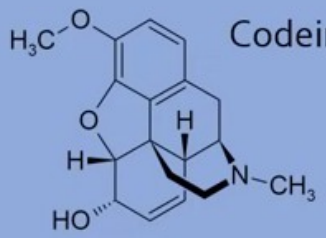
Opioid Functions

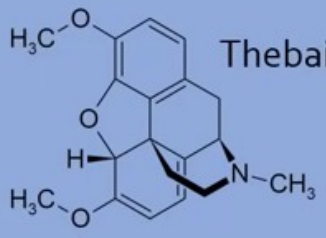
Opioid Drugs

Opiates
(Isolated from the Opium Poppy)

Morphine

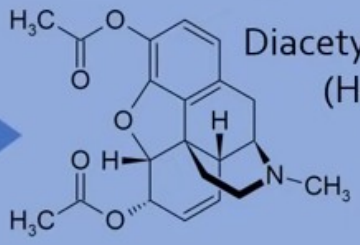


Codeine

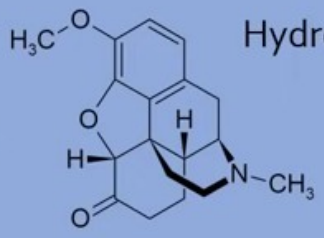


Thebaine

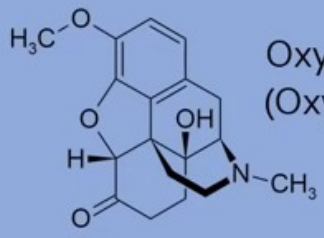
Semi-Synthetic
(Chemically Modified Opiates)



Diacetylmorphine
(Heroin)

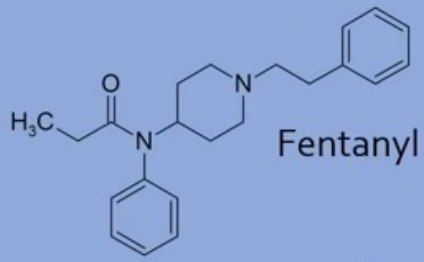


Hydrocodone

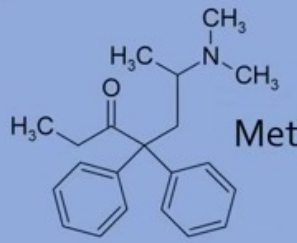


Oxycodone
(Oxycontin)

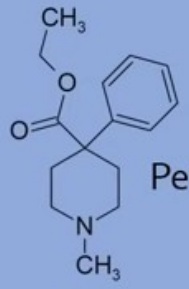
Synthetic
(Chemically Formulated)



Fentanyl



Methadone



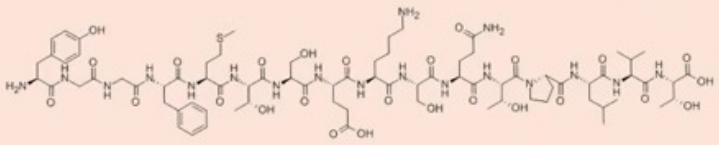
Pethidine/Meperidine
(Demerol)

Endogenous Opioids

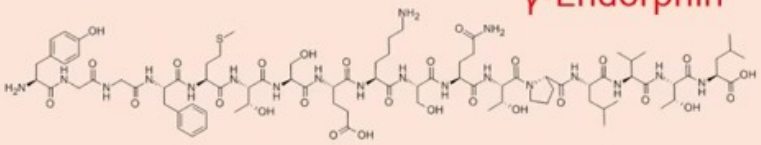
Produced naturally by the body

Endorphins

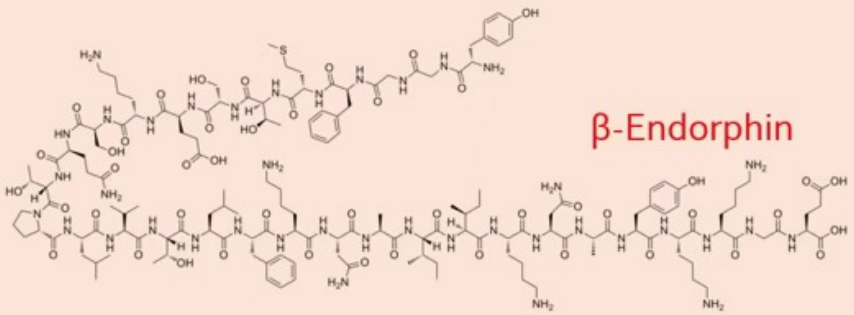
α-Endorphin



γ-Endorphin

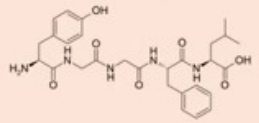


β-Endorphin

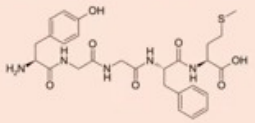


Enkephalins

Leu-Enkephalin

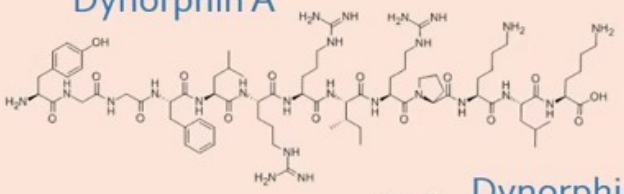


Met-Enkephalin

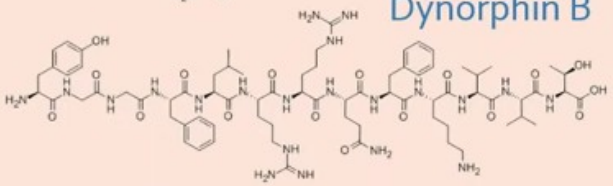


Dynorphins

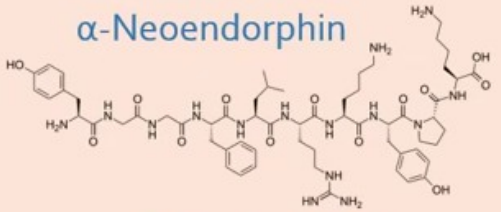
Dynorphin A



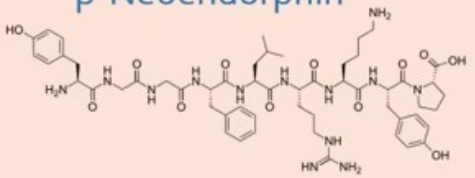
Dynorphin B



α-Neoendorphin



β-Neoendorphin

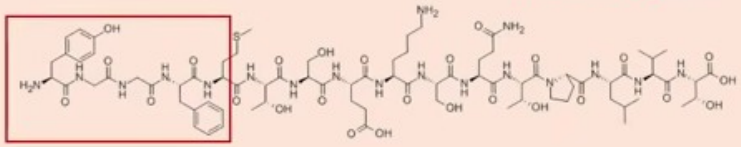


Endogenous Opioids

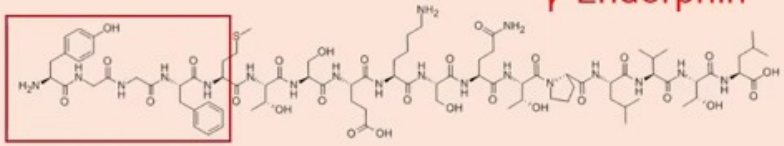
Produced naturally by the body

Endorphins

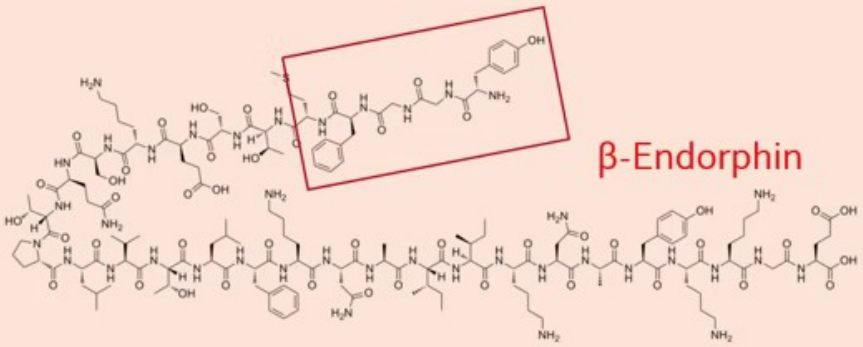
α-Endorphin



γ-Endorphin

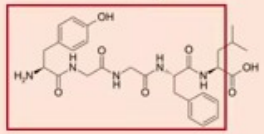


β-Endorphin

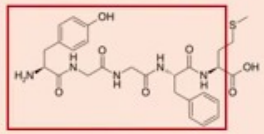


Enkephalins

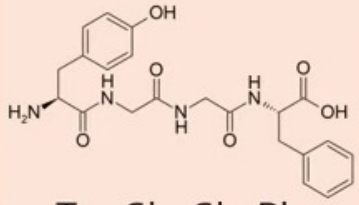
Leu-Enkephalin



Met-Enkephalin



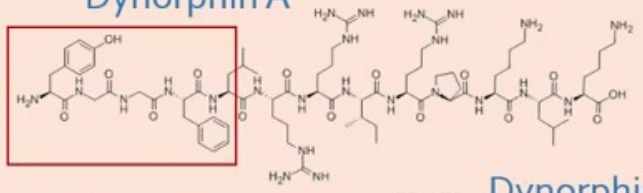
All have the



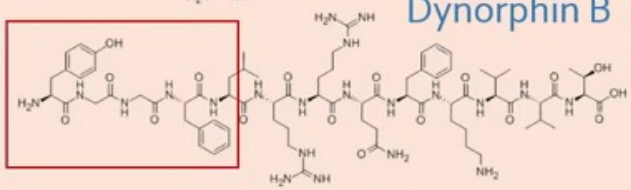
Tyr-Gly-Gly-Phe motif

Dynorphins

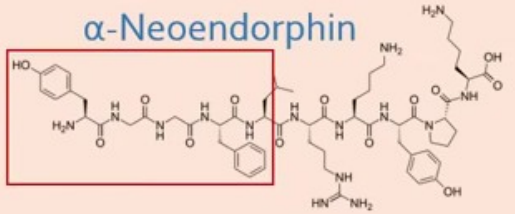
Dynorphin A



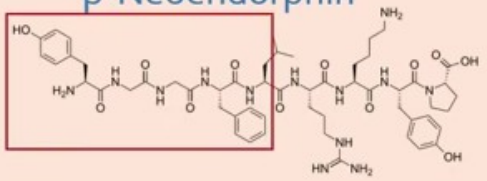
Dynorphin B

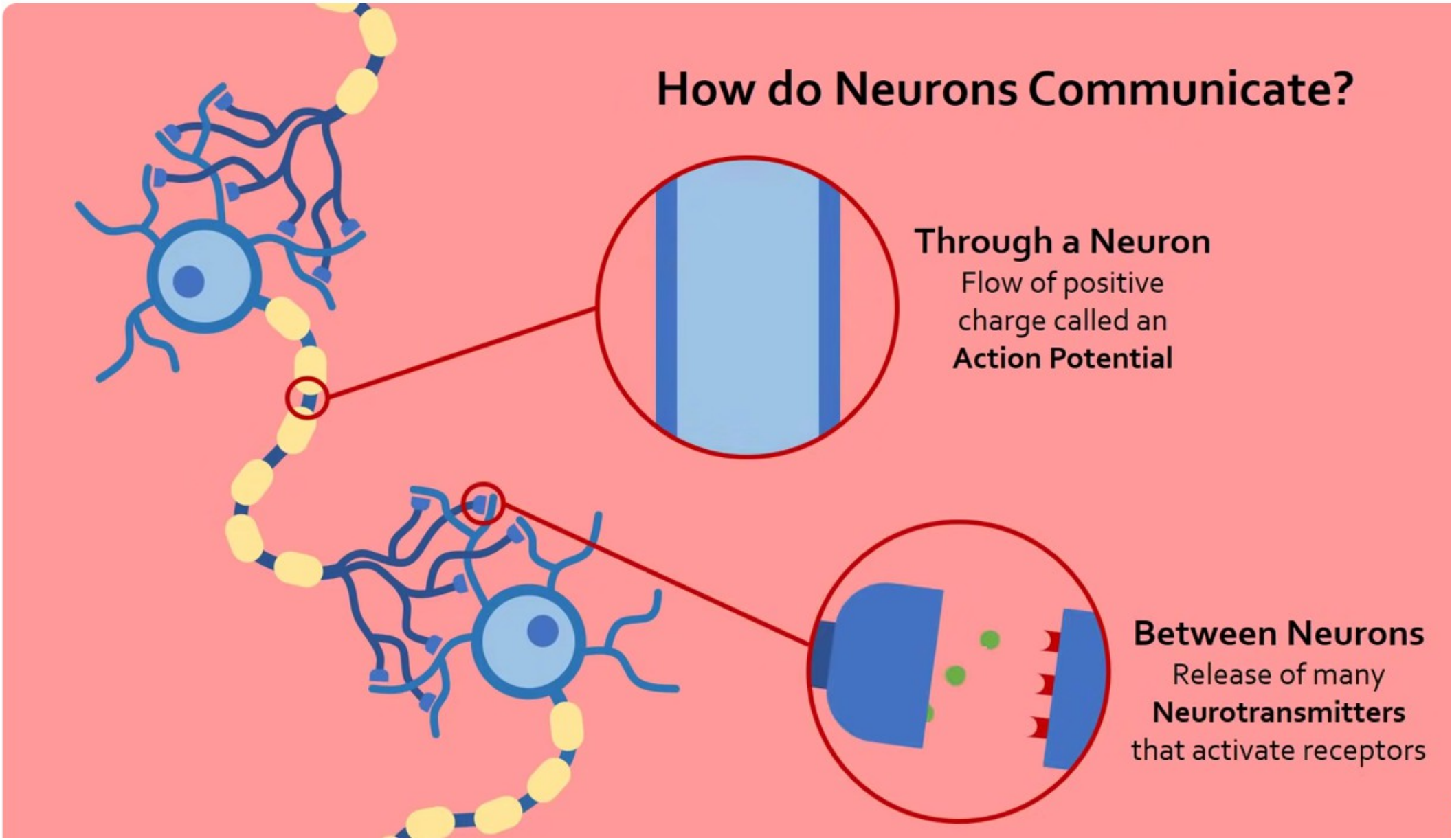


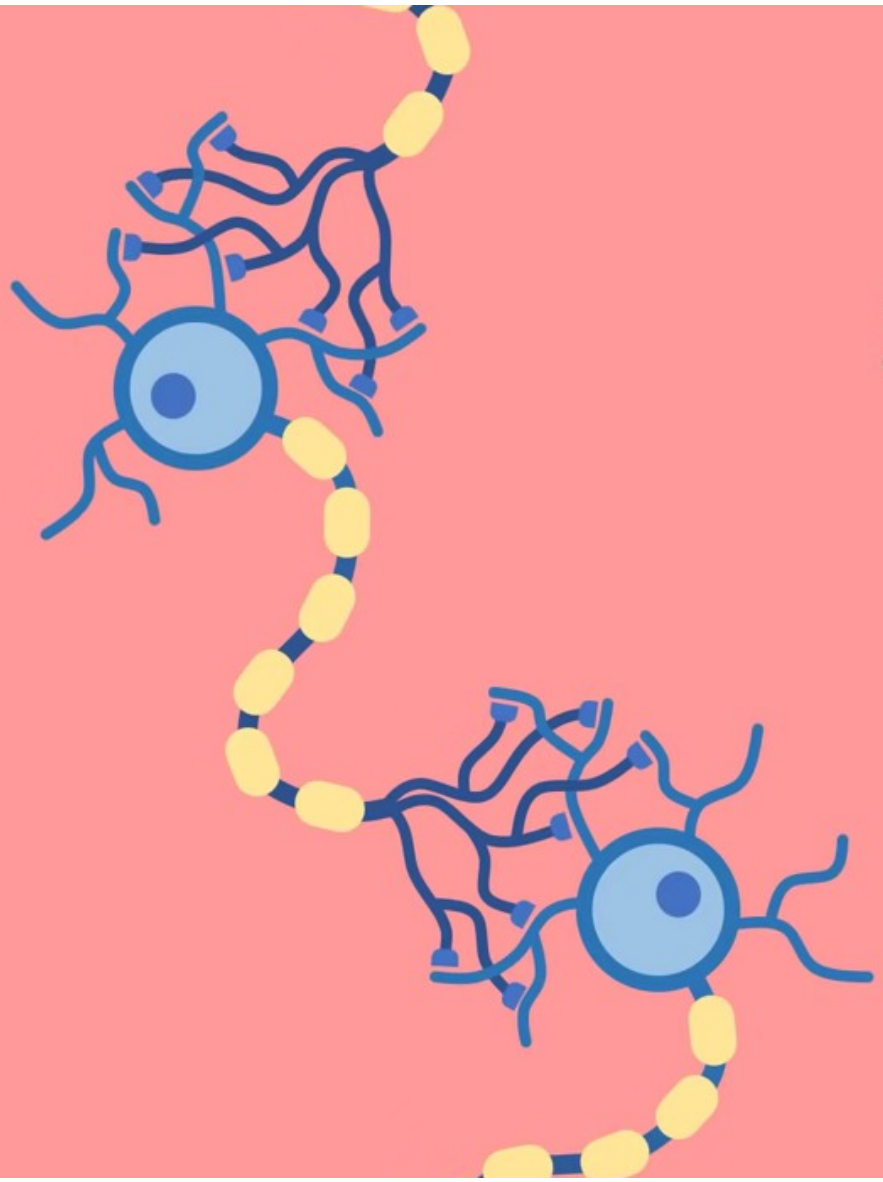
α-Neoendorphin



β-Neoendorphin




How do Neurons Communicate?
Through a Neuron
Flow of positive charge called an Action Potential
Between Neurons
Release of many Neurotransmitters that activate receptors



How do neurons communicate?

Presynaptic neuron releases **excitatory** neurotransmitter (e.g. Glutamate)

↓

Depolarization in postsynaptic neuron (**Increase** positive charge)

↓

Action potential **forms** in postsynaptic neuron

↓

Signal continues

Presynaptic neuron releases **inhibitory** neurotransmitter (e.g. GABA)

↓

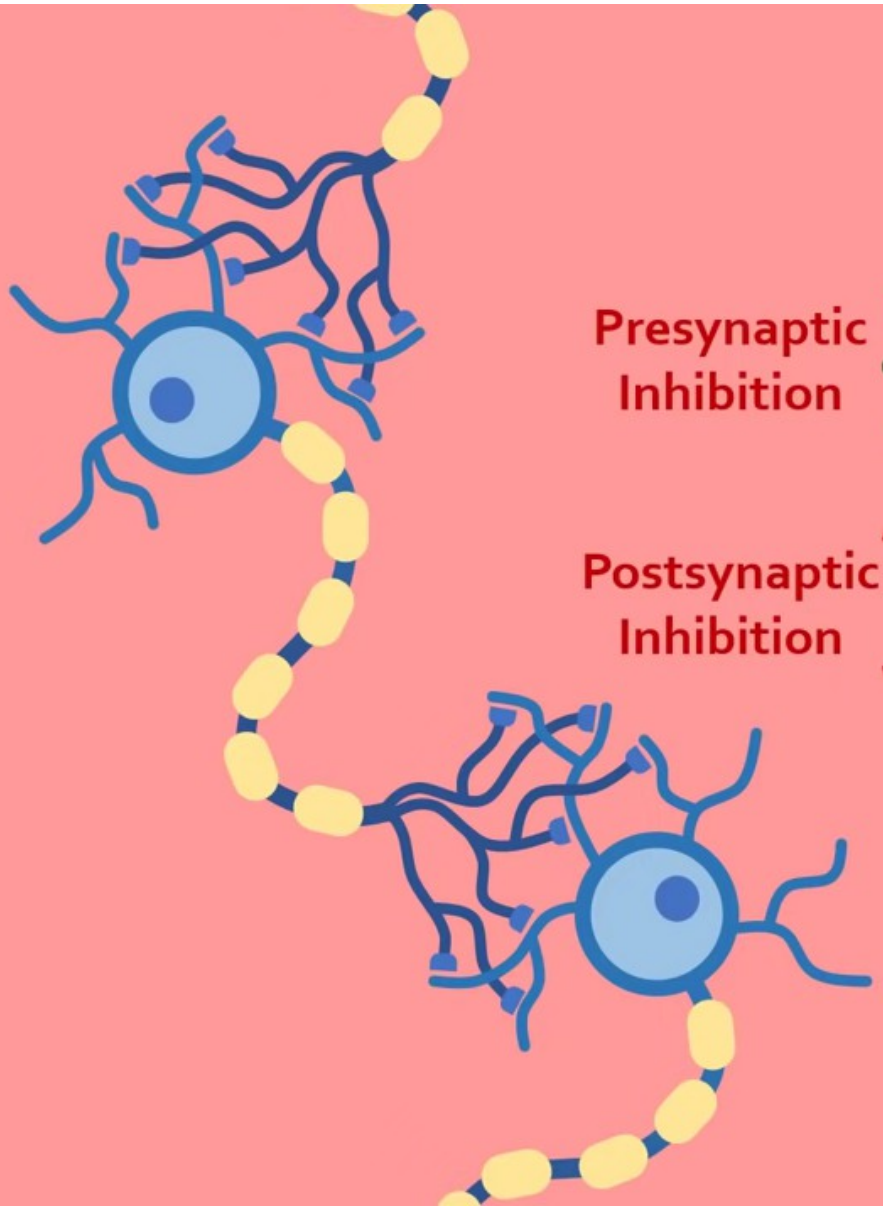
Hyperpolarization in postsynaptic neuron (**Decrease** positive charge)

↓

Action potential **does not form** in postsynaptic neuron

↓

Signal stops



How do neurons communicate?

Presynaptic Inhibition

~~Presynaptic neuron releases excitatory neurotransmitter (e.g. Glutamate)~~

Presynaptic neuron releases **inhibitory** neurotransmitter (e.g. GABA)

↓

Postsynaptic Inhibition

~~**Depolarization** in postsynaptic neuron (**Increase** positive charge)~~

Hyperpolarization in postsynaptic neuron (**Decrease** positive charge)

↓

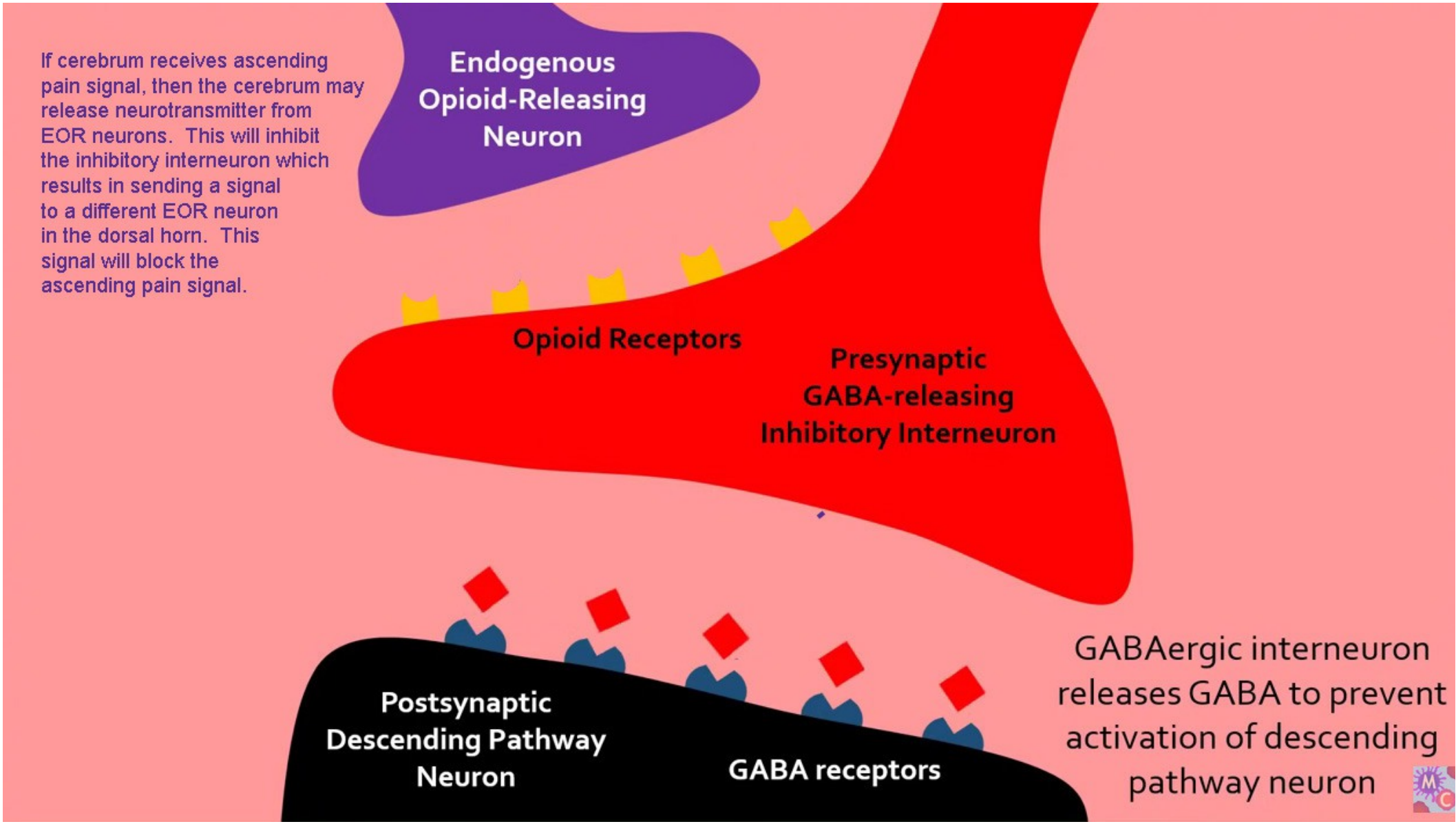
Action potential **forms** in postsynaptic neuron

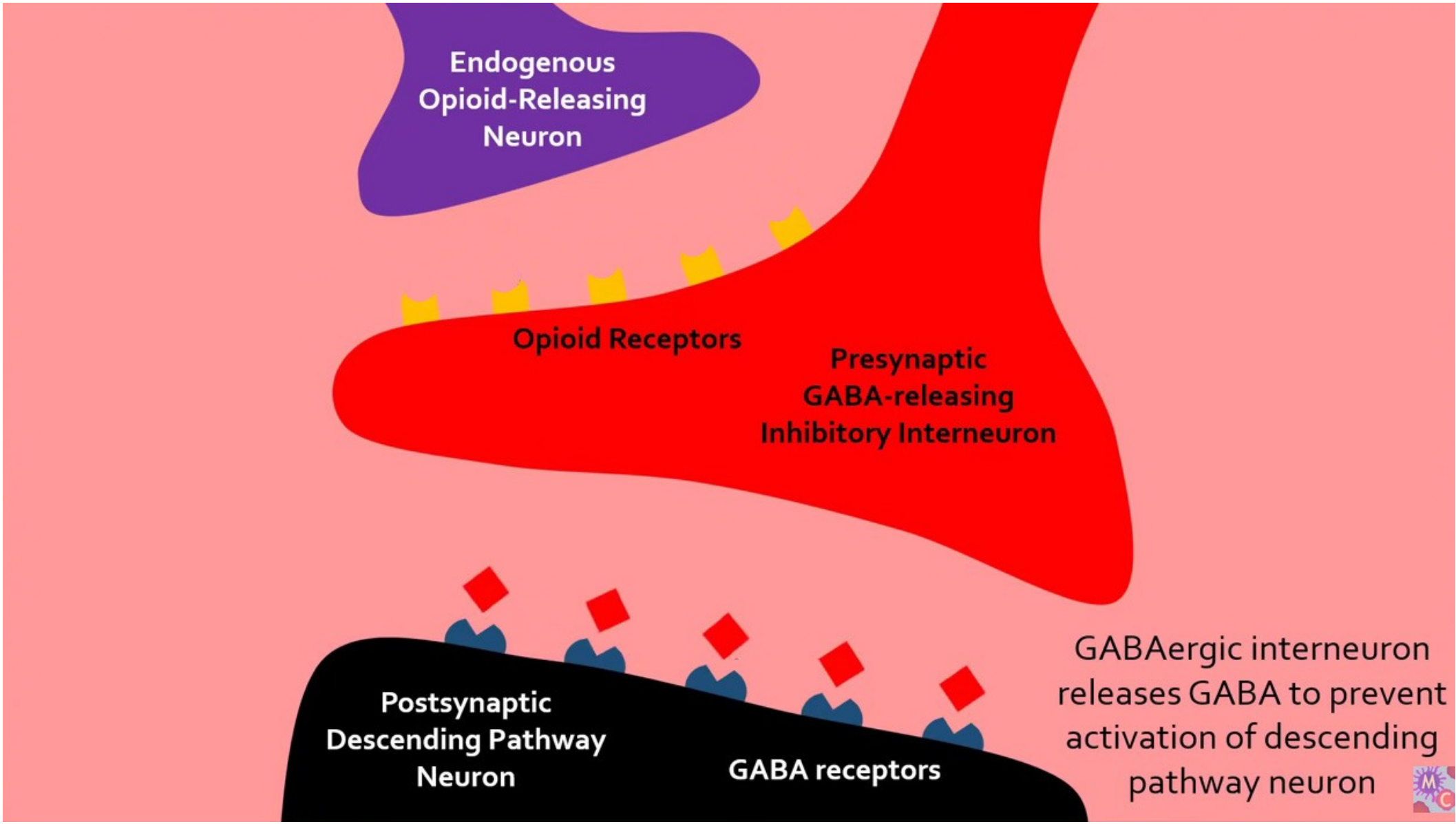
Action potential **does not form** in postsynaptic neuron

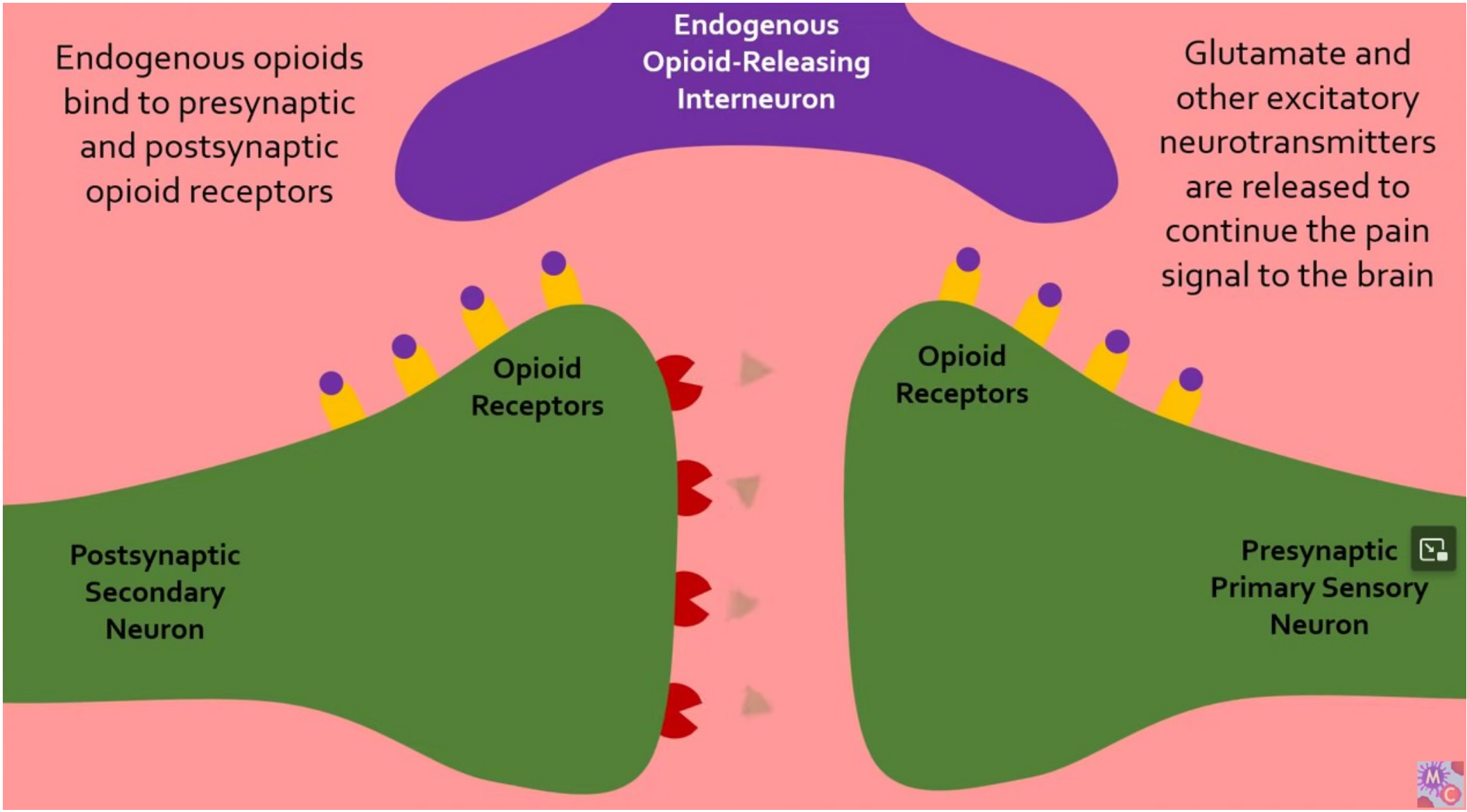
↓

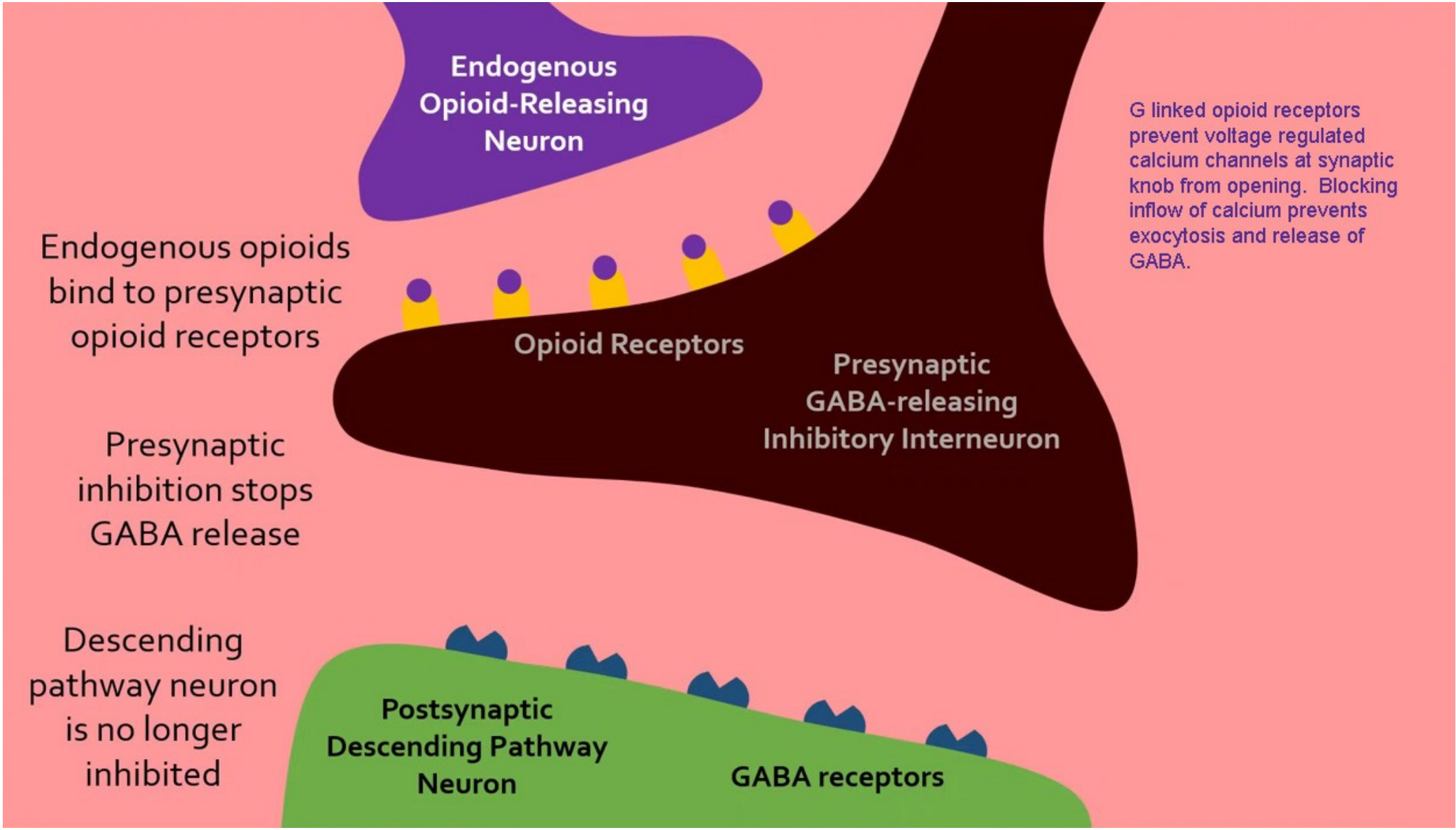
Signal continues

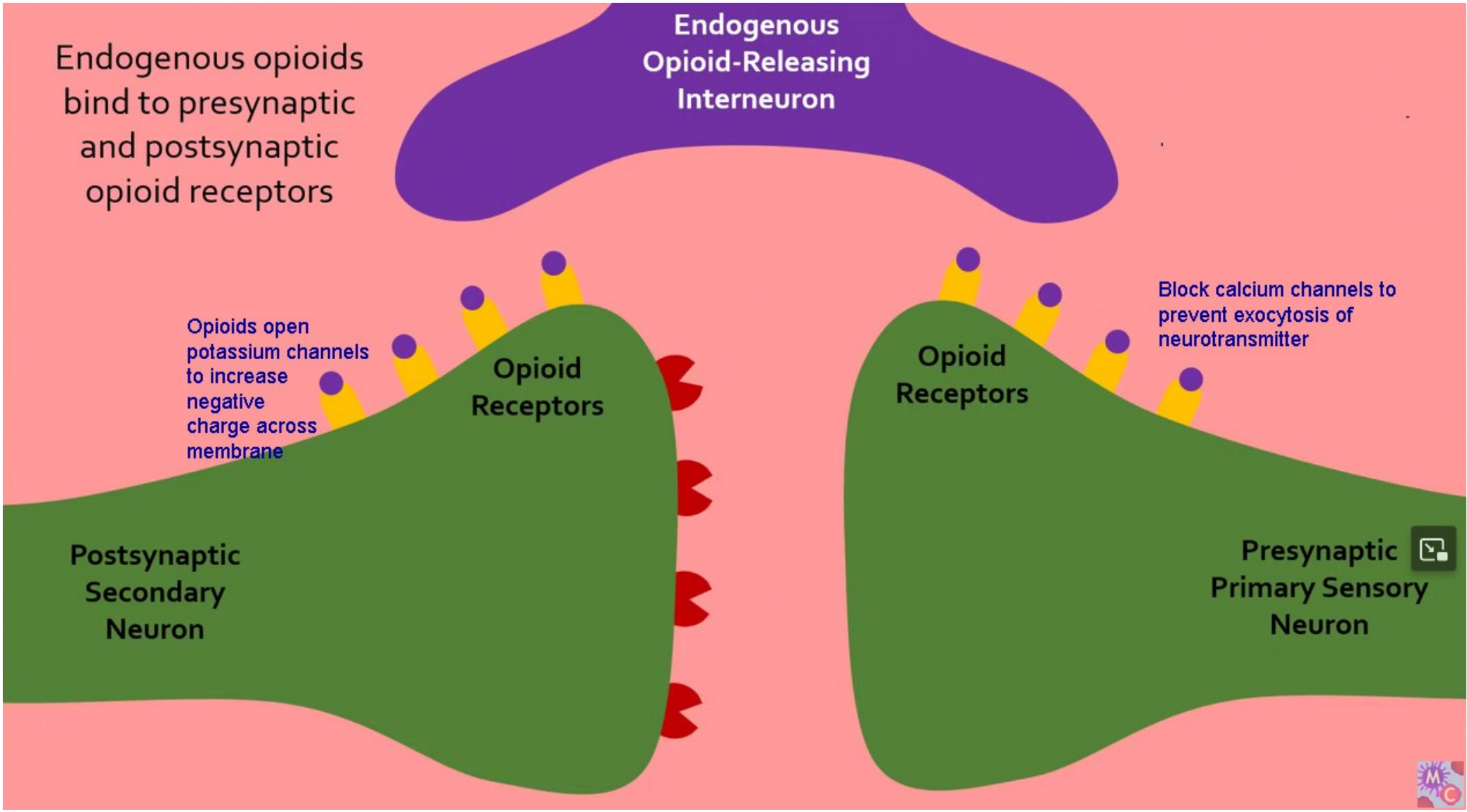
Signal stops


If cerebrum receives ascending pain signal, then the cerebrum may release neurotransmitter from EOR neurons. This will inhibit the inhibitory interneuron which results in sending a signal to a different EOR neuron in the dorsal horn. This signal will block the ascending pain signal.
Endogenous Opioid-Releasing Neuron
Opioid Receptors
Presynaptic GABA-releasing Inhibitory Interneuron
Postsynaptic Descending Pathway Neuron
GABA receptors
GABAergic interneuron releases GABA to prevent activation of descending pathway neuron


Endogenous Opioid-Releasing Neuron
Opioid Receptors
Presynaptic GABA-releasing Inhibitory Interneuron
Postsynaptic Descending Pathway Neuron
GABA receptors
GABAergic interneuron releases GABA to prevent activation of descending pathway neuron


Endogenous opioids bind to presynaptic and postsynaptic opioid receptors
Endogenous Opioid-Releasing Interneuron
Glutamate and other excitatory neurotransmitters are released to continue the pain signal to the brain
Opioid Receptors
Opioid Receptors
Postsynaptic Secondary Neuron
Presynaptic Primary Sensory Neuron

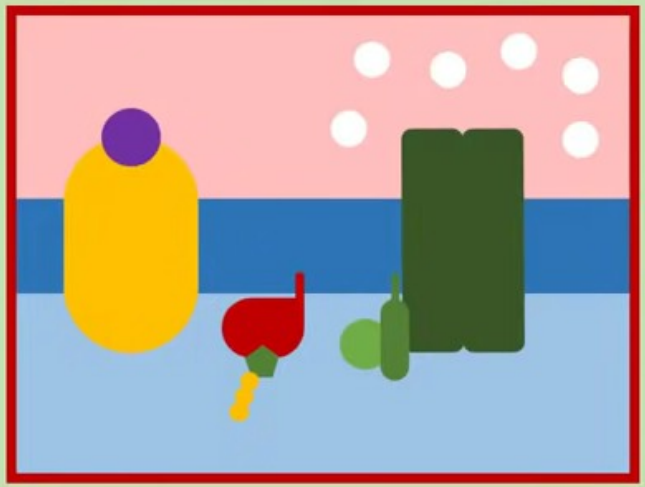

Endogenous Opioid-Releasing Neuron
Endogenous opioids bind to presynaptic opioid receptors
Opioid Receptors
Presynaptic GABA-releasing Inhibitory Interneuron
G linked opioid receptors prevent voltage regulated calcium channels at synaptic knob from opening. Blocking inflow of calcium prevents exocytosis and release of GABA.
Presynaptic inhibition stops GABA release
Descending pathway neuron is no longer inhibited
Postsynaptic Descending Pathway Neuron
GABA receptors


Endogenous opioids bind to presynaptic and postsynaptic opioid receptors
Endogenous Opioid-Releasing Interneuron
Opioids open potassium channels to increase negative charge across membrane
Opioid Receptors
Postsynaptic Secondary Neuron
Block calcium channels to prevent exocytosis of neurotransmitter
Opioid Receptors
Presynaptic Primary Sensory Neuron

Presynaptic Inhibition

Interaction with $G_{\beta\gamma}$ stops voltage-gated calcium channels from opening in the presynaptic neuron

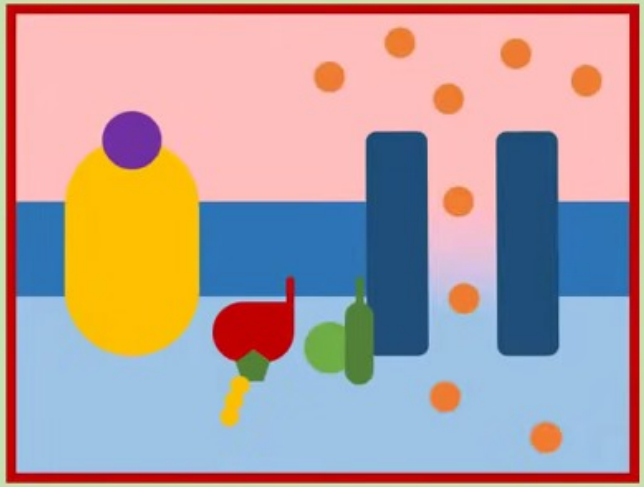
No neurotransmitter released



Postsynaptic Inhibition

Interaction with $G_{\beta\gamma}$ opens KIR3 potassium channels to allow potassium ions to flow out of the postsynaptic neuron

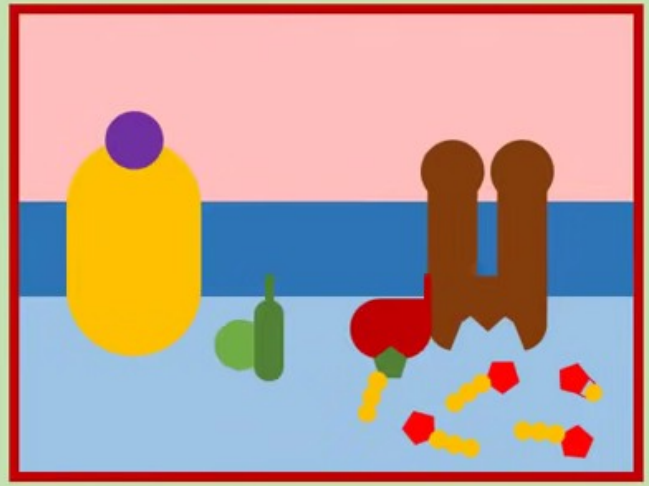
Neuron does not depolarize

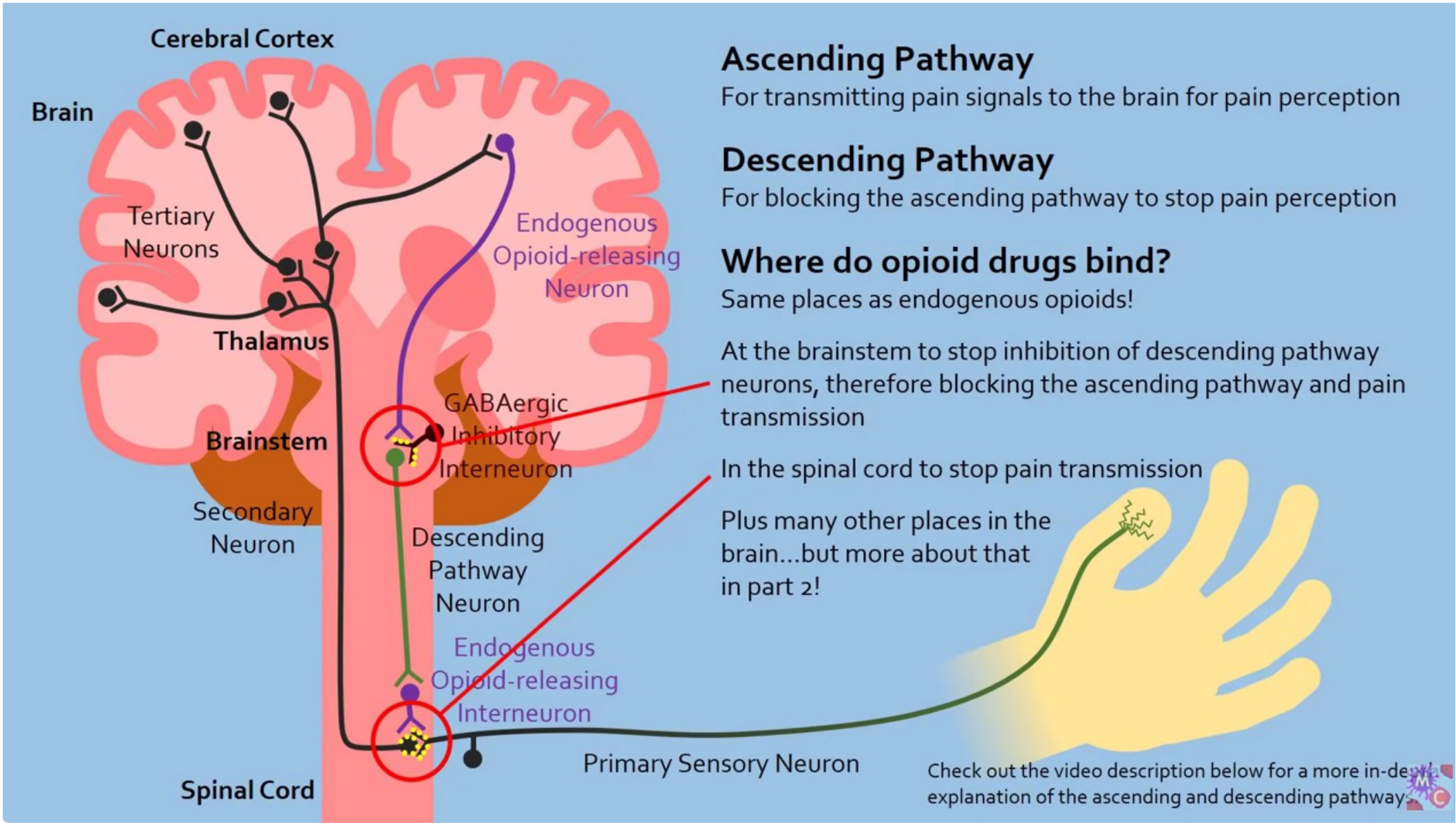


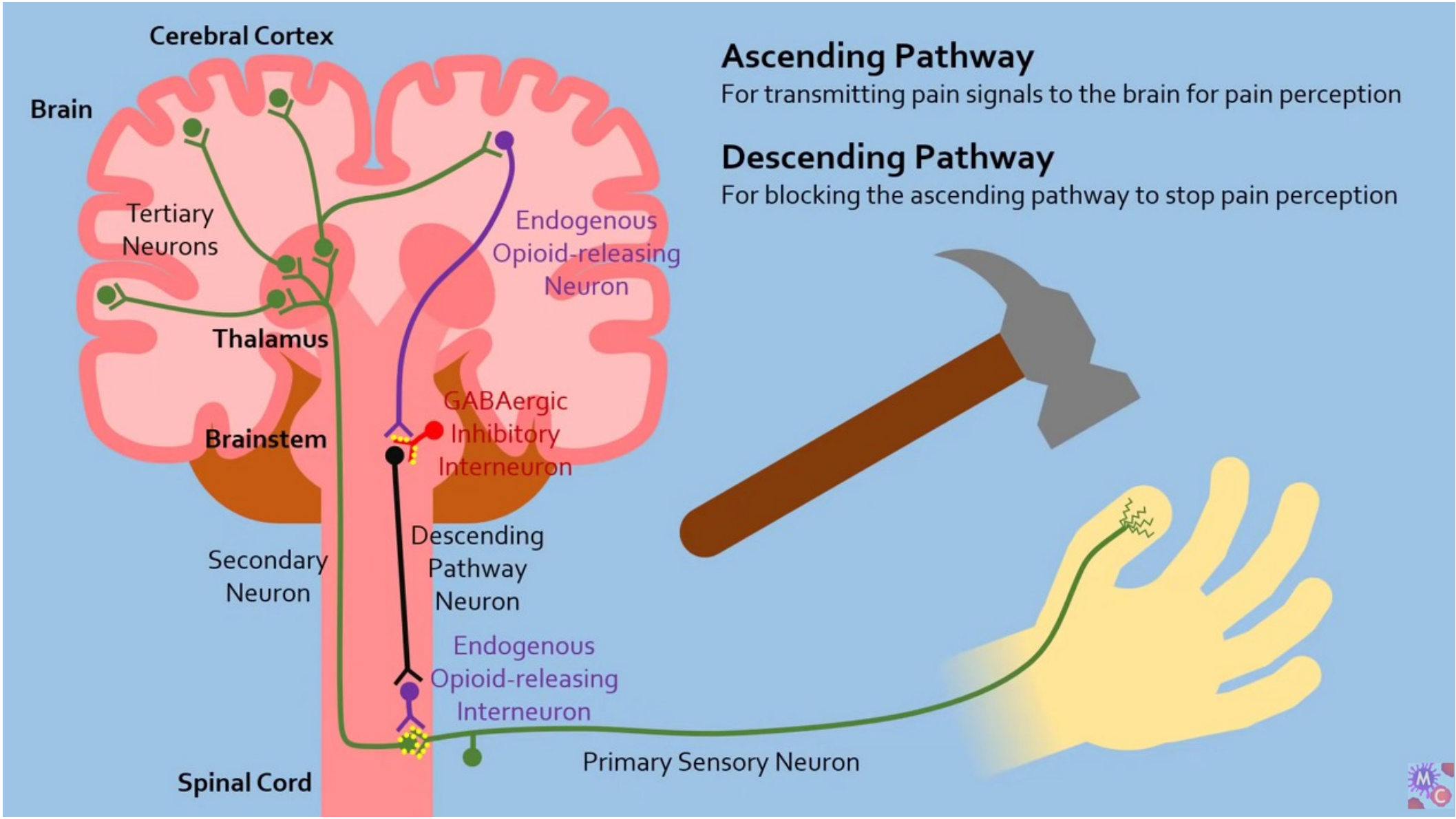
Decreased cAMP

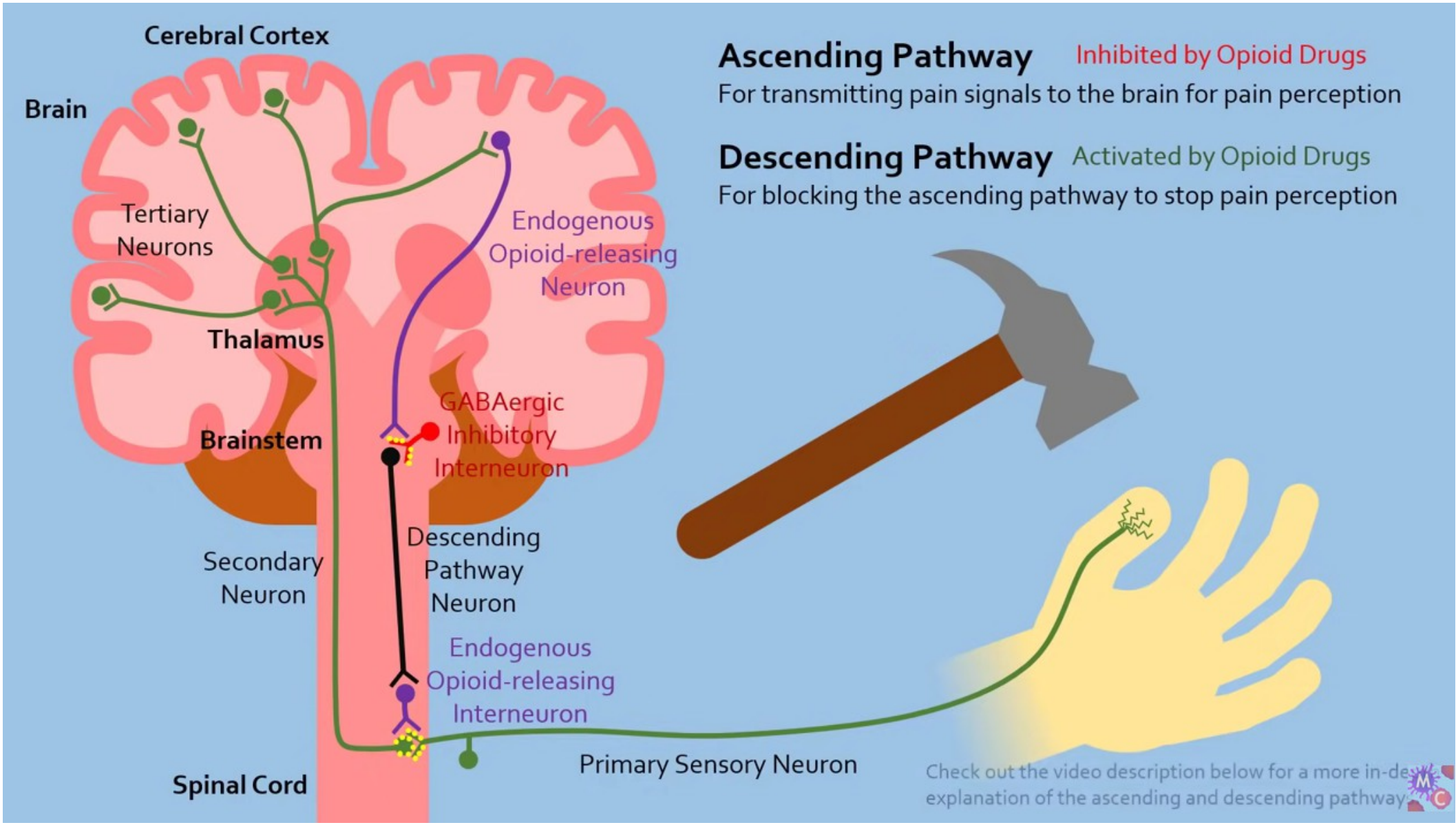
Interaction with $G_{\alpha i/o}$ inhibits adenylyl cyclase, stopping cAMP synthesis and decreasing cAMP levels in the neuron

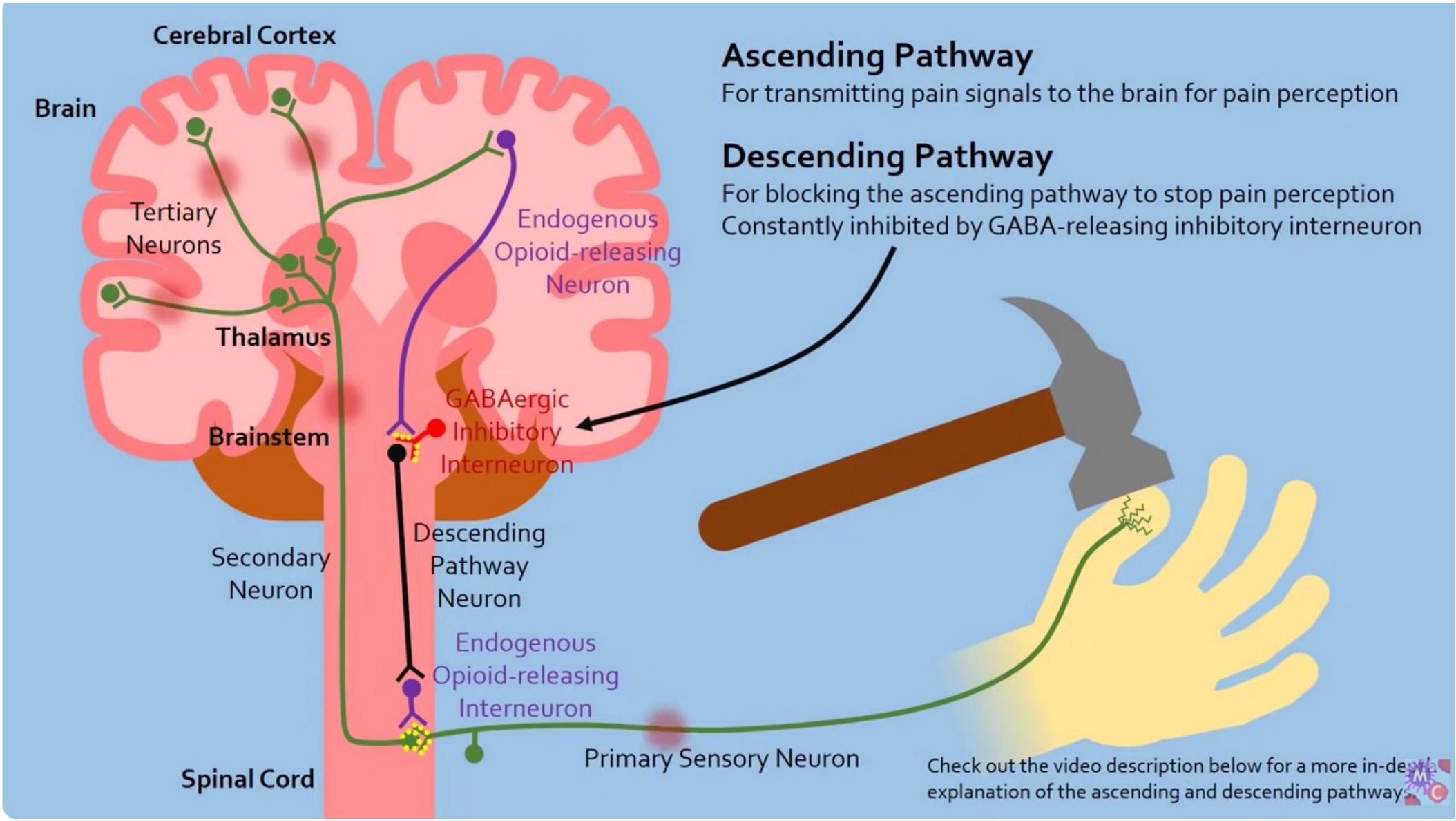
Variety of signaling changes

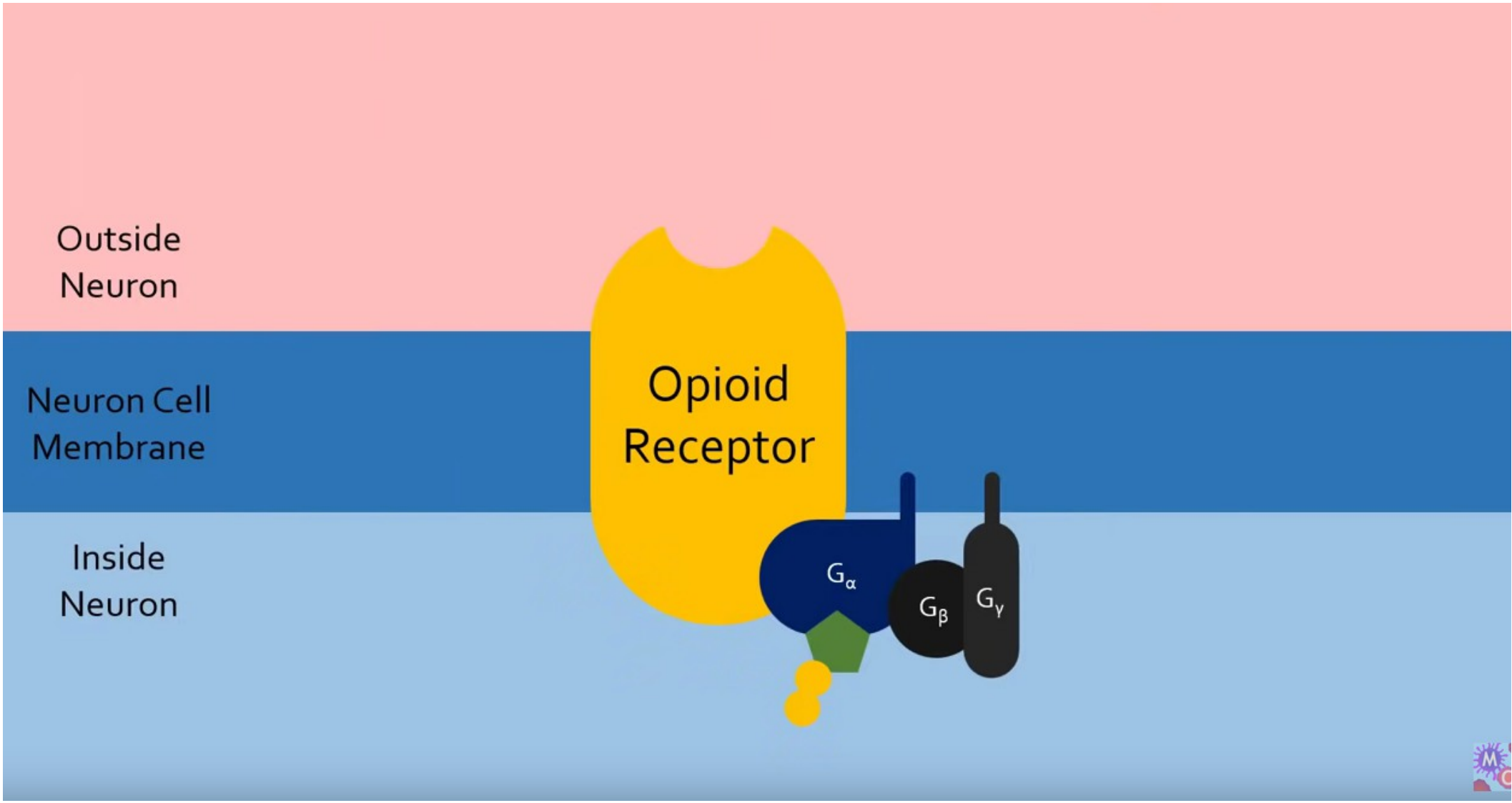



Cerebral Cortex
Brain
Tertiary Neurons
Endogenous Opioid-releasing Neuron
Thalamus
GABAergic Inhibitory Interneuron
Brainstem
Secondary Neuron
Descending Pathway Neuron
Endogenous Opioid-releasing Interneuron
Primary Sensory Neuron
Spinal Cord
Ascending Pathway
For transmitting pain signals to the brain for pain perception
Descending Pathway
For blocking the ascending pathway to stop pain perception
Where do opioid drugs bind?
Same places as endogenous opioids!
At the brainstem to stop inhibition of descending pathway neurons, therefore blocking the ascending pathway and pain transmission
In the spinal cord to stop pain transmission
Plus many other places in the brain...but more about that in part 2!
Check out the video description below for a more in-de
explanation of the ascending and descending pathway

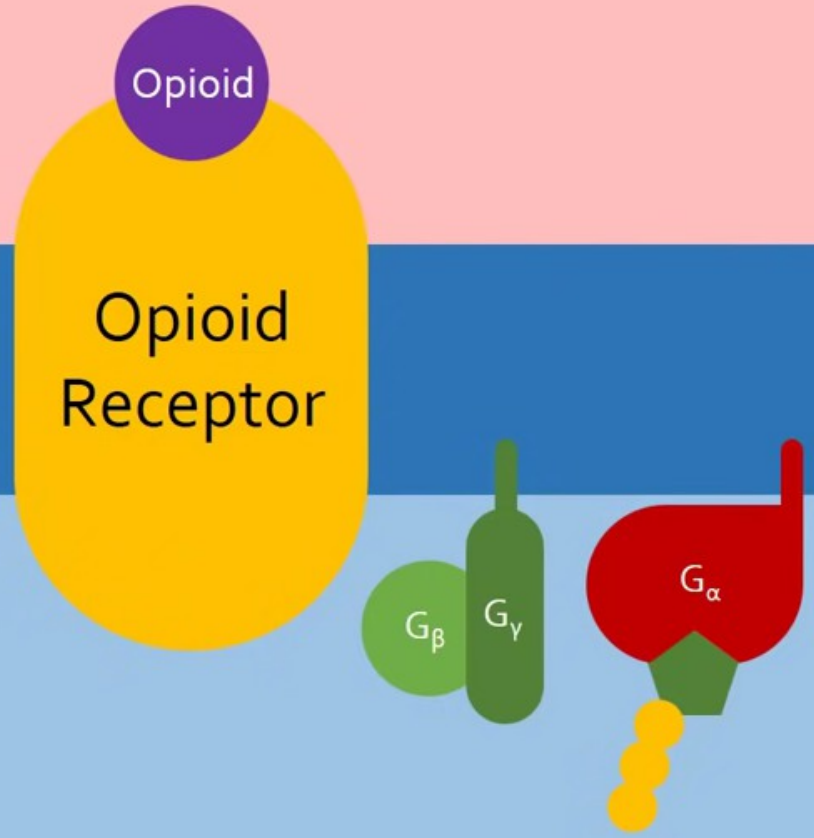

Cerebral Cortex
Brain
Tertiary Neurons
Endogenous Opioid-releasing Neuron
Thalamus
GABAergic Inhibitory Interneuron
Brainstem
Secondary Neuron
Descending Pathway Neuron
Endogenous Opioid-releasing Interneuron
Primary Sensory Neuron
Spinal Cord
Ascending Pathway
For transmitting pain signals to the brain for pain perception
Descending Pathway
For blocking the ascending pathway to stop pain perception


Cerebral Cortex
Brain
Tertiary Neurons
Endogenous Opioid-releasing Neuron
Thalamus
GABAergic Inhibitory Interneuron
Brainstem
Secondary Neuron
Descending Pathway Neuron
Endogenous Opioid-releasing Interneuron
Primary Sensory Neuron
Spinal Cord
Ascending Pathway
Inhibited by Opioid Drugs
For transmitting pain signals to the brain for pain perception
Descending Pathway
Activated by Opioid Drugs
For blocking the ascending pathway to stop pain perception
Check out the video description below for a more in-de
explanation of the ascending and descending pathway


Cerebral Cortex
Brain
Tertiary Neurons
Thalamus
Brainstem
Secondary Neuron
Endogenous Opioid-releasing Neuron
GABAergic Inhibitory Interneuron
Descending Pathway Neuron
Endogenous Opioid-releasing Interneuron
Primary Sensory Neuron
Spinal Cord
Ascending Pathway
For transmitting pain signals to the brain for pain perception
Descending Pathway
For blocking the ascending pathway to stop pain perception
Constantly inhibited by GABA-releasing inhibitory interneuron
Check out the video description below for a more in-de
explanation of the ascending and descending pathways


Outside
Neuron
Neuron Cell
Membrane
Inside
Neuron
Opioid
Receptor
Gα
Gβ
Gγ

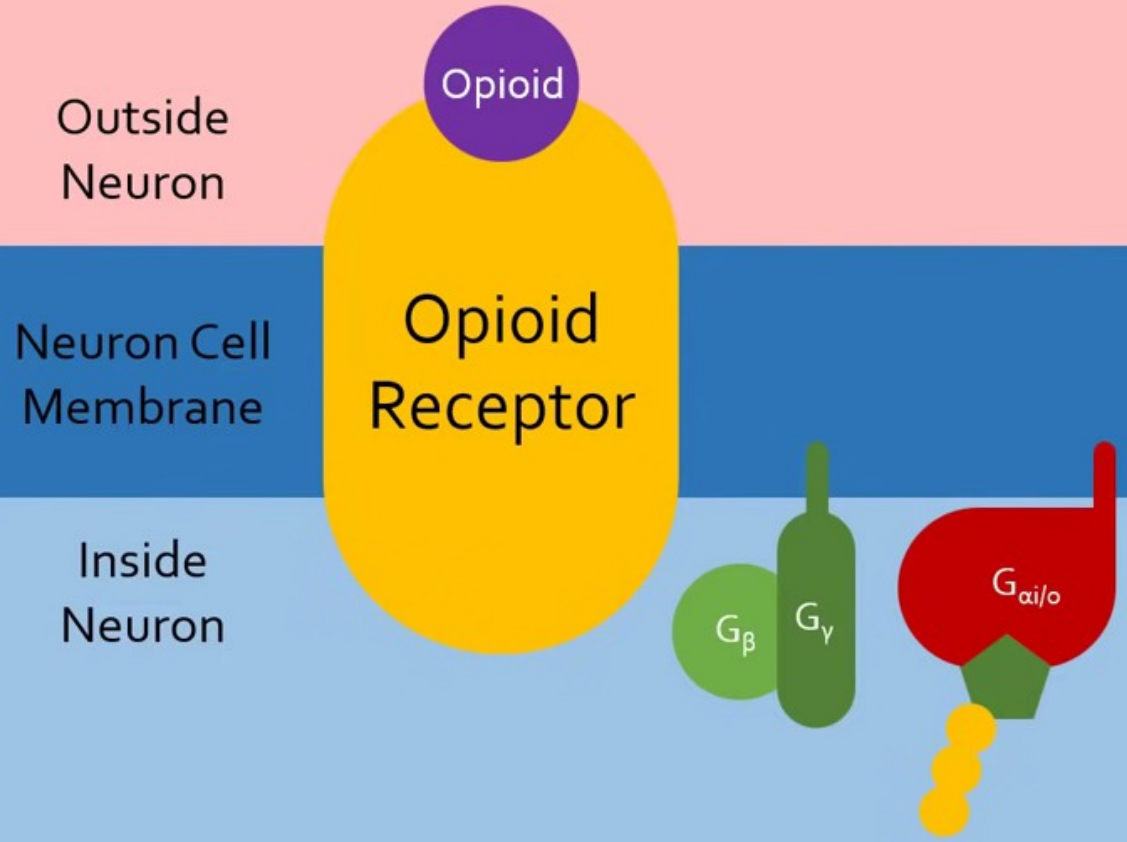
What does the G_α subunit do?



Different classes of G_α subunits

$G_{\alpha s}$	Stimulates cAMP synthesis
$G_{\alpha i/o}$	Inhibits cAMP synthesis
$G_{\alpha q/11}$	Activates Phospholipase C
$G_{\alpha 12/13}$	Remodels cytoskeleton

What does the G_α subunit do?



Different classes of G_α subunits

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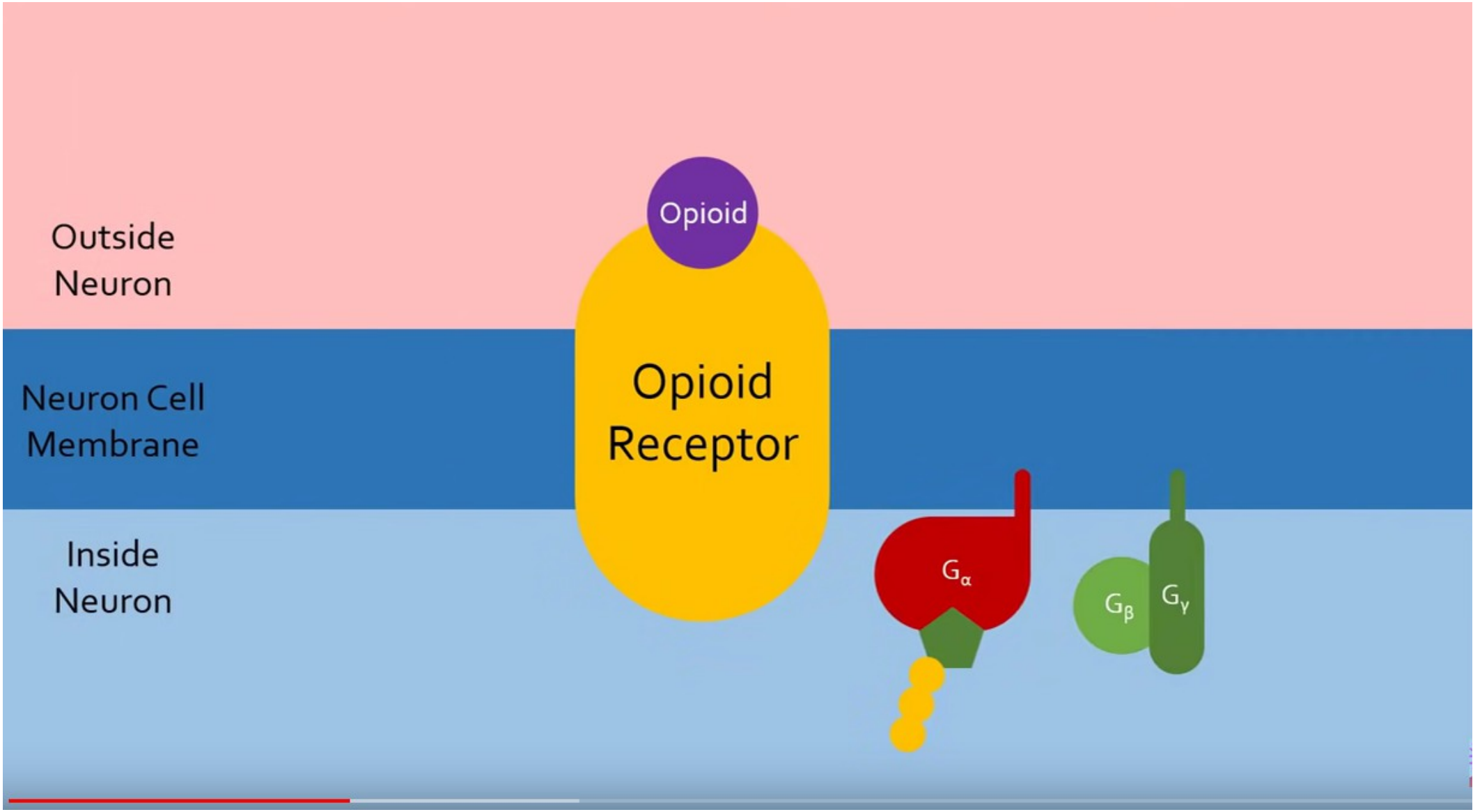
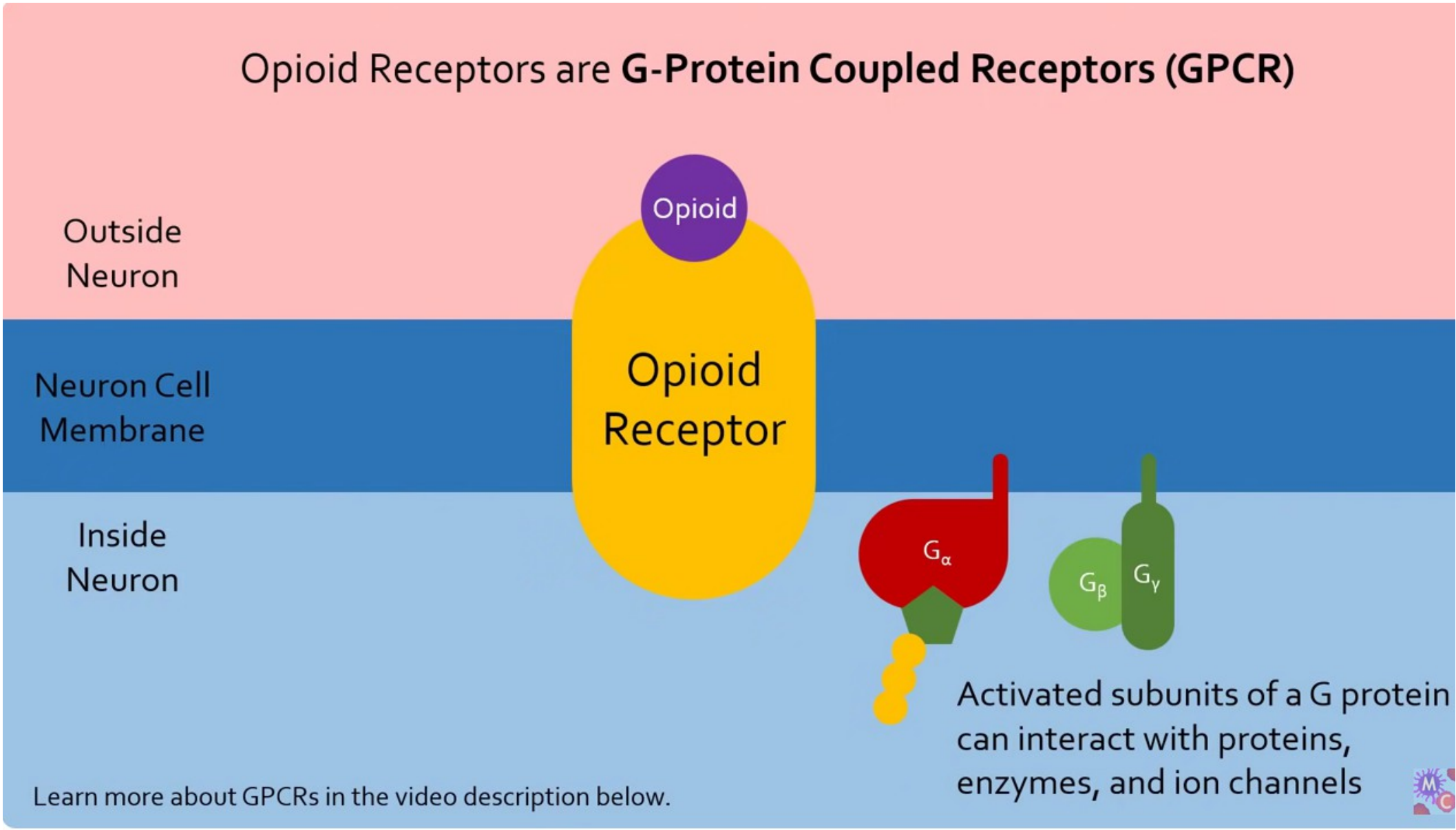
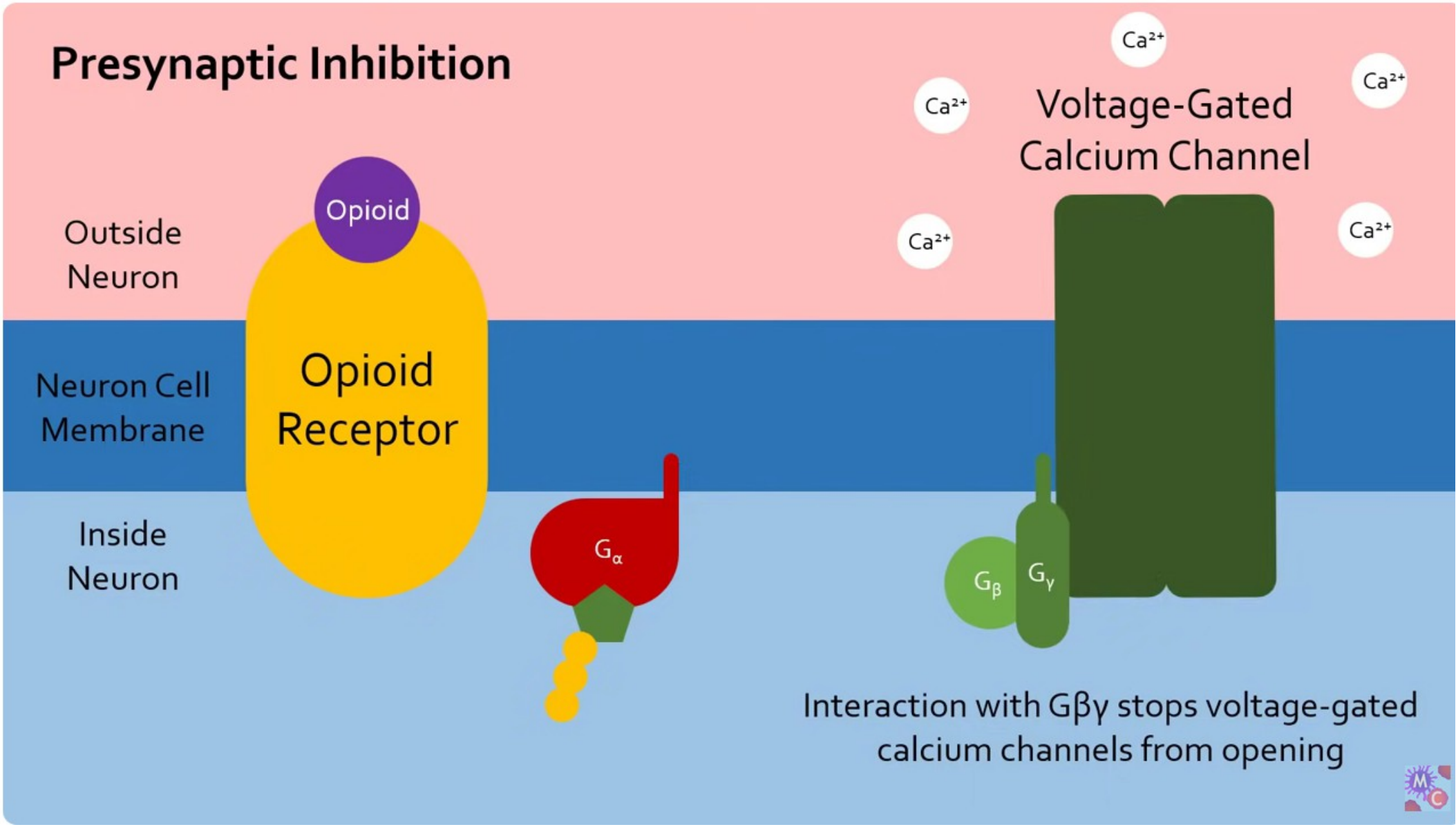
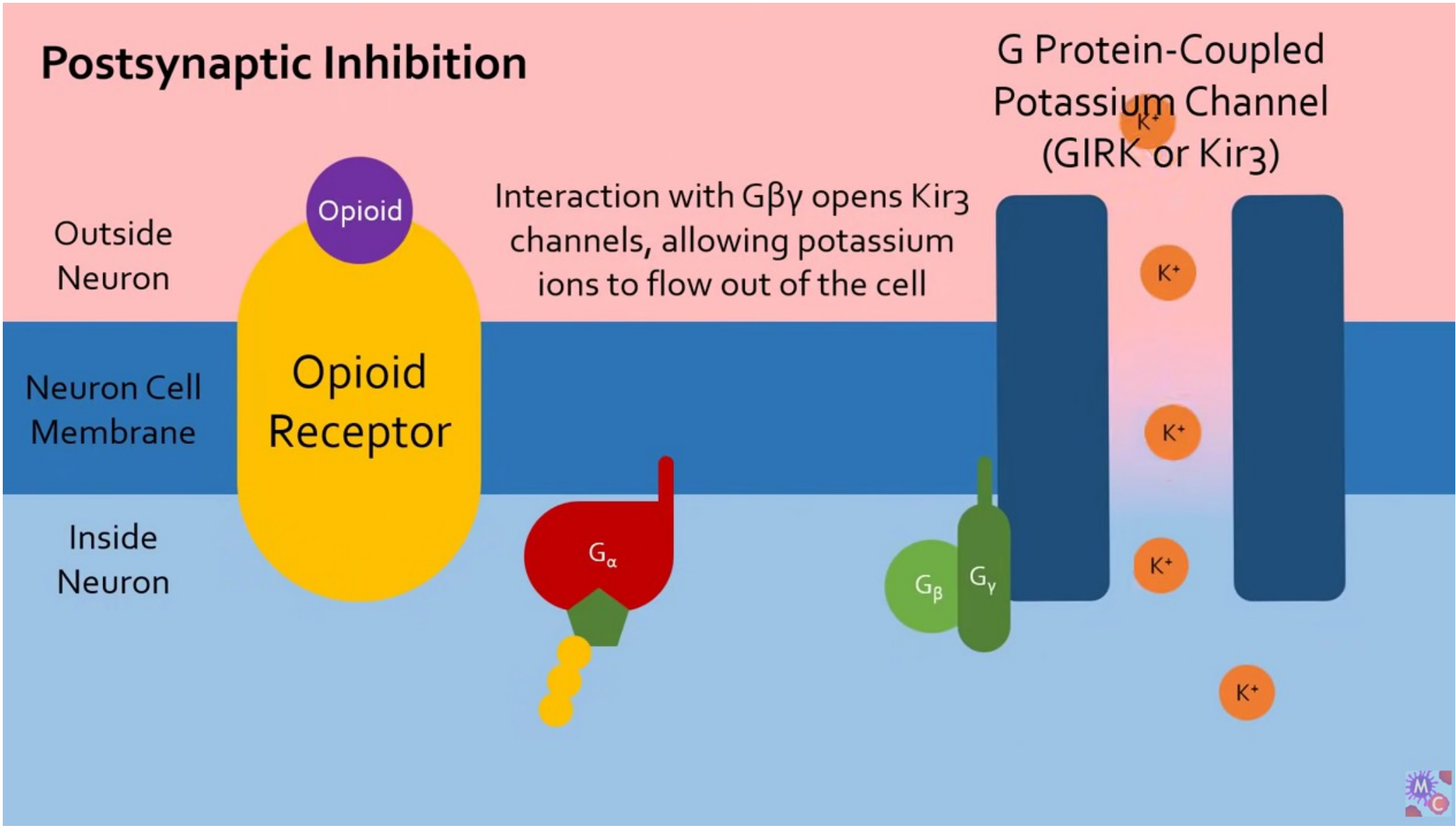
$G_{\alpha 12/13}$	Remodels cytoskeleton

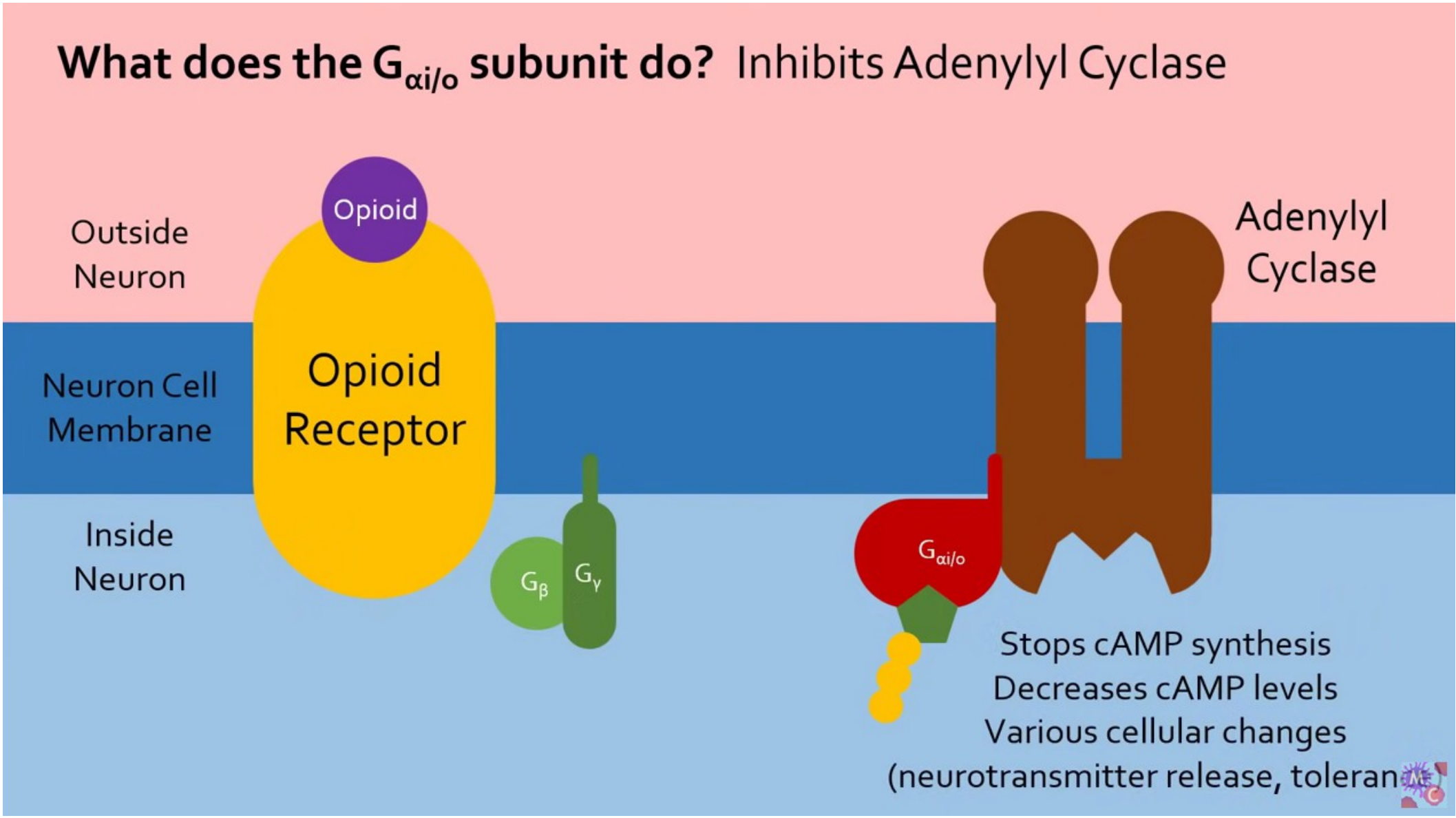

Outside
Neuron
Neuron Cell
Membrane
Inside
Neuron
Opioid
Opioid
Receptor
Gα
Gβ
Gγ

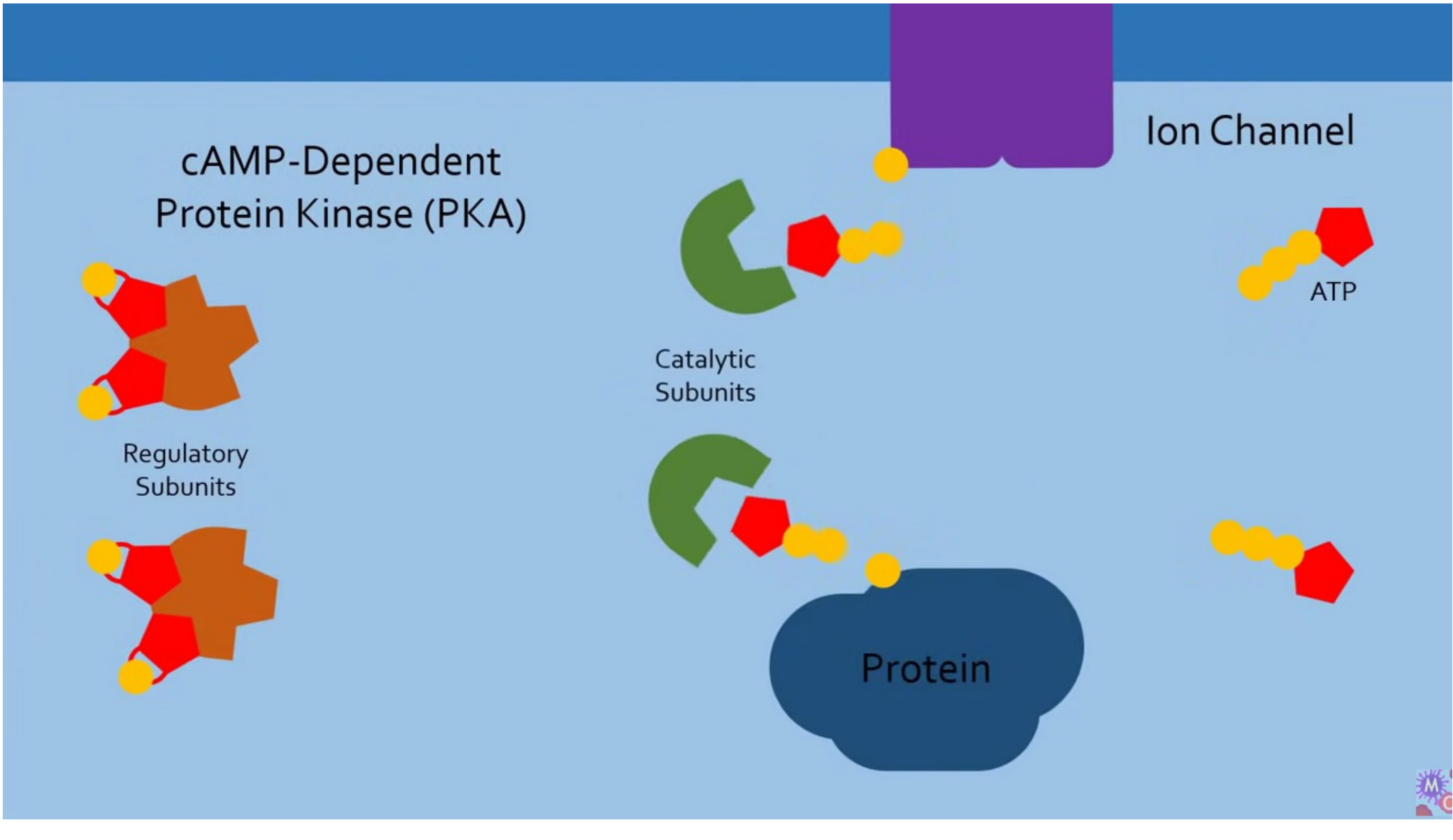
Opioid Receptors are **G-Protein Coupled Receptors (GPCR)**

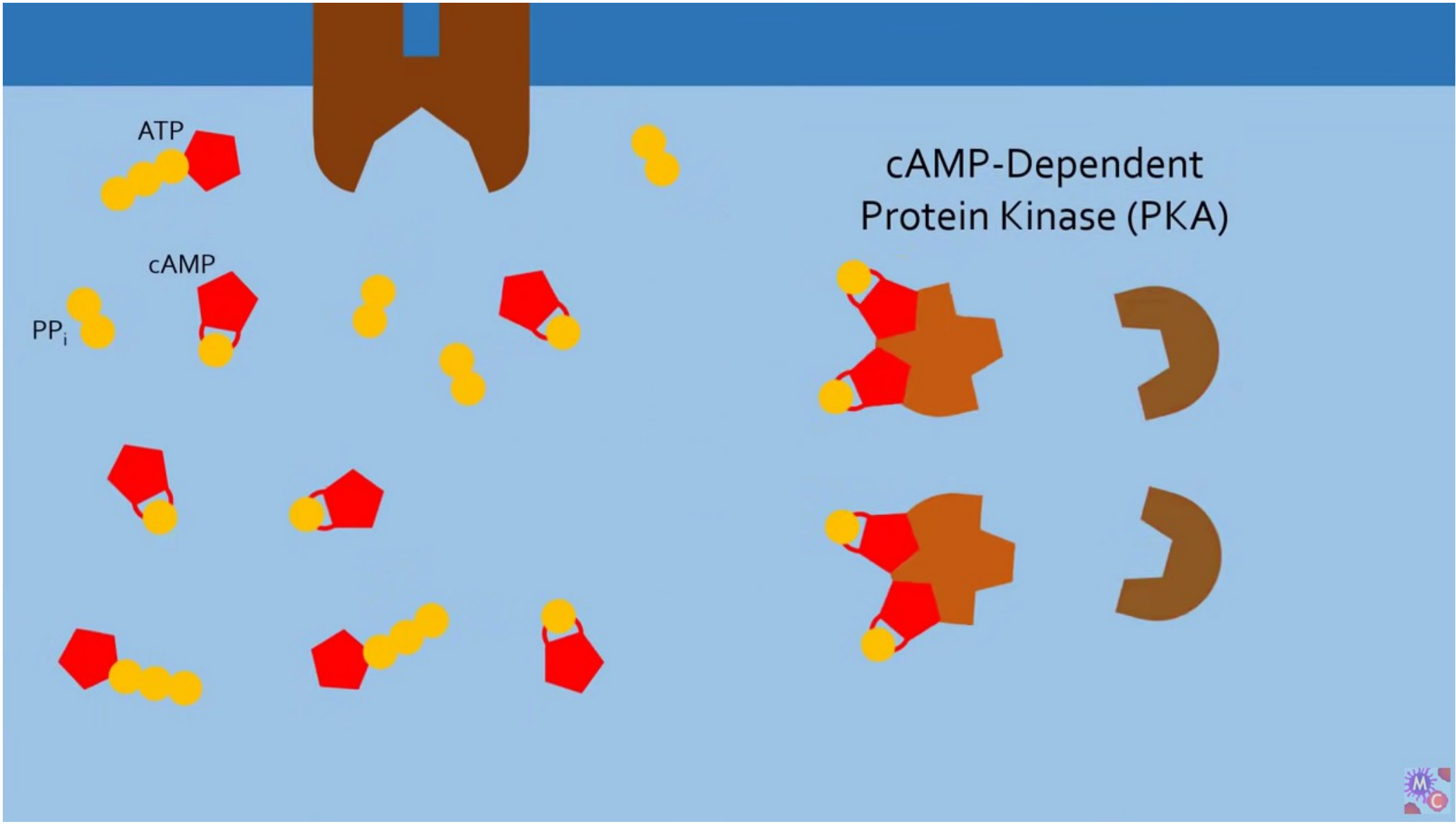


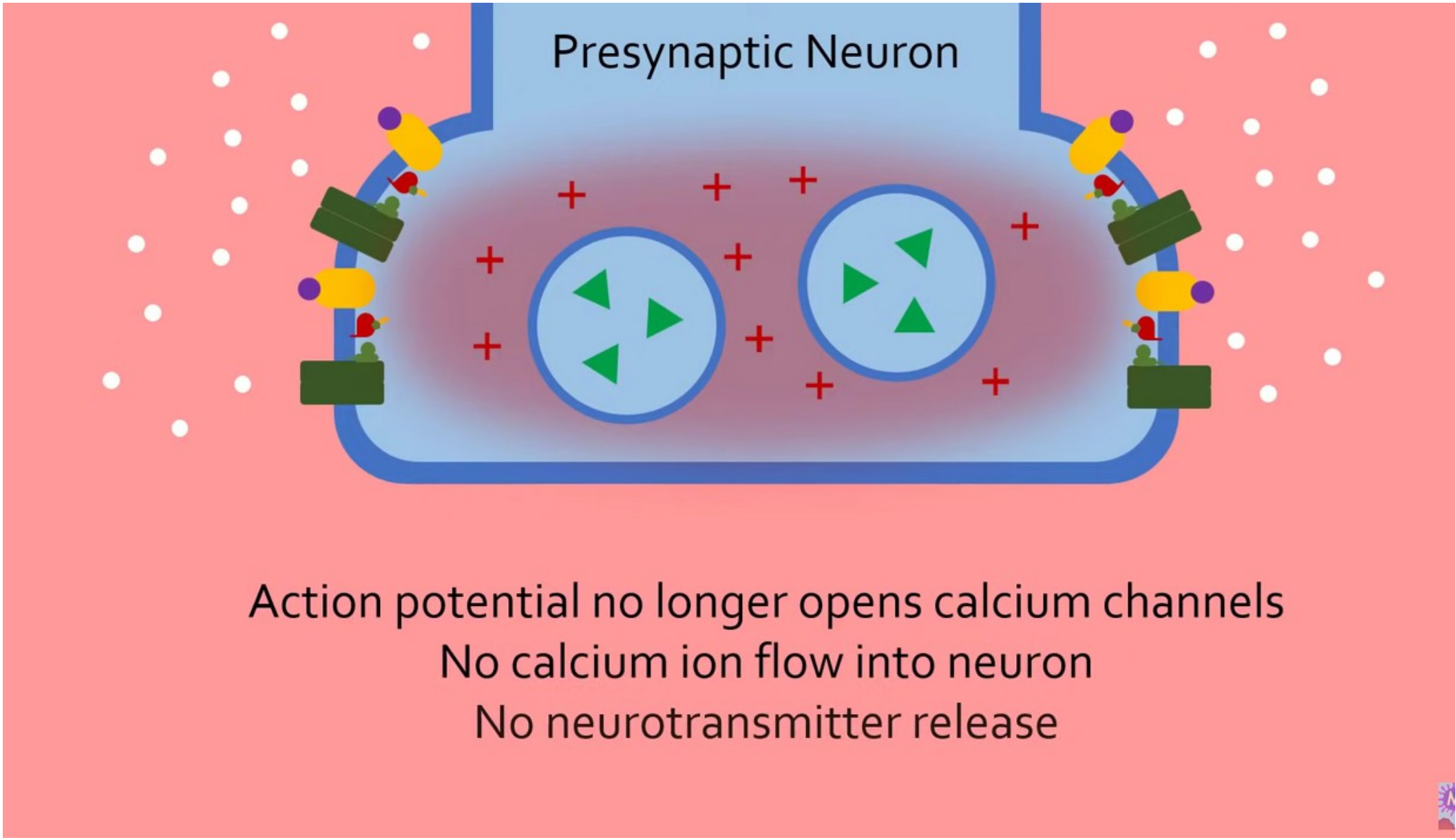

Presynaptic Inhibition
Ca2+
Ca2+
Ca2+
Voltage-Gated
Calcium Channel
Ca2+
Ca2+
Outside
Neuron
Opioid
Neuron Cell
Membrane
Opioid
Receptor
Inside
Neuron
Gα
Gβ
Gγ
Interaction with Gβγ stops voltage-gated
calcium channels from opening


Postsynaptic Inhibition
G Protein-Coupled Potassium Channel (GIRK or Kir3)
Outside Neuron
Opioid
Interaction with Gβγ opens Kir3 channels, allowing potassium ions to flow out of the cell
Neuron Cell Membrane
Opioid Receptor
Inside Neuron
Gα
Gβ
Gγ
K+
K+
K+
K+
K+

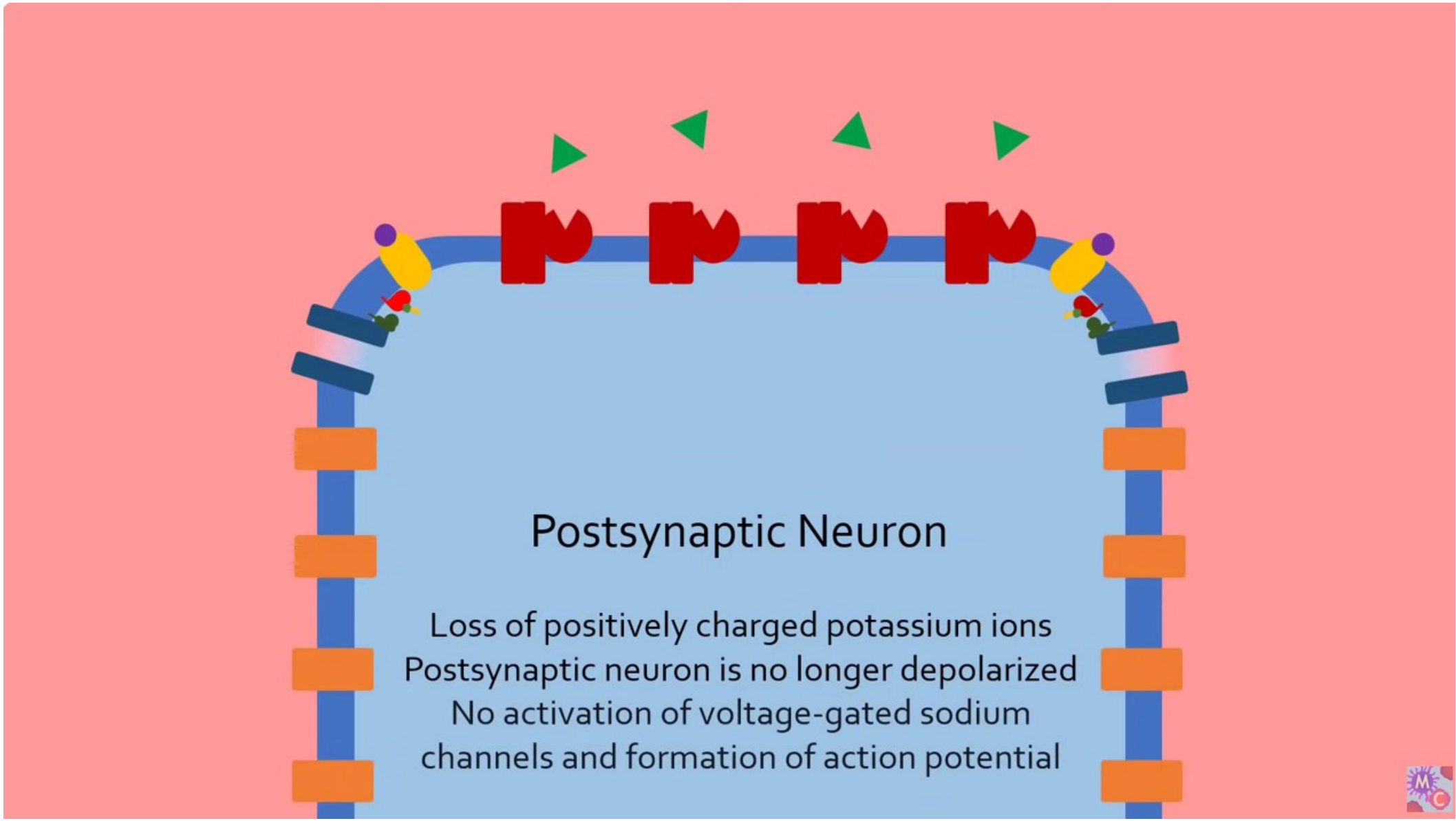

What does the $G_{\alpha i/o}$ subunit do? Inhibits Adenylyl Cyclase
Outside Neuron
Neuron Cell Membrane
Inside Neuron
Opioid
Opioid Receptor
G_β
G_γ
$G_{\alpha i/o}$
Adenylyl Cyclase
Stops cAMP synthesis
Decreases cAMP levels
Various cellular changes
(neurotransmitter release, toleran


cAMP-Dependent
Protein Kinase (PKA)
Regulatory
Subunits
Catalytic
Subunits
Ion Channel
ATP
Protein


ATP
cAMP
PP_i
cAMP-Dependent
Protein Kinase (PKA)



Action potential no longer opens calcium channels
No calcium ion flow into neuron
No neurotransmitter release


Postsynaptic Neuron
Loss of positively charged potassium ions
Postsynaptic neuron is no longer depolarized
No activation of voltage-gated sodium
channels and formation of action potential

Opioid Use Disorder

Diagnosed if meeting **at least 2 of the criteria** below within a year

Mild: 2-3 criteria Moderate: 4-5 criteria Severe: 6 or more

Loss of Control

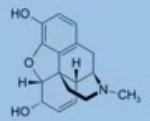
1. Opioids are used at higher doses or longer times than intended.
2. Patient wants to stop using opioids but is unsuccessful.
3. Excessive time is used to find and use the opioid.
4. There is a craving to use opioids.

Risky Use of Opioids

5. Repeated use of opioids in situations in which it is physically dangerous to do so.
6. Continued use despite knowing opioids have negative health and mental consequences.

Social Problems

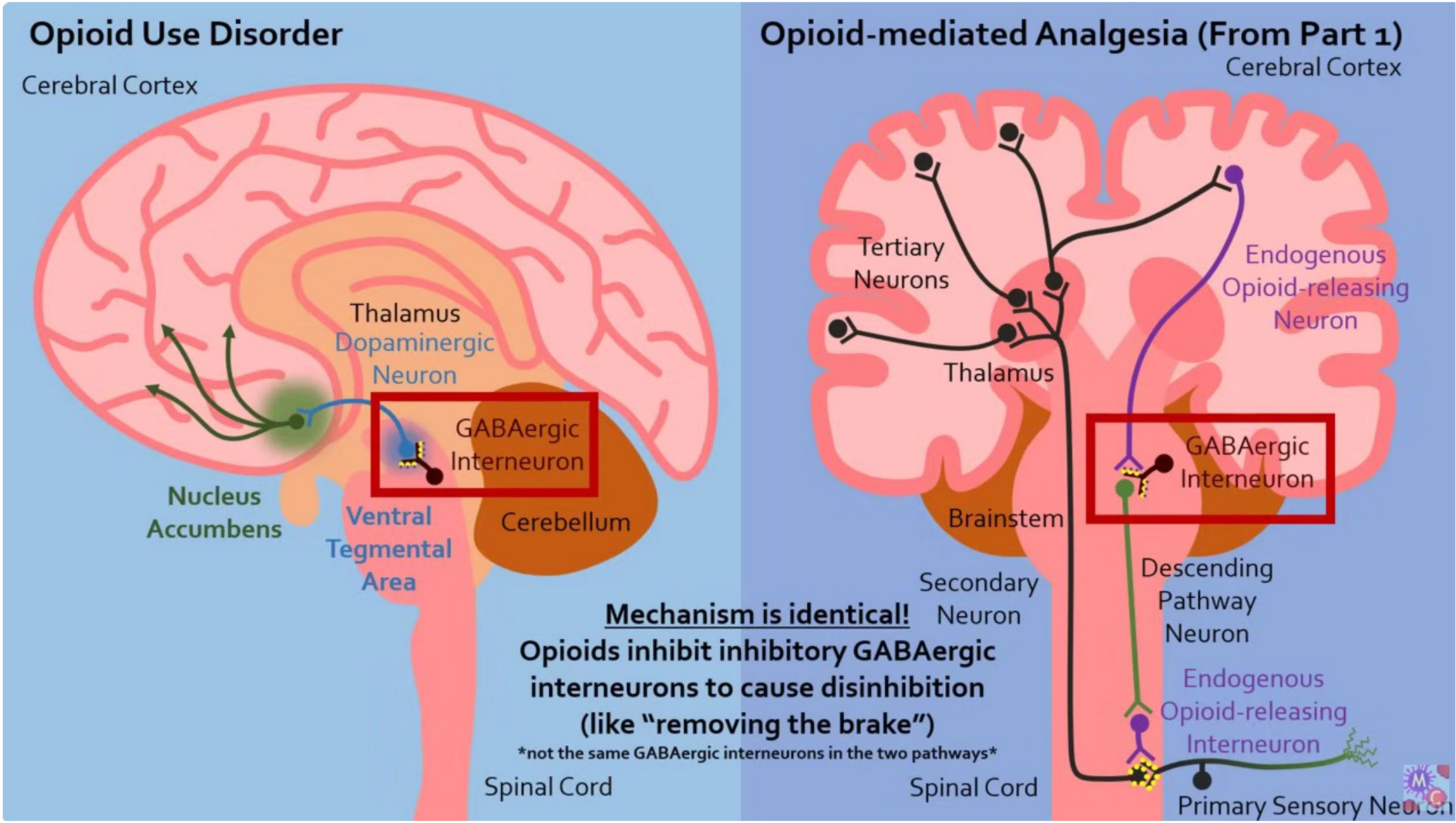
7. Opioid use is negatively affecting the ability to fulfill responsibilities at work, school, or home.
8. Continued opioid use despite social problems caused or worsened by opioid use.
9. Important social, work, or recreational activities are given up or reduced because of opioid use.

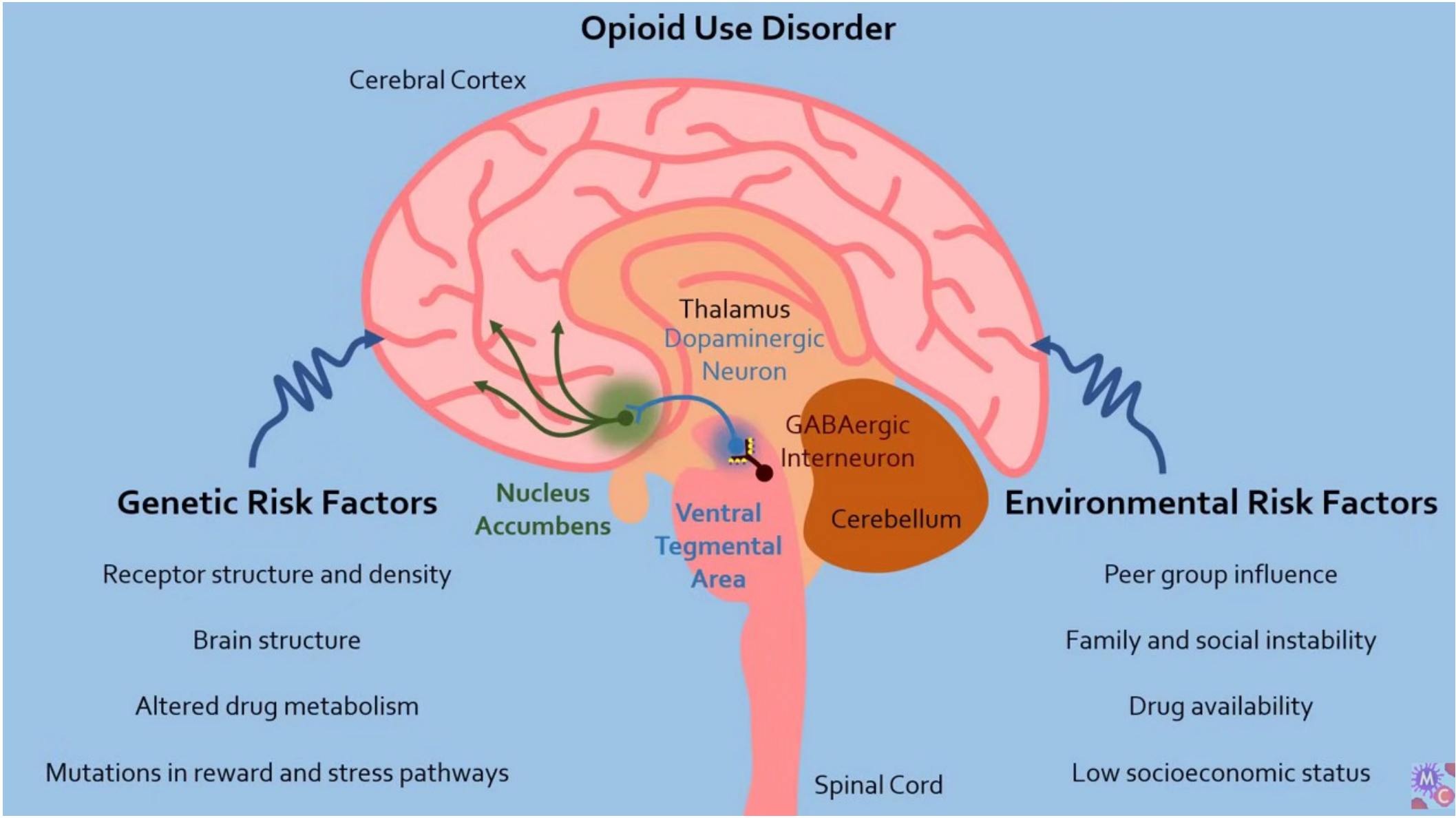


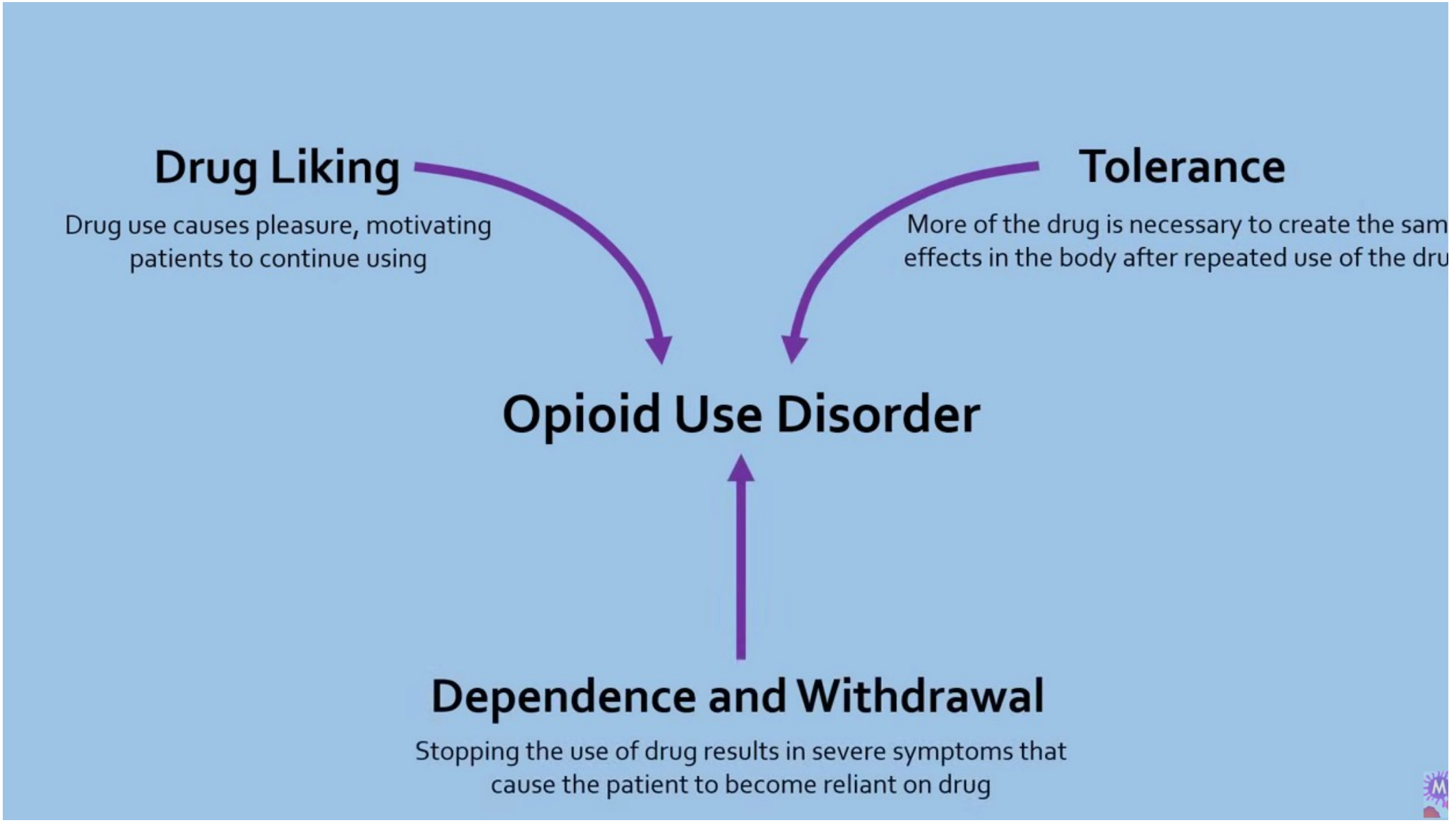
Pharmacological Problems

10. *Development of tolerance, when the opioid dose needs to increase in order to have the same effect
11. *Development of withdrawal symptoms

*Patients prescribed opioids can satisfy these criteria but not necessarily have opioid use disorder

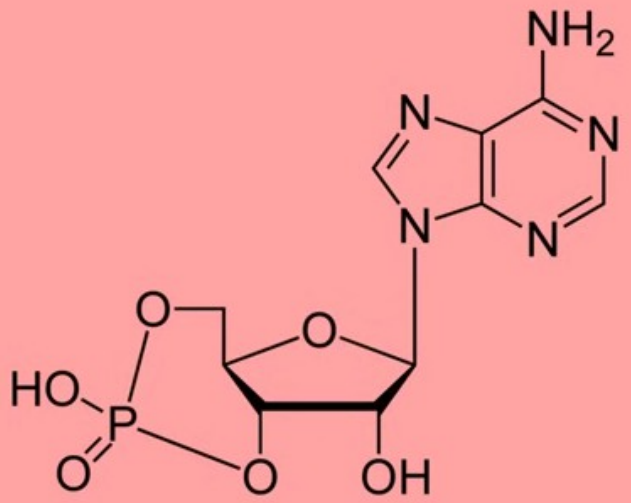

Opioid Use Disorder
Cerebral Cortex
Thalamus
Dopaminergic
Neuron
GABAergic
Interneuron
Nucleus
Accumbens
Ventral
Tegmental
Area
Cerebellum
Spinal Cord
Opioid-mediated Analgesia (From Part 1)
Cerebral Cortex
Tertiary
Neurons
Endogenous
Opioid-releasing
Neuron
Thalamus
GABAergic
Interneuron
Brainstem
Secondary
Neuron
Descending
Pathway
Neuron
Endogenous
Opioid-releasing
Interneuron
Spinal Cord
Primary Sensory Neuron
Mechanism is identical!
Opioids inhibit inhibitory GABAergic
interneurons to cause disinhibition
(like "removing the brake")
not the same GABAergic interneurons in the two pathways


Opioid Use Disorder
Cerebral Cortex
Thalamus
Dopaminergic
Neuron
GABAergic
Interneuron
Cerebellum
Nucleus
Accumbens
Ventral
Tegmental
Area
Spinal Cord
Genetic Risk Factors
Receptor structure and density
Brain structure
Altered drug metabolism
Mutations in reward and stress pathways
Environmental Risk Factors
Peer group influence
Family and social instability
Drug availability
Low socioeconomic status


Drug Liking
Drug use causes pleasure, motivating patients to continue using
Tolerance
More of the drug is necessary to create the sam
effects in the body after repeated use of the dru
Opioid Use Disorder
Dependence and Withdrawal
Stopping the use of drug results in severe symptoms that cause the patient to become reliant on drug

Currently most-studied theory of opioid tolerance:

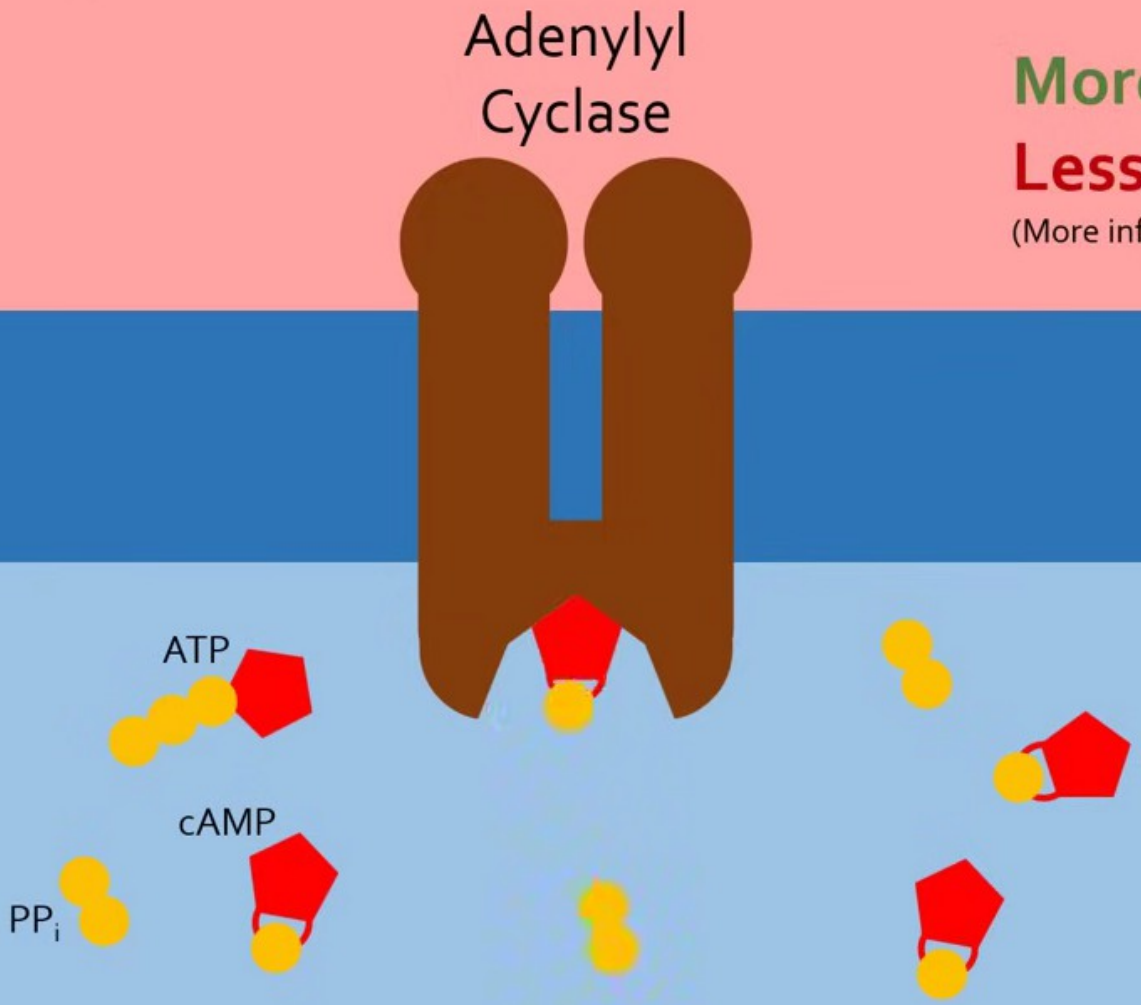
Cyclic AMP (cAMP) dependent tolerance pathways



cAMP is a secondary messenger molecule involved in many signaling pathways in the neuron

Other theories also exist – check out the video description to learn more.

Adenylyl Cyclase synthesizes cAMP from ATP



More cAMP = Activate Neurons

Less cAMP = Inhibit Neurons

(More information on why this occurs in the video description)

cAMP-dependent pathways involve…

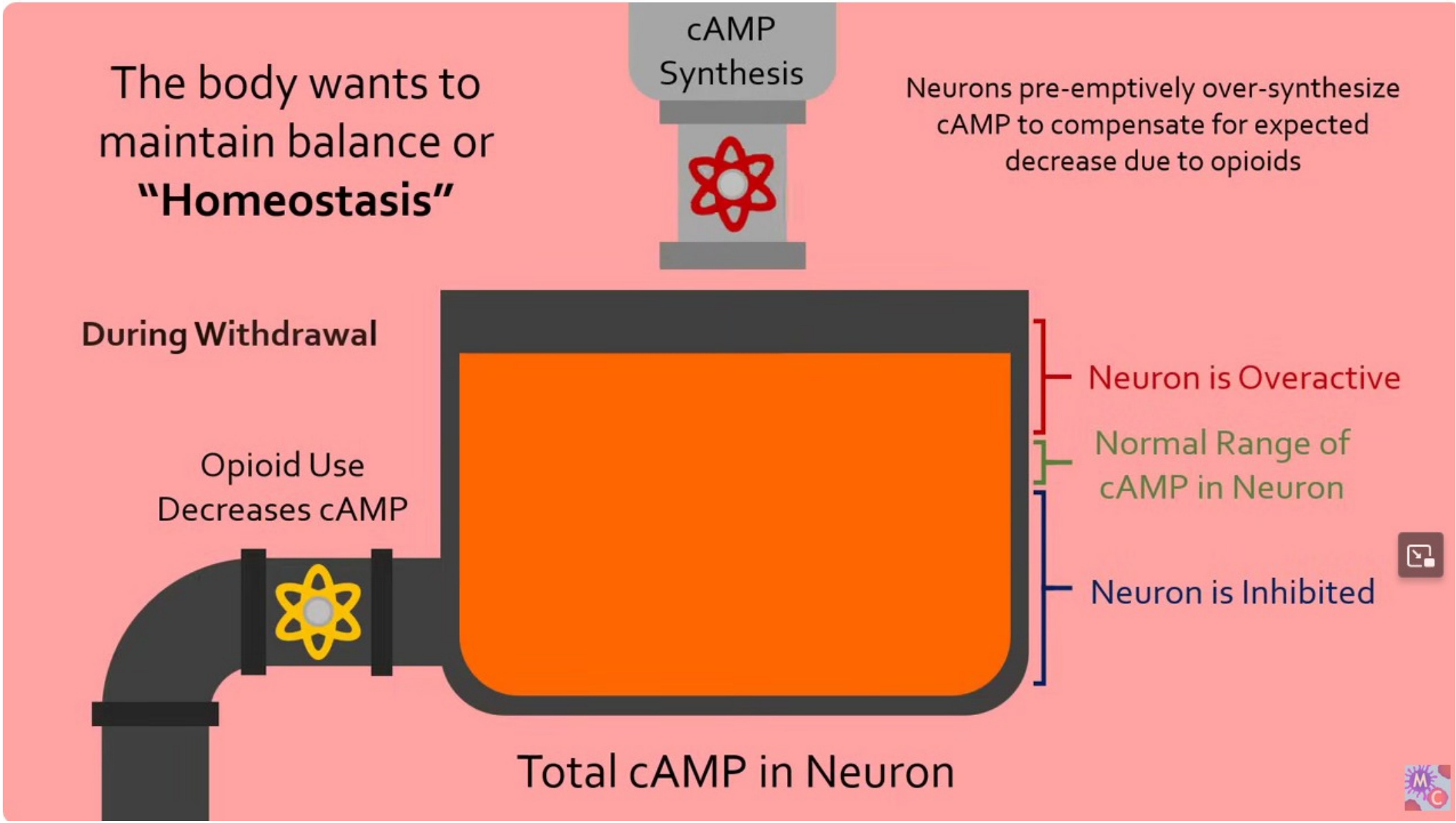
Neurotransmitter Release

Opening/Closing Ion Channels

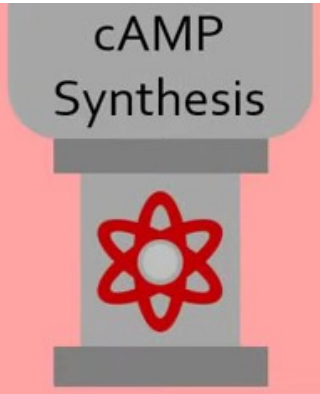
Receptor Sensitivity

Receptor Internalization

Gene Expression Changes

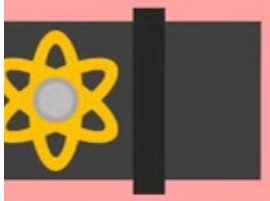

The body wants to maintain balance or "Homeostasis"
cAMP Synthesis
Neurons pre-emptively over-synthesize cAMP to compensate for expected decrease due to opioids
During Withdrawal
Opioid Use Decreases cAMP
Neuron is Overactive
Normal Range of cAMP in Neuron
Neuron is Inhibited
Total cAMP in Neuron

The body wants to maintain balance or **"Homeostasis"**



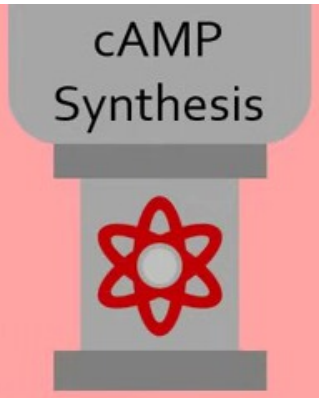
Neurons pre-emptively over-synthesize cAMP to compensate for expected decrease due to opioids

During Withdrawal



Total cAMP in Neuron

The body wants to maintain balance or **"Homeostasis"**



Neurons pre-emptively over-synthesize cAMP to compensate for expected decrease due to opioids

During Withdrawal

If opioid use is stopped

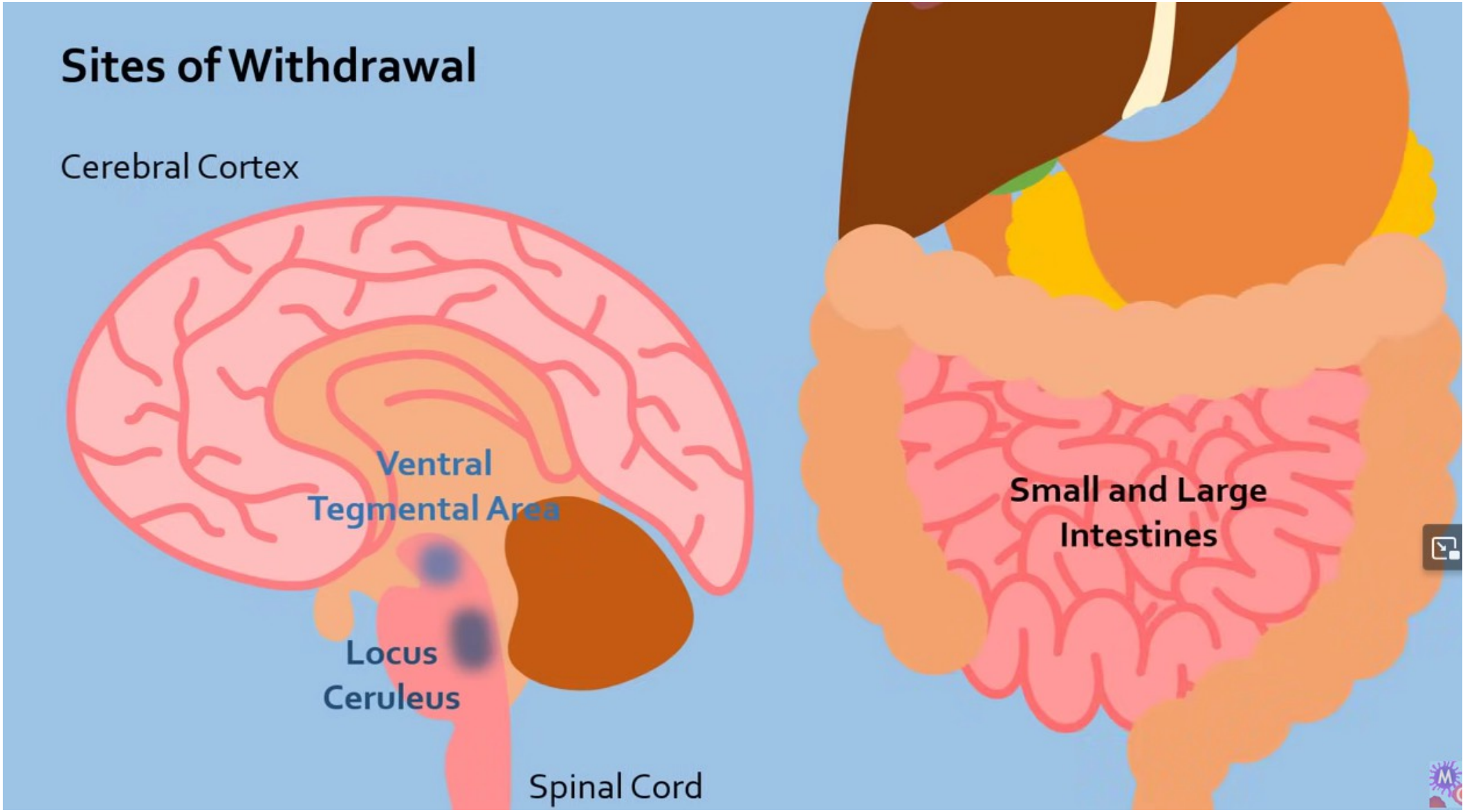
↓

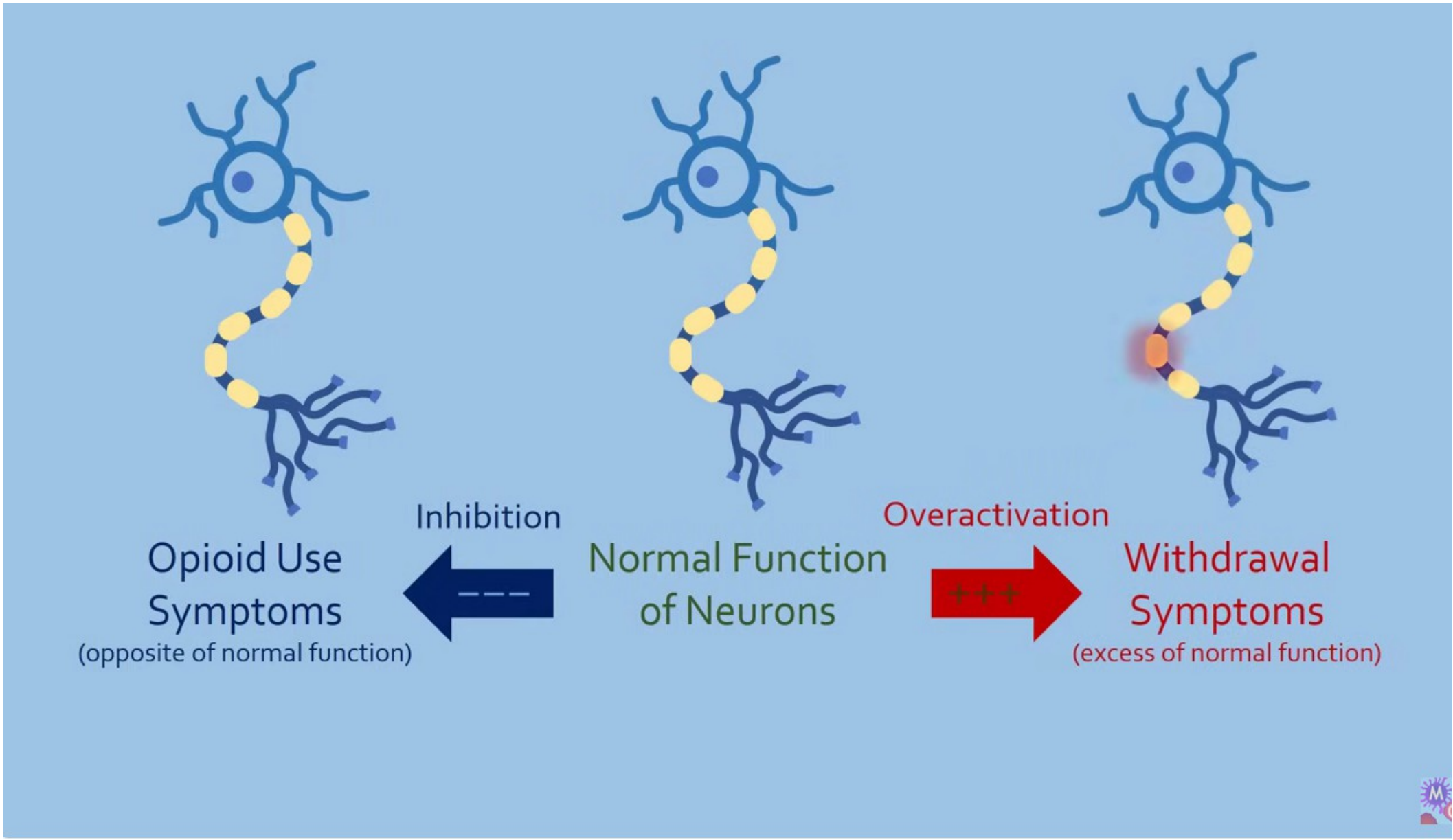
cAMP levels remain high

↓

Certain neurons become overactive and cause withdrawal symptoms

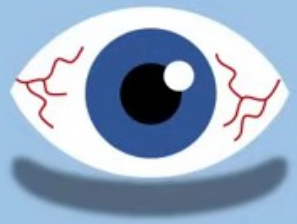
Total cAMP in Neuron


Sites of Withdrawal
Cerebral Cortex
Ventral
Tegmental Area
Locus
Ceruleus
Spinal Cord
Small and Large
Intestines


Inhibition
Overactivation
Opioid Use Symptoms
(opposite of normal function)
Normal Function of Neurons
Withdrawal Symptoms
(excess of normal function)

Main Roles of the Locus Ceruleus

During Withdrawal...



Withdrawal symptoms are **EXTREME VERSIONS OF** normal Locus Ceruleus function

"Fight or Flight"

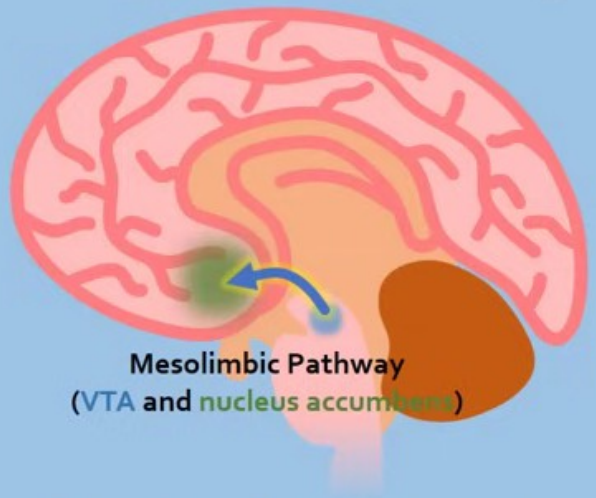
Jitteriness/Insomnia — **Sympathetic Overactivation** — **Anxiety/Panic/Stress**

Excessive sweating

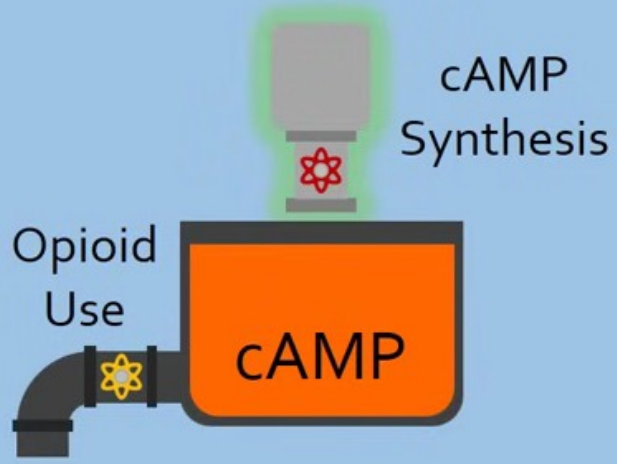
Very large pupils

Rapid heart and breathing rate

Progression of Opioid Use Disorder



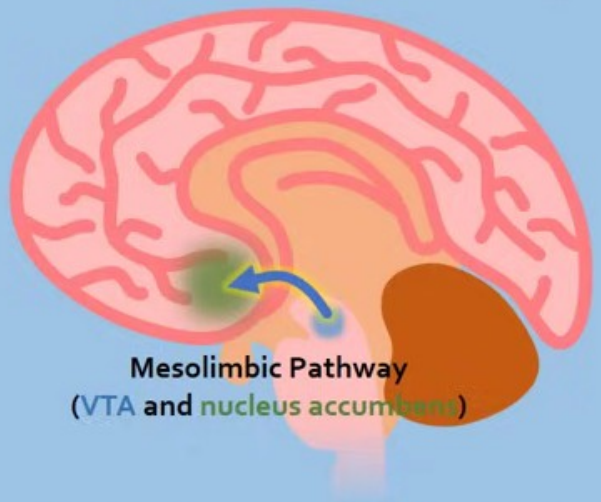
1. Association between drug and pleasure is formed after repeated opioid use

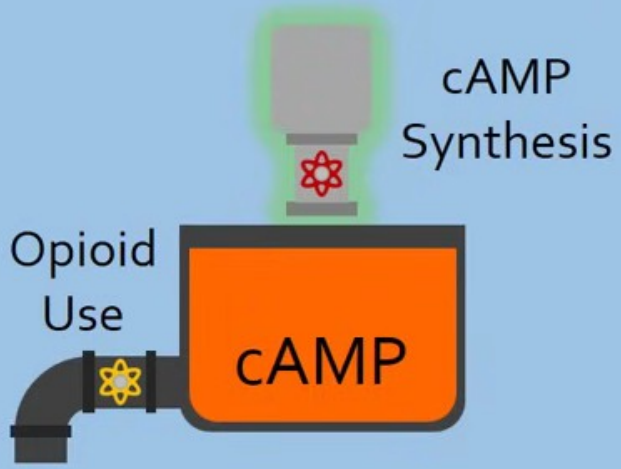


2. Tolerance results from pre-emptive cAMP increase due to repeated opioid use

3. Withdrawal symptoms prevent patient from stopping opioid use

Progression of Opioid Use Disorder





1. Association between drug and pleasure is formed after repeated opioid use
2. Tolerance results from pre-emptive cAMP increase due to repeated opioid use
3. Withdrawal symptoms prevent patient from stopping opioid use

If opioid use is stopped, tolerance and withdrawal symptoms disappear after a few weeks, but this process is extremely painful and often unsuccessful