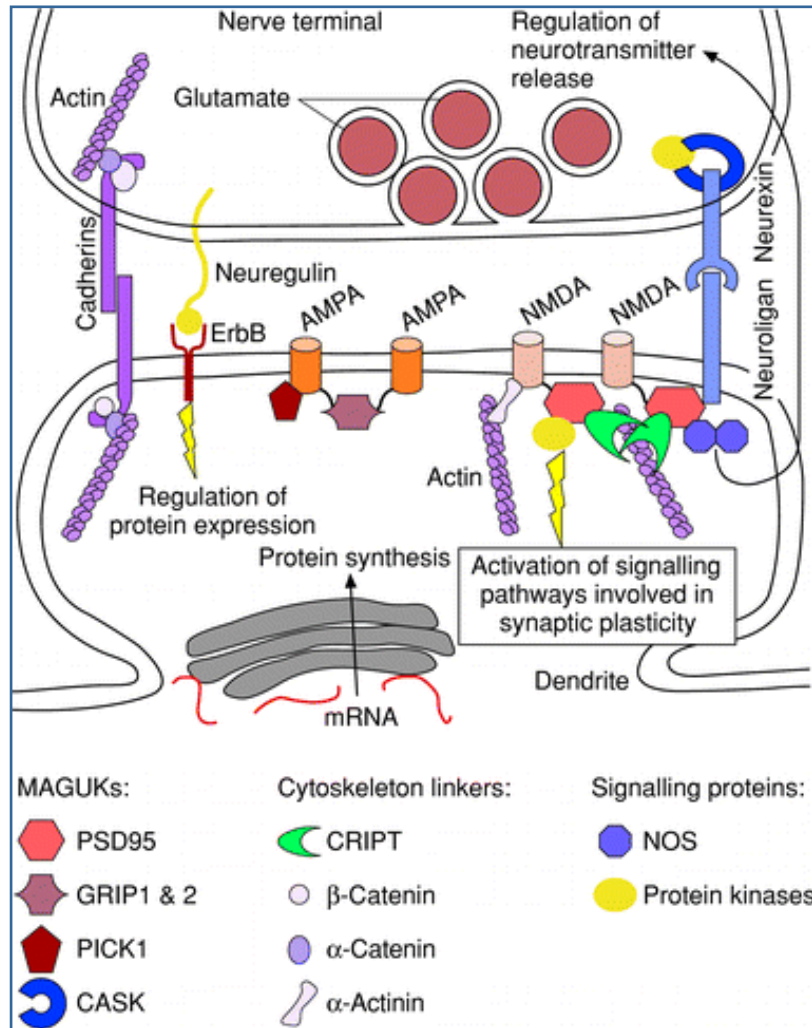
# Basics of Neurobiology: Ionotropic receptors

## AMPA receptor



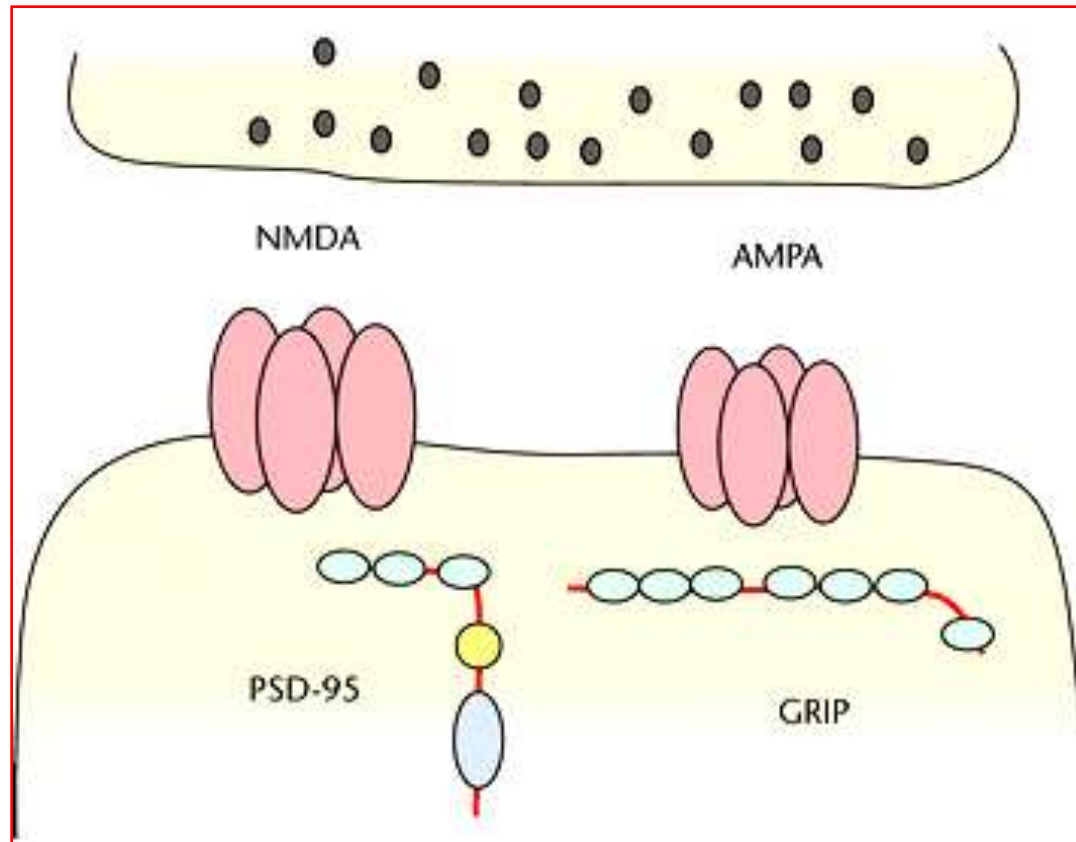
Structure of a prototype **a-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)** receptor subunit. The common transmembrane topology of all AMPA receptors is shown with individual features taken from glutamate receptor (GluR) subunit 1, GluR2 and GluR3. The glutamate binding site, the glutamine/arginine site and the flipflop cassette are common to all AMPA receptor subunits. The phosphorylation sites are specific to GluR1, the N-ethyl-maleimide sensitive factor (NSF) site is specific to GluR2, and the glutamate receptor interacting protein, AMPA receptor binding protein and protein interacting with Ckinase (GRIPABP Pick1) site is specific to GluR2 and GluR3.

# Basics of Neurobiology: Ionotropic receptors

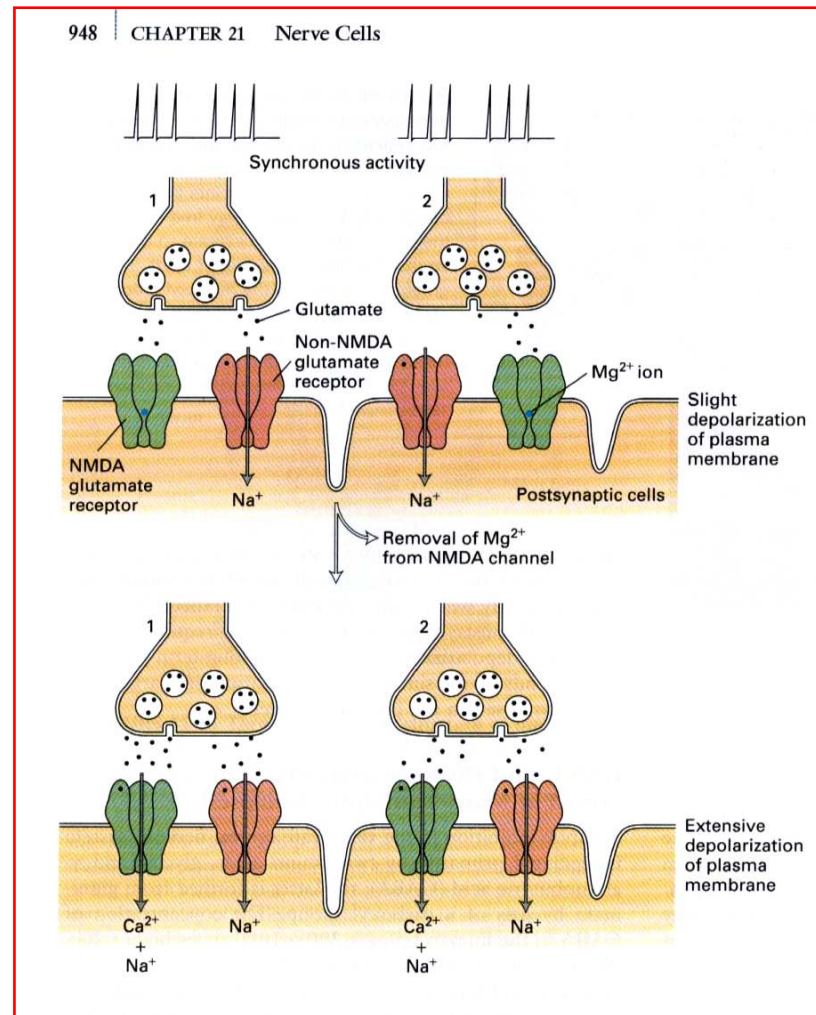


AMPA and NMDA receptors in glutamatergic synapse

## Basics of Neurobiology: Ionotropic receptors



# Basics of Neurobiology: Ionotropic receptors



[http://www.sumanasinc.com/webcontent/animations/content/ampa\\_and\\_nmda.html](http://www.sumanasinc.com/webcontent/animations/content/ampa_and_nmda.html)

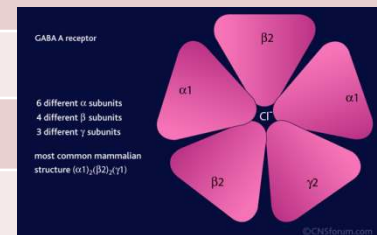
## Basics of Neurobiology: Ionotropic receptors

| KAINATE RECEPTOR |                                                                                                                                                            |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATTRIBUTE        | DESCRIPTION                                                                                                                                                |
| NAME             | KAINATE RECEPTOR                                                                                                                                           |
| SUPERFAMILY      | GLUTAMATE RECEPTOR                                                                                                                                         |
| STRUCTURE        | TETRAMERIC                                                                                                                                                 |
| SUBUNITS         | GluR5-GluR7, KA1-KA2                                                                                                                                       |
| EXPRESSION TYPES | SUBUNITS FORM HOMO- AND HETERODIMERS                                                                                                                       |
| LIGAND BINDING   | POCKET AT GluR6                                                                                                                                            |
| BASIC ROLE(S)    | EXCITATORY AT POSTSYNAPTIC SITES, INHIBITORY AT PRESYNAPTIC LOCI. PORES ARE PERMEABLE FOR SODIUM AND POTASSIUM. KEPT OPEN SHORTER THAN AMPA RECEPTOR PORES |
| AGONISTS         | SYM 2081, KAINIC ACID, DOMOIC ACID                                                                                                                         |
| ANTAGONISTS      | NS102, KYNURENIC ACID                                                                                                                                      |
| FUNCTIONAL ROLES | FUNCTION-DEPENDENT SYNAPTIC PLASTICITY                                                                                                                     |
| DISEASES         | EPILEPSY                                                                                                                                                   |

# Basics of Neurobiology: Ionotropic receptors

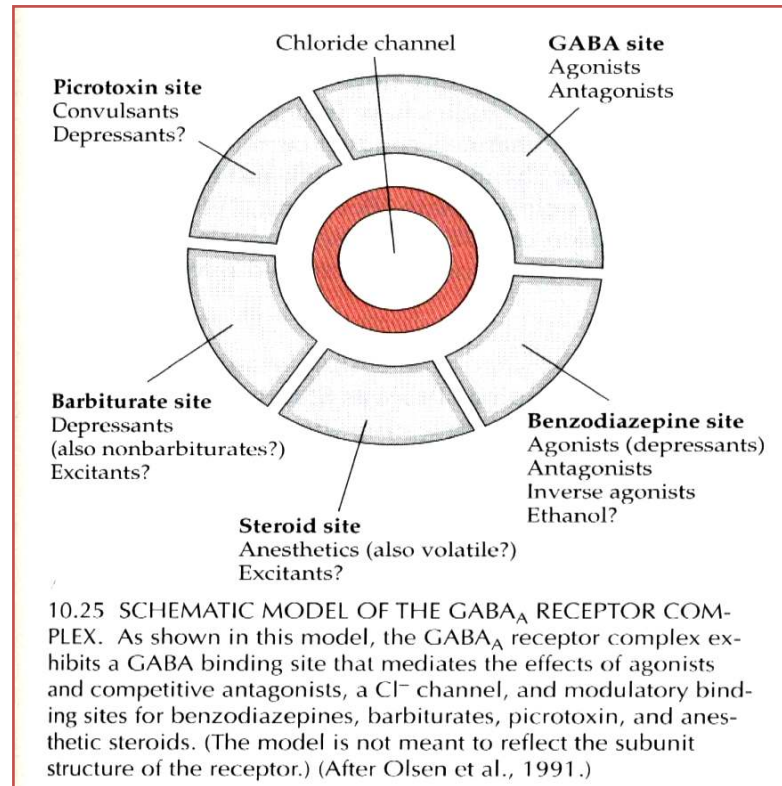
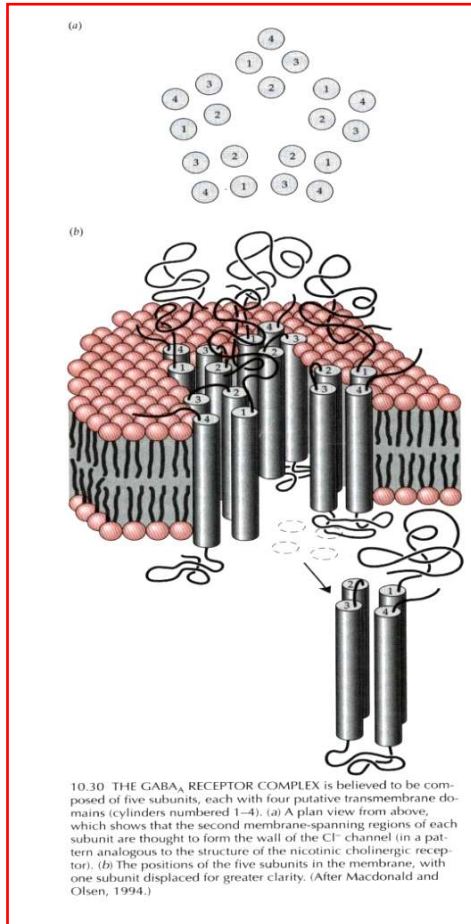
## GAMMA-AMINOBUTYRIC ACID A RECEPTOR (GABA-A)

| ATTRIBUTE        | DESCRIPTION                                                                                                                                    |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| NAME             | GAMMA-AMINOBUTYRIC ACID A RECEPTOR (GABA-A)                                                                                                    |
| SUPERFAMILY      | NICOTINIC ACETYLCHOLINE RECEPTOR                                                                                                               |
| STRUCTURE        | PENTAMERIC                                                                                                                                     |
| SUBUNITS         | $\alpha$ , $\beta$ , $\gamma$ , $\delta$ , $\varepsilon$ , $\pi$ , $\psi$ , ISOFORMS: $\alpha 1-6$ , $\beta 1-3$ , $\gamma 1-3$ , $\rho 1-3$ . |
| EXPRESSION TYPES | MORE THAN 100 SUBTYPES                                                                                                                         |
| LIGAND BINDING   | GABA AGONIST AND ANTAGONIST BINDING SITE, BENZODIAZEPINE SITE, STEROID SITE, BARBITURATE SITE, PICROTOXIN SITE                                 |
| BASIC ROLE(S)    | REGULATES CHLORIDE CHANNEL, IPSP                                                                                                               |
| AGONISTS         | MUSCIMOL, BACLOFEN, ETHANOL, BARBITURATES, BENZODIAZEPINES                                                                                     |
| ANTAGONISTS      | BICUCULINE                                                                                                                                     |
| FUNCTIONAL ROLES | AGONISTS EXERT ANXIOLYTIC, ANTICONVULSANT, AMNESIC, SEDATIVE, HYPNOTIC AND MUSCLE RELAXANT EFFECTS                                             |
| DISEASES         | EPILEPSY, ANXIETY                                                                                                                              |

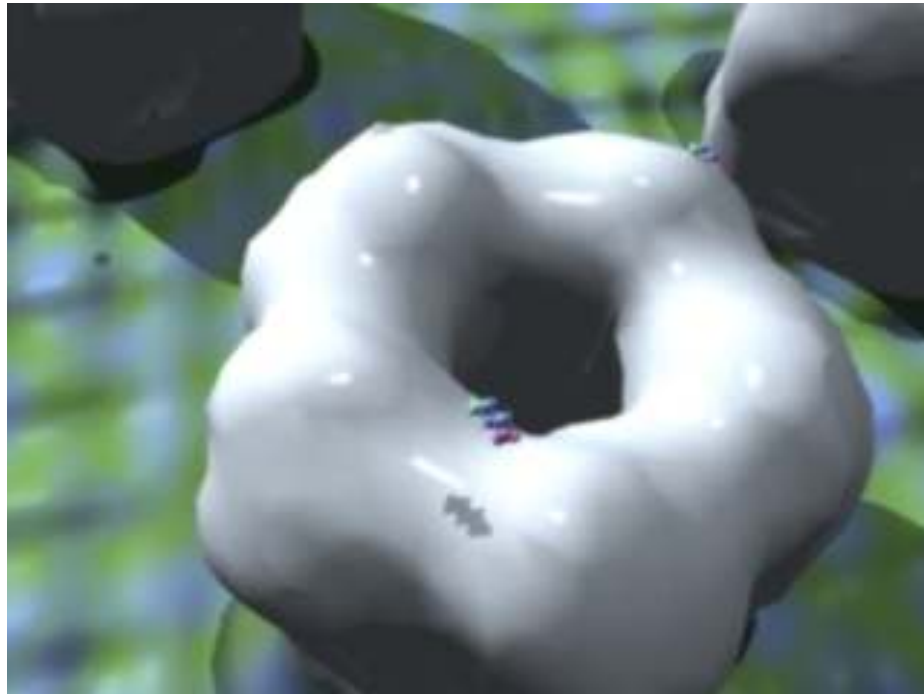


# Basics of Neurobiology: Ionotropic receptors

## GABA-A-R



## Ionotropic GABA-A receptor *animation*



## Basics of Neurobiology: Ionotropic receptors

| GLYCINE RECEPTOR |                                                                       |
|------------------|-----------------------------------------------------------------------|
| ATTRIBUTE        | DESCRIPTION                                                           |
| NAME             | GLYCINE RECEPTOR                                                      |
| SUPERFAMILY      | NICOTINIC ACETYLCHOLINE RECEPTOR                                      |
| STRUCTURE        | PENTAMERIC                                                            |
| SUBUNITS         | 5 SUBUNITS                                                            |
| EXPRESSION TYPES | $(\alpha 1)_3 \beta_2$ or $(\alpha 1)_4 \beta$                        |
| LIGAND BINDING   | GLYCINE, TAURINE, SERINE                                              |
| BASIC ROLE(S)    | REGULATES CHLORIDE CHANNEL, IPSP                                      |
| AGONISTS         | SERINE, TAURINE,                                                      |
| ANTAGONISTS      | STRYCHNINE, CAFFEINE                                                  |
| FUNCTIONAL ROLES | DOMINANT INHIBITORY NEUROTRANSMITTER IN THE SPINAL CORD AND BRAINSTEM |
| DISEASES         | HYPEREKPLEXIA, STIFFNESS                                              |