Basic Neuroscience

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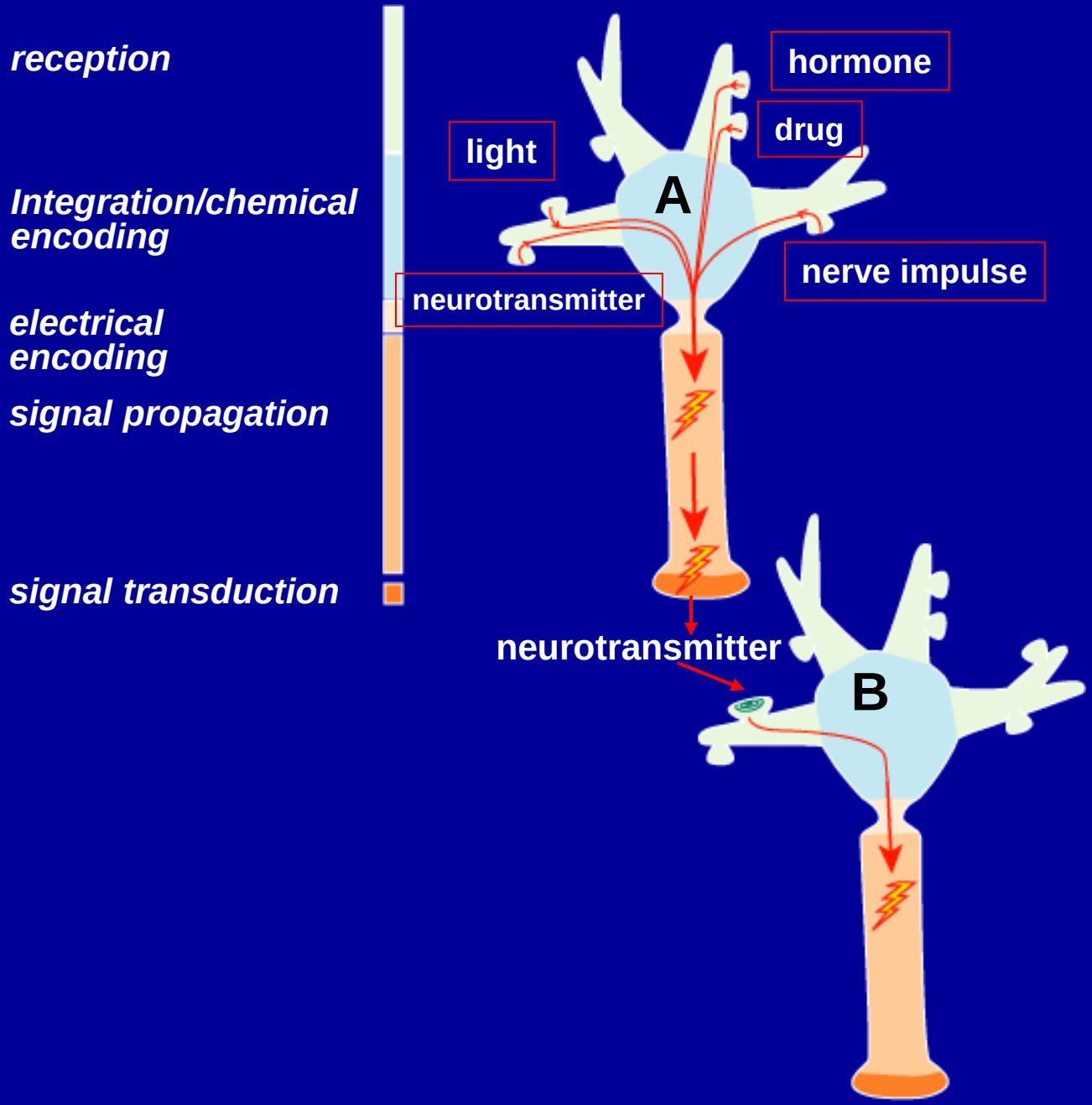
Objectives

- To review principles of chemical neurotransmission
- To explain G-protein systems as targets of psychotropic drugs
- To explain ion channels as targets of psychotropic drugs
  - Ligand gated
  - Voltage gated (voltage sensitive)

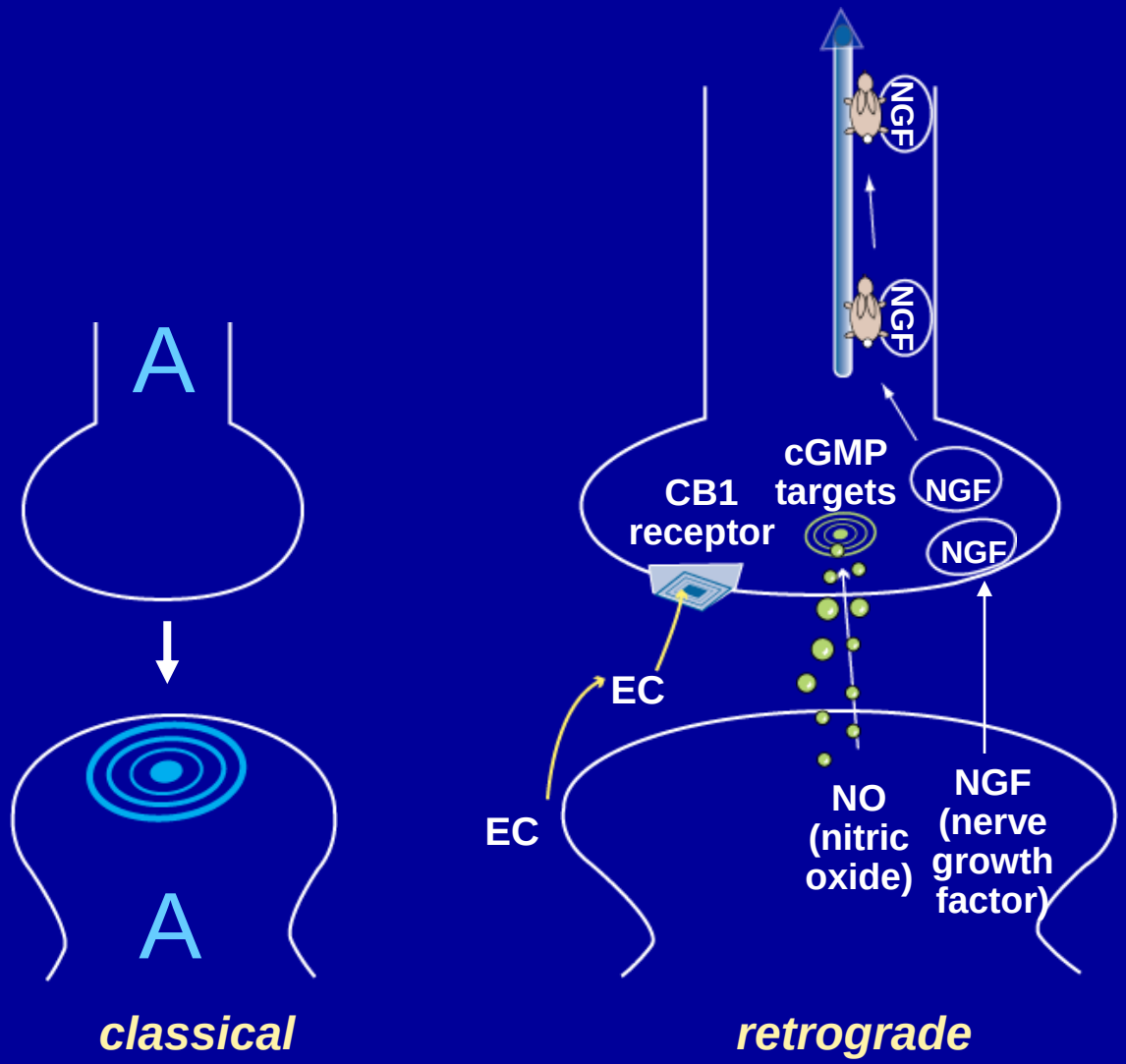
Three Types of Neurotransmission

- Classical synaptic
- Retrograde
- Volume (nonsynaptic) neurotransmission

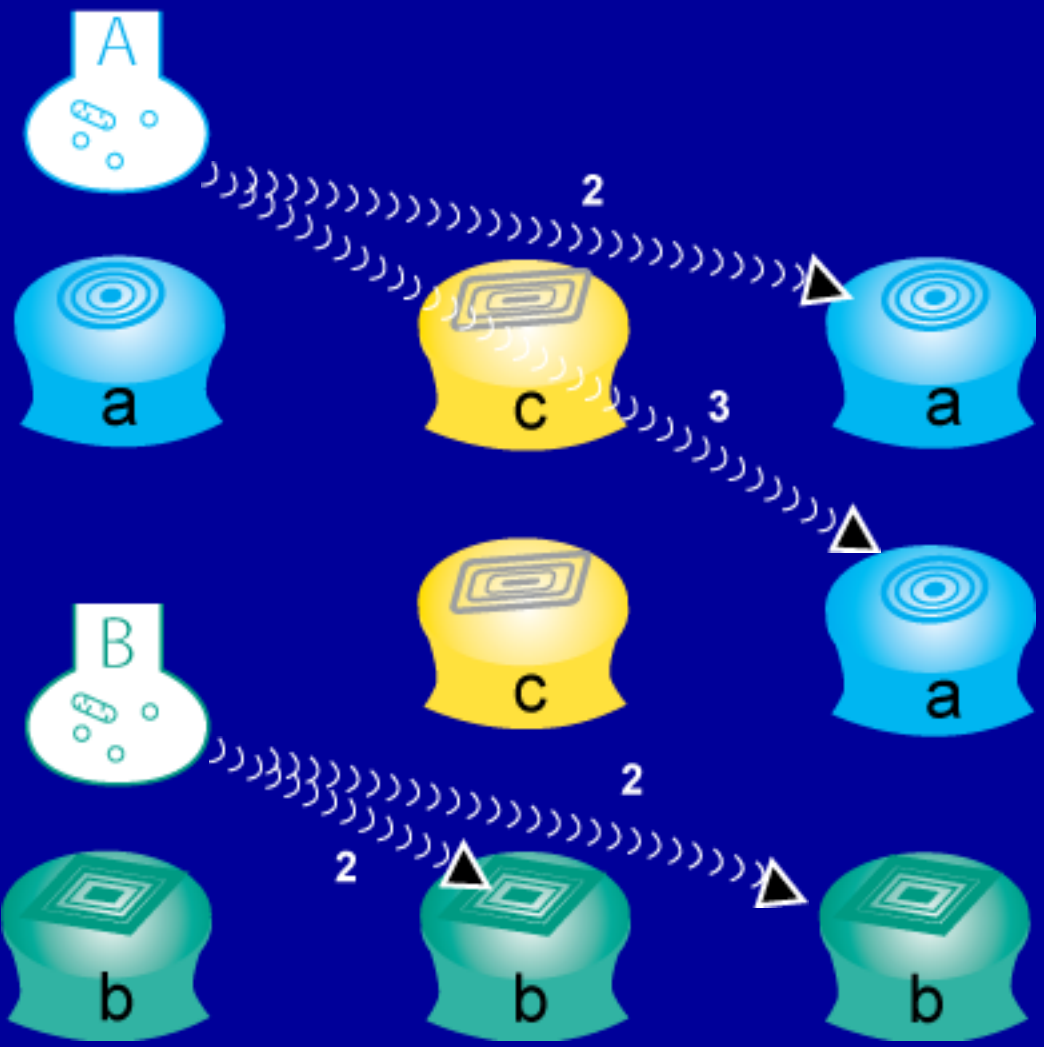
Classical Synaptic Neurotransmission



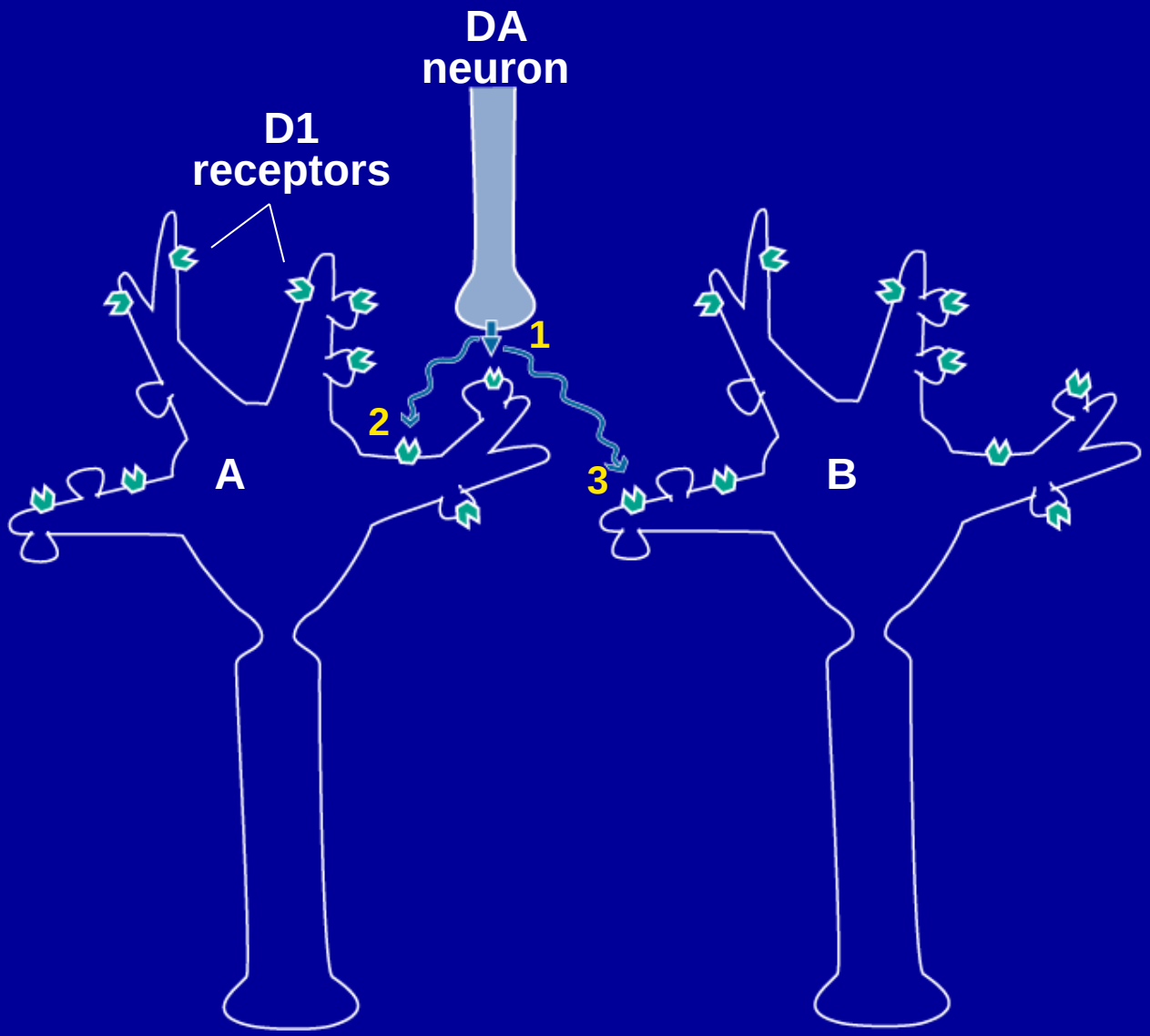
Classical Neurotransmission Versus Retrograde Neurotransmission



Classical Neurotransmission Versus Volume Neurotransmission



Volume Neurotransmission

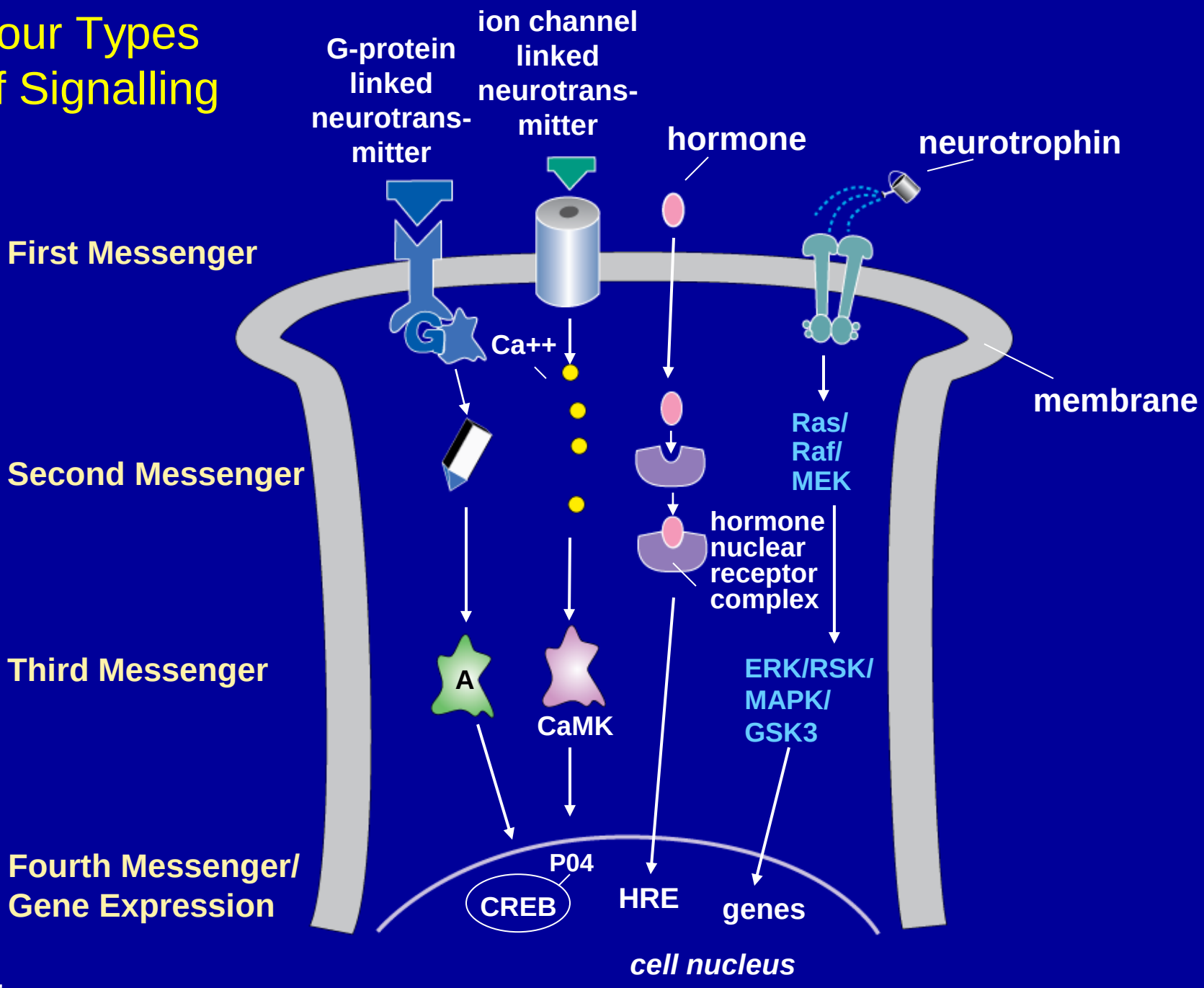


synaptic neurotransmission at 1 and diffusion to 2 and 3

Four Types of Signalling

- G-protein linked neurotransmission
- Ion-channel linked neurotransmission
- Hormones
- Neurotrophins

Four Types of Signalling



Four Types of Signalling

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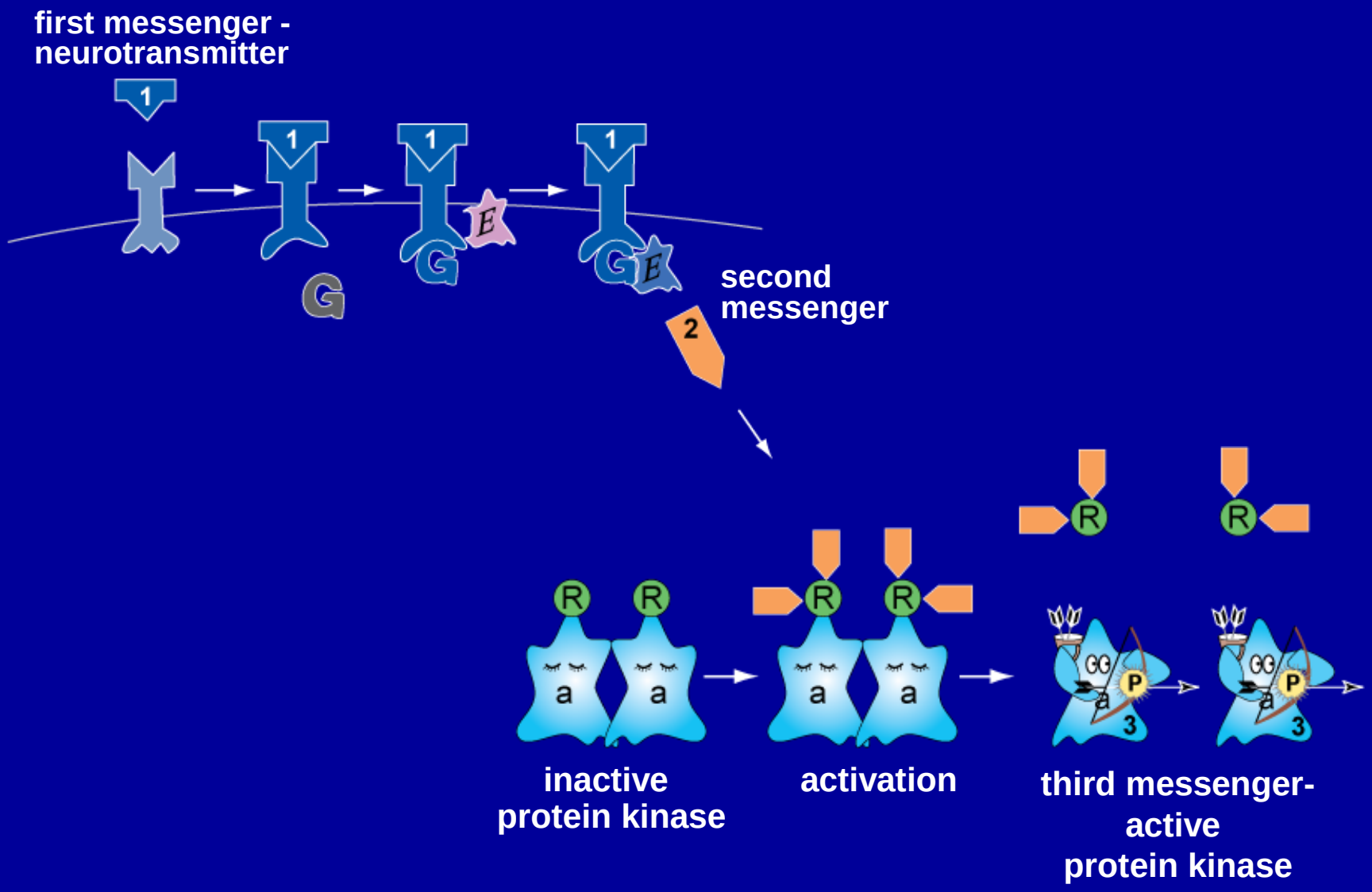
Activating a Third Messenger Kinase through Cyclic AMP



Four Types of Signalling

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- Ion-channel linked neurotransmission
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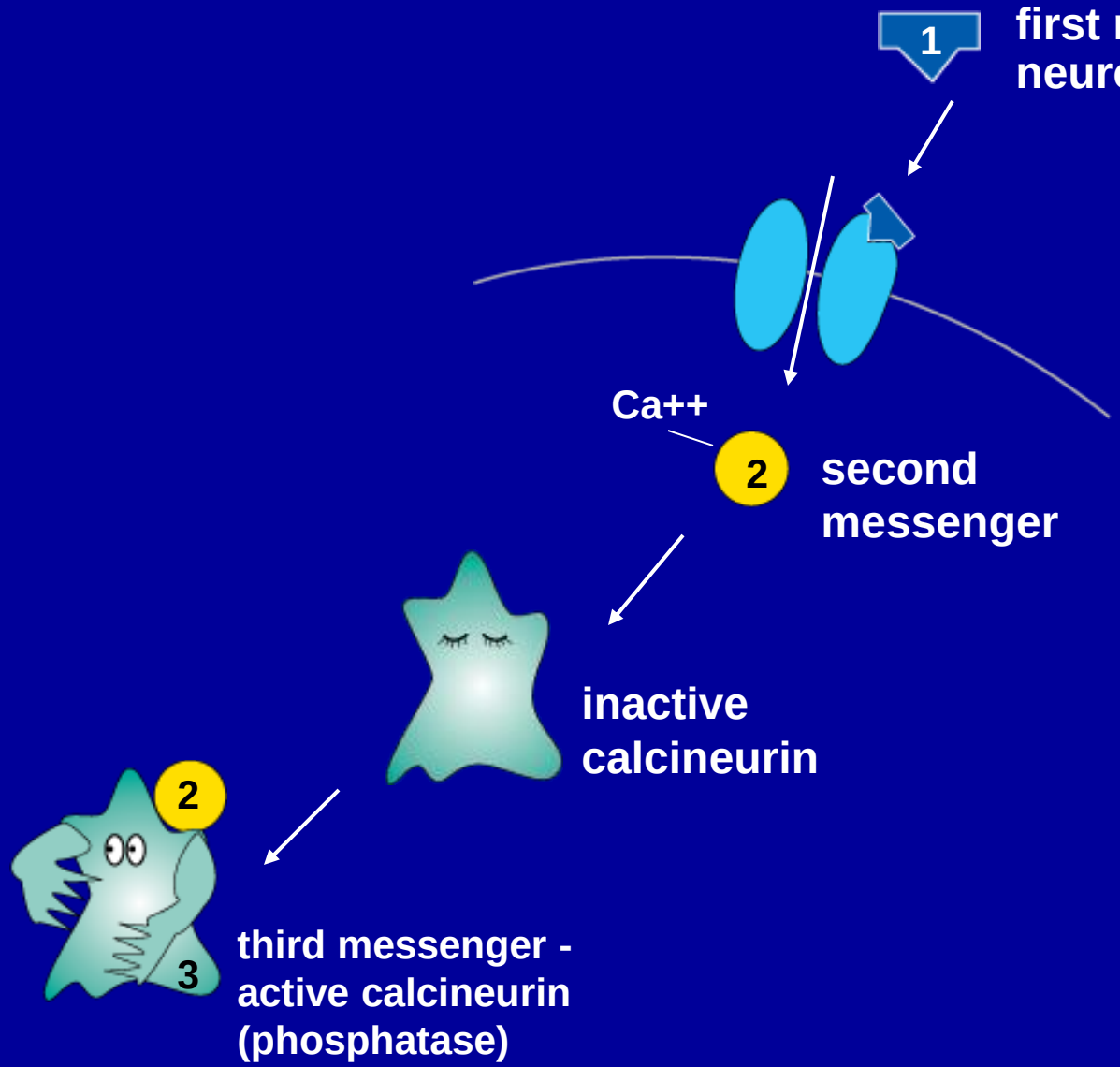
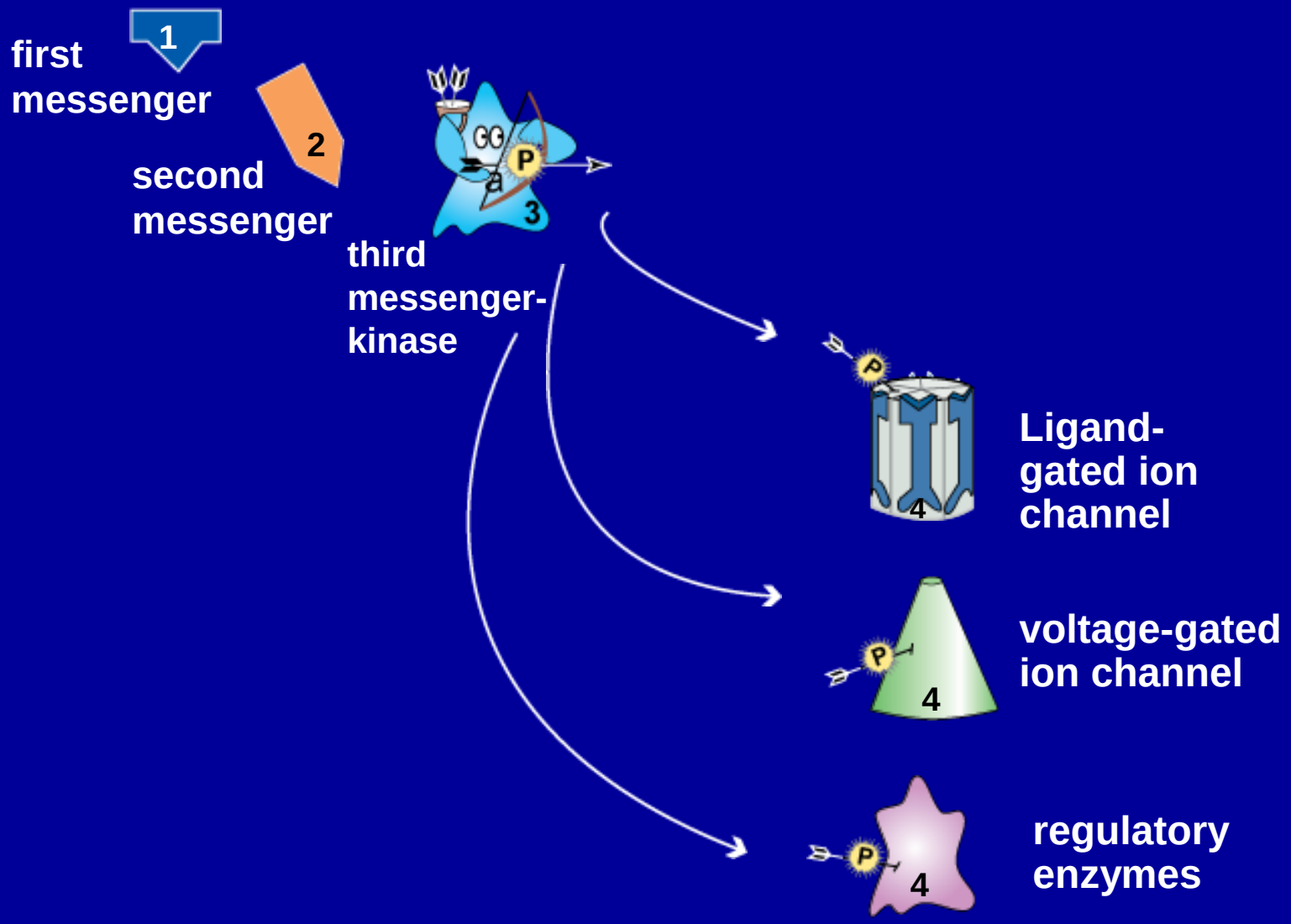
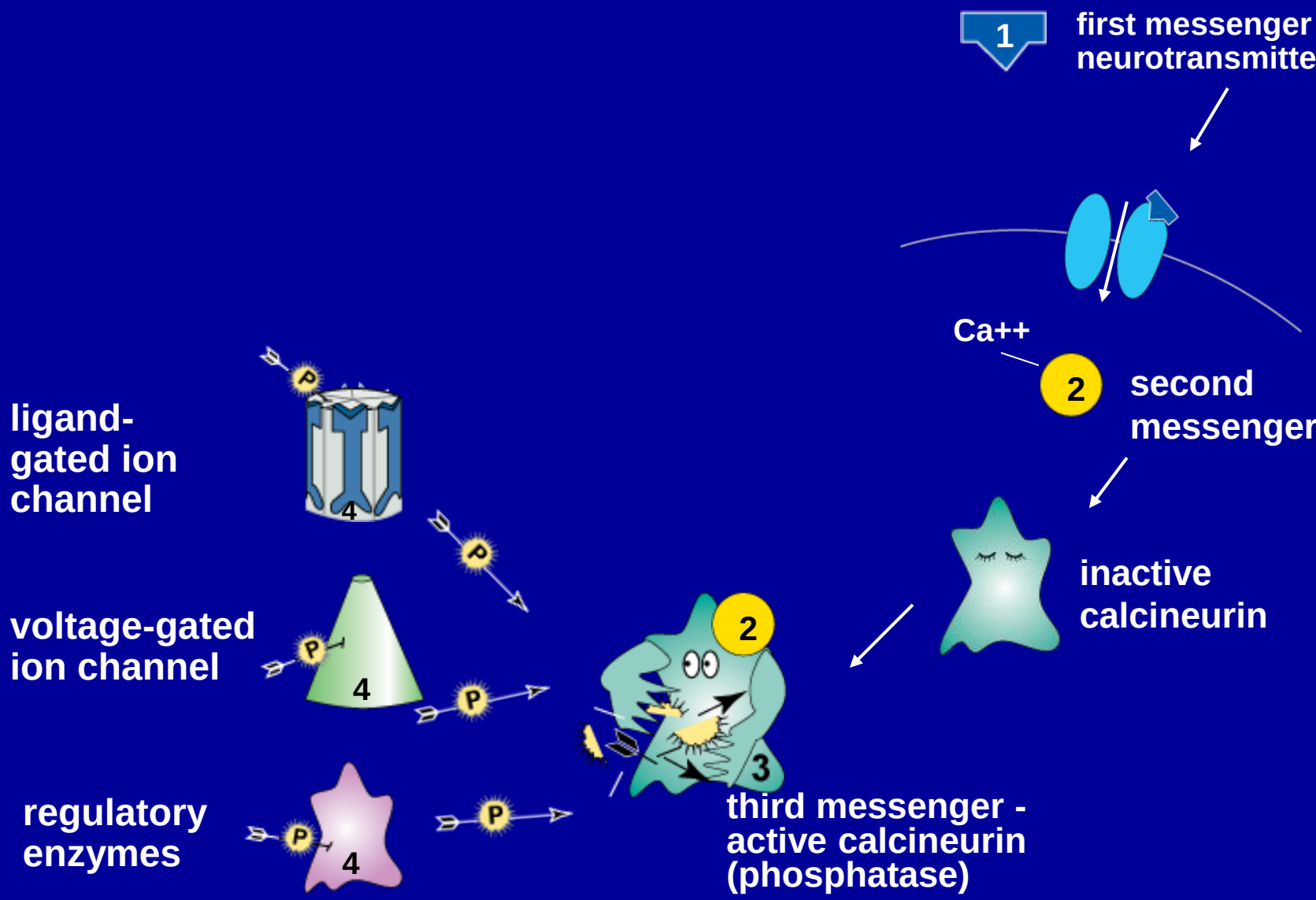
Activating a Third Messenger Phosphatase through Calcium

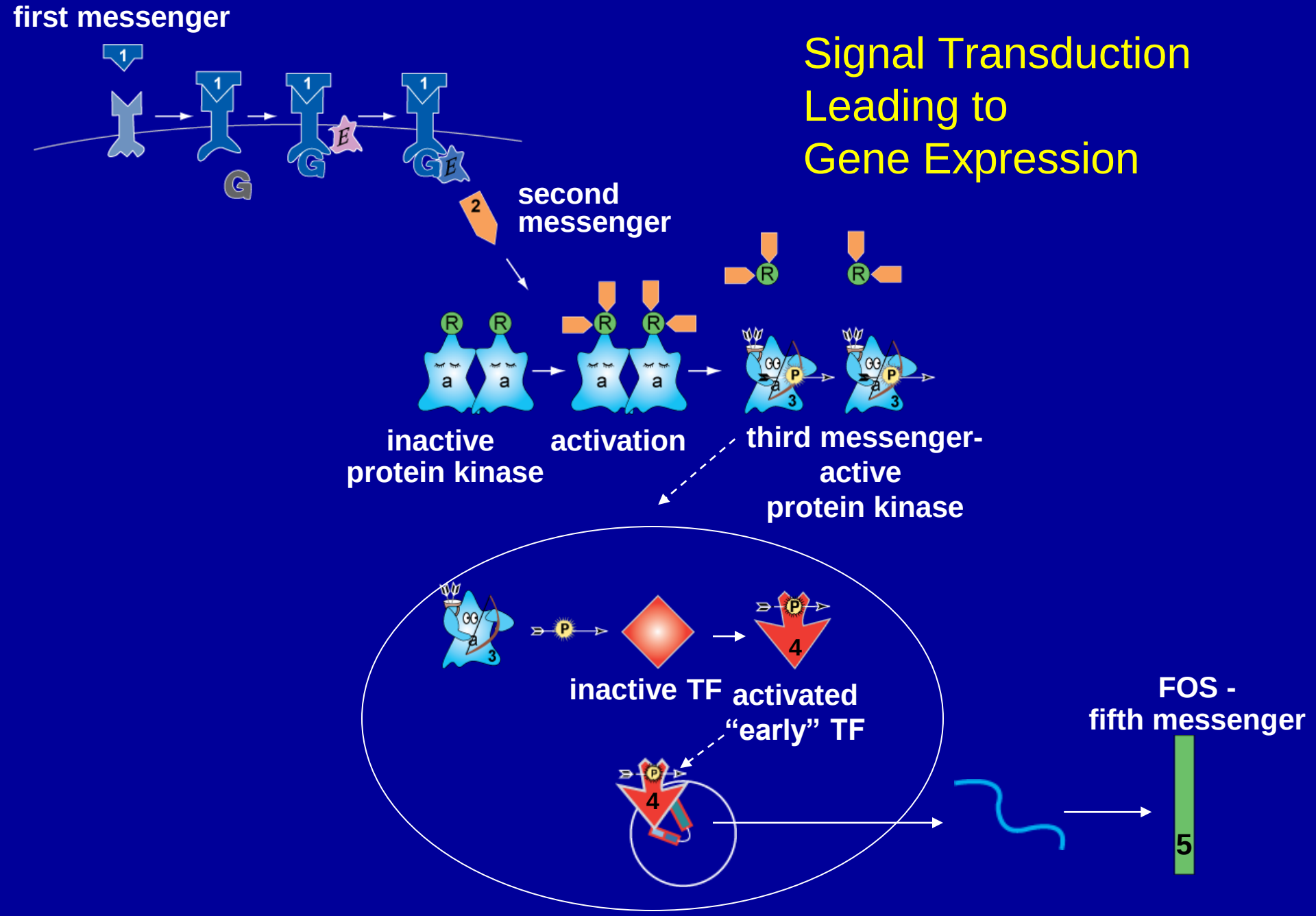


Third Messenger Kinases put Phosphates on Critical Proteins



Third Messenger Phosphatases Undo what Kinases Create - Take Phosphates Off Critical Proteins

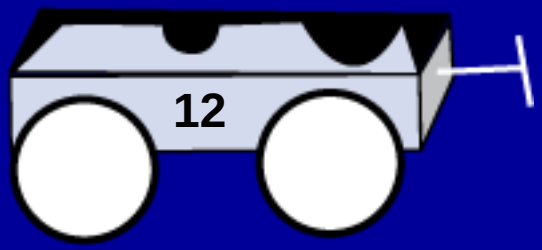



first messenger
Signal Transduction
Leading to
Gene Expression
second
messenger
inactive
protein kinase
activation
third messenger-
active
protein kinase
inactive TF
activated
"early" TF
FOS -
fifth messenger

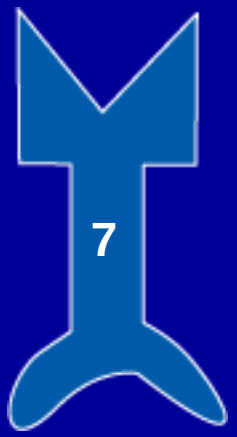
Five Major Targets of Psychotropic Drugs

- Transporters
- G-protein linked receptors
- Ligand Gated ion channels
- Voltage Gated Ion Channels
- Enzymes

Major Targets of Psychopharmacologic Drug Action



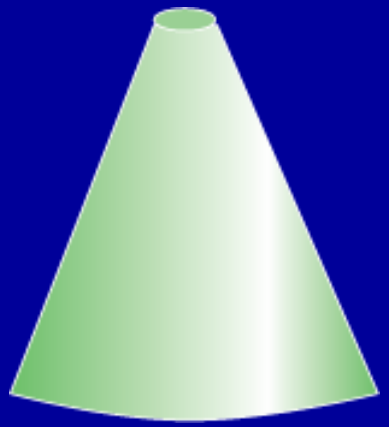
12 transmembrane region transporter
~ 30% of psychotropic drugs



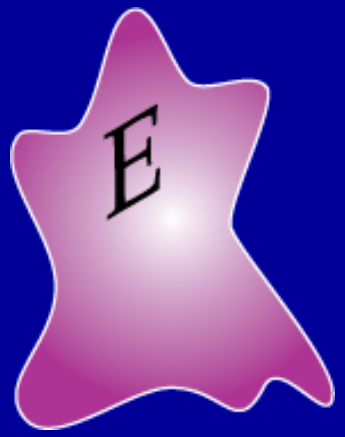
7 transmembrane region G protein-linked
~ 30% of psychotropic drugs

Other Targets of Psychopharmacologic Drug Action

4 transmembrane region
Ligand-gated ion channel
~ 20% of psychotropic drugs



6 transmembrane region
Voltage-gated ion channel
~ 10% of psychotropic drugs



enzyme
~ 10% of psychotropic drugs

Five Major Targets of Psychotropic Drugs

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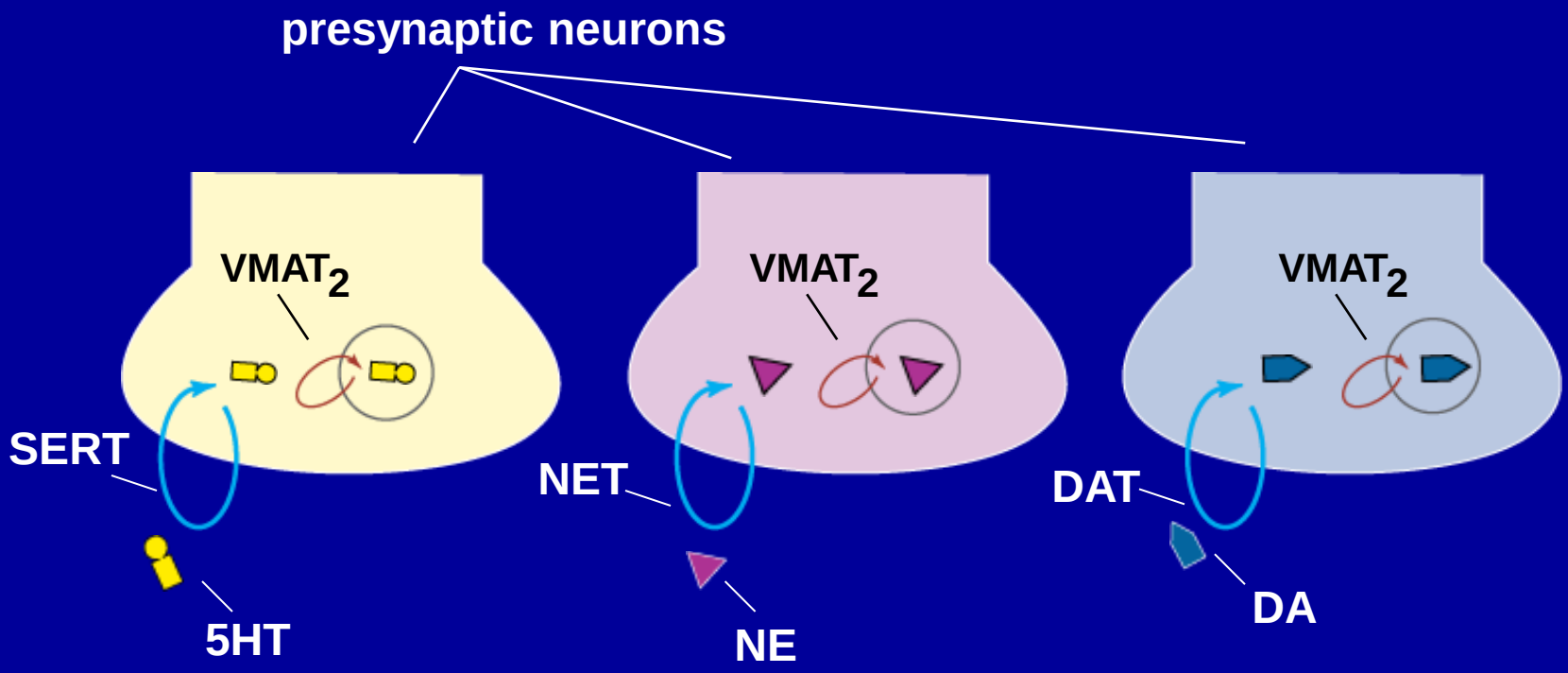
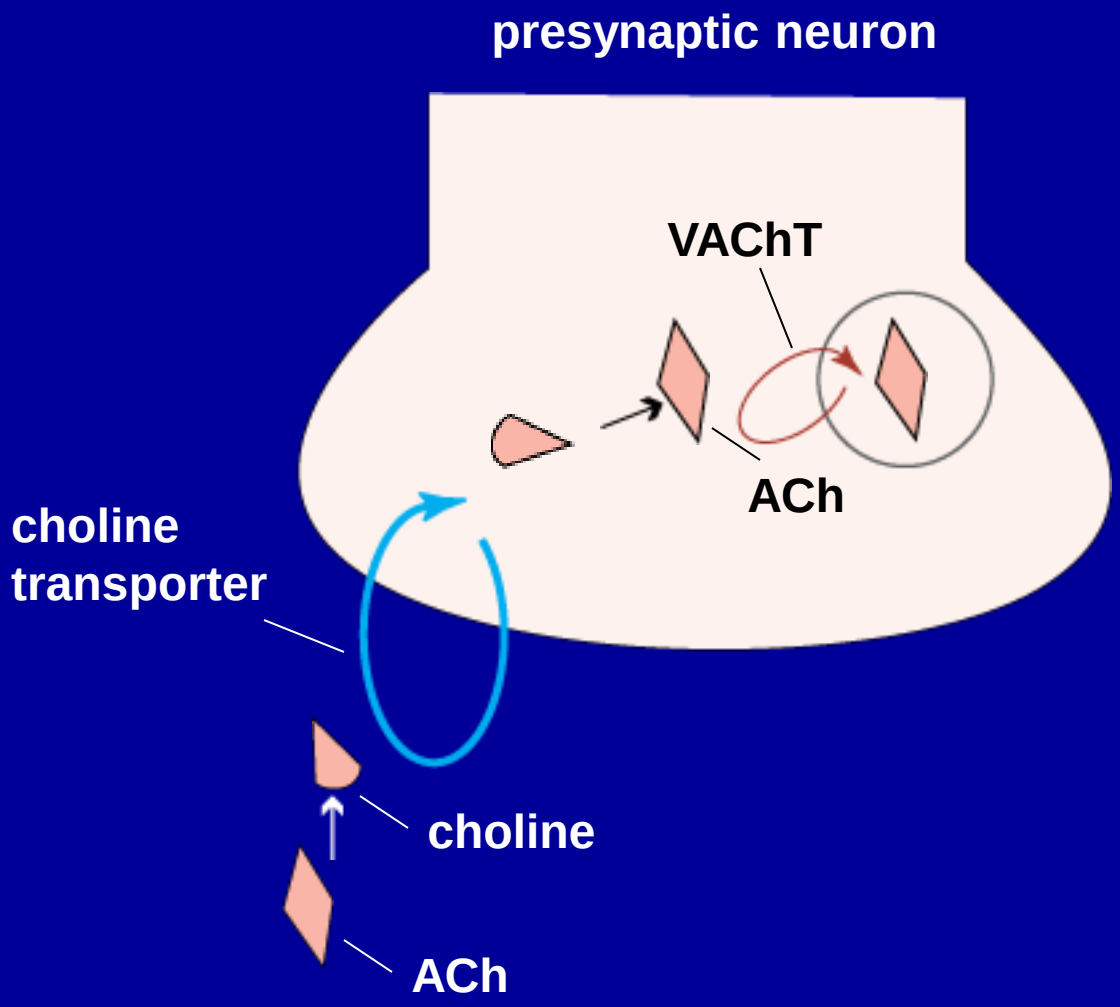
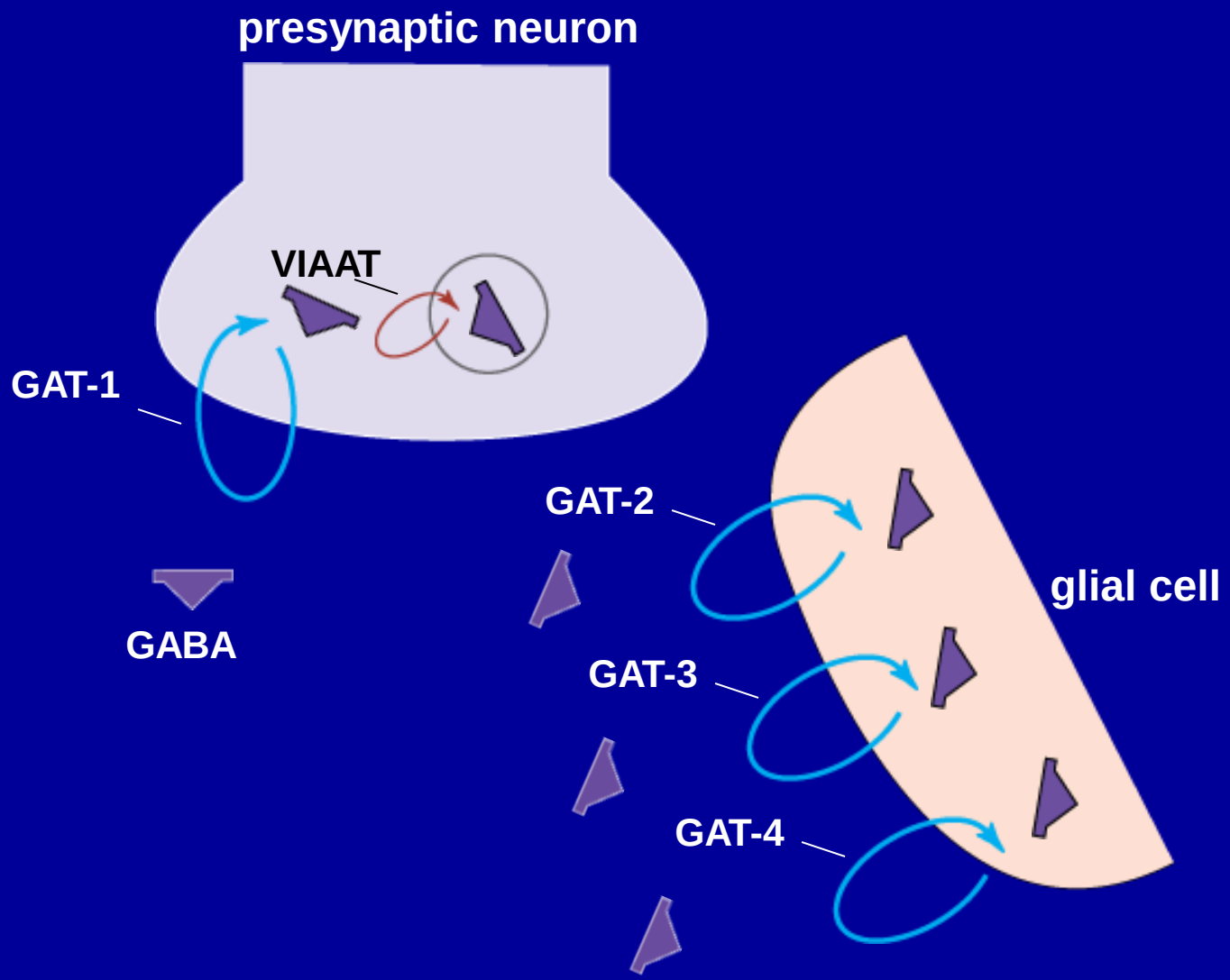
Monoamine Transporters



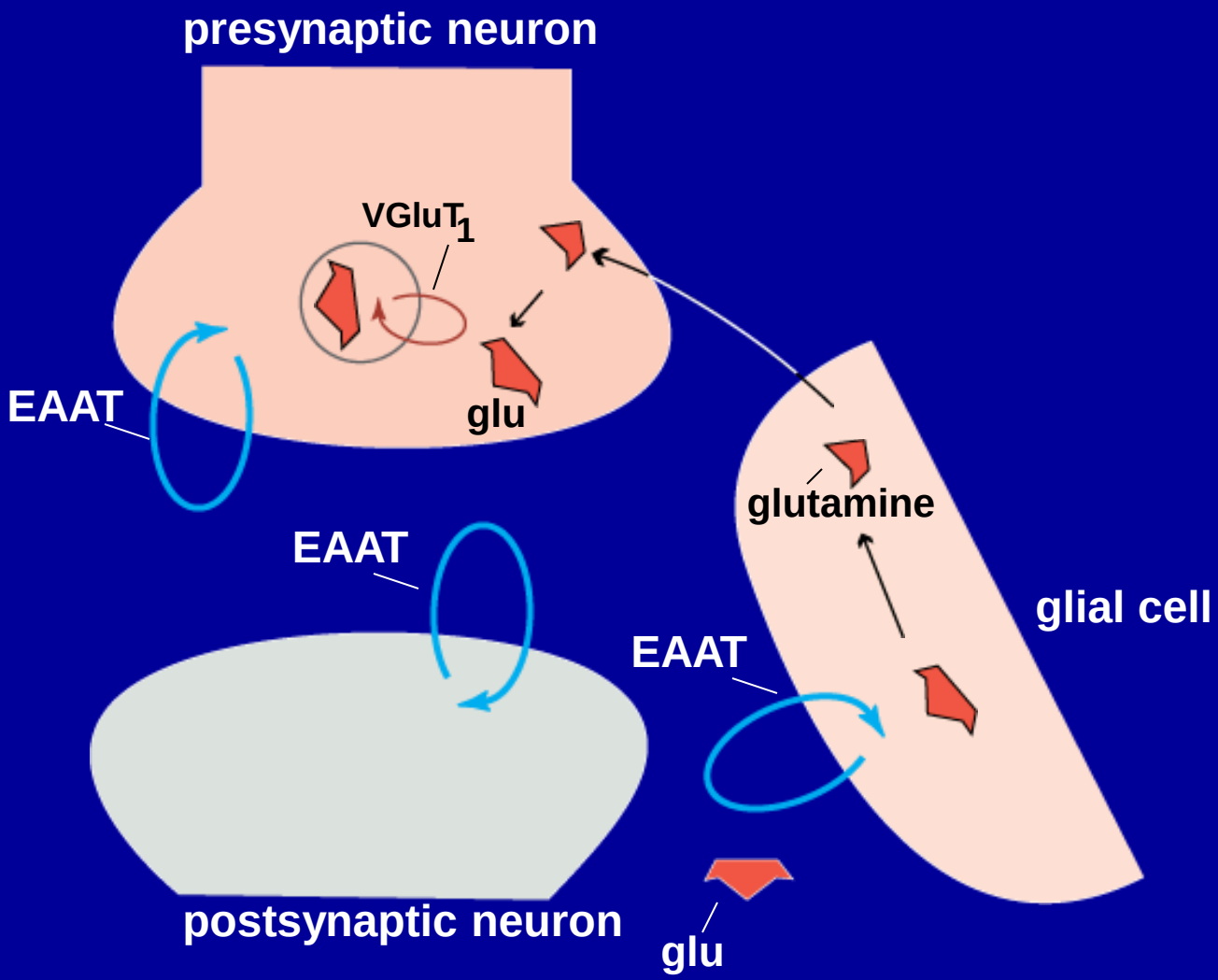
Acetylcholine and Choline Transporters



GABA Transporters



Glutamate Transporters



Five Major Targets of Psychotropic Drugs

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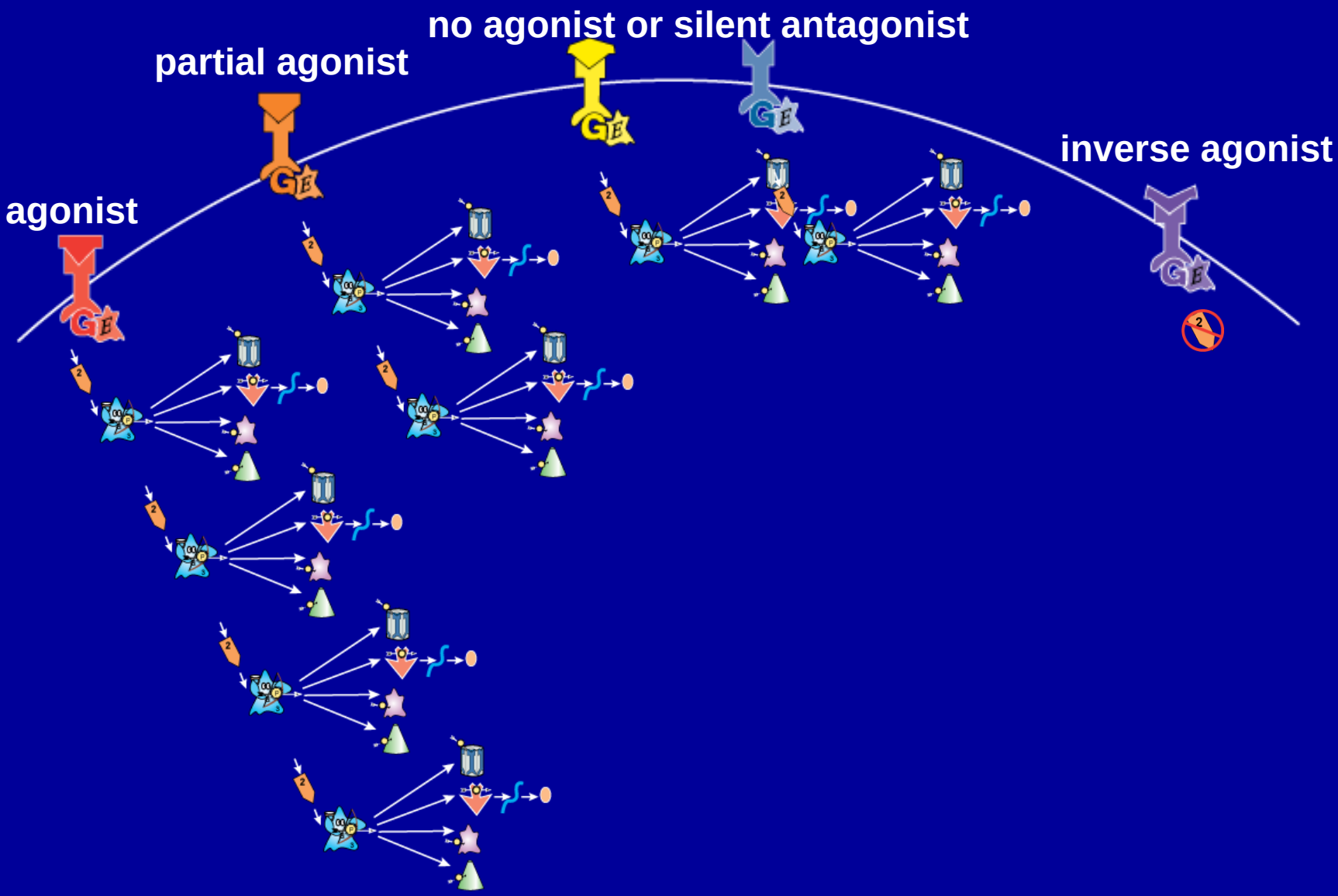
- G-protein linked receptors
- Ligand Gated ion channels
- Voltage Gated Ion Channels
- Enzymes

Agonist Spectrum: G protein linked receptors



Five Major Targets of Psychotropic Drugs

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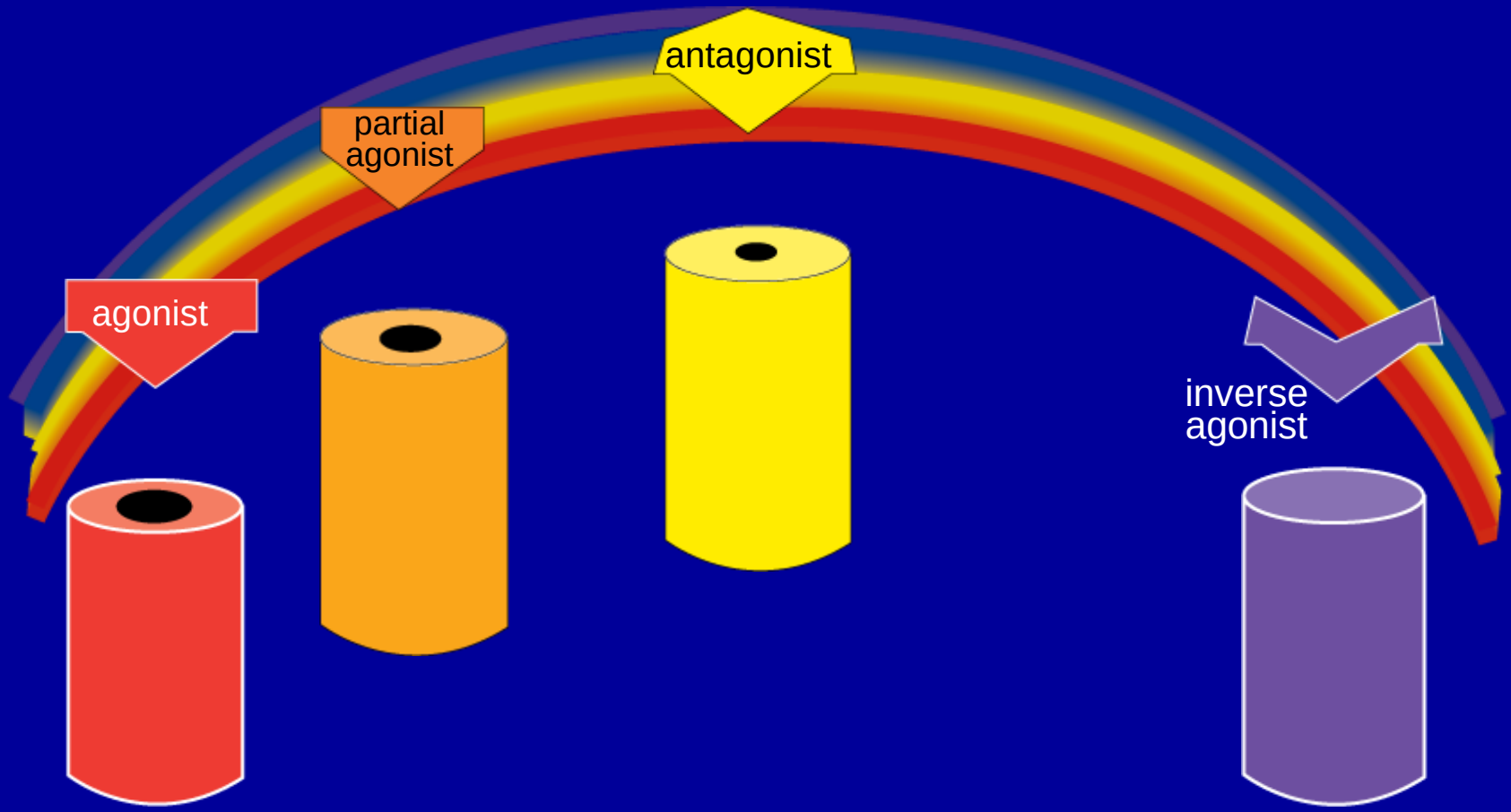
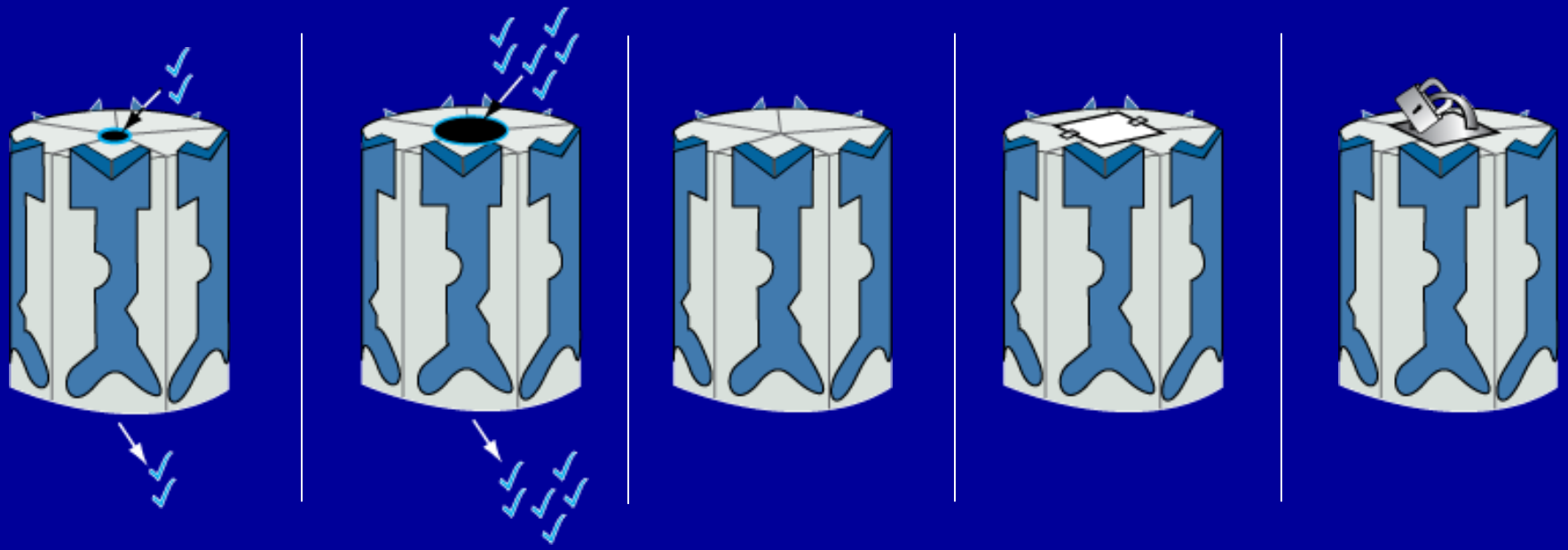
The Agonist Spectrum: Ion Channels



Five States of Ligand Gated Ion Channels



channel in resting state

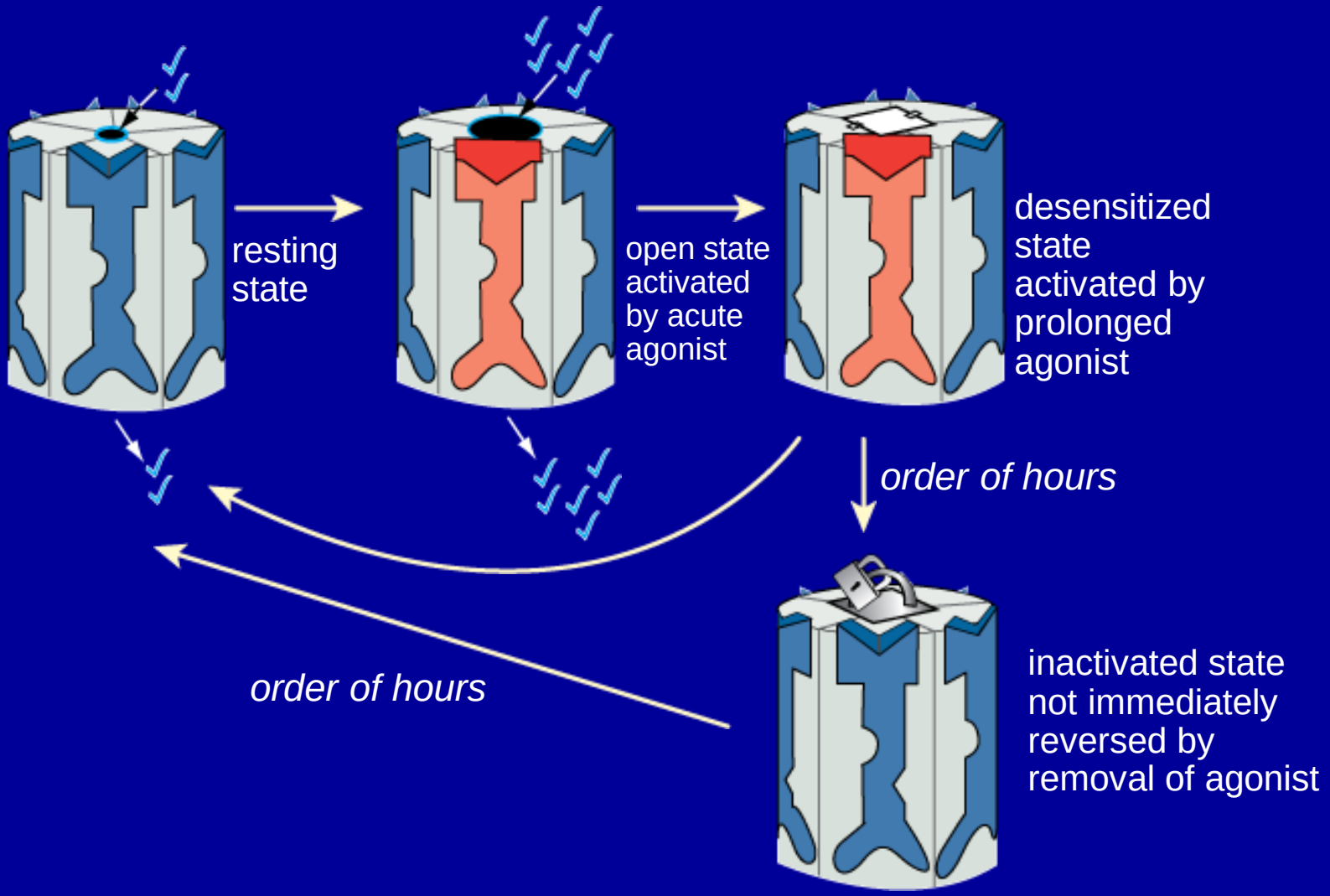
channel open

channel closed

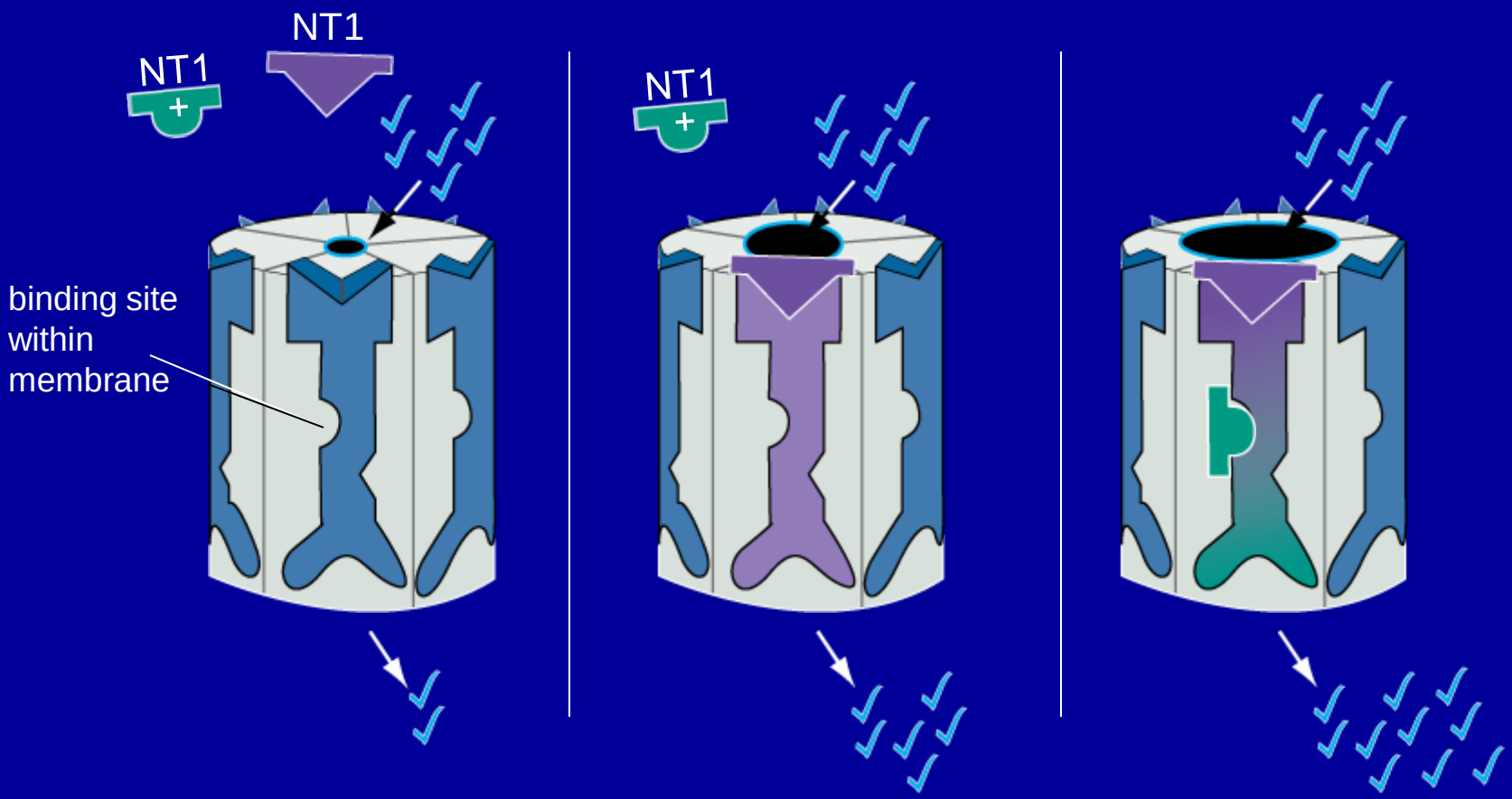
channel desensitized

channel inactivated

Opening, Desensitizing and Inactivating of Ligand-Gated Ion Channels by Agonists

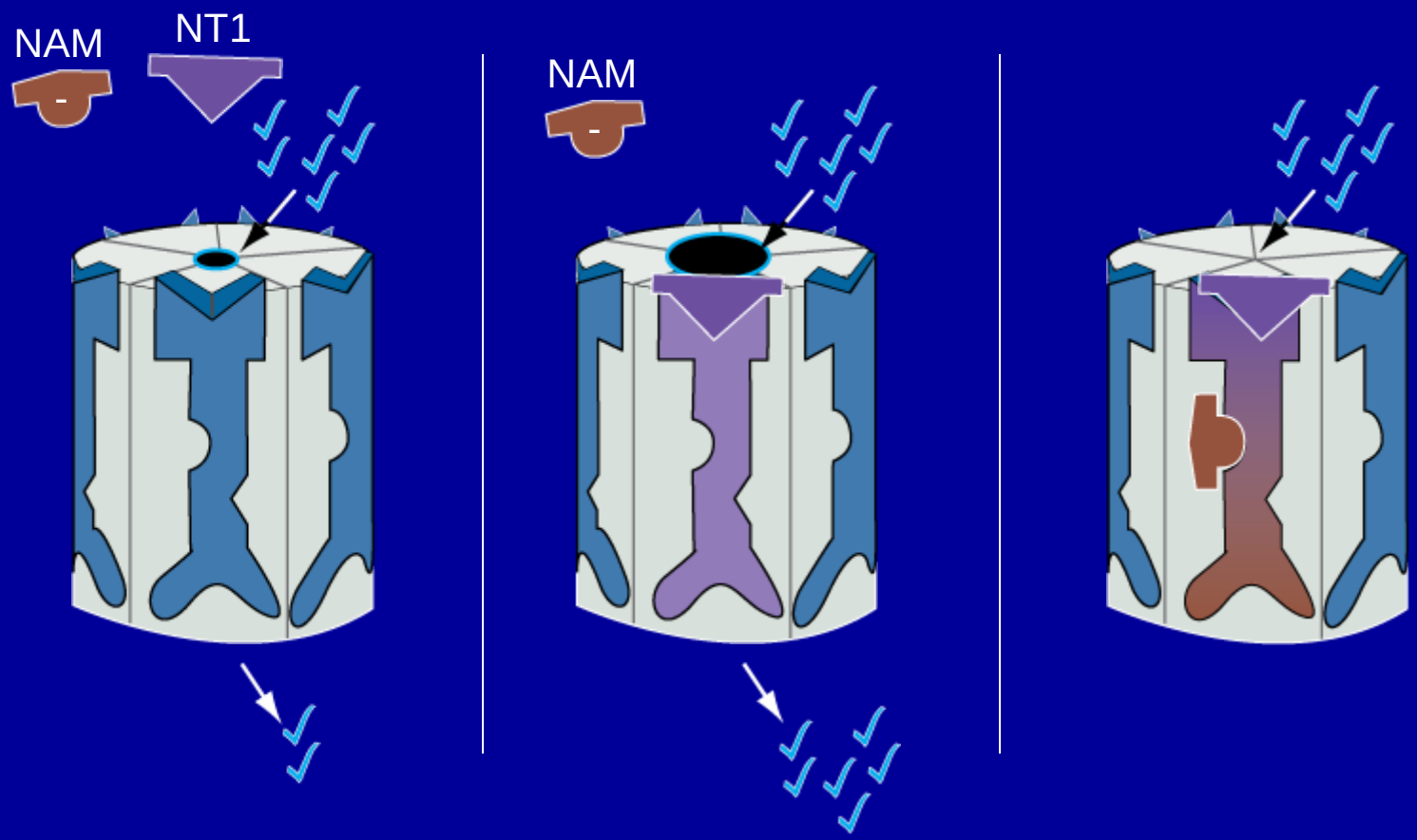


Positive Allosteric Modulation (PAM)



When a neurotransmitter binds to receptors making up an ion channel, the channel opens more frequently. However, when BOTH the neurotransmitter and a positive allosteric modulator (PAM) are bound to the receptor, the channel opens much more frequently, allowing more ions into the cell.

Negative Allosteric Modulation (NAM)

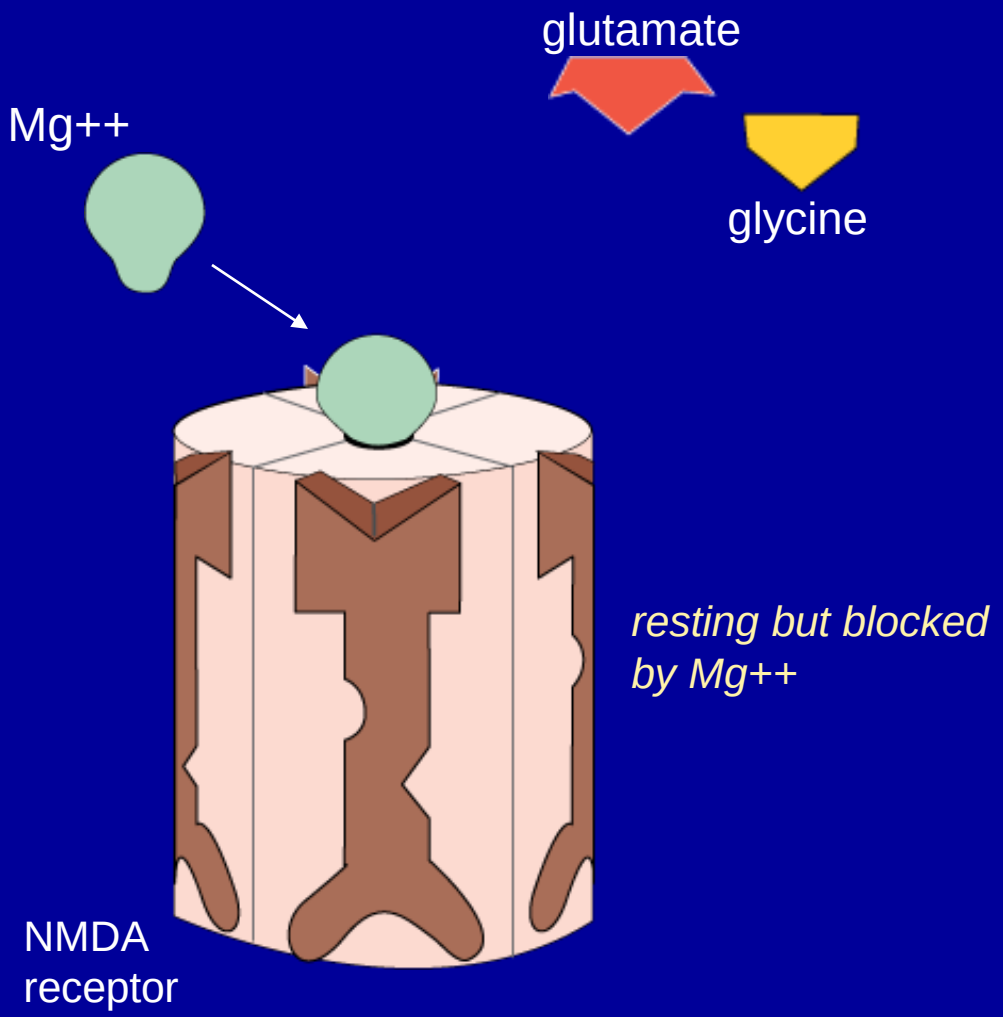


When a neurotransmitter binds to receptors making up an ion channel, the channel opens more frequently. However, when BOTH the neurotransmitter and a negative allosteric modulator (NAM) are bound to the receptor, the channel opens much less frequently, allowing less ions into the cell.

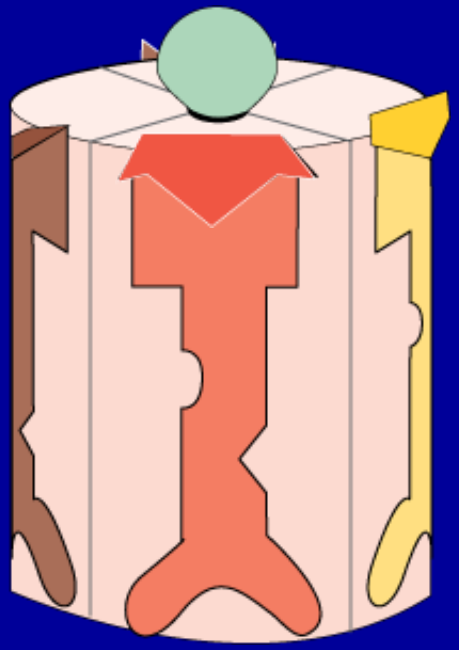
Five Major Targets of Psychotropic Drugs

- Transporters
- G-protein linked receptors
- Ligand Gated ion channels
  - The glutamate system as an example
- Voltage Gated Ion Channels
- Enzymes

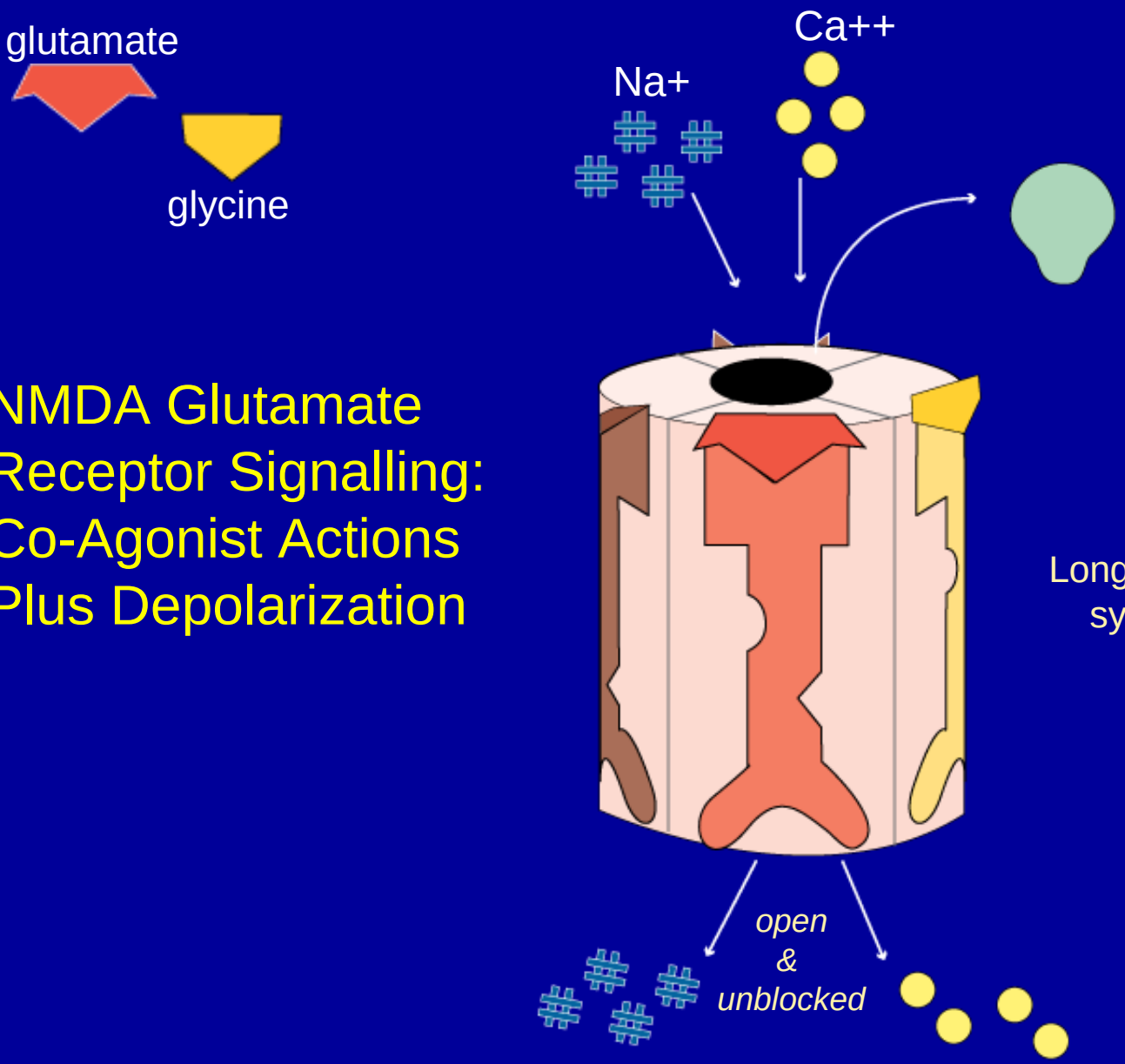
NMDA Glutamate Receptor Signalling: Resting State



NMDA Glutamate Receptor Signalling: Occupancy by Both Co-Agonists in the Absence of Neuronal Depolarization



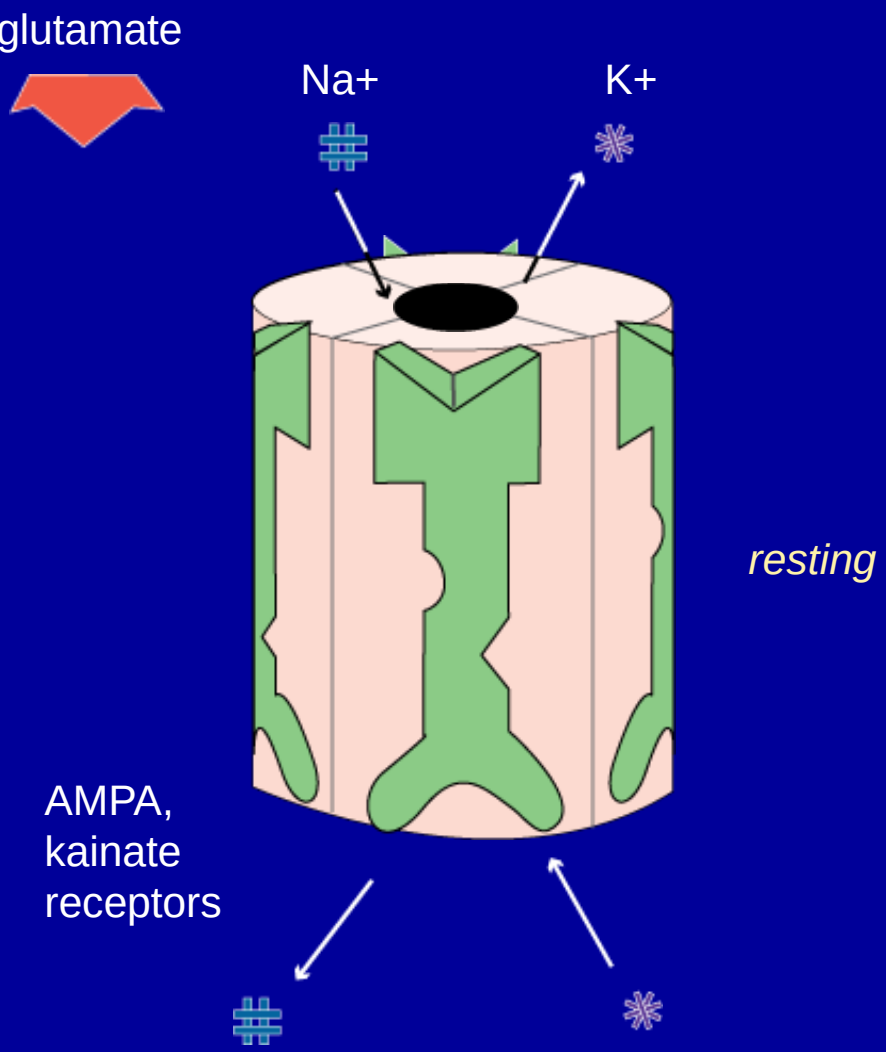
co-agonists open the channel,
but it is blocked by Mg++
- not depolarized



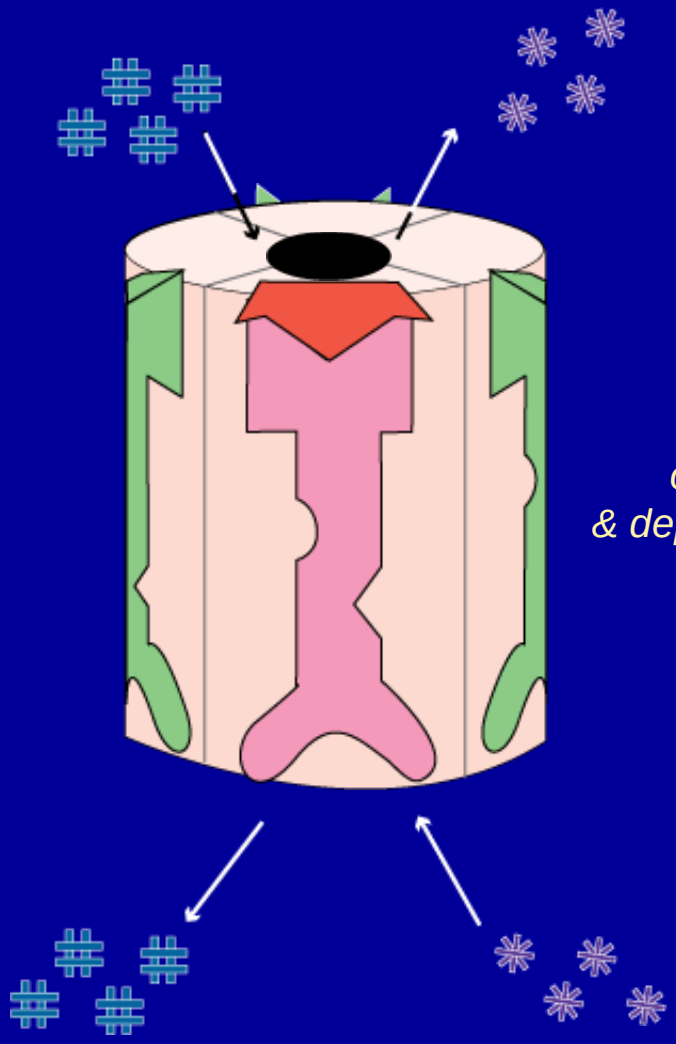
NMDA Glutamate Receptor Signalling: Co-Agonist Actions Plus Depolarization

Long-term potentiation
synaptic plasticity

AMPA/Kainate Glutamate Receptor Signalling: Resting State



AMPA/Kainate Glutamate Receptor Signalling: Glutamate Actions



open
& depolarized

Stahl. Stahl's Essential Psychopharmacology, 3rd ed., 2008.

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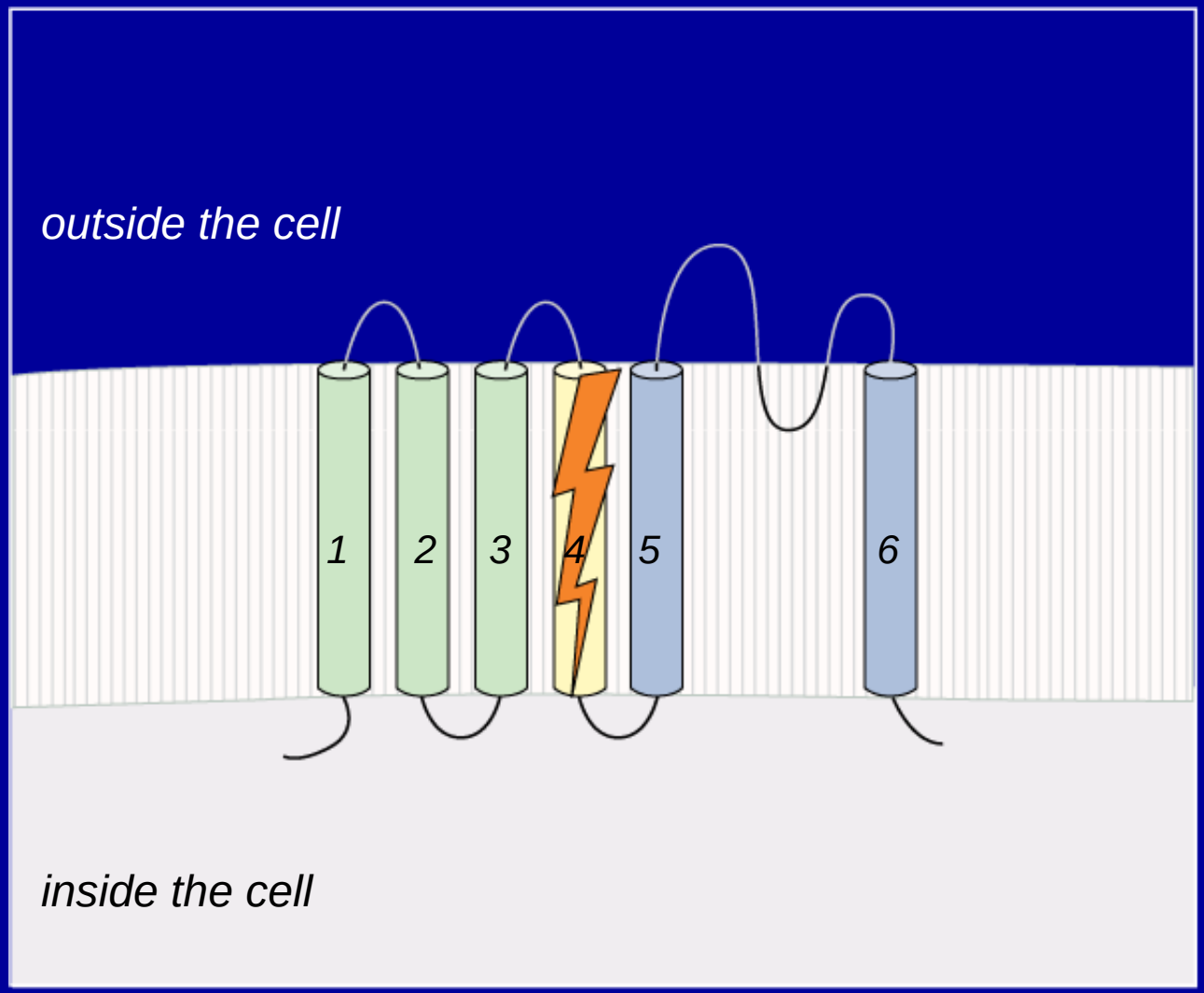
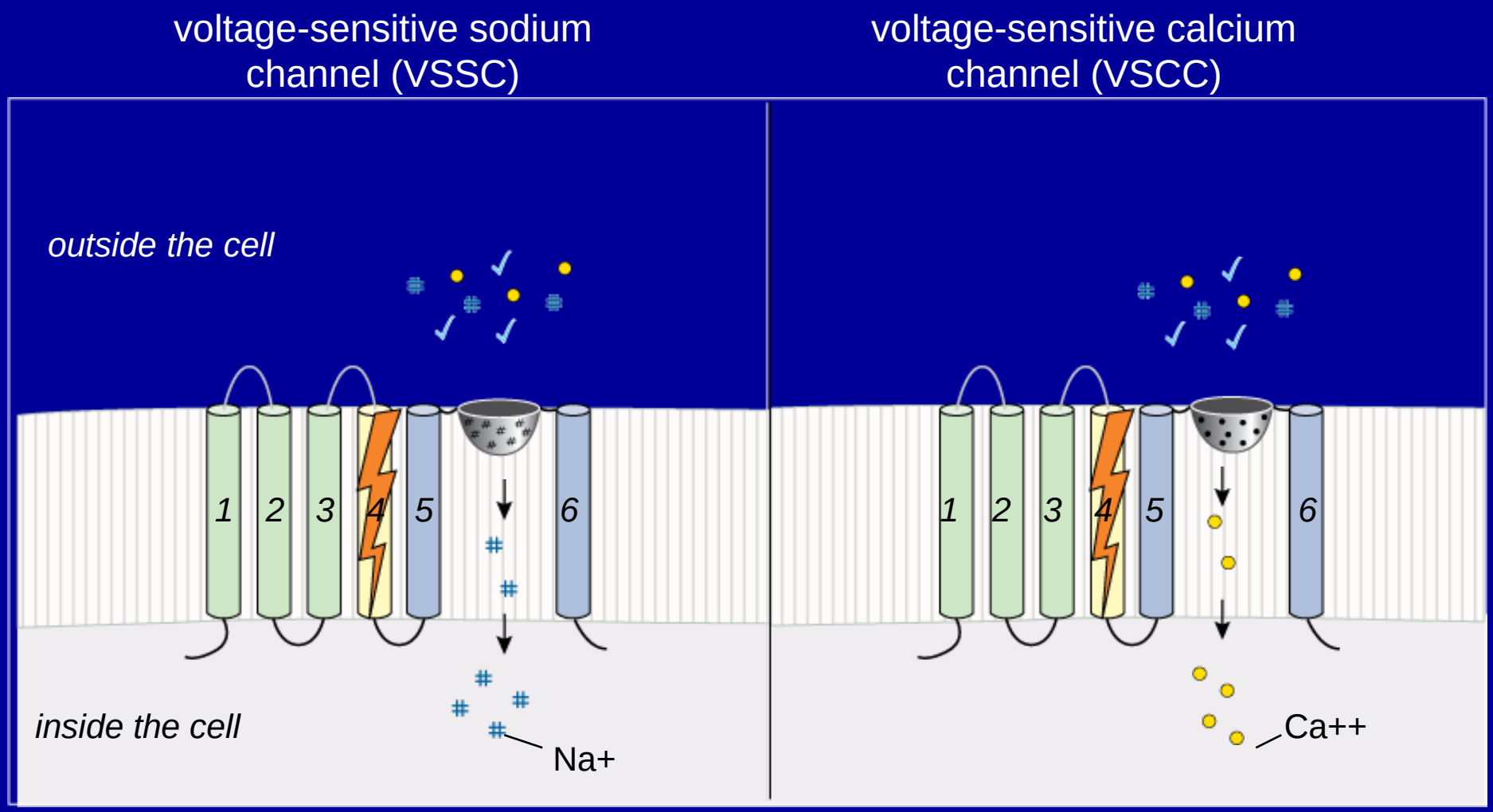
The Pore of a Voltage-Sensitive Ion Channel has Six Transmembrane Regions



The Loop Between Regions 5 and 6 is an Ionic Filter



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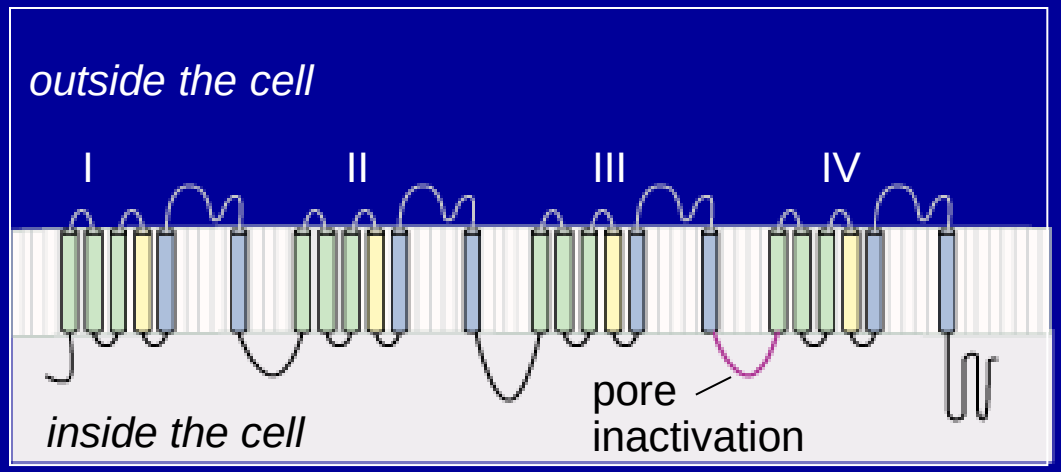
  - Voltage gated (voltage sensitive) sodium channels as an example
- Enzymes

Four Subunits Combine to Form the Alpha Pore Subunit, or Channel, for Sodium of a VSSC (Voltage-Sensitive Sodium Channel)



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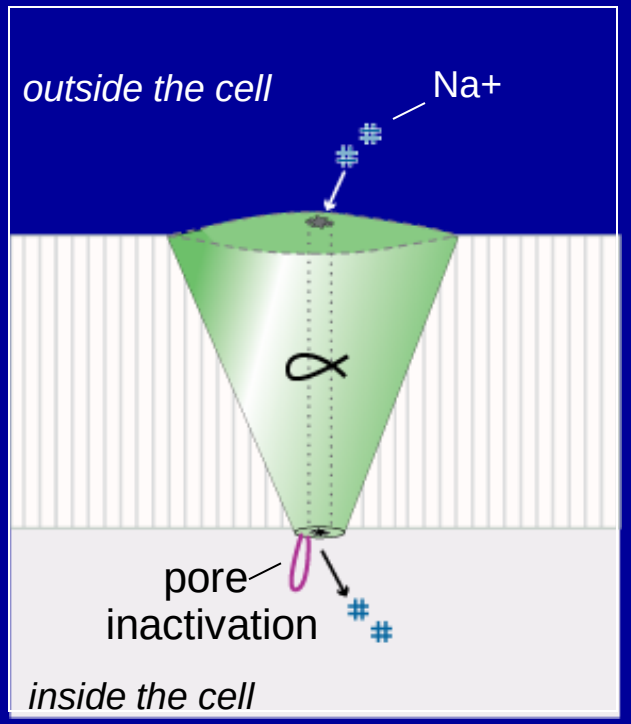
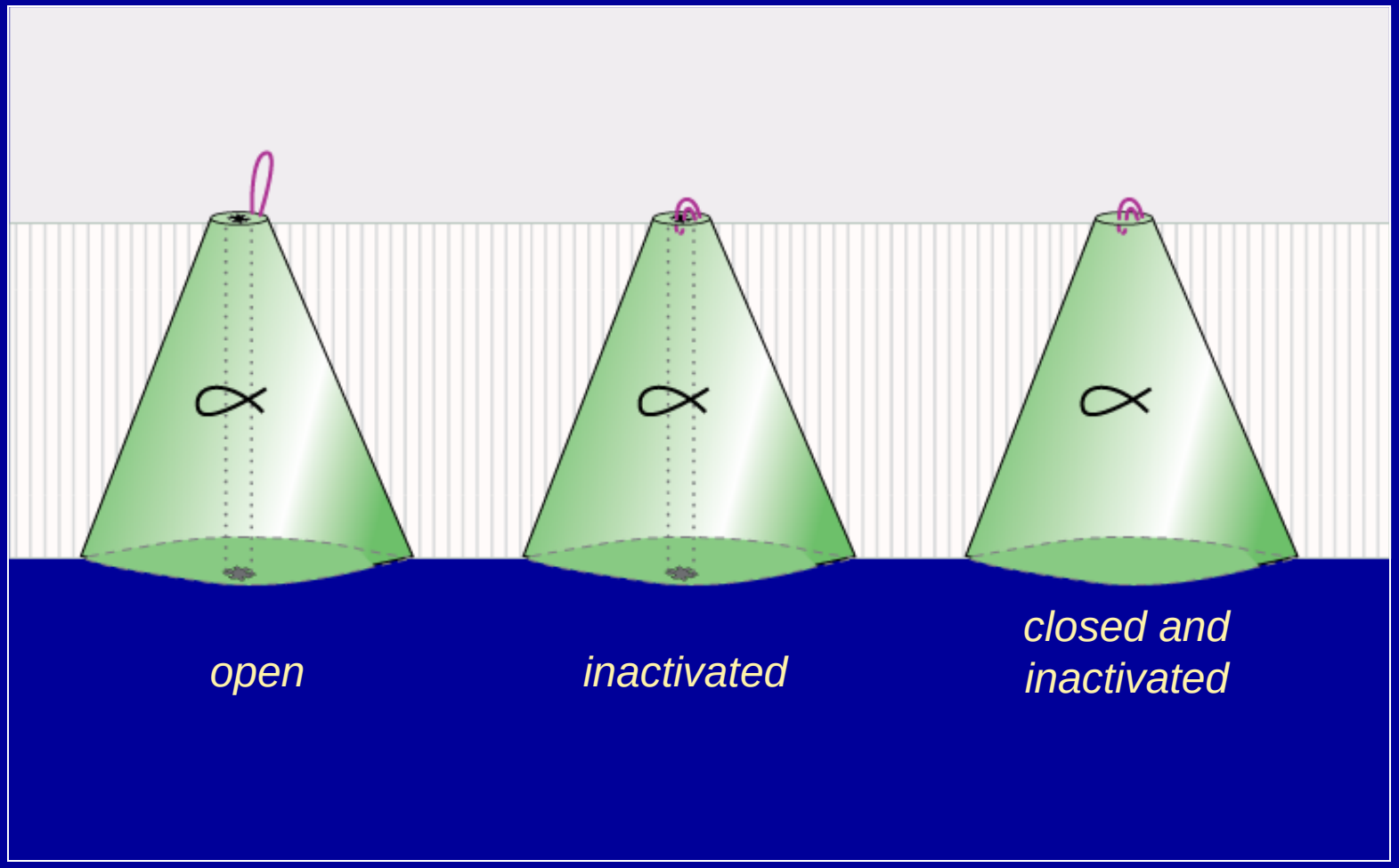
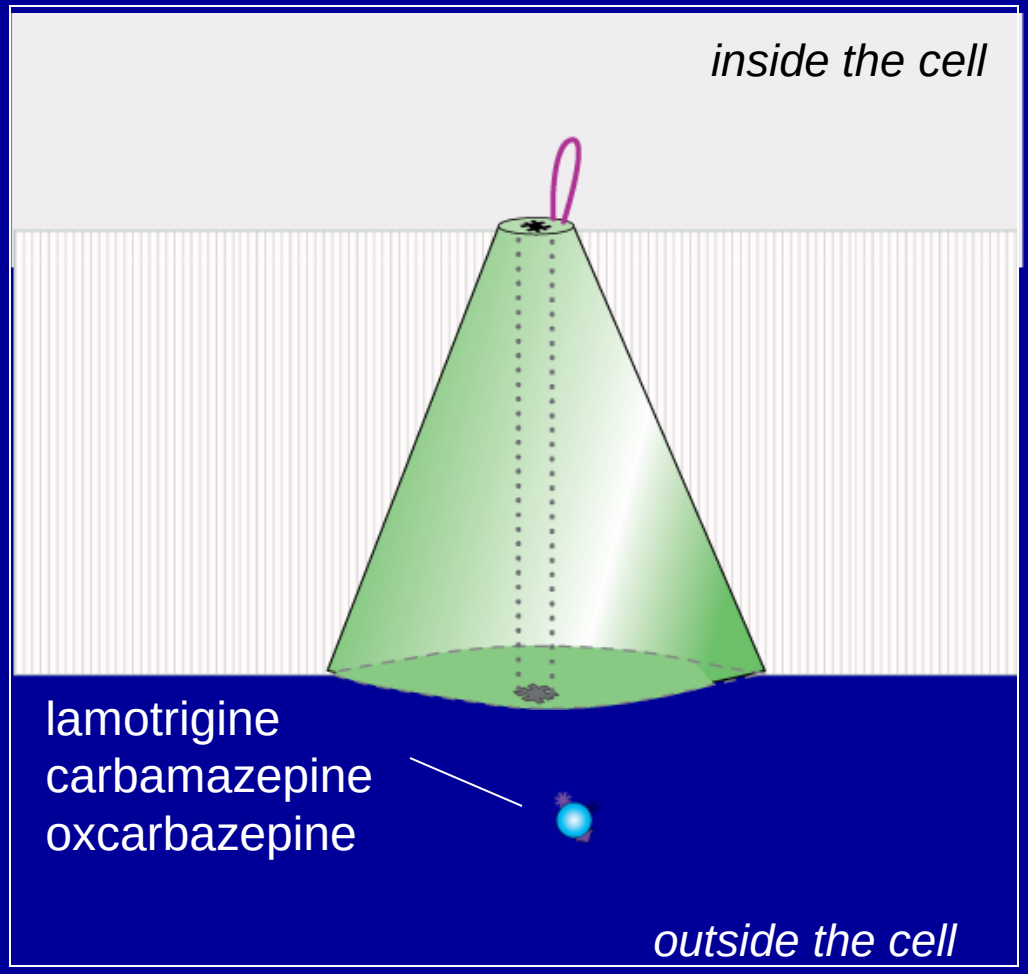


Three States of a Voltage-Sensitive Sodium Channel (VSSC)



Possible Binding Sites for Certain Mood Stabilizers on VSSCs



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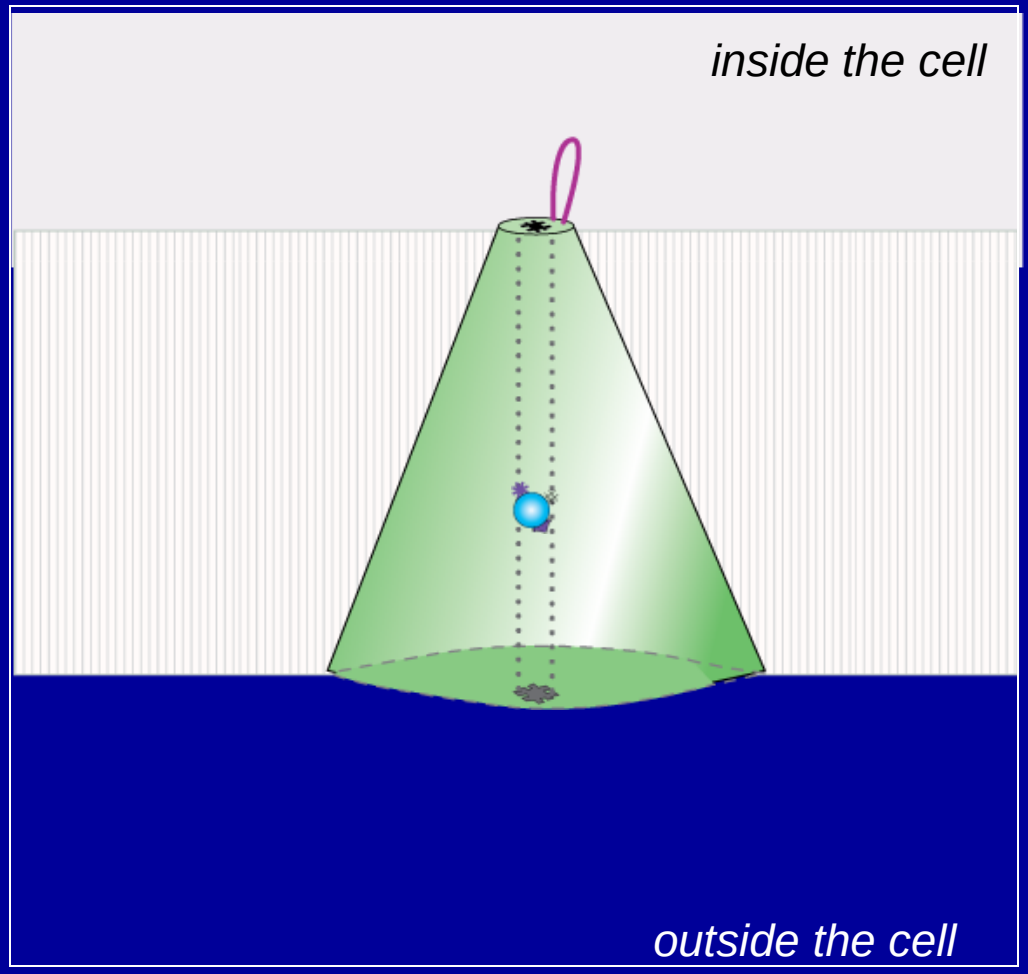

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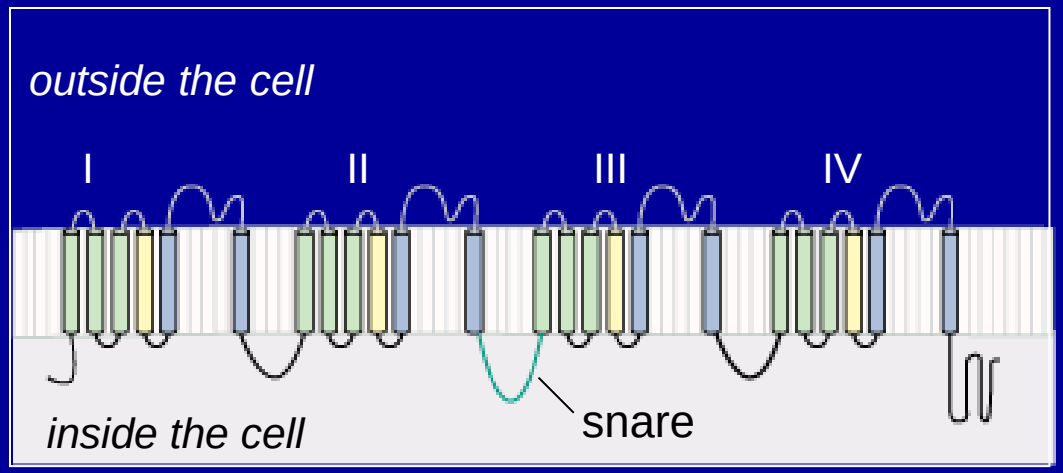
Four Subunits Combine to Form the Alpha1 Pore Subunit, or Channel, for Calcium of a VSCC (Voltage-Sensitive Calcium Channel)



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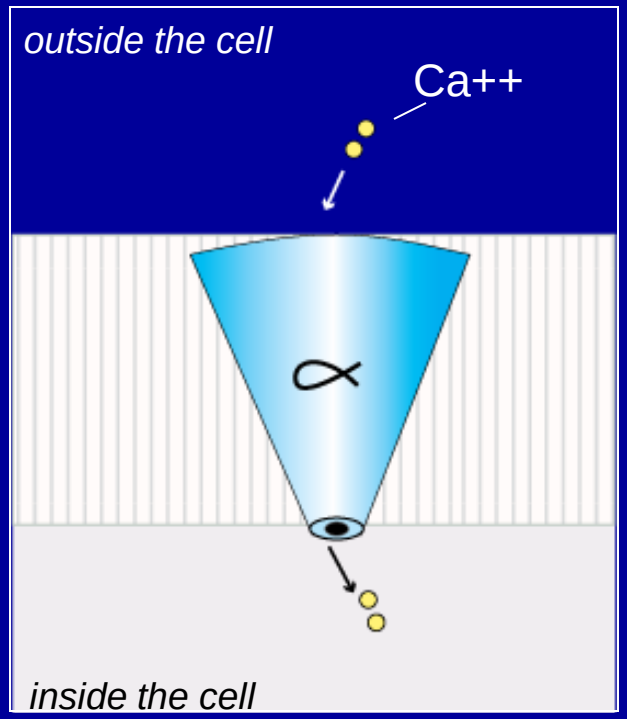
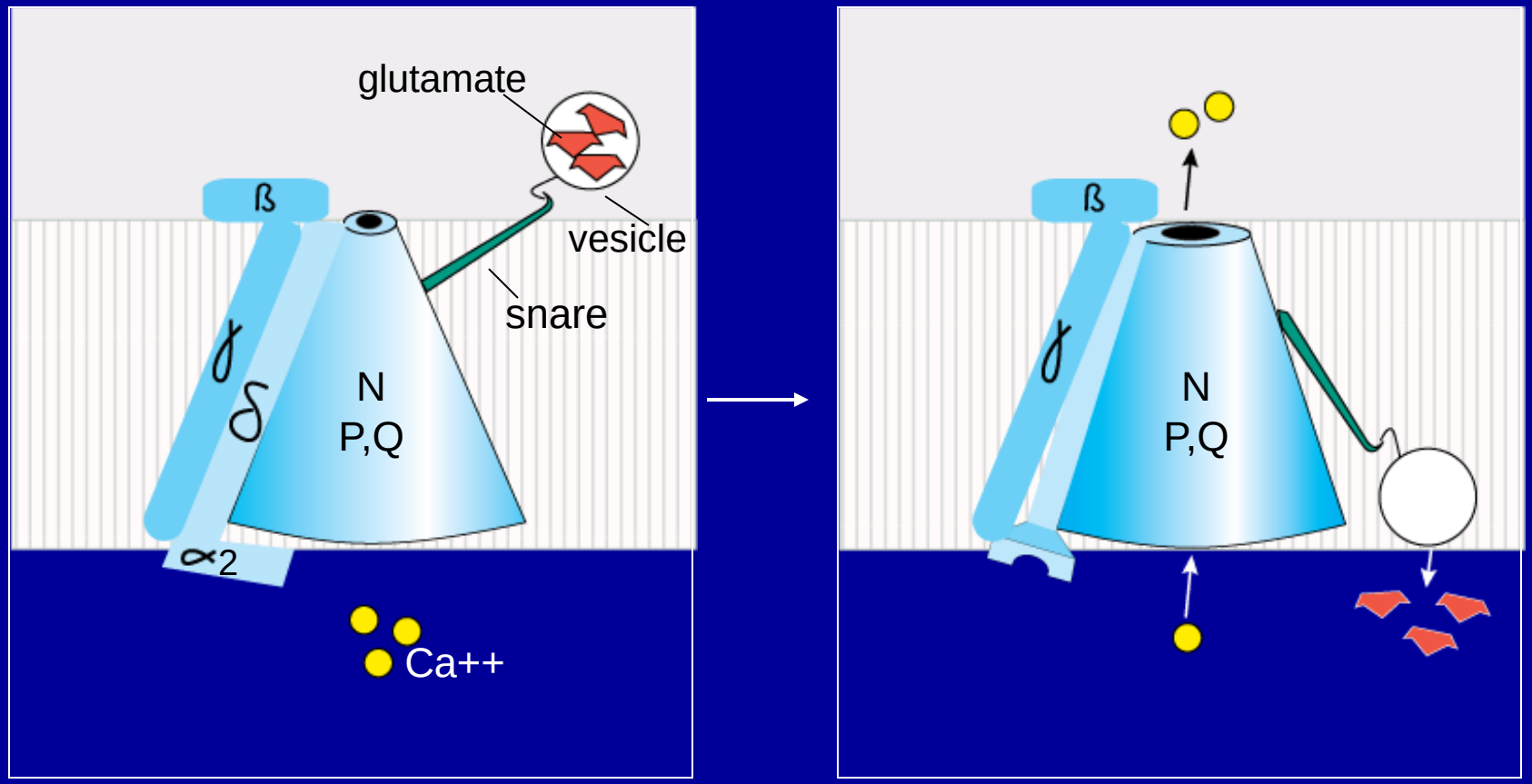
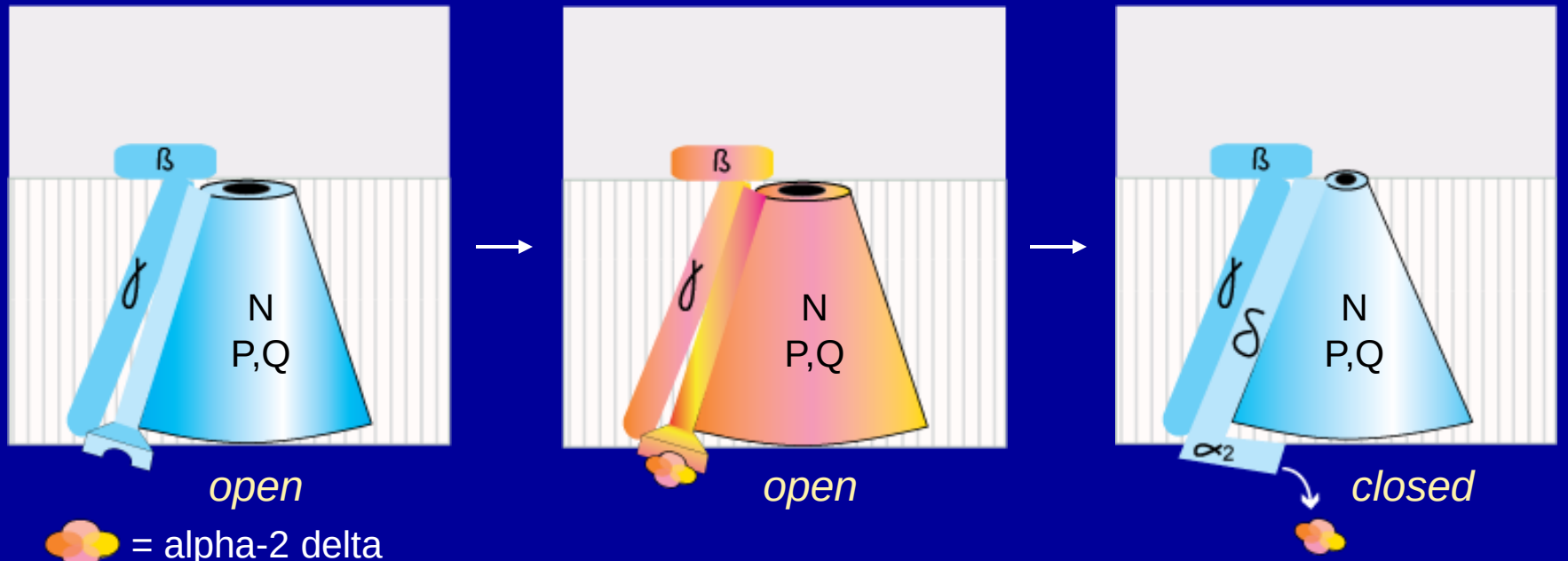


Opening a Presynaptic Voltage-Sensitive N or P/Q Calcium Channel Triggers Neurotransmitter Release



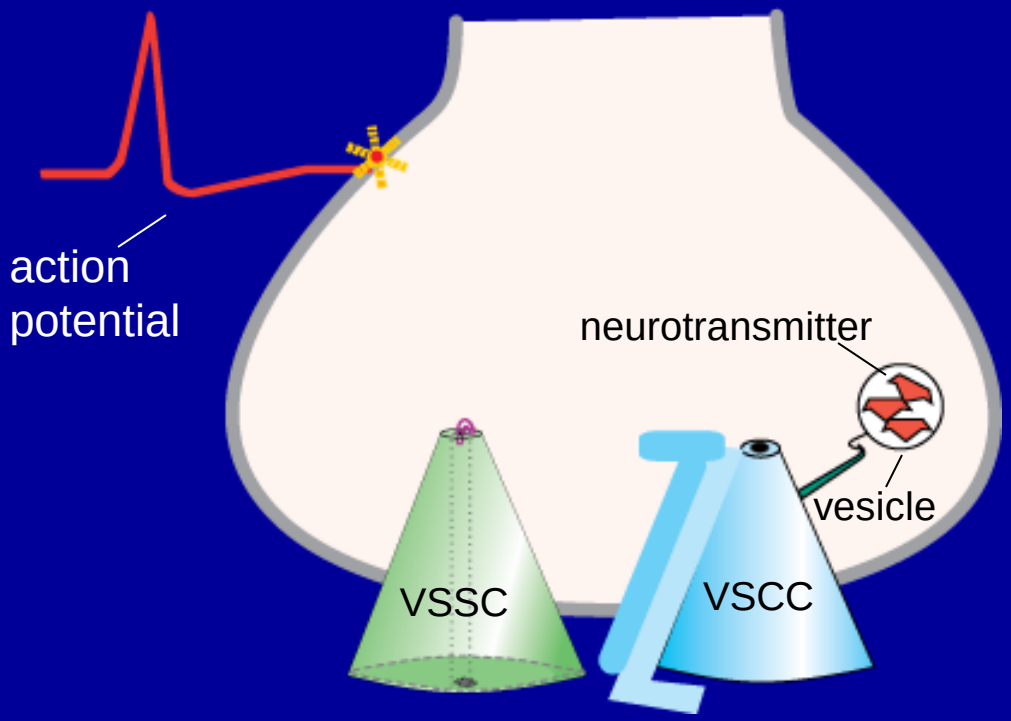
Site of Action of Alpha-2 Delta Ligands as Selective Inhibitors of Presynaptic Voltage-Sensitive N and P/Q Calcium Channels



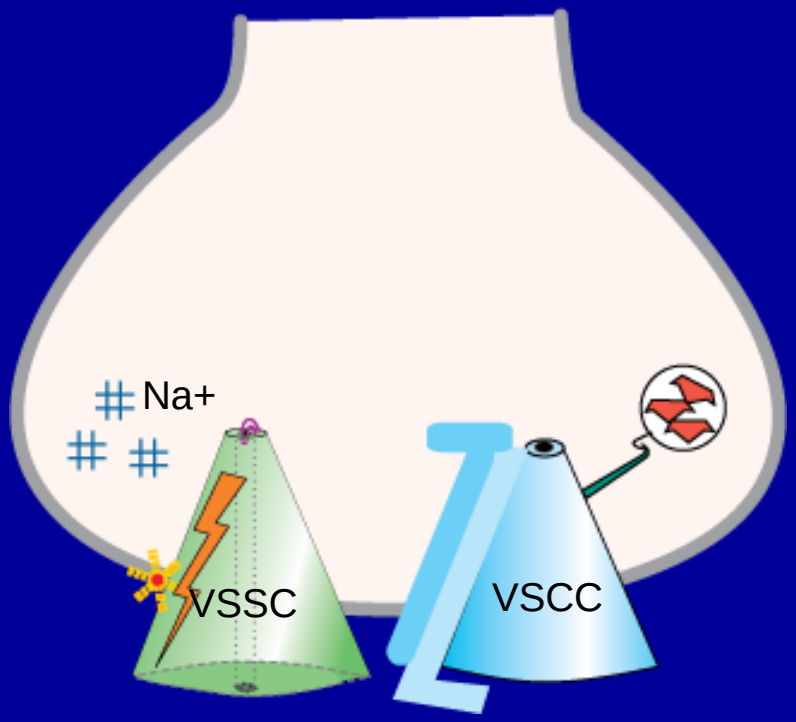
Pre-Synaptic Neurotransmission and Voltage Gated Ion Channels

- Nerve impulse propagation along axonal sodium channels
- Invasion of nerve impulse into presynaptic sodium channels
- Opening of axon terminal sodium channels
- Causes presynaptic voltage changes detected by calcium channels in the axon terminal
- Opens calcium channels linked to synaptic vesicles
- Triggers excitation secretion coupling with release of neurotransmitter into the synapse

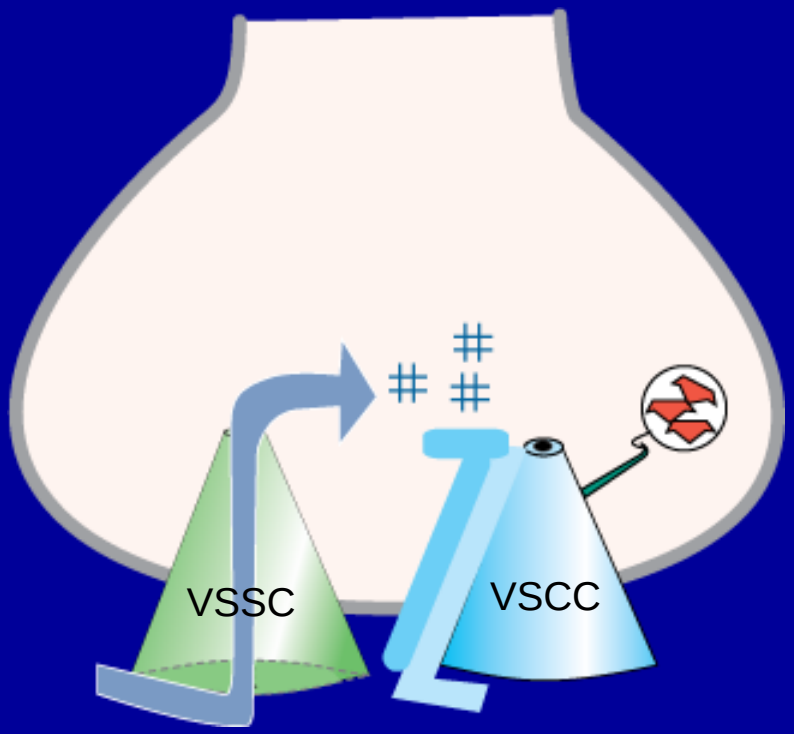
Nerve impulse propagation along axonal sodium channels



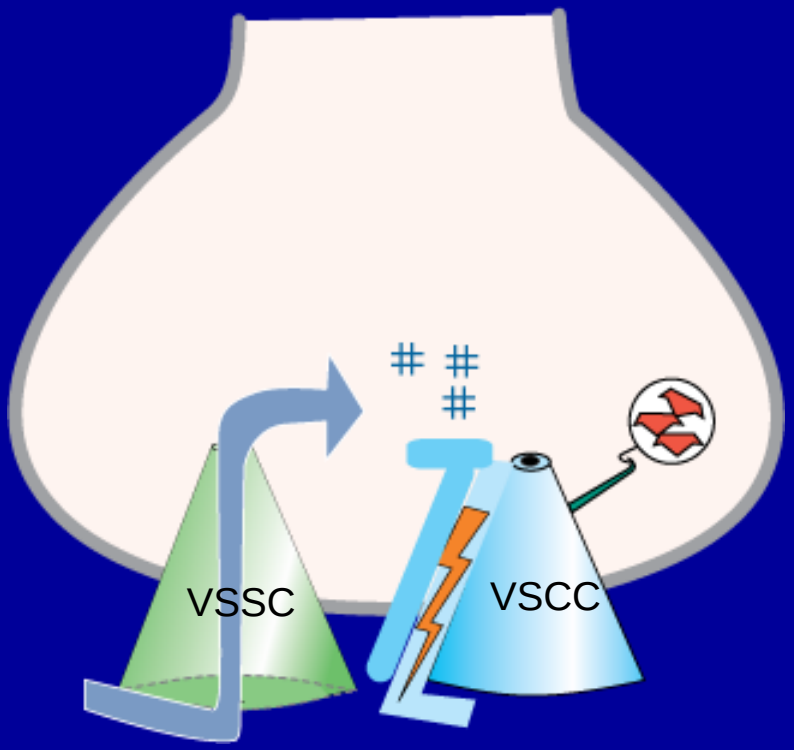
Invasion of nerve impulse into presynaptic sodium channels



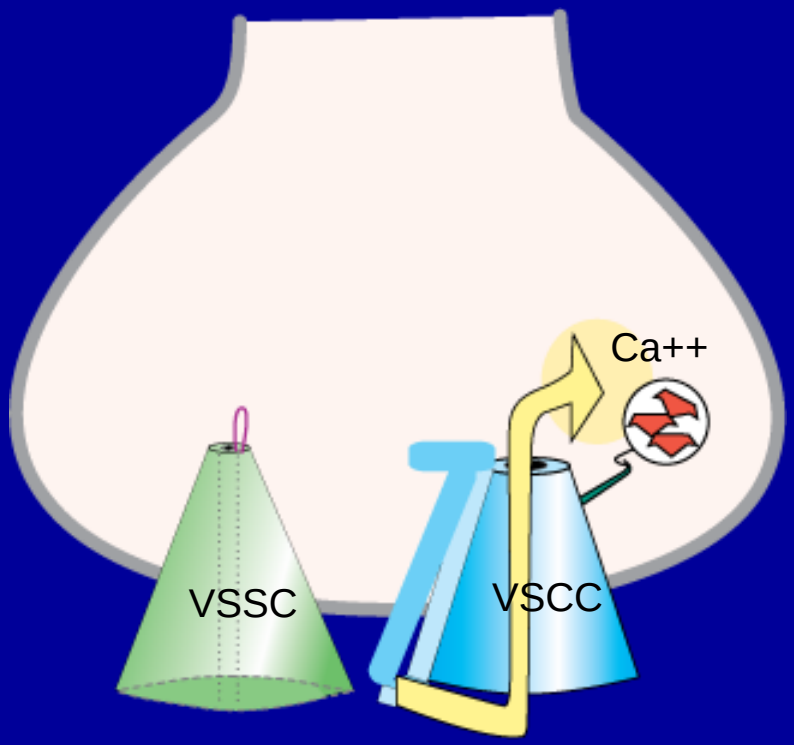
Opening of axon terminal sodium channels



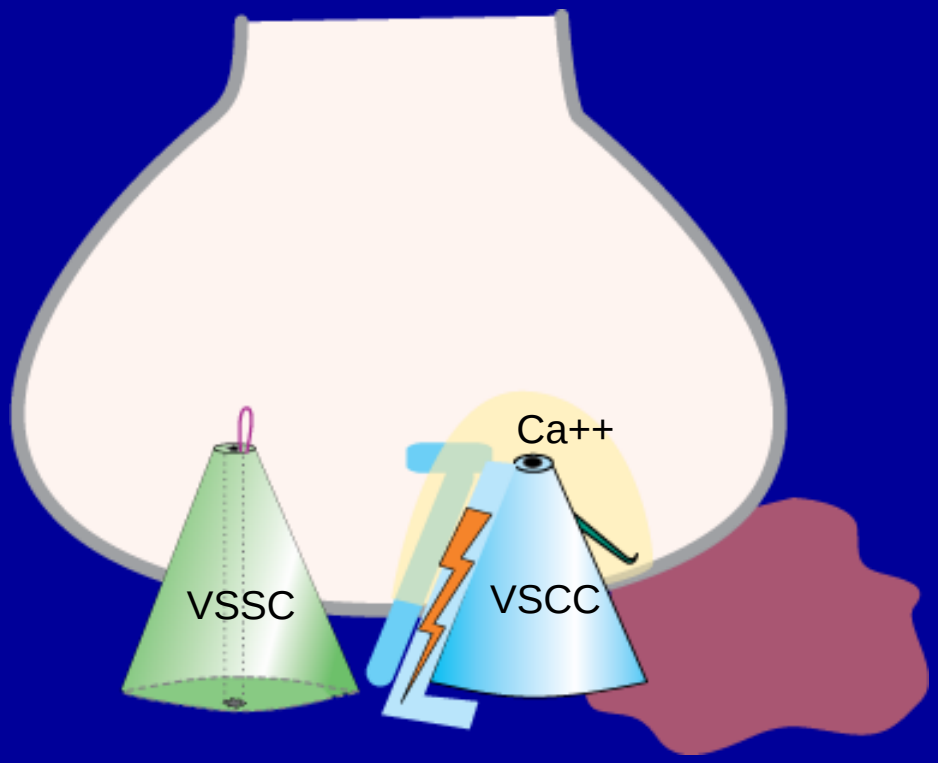
Causes presynaptic voltage changes detected by calcium channels in the axon terminal



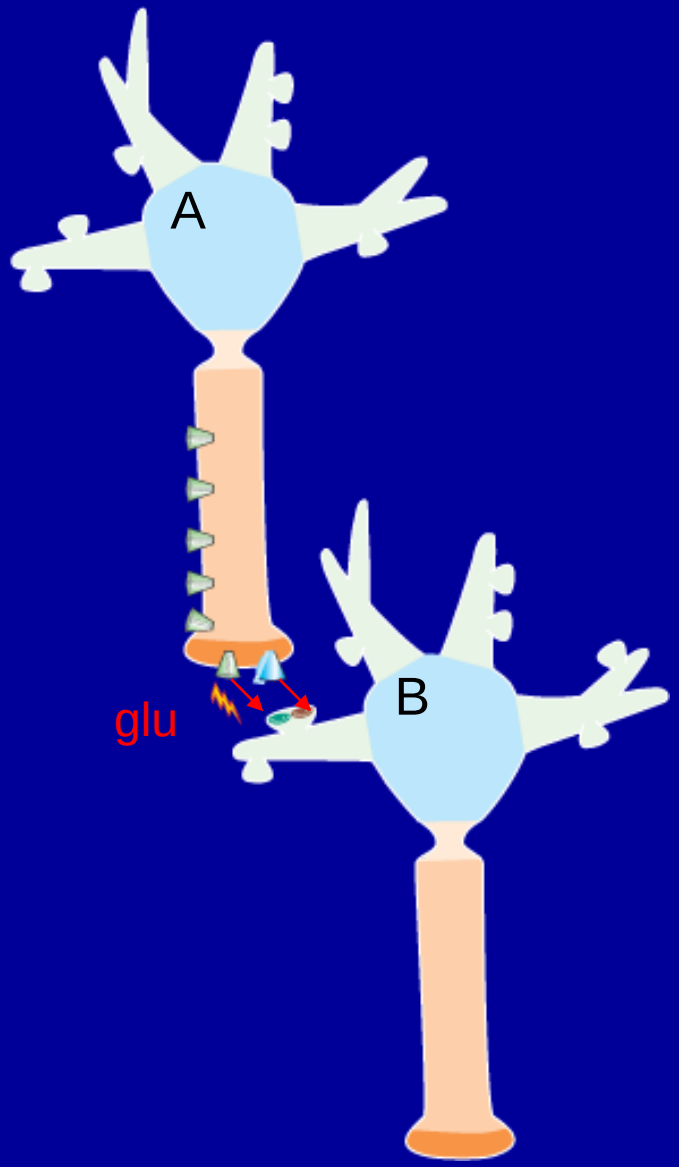
Opens calcium channels linked to synaptic vesicles



Triggers excitation secretion coupling with release of neurotransmitter into the synapse



Signal Transduction of Glutamate into Excitatory Neurotransmission and Signal Propagation in the Postsynaptic Neuron

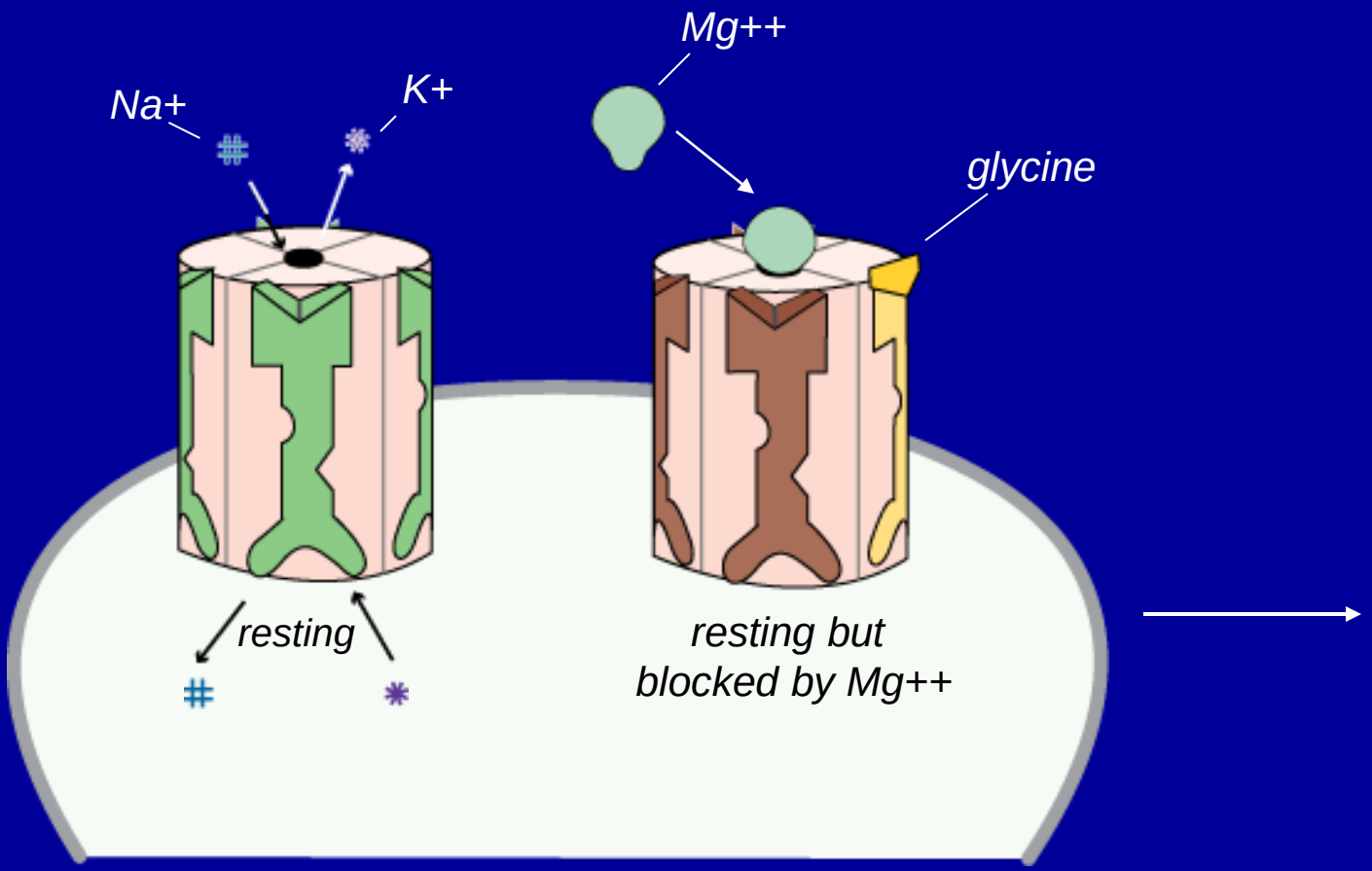


signal transduction

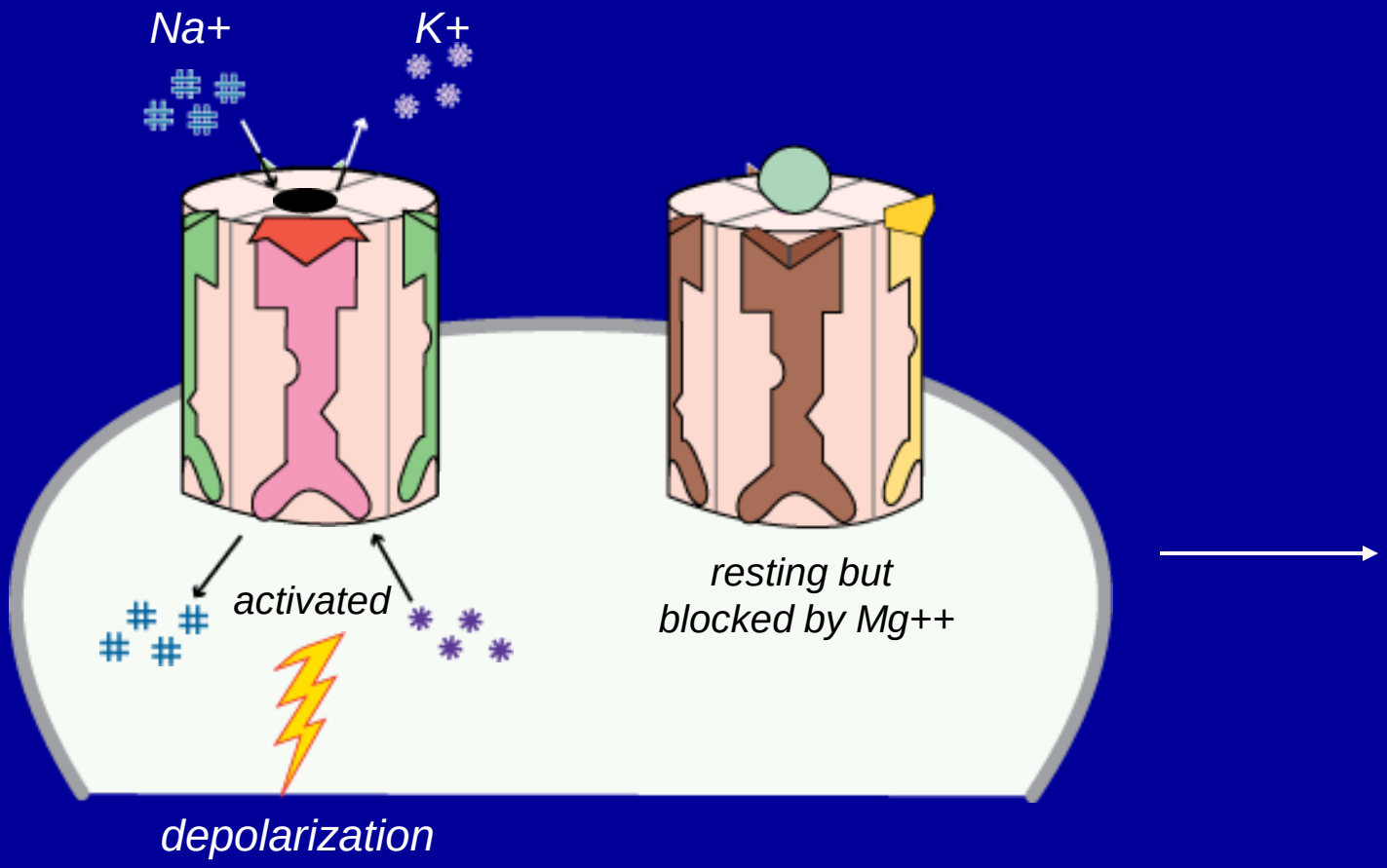
Post-Synaptic Neurotransmission and Ligand Gated Ion Channels (Glutamate)

- Resting state prior to arrival of glutamate
- Glutamate activates AMPA receptors and post synaptic neuron is depolarized
- Simultaneous depolarization, glutamate and glycine actions activates NMDA receptors and long term potentiation postsynaptically

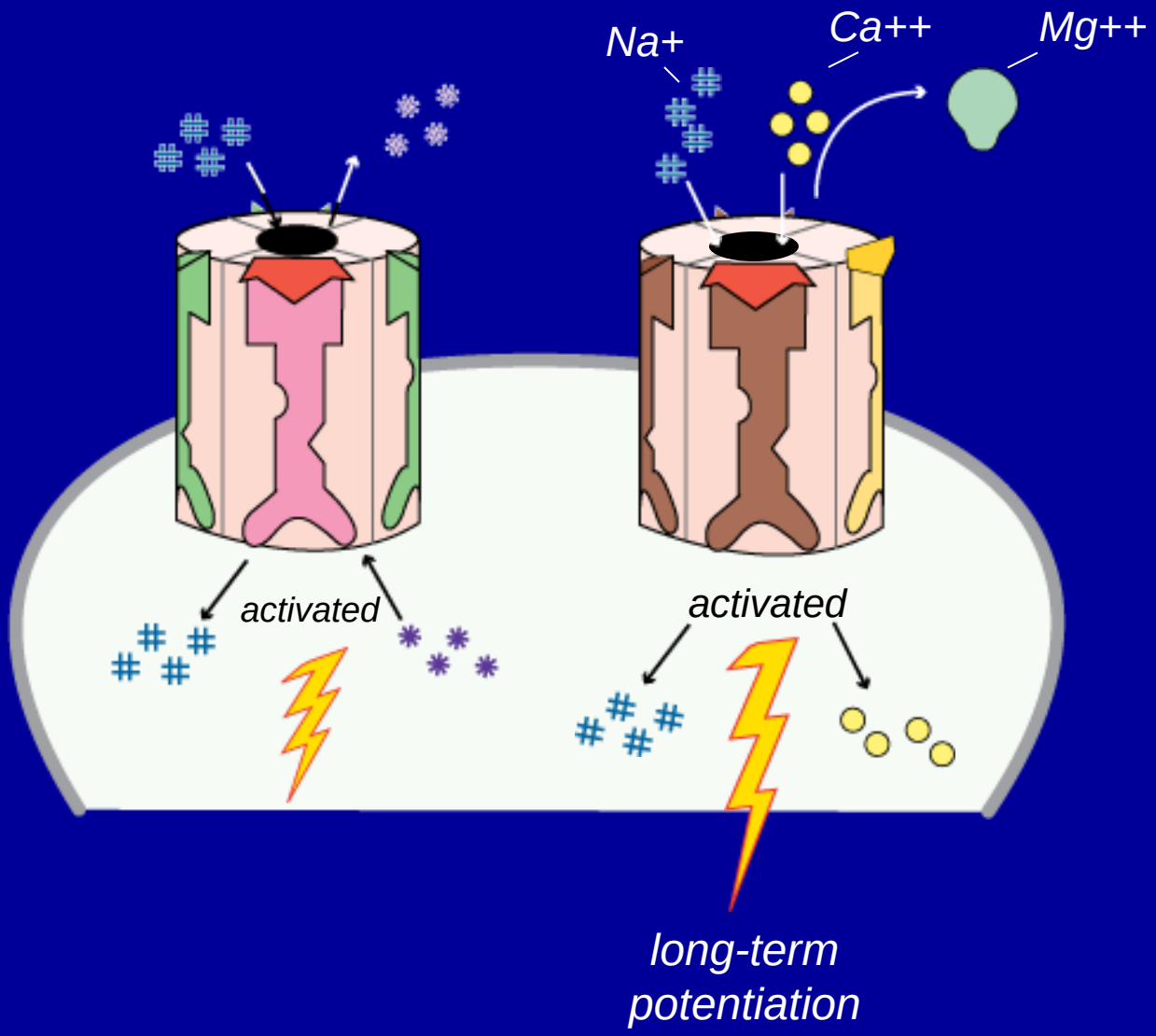
Resting state prior to arrival of glutamate
AMPA receptor (left) and NMDA receptor (right)



Glutamate activates AMPA receptors and post synaptic neuron is depolarized



Simultaneous depolarization, glutamate and glycine actions activates NMDA receptors and long term potentiation postsynaptically



5-43C

Summary

- Principles of chemical neurotransmission include classical synaptic, retrograde and volume nonsynaptic
- Major targets of psychopharmacologic drugs include transporters, G-protein systems as targets of psychotropic drugs
- Neurotransmission involves the cooperation of presynaptic and post synaptic receptors and ion channels