Introduction to Physiology for medical and dental students

Synapses

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Synapses

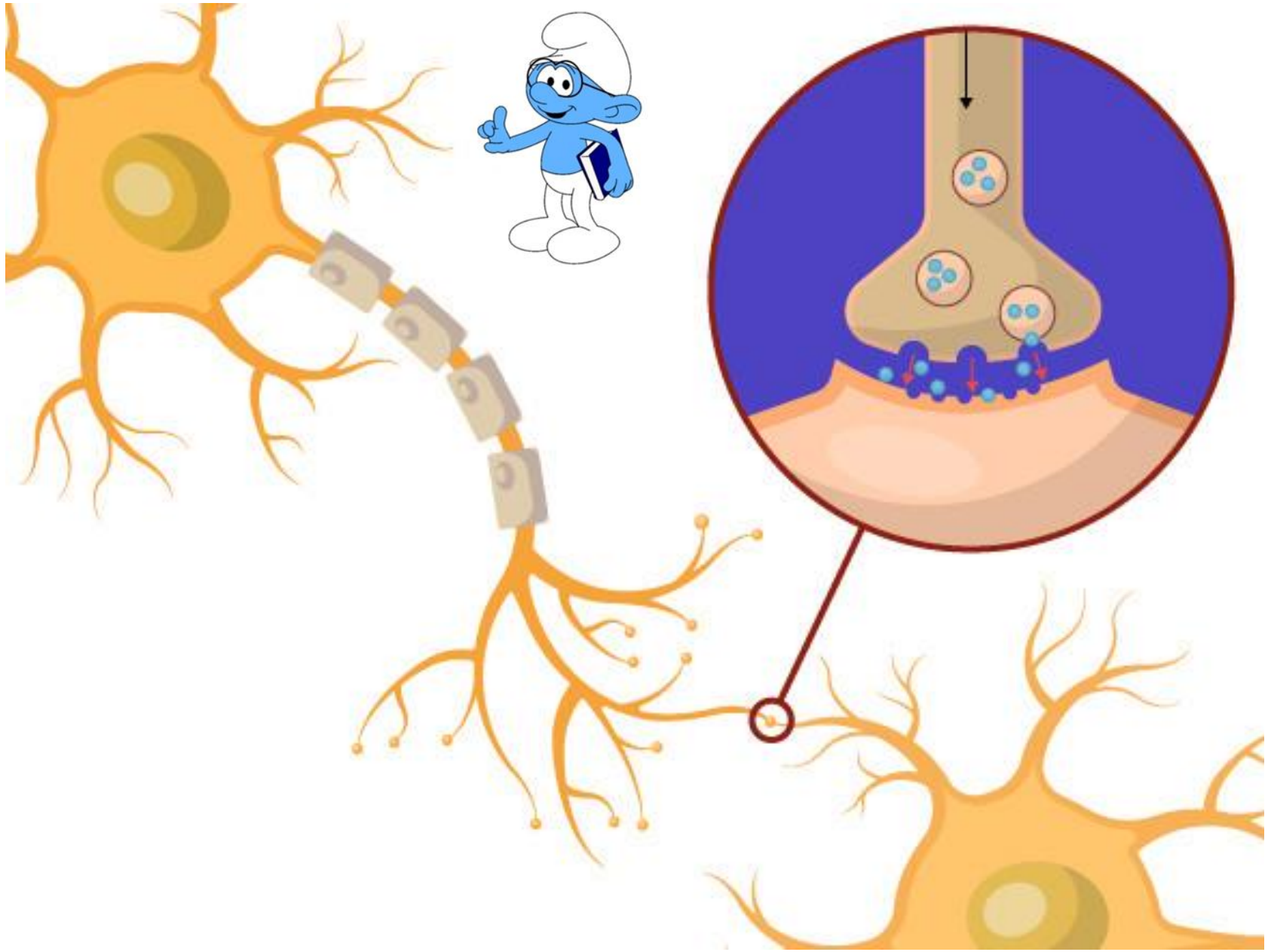
- The synapse is a region where communication occurs between two neurons or between a neuron and an effector cell (muscle cell or glandular cell).

Synaptic functions of neurons

Information is transmitted in the central nervous system mainly in the form of nerve action potentials, called nerve impulses, through a succession of neurons, one after another.

However, this impulse may be blocked, changed into repetitive impulses, or integrated with other impulses.

These functions are called **synaptic functions of neurons**.



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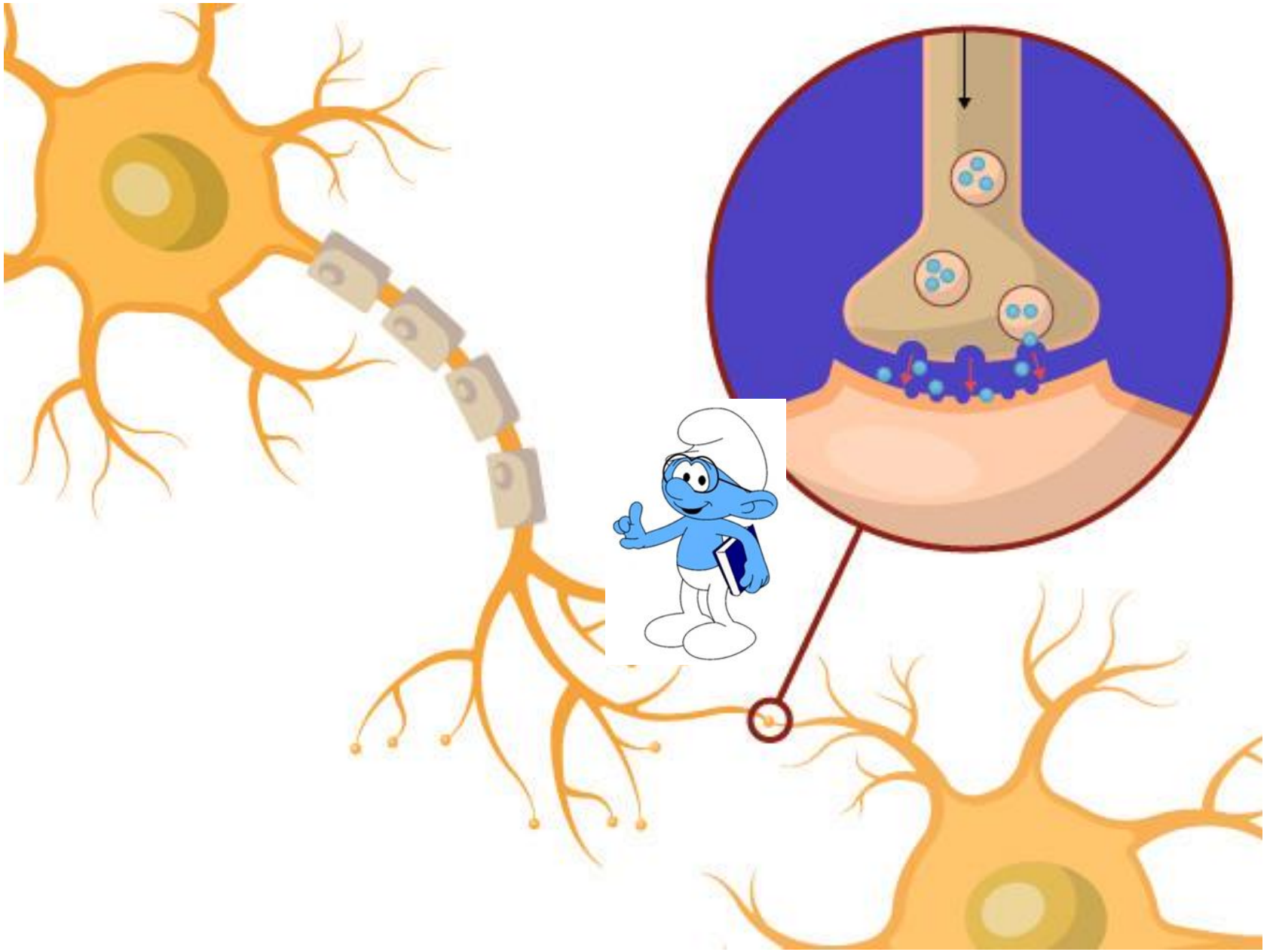

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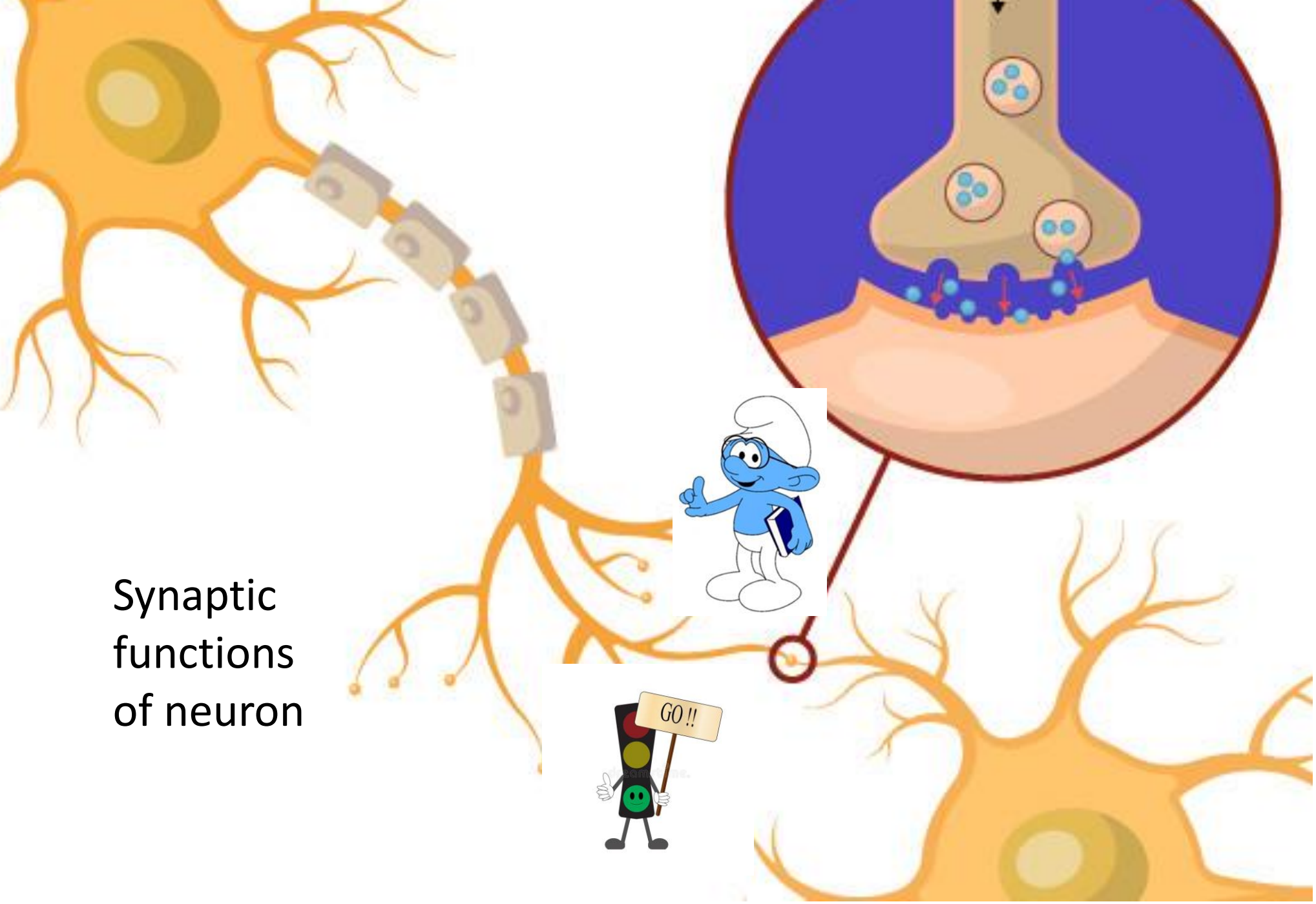
Synaptic functions of neuron



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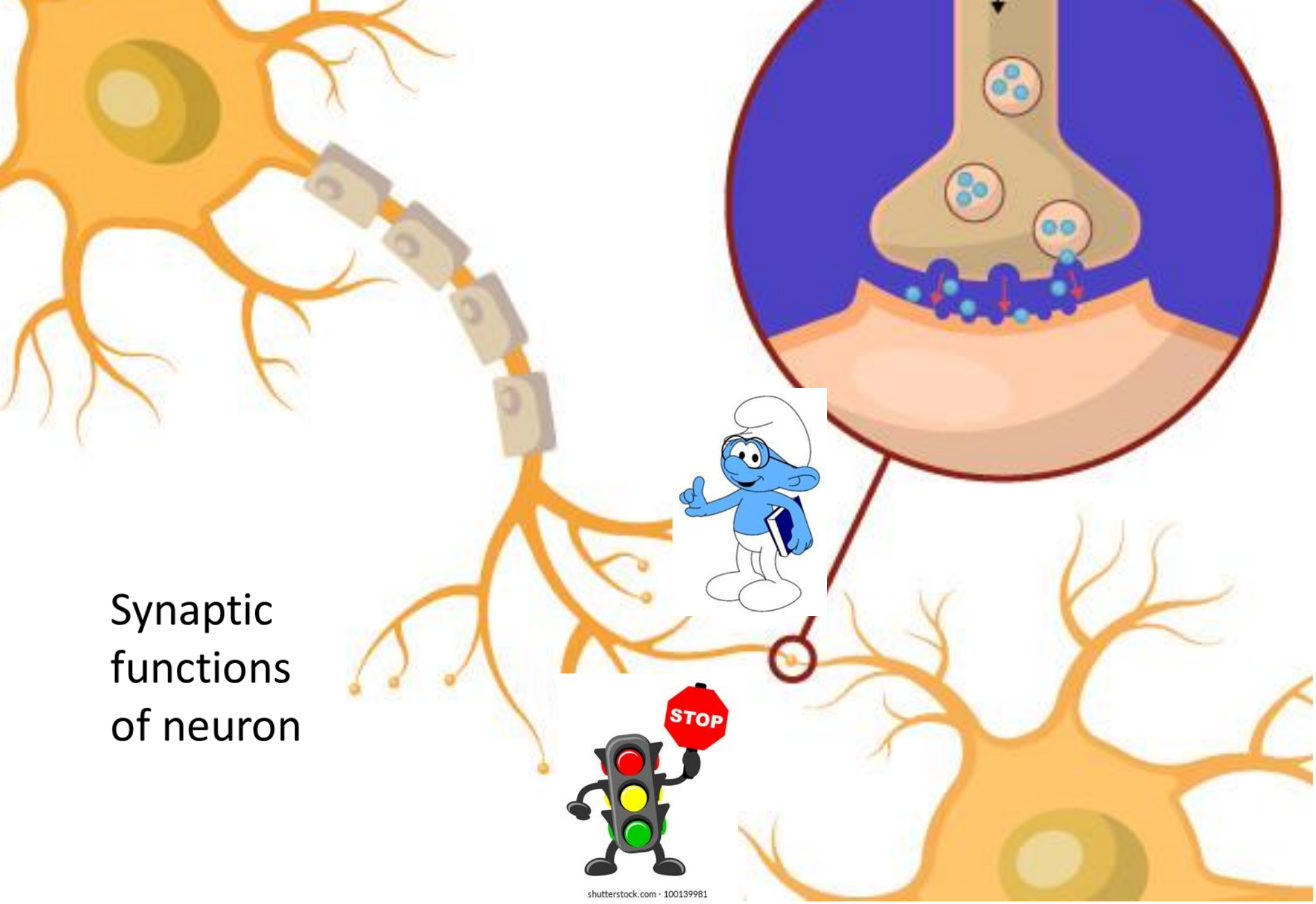
Synaptic functions of neuron



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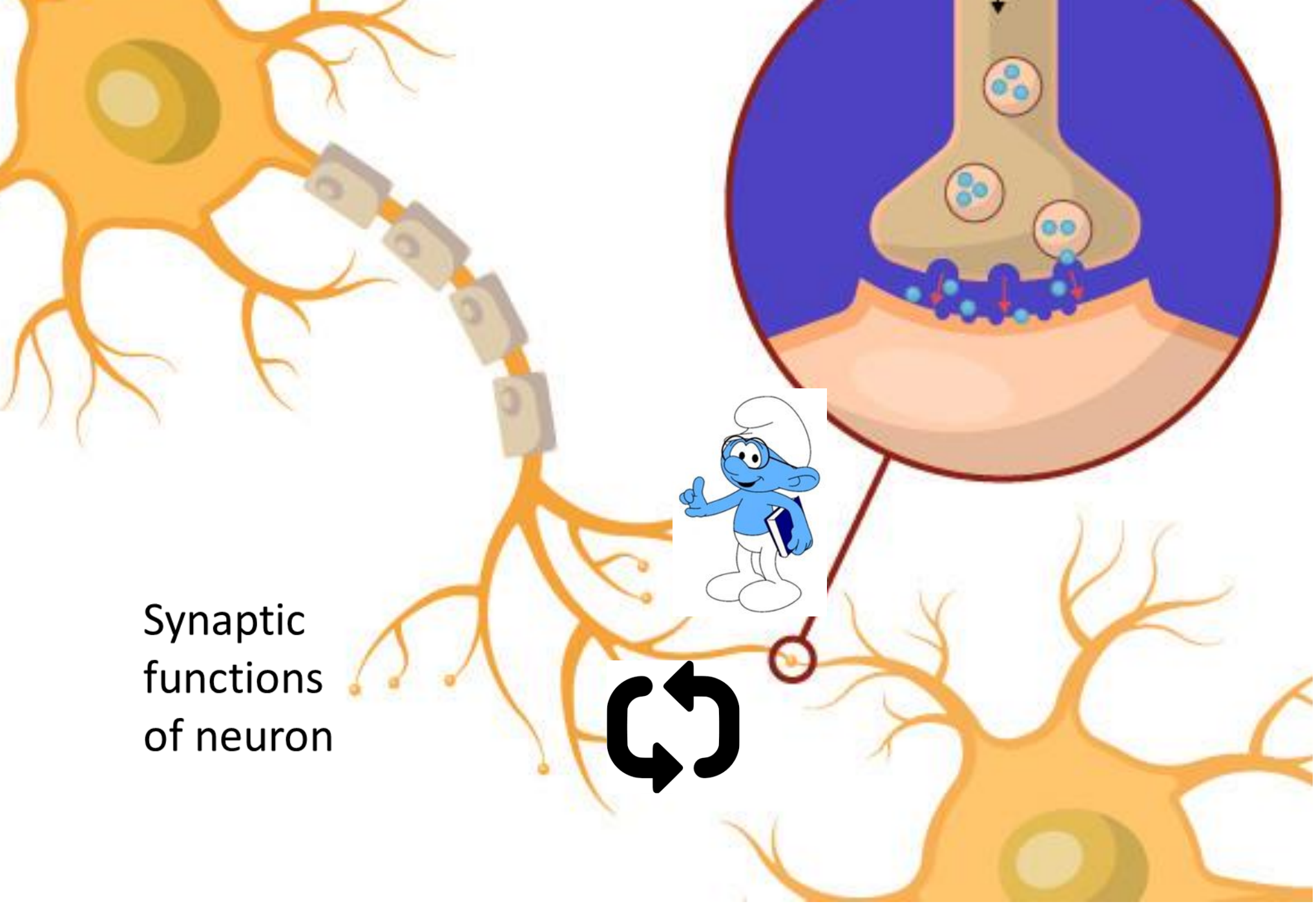

Synaptic functions of neuron

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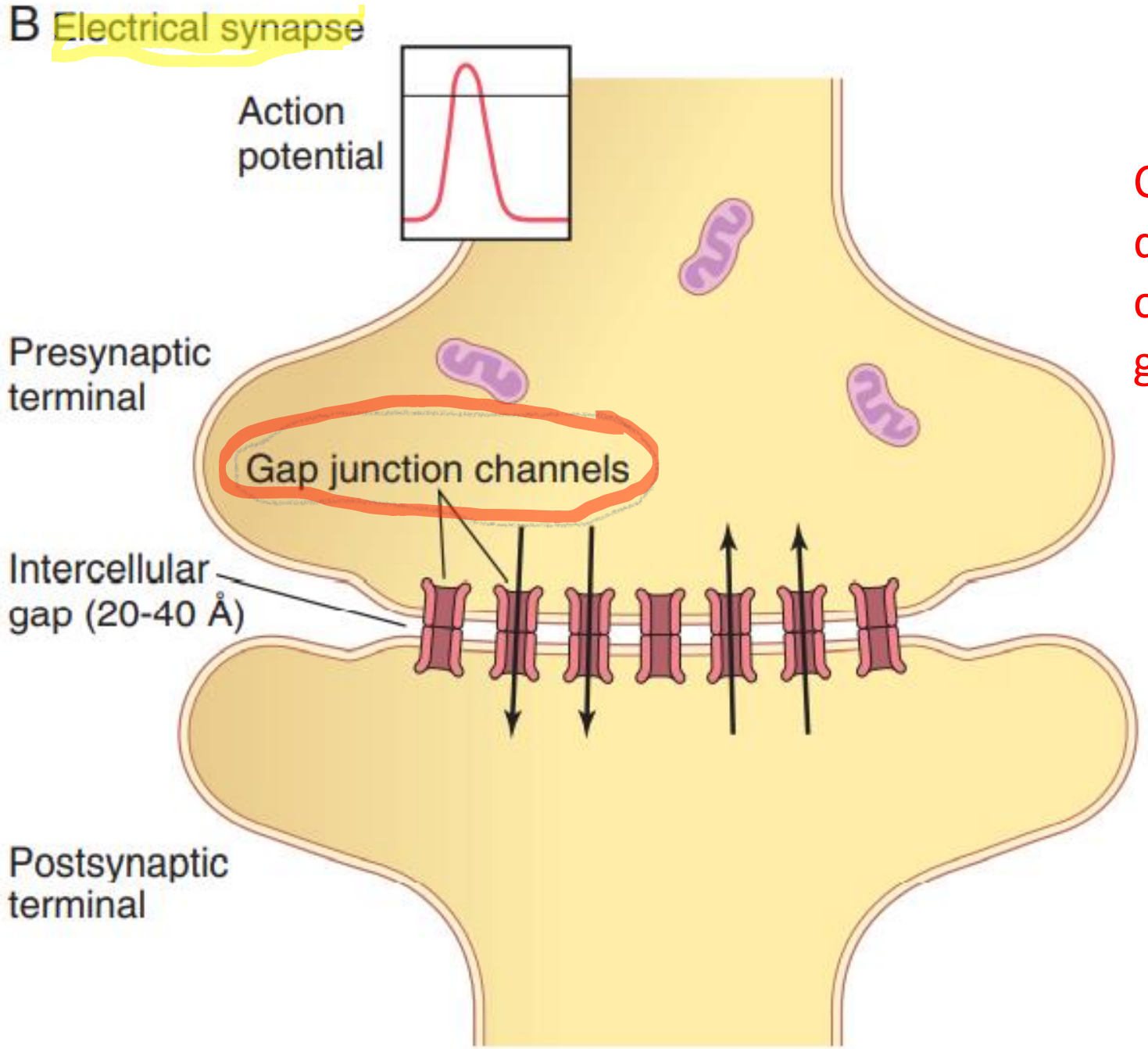
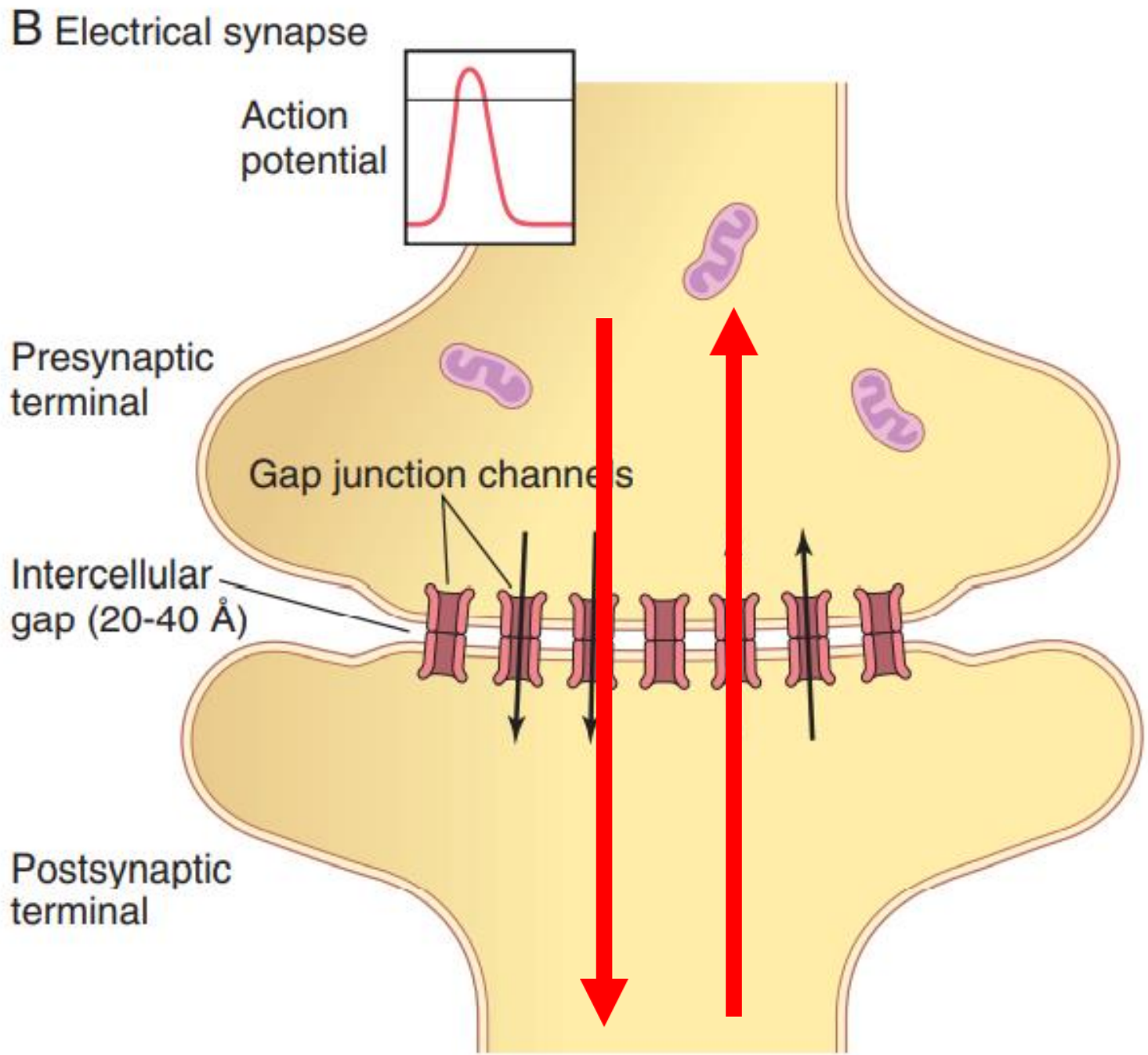
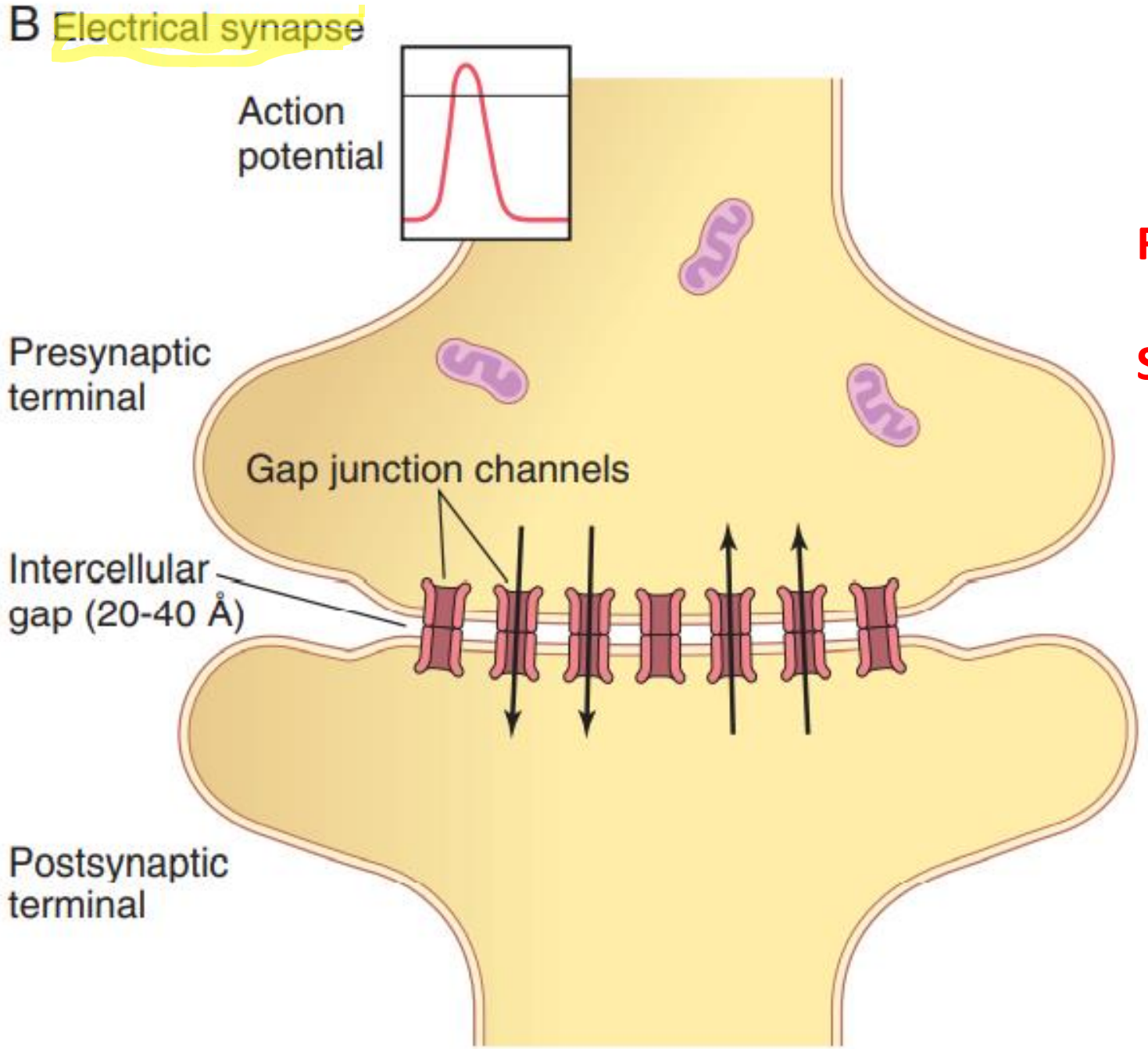
Types of Synapses

- Chemical synapses.
- Electrical synapses.



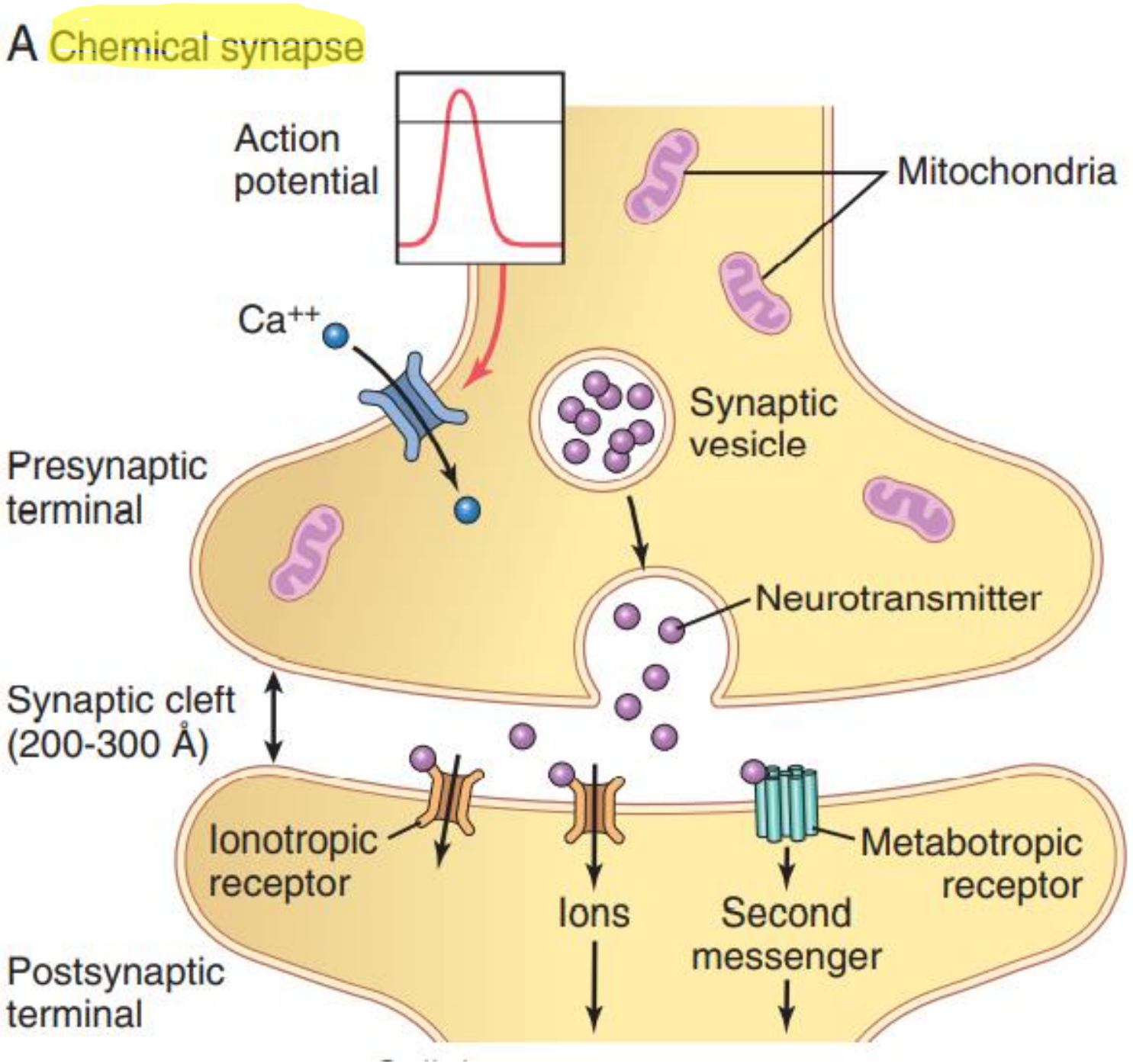
Cytoplasms are directly connected by gap junctions


B Electrical synapse
Action potential
Presynaptic terminal
Gap junction channels
Intercellular gap (20-40 Å)
Postsynaptic terminal



FAST

Synchronization


A Chemical synapse
Action potential
Mitochondria
Ca++
Synaptic vesicle
Presynaptic terminal
Neurotransmitter
Synaptic cleft (200-300 Å)
Ionotropic receptor
Ions
Metabotropic receptor
Second messenger
Postsynaptic terminal

More common

A Chemical synapse

Action potential

Mitochondria

Ca^{++}

Synaptic vesicle

Presynaptic terminal

Neurotransmitter

Synaptic cleft (200-300 Å)

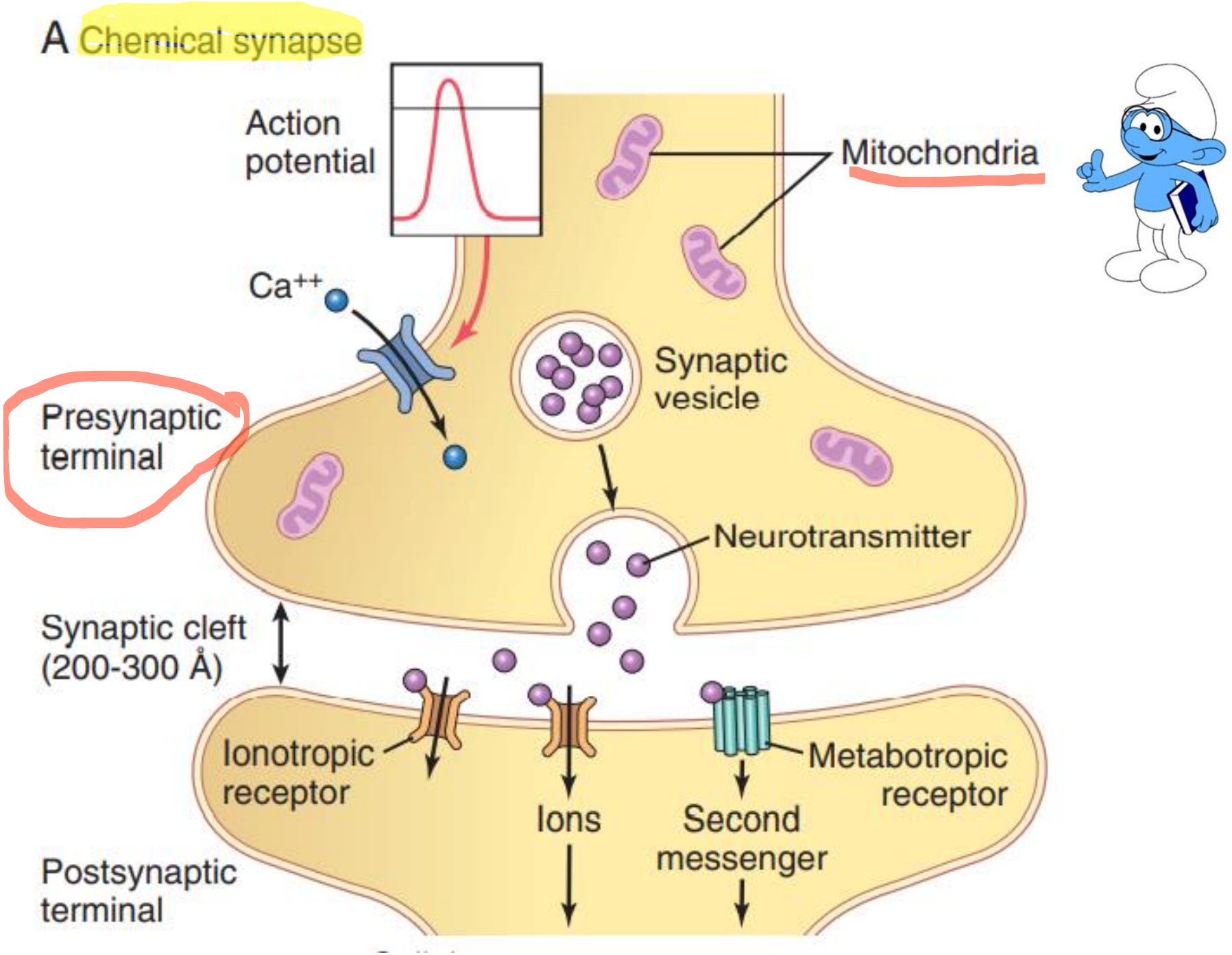
Ionotropic receptor

Ions

Metabotropic receptor

Second messenger

Postsynaptic terminal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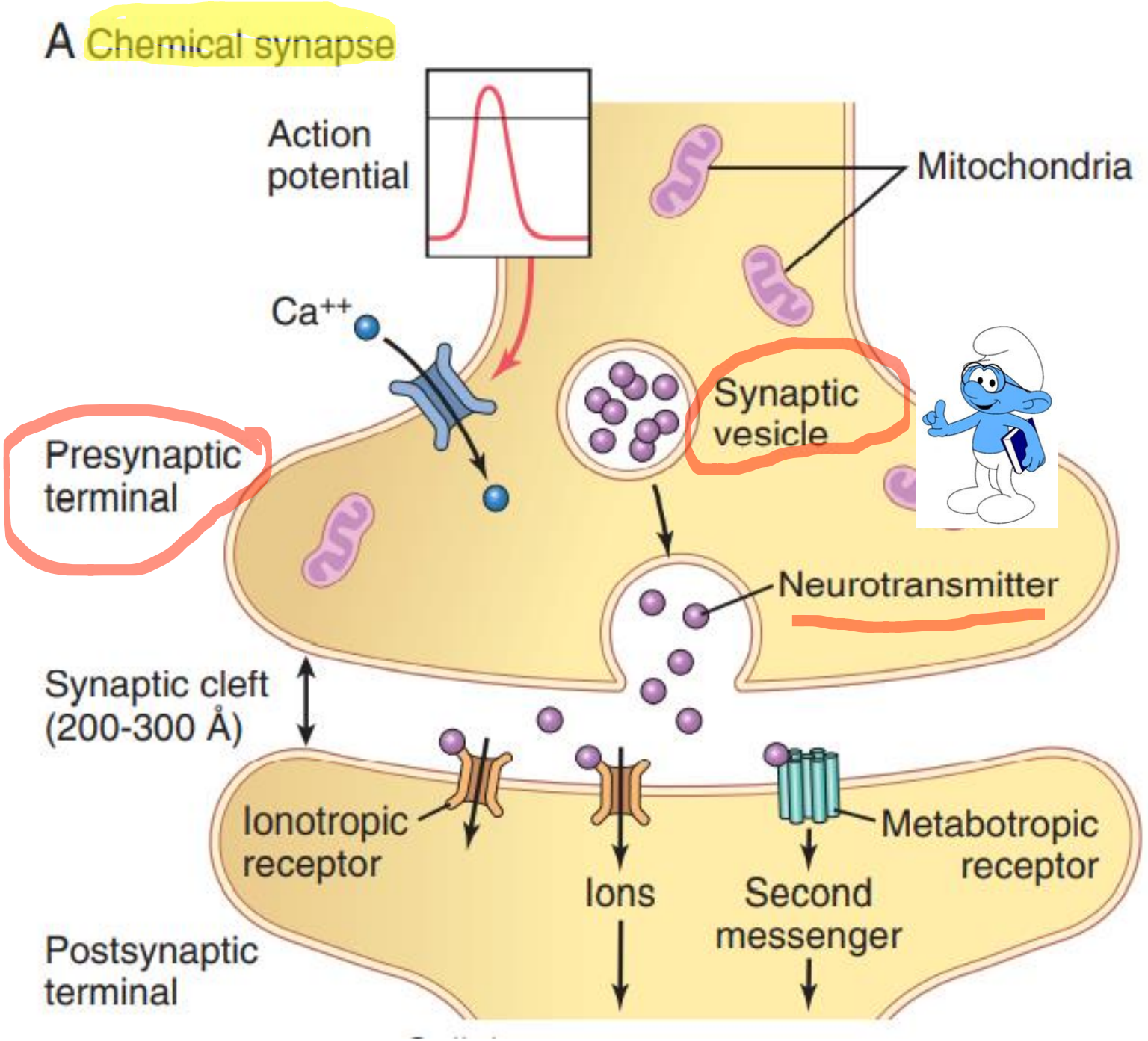
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Ca++
Synaptic vesicle
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Neurotransmitter
Synaptic cleft (200-300 Å)
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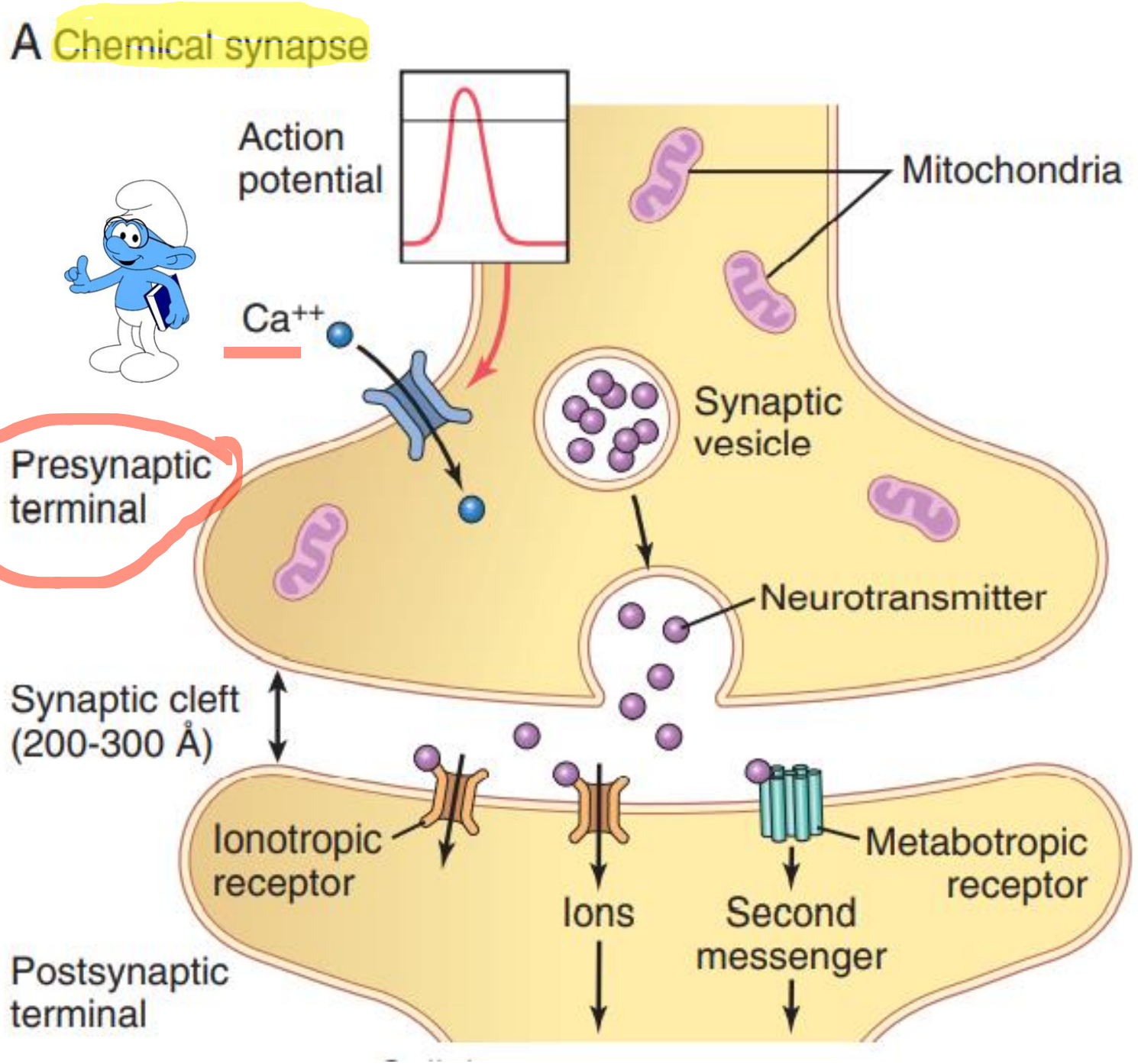
Postsynaptic terminal

More Ca++
More NT



A Chemical synapse

Action potential

Mitochondria

Ca^{++}

Synaptic vesicle

Presynaptic terminal

Neurotransmitter

Synaptic cleft (200-300 Å)

Ionotropic receptor

Ions

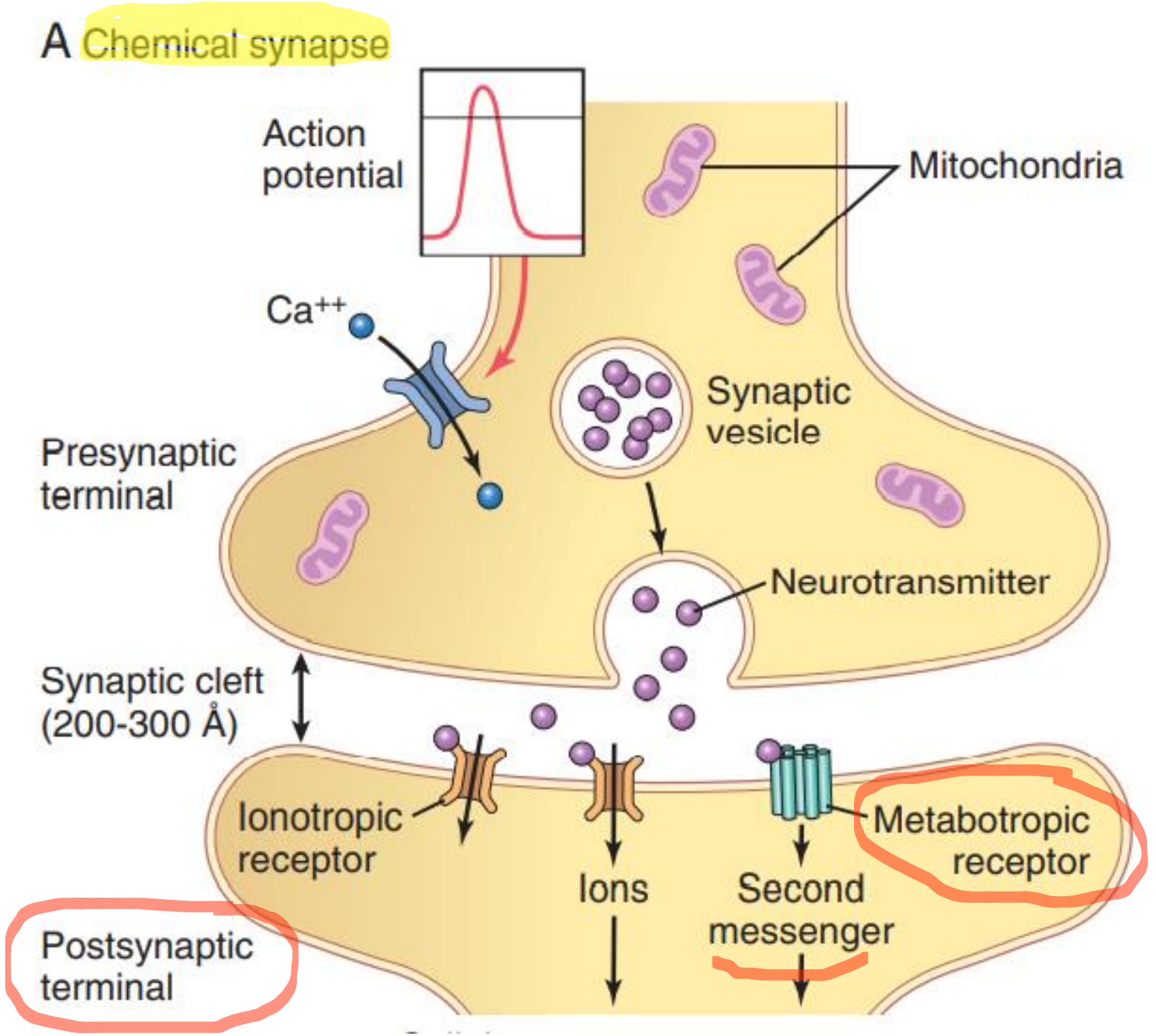
Metabotropic receptor

Second messenger

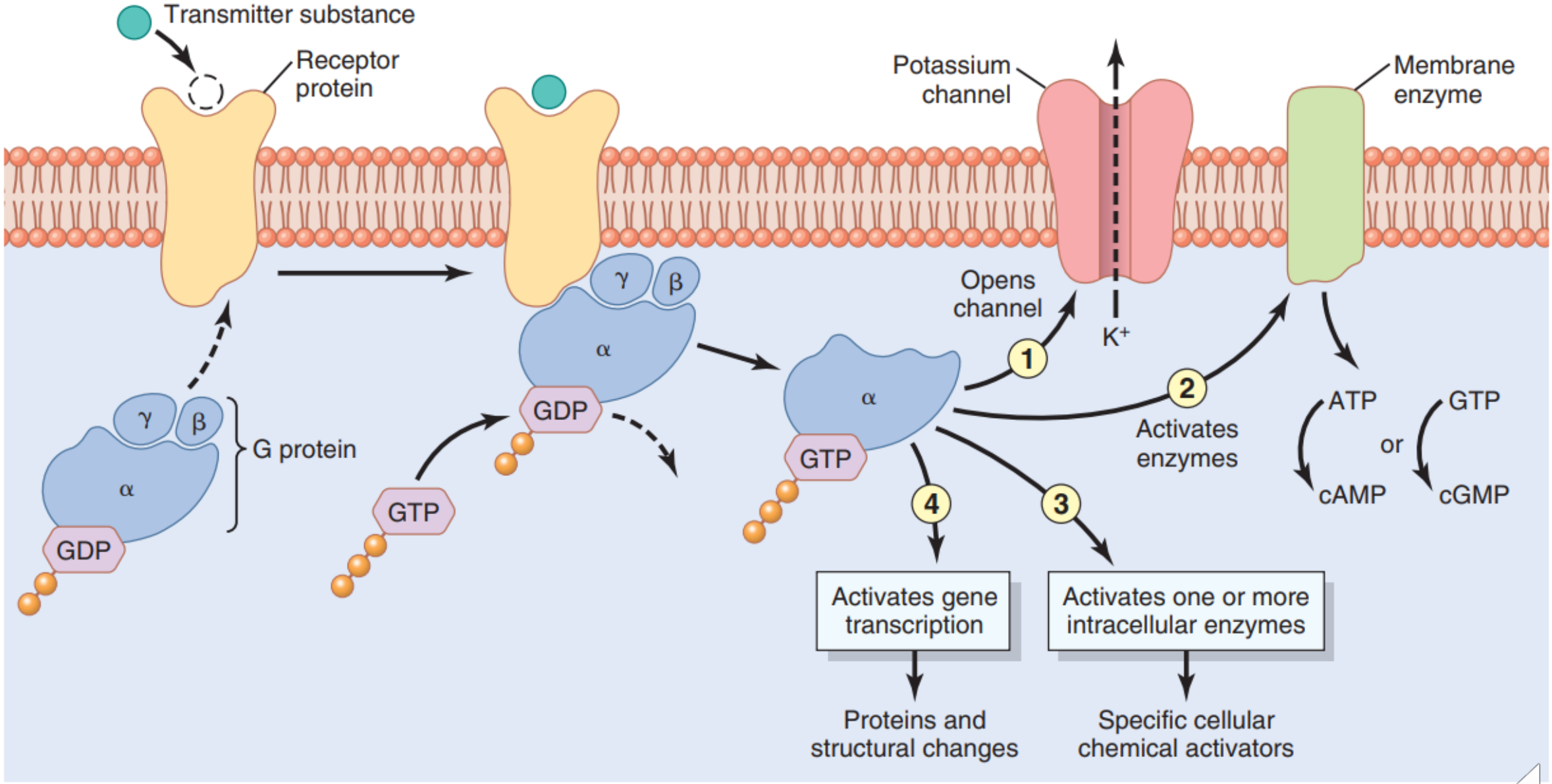
Postsynaptic terminal

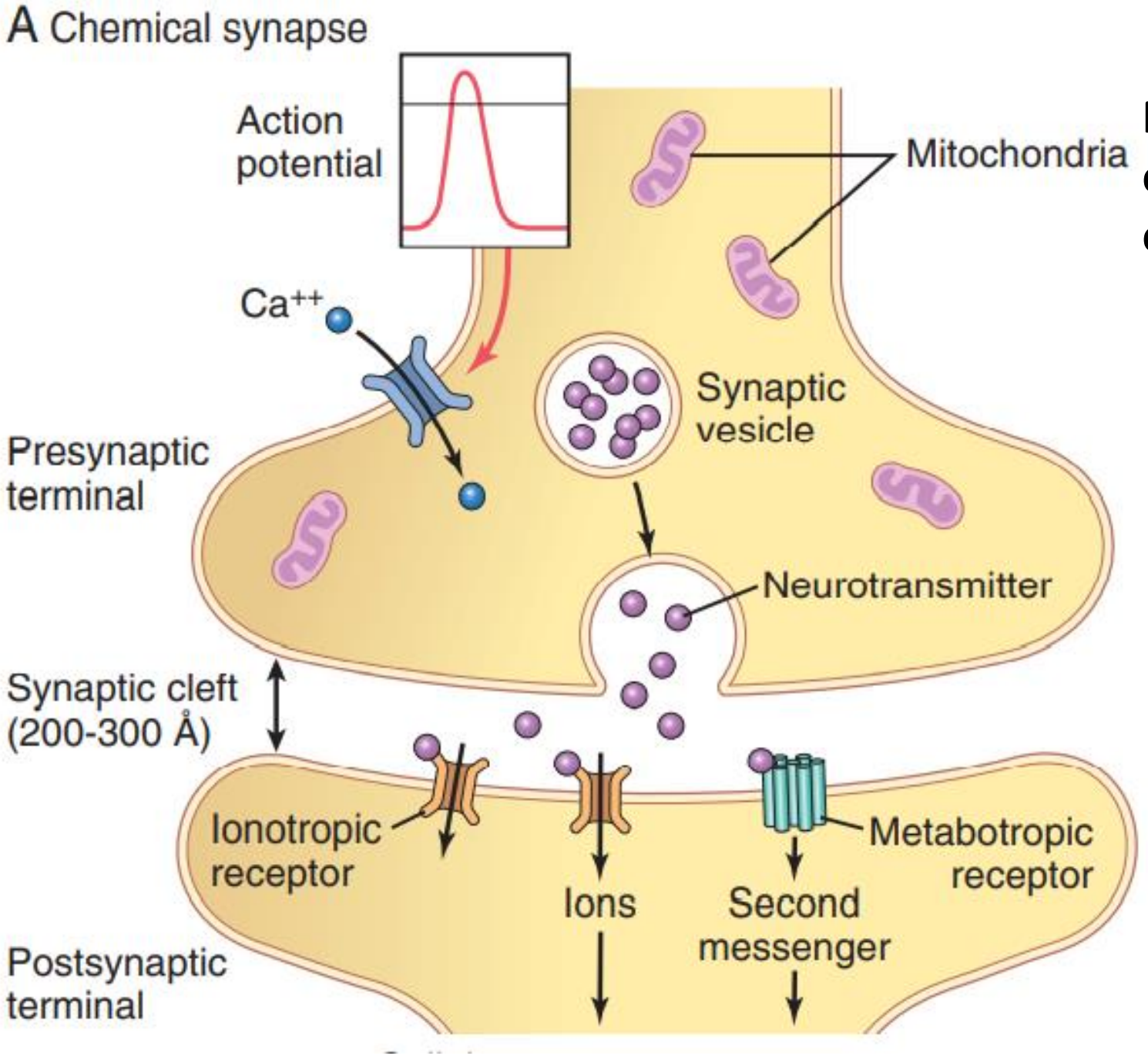
Cation and anion channels

Excitation (Na+) or inhibition (Cl-)

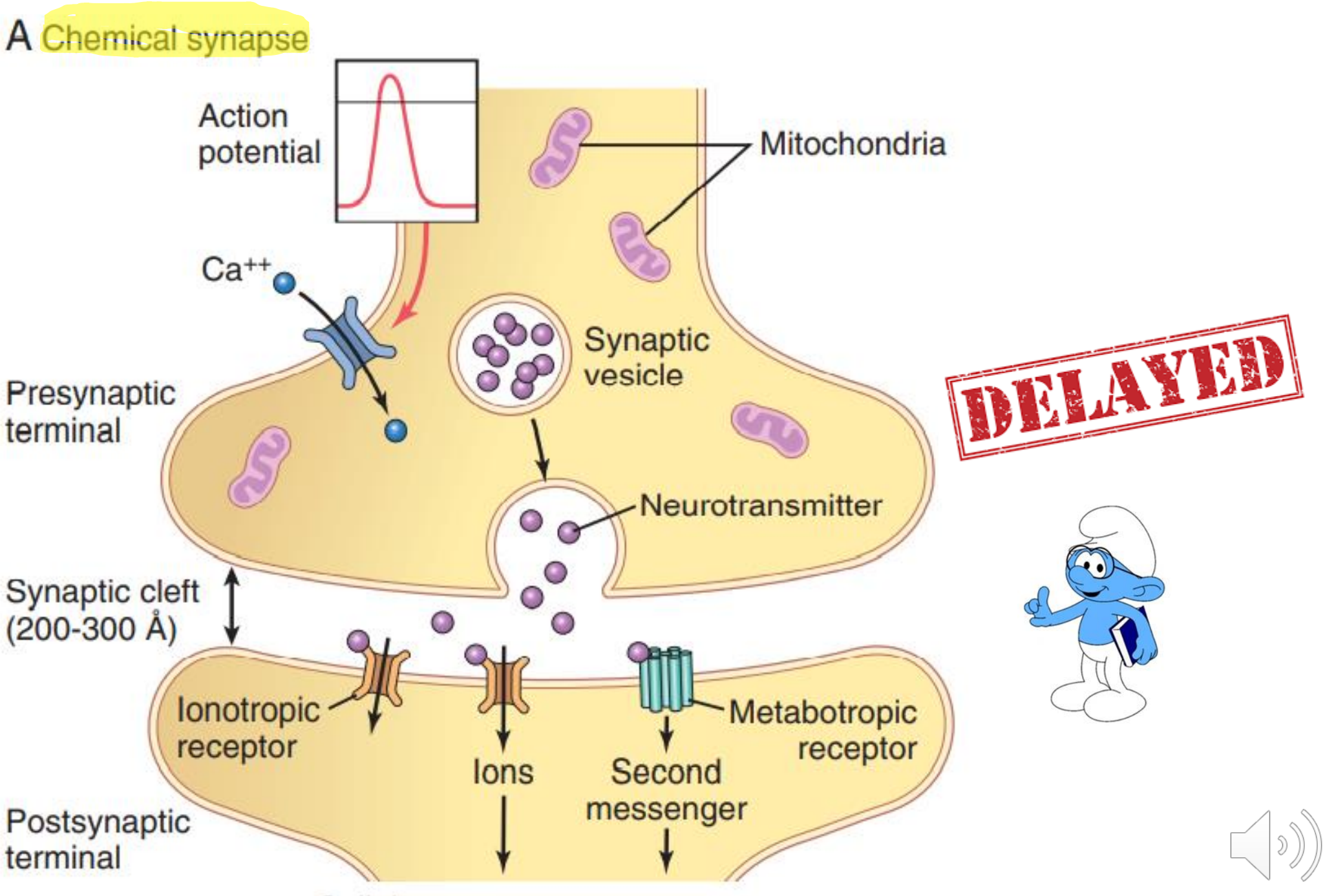


Prolonged action e.g. memory


Transmitter substance
Receptor protein
Potassium channel
Membrane enzyme
Opens channel
K+
γ
β
α
GDP
G protein
GTP
1
2
Activates enzymes
ATP
or
GTP
cAMP
cGMP
3
4
Activates gene transcription
Activates one or more intracellular enzymes
Proteins and structural changes
Specific cellular chemical activators



Principle of one-way conduction at chemical synapse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Presynaptic terminal
Neurotransmitter
Synaptic cleft (200-300 Å)
Ionotropic receptor
Ions
Metabotropic receptor
Second messenger
Postsynaptic terminal
DELAYED

Electrical Synapses

- The **cytoplasms of adjacent cells are directly connected by gap junctions** that allow free movement of ions between cells.

- Similar to the ones in smooth muscles and cardiac muscles.

Bidirectional transmission of electrical synapses

Two main advantages:

- 1. **Faster communication**. Because action potentials conduct directly through gap junctions, electrical synapses are faster than chemical synapses.

- 2. **Synchronization**. Electrical synapses can synchronize (coordinate) the activity of a group of neurons or muscle fibers. As well as increasing neuronal sensitivity of connected neurons.

Chemical synapses

- **Most of the synapses** in the CNS are chemical synapses.

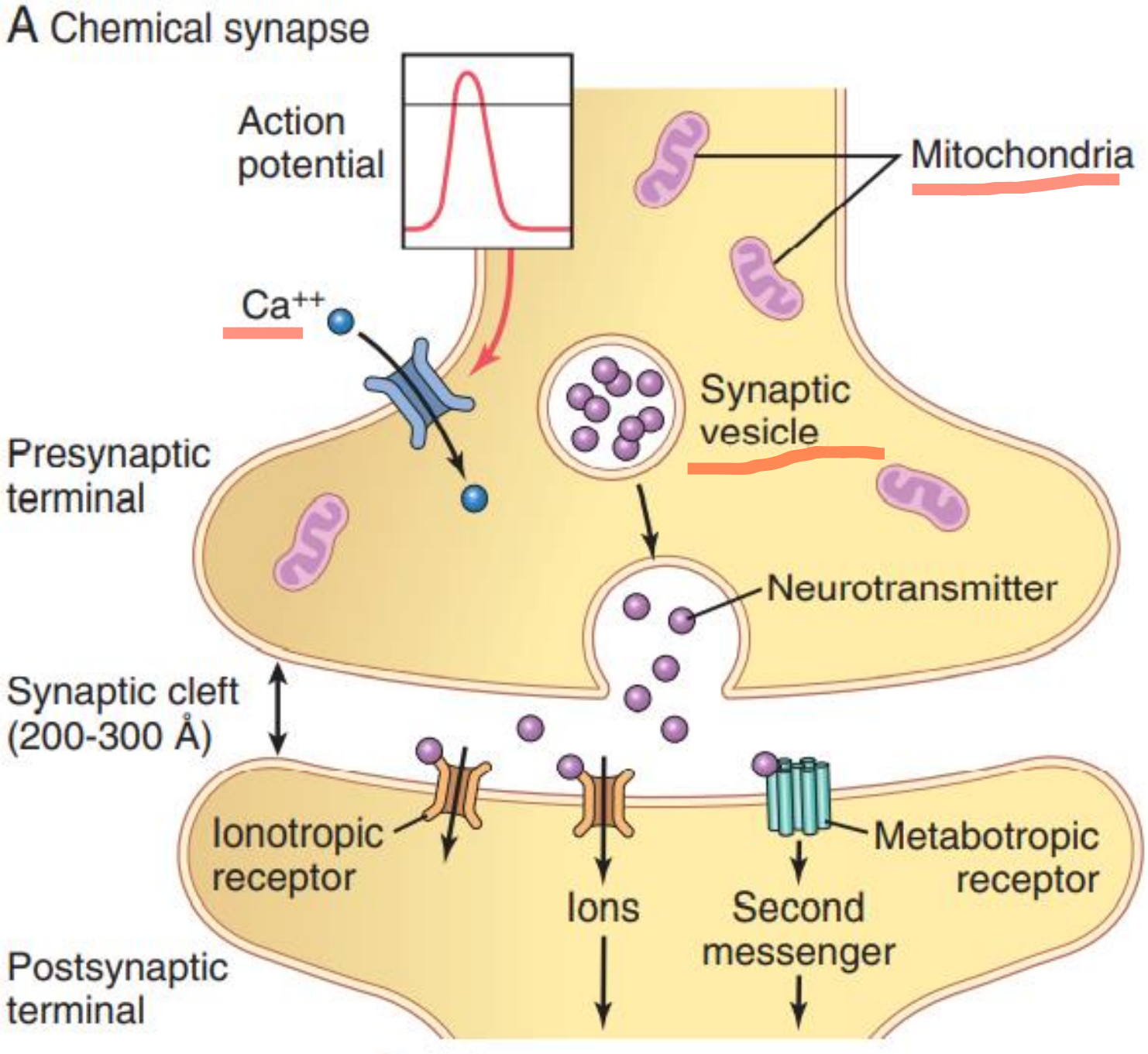
- The first neuron secretes at its nerve ending synapse a chemical substance called a **neurotransmitter.**

- Neurotransmitter acts on receptor proteins in the membrane of the next neuron **to excite the neuron, inhibit it, or modify its sensitivity in some other way**.

Principle of one-way conduction at chemical synapses

- **Always transmit the signals in one direction:** from the presynaptic neuron to the postsynaptic neuron.

- Allows signals to be directed toward specific goals and perform specific nervous functions.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Presynaptic terminals

- The terminal has two important internal structures:

- The transmitter vesicles contain the neurotransmitter that, when released into the synaptic cleft, either excites or inhibits the postsynaptic neuron.

- The mitochondria provide adenosine triphosphate (ATP), which in turn supplies the energy for synthesizing new transmitter substance.

Presynaptic terminals

- The presynaptic membrane contains large numbers of **voltage-gated calcium channels**.

- When an action potential depolarizes the presynaptic membrane, these calcium channels open.

- The quantity of neurotransmitter that is released is directly related to the number of calcium ions that enter.

Synaptic delay

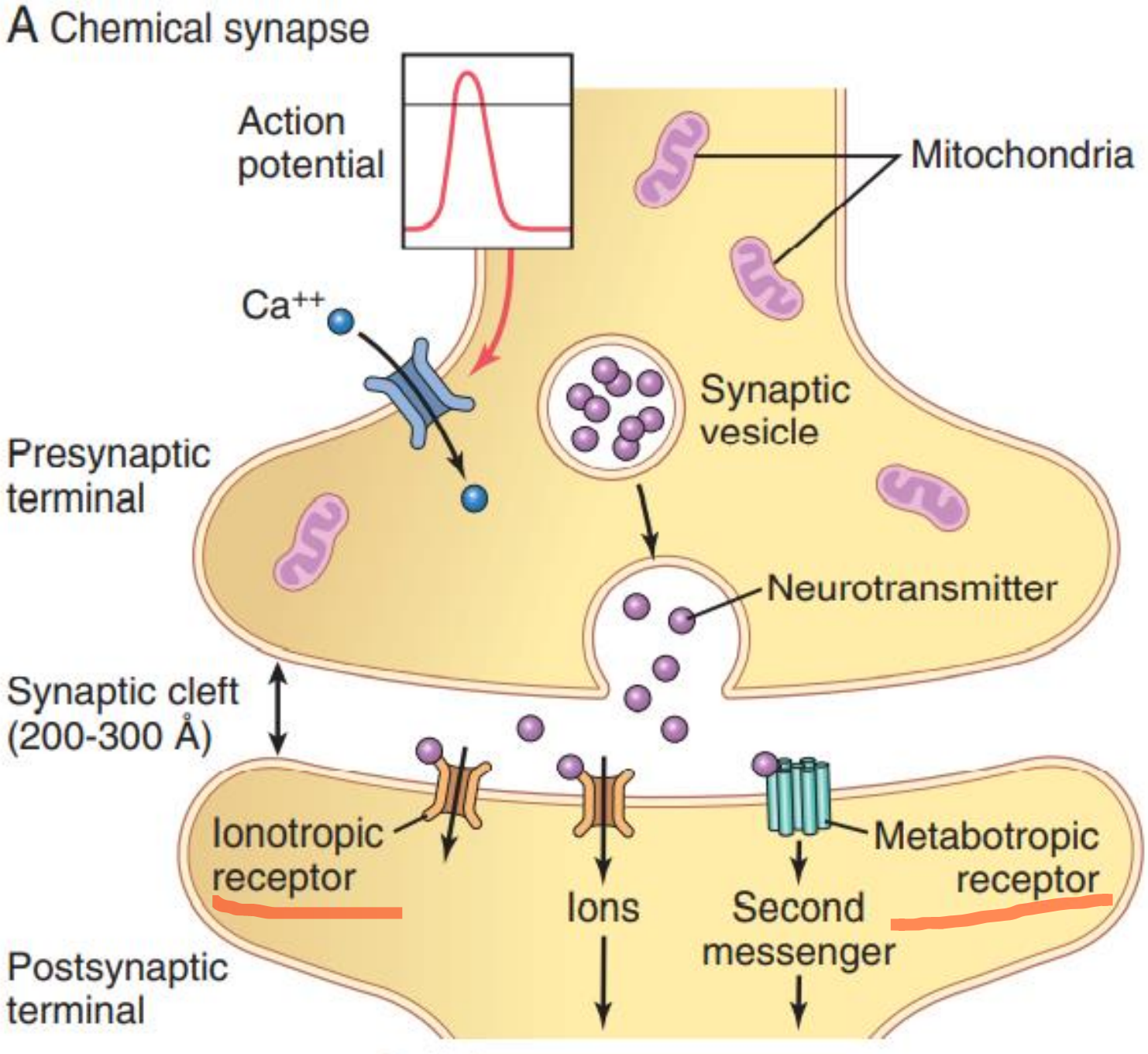
- During transmission of a neuronal signal from a presynaptic neuron to a postsynaptic neuron, a certain amount of time (0.5 msec) is consumed in the process of

- (1) discharge of the transmitter substance by the presynaptic terminal,

- (2) diffusion of the transmitter to the postsynaptic neuronal membrane,

Synaptic delay

- (3) action of the transmitter on the membrane receptor,
- (4) action of the receptor to increase the membrane permeability,
- (5) inward diffusion of sodium to raise the EPSP to a high enough level to elicit an action potential.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Postsynaptic neurons

- Receptor activation controls the opening of ion channels in the postsynaptic cell in one of two ways:

(1) by gating ion channels directly (Ionotropic receptors).

(2) by activating a second messenger (metabotropic receptors).

Excitation of postsynaptic neuron

- 1. Opening of sodium channels.
- 2. Depressed conduction through chloride or potassium channels, or both.
- 3. Changes in the internal metabolism of the postsynaptic neuron to excite cell activity or to increase the number of excitatory membrane receptors or decrease the number of inhibitory membrane receptors.

Inhibition of postsynaptic neuron

- 1. Opening of chloride ion channels through the postsynaptic neuronal membrane.

- 2. Increase in conductance of potassium ions out of the neuron.

- 3. Activation of receptor enzymes that inhibit cellular metabolic functions or that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors.

Ion channels

- The ion channels in the postsynaptic neuronal membrane are usually of two types:

(1) cation channels that most often allow sodium ions to pass when opened but sometimes also allow potassium and/or calcium ions to pass.

(2) anion channels that mainly allow chloride ions to pass but allow minute quantities of other anions to pass as well.

Ion channels

- When cation channels open and allow positively charged sodium ions to enter, the positive electrical charges of the sodium ions will in turn excite this neuron.

- Therefore, a neurotransmitter that opens cation channels is called an **excitatory transmitter**.

Ion channels

- Opening anion channels allows negative electrical charges to enter. Therefore, neurotransmitters are called **inhibitory transmitters.**

- When a neurotransmitter activates an ion channel, the channel usually opens within a fraction of a millisecond; when the transmitter is no longer present, the channel closes rapidly. The opening and closing of ion channels provide a means for very **rapid control of postsynaptic neurons**.

Second-messenger system

- Many functions of the nervous system—for instance, the process of memory—require prolonged changes in neurons for seconds to months after the initial transmitter substance is gone.

- The ion channels are not suitable for causing prolonged postsynaptic neuronal changes because these channels close within milliseconds after the transmitter substance is no longer present.

Second-messenger system

- However, in many instances, **prolonged** postsynaptic neuronal excitation or inhibition is achieved by activating a “second messenger” chemical system inside the postsynaptic neuronal cell itself, and then it is the second messenger that causes the prolonged effect.

Types of synaptic transmitters

- The **small-molecule, rapidly acting transmitters:** cause most acute responses of the nervous system, such as transmission of sensory signals to the brain and of motor signals back to the muscles.

- The **neuropeptides,** in contrast, usually cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, long-term opening or closure of certain ion channels, and possibly long-term changes in numbers of synapses or sizes of synapses.

Small-molecule, rapidly acting transmitter

- In most cases, they are synthesized in the cytosol of the presynaptic terminal and are absorbed by means of active transport into the transmitter vesicles in the terminal.

- Each time an action potential reaches the presynaptic terminal, a few vesicles at a time release their transmitter into the synaptic cleft. This action usually occurs within a millisecond or less.

Small-molecule, rapidly acting transmitter

- The subsequent action on the membrane receptors of the postsynaptic neuron usually also occurs within another millisecond or less.

- Most often the effect is to increase or decrease conductance through ion channels.

Small-molecule, rapidly acting transmitter

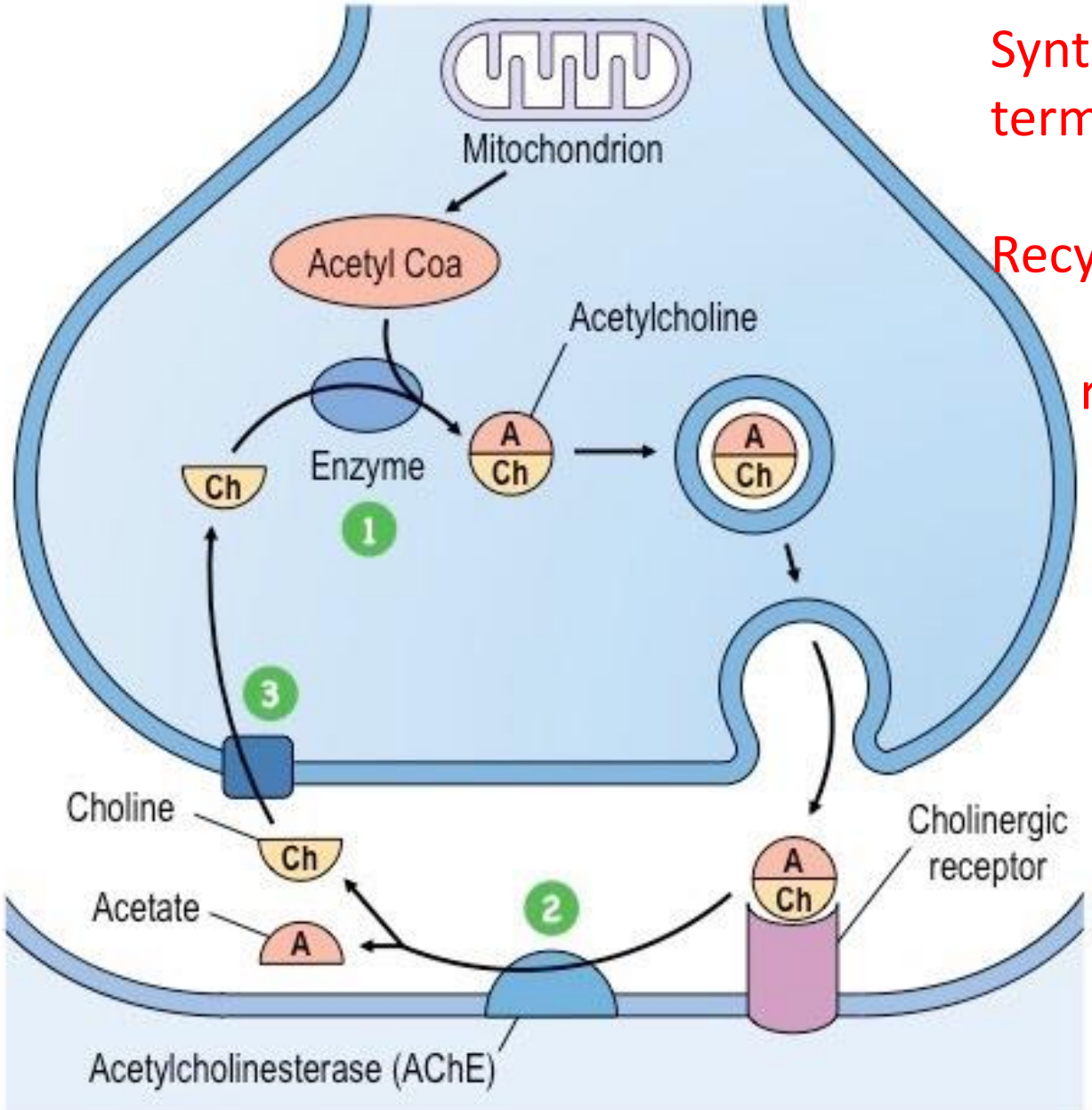
- Vesicles that store and release small-molecule transmitters are continually recycled and used over and over again.

- After they fuse with the synaptic membrane and open to release their transmitter substance, the vesicle membrane at first simply becomes part of the synaptic membrane.

Small-molecule, rapidly acting transmitter

- Within seconds to minutes, the vesicle portion of the membrane invaginates back to the inside of the presynaptic terminal and pinches off to form a new vesicle.

- The new vesicular membrane still contains appropriate enzyme proteins or transport proteins required for synthesizing and/or concentrating new transmitter substance inside the vesicle.



Synthesis in presynaptic terminal

1. Acetylcholine (ACh) is made from choline and acetyl CoA

Recycling

rapid

2. In the synapse, ACh is rapidly broken down by the enzyme **acetylcholinesterase (AChE)**

3. Choline is transported back into the axon terminal and used to make more ACh

Acetylcholine

- Acetylcholine is secreted by neurons in many areas of the nervous system.

- For example, the preganglionic neurons of the autonomic nervous system, the postganglionic neurons of the parasympathetic system, and at neuromuscular junctions (NMJ).

- In most instances, it has an excitatory effect.

Norepinephrine

- Secreted by the terminals of many neurons whose cell bodies are located in the **brain stem and hypothalamus**.

- In most areas, norepinephrine probably activates excitatory receptors, but in a few areas, it activates inhibitory receptors instead.

Glutamate

- **Glutamate** is secreted by the presynaptic terminals in many of the **sensory** pathways entering the central nervous system, as well as in many areas of the **cerebral cortex**.

- It probably always causes **excitation**.

Glycine

- **Glycine** is secreted mainly at synapses in the **spinal cord**.

- It is believed to always act as an inhibitory transmitter

Dopamine

- Dopamine is secreted by neurons that originate in the **substantia nigra**. The termination of these neurons is mainly in the striatal region of the **basal ganglia**.

- The effect of dopamine is usually inhibition.

GABA

- **GABA** (gamma-aminobutyric acid) is secreted by nerve terminals in the **spinal cord, cerebellum, basal ganglia, and many areas of the cortex**.

- It is believed to always cause **inhibition**.

Serotonin

- **Serotonin** is secreted by nuclei that originate in the median raphe of the **brain stem** and project to many brain and spinal cord areas, especially to the dorsal horns of the spinal cord and to the hypothalamus.

- Serotonin acts as an **inhibitor of pain pathways** in the cord, and an inhibitor action in the higher regions of the nervous system is believed to **help control the mood** of the person, perhaps even to cause sleep.

Nitric Oxide

- **Nitric oxide** is especially secreted by nerve terminals in areas of the brain responsible **for long-term behavior and memory**.

- Nitric oxide is different from other small-molecule transmitters.

Nitric Oxide

- **It is not preformed and stored in vesicles** in the presynaptic terminal as are other transmitters.

- Instead, it is **synthesized almost instantly as needed and then diffuses out** of the presynaptic terminals over a period of seconds rather than being released in vesicular packets.

- Next, it diffuses into postsynaptic neurons nearby.

Nitric Oxide

- In the postsynaptic neuron, it usually does not greatly alter the membrane potential but instead changes intracellular metabolic functions that modify neuronal excitability for seconds, minutes, or longer.

Neuropeptides

- Actions are usually **slow** and in other ways quite different from those of the small-molecule transmitters.

- **Not synthesized in the cytosol of the presynaptic terminals but by ribosomes in the neuronal cell body**.

Neuropeptides

- Because of this laborious method of forming the neuropeptides, much **smaller quantities** of neuropeptides than of the small-molecule transmitters are usually released.

- This difference is partly compensated for by the fact that the neuropeptides are generally a thousand or more times as **potent** as the small-molecule transmitters.

Neuropeptides

- The vesicles are transported by axonal streaming of the axon cytoplasm, **traveling at the slow rate** of only a few centimeters per day.
- Vesicle is autolyzed and is not reused.
- Small quantities are released, but more potent.
- Prolonged action.

Neuropeptides

- Another important characteristic of the neuropeptides is that they often cause much more **prolonged actions**.

- Some of these actions include prolonged closure of calcium channels, prolonged changes in the metabolic machinery of cells, prolonged changes in activation or deactivation of specific genes in the cell nucleus, and/or prolonged alterations in numbers of excitatory or inhibitory receptors. Some of these effects last for days, but others last perhaps for months or years.

Neuropeptides

Hypothalamic-Releasing Hormones
Thyrotropin-releasing hormone
Luteinizing hormone–releasing hormone
Somatostatin (growth hormone inhibitory factor)
Pituitary Peptides
Adrenocorticotropic hormone
β-Endorphin
α-Melanocyte-stimulating hormone
Prolactin
Luteinizing hormone
Thyrotropin
Growth hormone
Vasopressin
Oxytocin

Peptides that Act on Gut and Brain
Leucine enkephalin
Methionine enkephalin
Substance P
Gastrin
Cholecystokinin
Vasoactive intestinal polypeptide
Nerve growth factor
Brain-derived neurotropic factor
Neurotensin
Insulin
Glucagon

From Other Tissues
Angiotensin II
Bradykinin
Carnosine
Sleep peptides
Calcitonin

Fatigue of synaptic transmission

- The mechanism of fatigue is mainly **exhaustion or partial exhaustion of the stores of transmitter substance in the presynaptic terminals**.

- The excitatory terminals on many neurons can store enough excitatory transmitter to cause only about 10,000 action potentials, and the transmitter can be exhausted in only a few seconds to a few minutes of rapid stimulation.

Fatigue of synaptic transmission

- Depletion of transmitter stores.
- Progressive inactivation of postsynaptic membrane receptors.
- Slow development of abnormal concentrations of ions inside the postsynaptic neuronal cell.

Fatigue of synaptic transmission

- Other factors:
- (1) **progressive inactivation of many of the postsynaptic membrane receptors.**

- (2) **slow development of abnormal concentrations of ions inside the postsynaptic neuronal cell.**

Effect of alkalosis on synaptic transmission

- **Most neurons are highly responsive to changes in pH** of the surrounding interstitial fluids.

- **Alkalosis increases neuronal excitability** and may cause cerebral **epileptic seizures**.

- In a person who is predisposed to epileptic seizures, even a short period of hyperventilation, which lowers CO2 and elevates the pH, may precipitate an epileptic attack.

Effect of acidosis on synaptic transmission

- Conversely, **acidosis greatly depresses neuronal activity**; a fall in pH may cause a comatose state.

- For instance, in very severe **diabetic or uremic acidosis, coma** almost always develops.

Effect of hypoxia on synaptic transmission

- Neuronal excitability is also highly dependent on an adequate supply of oxygen.
- **Cessation of oxygen for only a few seconds can cause complete inexcitability of some neurons**.
- This effect is observed when the brain's blood flow is temporarily interrupted because within 3 to 7 seconds, the person becomes unconscious.

Effect of drugs on synaptic transmission

- Many drugs are known to increase the excitability of neurons, and others are known to decrease excitability.

- For instance, **caffeine, theophylline, and theobromine**, which are found in coffee, tea, and cocoa, respectively, all **increase neuronal excitability**, presumably by reducing the threshold for excitation of neurons.

Effect of drugs on synaptic transmission

- Most **anesthetics** increase the neuronal membrane threshold for excitation and thereby **decrease synaptic transmission** at many points in the nervous system.

Questions? Feedback?

Thank you