Neuropsychiatry Block: Week 1

Physiology of Synapses & Receptors

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Organization of the Nervous System, Basic Functions of Synapses, and Neurotransmitters

Chapter 46

(Guyton & Hall)

Objectives

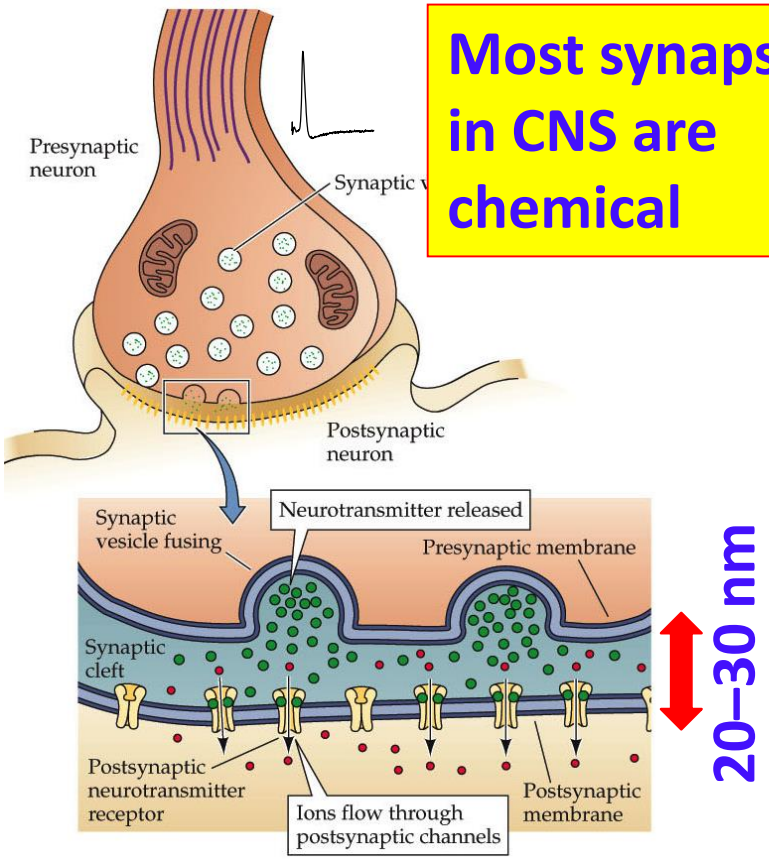
By the end of this lecture, students are expected to be able to:

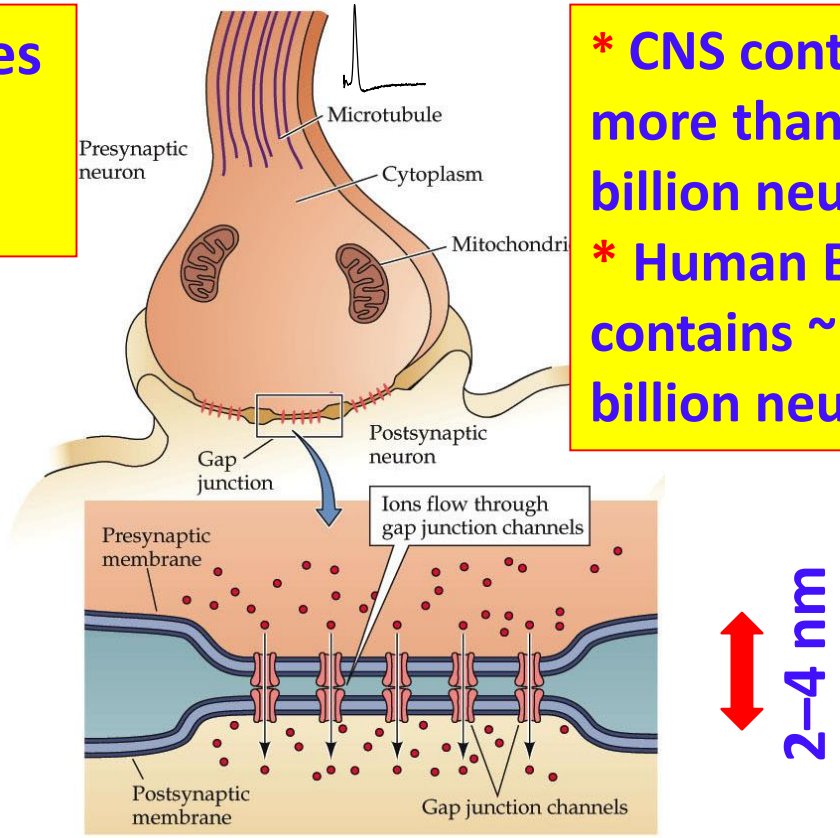
- Differentiate between chemical and electrical synapses.
- Explain what neurotransmitters are, their types and how they are released and removed.
- Differentiate between neurotransmitter receptors (**ionotropic** and **metabotropic**)
- Differentiate between postsynaptic & presynaptic inhibition, and between temporal & spatial **summation**.
- Appreciate that effectiveness of neurotransmitters can be modified by drugs and diseases

What is a Synapse?

Is a small gap, separating two neurons, that enables one neuron to pass an **electrical** or **chemical** signal to another neuron. **There are 2 types:**

Most synapses in CNS are chemical





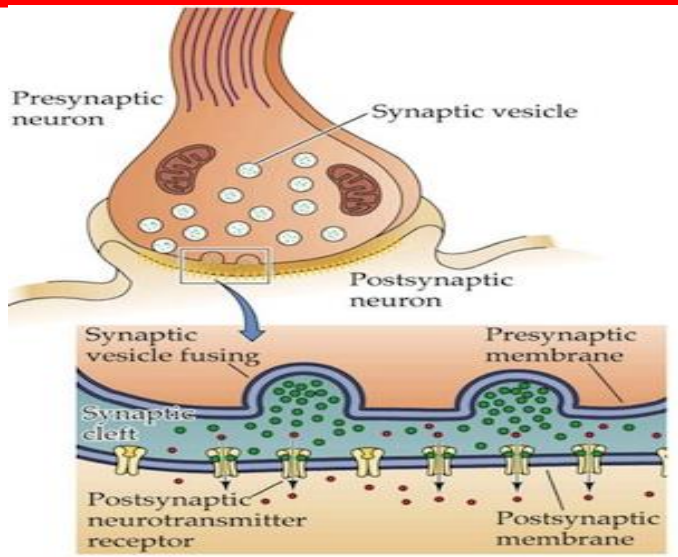
*** CNS contains more than 100 billion neurons**
*** Human Brain contains ~ 86 billion neurons**

1. CHEMICAL: neuronal communication *via* secretion of **neurotransmitters** (NTs)

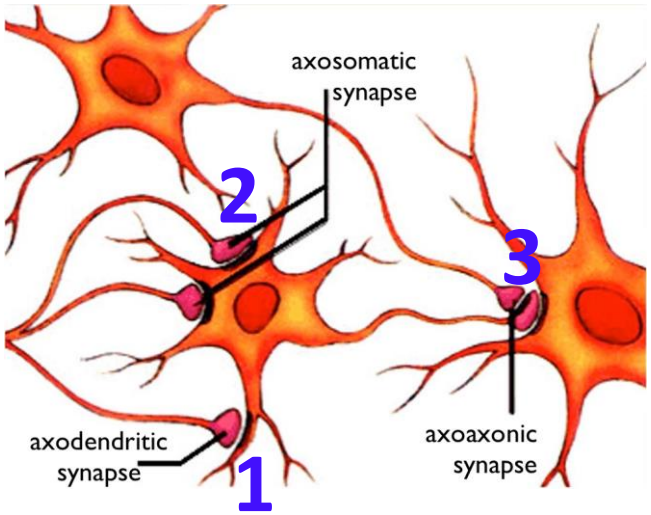
2. ELECTRICAL: communication *via* current flowing through **gap junctions**

Types of Synapses: 1. Chemical

- A junction where the axon of a neuron terminates on one of the following of another neuron:
  1. **Dendrites (axo-dendritic)**
  2. **Soma (axo-somatic) or**
  3. **Axon (axo-axonic)**
- The **presynaptic** neuron releases a chemical (**neurotransmitter, NT**)
- NT binds to a **specific receptor** on postsynaptic neuron enabling an electrical signal (post synaptic potential or action potential, **AP**) to be generated in **postsynaptic N**

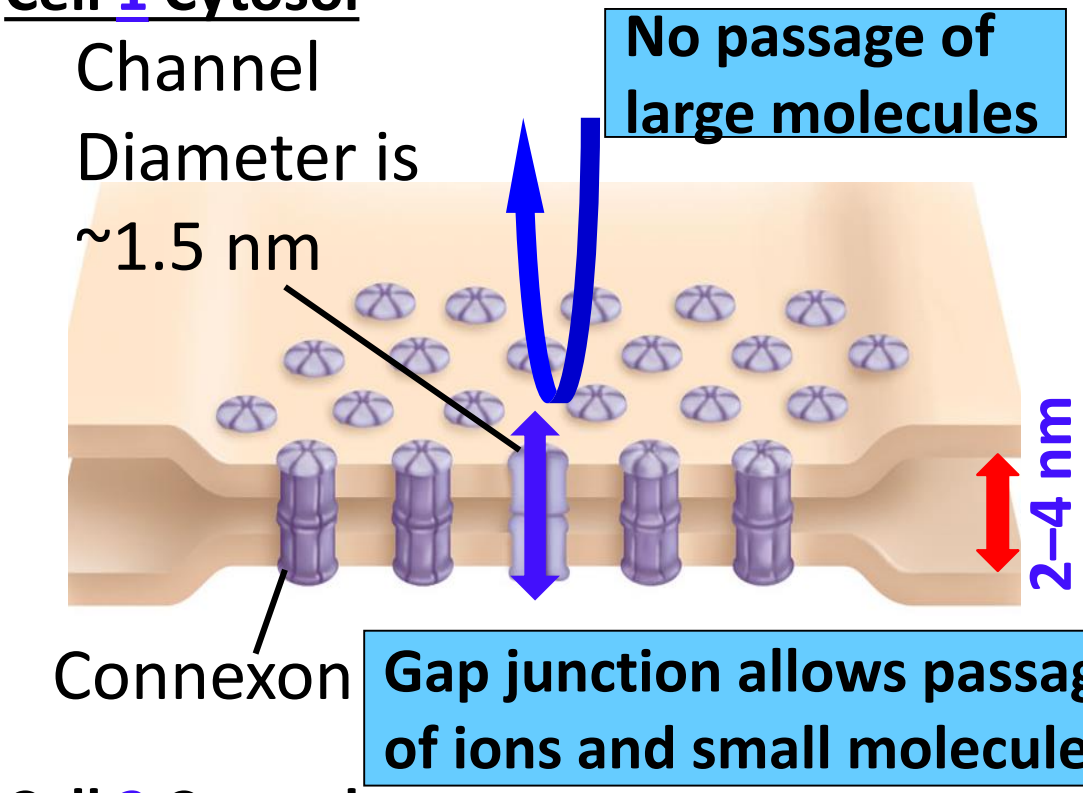


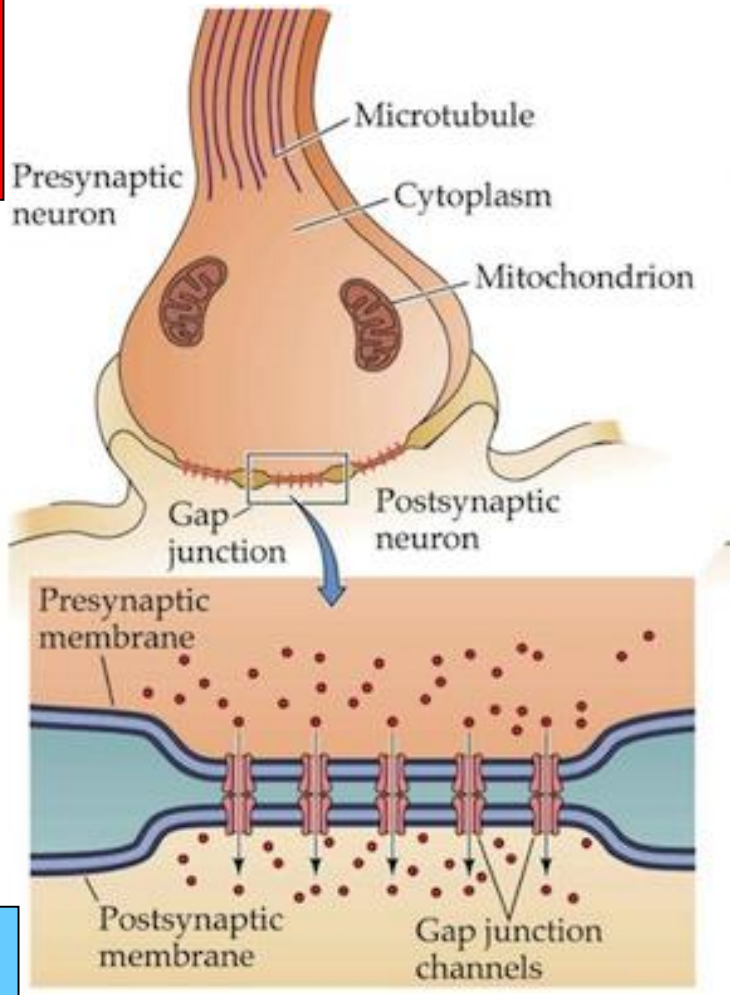
One-direction transmission



Types of Synapses: 2. Electrical

- Very rare in the brain
- Used in attention, emotion & memory
- No synaptic vesicles or NT release



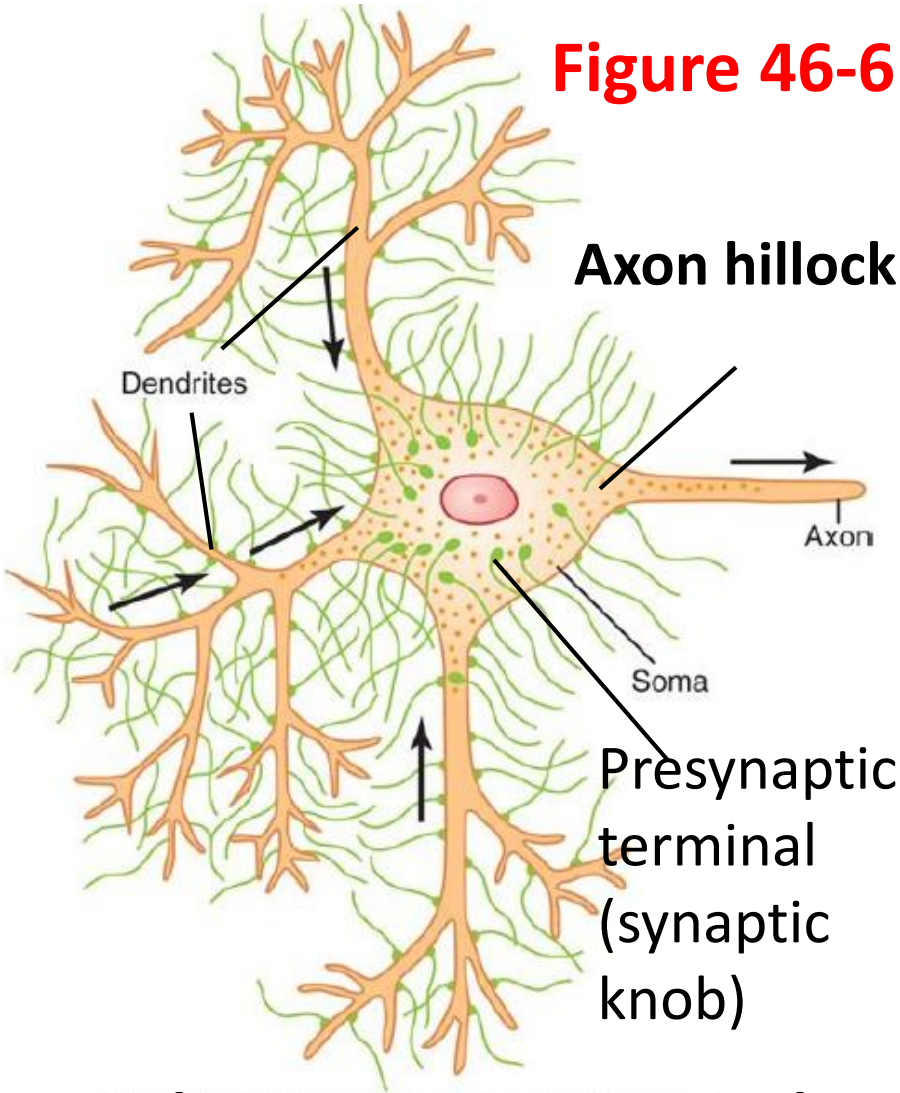


Bidirectional transmission

Physiological Anatomy of Chemical Synapse

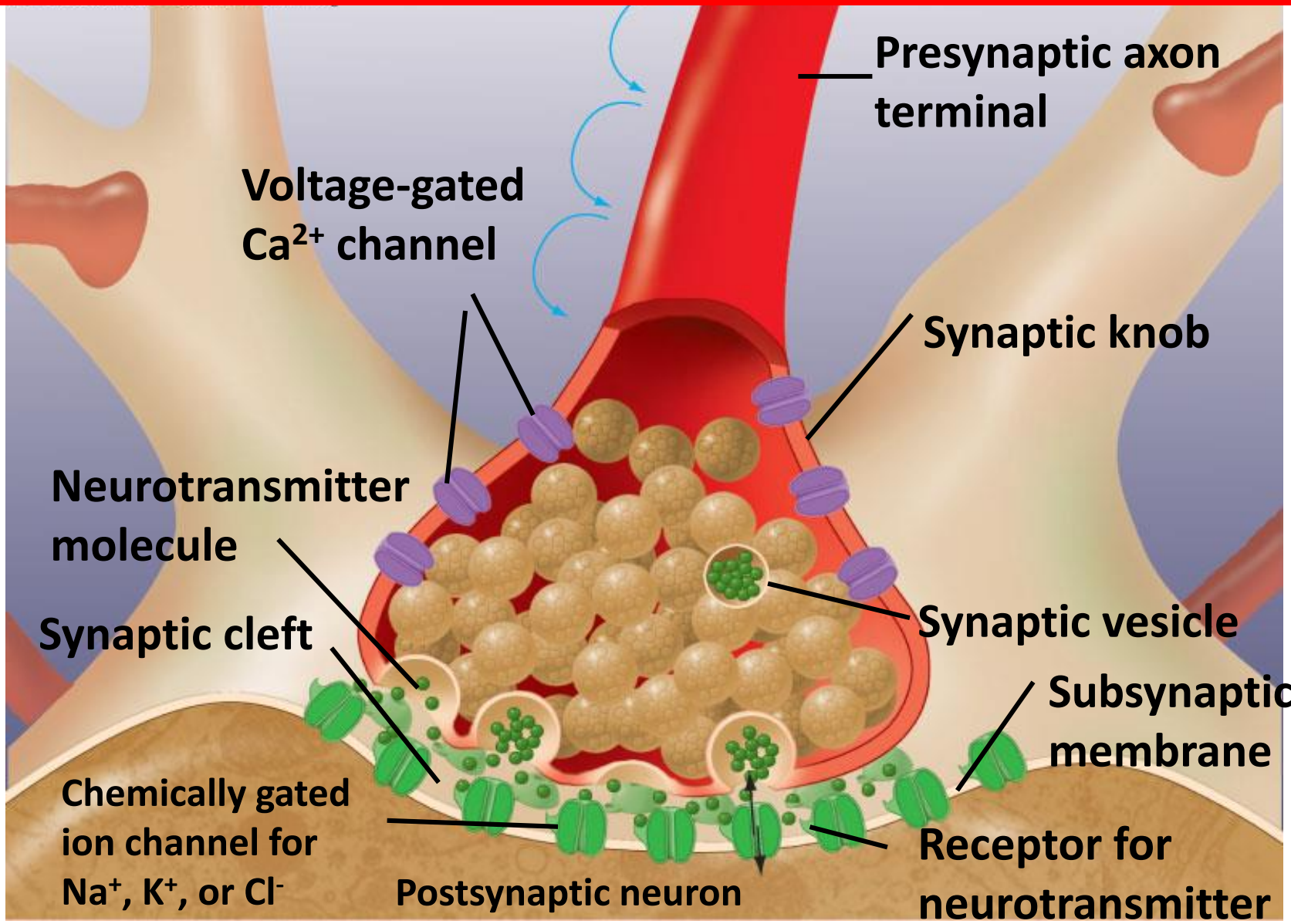
- The CNS contains more than **100 billion** neurons.
- Dendrites and soma receive **thousands of synaptic input**
- Some CNS neurons receive up to **20,000** synaptic input
- The input is converted to a nerve impulse (**AP**) at **axon hillock**
- The output signal (**AP**) travels by way of **a single axon** leaving the neuron.

Figure 46-6



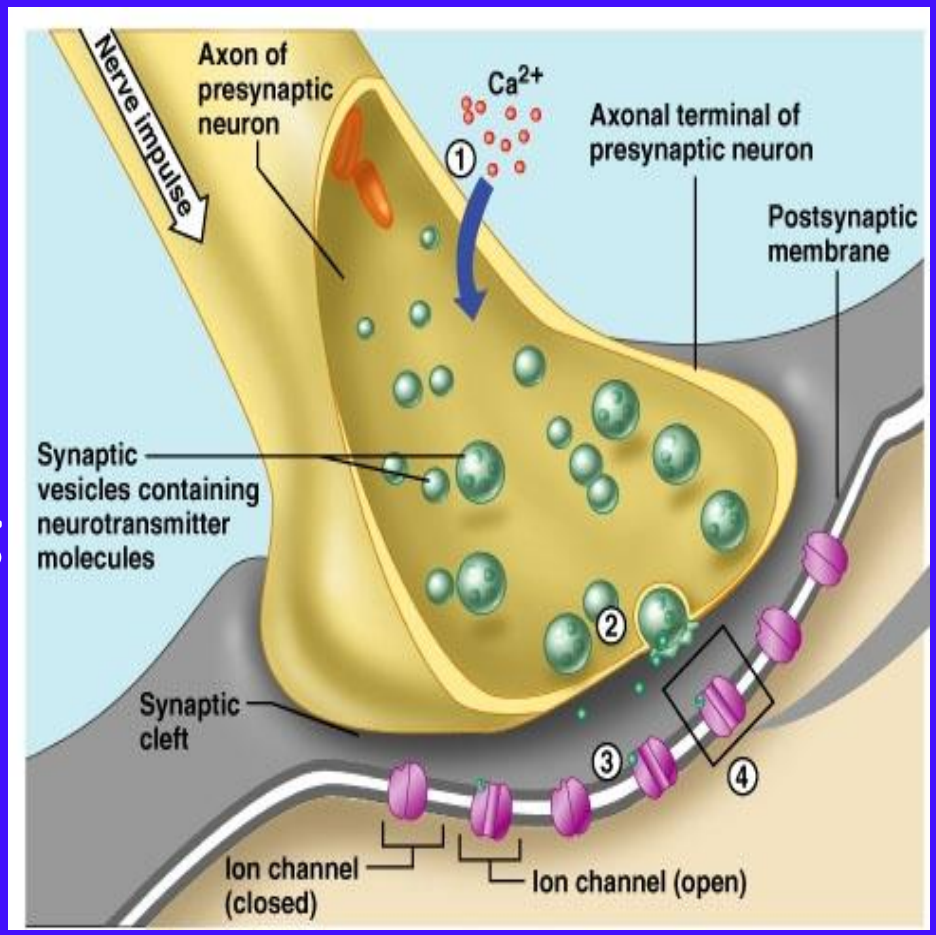
Typical motor neuron in spinal cord

Anatomy of a Chemical Synapse



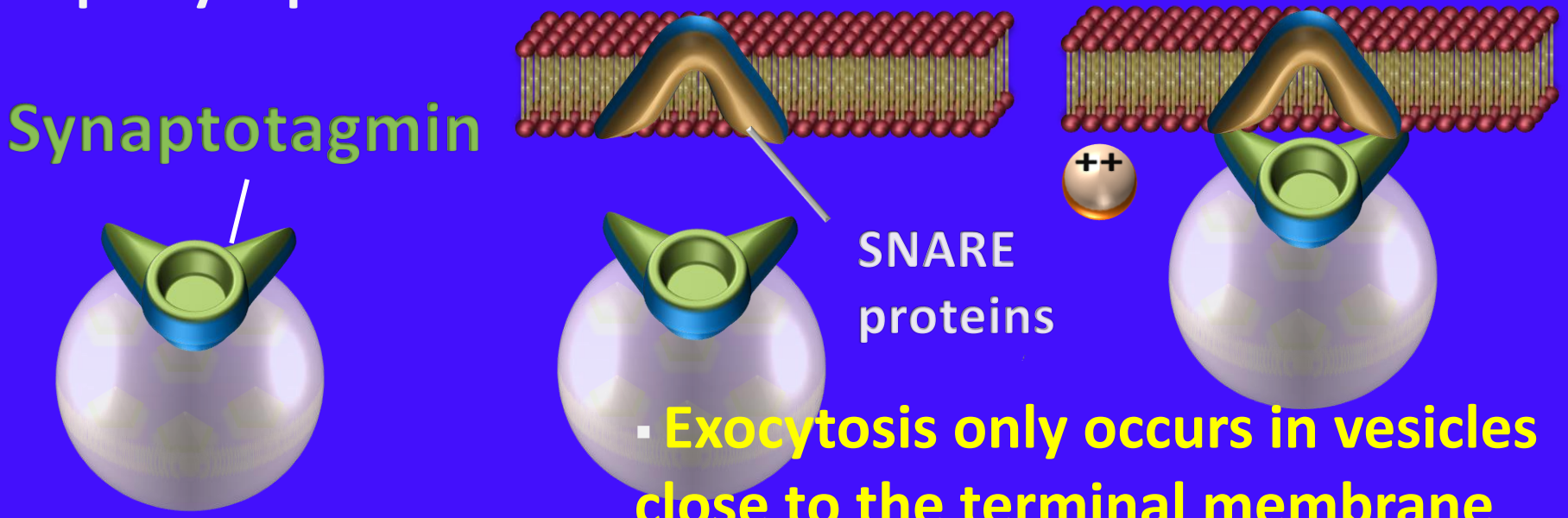
What are Synaptic Vesicles

- Are abundant organelles of with a diameter of ~40 nm
- Can accommodate only a limited number of NTs
- Each vesicle contains only one type of a NT
- Different vesicles containing different types of NTs are often found in a single synaptic terminal
- Synaptotagmin and SNAREs are proteins involved in the vesicle fusion



Synaptic Vesicular Membrane

- *Synaptotagmin (on the vesicle)* helps the vesicle to bind to the terminal membrane without Ca^{2+}
- **SNARE proteins** on presynaptic membrane
- Ca^{2+} binds to synaptotagmin and initiates an interaction with SNARE proteins causing exocytosis



- Exocytosis only occurs in vesicles close to the terminal membrane

Classes of Neurotransmitters (NTs)

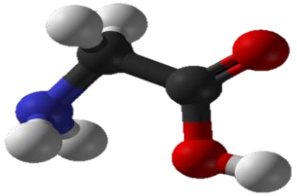
A. Large-molecule NTs (Slow)

- OXYTOCIN
- NEUROKININ
- SOMATOSTATIN
- SUBSTANCE P
- VASOPRESSIN

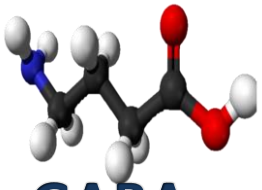
Neuropeptides

There are over 100 NTs

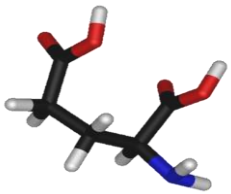
B. Small-molecule NTs (Fast)



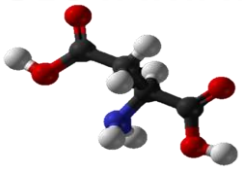
GLYCIN



GABA

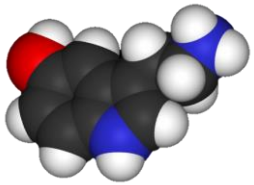


GLUTAMATE

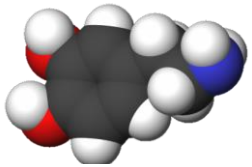


ASPARTATE

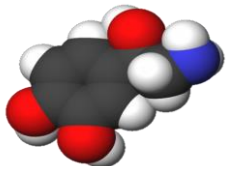
Amino Acids



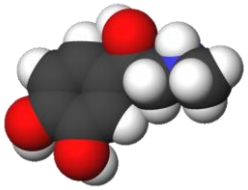
DOPAMINE



SEROTONIN

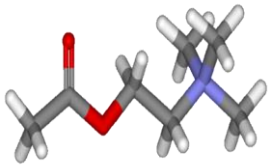


NORADRENALINE



ADRENALINE

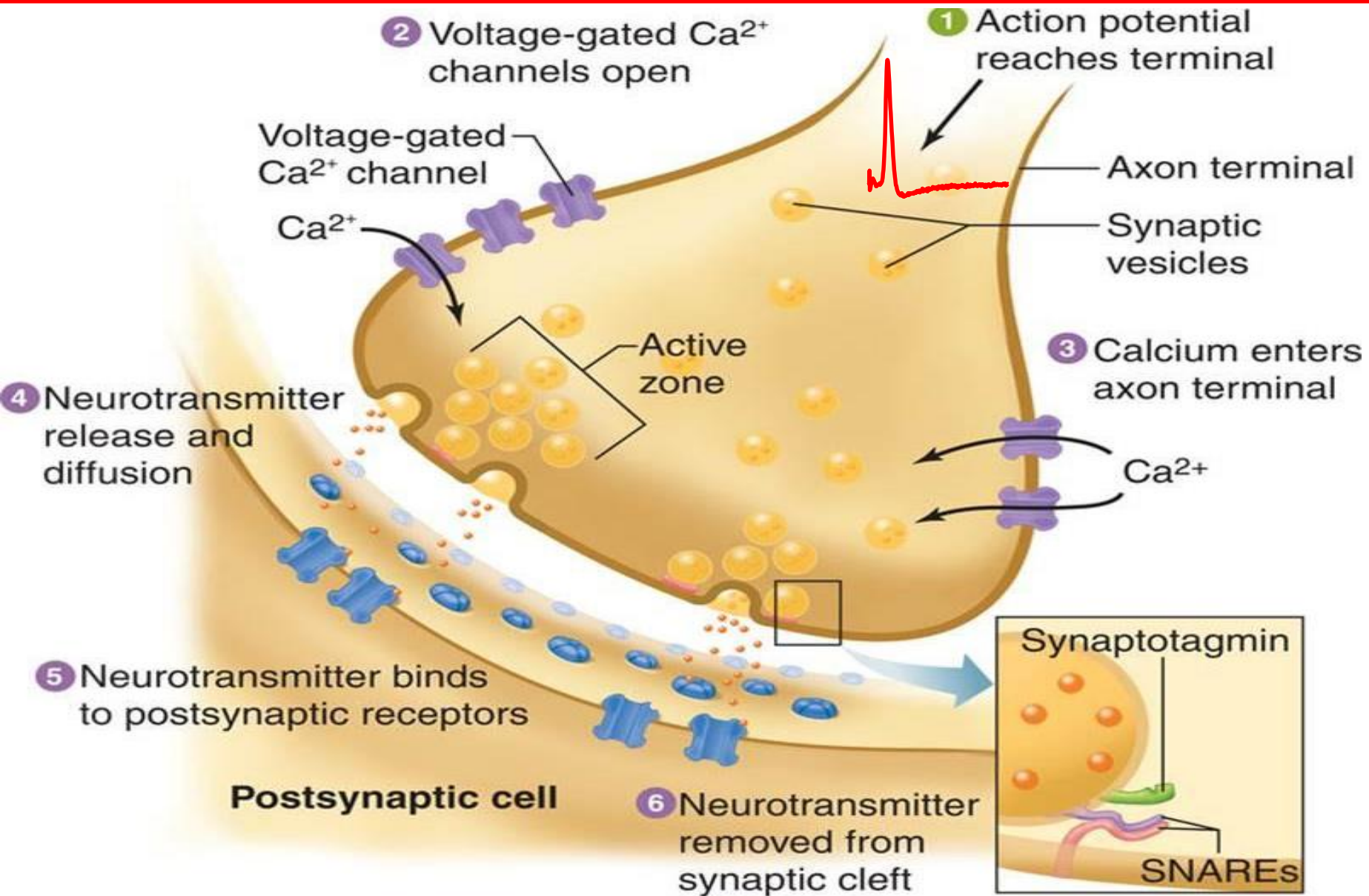
Monoamines



ACETYL CHOLINE

Choline ester

How Are Neurotransmitters Released?

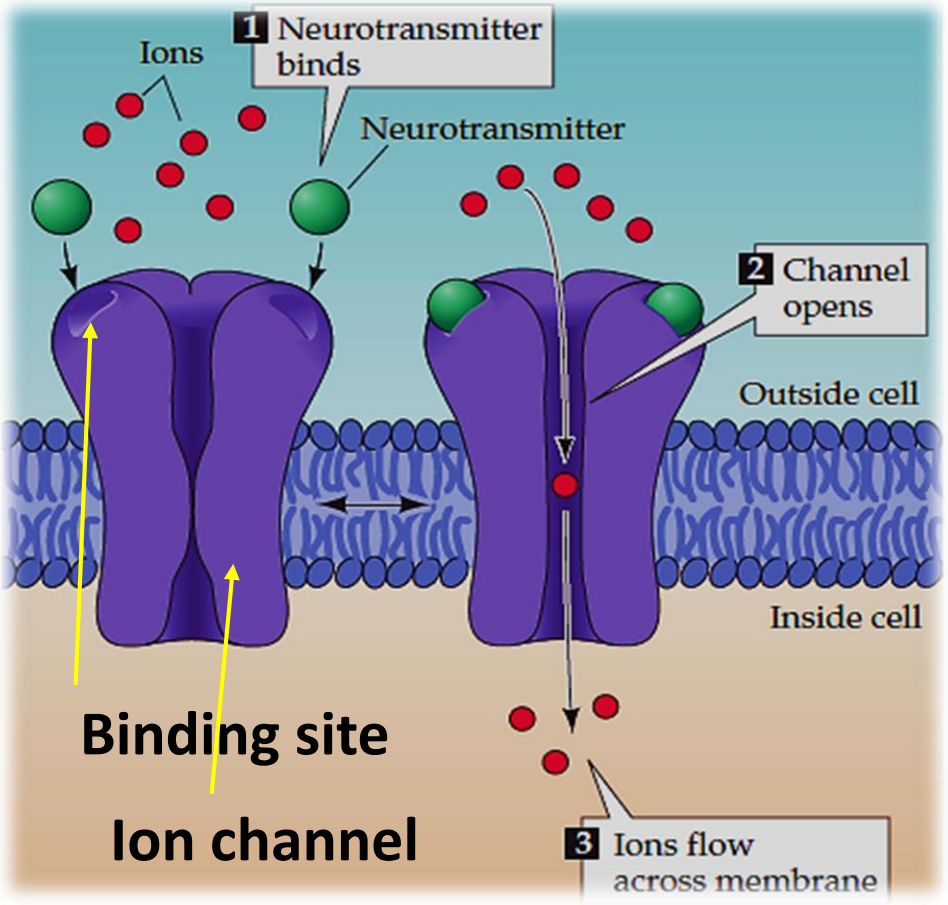


NT Receptors on Postsynaptic Membrane

- **There are 2 types of receptor proteins (NT receptors) on membranes of postsynaptic neurons:**
  - **Ionotropic receptors:** these **directly** gate ion channels (also known as **ligand-gated** ion channels)
  - **Metabotropic receptors**: these act through second messenger systems

Ionotropic Receptors

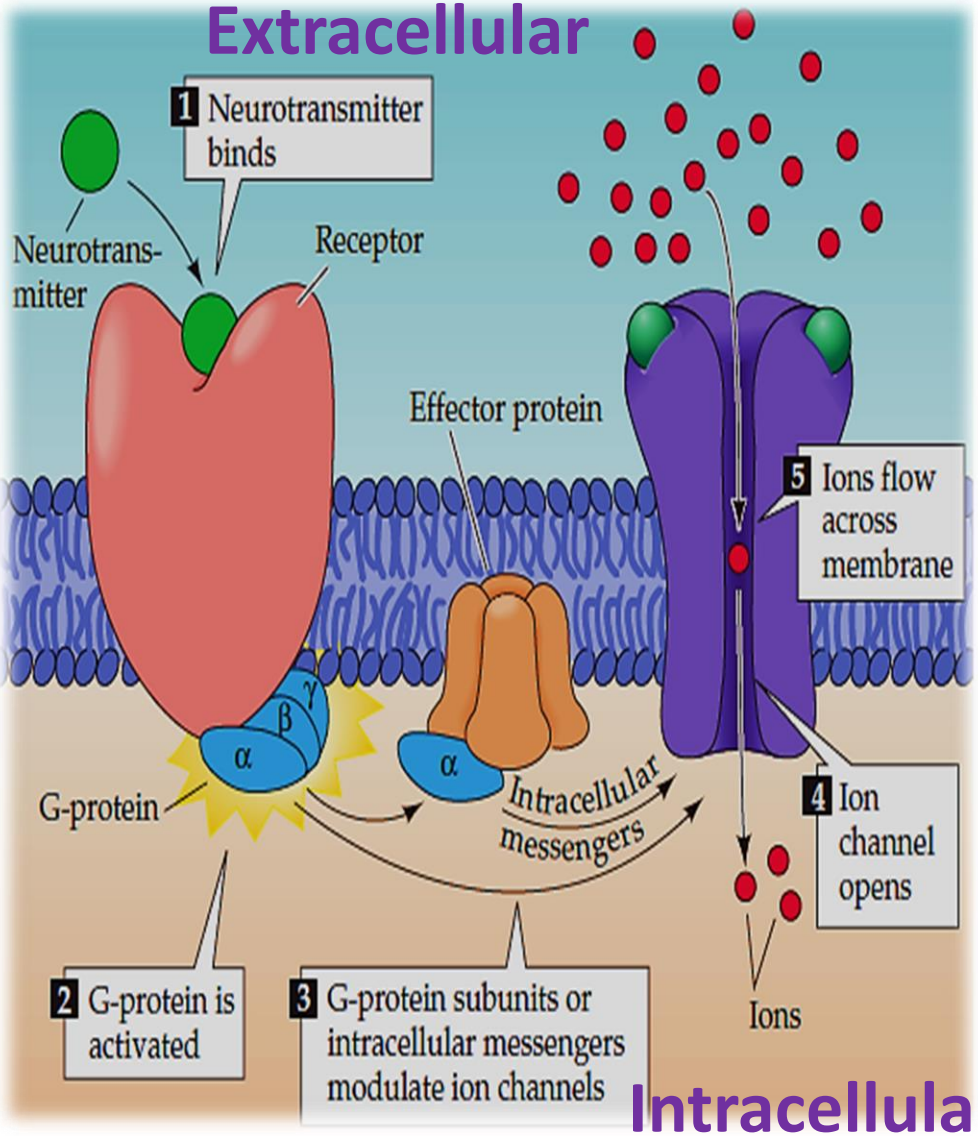
- Are linked directly to ion channels
- They contain two functional domains:
  - An extracellular site that binds NTs (**binding site**)
  - A membrane-spanning domain that forms an **ion channel**
    - **Cation channels (mainly Na^+, but also K^+ and Ca^{+2})**
    - **Anion channels (Cl^-)**



✓ **Whether a NT is excitatory or inhibitory depends on the receptor it binds to**

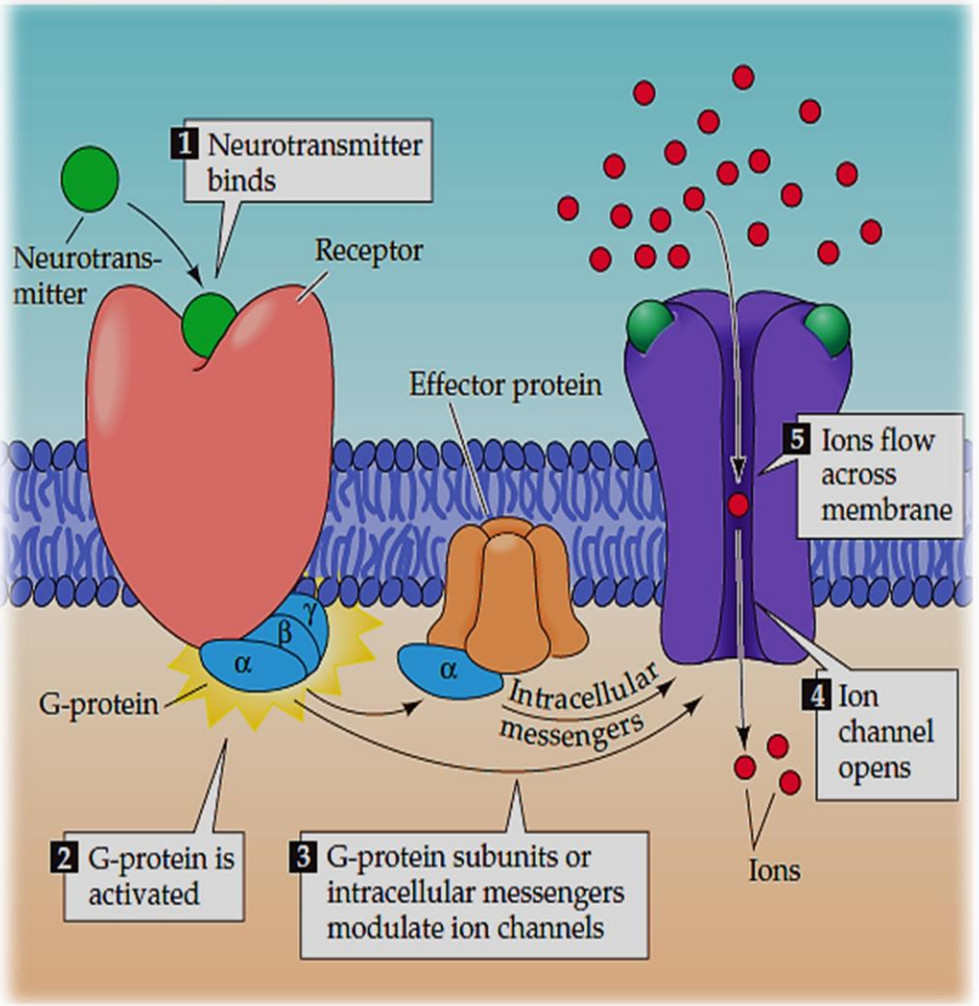
Metabotropic Receptors-1

- They are separated physically from the ion channel
- They are proteins with an extracellular domain that contains a NT **binding site** and an intracellular domain that binds to a **G-protein** (*guanine nucleotide-binding proteins*).
- They activate channels **indirectly** through activation of intermediate molecules called **G-proteins**



Metabotropic Receptors-2

- They are also called **G-protein-coupled receptors.**
- G protein dissociate from the receptor:
  - Directly interact with ion channels
  - Bind to other effector proteins, such as enzymes, that make intracellular **2nd messengers** that **open** or **close** ion channels.



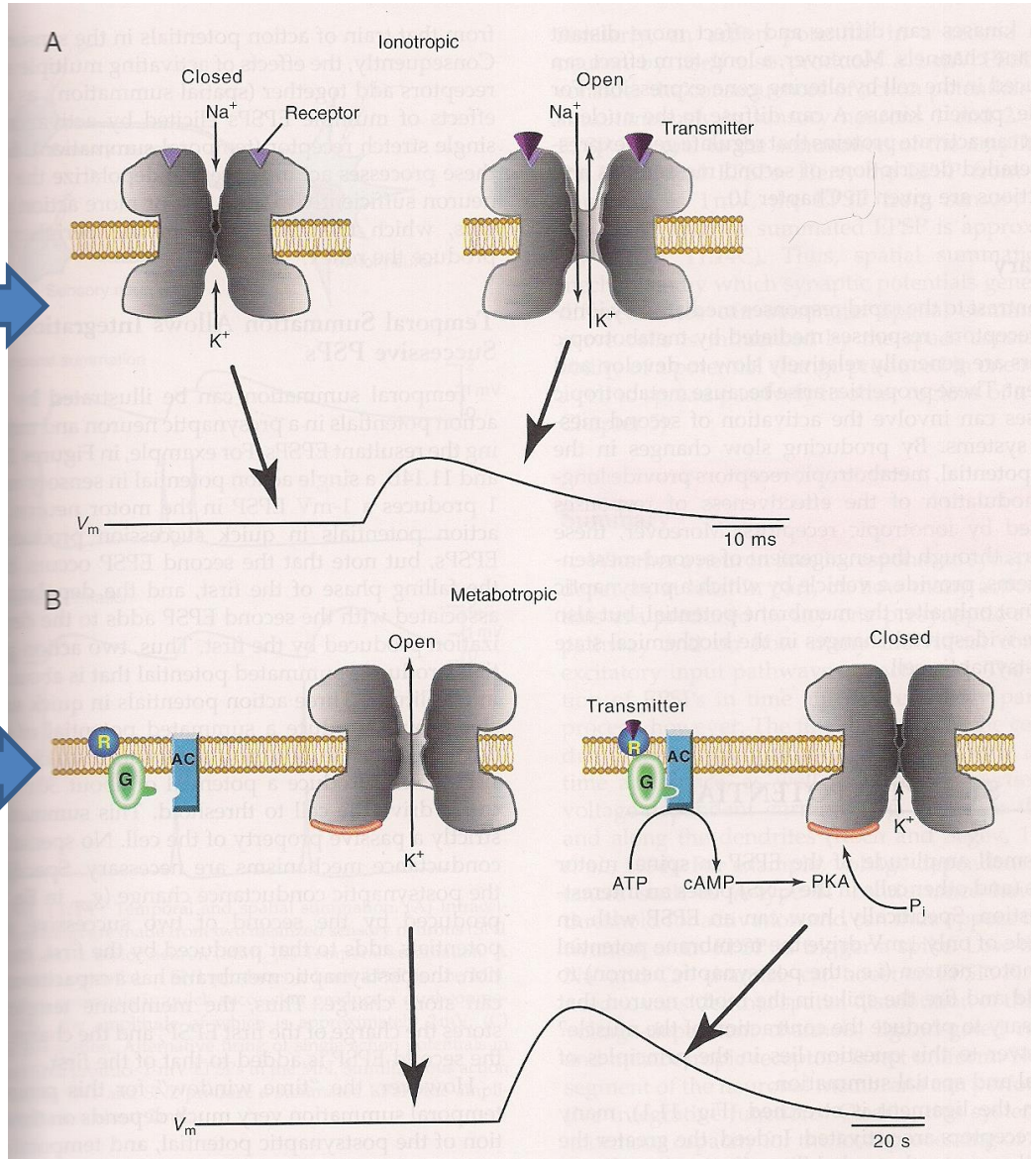
✓ **They are called metabotropic receptors because their end effects on ion channels involve one or metabolic steps**

Fast & Slow Postsynaptic Potentials

- **Fast postsynaptic potentials (PSPs)** are mediated by ionotropic receptors **(<30 ms)**

- **Slow postsynaptic potentials (PSPs):** are mediated by metabotropic receptors **(minutes or days!)**

Note the difference in the time scale 10 vs 20 ms



Functional Differences Between Ionotropic & Metabotropic Receptors

IONOTROPIC

- Mediate **rapid** PSPs.
- Duration of PSPs is **10-30 ms** or less
- PSPs (EPSP or IPSP) develop within 1-2 msec after an **AP** reaching the pre-synaptic terminal

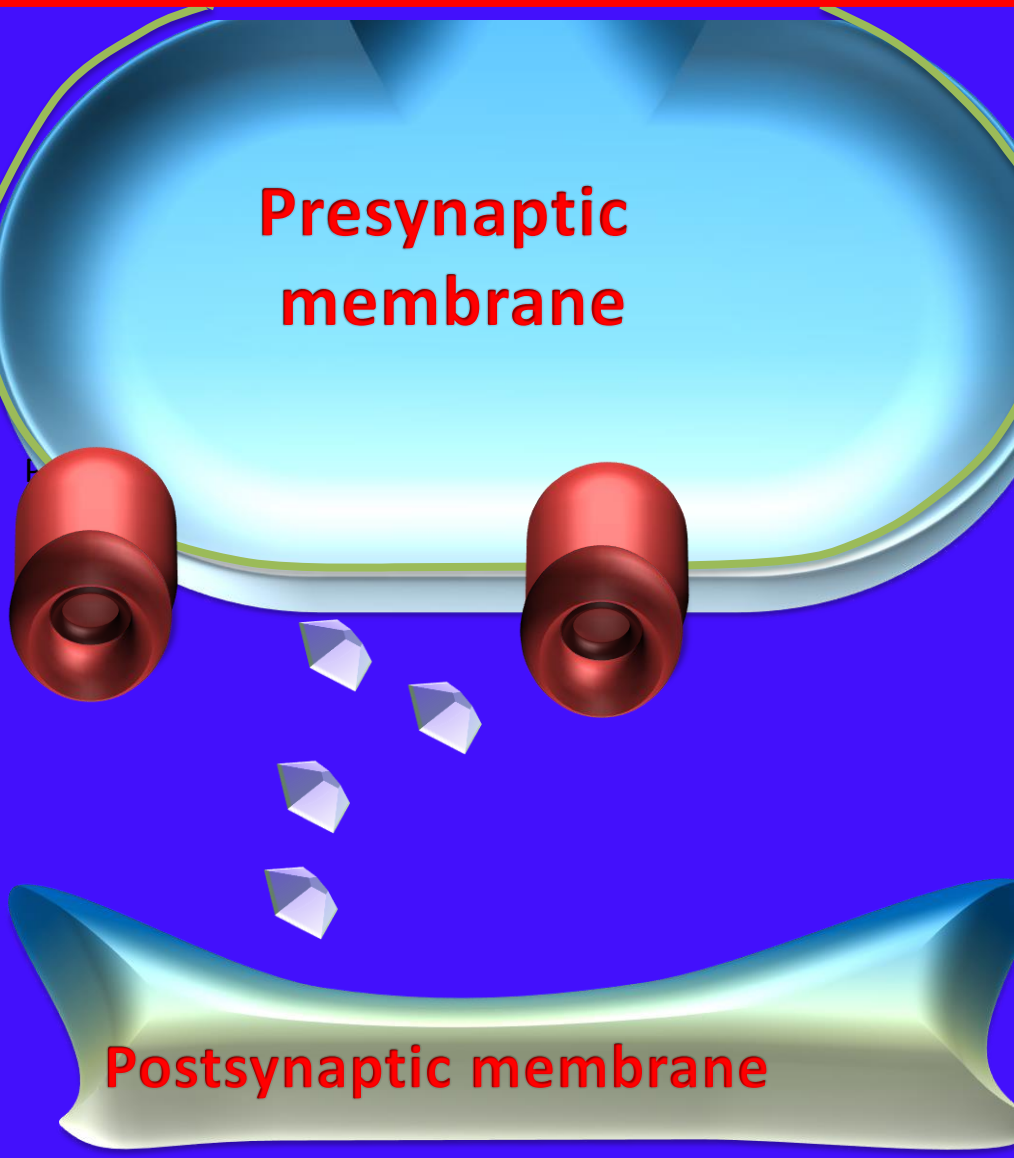
METABOTROPIC

- Mediate **slower** PSPs
- Duration from **100`s ms to minutes or longer.**
- This slowness is due to activation of second messengers leading to opening of ion channels

Note: a NT may activate both ionotropic and metabotropic receptors to produce both fast & slow postsynaptic potentials at the same synapse.

What is the Fate of Neurotransmitters?

- Inactivated by enzymes
- Actively pumped into synaptic knobs (reuptake)
- Diffuses away



Most drugs exert theirs actions at synapses:

- Specific serotonin reuptake inhibitors (SSRIs) e.g. Prozac for depression
- Cocaine blocks reuptake of dopamine

Excitatory & Inhibitory Synapses

- At rest **(A)**, resting membrane potential (**-65 mV**) is the same throughout the cell

- At **excitatory synapses (B)**, depolarization (EPSP): Na^+ influx (**20 mV change,** to -45mV)

- AT **inhibitory synapses (C)**, small hyperpolarization (IPSP): K^+ efflux or or Cl^- influx (**5 mV change**)

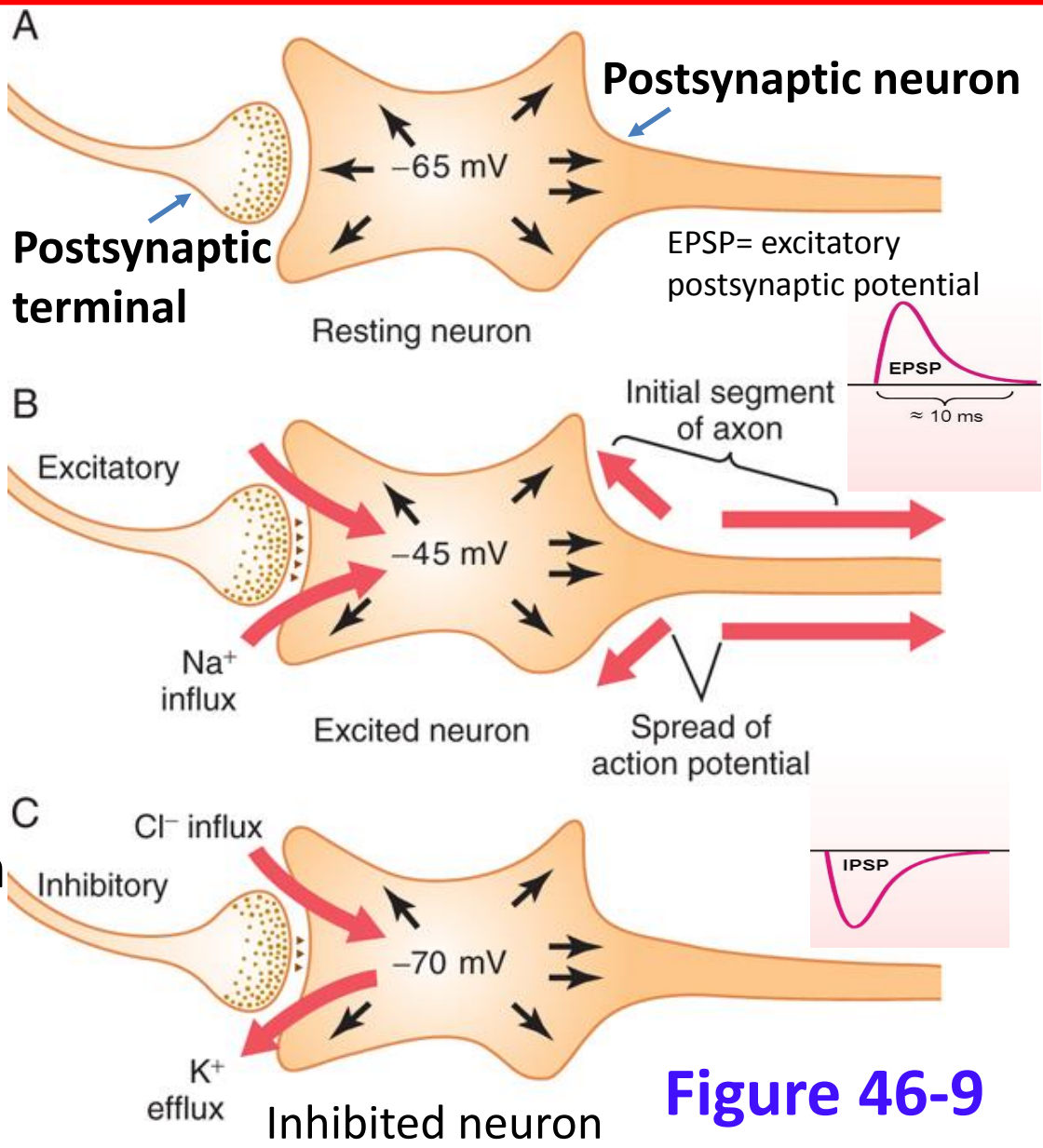


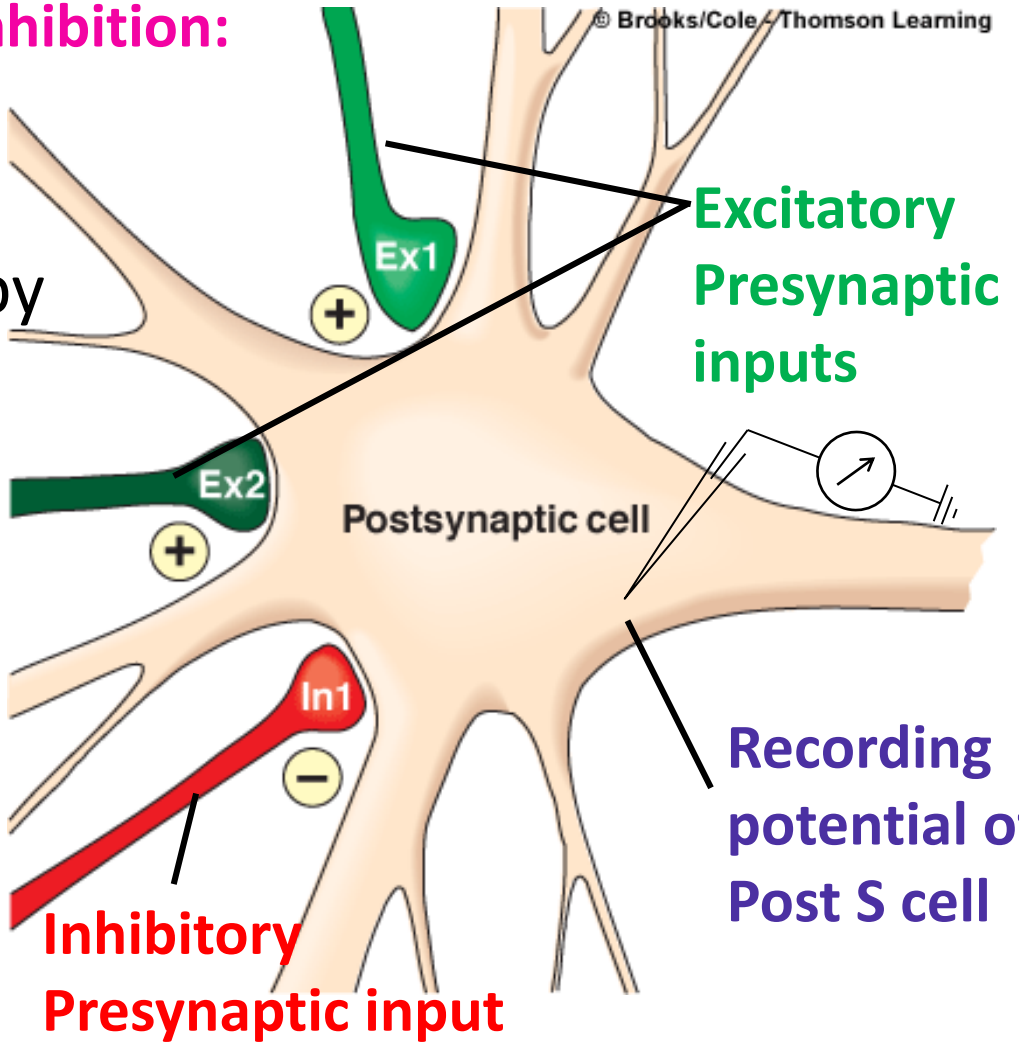
Figure 46-9

Synaptic Inhibition: 1.Postsynaptic

There are 2 types of synaptic inhibition: Postsynaptic & Presynaptic

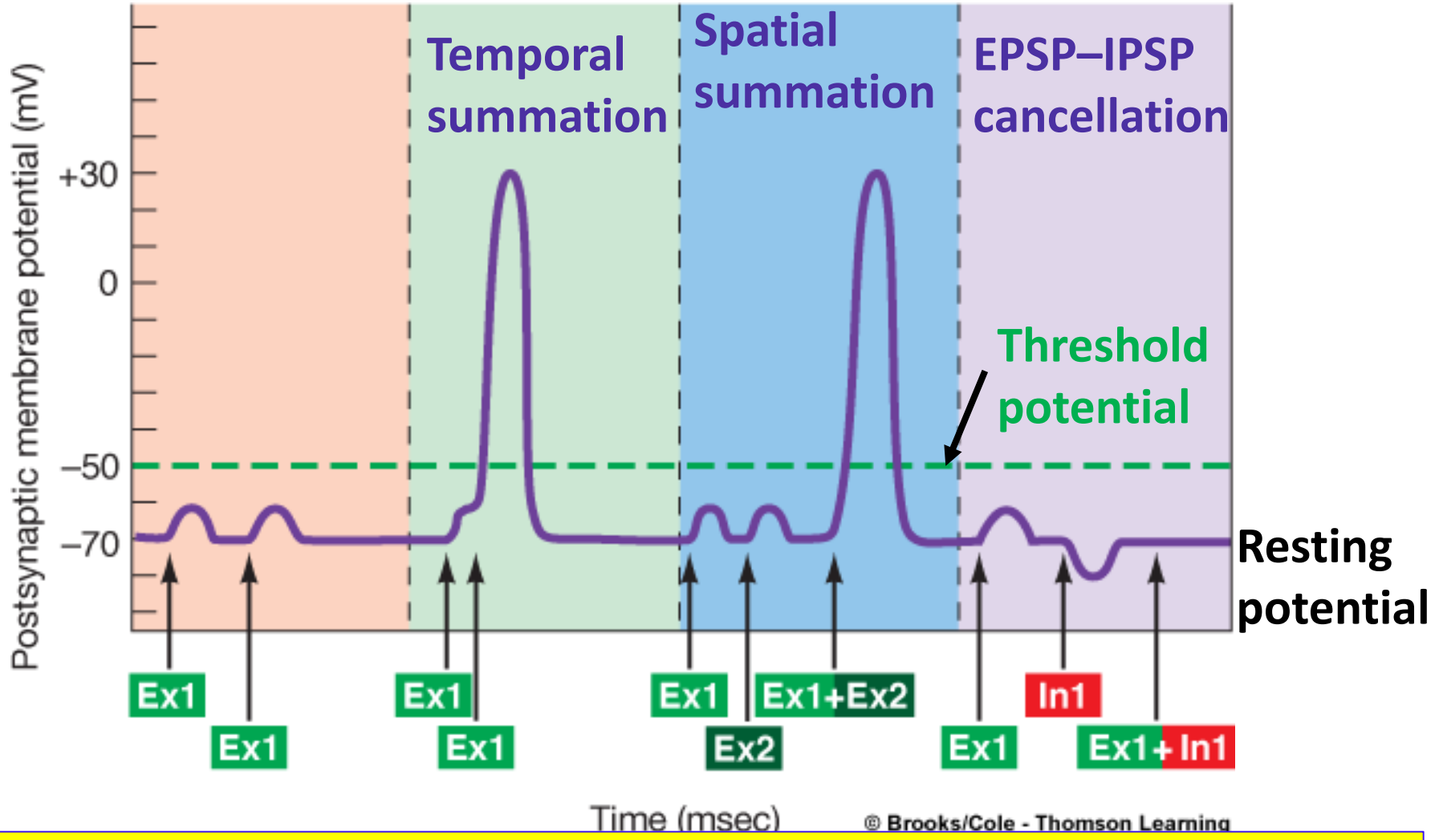
- Postsynaptic is accomplished directly by altering the membrane permeability of the postsynaptic cell.
- **EX1=excitatory**
- **In1= inhibitory**

Important note: A single presynaptic terminal can never cause a large voltage change that reaches threshold



Summation is needed

Temporal & Spatial Summation



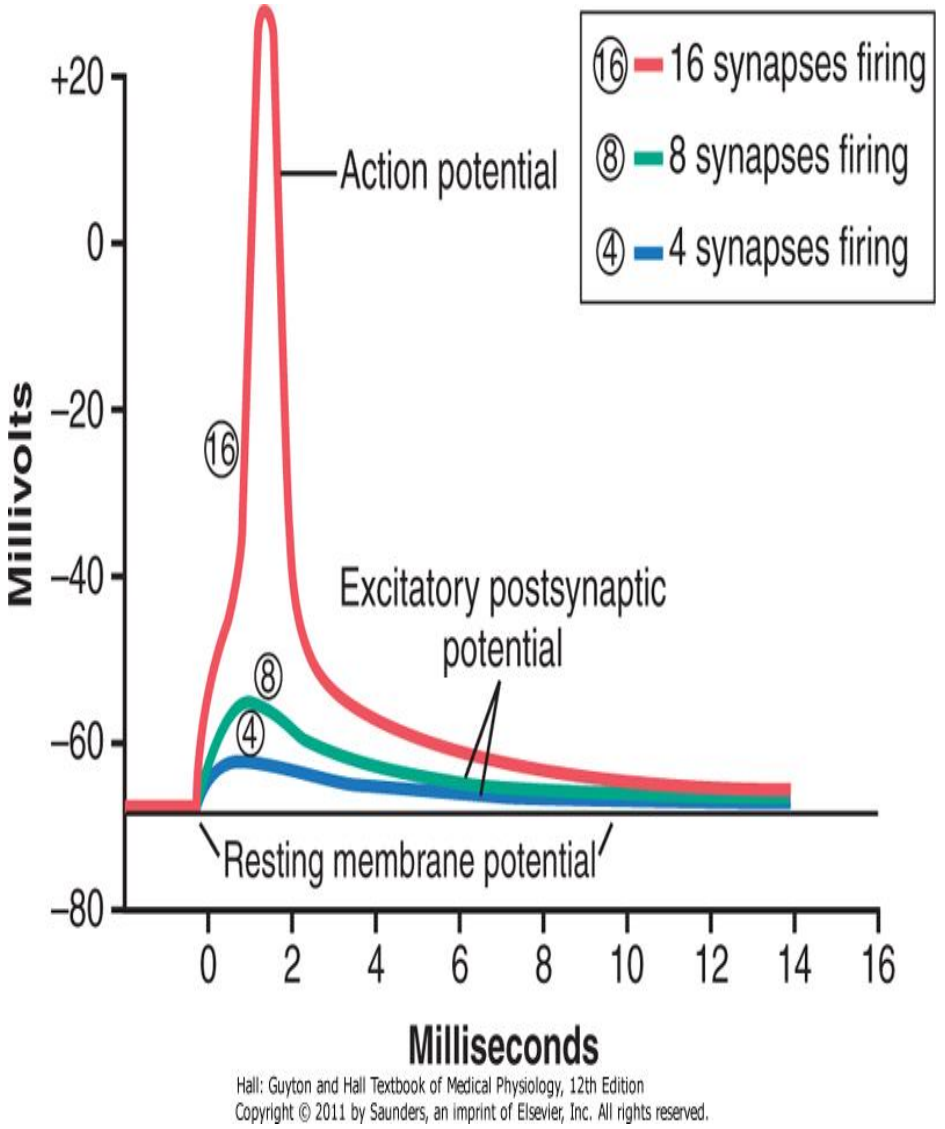
Post-synaptic potential can be of varying amplitude (graded); it can be summed (added on top of each other)

Time Course of Postsynaptic Potentials

- Postsynaptic potentials (PSPs) decline within 15 ms (**not long enough**)

- This is the time needed for excess positive charges to leak out of the excited cell

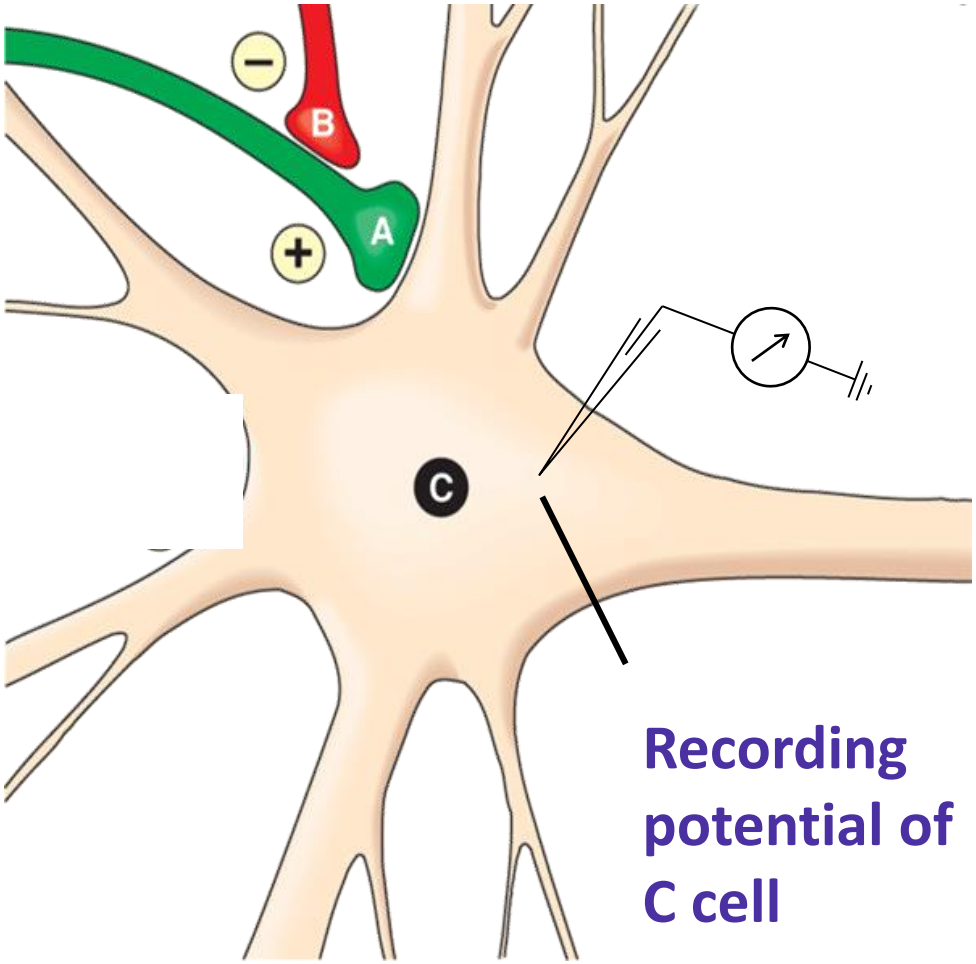
- Firing of only few synapses (4 or 8) will cause PSPs, but these are not large enough to reach **threshold**



Synaptic Inhibition: 2. Presynaptic

- it is accomplished **indirectly** through the membrane of an excitatory pre-synaptic terminal

- Inhibitory terminal reduces (**through Cl^- channels**) influx of Ca^{2+} into excitatory terminal during an action potential (**AP**)



(see next slide)

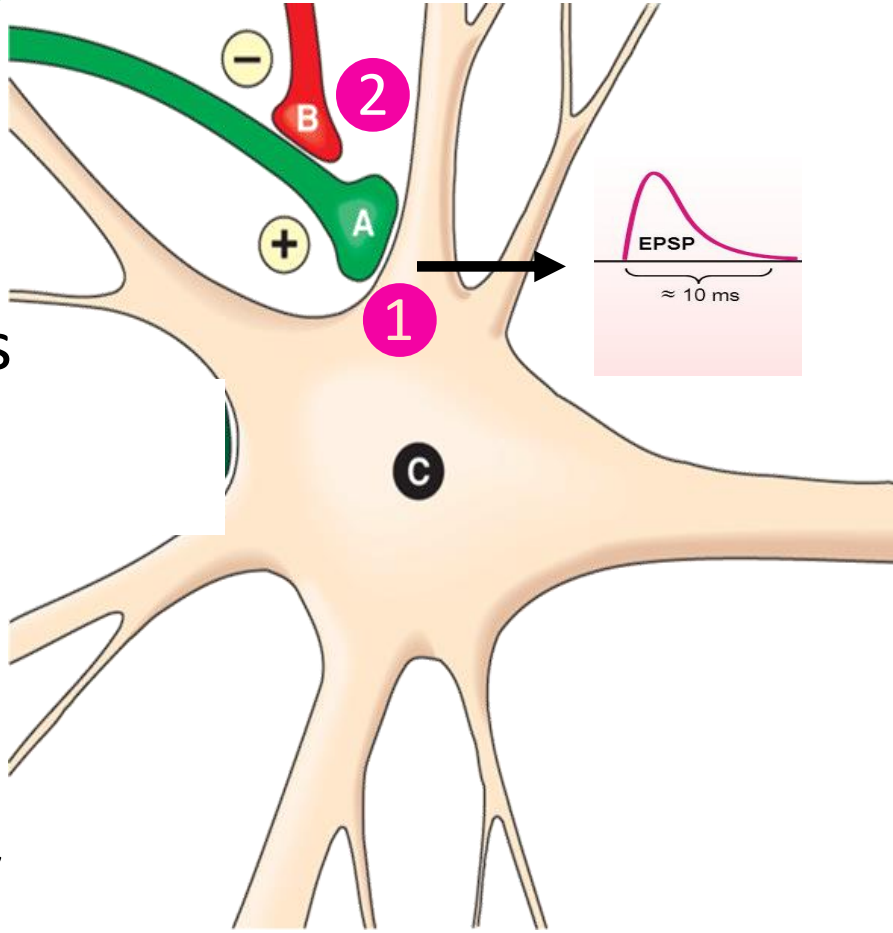
Synaptic Inhibition: 2. Presynaptic

1. Firing of presynaptic **A alone** will result in EPSP

2. Activation of **pre-synaptic B** will cause opening of Cl^- channels in **terminal A**

- Entry of Cl^- into terminal A will reduce **depolarization**.

- **This** results in reduced Ca^{2+} entry which causes reduced NT release from **A** and prevention of **EPSP**.



Most CNS Drugs Affect Synaptic Mechanisms

- **Drugs could influence the effectiveness of synaptic transmission by**:
  - Altering **synthesis, storage** or **release** of neurotransmitter
  - Modifying interaction of neurotransmitter with post synaptic receptor
  - **Influencing reuptake or destruction of neurotransmitter**

Some Drugs that Affect Neurotransmitters

- **Cocaine:** blocks the reuptake of **Dopamine** by binding competitively with dopamine reuptake transporters. This causes prolonged activation of pleasure pathway (euphoria).
- **Strychnine** competes with glycine; it combines with the glycine receptor & blocks it (no IPSPs).
- **Prozac**, an example of a **Selective Serotonin Reuptake Inhibitor (SSRIs)**
  - Serotonin is involved in neural pathways regulating mood & behavior.
  - **Prozac is used for treating** depression, which is characterized by deficiency of serotonin.

Some Diseases that Affect NTs or their Receptors-1

Parkinson's disease: is due to

- A deficiency of **Dopamine** in a brain region (substantia nigra) controlling complex movements.
- The main features are:
  - Involuntary tremor (shaking of hands)
  - Muscle rigidity

Parkinson's disease Treatment:

- **Levodopa** (L-dopa), a precursor of dopamine, which crosses the blood-brain barrier (unlike dopamine).
- Once inside the brain, it is converted to dopamine & relieves the symptoms of disease

Some Diseases that Affect NTs or their Receptors-2

Myasthenia Gravis: autoimmune disease that targets nicotinic ACh receptors on skeletal muscle fibers (antibodies directed against these receptors)

- The hallmark of the disorder is **muscle weakness**, particularly during sustained activity
- Can be improved by treatment with inhibitors of **Acetylcholinesterase,** the enzyme that normally degrades Ach at the neuromuscular junction.


Thank You
Any Questions
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Factors Affecting Synaptic Transmission

- **Alkalosis:**
  - Increases neuronal excitability.
  - Causes cerebral epileptic seizures (e. g. overbreating in person with epilepsy blows off carbon dioxide and therefore elevates the pH of the blood)
- **Acidosis:**
  - Depresses neuronal excitability
  - pH around 7.0 usually causes a coma
- **Drugs:**
  - Caffeine (coffee, tea) increases neuronal excitability, by reducing the threshold for excitation of neurons.