

Introduction to Neurophysiology 3

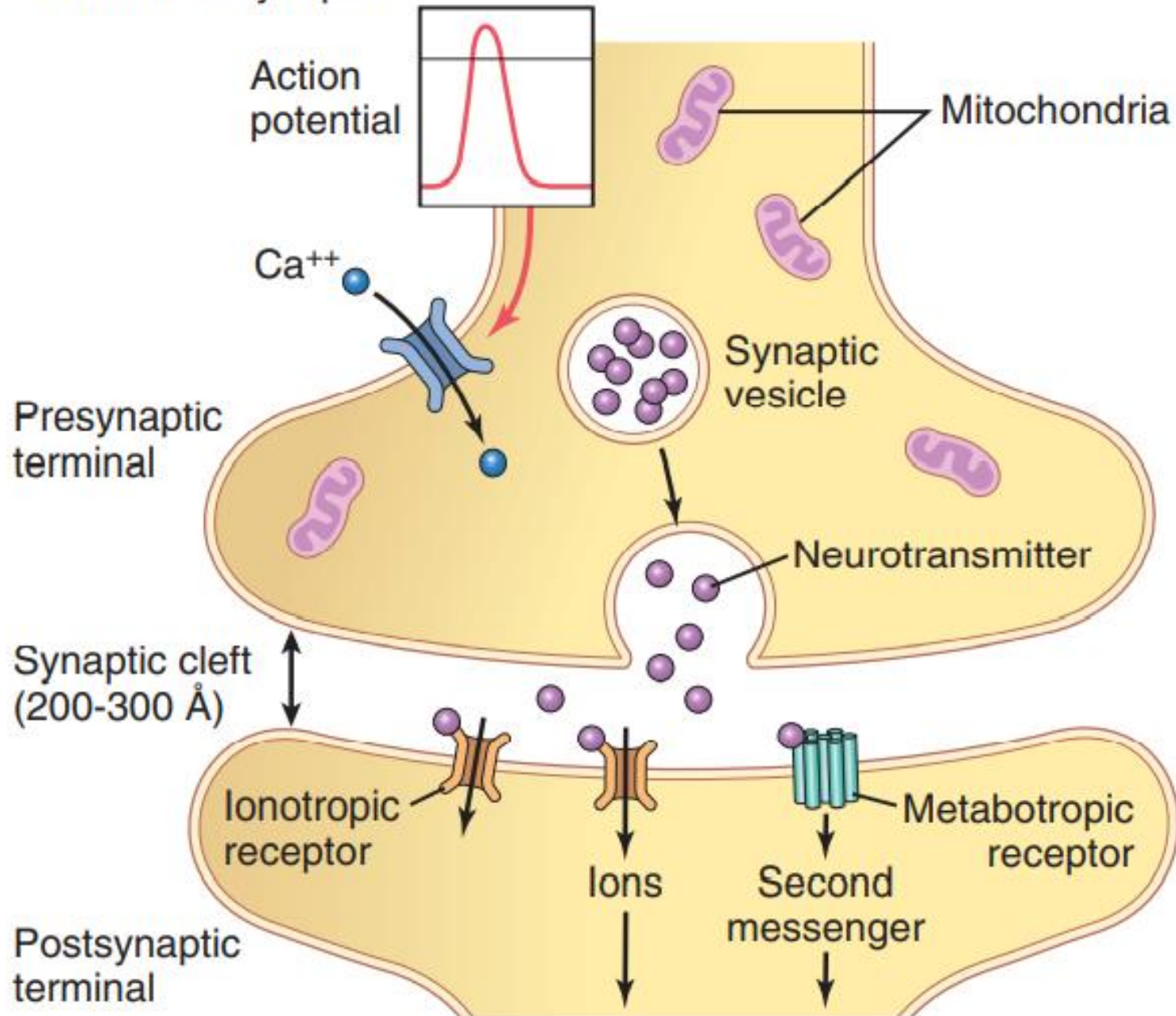
Neurotransmitters and changes in membrane potential

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A Chemical synapse



Neuromodulators (Neurotransmitters) are chemicals that adjust how neurons communicate, by changing the strength or duration of signals rather than directly causing a response.

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 Transmitters

Class I

Acetylcholine

Class II: The Amines

Norepinephrine

Epinephrine

Dopamine

Serotonin

Melatonin

Histamine

Can be inhibitory
or excitatory

Class III: Amino Acids

Gamma-aminobutyric acid

Glycine

Glutamate

Aspartate

Inhibitory

excitatory

Class IV

ATP

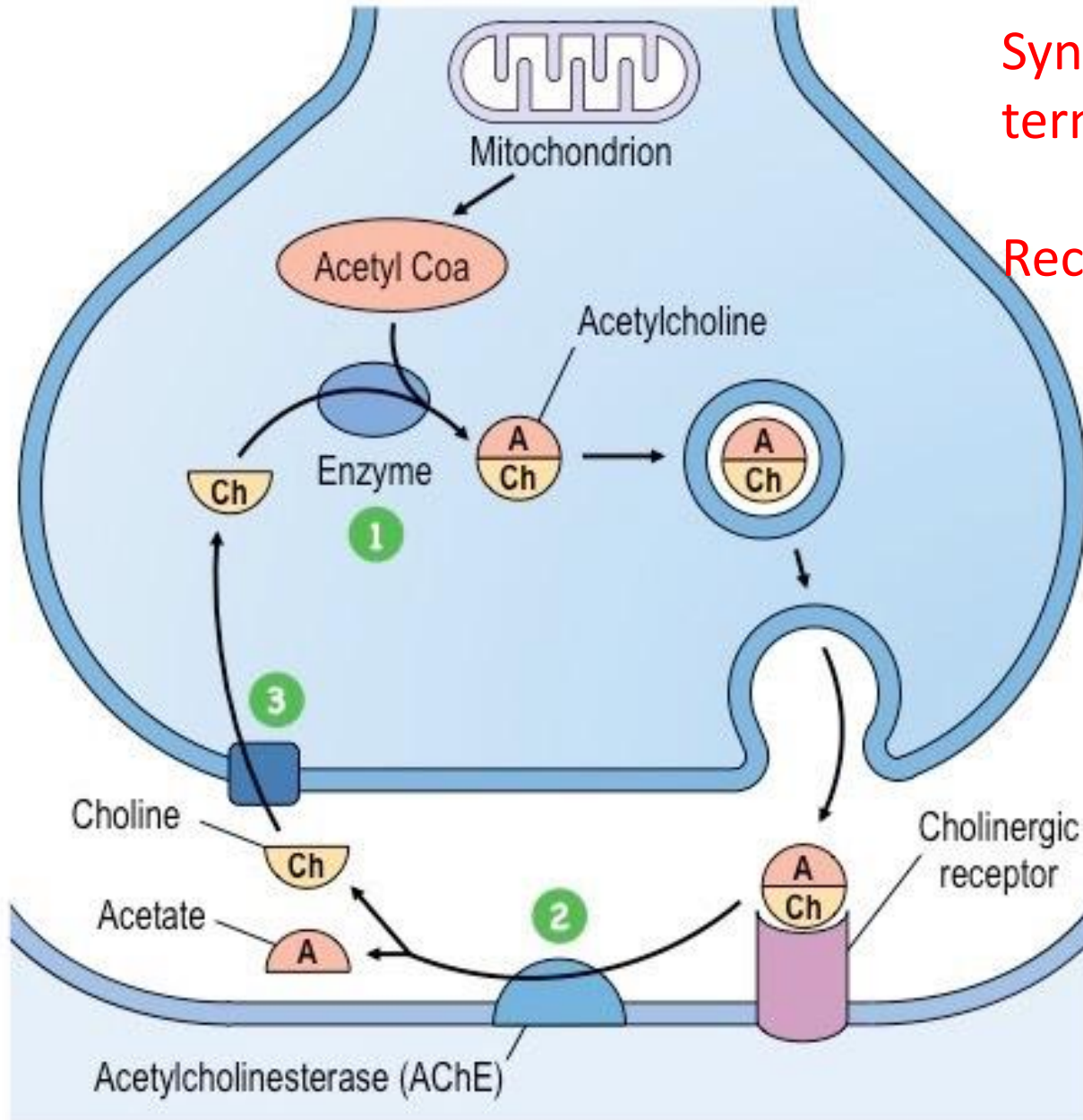
Arachidonic acid

Nitric oxide

Carbon monoxide

Gas

Excitatory or Inhibitory
depends on the complex → the (neurotransmitter
receptor) complex which is formed when the
neurotransmitter binds to its receptor



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



- A small molecule neurotransmitter has several important characteristics. Take **acetylcholine** as an example—it can be synthesized **locally** within the **presynaptic neuron at its terminal**, because the **enzymes, energy substrates, and necessary machinery** are all present in this region. Specifically, **choline** combines with **acetyl-CoA** in the presence of the enzyme **choline acetyltransferase**, resulting in the synthesis of **acetylcholine**.
- Once synthesized, acetylcholine is **packaged and stored in vesicles** within the presynaptic terminal, ready for release when a signal arrives. Upon stimulation, **calcium influxes** through **voltage-gated calcium channels**, triggering **exocytosis**. This causes the vesicles to fuse with the membrane and release acetylcholine into the **synaptic cleft**.
- In the cleft, acetylcholine **binds to specific receptors** on the **postsynaptic neuron**, specifically **cholinergic receptors**. This binding commonly activates **ionotropic receptors**, which then change the **permeability of the postsynaptic membrane**, resulting in a **postsynaptic potential**.
- However, this binding **must not last indefinitely**. Therefore, mechanisms exist to **remove acetylcholine from the synaptic cleft**, particularly for small molecule neurotransmitters. These mechanisms include:
 - **Diffusion** of some neurotransmitter molecules away from the cleft,
 - **Reuptake** of some molecules into the presynaptic neuron,
 - **Enzymatic degradation**—in this case, by **acetylcholinesterase**, which breaks down acetylcholine into **choline** and **acetate**.
 - Finally, the **choline is reuptaken** into the presynaptic terminal, where it can be **recycled and used again** for acetylcholine synthesis.

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.

Neurotransmitters

- Acetylcholine is secreted by motor neurons at neuromuscular junctions (NMJ).

- Glutamate is an excitatory neurotransmitter.

- Glycine and GABA are inhibitory transmitters.

- Serotonin is related to mood pathways, and pain inhibitory pathways.

Certain infections can interfere with **GABA function**. For example, the **tetanus toxin** prevents the **release of GABA** from specific neurons. As a result, the **absence of inhibitory signaling** leads to **unopposed excitatory activity**, which in turn causes **muscle spasms** in affected patients.

Serotonin

- Serotonin is derived from tryptophan.
- Foods containing tryptophan can help improve mood.
- Serotonin plays an important role in patients with depression.
- Patients with depression are treated with Selective Serotonin Reuptake Inhibitors (SSRIs).
- SSRIs prevent the reuptake of serotonin.
- Preventing reuptake increases serotonin concentration in the synaptic clefts.
- Higher serotonin levels enhance its effect in the brain.
- Serotonin is linked to mood improvement pathways.
- SSRIs improve mood in depressed patients by increasing serotonin activity.

Dopamine

- Dopamine is secreted by neurons that originate in the substantia nigra to control movement of muscles.
- Dopamine is present in pleasure pathways.
- The effect of dopamine can be inhibitory or excitatory depends on the type of the receptor.

Dopamine

- Disorders in dopaminergic neurons in the **substantia nigra** (located in the brainstem) affect **muscle movement control**.
- The substantia nigra is part of the **basal nuclei**, which are involved in motor regulation.
- Impairment in this area leads to **muscle movement issues**, most notably seen in **Parkinson's disease**.
- **Dopamine** is also involved in the **pleasure sensation pathway**.
- **Cocaine** prevents the **reuptake of dopamine**, causing **dopamine accumulation in the synaptic cleft**.
- This leads to **continued stimulation of postsynaptic neurons** by dopamine.
- As dopamine is linked to pleasure, cocaine use **produces a strong sensation of pleasure**.
- Repeated use eventually leads to **addiction** and its **negative consequences**.

Nitric Oxide gas

- 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

Hypothalamic-Releasing Hormones

Thyrotropin-releasing hormone

Luteinizing hormone–releasing hormone

Somatostatin (growth hormone inhibitory factor)

Pituitary Peptides

Adrenocorticotrophic 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

Neuropeptides

- **Neuropeptides** have a **delayed or more prolonged action** compared to other neurotransmitters.
- This is because most neuropeptides act on **metabotropic receptors** rather than **ionotropic receptors**.
- Metabotropic receptor activation leads to changes in the **metabolism of the neuronal cell**.
- Effects can include **upregulation or downregulation of certain receptors**, **changes in the synapse area**, and **alteration of enzymatic activity** within the **postsynaptic neuron**.
- Due to these effects, neuropeptides are often referred to as **neuromodulators** rather than simple neurotransmitters.
- Unlike ionotropic receptors that quickly change membrane **permeability** to transmit signals, neuropeptides **modulate** postsynaptic function.
- This modulation results in a **more prolonged effect** compared to **small molecular neurotransmitters**.

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 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.

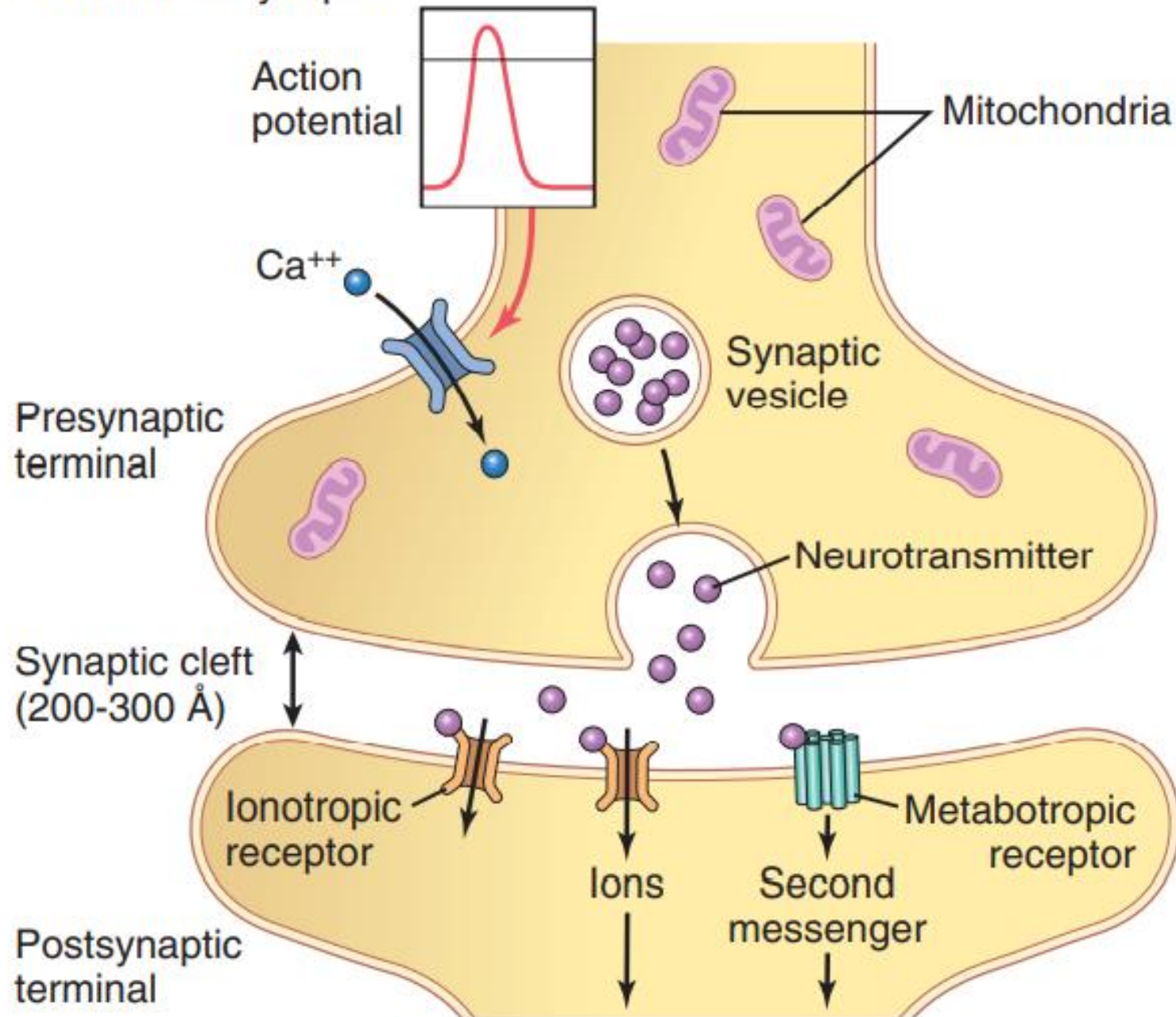
Neuropeptides

- 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.

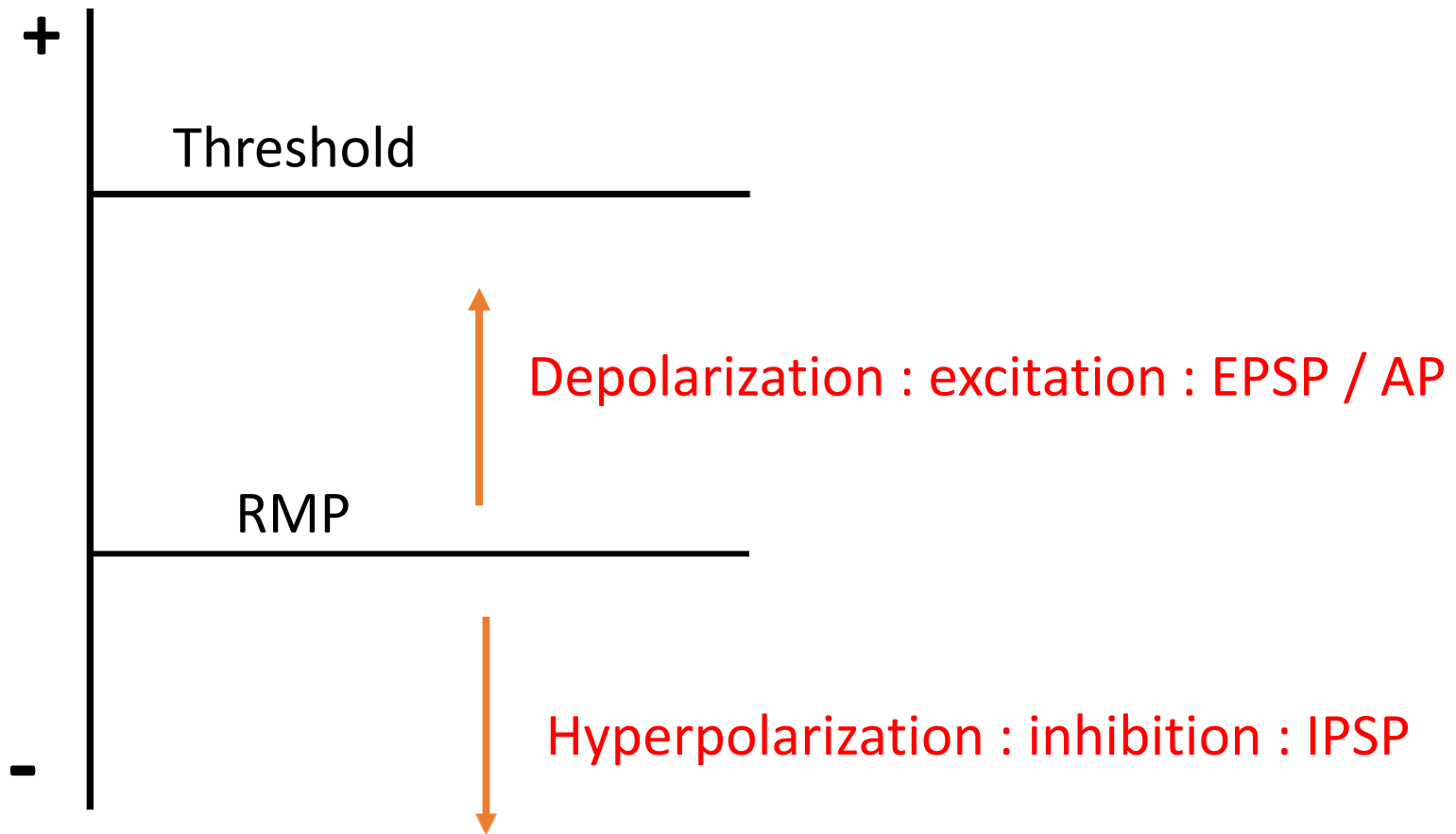
Neuropeptides

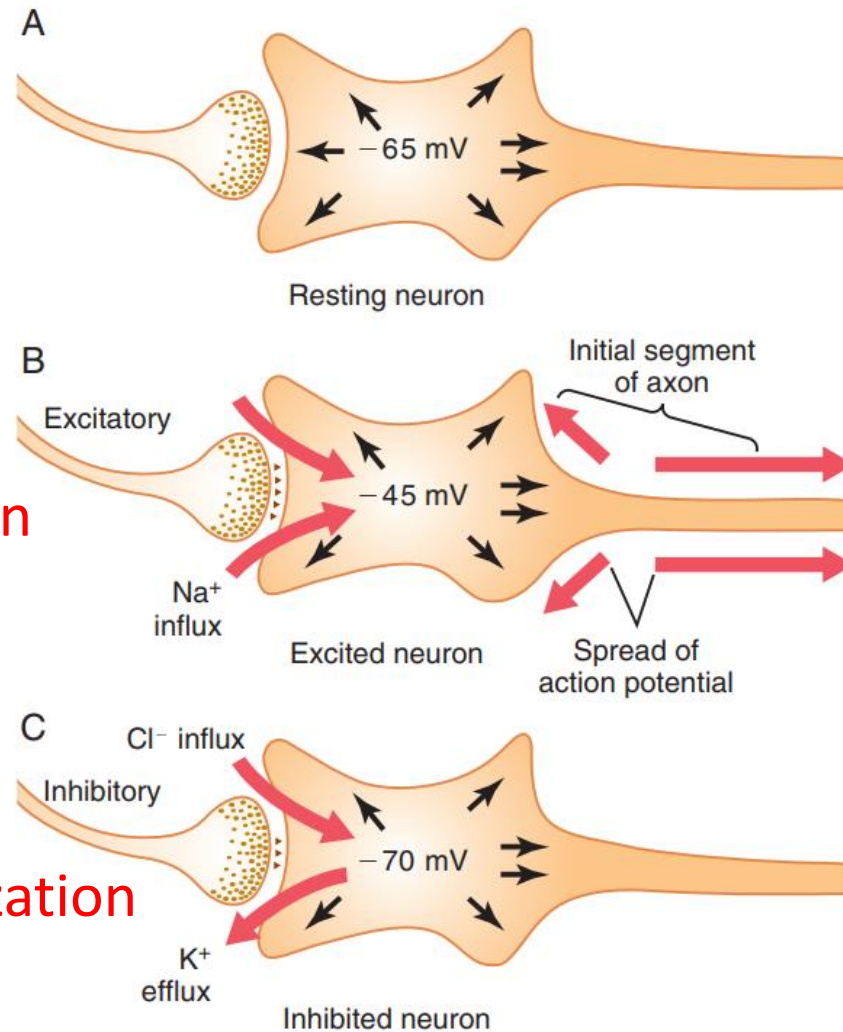
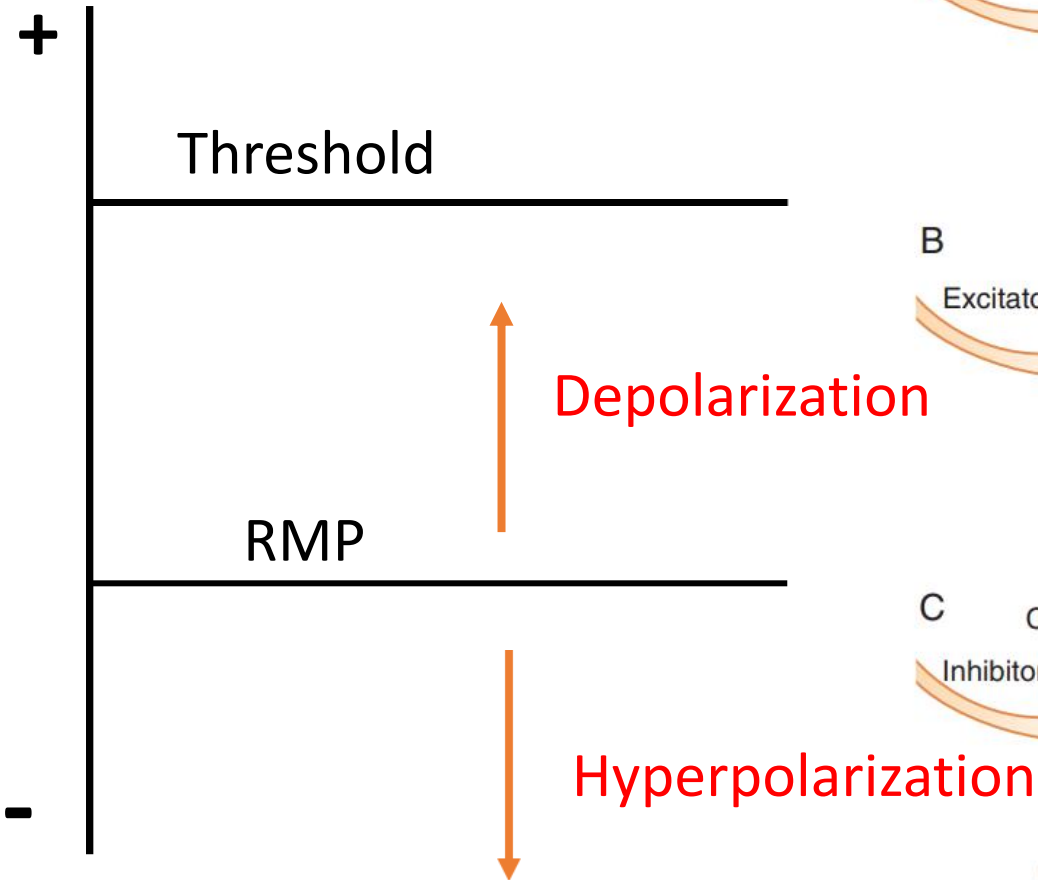
- Another important characteristic of the neuropeptides is that they often cause much more **prolonged actions**.
- Some of these actions include prolonged closure of calcium channels, prolonged changes in the metabolic machinery of cells, prolonged changes in activation or deactivation of specific genes 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.

A Chemical synapse



Basics of the membrane potential revision !





- A neuron at rest has a **resting membrane potential of -65 millivolts**.
- A **trigger causing sodium ion influx** leads to **depolarization** and **neuron excitation**.
- If **depolarization reaches the threshold**, an **action potential** is generated.
- If the threshold is **not reached**, the change remains as a **localized excitatory postsynaptic potential (EPSP)**, which is a **graded potential**.
- If the trigger causes **chloride ion influx** or **potassium ion efflux**, this results in **hyperpolarization**.
- Hyperpolarization** makes the membrane potential **more negative** and **inhibits the neuron**.

Resting membrane potential

- The basic cause of the change in membrane potential is a change in membrane permeability of the neuron, which allows ions to diffuse more or less readily through the membrane and thereby to change the membrane potential.

Graded potential vs Action potential

Comparison of Graded Potentials and Action Potentials in Neurons

CHARACTERISTIC	GRADED POTENTIALS	ACTION POTENTIALS
Origin	Arise mainly in dendrites and cell body.	Arise at trigger zones and propagate along axon.

Graded potential vs Action potential

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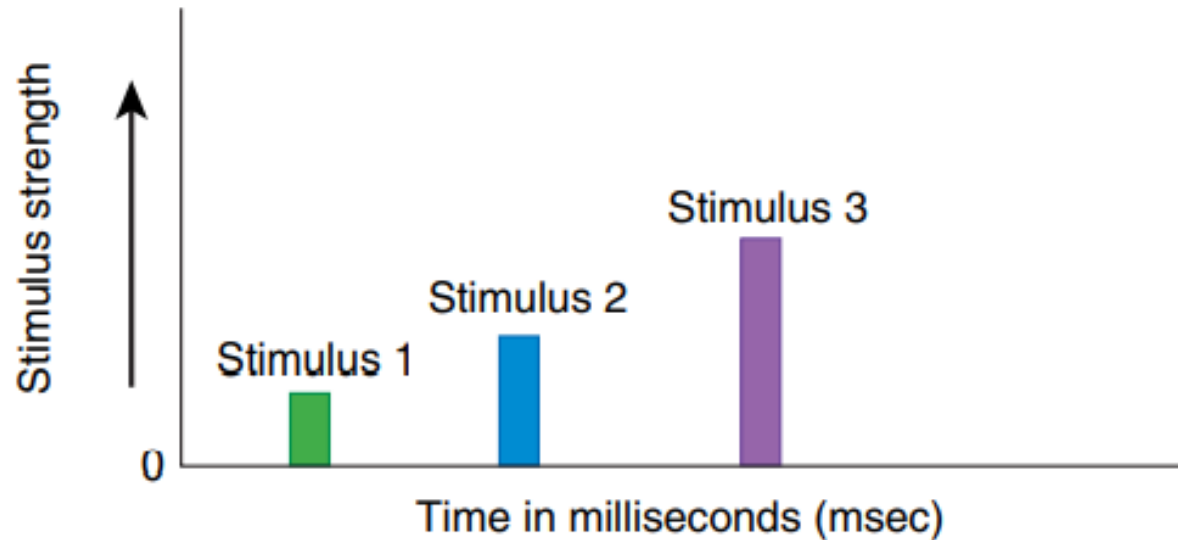
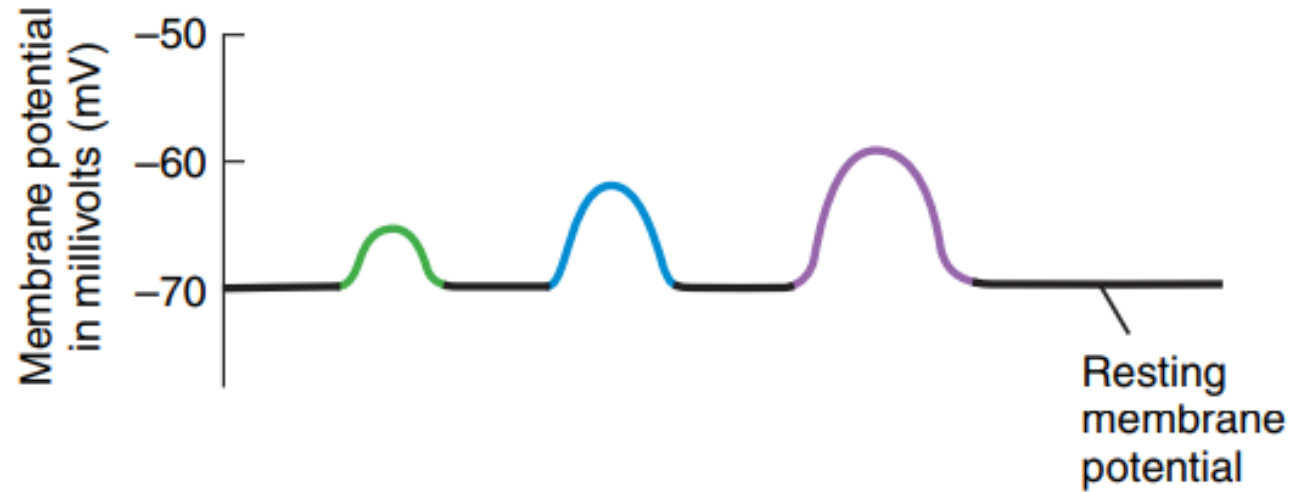
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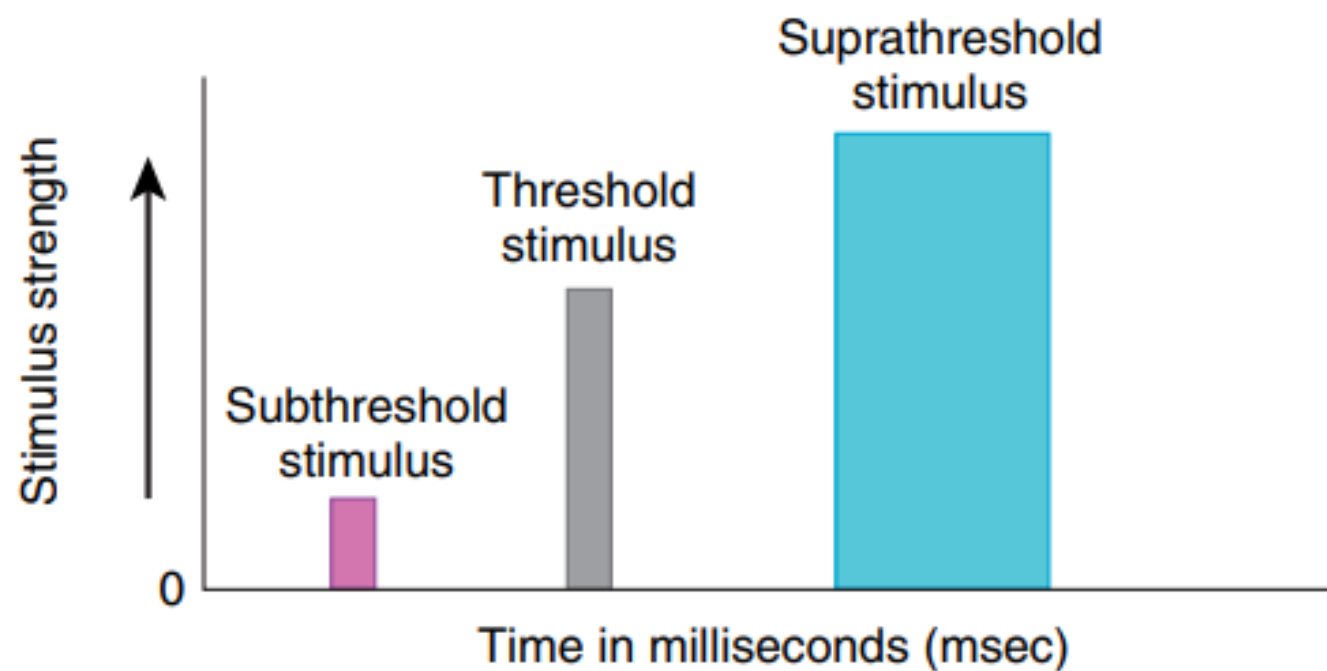
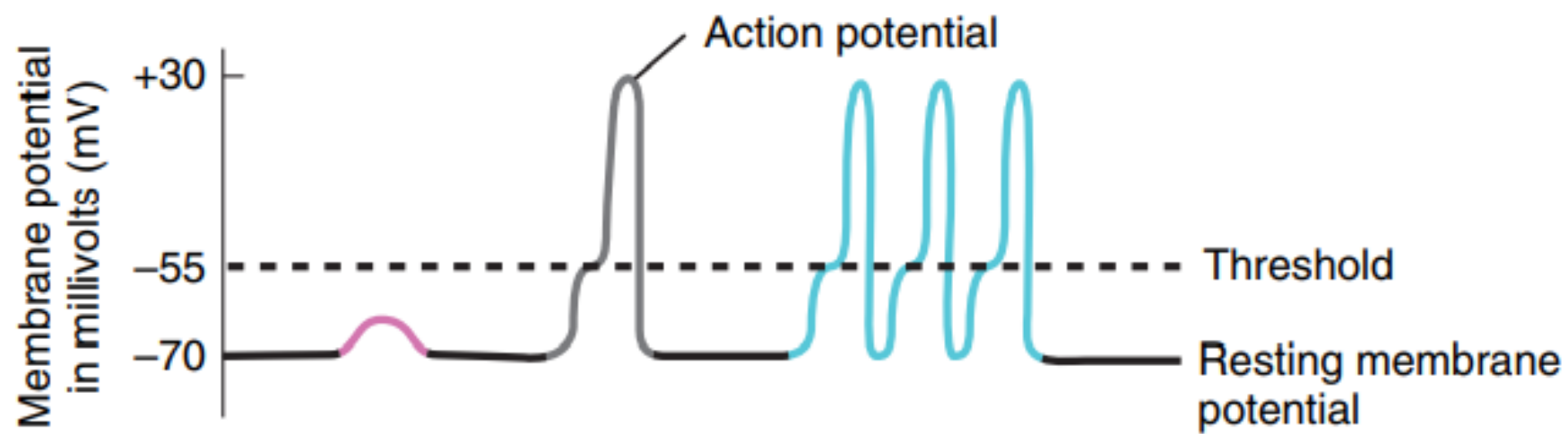
Graded potential vs Action potential

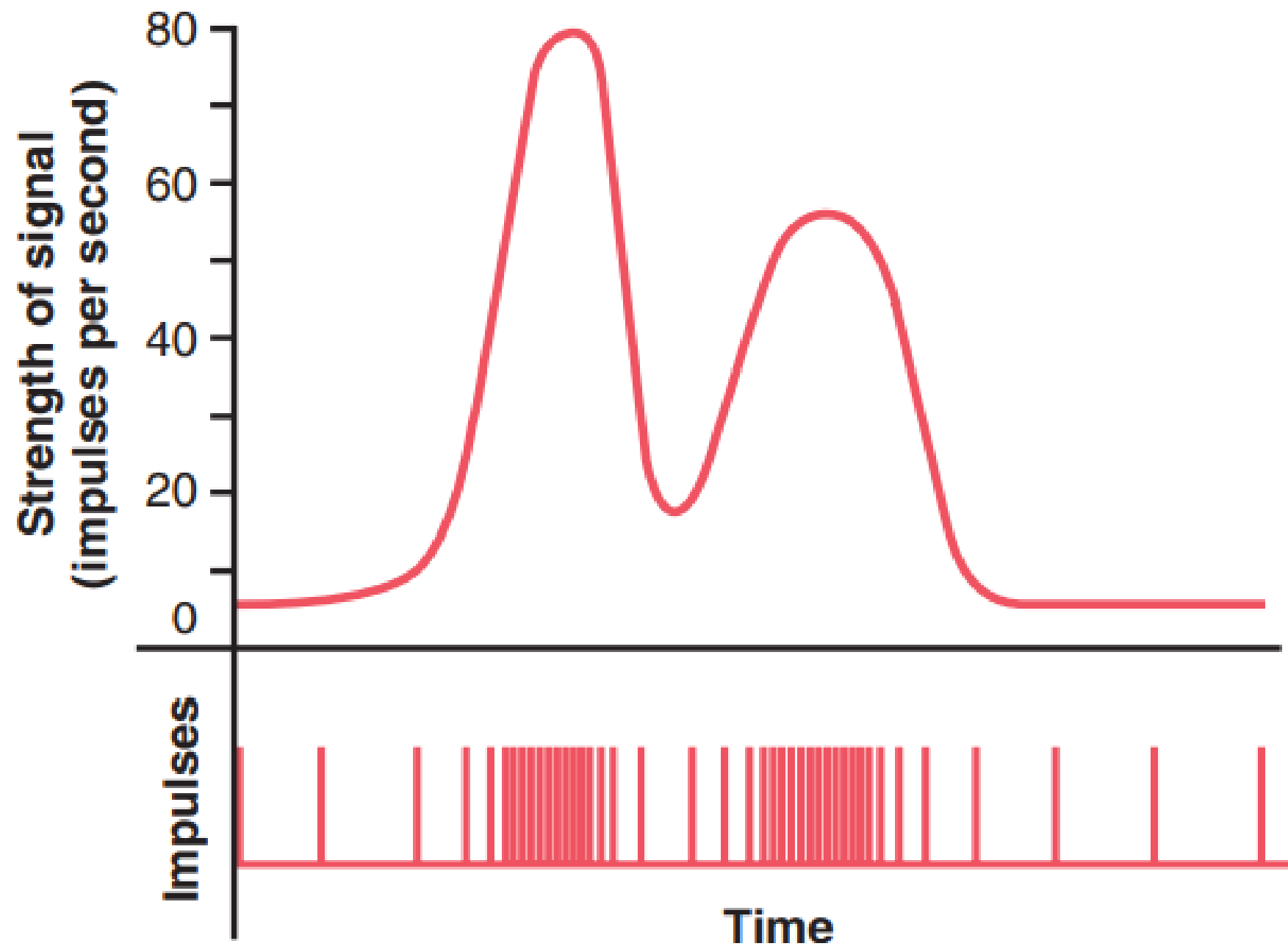
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Amplitude (size)	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All or none; typically about 100 mV.

The amplitude of a graded potential depends on the stimulus strength. The greater the stimulus strength, the larger the amplitude of the graded potential.







Graded potential vs Action potential

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Duration	Typically longer, ranging from several milliseconds to several minutes.	Shorter, ranging from 0.5 to 2 msec.

Graded potential vs Action potential

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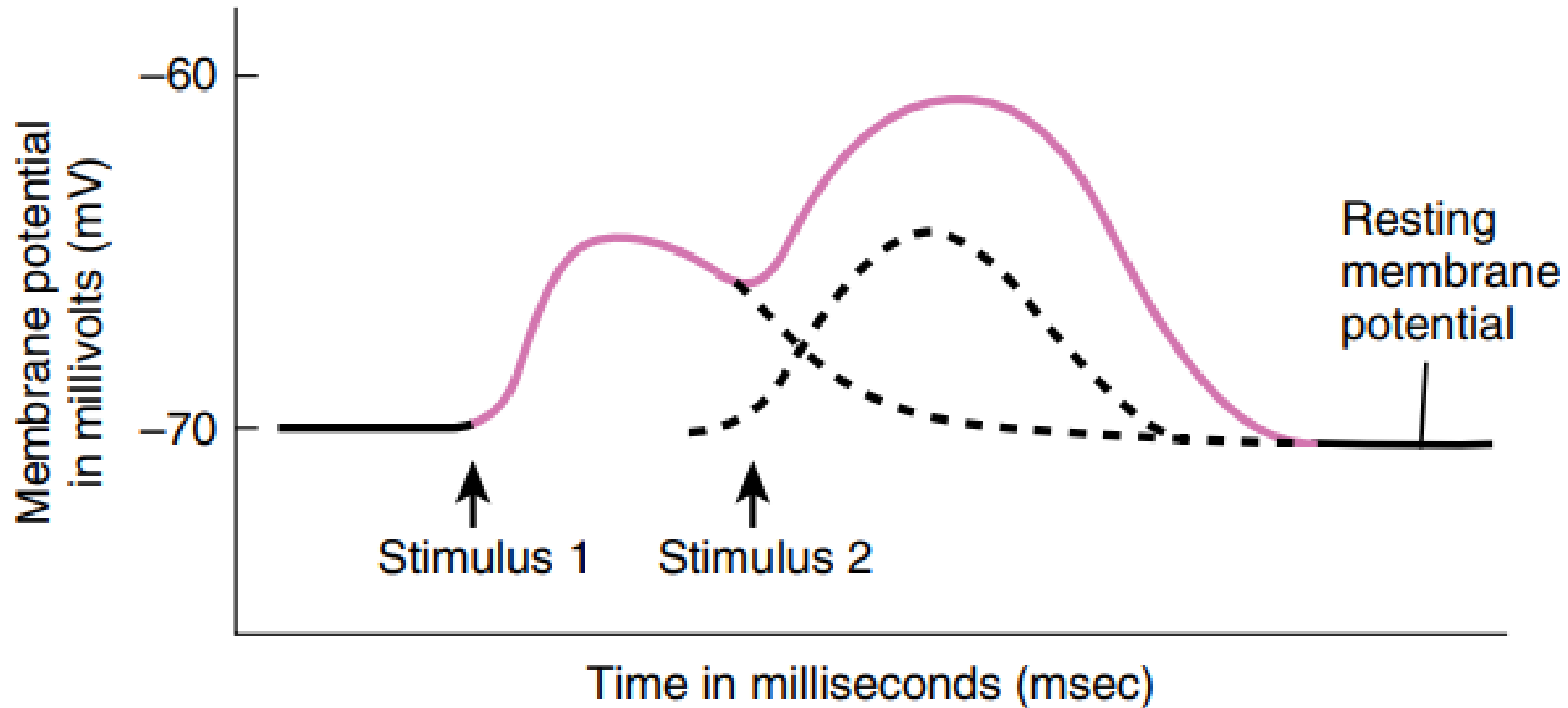
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Graded potential vs Action potential

Comparison of Graded Potentials and Action Potentials in Neurons

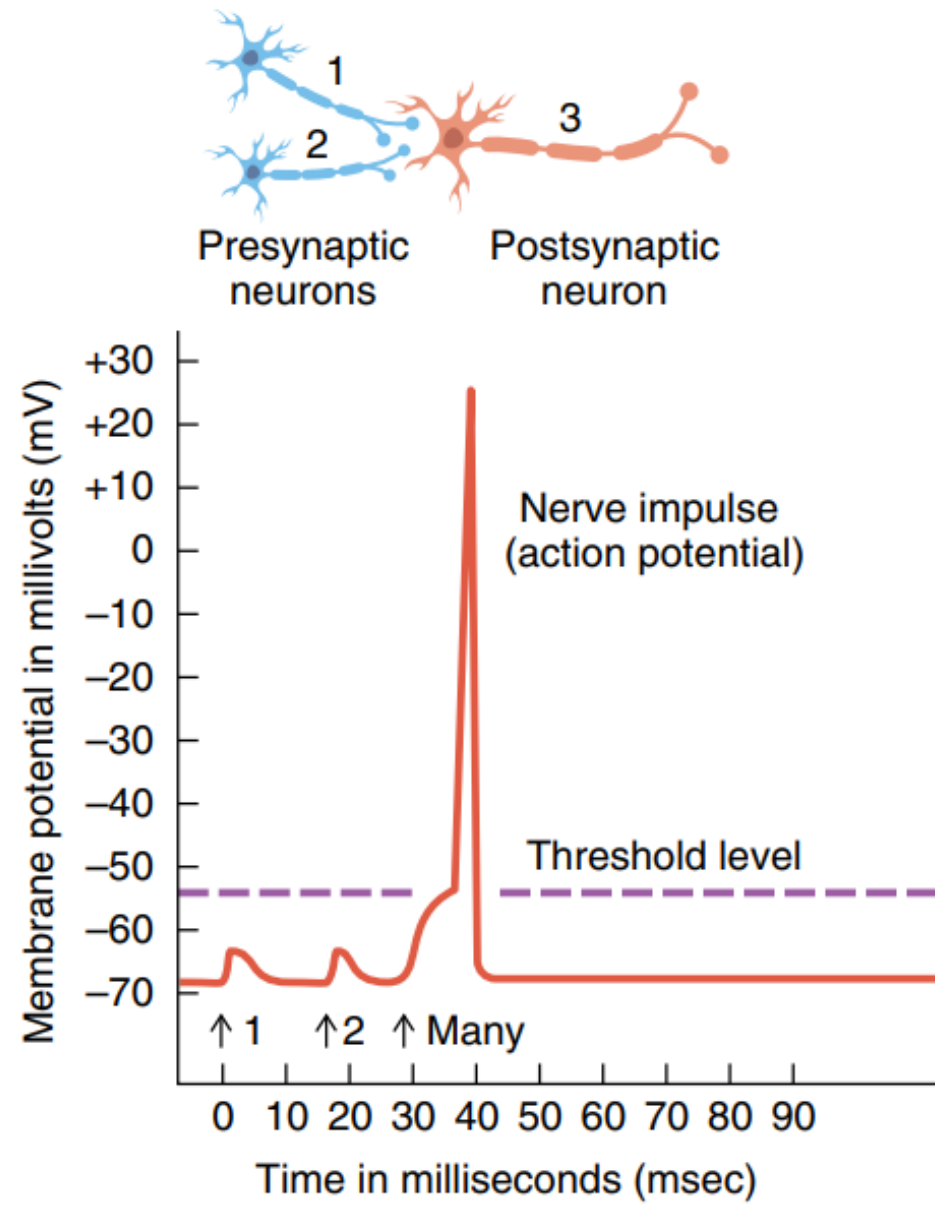
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Polarity	May be hyperpolarizing (inhibitory to generation of action potential) or depolarizing (excitatory to generation of action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present; summation can occur.	Present; summation cannot occur.

Summation in graded potential



Spatial summation in neurons

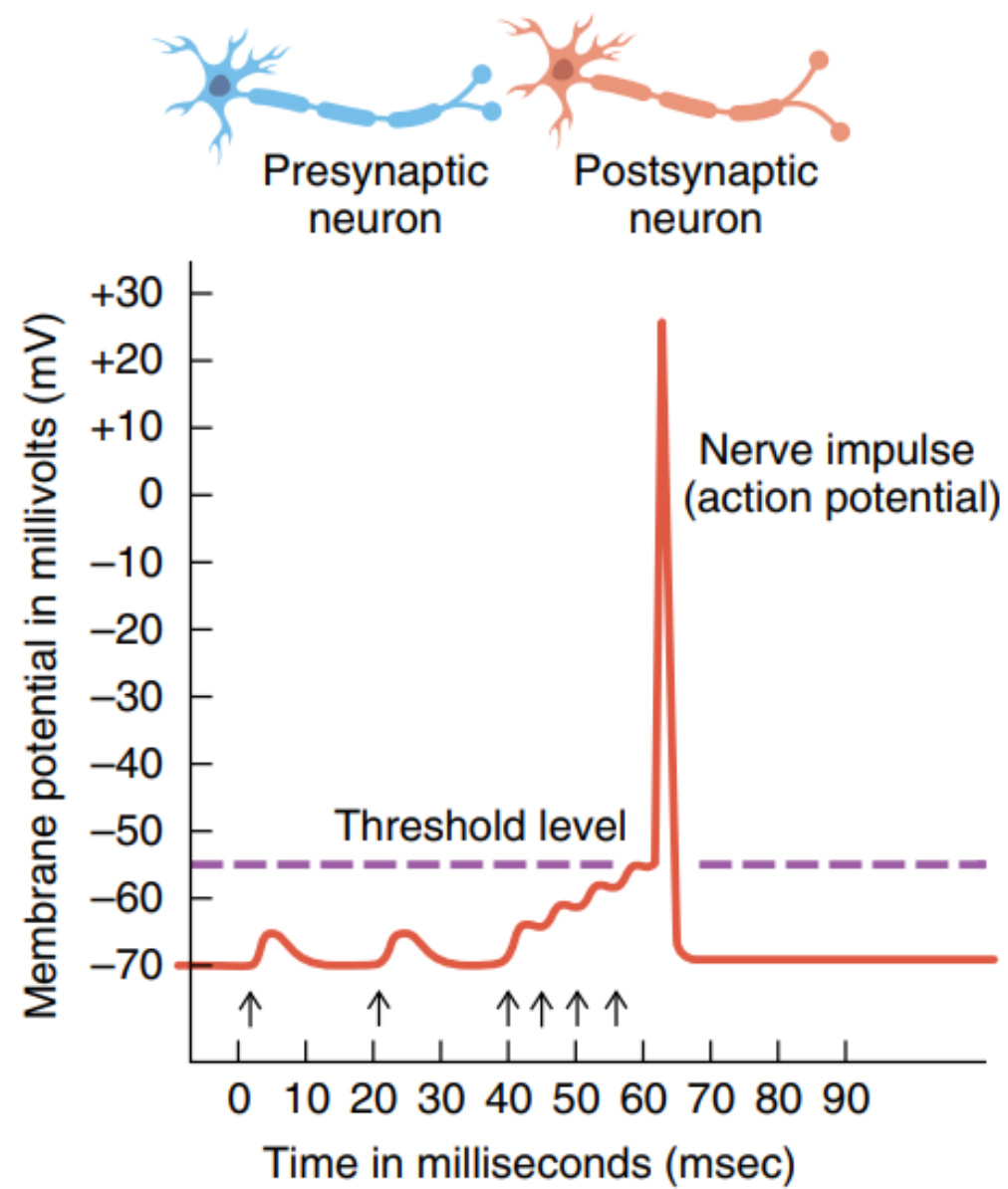
- The effect of summing simultaneous postsynaptic potentials by activating multiple terminals on widely spaced areas of the neuronal membrane is called **spatial summation**.



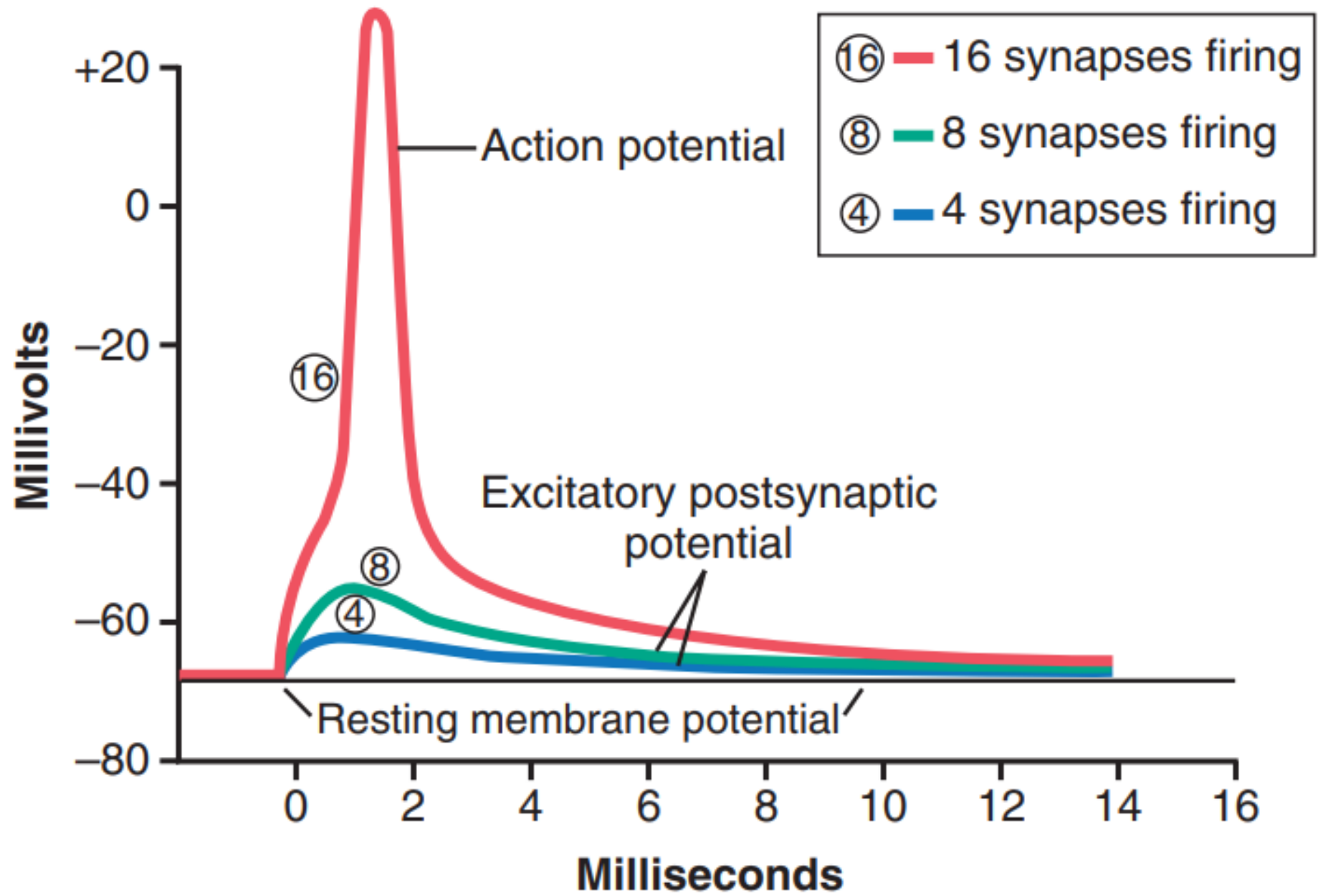
(a) Spatial summation

Temporal summation in neurons

- Each time a presynaptic terminal fires, the released transmitter substance opens the membrane channels for at most a millisecond or so. However, the changed postsynaptic potential lasts up to 15 milliseconds after the synaptic membrane channels have already closed.
- Therefore, a second opening of the same channels can increase the postsynaptic potential to a still greater level, and the more rapid the rate of stimulation, the greater the postsynaptic potential becomes. Thus, successive discharges from a single presynaptic terminal, if they occur rapidly enough, can add to one another; that is, they can “summate.” This type of summation is called temporal summation.



(b) Temporal summation



Time course of postsynaptic potentials

- When an excitatory synapse excites the anterior motor neuron, the neuronal membrane becomes highly permeable to sodium ions for 1 to 2 milliseconds.
- During this very short time, enough sodium ions diffuse rapidly to the interior of the postsynaptic motor neuron to increase its intraneuronal potential by a few millivolts, thus creating the EPSP.
- This potential then slowly declines over the next 15 milliseconds because this is the time required for the excess positive charges to leak out of the excited neuron and to re-establish the normal resting membrane potential.

Time course of postsynaptic potentials

- The opposite effect occurs for an **IPSP**;
- The inhibitory synapse increases the permeability of the membrane to potassium or chloride ions, or both, for 1 to 2 milliseconds, and this action decreases the intraneuronal potential to a more negative value than normal, thereby creating the IPSP.
- This potential also dies away in about 15 milliseconds.

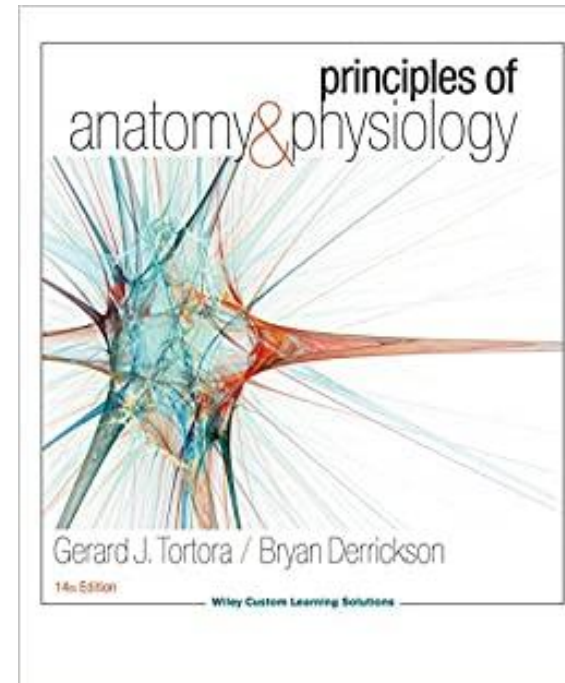
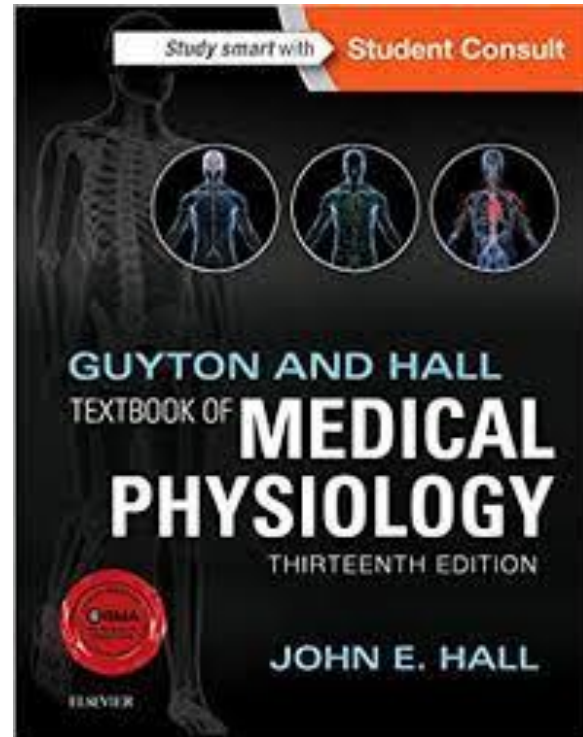
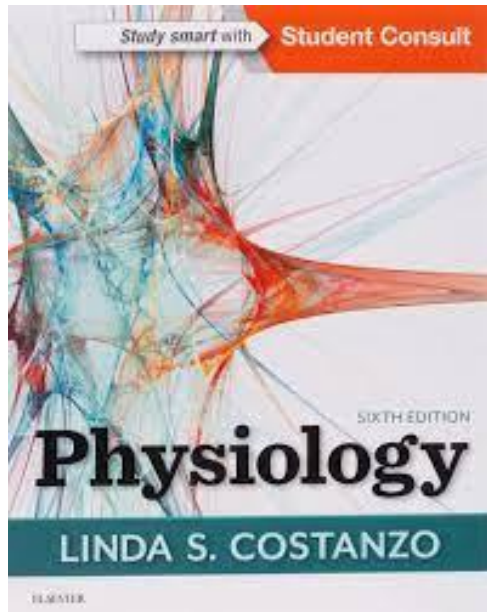
Time course of postsynaptic potentials

- Other types of transmitter substances can excite or inhibit the postsynaptic neuron for much longer periods— for hundreds of milliseconds or even for seconds, minutes, or hours. This is especially true for some of the **neuropeptide transmitters**.

Summation of IPSP and EPSP

- If an IPSP is tending to decrease the membrane potential to a more negative value while an EPSP is tending to increase the potential at the same time, these two effects can either completely or partially nullify each other.

References



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Edition

Human Physiology

From Cells to Systems

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