GLUTAMATE RECEPTORS

SUBMITTED BY

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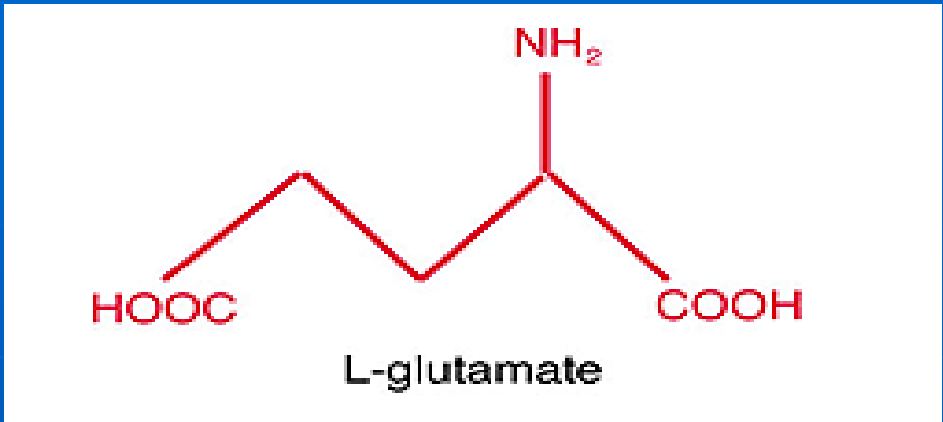


- Glutamate is the major excitatory neurotransmitter in the mammalian CNS, acting through both ligand gated ion channels (ionotropic receptors) and G-protein coupled (metabotropic) receptors

- Glutamate receptors play a vital role in the mediation of excitatory synaptic transmission

Glutamate acts on:

Ionotropic receptors

- NMDA-receptor family
  - NMDAR1
  - NMDAR2A, ...
- AMPA-receptor family
  - GluR1
  - GluR2
  - GluR3
- Kainate-receptor family
  - ...
  - GluR6

Metabotropic receptors

- Group I (Phospholipase C activation)
  - mGlu1A
  - mGlu5A
- Group II (Adenylyl cyclase inhibition)
  - mGlu2
  - mGlu3
- Group III (Adenylyl cyclase inhibition)
  - mGlu4, mGlu8
  - mGlu6, mGlu6

Receptor subunits

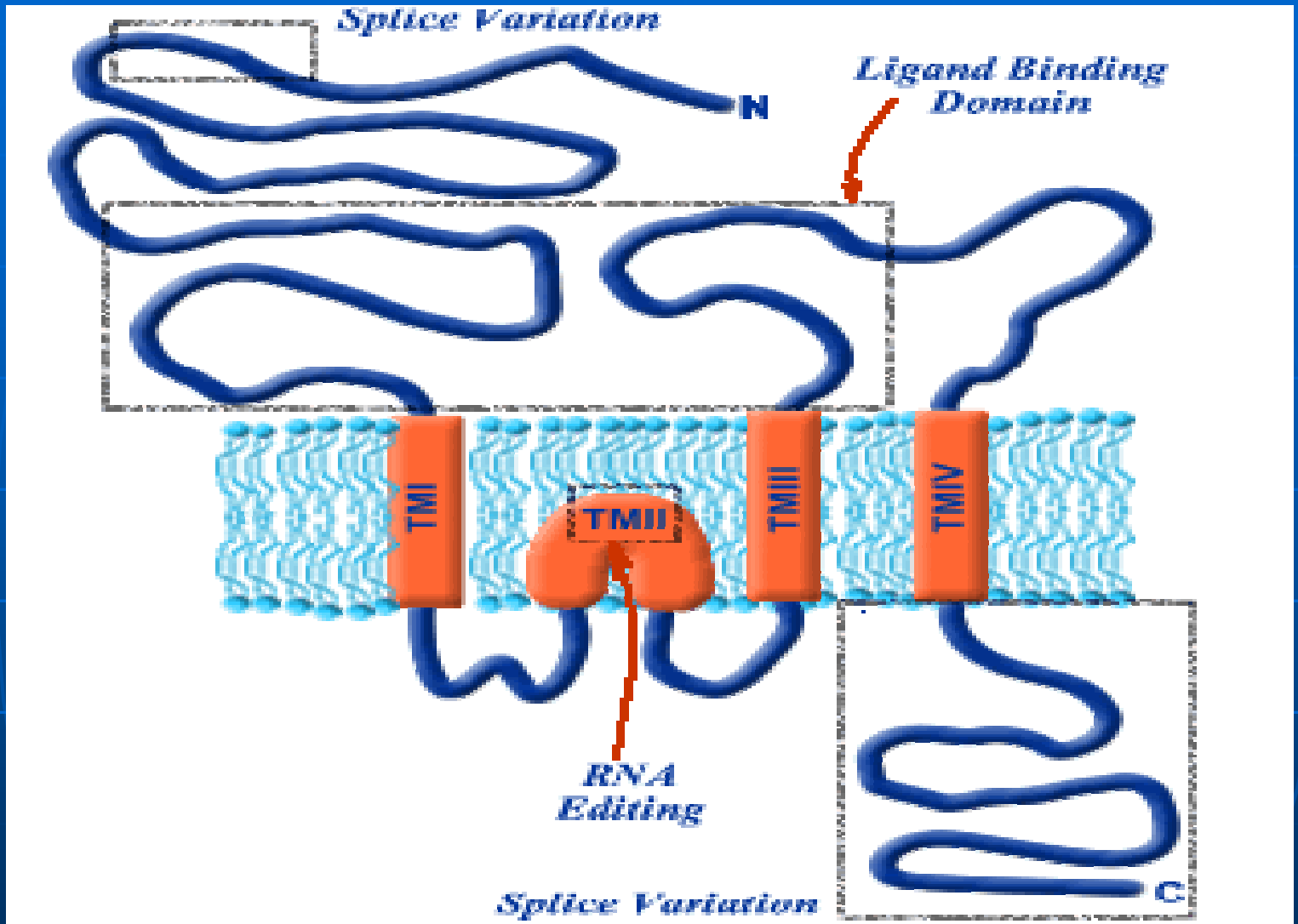
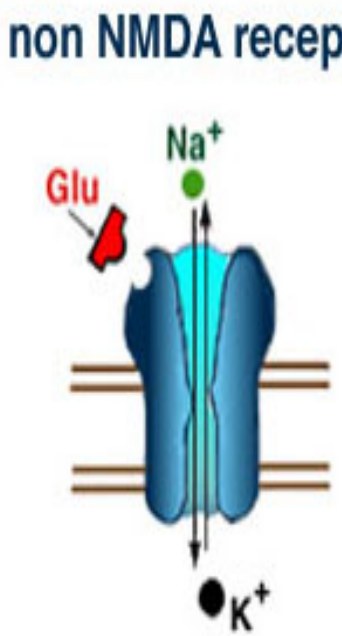


Figure 2. General structure of an ionotropic glutamate receptor subunit. Ionotropic glutamate receptor subunits follow the same basic structural pattern with an extracellular N-terminus and large loop that together form the ligand binding domain. The C-terminus is intracellular and is often the site of splice variation and interaction sites with intracellular proteins.



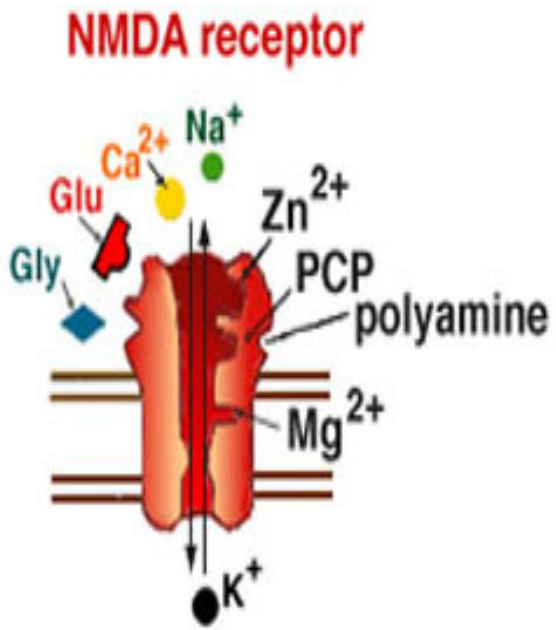


Fig. 6a. Non-NMDA receptors are selectively agonized by kainate, AMPA and quisqualate. The associated ion channels are more perm eable to Na+ and K+ ions tha Ca+2 (from Kandel et al,.1991).

Fig. 6b. NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine MG+2, Zn+2 and polyamines. NMDA-gated channels are more permeable to Ca+2 than Na+ ions (from Kandel et al., 1991).

NON-NMDA RECEPTORS

- Give immediate response upon binding of glutamate
- More permeable to Na^+ & K^+ than $Ca^{+\ +}$
- Influx of Na^+ causes depolarization of the membrane which is the major factor for activating NMDA type receptors

NMDA RECEPTORS

- Unlike non NMDA receptors, they require a co-agonist GLYCINE

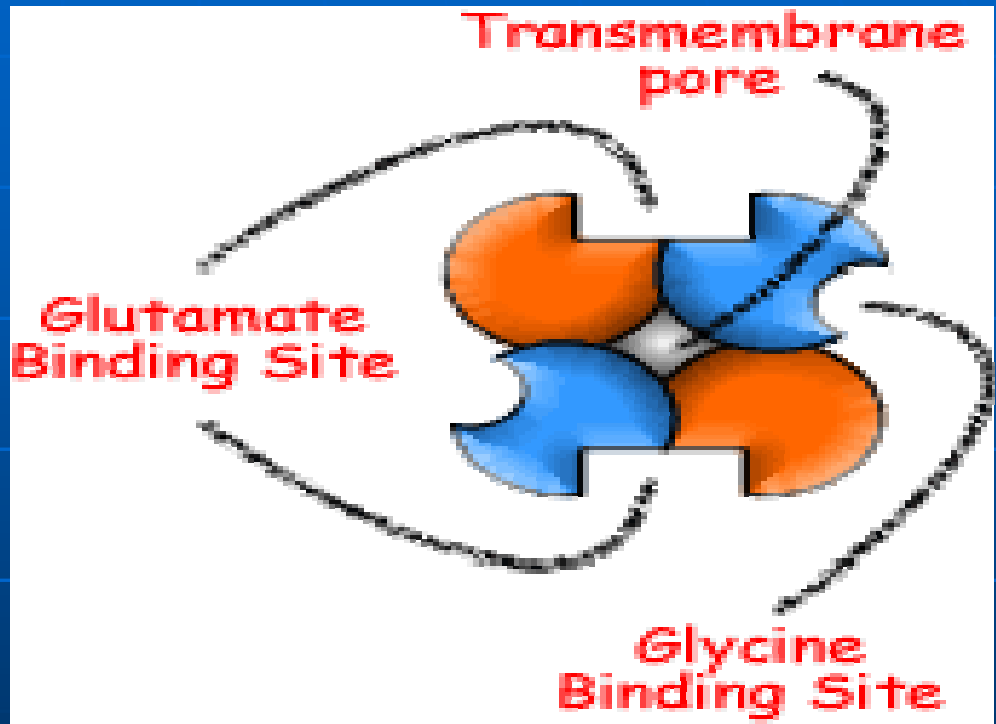
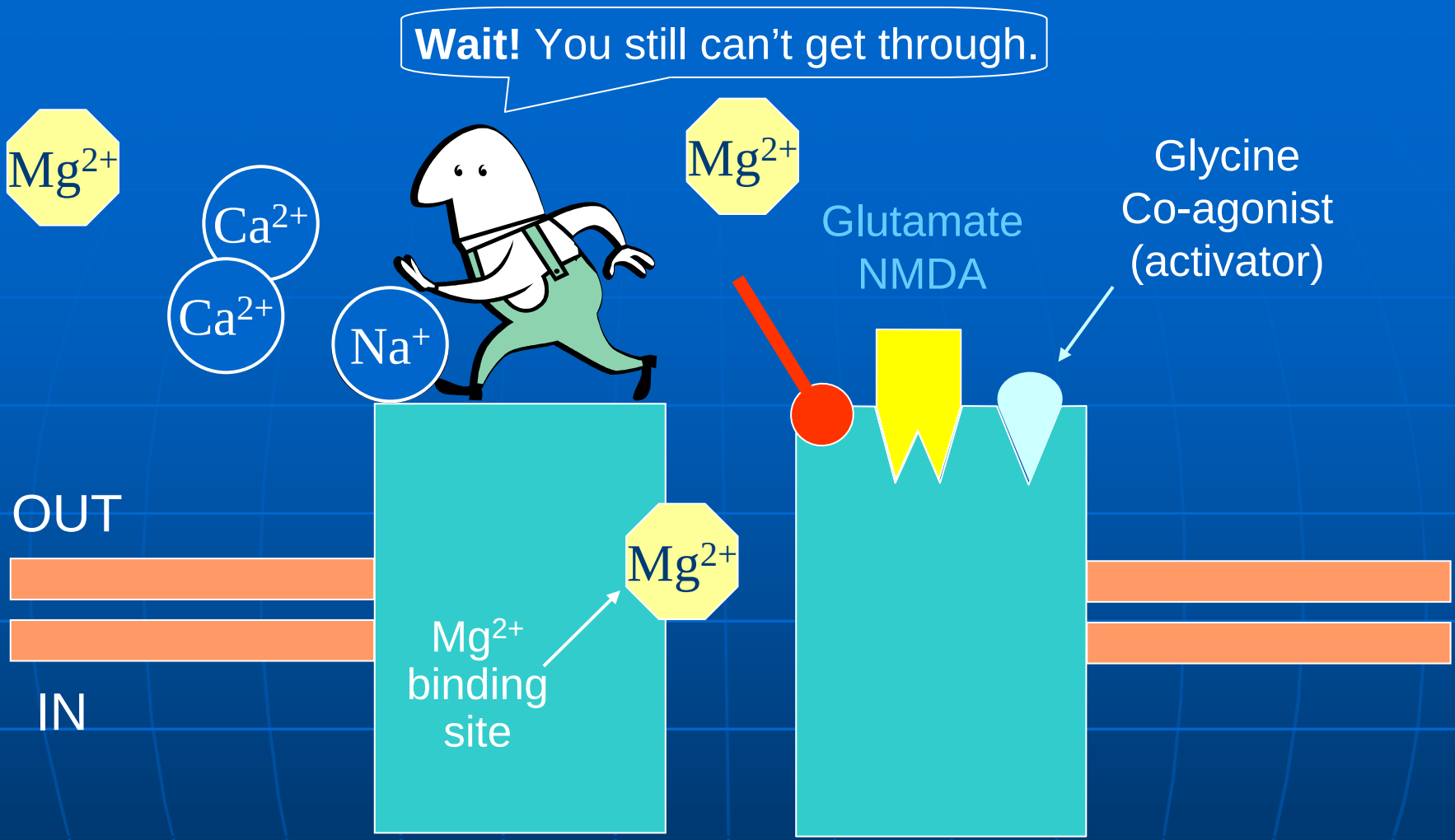


Figure 3. Binding sites on the NMDA receptor. Note - the stoichiometry of the reeptor complex is schematic only. It is not known as yet whether the complex is a tetramer or a pentamer



Because, as long as the membrane remains polarised, the pore of the channel is blocked by physiological, extracellular concentration of Mg^{2+}.

Metabotropic Glutamate (mGlu) Receptors

- Metabotropic glutamate (mGlu) receptors are G-protein coupled receptors (GPCRs)

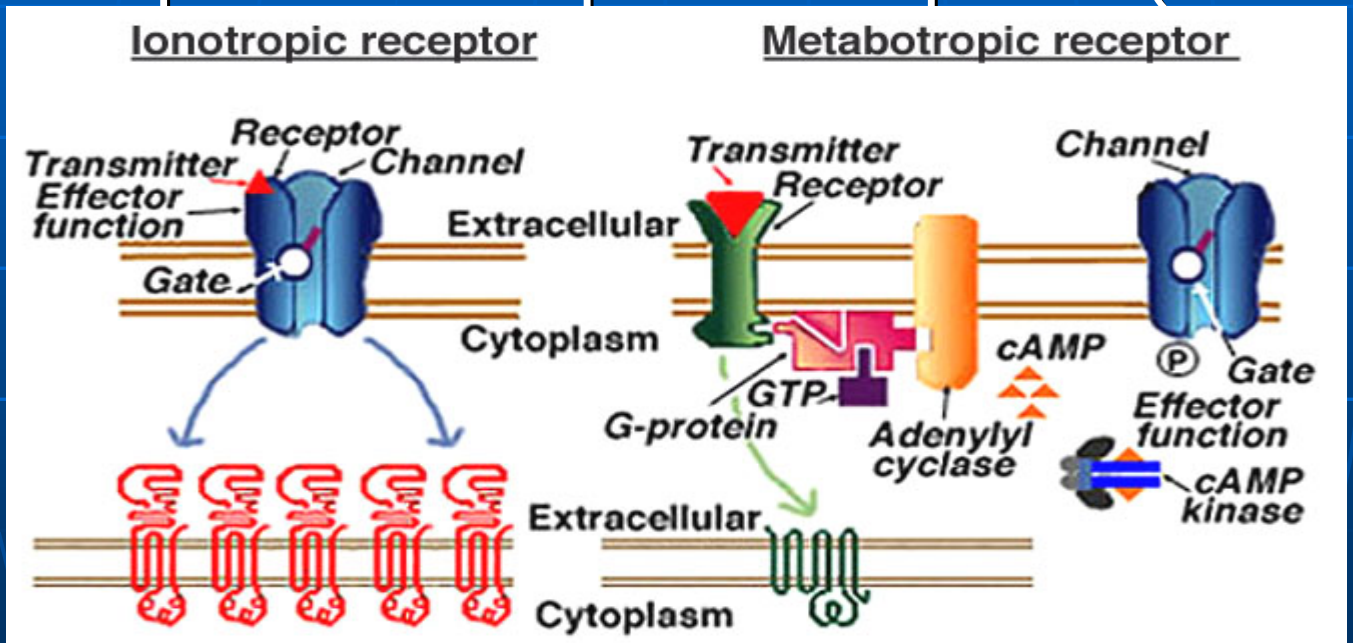


Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

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).

- They are not co-assembled from multiple subunits, but are one polypeptide with common 7 transmembrane domain

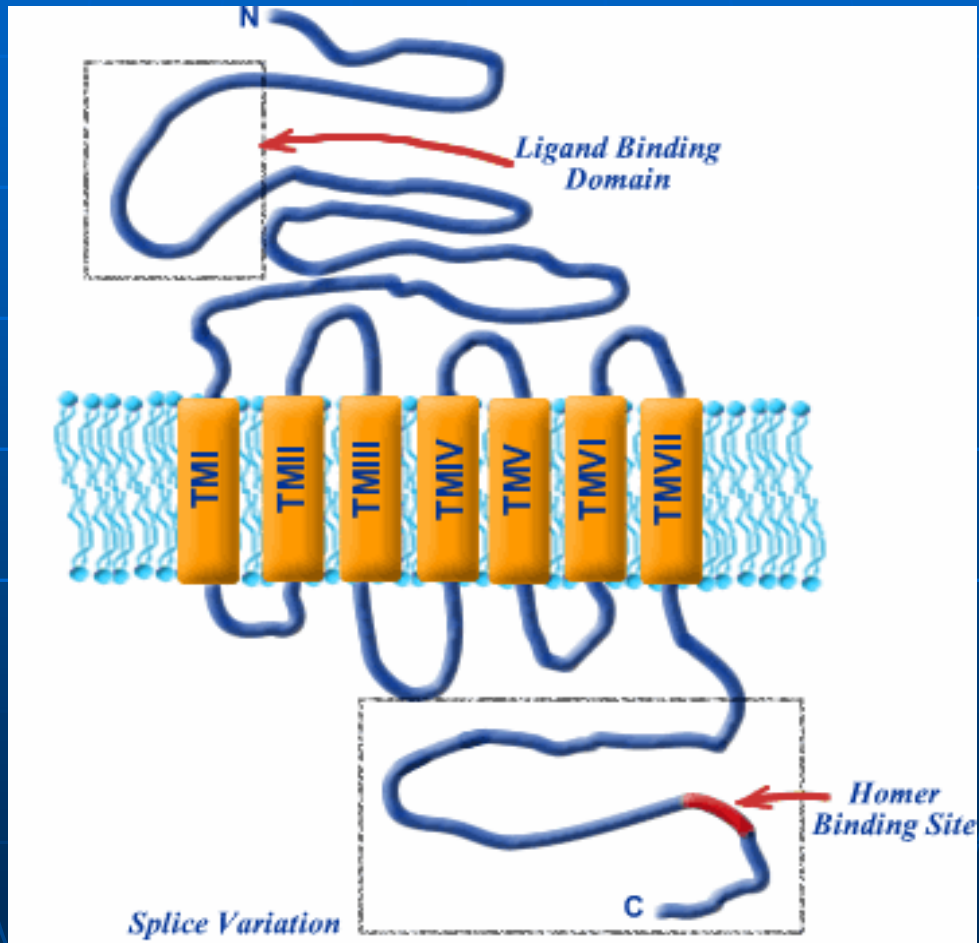


Figure 8. General structure of the metabotropic glutamate receptors. The mGlu receptors are coupled to G-proteins and possess the common 7-transmembrane domain motifly found in these receptor types. However, the N-terminus is much larger than in the adrenergic family of GPCRs and contains the ligand binding domain. The C-terminus generally undergoes extensive splice variation.

They have been subdivided into three groups, based on

- sequence similarity,
- pharmacology
- intracellular signalling mechanisms

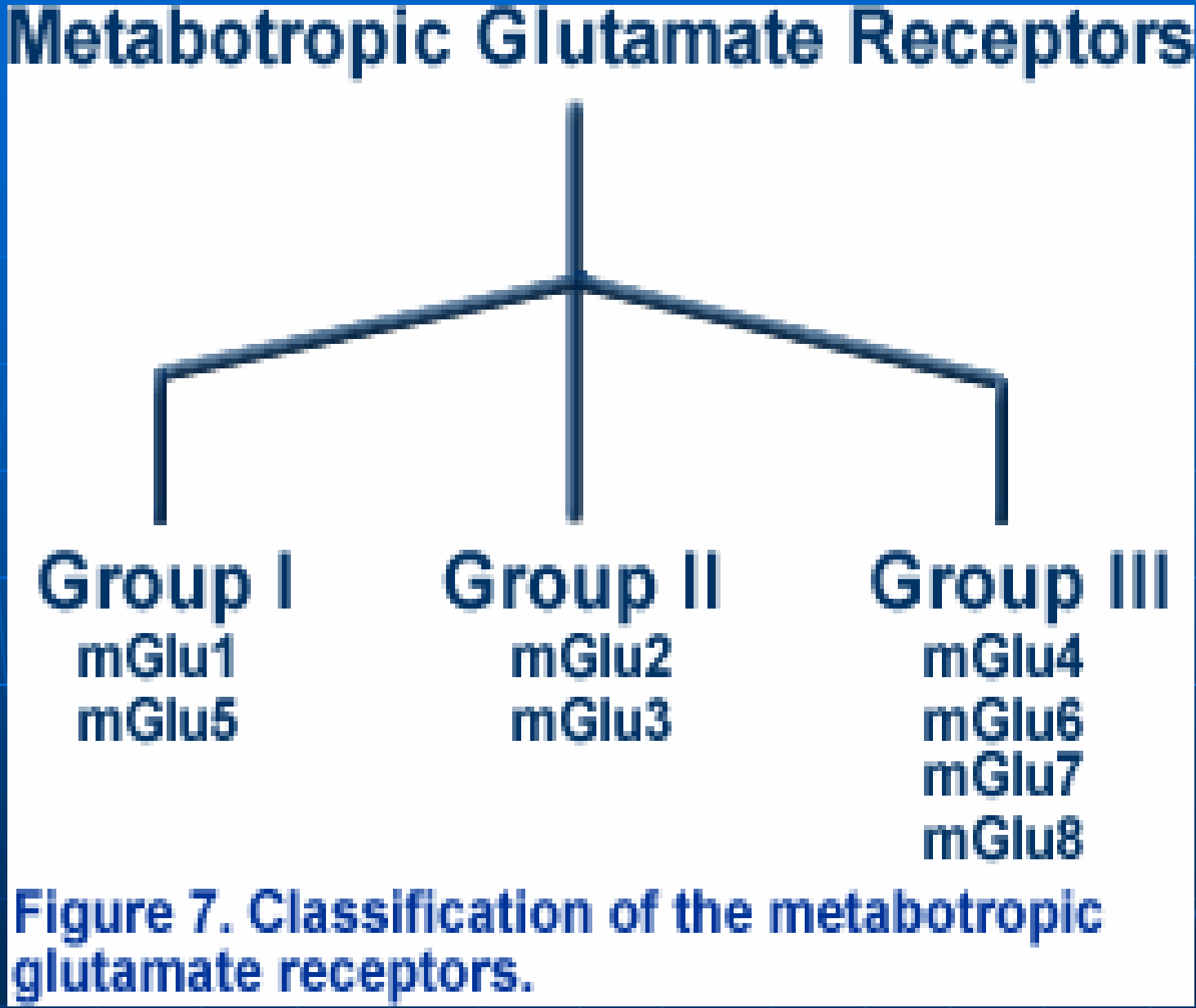


Figure 7. Classification of the metabotropic glutamate receptors.

Metabotropic glutamate receptor groups (from Pin and Duvoisin, 1995).

group	mGluR	agonist(s)	intracellular pathway
I	mGluR1, mGluR5	quisqualate, ACPD	increase phospholipase C activity, increase cAMP levels, increase protein kinase A activity
II	mGluR2, mGluR3	L-CCG-1, ACPD	decrease cAMP levels
III	mGluR4, mGluR6. mGluR7, mGluR8	L-AP4 (APB)	decrease cAMP or cGMP levels

? ?

REFERENCES

http://www.webvision.med.utah.edu/GLU.html

http://www.bris.ac.uk/Depts/Synaptic/info/glutamate.html

THANK YOU FOR YOUR ATTENTION