FAES Class: Foundations of Cellular Neuroscience

Synaptic Transmission II: Postsynaptic Mechanisms

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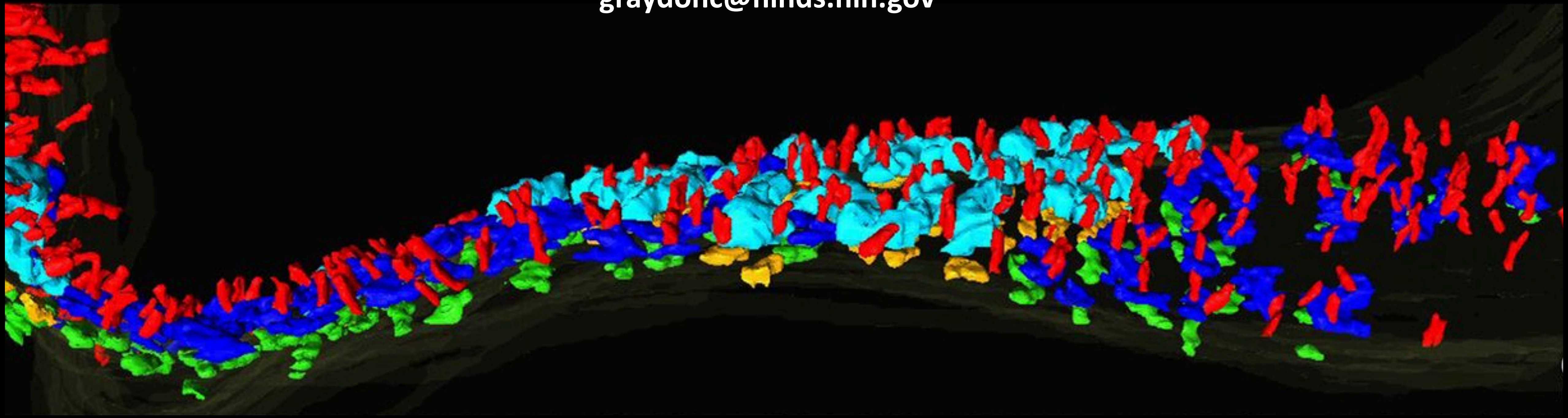


March 14, 2018

Structure of Lecture

Examining the beast in its natural habitat

The Beast

- Receptor Types (General)
- Receptor Types (Specific)

Natural Habitat

- Postsynaptic structures and molecular machinery
- Receptor trafficking and mobility, structural stability, and protein turnover
- A taste of postsynaptic receptor cycles

A note about transmitters and receptors

Huge total number of transmitters (100+)

Lots of diversity

Type	Examples
Amino acids	**GABA**, **glutamate**, **glycine**
Gases(!)	nitric oxide
Monoamines	dopamine, serotonin
Peptides	neuropeptide Y, substance P
Purines	ATP
Other Small Molecules	**acetylcholine**

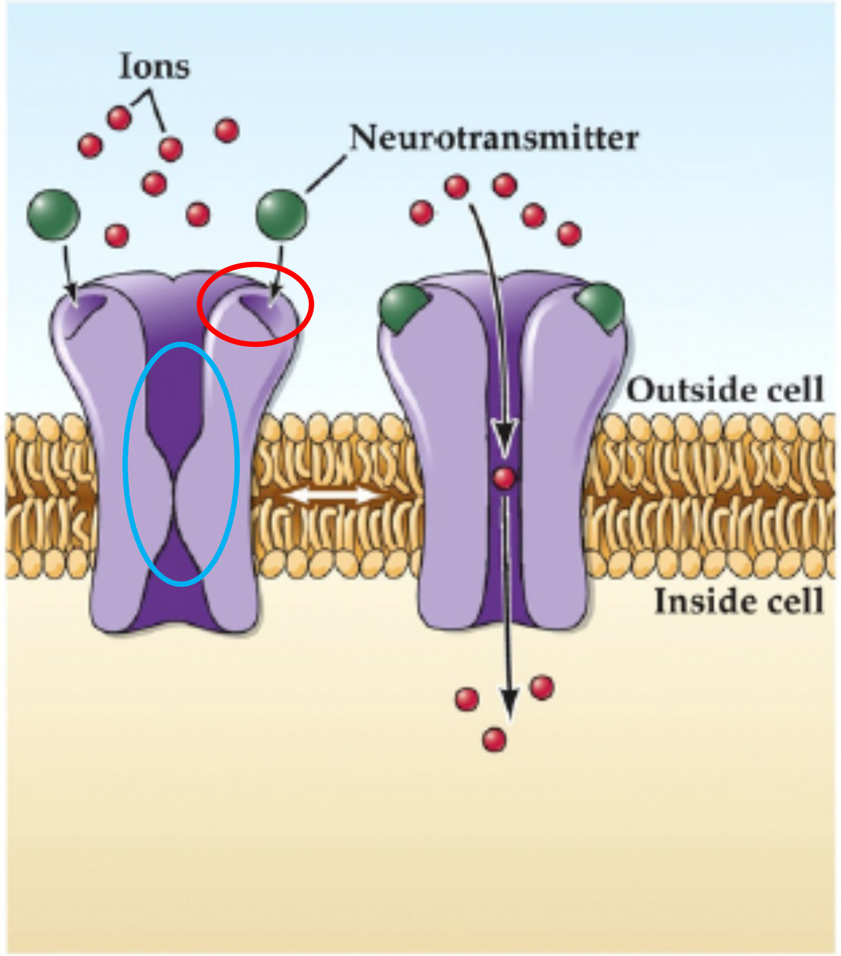
Disease/
Disorder

Disruption of Transmitter X => Receptor Y

Drugs!

Receptor Types (general): Ionotropic

Both receptor and ion channel



NEUROSCIENCE 5e, Figure 5.16 (Part 1)

Composed of multiple subunits (~4-5)

Subunits that line pore dictate selectivity

Fast time course (1-10ms)

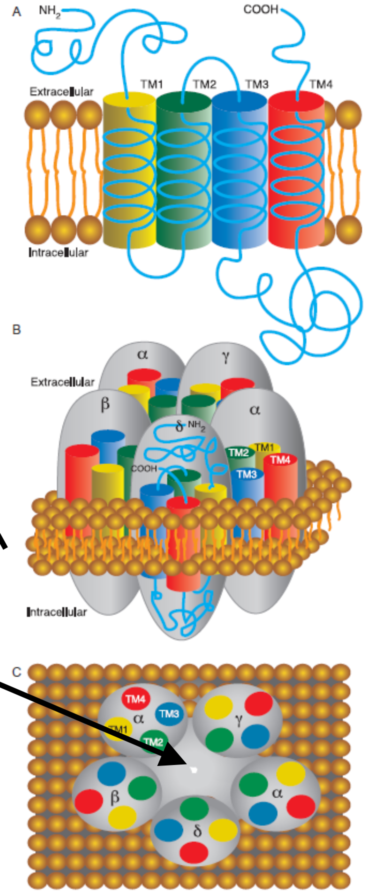
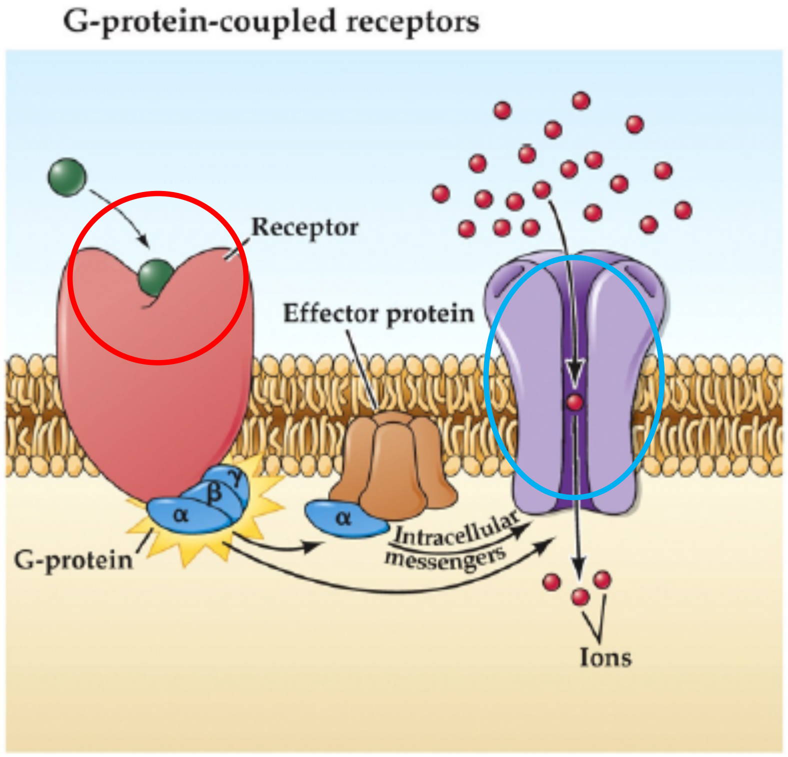


Figure 10.4

Receptor Types (general): Metabotropic

Receptor that interacts with ion channel (at some point)



NEUROSCIENCE 5e, Figure 5.16 (Part 2)

Metabolic step between NT binding and channel opening

Single protein

Can affect multiple channels

Slower time course (100+ ms)

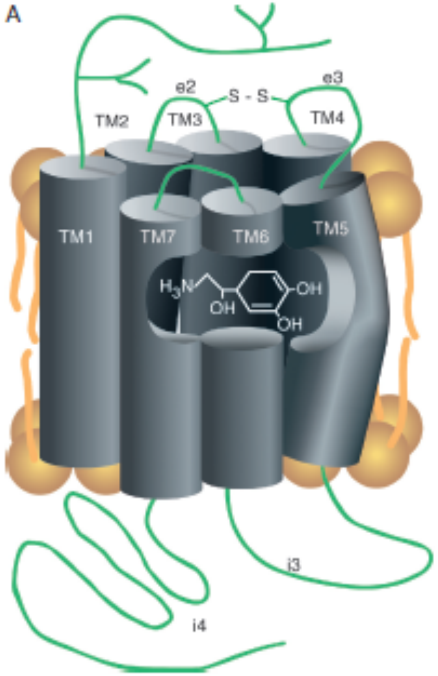
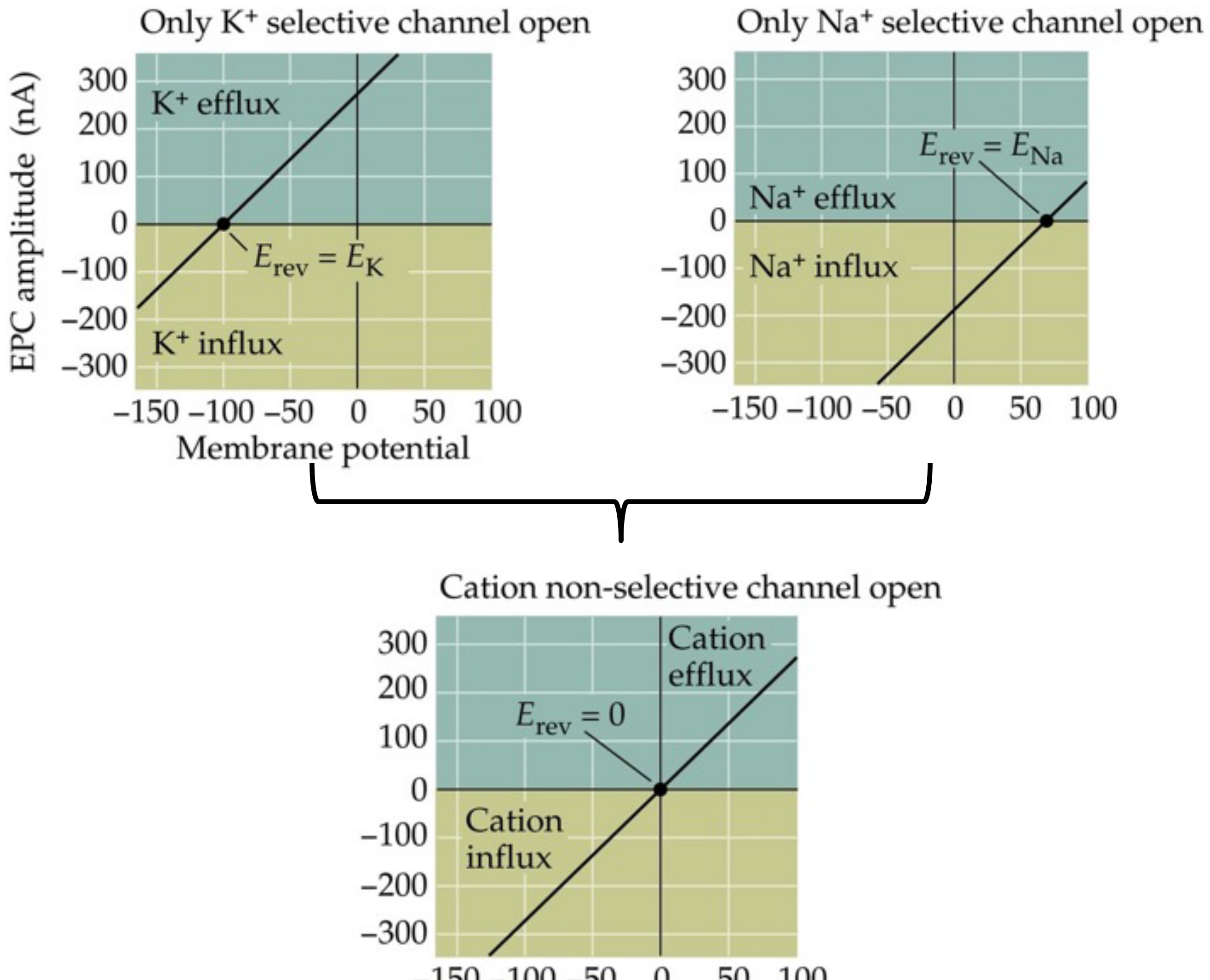


Figure 10.16

Terminology of “excitatory” and “inhibitory” synapses



Excitatory = E_{rev} above AP threshold

Inhibitory = E_{rev} below AP threshold

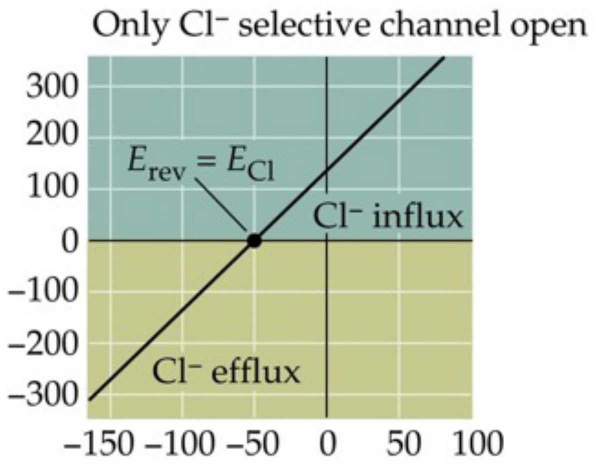
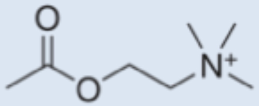


Figure 5.17 Neuroscience 3rd Ed.

Receptor Types (specific): Acetylcholine (ACh)



Earliest to be identified and most studied receptor to date

Non-selective cation channel

Nicotinic – nACh receptor

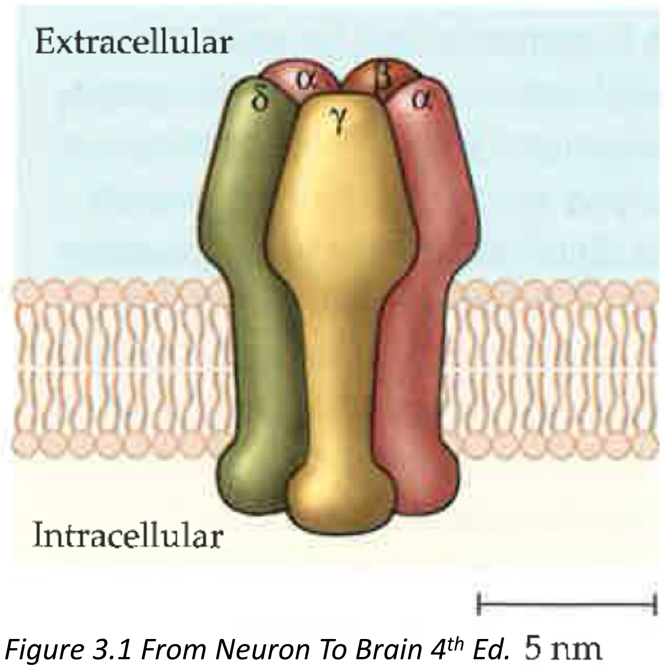
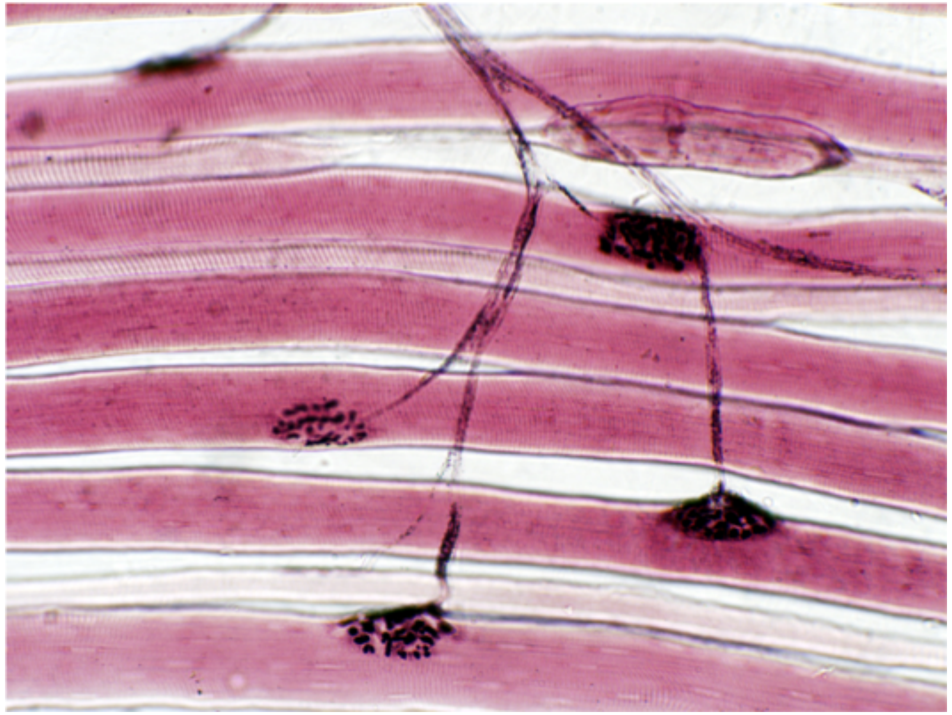


Figure 3.1 From Neuron To Brain 4th Ed.

5 subunits: 2 α, 1 β, 1 δ, 1 γ

Neuromuscular junction



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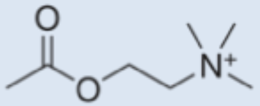


Muscarinic– mACh receptor

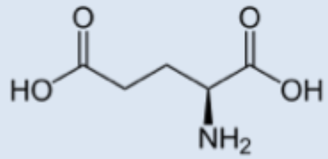
Single 7 transmembrane protein

Found in cardiac muscle cells

Coupled to opening of K+ channels by G-proteins

Muscarine – found in *A. muscaria*

Receptor Types (specific): Glutamate



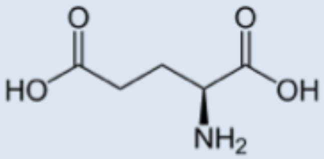
Receptor:	AMPA	KAINATE	NMDA	metabotropic I	metabotropic II	metabotropic III
	GluA1	GluK1	GluN1	mGluR1	mGluR2	mGluR4
	GluA2	GluK2	GluN2A	mGluR5	mGluR3	mGluR6
	GluA3	GluK3	GluN2B			mGluR7
	GluA4	GluK4	GluN2C			mGluR8
		GluK5	GluN2D			
			GluN3A			
			GluN3B			

Named after agonists

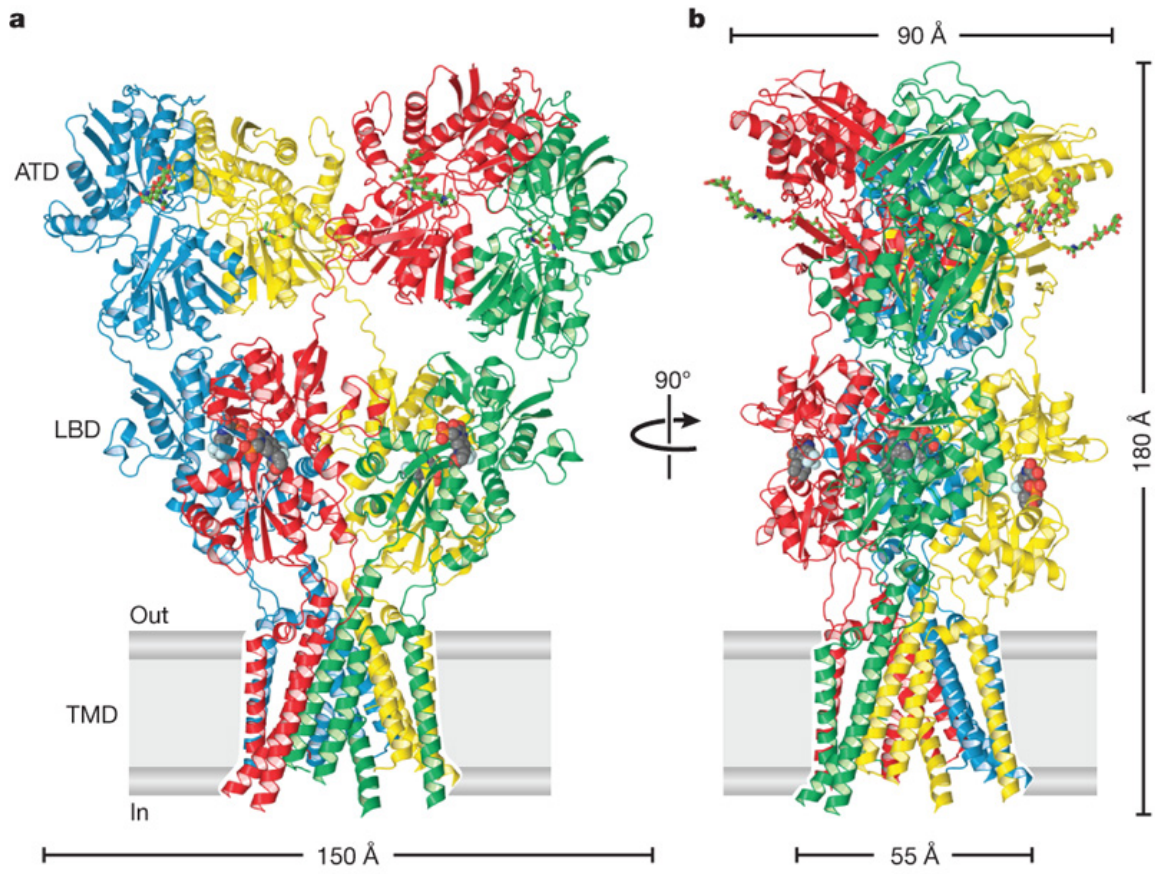
Non-selective ion channels with reversal potential ≈ 0 mV

Many different combinations of subunits give rise to functional diversity

Receptor Types (specific): Glutamate



The AMPA/Kainate receptor



Sobolevsky et al. (2009) Nature 462:745-756.

Four subunits each with 4 TM domains

Permeable to Na^+ and K^+

AMPA more common than Kainate

Produce fast postsynaptic events

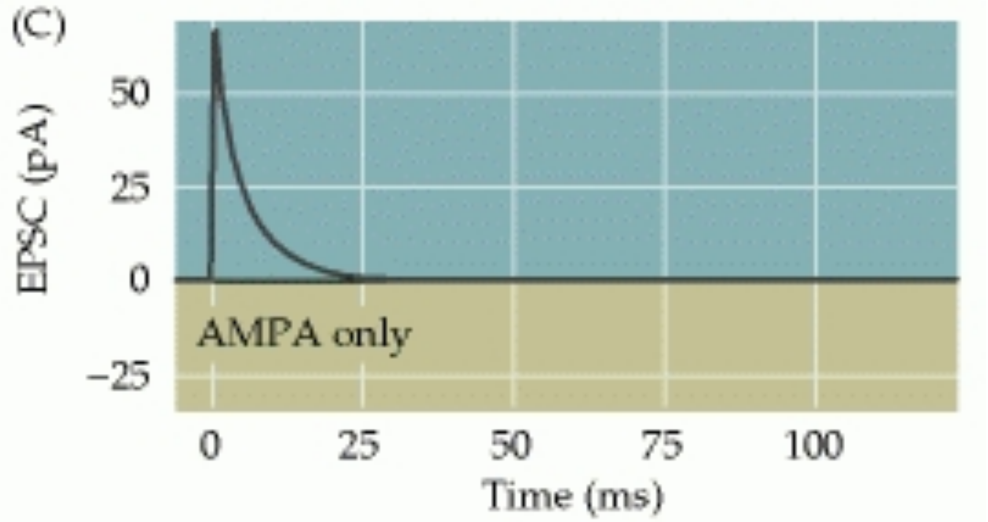
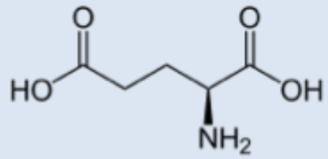
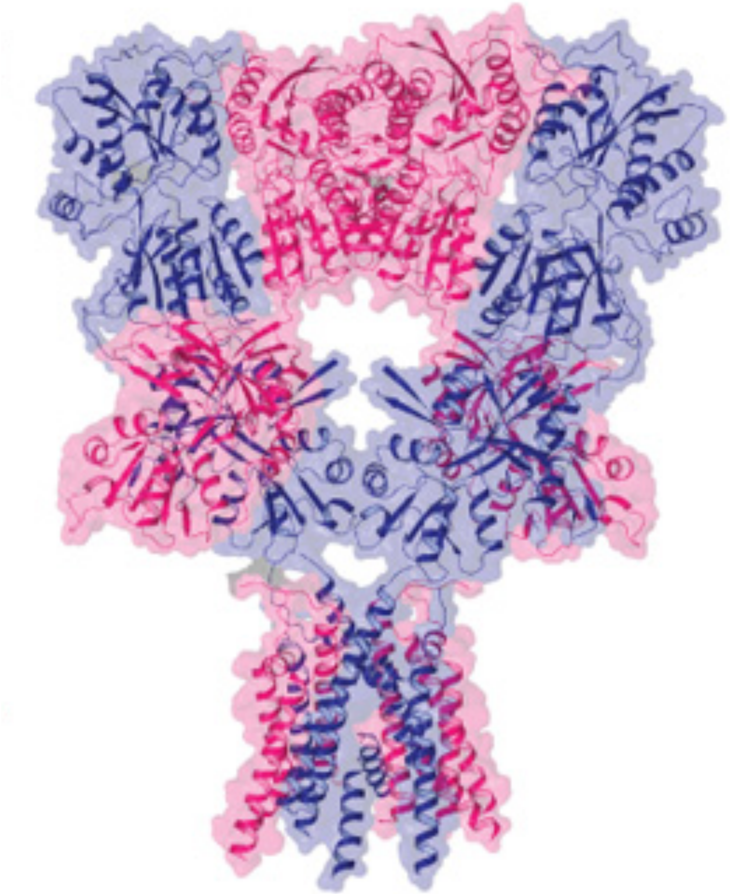


Figure 6.7 Neuroscience 3rd Ed.

Receptor Types (specific): Glutamate



The NMDA receptor



Sobolevsky et al. (2009) Nature 462:745-756.

Four subunits each with 4 TM domains

Ca^{2+} permeable (in addition to Na^{+} and K^{+})

Slower and longer events than AMPARs

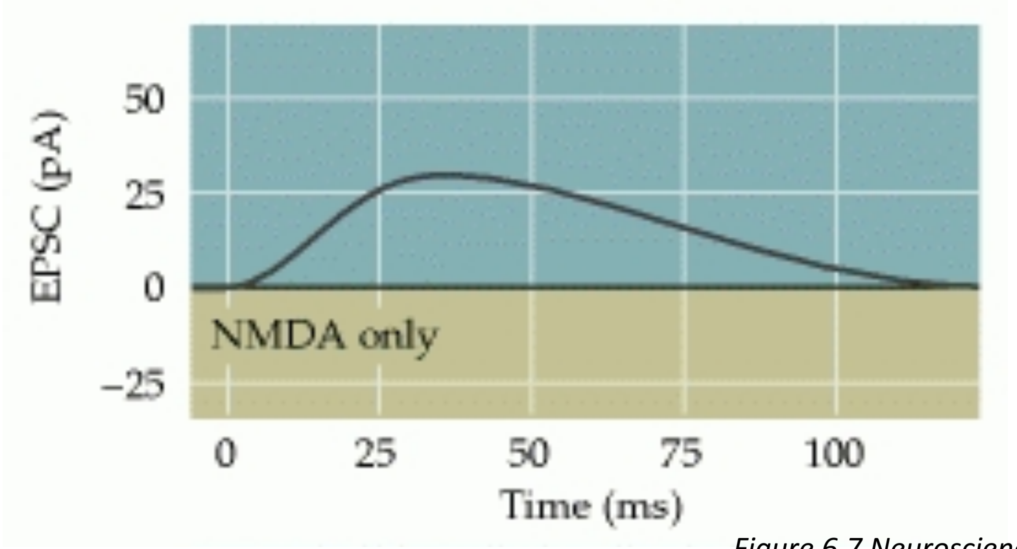
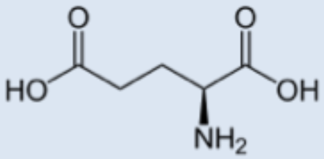
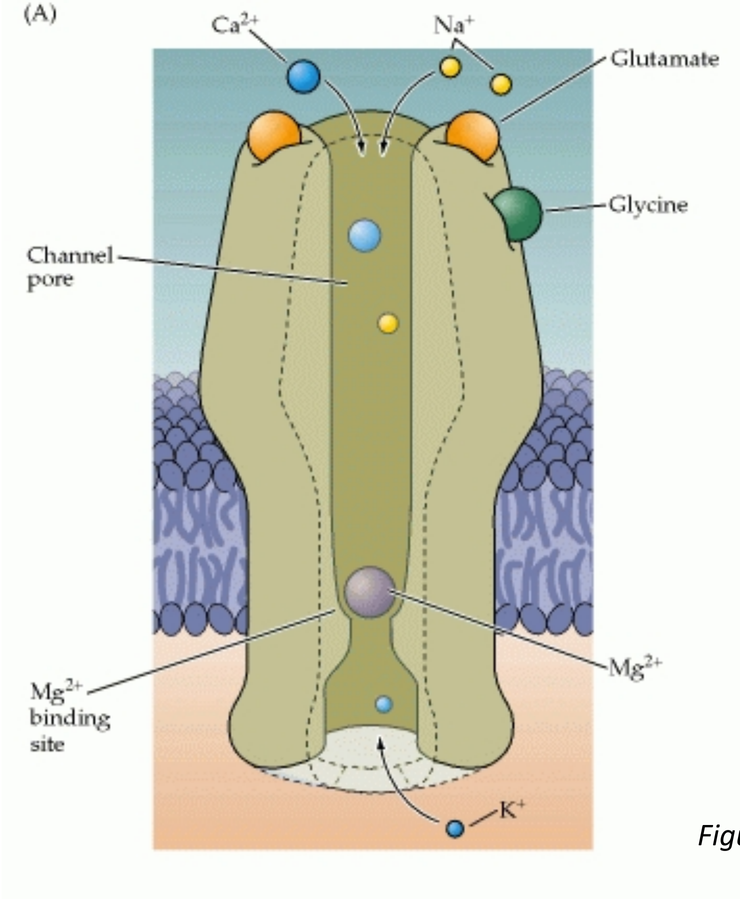


Figure 6.7 Neuroscience 3rd Ed.

Receptor Types (specific): Glutamate



The NMDA receptor



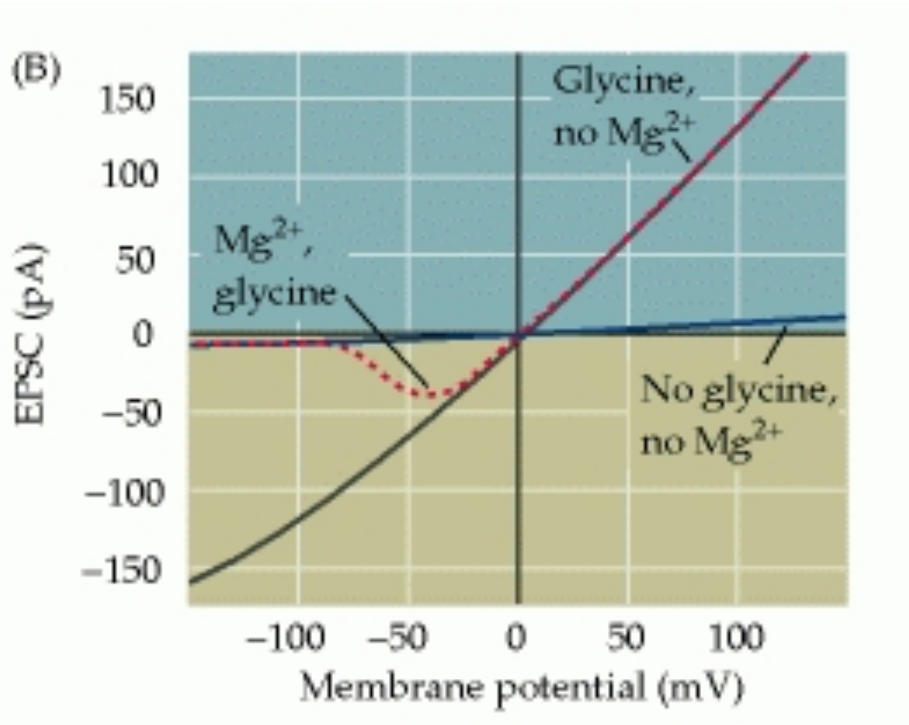
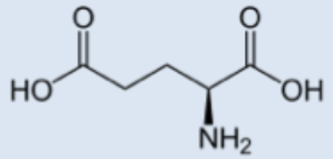


Figure 6.7 Neuroscience 3rd Ed.

Glycine required as co-agonist

Extracellular Mg^{2+} blocks current at hyperpolarized membrane potentials

Receptor Types (specific): Glutamate



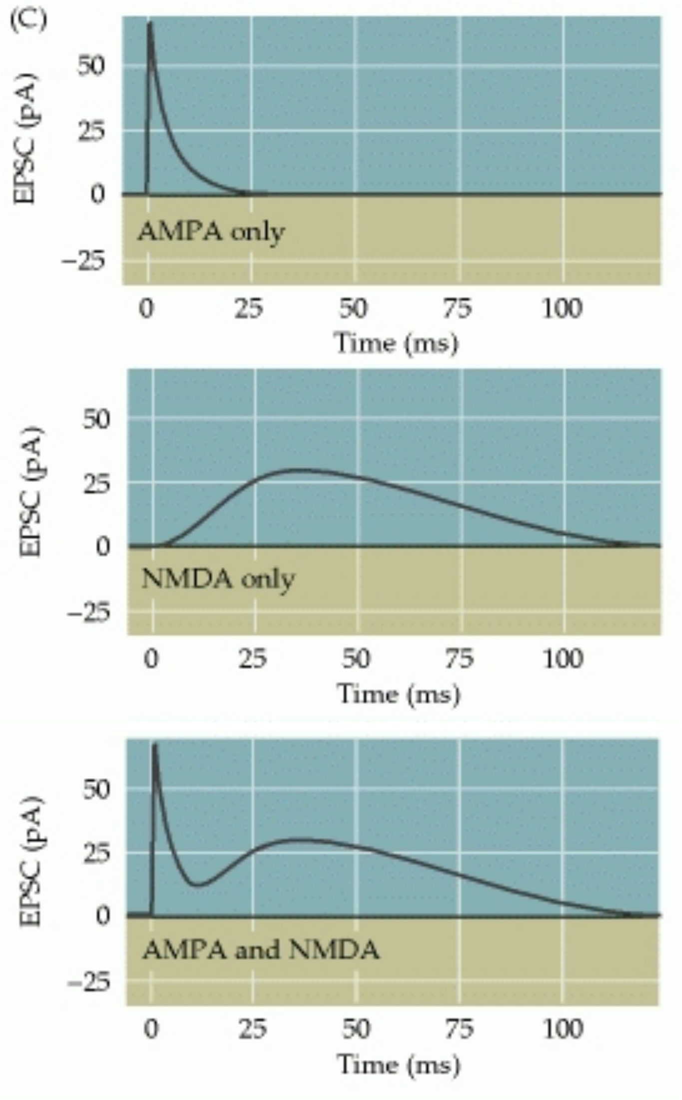


Figure 6.7 Neuroscience 3rd Ed.

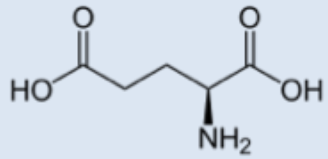
<u>AMPA/kainate and NMDA receptors</u>

Most glutamatergic synapses have **both** AMPA/Kainate and NMDA receptors

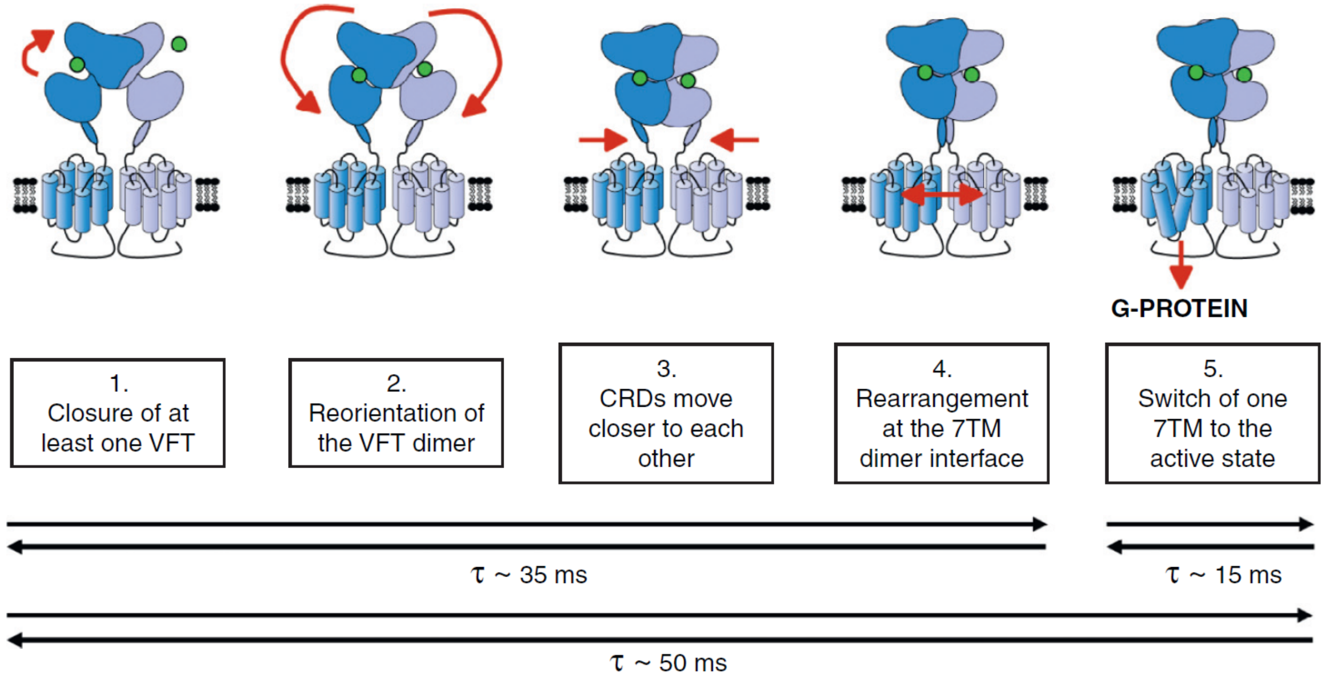
(Some only AMPARs, some only NMDARs)

If NMDA current is blocked at resting Vm, will a released vesicle cause a current through NMDARs?

Receptor Types (specific): Glutamate



Metabotropic glutamate receptors (mGluRs)



Rondard and Pin (2015) Curr Opin Pharm 20:95-101.

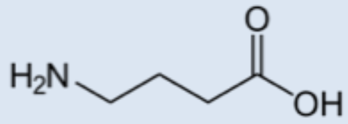
Activation often results in inhibition of Ca^{2+} and Na^{+} channels

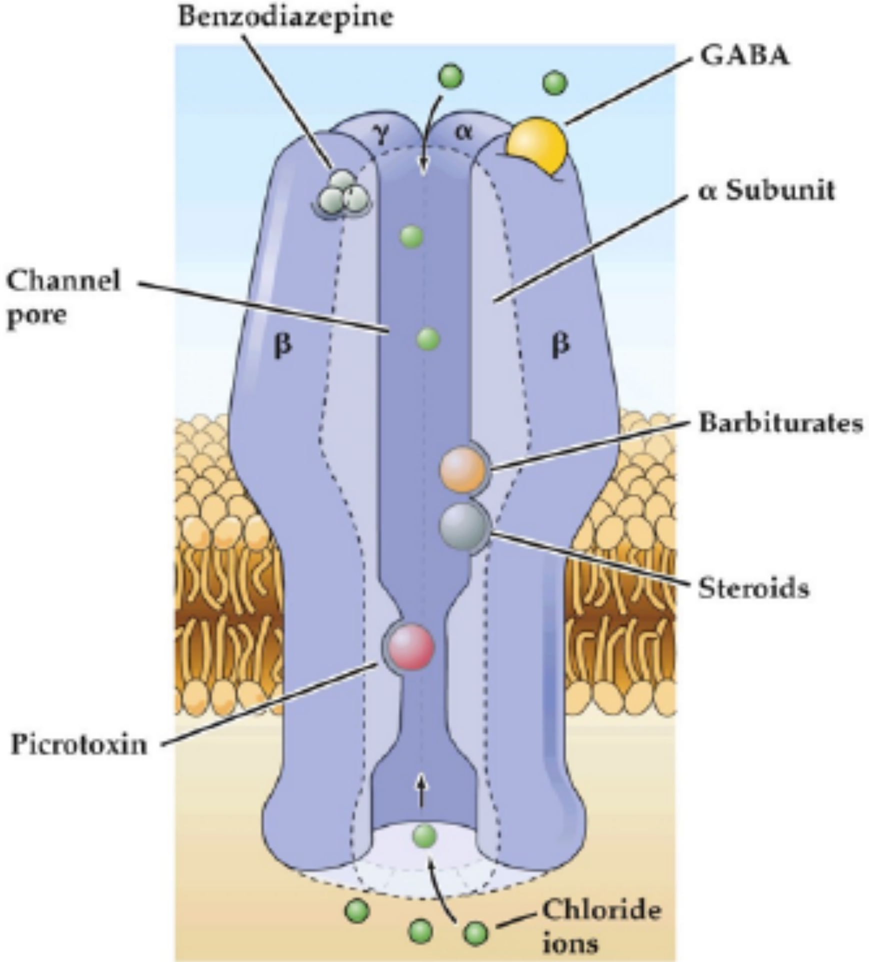
Can be located **pre-** or **post**synaptic

Generally slow time course of effects

Often role is to modulate the activity of other receptors

Receptor Types (specific): GABA





NEUROSCIENCE 5e, Figure 6.9 (Part 1)

<u>γ-aminobutyric acid receptors</u>

Ionotropic	*Metabotropic*
$GABA_A$	$GABA_B$
$GABA_C$	

<u>Ionotropic:</u>

Widespread and large % throughout CNS

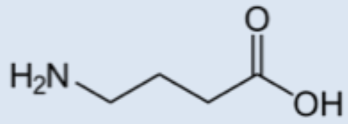
(1 in 5 neurons in some brain regions)

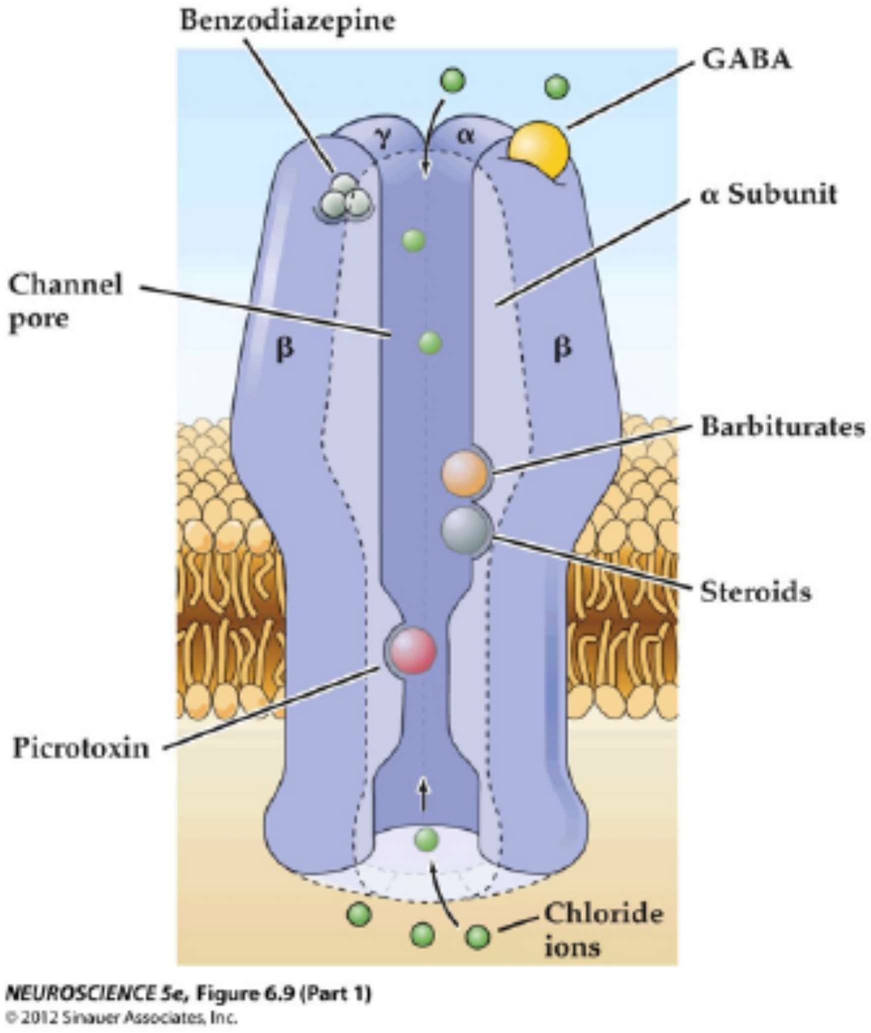
$GABA_A$ has sequence homology with nAChR

5 subunit composition
(mix and match for different properties)

Permeable to Cl^- (generally inhibitory)

Receptor Types (specific): GABA





Allosteric Modulation

other, different

spatial arrangement, position

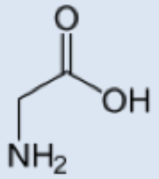
Sedative

Barbiturates Benzodiazepines Steroids progesterone testosterone corticosterone	Potentiate GABA binding ↑ inhibition

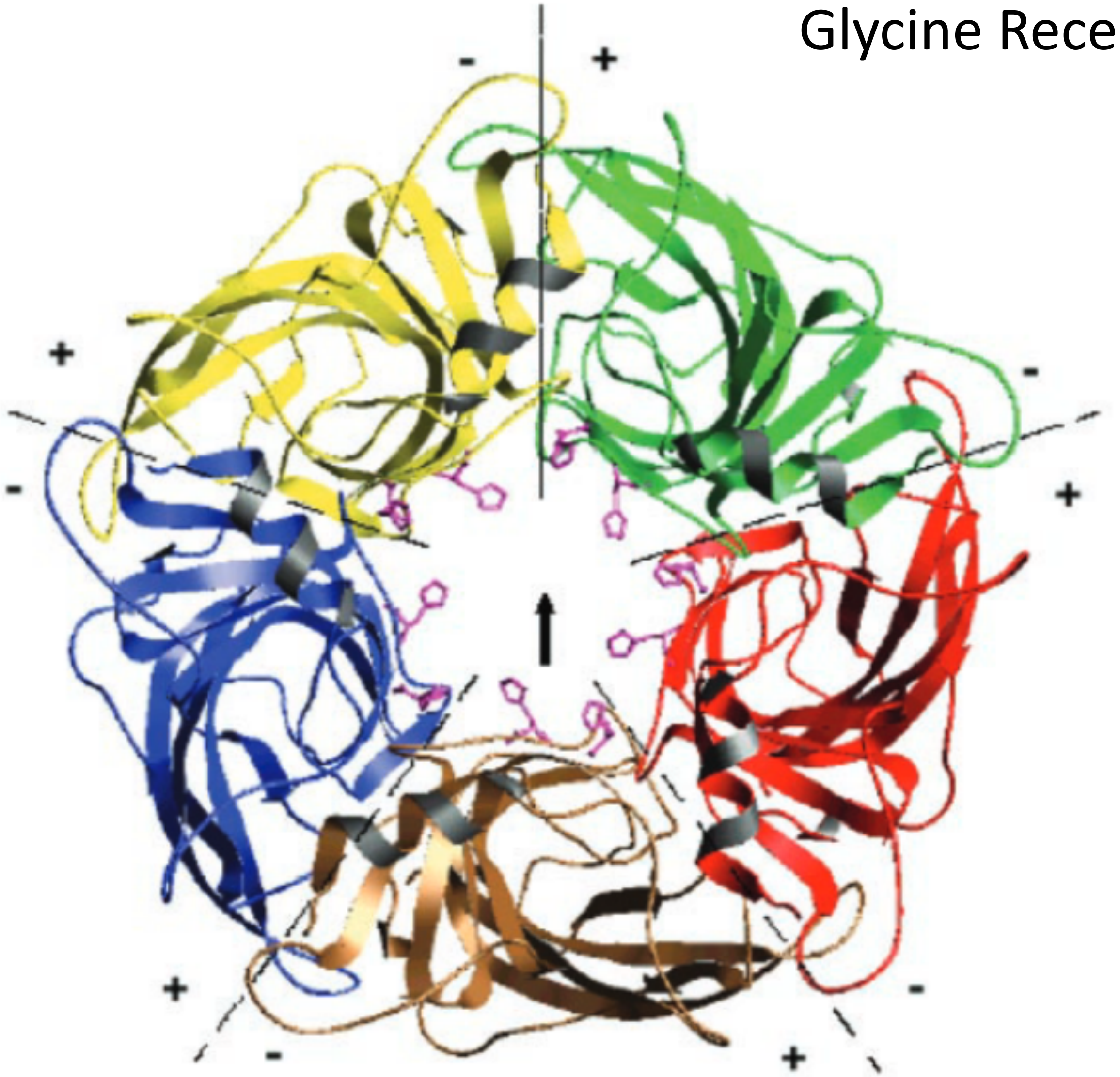
Picrotoxin Bicuculline Penicillin	Blocks channel Blocks GABA binding Inhibits channel ↓ inhibition

Convulsing

Receptor Types (specific): Glycine



Glycine Receptors



Generally similar properties as $GABA_{A\&C}$ receptors

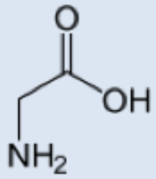
Structurally (e.g. 5 subunits similar to nAChR) and conductance (e.g. Cl^-)

No metabotropic receptor

Found particularly in brainstem and spinal cord (and retina)

Lynch(2004) Physiol Rev 84:1051-1095.

Receptor Types (specific): Glycine



Glycine Receptors

Strychnine -> muscle convulsions -> asphyxia -> 

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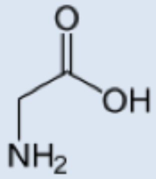


Glycine Receptors

Strychnine -> muscle convulsions -> asphyxia -> 

Performance enhancer [edit]

Strychnine was popularly used as an athletic performance enhancer and recreational stimulant in the late 19th century and early 20th century, due to its convulsant effects. It was thought to be similar to coffee.[7][8] Its effects are well described in H. G. Wells' novella *The Invisible Man*: the title character states: " Strychnine is a grand tonic ... to take the flabbiness out of a man." The protagonist replies: "It's the devil, ... It's the palaeolithic in a bottle."[9]

(Wikipedia: Strychnine)

Generally similar properties as $GABA_{A\&C}$ receptors

Structurally (e.g. 5 subunits similar to nAChR) and conductance (e.g. Cl^-)

No metabotropic receptor

Found particularly in brainstem and spinal cord (and retina)

Postsynaptic structures and molecular machinery

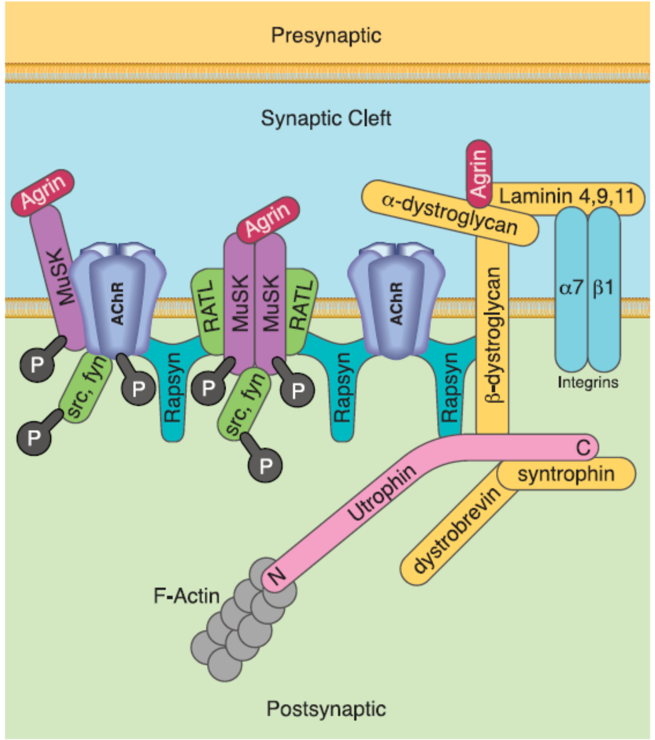


Figure 10.9

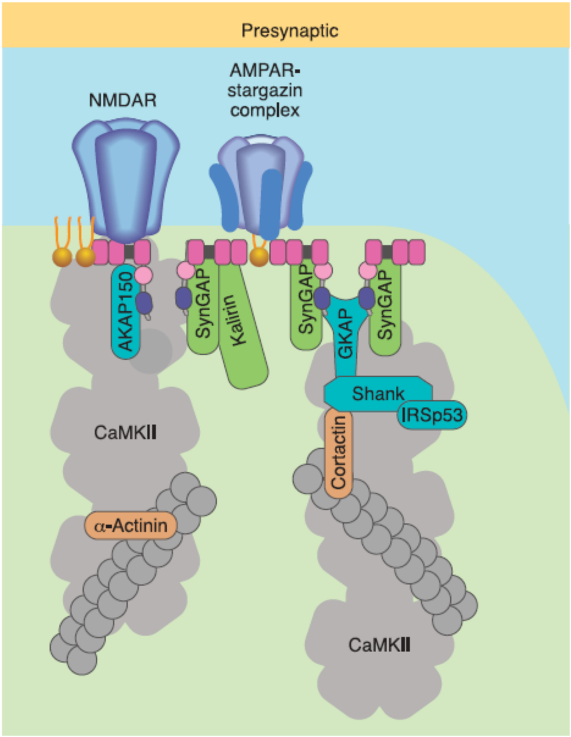
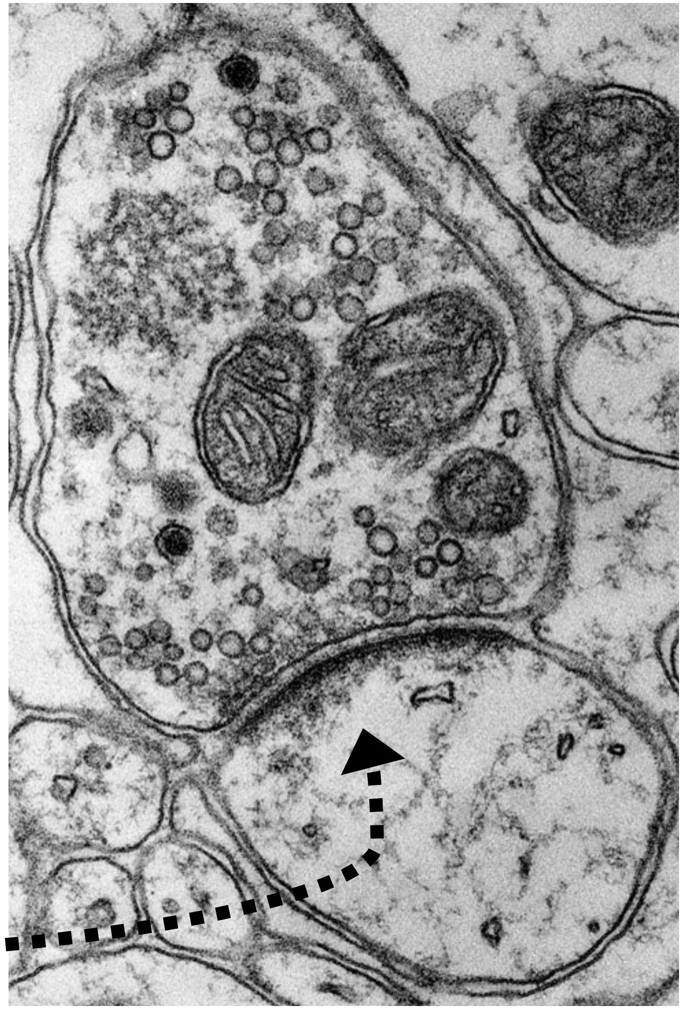


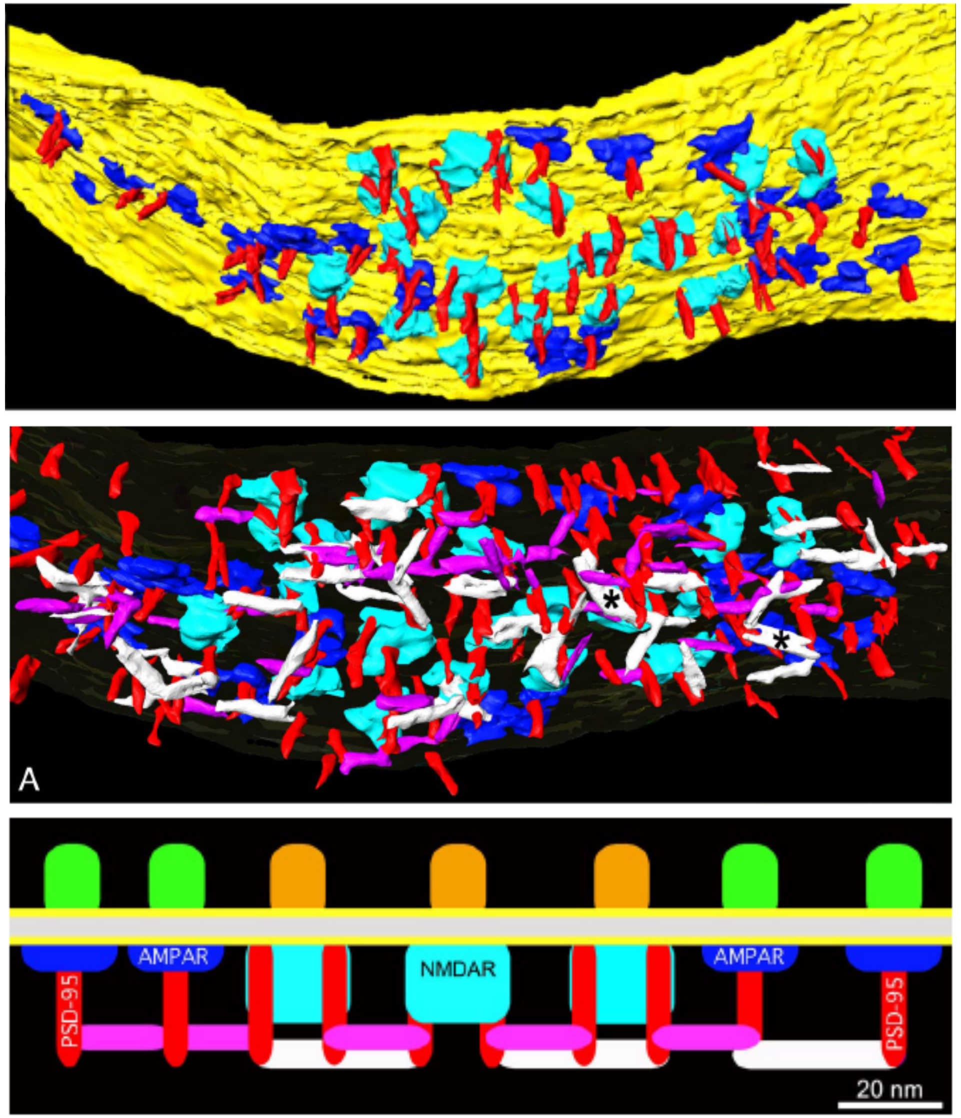
Figure 10.15



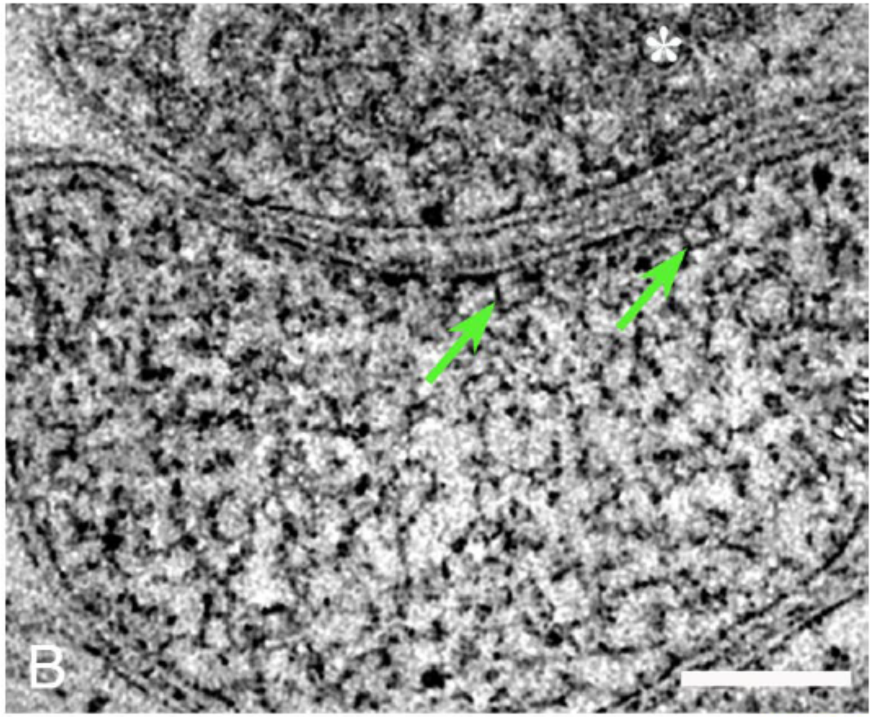
Dense labeling of postsynaptic membrane in electron micrographs

http://medcell.med.yale.edu/image_gallery/nervous_images/synapse_em.jpg

Postsynaptic structures and molecular machinery

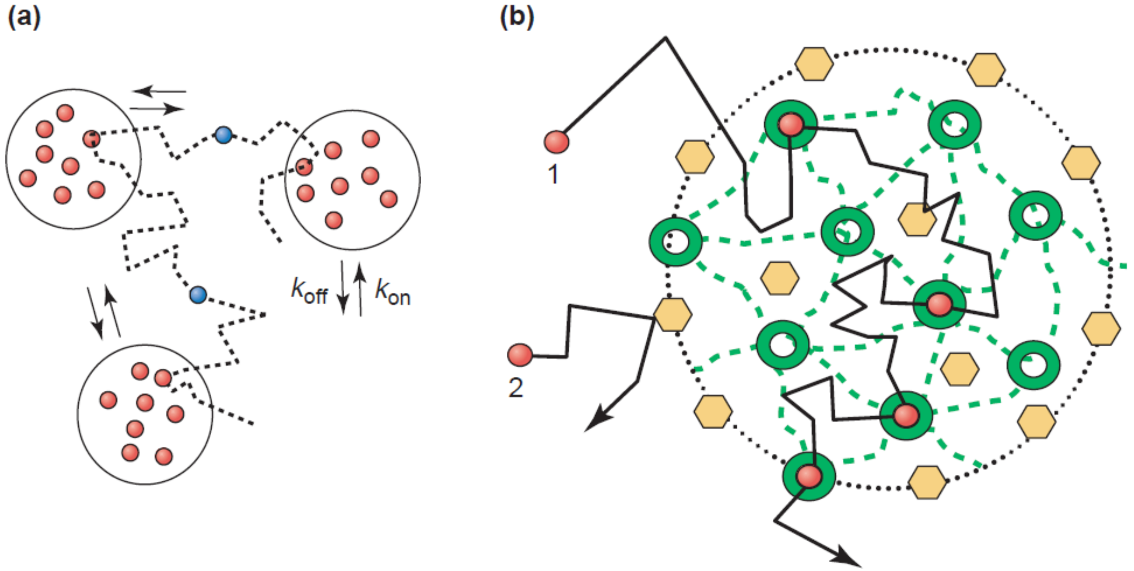


Reconstructing the postsynaptic density (PSD) of cultured rat hippocampal neurons

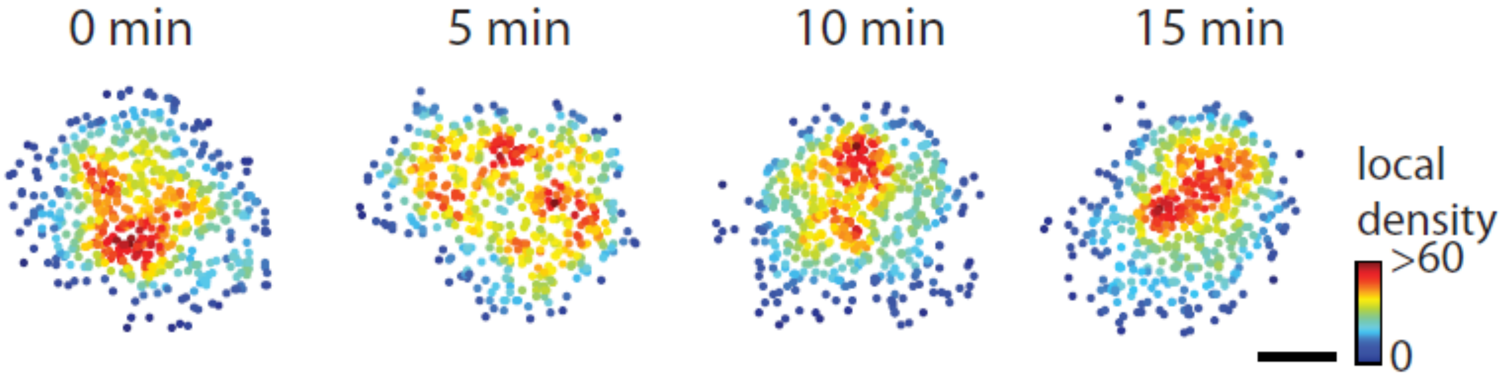


Chen et al (2008) PNAS 105:4453-4458

Receptor trafficking and mobility



Triller and Choquet (2005) TINS 28:133-139



MacGillavry et al (2013) Neuron 78:615-622

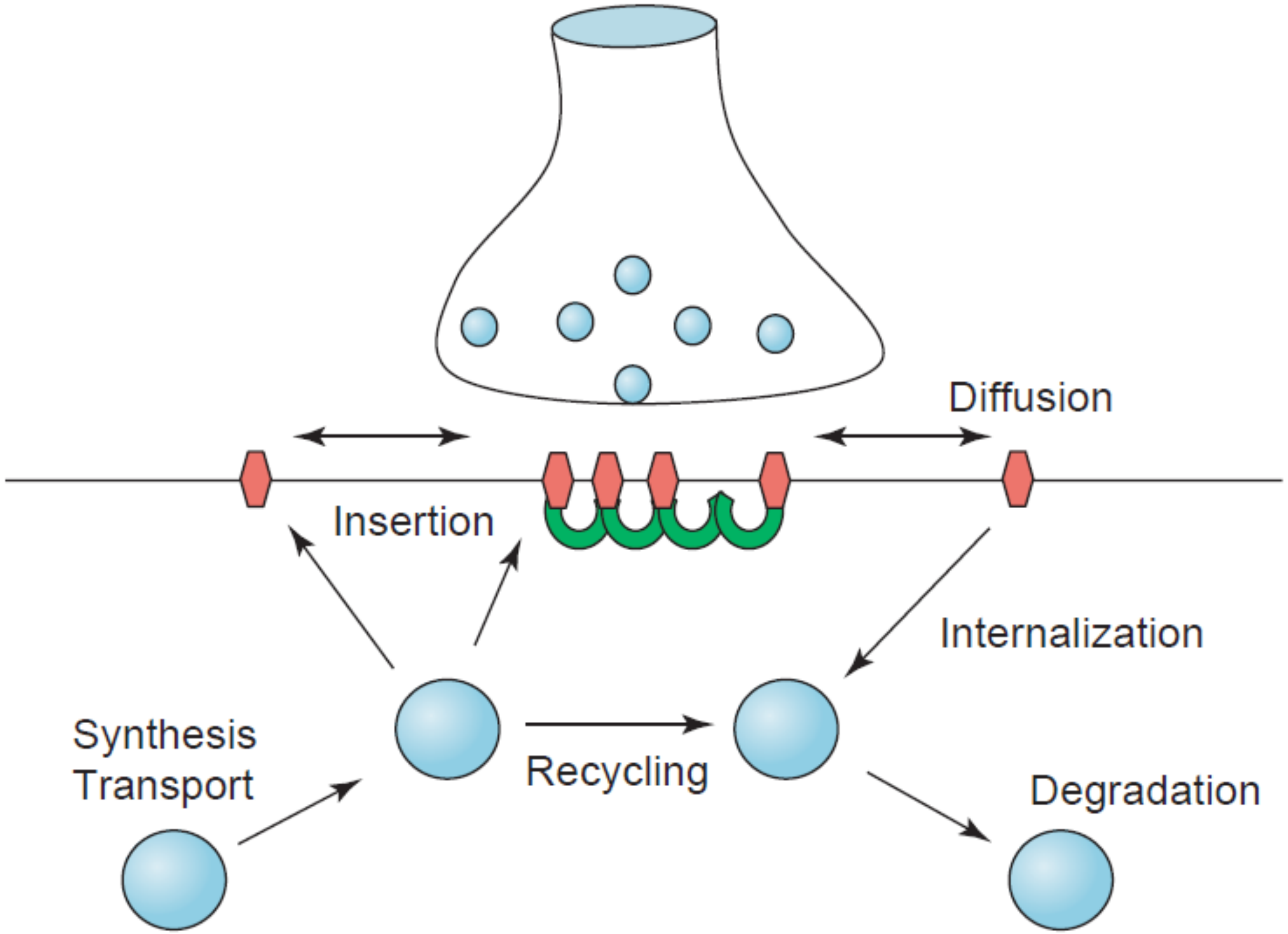
<u>Current thinking:</u>

Receptors diffuse laterally *into*, *out of*, and *between* PSDs

Other proteins in PSD help retain receptors by binding to them or steric effects

Overall structure of PSD is dynamic through time

A taste of postsynaptic receptor cycles



<u>Current thinking:</u>
Composition of receptors can be changed by *insertion* and *internalization* via vesicles

This can change the strength/properties of the postsynaptic response

(covered in later lectures)

Triller and Choquet (2005) TINS 28:133-139

Journal Article

Journal Article:

Maternal oxytocin triggers a transient inhibitory switch in GABA signaling in the fetal brain during delivery.

Tyzio et al., 2006

Science

Any questions/difficulties:
graydonc@ninds.nih.gov