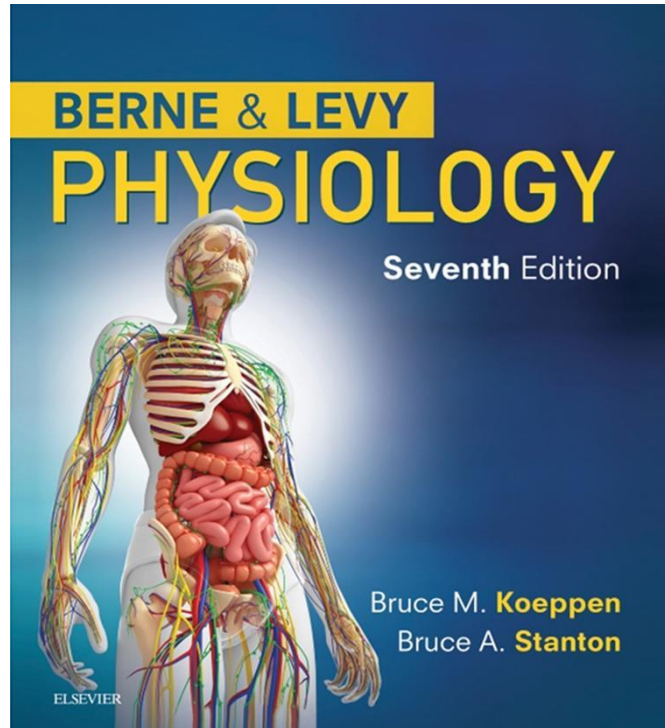
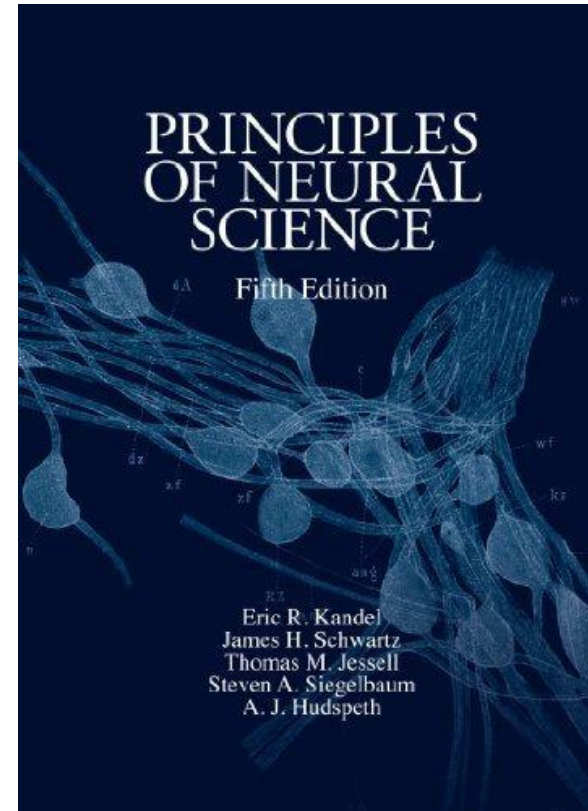


# Synapses



Chapter 6



Chapters 8 -13

Nerve cells have the capability to communicate with one another rapidly and with great precision, sometimes at very long distances. This is possible because of two mechanisms: axonal conduction of the action potential and synaptic transmission.

The term [synapse](#) was introduced by the great British neurophysiologist [Charles S. Sherrington](#) in 1897 in the book “Textbook of Physiology” written as a co-author with his older colleague Michael Foster.

[Sherrington](#) wrote:

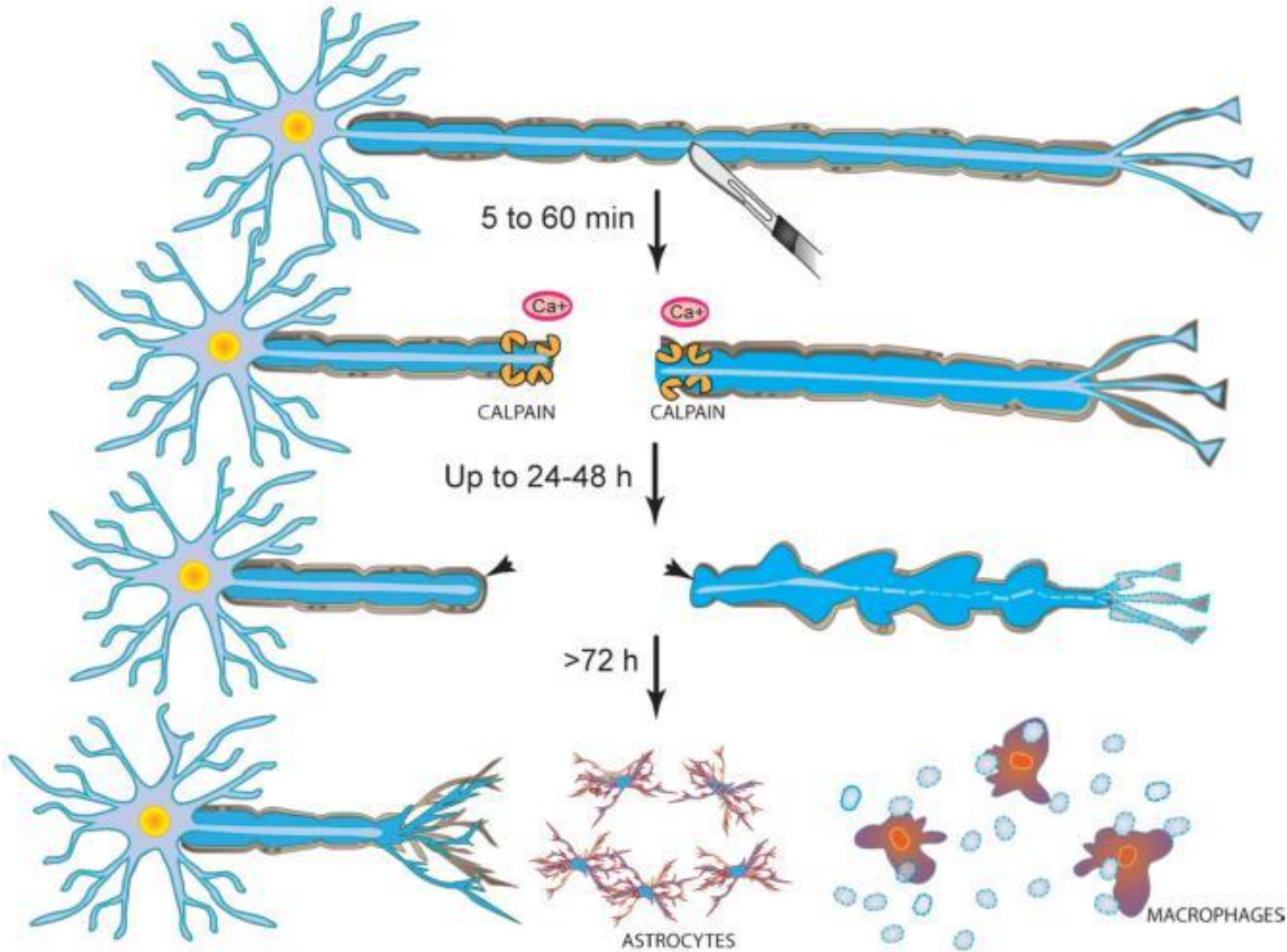
‘So far as our present knowledge goes, we are led to think that the tip of a twig of the arborescence is not continuous with but merely in contact with the substance of the dendrite or cell body on which it impinges. Such a special connection of one nerve cell with another might be called a [synapse](#).’

In that time, it was known that neurons were sending one-way electric signal from the body to the axons, but the modality of conduction of the signal along the cell was still ignored as well as the way signals were passing from neuron to neuron.

[Camillo Golgi](#) and [Santiago Ramon Y Cajal](#) were also in the middle of a scientific dispute. [Golgi](#), who invented an extraordinary way to color neurons, was convinced that neurons were organized in a large and continuous reticular matrix (the reticular theory), whereas [Cajal](#) was proposing that neurons were individual cells, separated one from the other and that neuronal fibers were not continuous with the other cells (the neuron theory).

The neuron theory was not just based on anatomical data, but also on the evidence provided by the [wallerian degeneration](#), described by [Augustus Volney Waller](#) in 1850.

## Wallerian degeneration



(JT Wang et al., 2012)

As early as 5–30 min after nerve injury, the axonal segments proximal (left) and distal (right) to the injury site exhibit acute axon degeneration an event that is principally mediated by extracellular  $\text{Ca}^{2+}$  influx and activation of the intracellular Ca-dependent protease **calpain**.

This event is followed by a slower axonal retraction and formation of axonal bulbs at the injury sites.

For the next 24 to 48 h after injury the distal axon remains morphologically stable and electrically excitable. At more than 72 h after injury, rapid fragmentation and cytoskeletal breakdown occur along the full length of the distal axon, followed by increased glial (astrocytes, macrophages and, in the PNS, Schwann cells) influx to clear axonal remnants and to promote regenerative attempts by the proximal axon.

## Electrical synapse

Many different tissues (heart, liver, smooth muscles, nervous system). Very rapid but stereotyped. It is used to send simple depolarizing or hyperpolarizing signals. It does not induce long-term modifications in the post-synaptic cell

## Chemical synapse

Involved in more variable signaling and thus can produce more complex behaviors. They can mediate either excitatory or inhibitory actions in postsynaptic cells and produce electrical changes in the postsynaptic cell that last from milliseconds to many minutes.

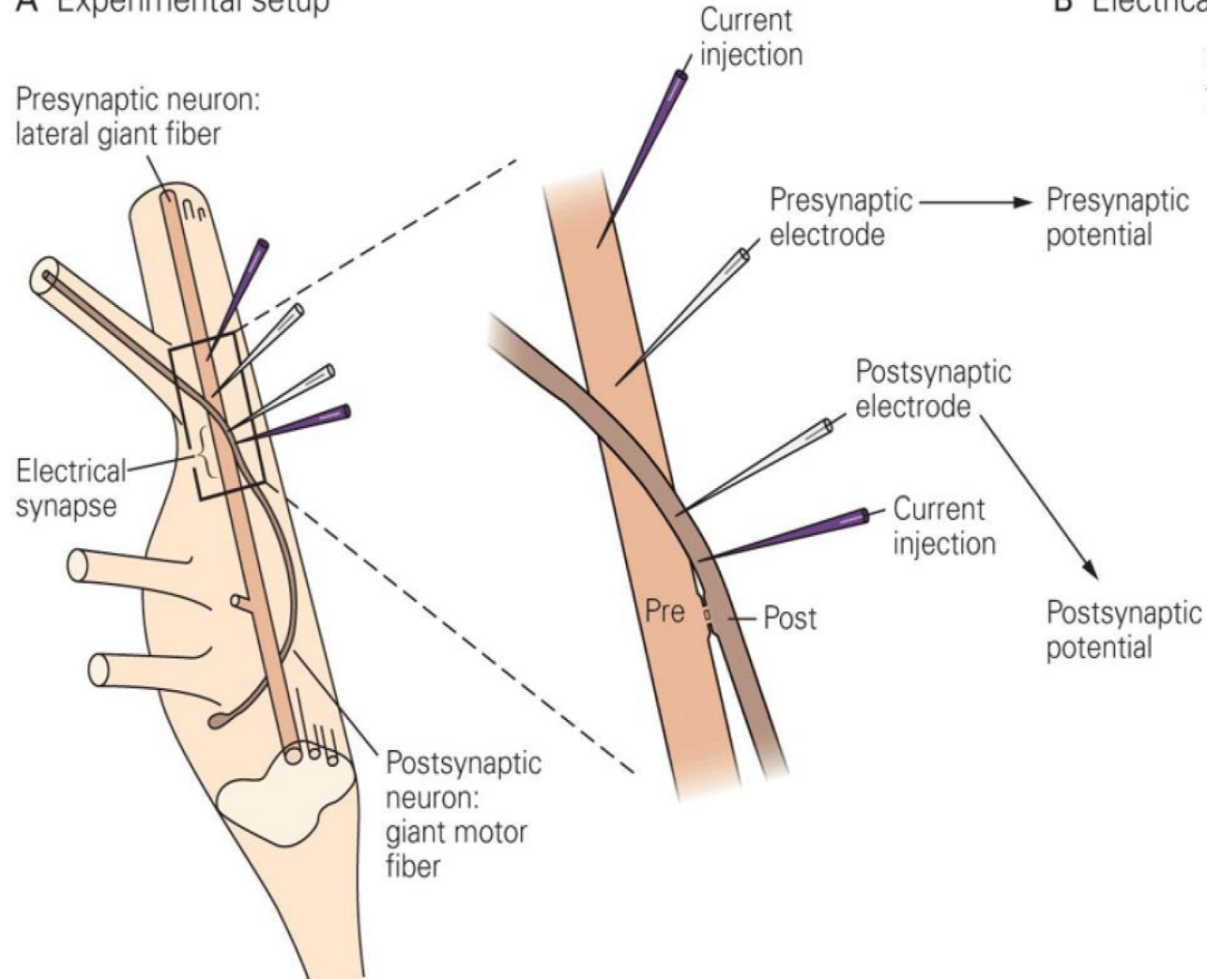
Chemical synapses also serve to amplify neuronal signals, so even a small presynaptic nerve terminal can alter the response of large postsynaptic cells. Not surprisingly, most synapses in the brain are chemical.

Type of synapse	Distance between pre- and postsynaptic cell membranes	Cytoplasmic continuity between pre- and postsynaptic cells	Ultrastructural components	Agent of transmission	Synaptic delay	Direction of transmission
Electrical	4 nm	Yes	Gap-junction channels	Ion current	Virtually absent	Usually bidirectional
Chemical	20–40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Chemical transmitter	Significant: at least 0.3 ms, usually 1–5 ms or longer	Unidirectional

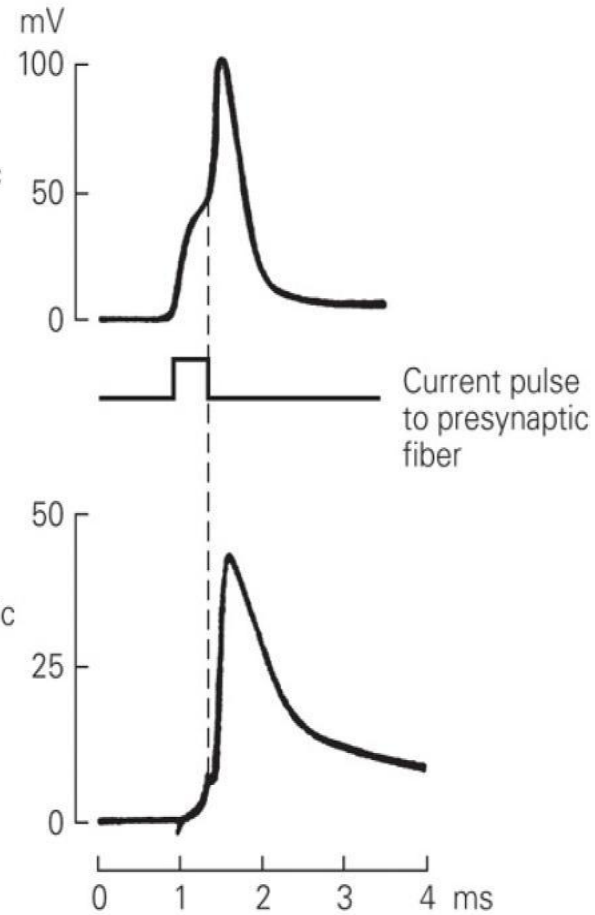
Table 8.1 Kandell

# Electrical synapse (Gap junctions)

## A Experimental setup



## B Electrical synaptic transmission



Latency between pre-synaptic and post-synaptic action potential is almost null. An action potential in the pre-synaptic cell is not necessary to evoke a response in the post-synaptic cell. This is because there is cytoplasmic continuity. Variation of  $V_m$  in the post-synaptic cell is proportional to the variation of  $V_m$  in the pre-synaptic cell.

Signal transmission at electrical synapses is similar to the passive propagation of subthreshold electrical signals along axons and therefore is also referred to as *electrotonic transmission*.

Fig 8.2 Kandell

## Electrical synapse

The specialized region of contact between two neurons at an electrical synapse is termed the *gap junction*. Here the separation between the two neurons (4 nm) is much less than the normal nonsynaptic space between neurons (20 nm). This narrow gap is bridged by the gap-junction channels, specialized protein structures that conduct ionic current from the presynaptic to the postsynaptic cell.

Gap-junction channels consist of a pair of hemichannels that form a continuous bridge. Each hemichannel is composed of six identical subunits, called *connexins*.

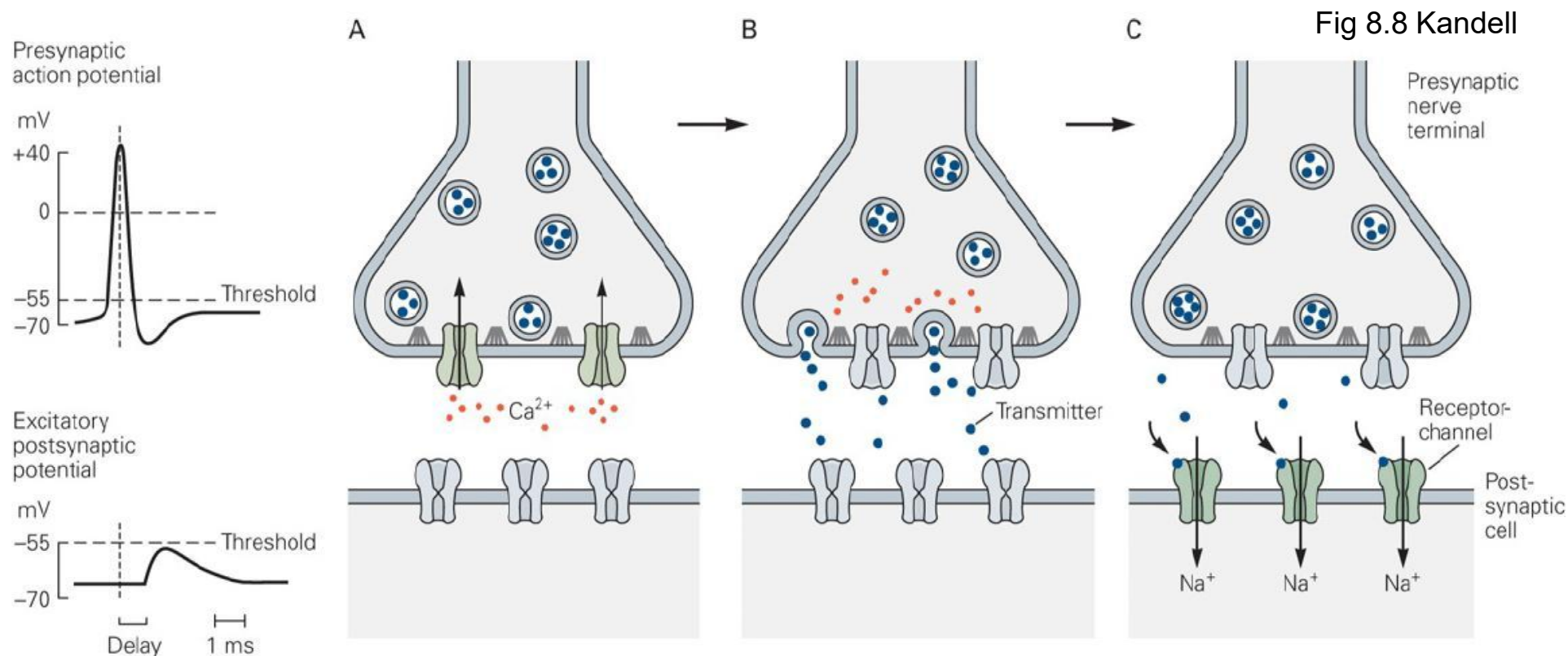
Many gap-junction channels in different cell types respond differently to modulatory factors that control their opening and closing. Some channels close in response to a decrease in ICF pH or ICF high concentrations of  $\text{Ca}^{2+}$ , others are voltage-sensitive, while in others channel proteins are phosphorylated in response to the activity of close-by chemical synapses.

Electrical transmission is useful for orchestrating the actions of large groups of cells. Because current crosses the membranes of all electrically coupled cells at the same time, several small cells can act coordinately as one large cell. Moreover, because of the electrical coupling between the cells, the effective resistance of the coupled network of neurons is rather small. Thus, from Ohm's law, the synaptic current required to fire electrically coupled cells is relatively large because it tends to dissipate. Once the threshold is surpassed, however, electrically coupled cells fire synchronously because voltage-activated  $\text{Na}^{+}$  currents generated in one cell are very rapidly conducted to other cells. In the nervous system, electrical synapses are formed between glial cells (astrocytes, Schwann cells) but also between neurons

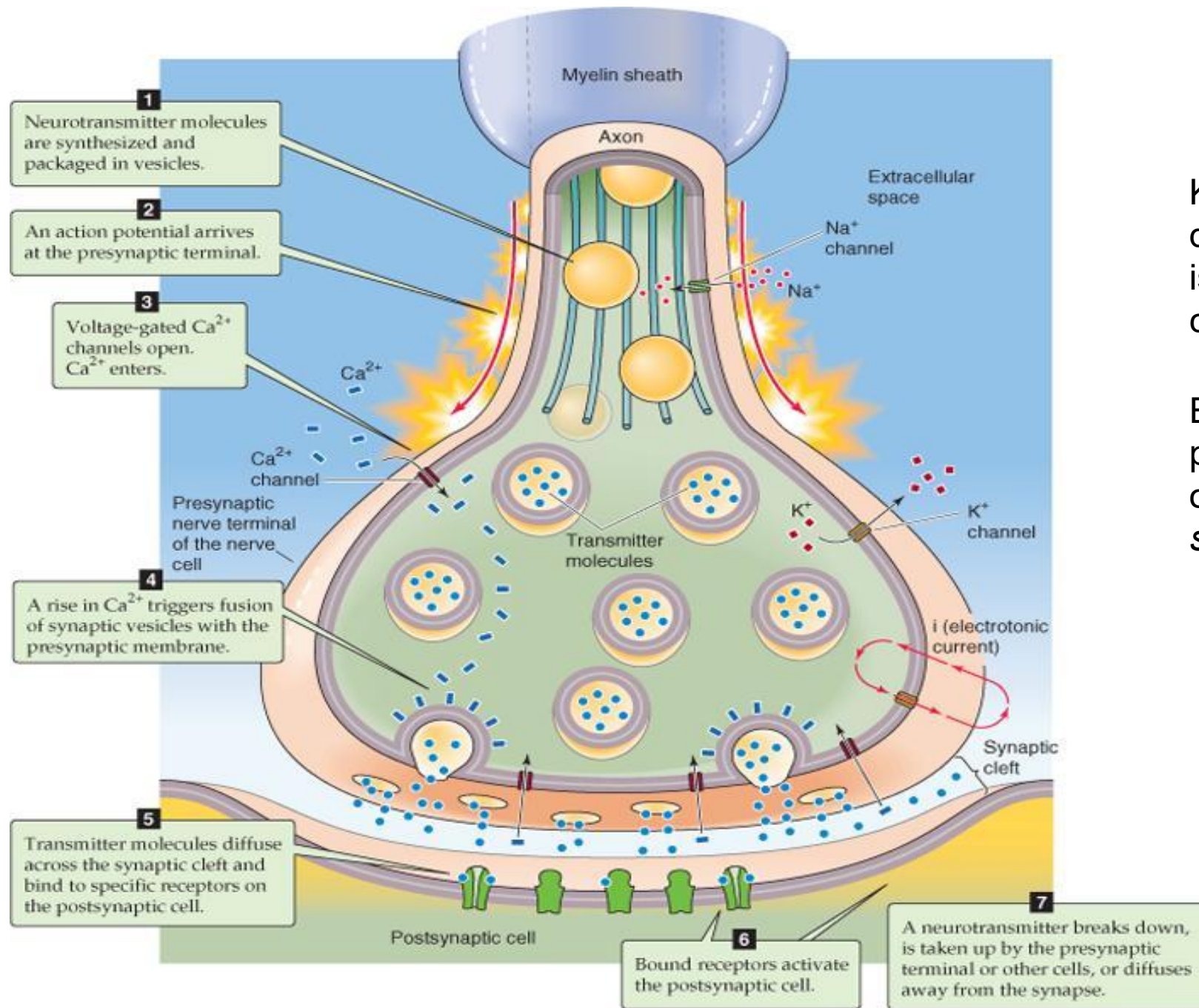


# Chemical synapse

Chemical synaptic transmission depends on the diffusion of a neurotransmitter across the synaptic cleft. A neurotransmitter is a chemical substance that binds receptors in the postsynaptic membrane of the target cell. At most chemical synapses, transmitter is released from specialized swellings of the axon, the presynaptic terminals, which typically contain 100 to 200 synaptic vesicles, each of which is filled with several thousand molecules of the neurotransmitter. This happens in specialized regions of the presynaptic membrane called *active zones*.



The rise in intracellular Ca<sup>2+</sup> concentration triggers a biochemical reaction that causes the vesicles to fuse with the presynaptic membrane and release neurotransmitter into the synaptic cleft, a process termed *exocytosis*. The transmitter molecules then diffuse across the synaptic cleft and bind to their receptors on the postsynaptic cell membrane. This in turn activates the receptors, leading to the opening or closing of ion channels. The resulting flux of ions alters the membrane conductance and potential of the postsynaptic cell.



Katz and his colleagues discovered that neurotransmitter is released in discrete amounts, called *quanta*.

Each quantum of transmitter produces a postsynaptic potential of fixed size, called the *quantal synaptic potential*.

The neurotransmitter release is consequence of  $\text{Ca}^{2+}$  influx in the pre-synaptic terminals. More precisely  $\text{Ca}^{2+}$  increases the probability that one quantum of neurotransmitter is released without influencing the number of molecules inside each vesicle. Two-fold increase in  $\text{Ca}^{2+}$  influx can increase the amount of transmitter released by 16-fold.

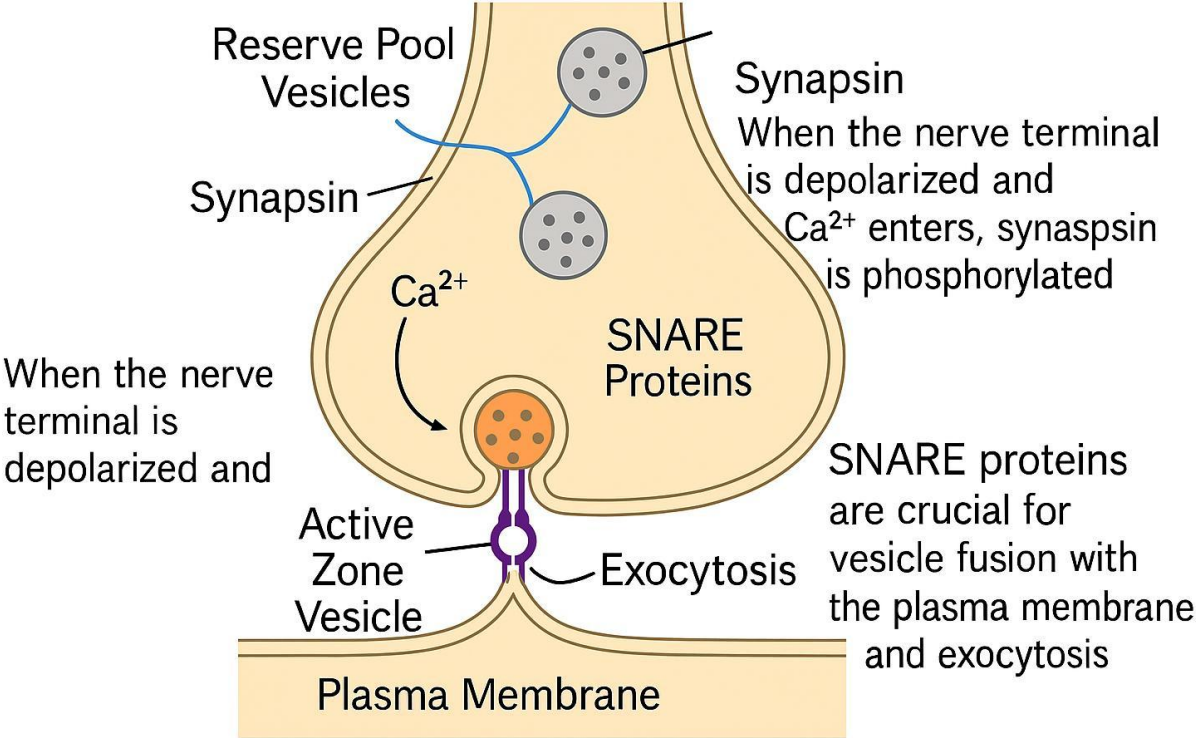
Experimental recordings revealed a brief lag of 1 to 2 ms between the onset of the presynaptic action potential and the postsynaptic excitatory synaptic potential, which accounts for what Sherrington termed the *synaptic delay*. Because  $\text{Ca}^{2+}$  channels open more slowly than  $\text{Na}^{+}$  channels,  $\text{Ca}^{2+}$  reaches its concentration peak when the membrane has begun to repolarize. Surprisingly, once  $\text{Ca}^{2+}$  enters the terminal, transmitter is rapidly released with a delay of only a few hundred microseconds. Thus, the synaptic delay is largely attributable to the time required to open  $\text{Ca}^{2+}$  channels.

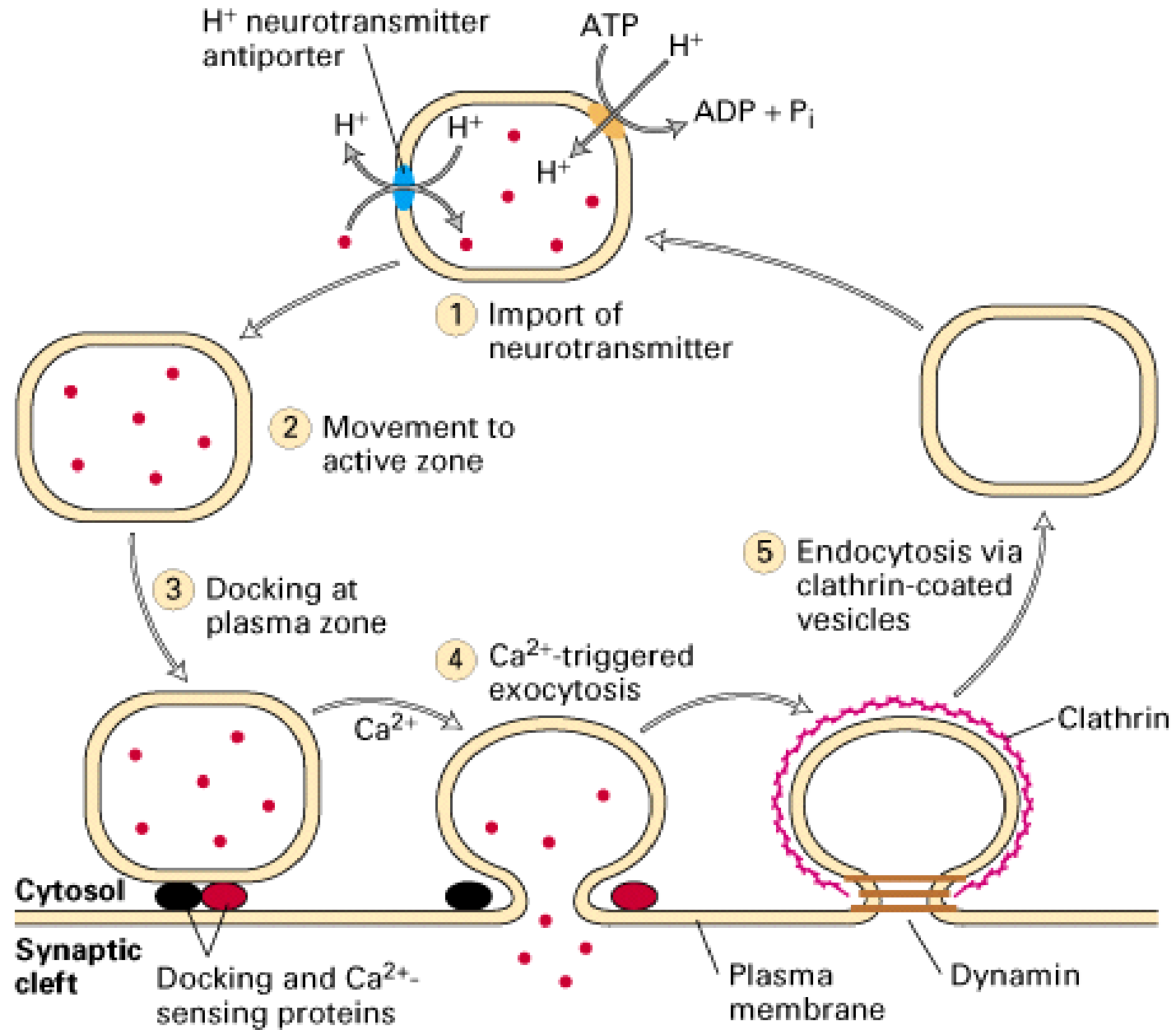
Approximately 10 to 30  $\mu\text{M}$   $\text{Ca}^{2+}$  is required to release the amount of neurotransmitter normally observed during an action potential.

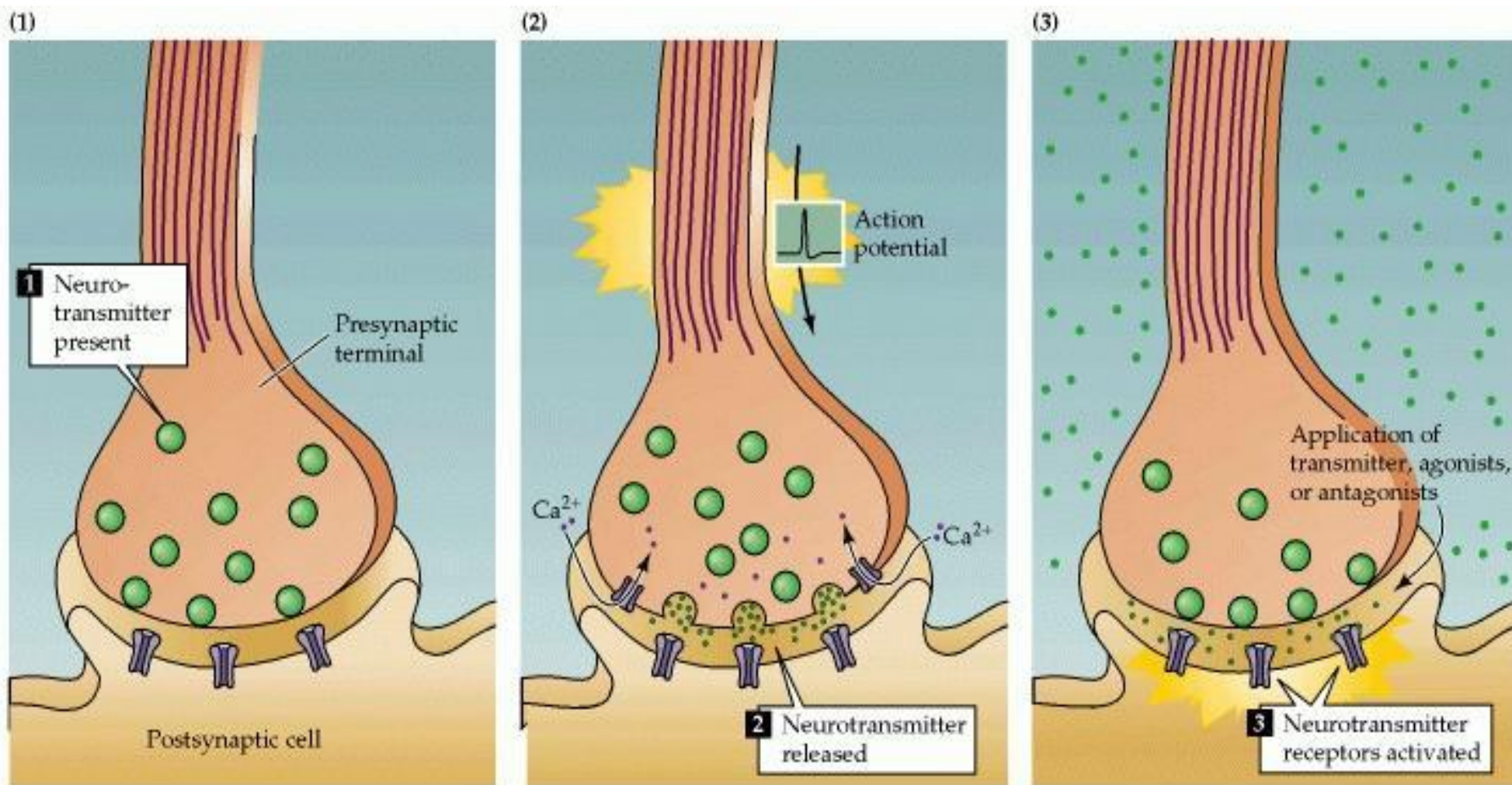
Neurons contain five classes of voltage-gated  $\text{Ca}^{2+}$  channels: the **L-type**, **P/Q-type**, **N-type**, **R-type**, and **T-type**. Calcium channels are multimeric proteins with the  $\alpha 1$ -subunit being their pore forming subunit. The  $\alpha 1$ -subunit is homologous to the  $\alpha$ -subunit of the voltage-gated  $\text{Na}^{+}$  channel, comprised of four repeats of a domain with six membrane-spanning segments that includes the S4 voltage-sensor and pore-lining P region. Calcium channels also have auxiliary subunits (termed  $\alpha 2$ ,  $\beta$ ,  $\gamma$ , and  $\Delta$ ). In neurons the rapid release of conventional transmitters associated with fast synaptic transmission is mediated mainly by the P/Q-type and N-type  $\text{Ca}^{2+}$  channels because these are the channel types concentrated at the active zone.

When firing at high frequency, a typical neuron is able to maintain a high rate of transmitter release. This can result in the exocytosis of a large number of vesicles, more than the number originally present within the presynaptic terminal. To prevent the supply of vesicles from being rapidly depleted, used vesicles are rapidly retrieved (e.g. usually clathrin mediated process) and recycled.

The vesicles outside the active zone represent a reserve pool of transmitter. *Synapsins* are important regulators of the reserve pool of vesicles. The synapsins are substrates for both PKA and  $Ca^{2+}$ /calmodulin-dependent protein kinase I. When the nerve terminal is depolarized and  $Ca^{2+}$  enters, the synapsins become phosphorylated by the kinase and are thus released from the vesicles. SNARE proteins are fundamental for vesicle fusion with plasma mb and exocytosis.







Demonstrating that a substance acts as a **neurotransmitter** at a synapse requires showing (1) its presence in the presynaptic terminal, (2) its release because of presynaptic terminal depolarization and (3) the postsynaptic presence of specific receptors.

Fulfilling these criteria establishes unambiguously that a substance is used as a transmitter at a given synapse. Practical difficulties, however, have prevented these standards from being applied at many types of synapses. It is for this reason that so many substances must be referred to as "**putative**" **neurotransmitters**.

## NEUROTRANSMITTERS

More than 50 different neurotransmitters have been identified so far. This shows that the nervous system uses a chemically diversified code. Neurotransmitters are classified chemically and functionally.

### CHEMICAL CLASSIFICATION

(independent from postsynaptic organization)

i) Acetylcholine (ACh); ii) Biogenic amines; iii) Amino acids; iv) Peptides; v) Novel messengers

### FUNCTIONAL CLASSIFICATION

(dependent from postsynaptic organization)

A: i) **Excitatory**; excitatory neurotransmitters cause depolarizations (e.g., glutamate); ii) **Inhibitory**; inhibitory neurotransmitters cause hyperpolarizations (e.g., GABA).

A neurotransmitter may have both excitatory and inhibitory effects determined by the receptor type of the postsynaptic neuron (the diversity of receptors for the same neurotransmitter amplifies the chemical diversification of the neuronal code). For example, acetylcholine (ACh) is excitatory for the skeletal muscle (presence of nicotinic receptors) and inhibitory for the cardiac muscle (presence of muscarinic receptors).

B: Acting on different type of receptors: i) **Ionotropic** (open ion channels) promote rapid responses; ii) **Metabotropic** (activate G-proteins and act through second messengers) create a metabolic change in cell and promote long-lasting effects.

# CHEMICAL CLASSIFICATION OF NEUROTRANSMITTERS

## CLASSICAL NEUROTRANSMITTERS

### Acetylcholine

**Biogenic amines;** Catecholamines: dopamine (DA), norepinephrine (NE) or noradrenaline (NA), and epinephrine (EP) or adrenaline (A); Indolamines: serotonin (5-HT) and histamine (H).

**Amino acids;** Gamma-aminobutyric acid (GABA), Glycine, Glutamic acid.

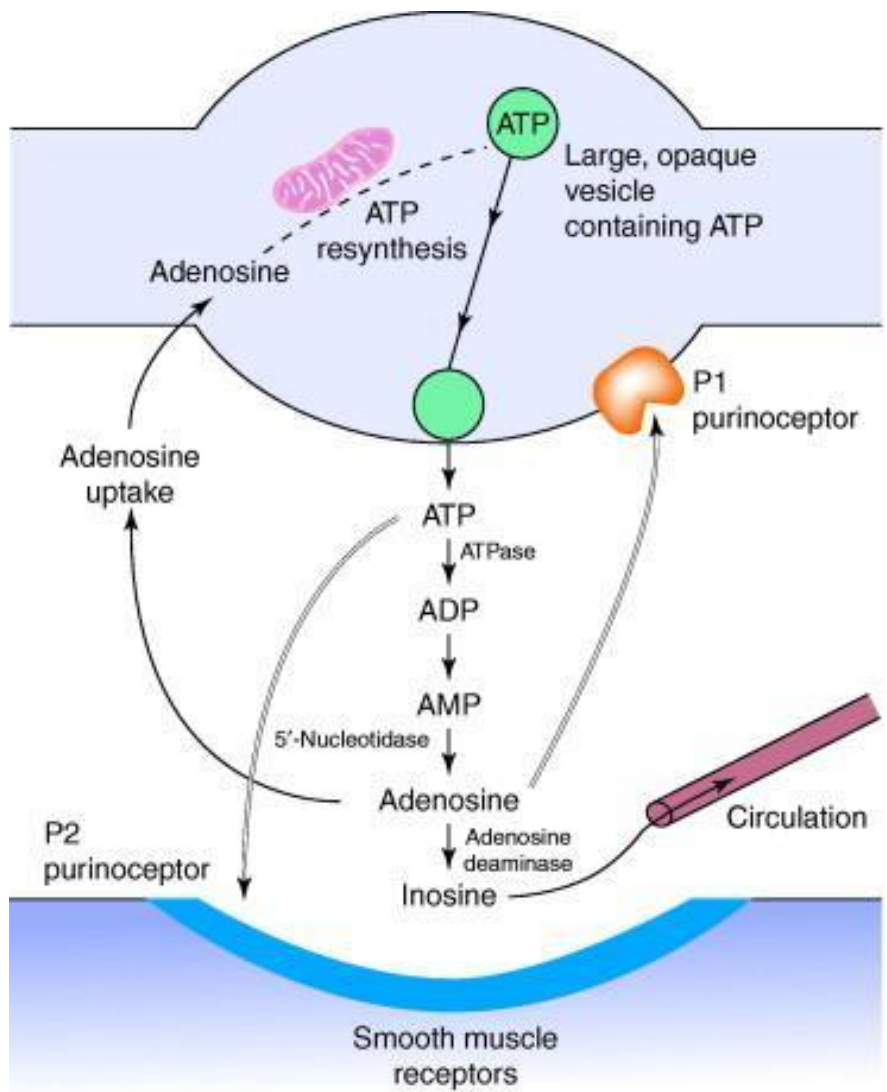
## NON CLASSICAL NEUROTRANSMITTERS

**Neuropeptides:** All Neuropeptide receptors are G-protein linked (alter levels of intracellular second messengers): Substance P – mediator of pain signals; Neuropeptide Y - stimulates appetite and food intake; Endogenous Opioids (Endorphins, Enkephalins, Dynorphin) which bind to the same receptor as opiates and morphine, reducing our perception of pain.

**Novel messengers:** Nitric oxide (NO), the same substance produced by sublingual nitroglycerin (a drug producing an increase vasodilation in relief of angina). A short-lived gas, NO diffuses through membranes to bind with its intracellular receptor which is an enzyme (guanylyl cyclase). Also, NO is a free radical and, therefore, a highly reactive compound.

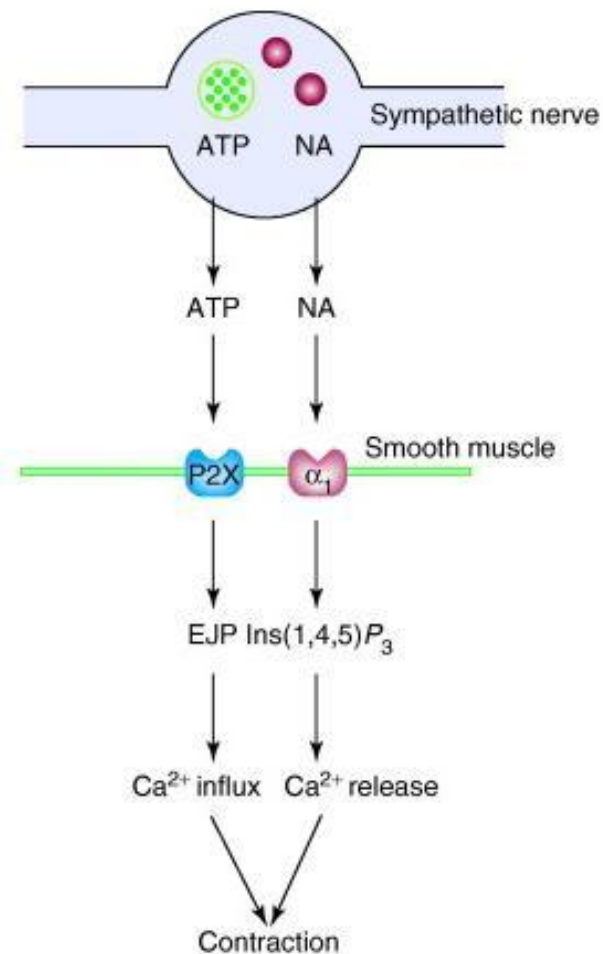
ATP

Purinergetic neuromuscular junction depicting the synthesis, storage, release and inactivation of ATP. ATP, stored in vesicles in nerve varicosities, is released by exocytosis to act on postjunctional P2 purinoceptors on smooth muscle. ATP is broken down extracellularly by ATPases and 5'-nucleotidase to adenosine, which is taken up by varicosities to be resynthesised and restored in vesicles. Adenosine acts prejunctionally on P1 purinoceptors to modulate transmitter release. If adenosine is broken down further by adenosine deaminase to inosine, it is removed by the circulation.

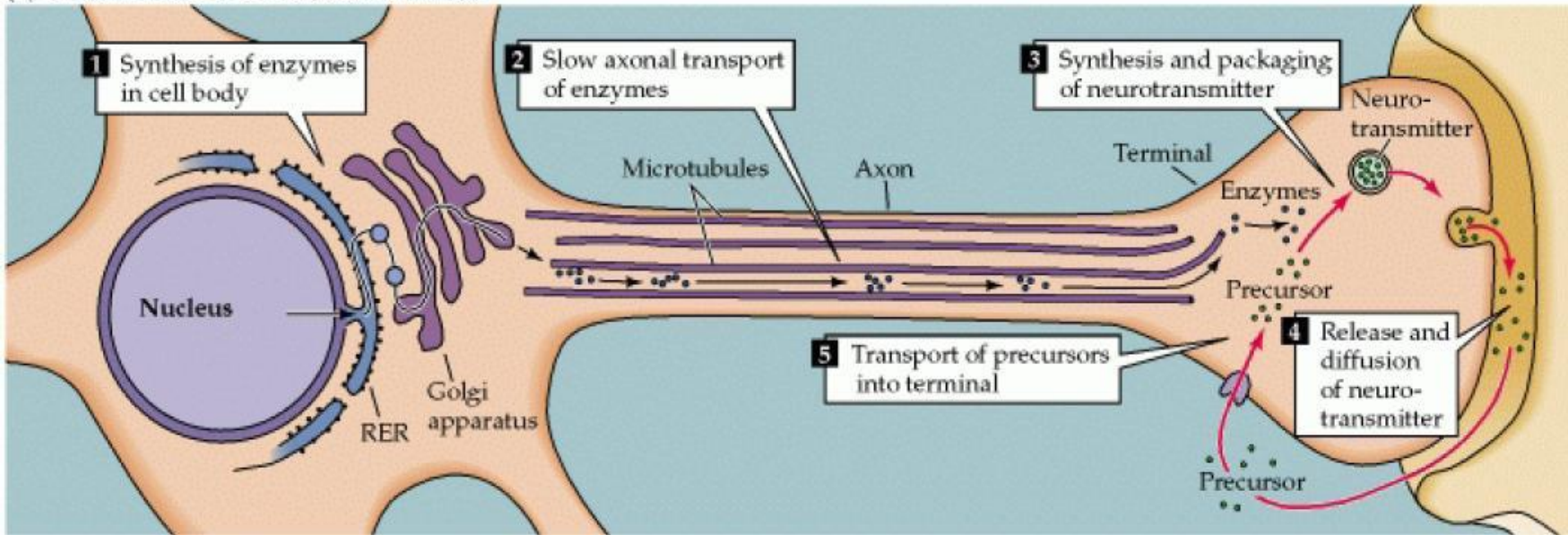


*TRENDS in Pharmacological Sciences*

Burnstock, 2006



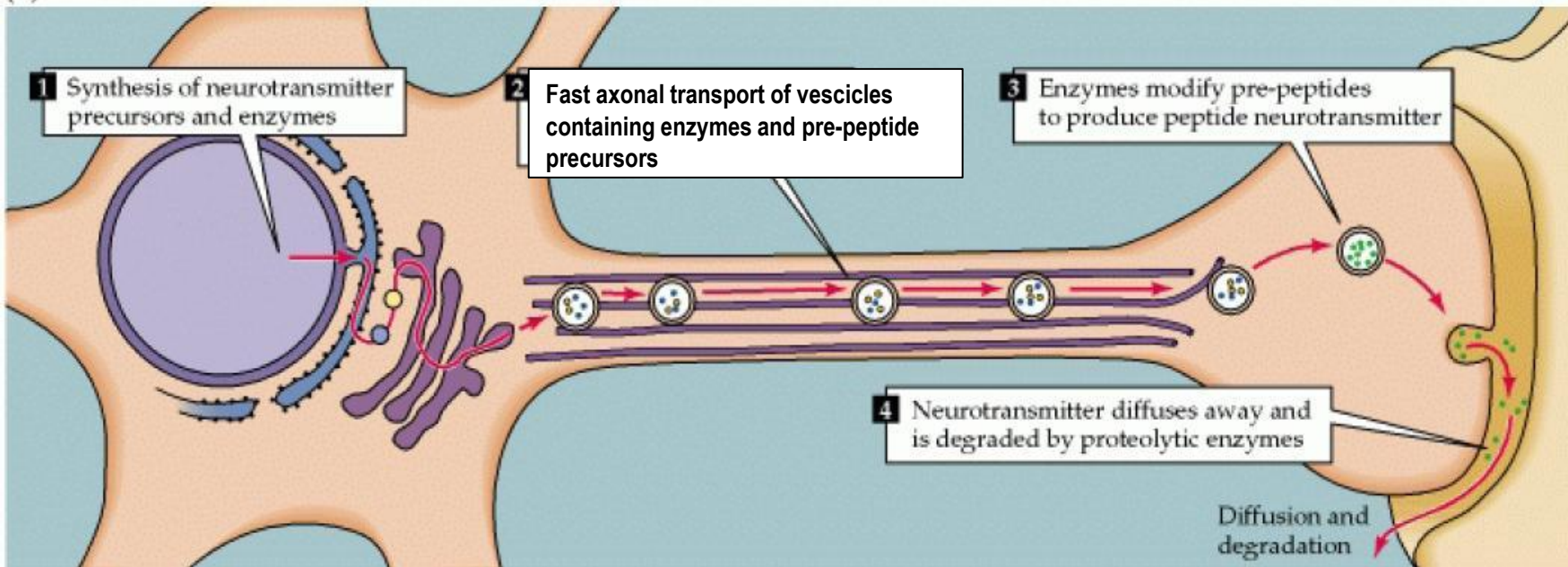
## (B) SMALL-MOLECULE TRANSMITTERS



Axonal transport can be: **anterograde** (towards the synapse) or **retrograde** (towards the cell body). The anterograde transport is mediated by a class of protein called **kinesin**. The retrograde transport is mediated by the **dynein**.

Axonal transport can be **slow** (0,2 - 8,0 mm / day) or **fast** (200 - 400 mm / day):

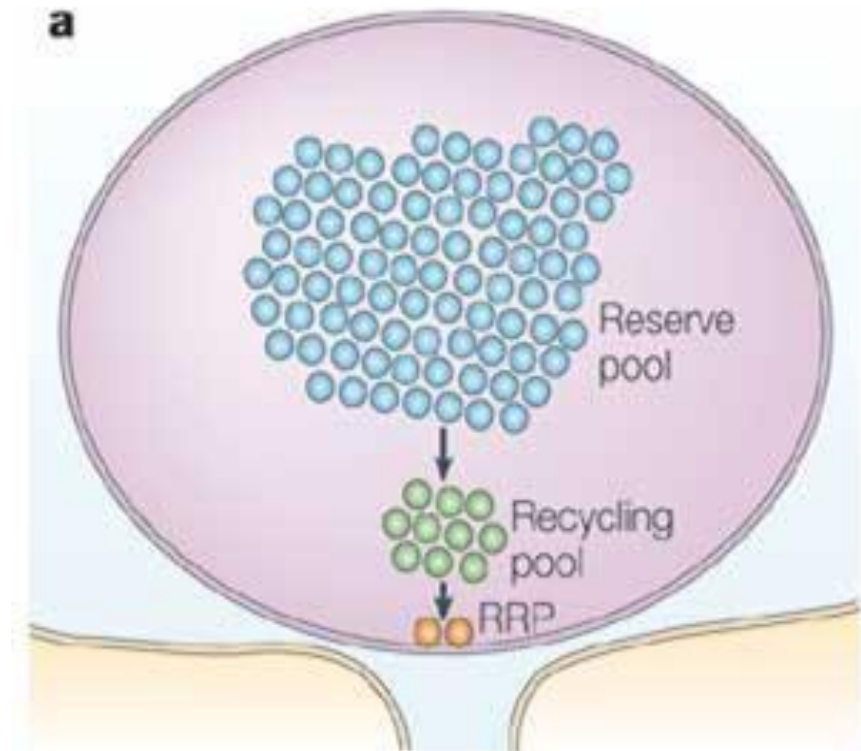
## (C) PEPTIDE TRANSMITTERS



The slow axonal transport is for enzyme and RNA  
The fast axonal transport is for vesicles and mitochondria.

The axonal transport makes use of **microtubuli** (23-24 nm diameter), which can be considered as rails

Microtubuli are one of the component of the cytoskeleton of the neuron, together with the **neurofilament** (10nm) and the **microfilament** (5 nm)



[Nat Rev Neurosci.](#) 2005 Jan;6(1):57-69.

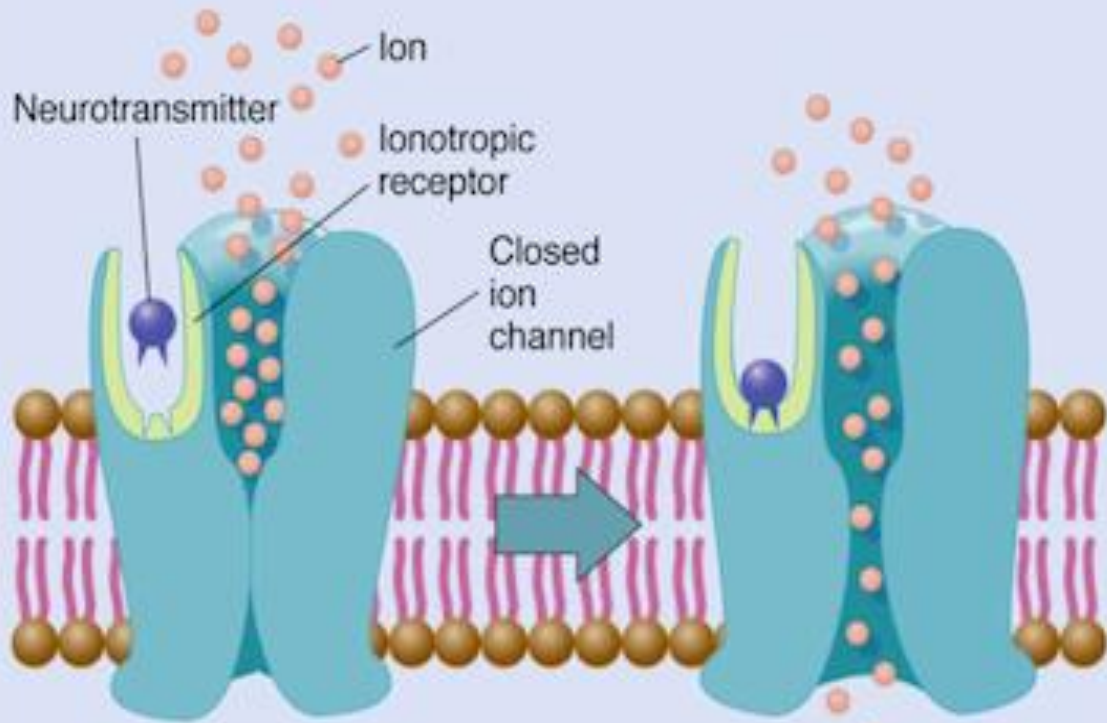
The classic three-pool model. The **reserve pool** makes up 80–90% of the total pool, and the **recycling pool** is significantly smaller (10–15%). The **readily releasable pool (RRP)** consists of a few vesicles (1%) that seem to be docked and primed for release.

Once released in the synaptic cleft, the neurotransmitter is recognized and binds to its own receptor on the post-synaptic cell. All receptors have two bio-chemical common features:

1. They are trans-membrane proteins that span the entire lipid bilayer, with the external (ECF) portion which has the function to recognize and bind its ligand released by the pre-synaptic cell.
2. They exert an effect on the target cell by modifying directly the gating of an ionic channel or by inducing specific metabolic effects and indirectly modifying the gating of an ionic channel.

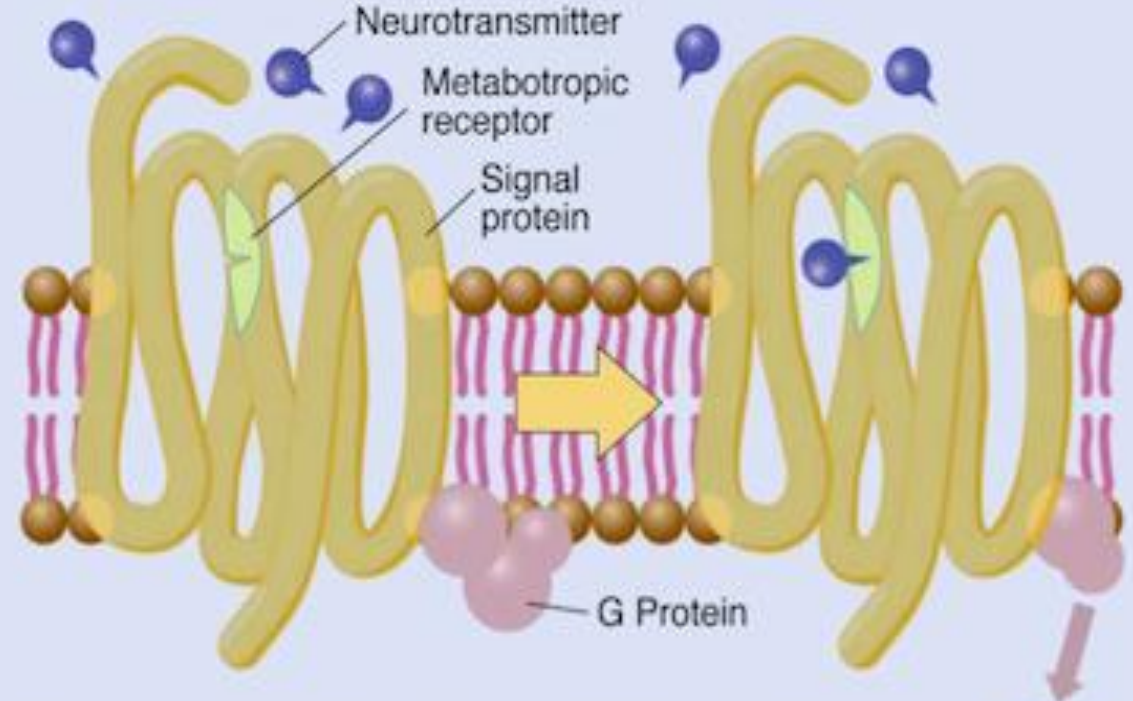
# Membrane receptors

## An Ionotropic Receptor



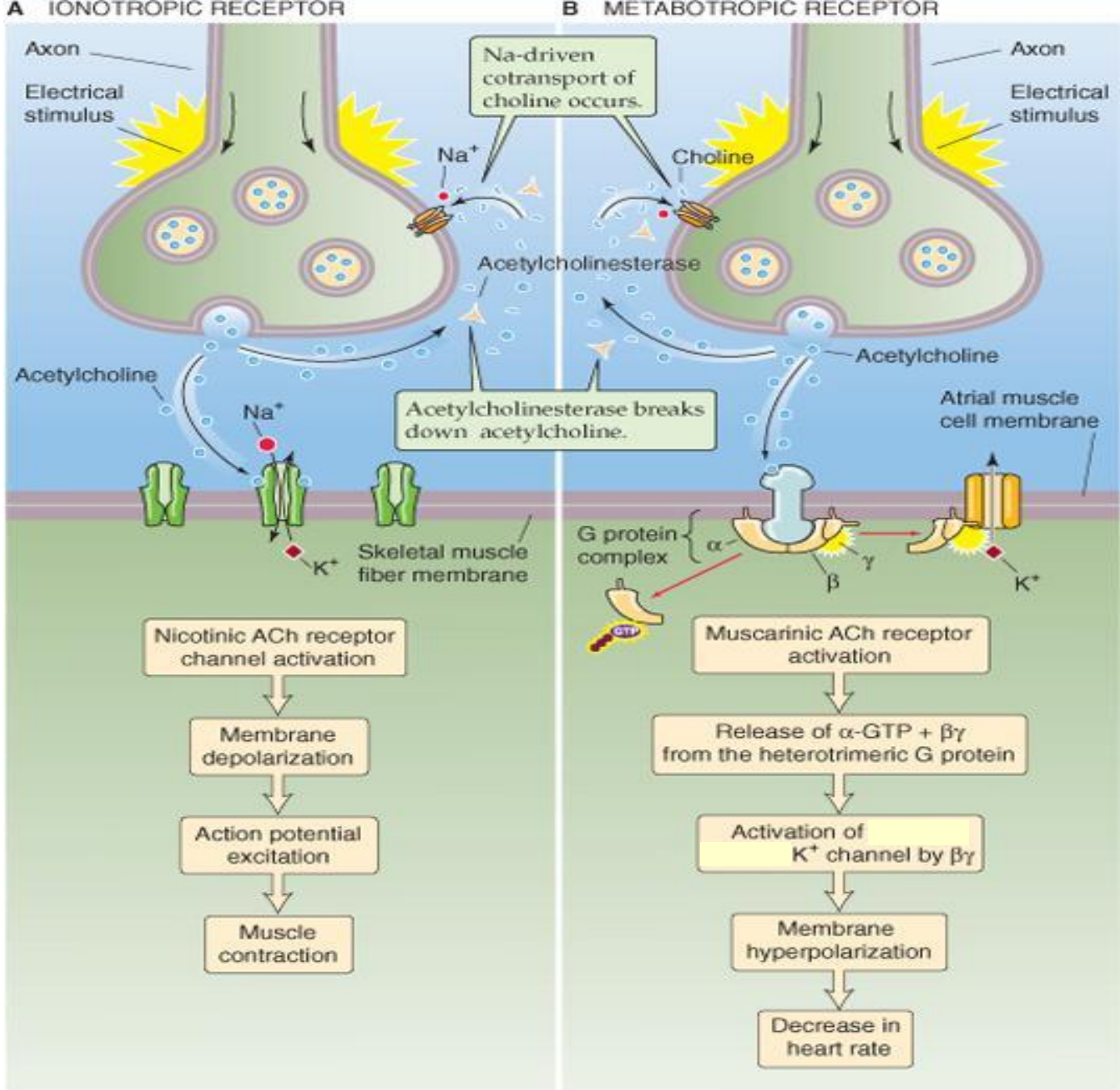
Some neurotransmitter molecules bind to receptors on ion channels. When a neurotransmitter molecule binds to an ionotropic receptor, the channel opens (as in this case) or closes, thereby altering the flow of ions into or out of the neuron.

## A Metabotropic Receptor



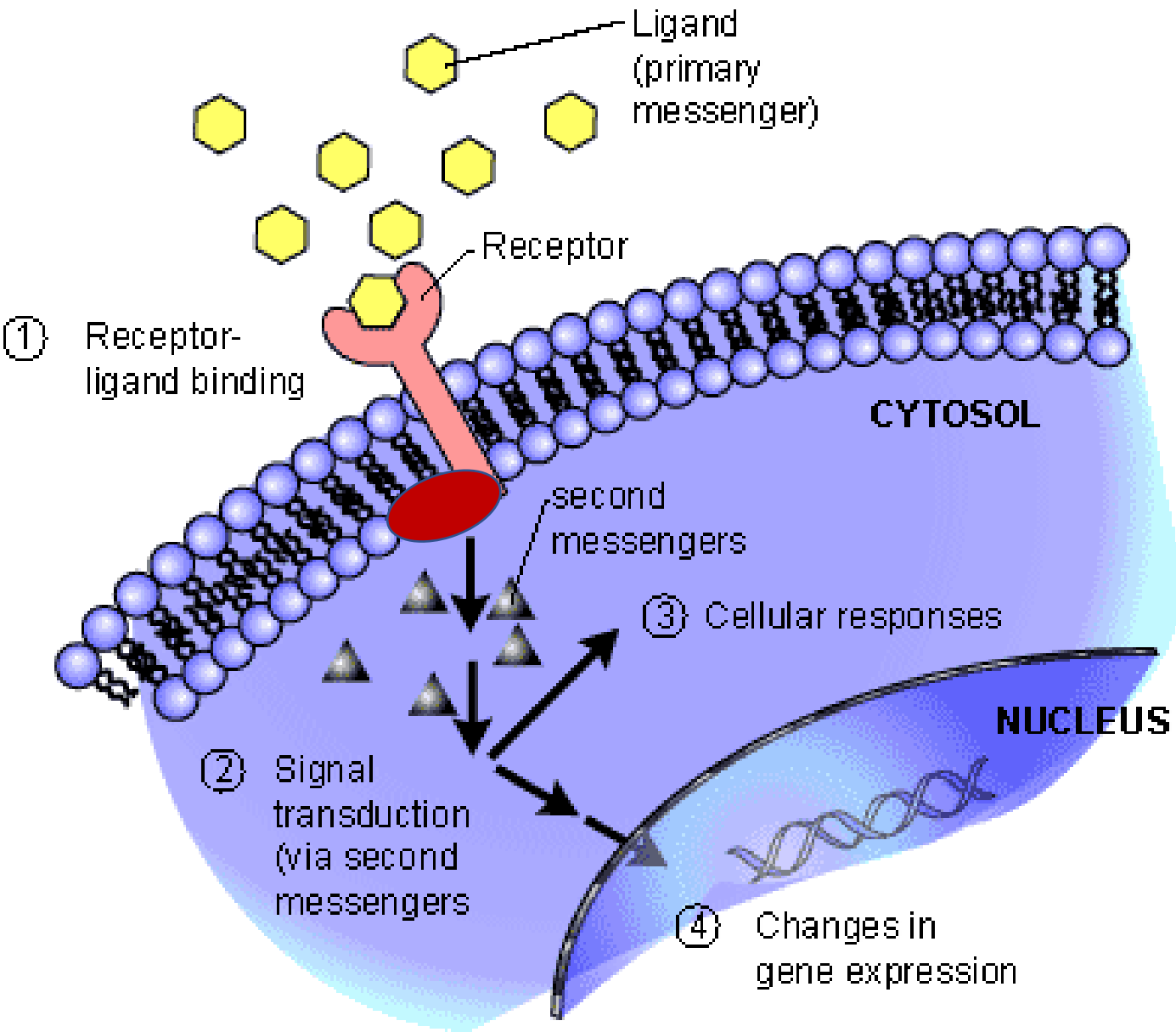
Some neurotransmitter molecules bind to receptors on membrane signal proteins, which are linked to G proteins. When a neurotransmitter molecule binds to a metabotropic receptor, a subunit of the G protein breaks off into the neuron and either binds to an ion channel or stimulates the synthesis of a second messenger.

Compared to ionotropic receptors, which are composed by several transmembrane subunits that form the channel-pore, metabotropic receptors are composed by one transmembrane polypeptide chain characterized by 7-alpha-helices



**Ionotropic** receptors mediate “fast” synaptic transmission. There is also “slow” synaptic transmission, mediated by what are called **metabotropic** receptors, in which the receptor and ion channel are not part of the same molecule, and binding of neurotransmitter to the receptor initiates biochemical cascades that lead to postsynaptic potentials with slow onsets

## Metabotropic receptor - functional scheme

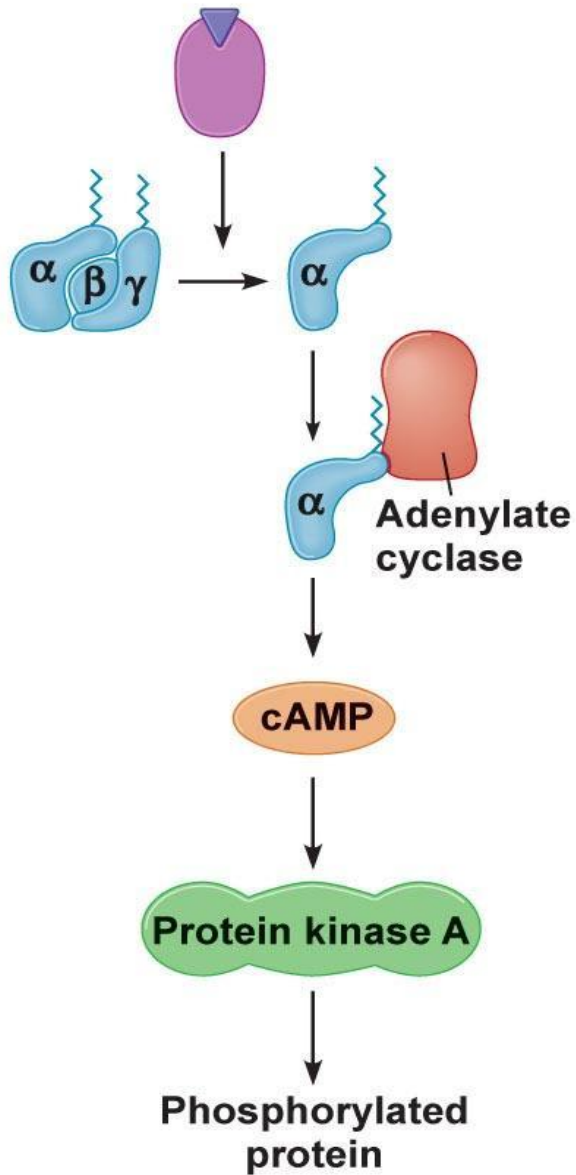


The function of metabotropic receptors is exerted through G-proteins (GTP-dependent).

G-proteins can act directly on channel proteins. Usually they couple the receptors to particular intracellular enzymes that catalyze the synthesis of intracellular second messengers (e.g. cAMP or DAG+IP3).

These second messengers act on ions channels or activate protein-kinases (e.g. PKA). Protein kinases phosphorylate channel proteins or start intracellular cascade signalling that influence the activity of channel proteins.

PKs action is not limited to modulate the gating of protein channels but can also modulate the activity of several other enzymes that control cell metabolism and transcription factors that control gene expression (long-lasting effects).



One messenger binds to one receptor

Several G proteins are activated

Each G protein activates an adenylate cyclase

Each adenylate cyclase generates hundreds of cAMP molecules

Each cAMP activates a protein kinase A

Each protein kinase A phosphorylates hundreds of proteins

Total number of product

1

10

10

5000

5000

2,500,000

One messenger molecule

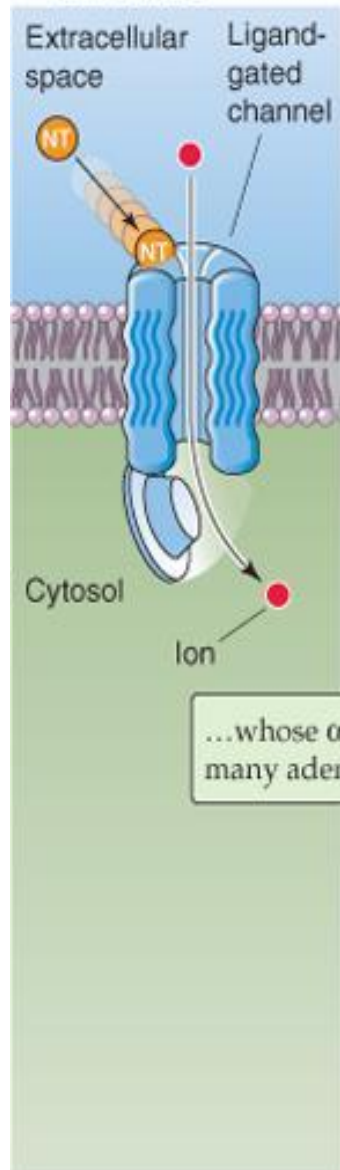
leads to...

phosphorylation of millions of proteins

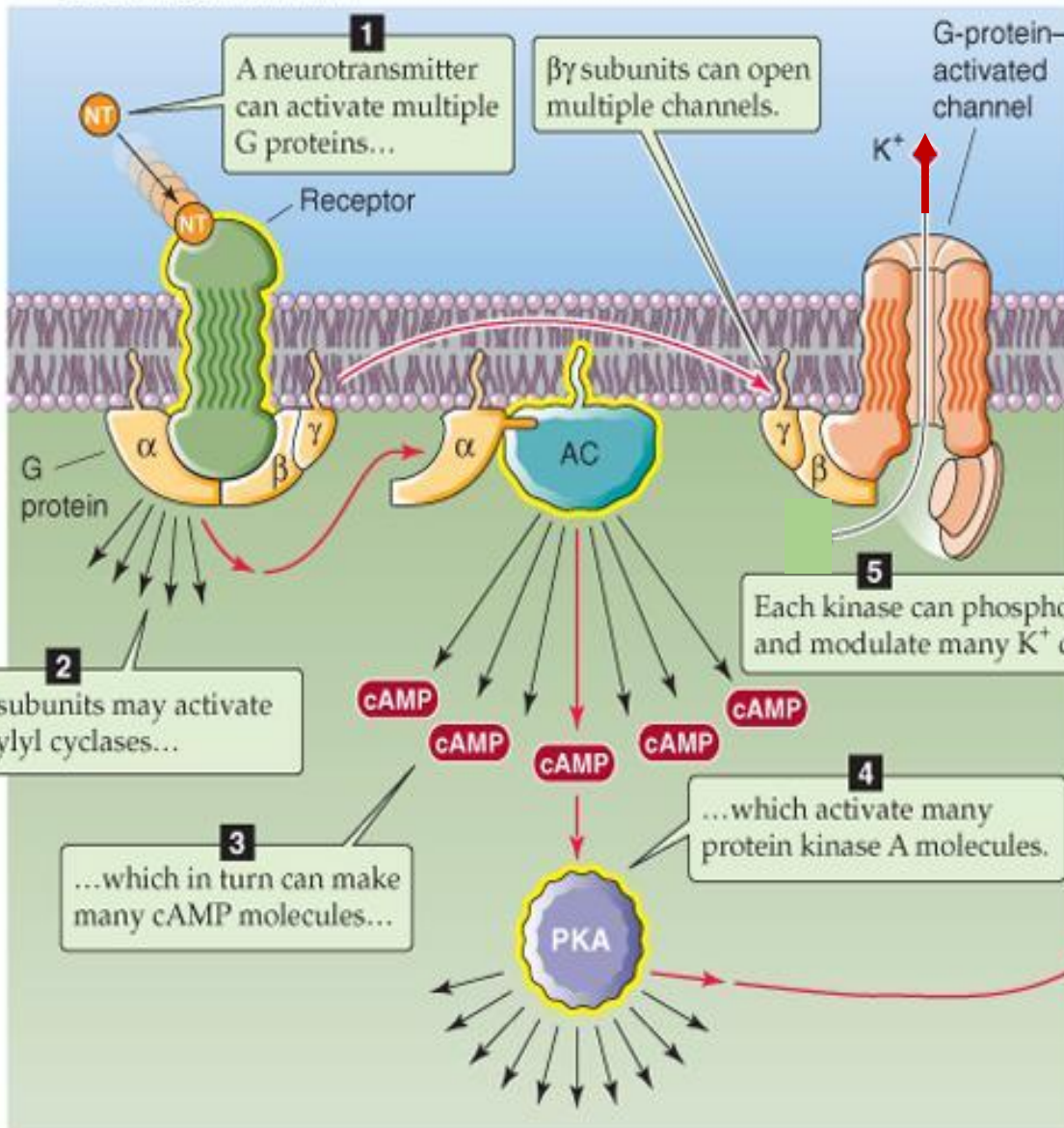
**The process of intracellular signal amplification has several consequences:**

- i) The amplification is differentiated: each second messenger activates different pathways;**
- ii) The amplification can affect gene expression, changing cell phenotype.**
- iii) Intracellular processes are mediated by regulatory steps both allosteric and covalent (phosphorylation), that can lead to the production of molecules that remain in the cytoplasm for a much longer time than the actual activation of the membrane receptor.**

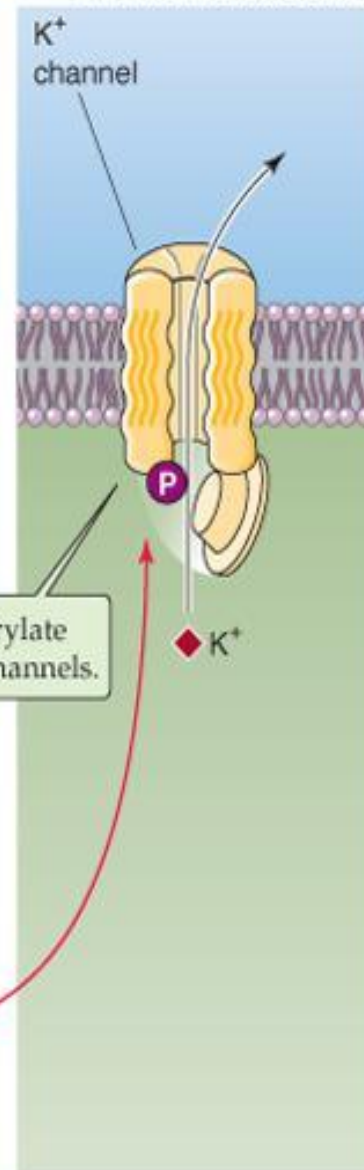
**A** LIGAND-GATED CHANNEL



**B** AMPLIFICATION BY A MEMBRANE-DELIMITED PATHWAY



**C** AMPLIFICATION BY A SIGNALING CASCADE



Bio-electrical effects on the post-synaptic cell, mediated by ion fluxes that travel through channels because of the electrochemical gradient, depends on:

1. Type of ion
2. Molecular characteristics of the channel
3. Resting state of the channel
4. Gating mechanism of the channel

Movement of the same ions through different channels can have different effects.

The binding of neurotransmitter generally changes the membrane potential of the postsynaptic cell, and these changes are referred to as **EPSPs** when they increase the excitability of the neuron and **IPSPs** when they inhibit the neuron from firing action potentials. EPSPs are always depolarizing potentials, and IPSPs are usually hyperpolarizing.

EPSP or IPSP depends on the channel that the neurotransmitter has activated. The same neurotransmitter can induce EPSP or IPSP

EPSPs are induced by opening of ion channels that allow passage of most cations ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ) with similar ease. ACh-gated channels at neuromuscular junction: If acetylcholine-gated channels open when the membrane is at its resting potential, a large inward  $\text{Na}^+$  current and a small outward  $\text{K}^+$  current will flow through the acetylcholine channel, thereby resulting in a net inward current, which acts to depolarize the membrane.

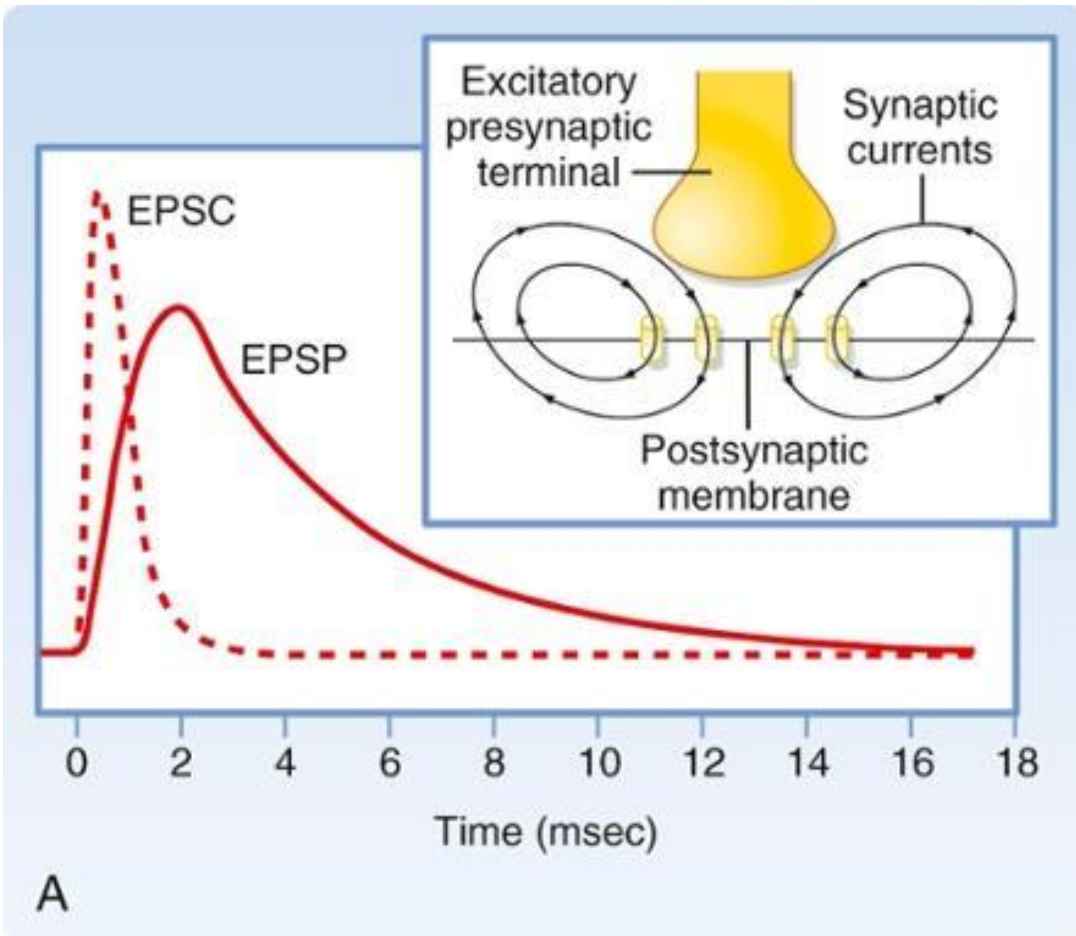
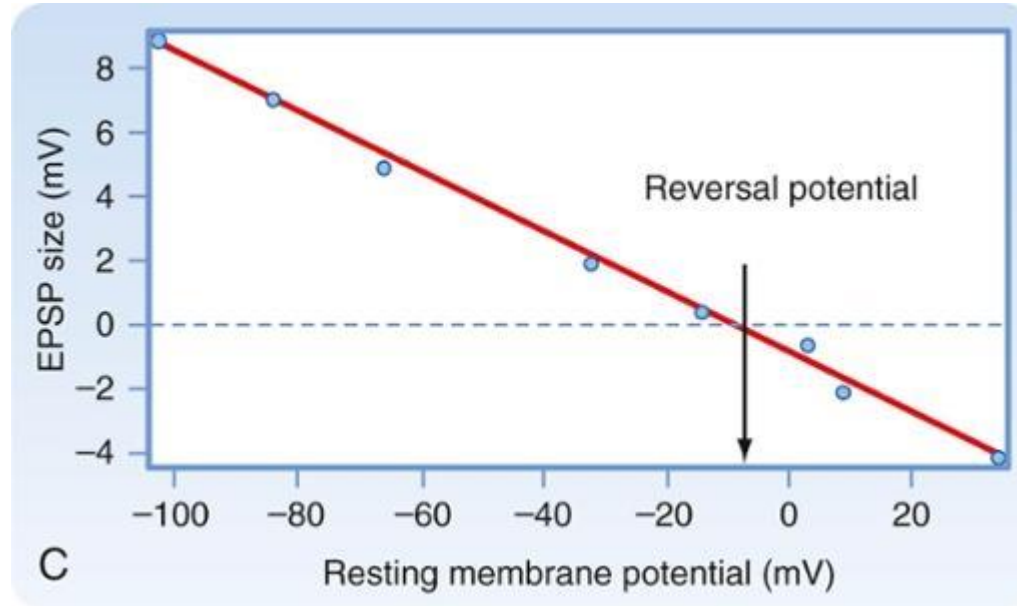


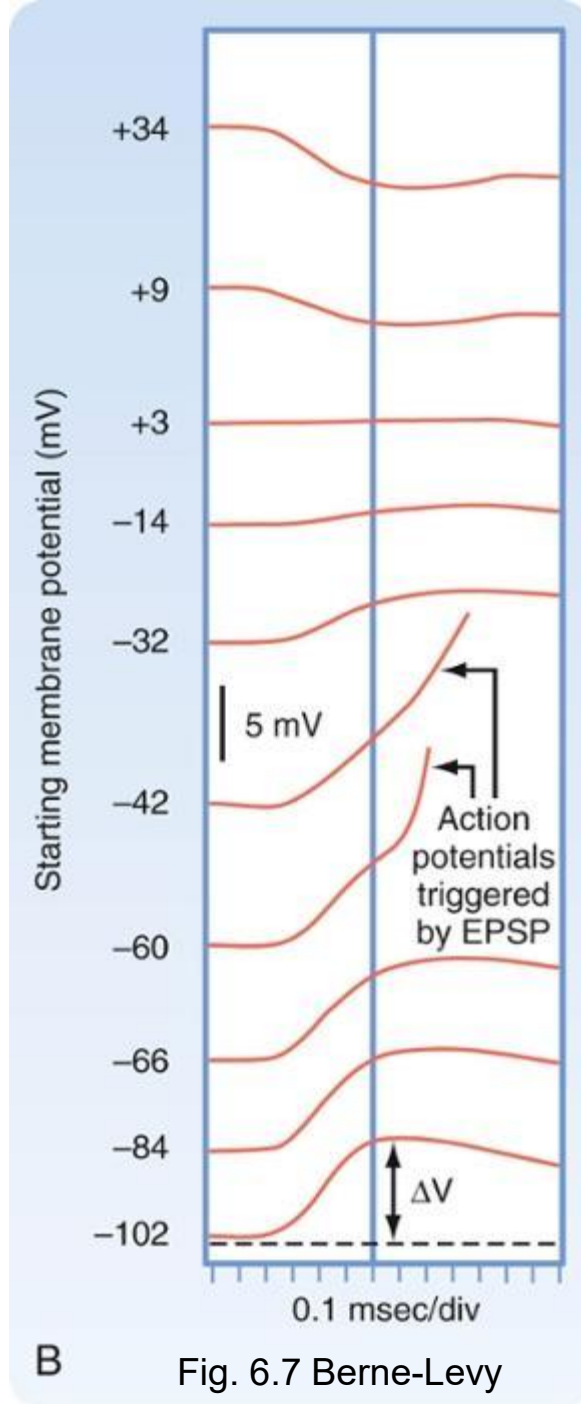
Fig. 6.7A Berne-Levy

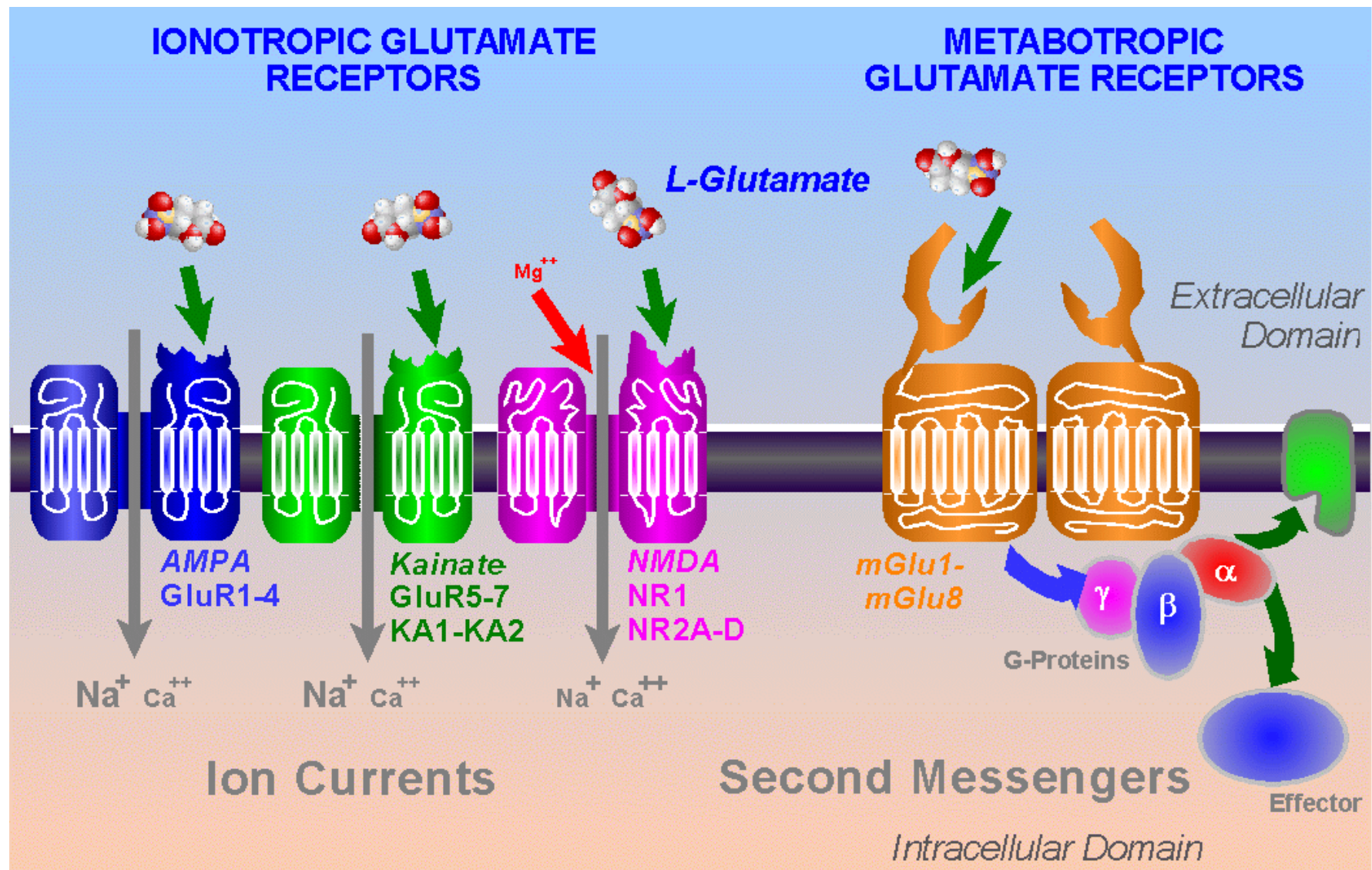
The net inward current that results from opening such channels is called the **excitatory postsynaptic current (EPSC)**. The time course of the EPSC and the resulting EPSP for fast synaptic transmission are different. The EPSC is much shorter ( $\approx 1$  to 2 msec in duration) and corresponds to the time the channels are actually open. The duration of the tail and the rate of the decay in EPSP amplitude reflect the passive membrane properties of the cell (i.e., its RC properties). In slow synaptic transmission, the duration of the EPSP reflects the activation and deactivation of biochemical processes more than the membrane properties. The long duration of even fast EPSPs (relative to EPSCs and action potentials) is functionally important because it allows EPSPs to overlap and thereby summate. Such summation is central to the integrative properties of neurons

$$I_x = g_x \times (V_m - E_x)$$



The potential at which there is no EPSP (or EPSC) is known as the **reversal potential**. For excitatory synapses, the reversal potential is usually around 0 mV ( $\pm 10$  mV), depending on the synapse





Glutamate also has ionotropic and metabotropic receptors. They are also built from different monomers, each with i) 4 transmembrane segments for the ionotropic ii) 7 transmembrane segments for the metabotropic ones.

The change in the membrane potential of a neuron caused by the activity of a synapse is called **postsynaptic potential (PSP)**. PSP could provide excitation (excitatory postsynaptic potential, EPSP), or inhibition (inhibitory postsynaptic potentials, IPSP). The amplitude of PSP is very small.

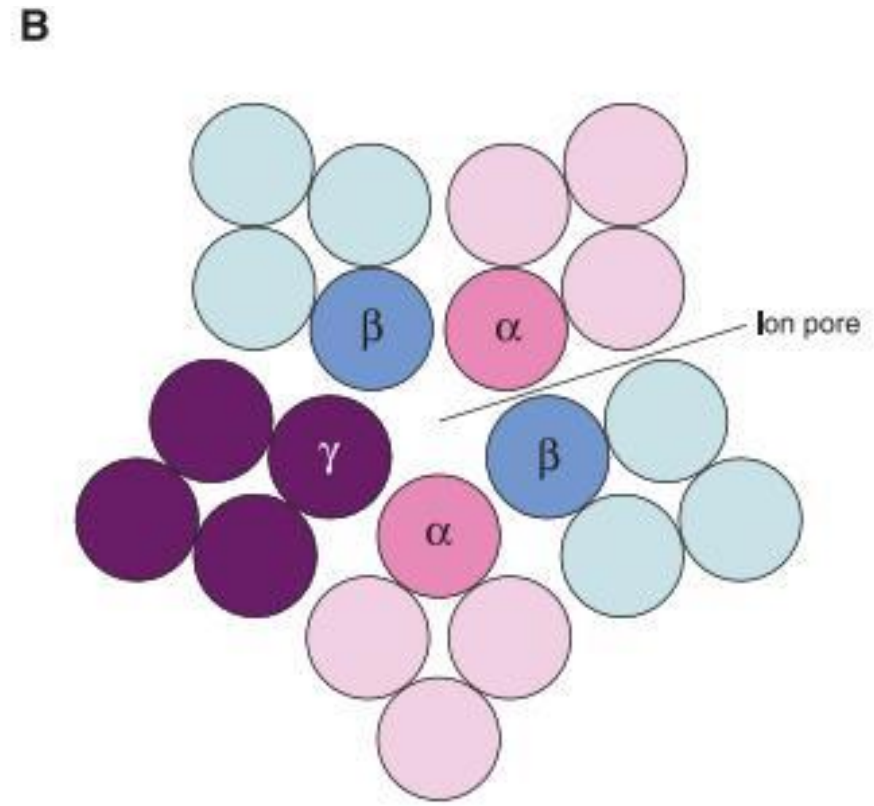
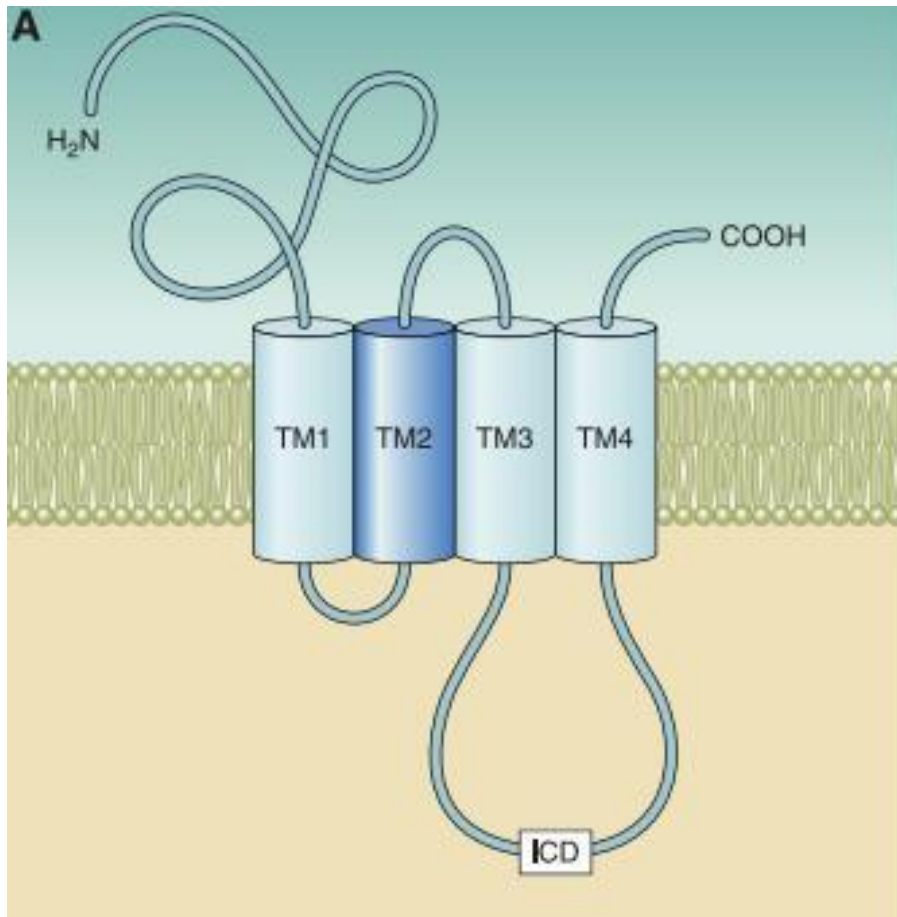
A neuron can fire an action potential only when the axon hillock reaches the threshold. EPSP can depolarize the membrane, but, since synapse are far from the hillock and small, it's highly unlikely that the threshold can be reached. More EPSPs have to sum to each other in order to reach the threshold.

EPSPs and IPSPs are subjected to:

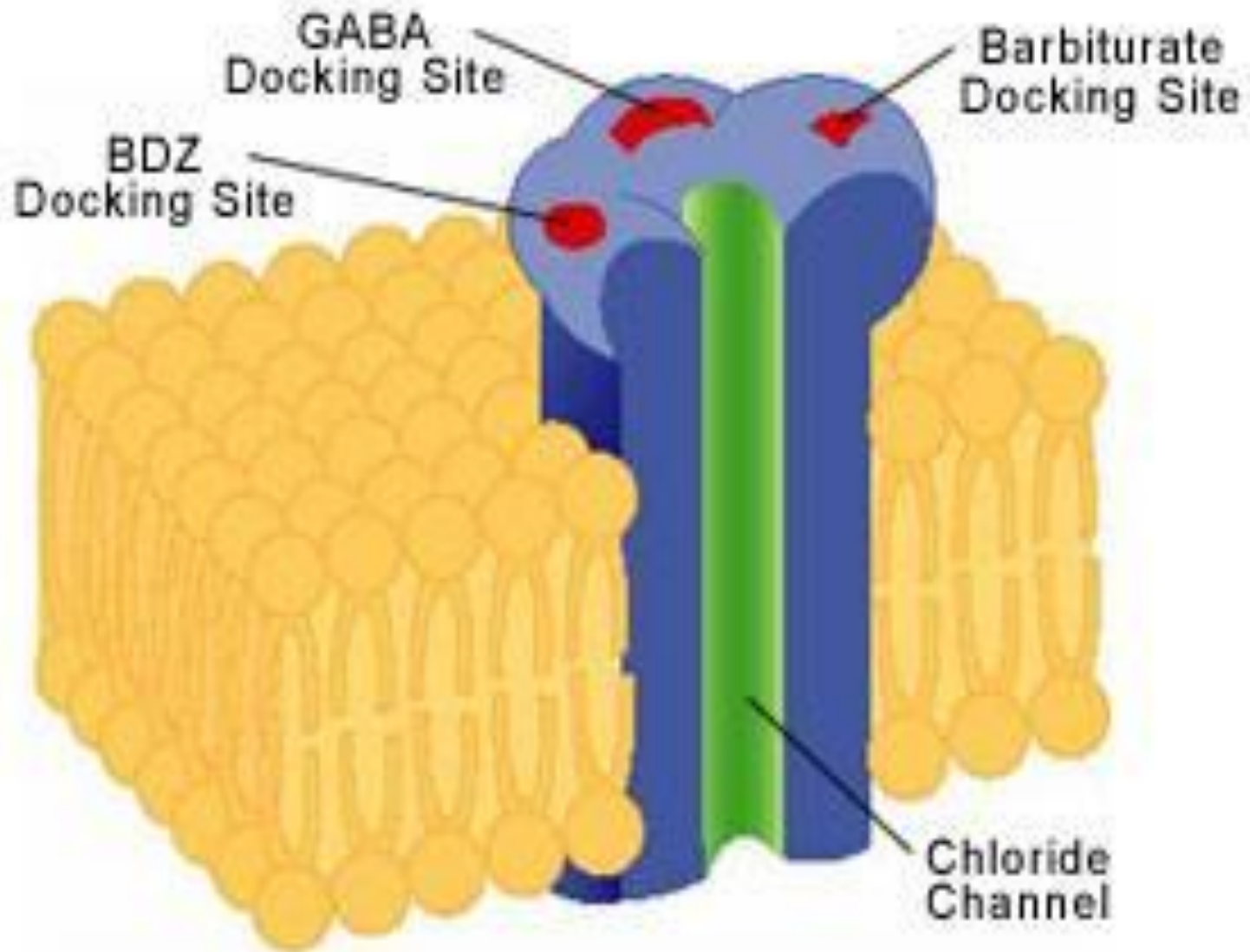
**Temporal summation**: when a synapse fires at such high frequency that the next EPSP is generated when the previous one is still having an effect.

**Spatial summation**: when more synapses are active at the same time and EPSP reach the hillock approximately at their maximum.

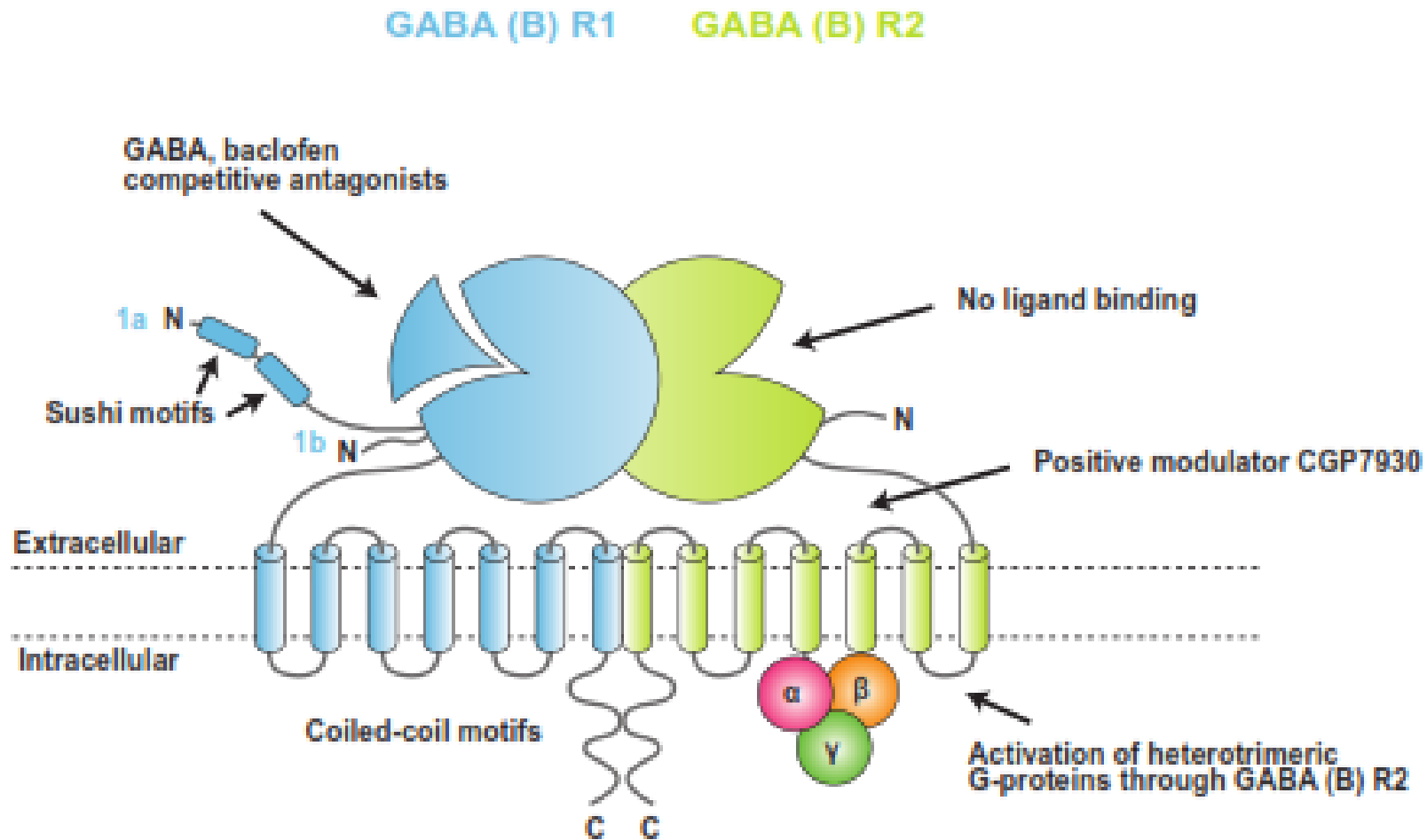
**IPSPs.** Like EPSPs, IPSPs are triggered by the binding of neurotransmitter to receptors on the postsynaptic membrane and typically involve an increase in membrane permeability as a result of the opening of ligand-gated channels. They differ in that IPSP channels are permeable to only a single ionic species, either  $\text{Cl}^-$  or  $\text{K}^+$ . Thus, IPSPs will have a reversal potential equal to the Nernst potential of the ion carrying the underlying current. Typically, the Nernst potential for these ions is somewhat negative relative to the resting potential, so when IPSP channels open, there is an outward flow of current through them that results in hyperpolarization of the membrane



The GABA<sub>A</sub> receptors is a Cl<sup>-</sup> channel built from 5 monomers each constituted of 4 transmembrane segments. There are alpha, beta and gamma monomers



Each different subunit of the GABA<sub>A</sub> receptor can bind different molecules that affect the function of the channel. Among these substances we can find ethanol, benzodiazepine (BDZ) and barbiturates.



The GABA<sub>B</sub> receptors is a metabotropic receptor. It's a dimer, built from 2 monomers, each constituted by 7 transmembrane segments.

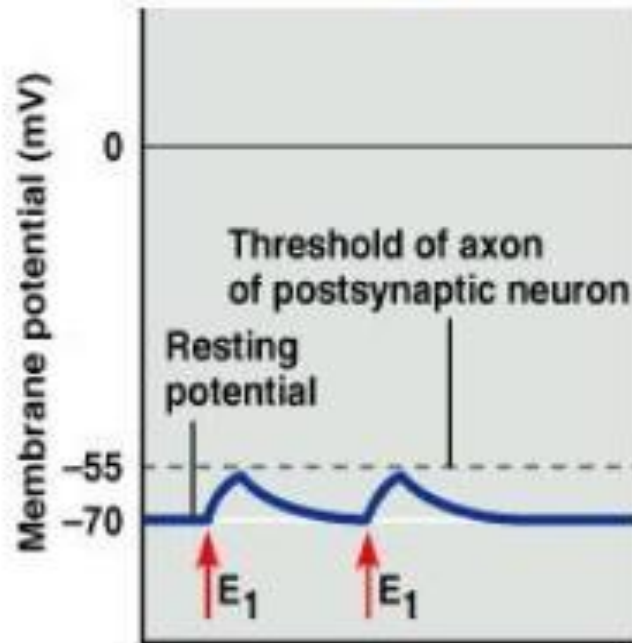
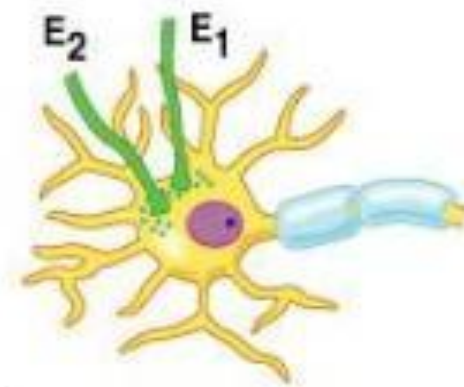
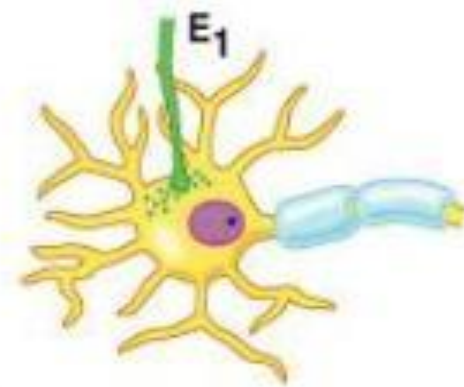
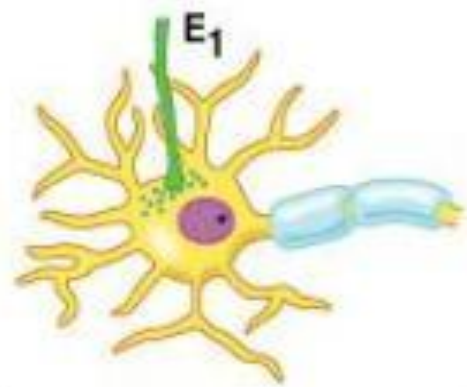
The change in the membrane potential of a neuron caused by the activity of a synapse is called **postsynaptic potential (PSP)**. PSP could provide excitation (excitatory postsynaptic potential, EPSP), or inhibition (inhibitory postsynaptic potentials, IPSP). The amplitude of PSP is very small.

A neuron can fire an action potential only when the axon hillock reaches the threshold. EPSP can depolarize the membrane, but, since synapse are far from the hillock and small, it's highly unlikely that the threshold can be reached. More EPSPs have to sum to each other in order to reach the threshold.

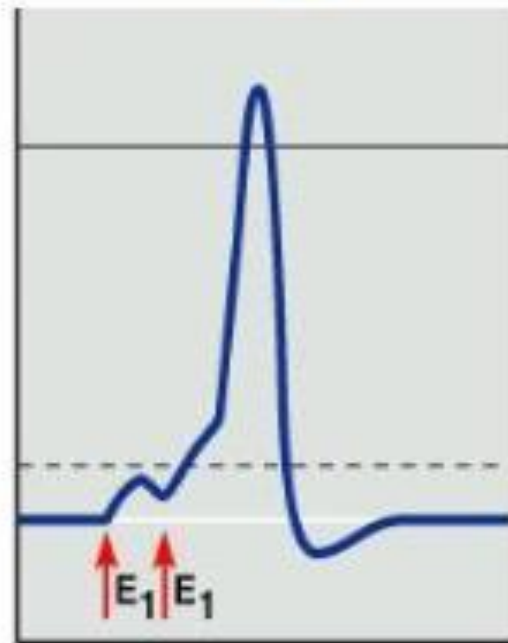
EPSPs and IPSPs are subjected to:

**Temporal summation**: when a synapse fires at such high frequency that the next EPSP is generated when the previous one is still having an effect.

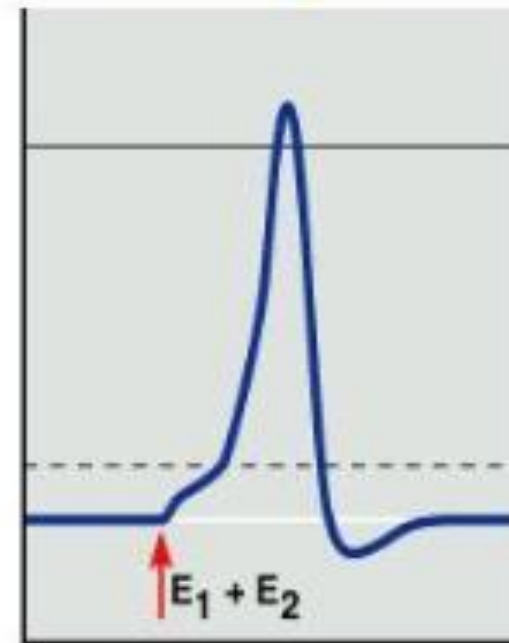
**Spatial summation**: when more synapses are active at the same time and EPSP reach the hillock approximately at their maximum.



(a) Subthreshold, no summation



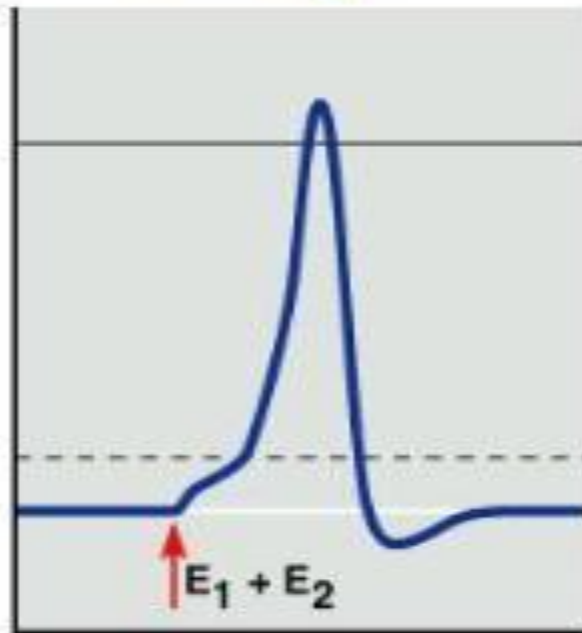
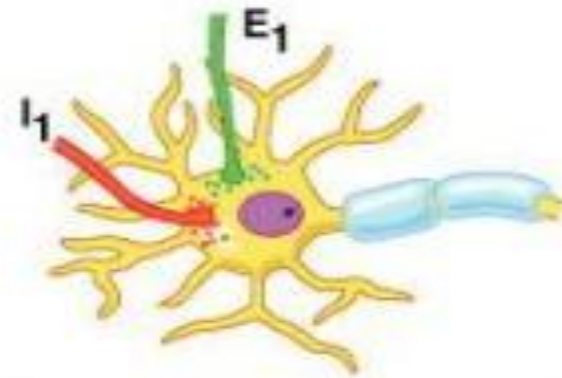
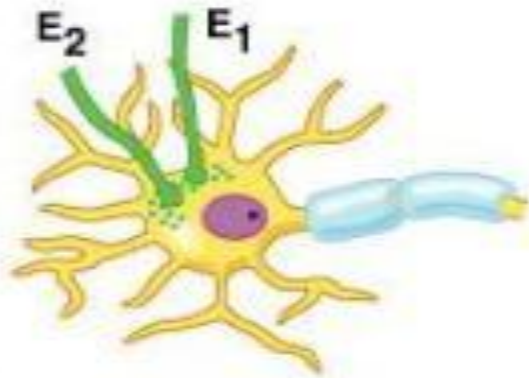
(b) Temporal summation



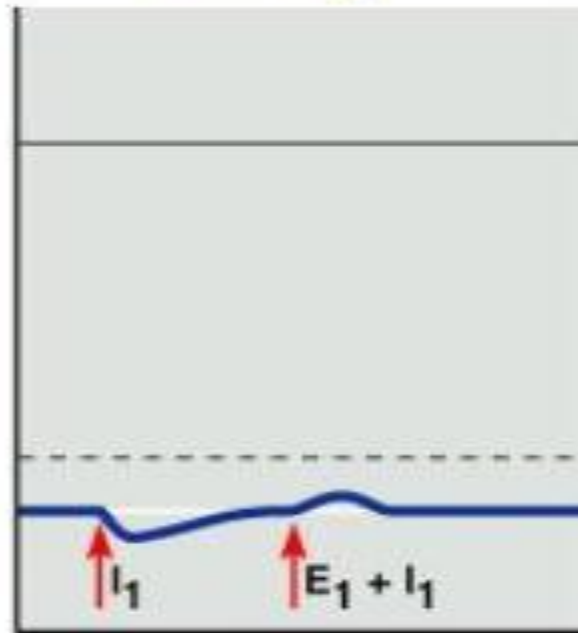
(c) Spatial summation

(a) Non-additive iteration ( $E_1 - E_1$ ) of EPSPs

(b,c) Additive iteration ( $E_1E_1, E_1+E_2$ ) of EPSPs

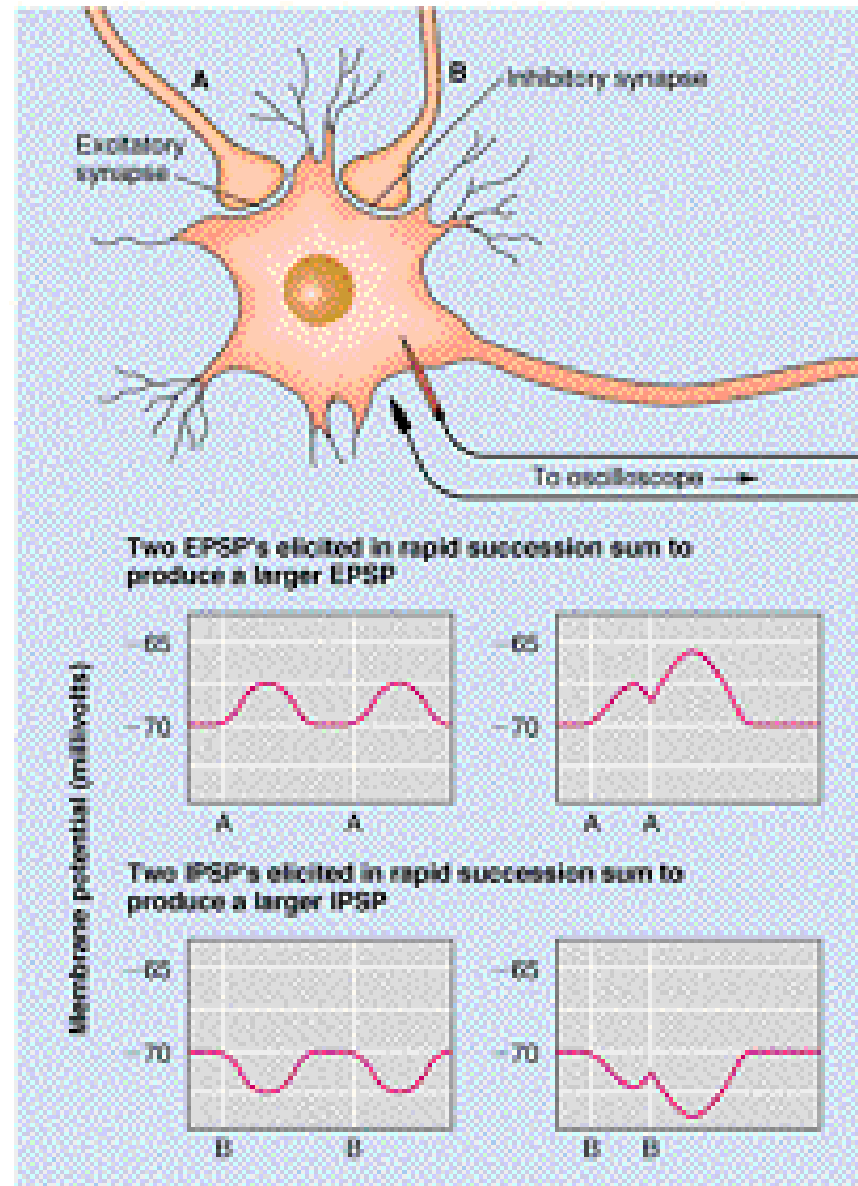


**(c) Spatial summation**

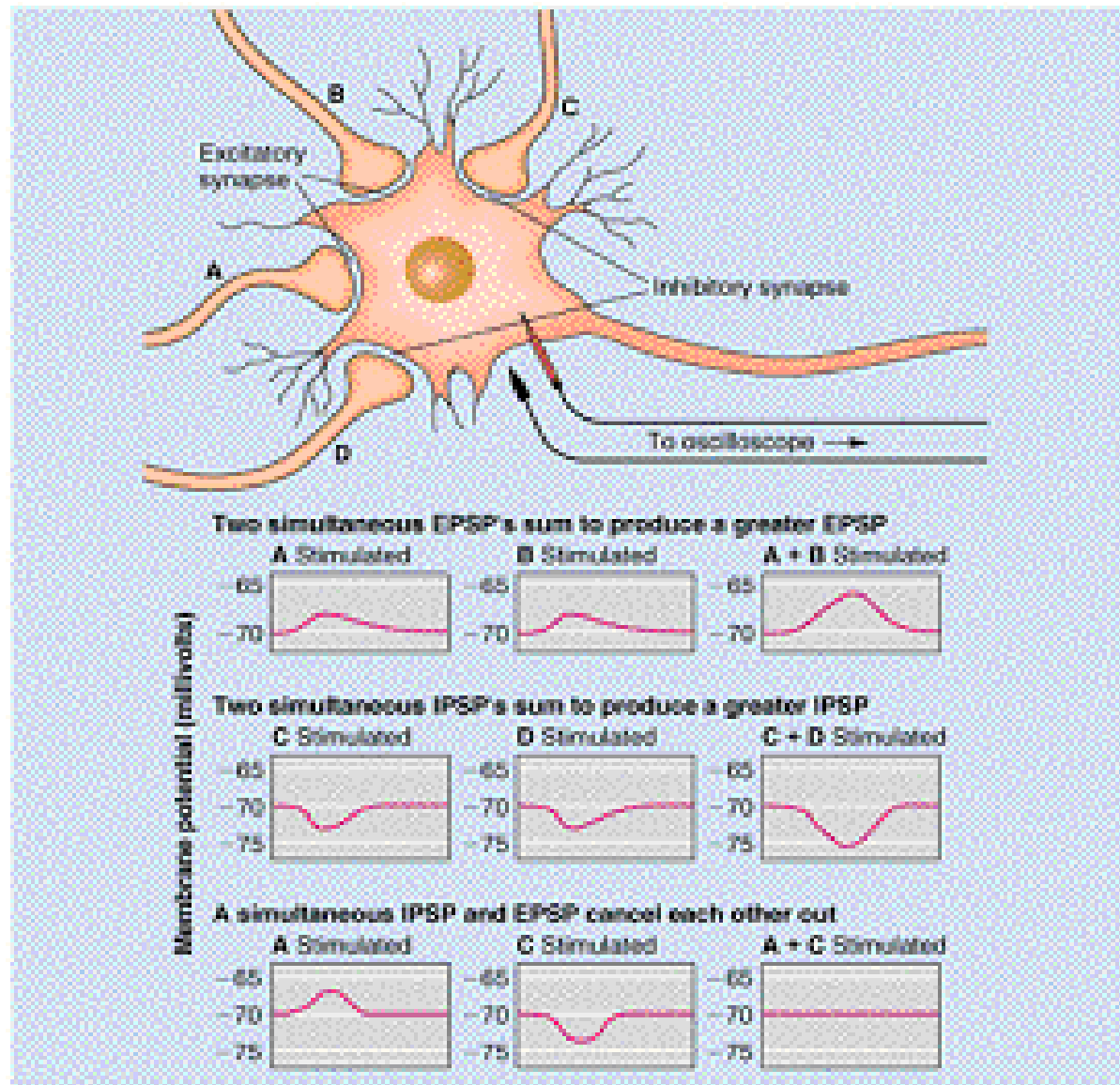


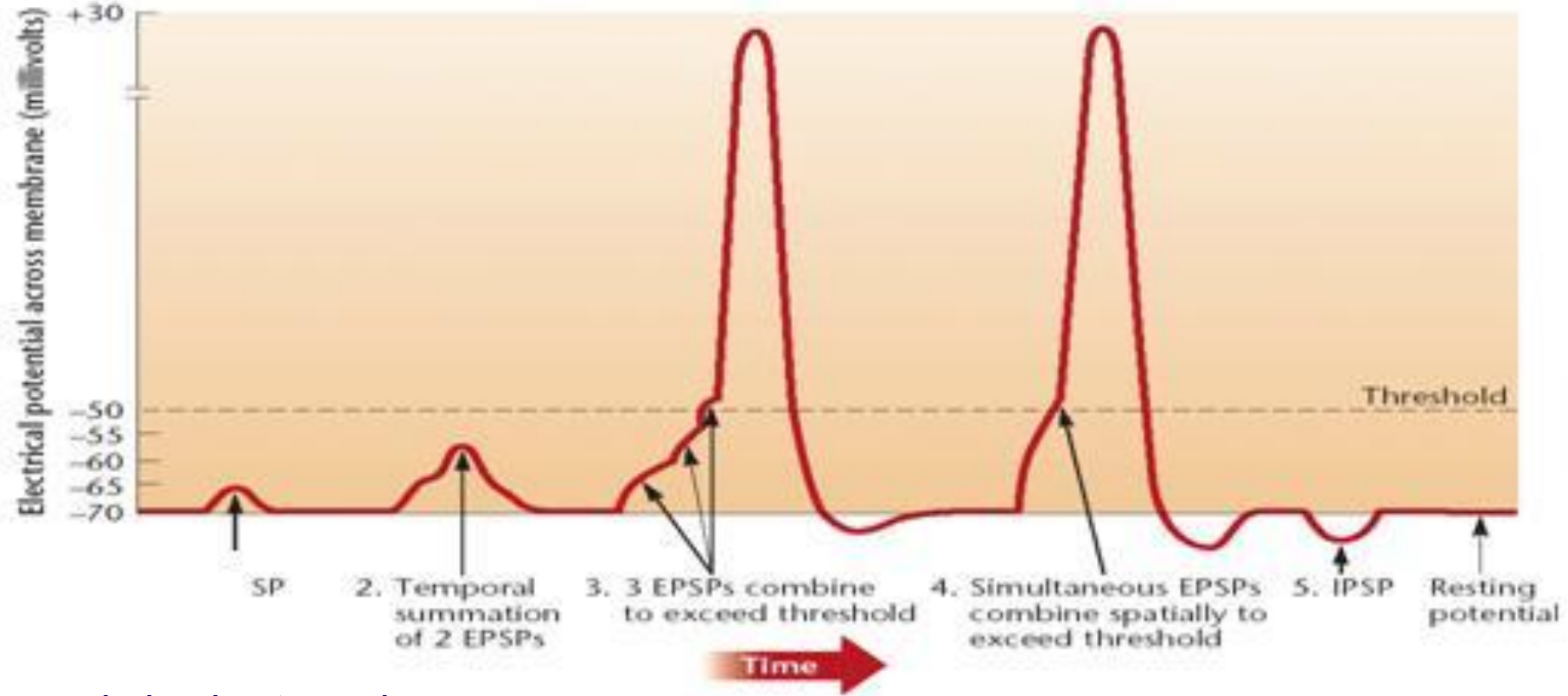
**(d) Spatial summation of EPSP and IPSP**

## ► Possible Combinations of Temporal Summation



► Possible Combinations of Spatial Summation

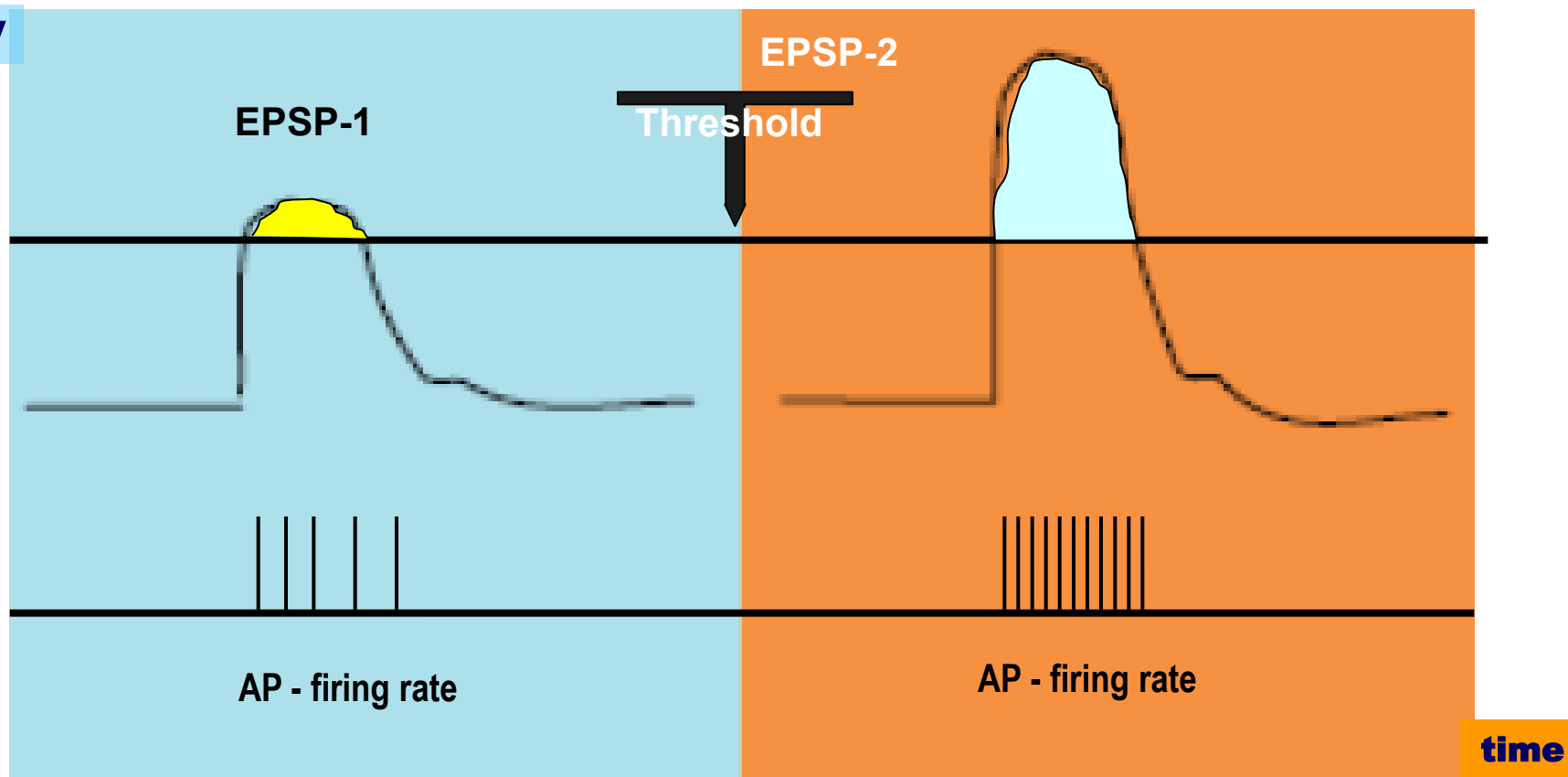




[www-dev.joomla.soton.ac.uk](http://www-dev.joomla.soton.ac.uk)

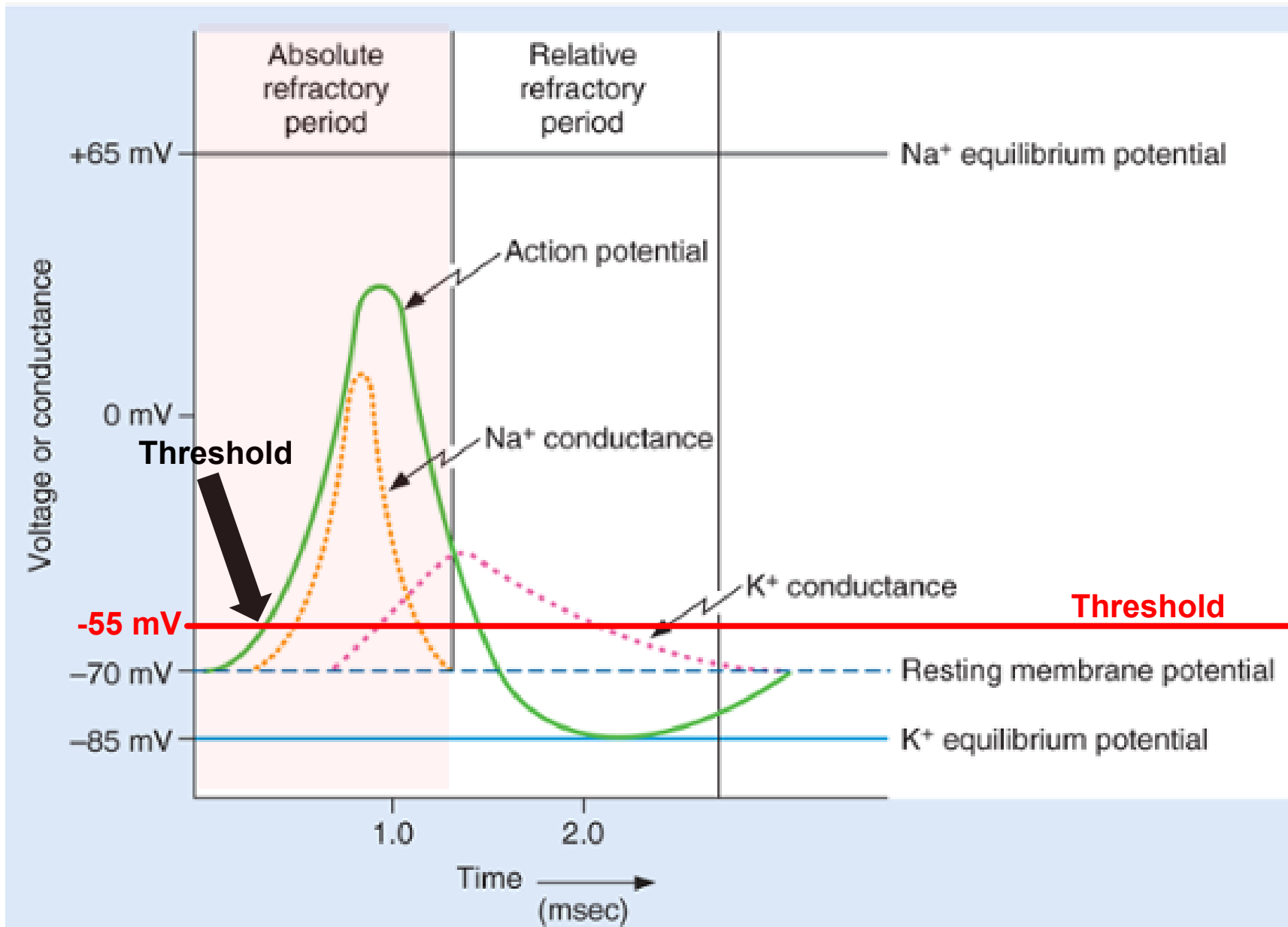
Summary

mV



The number of action potential fired in a second is termed **firing rate**.

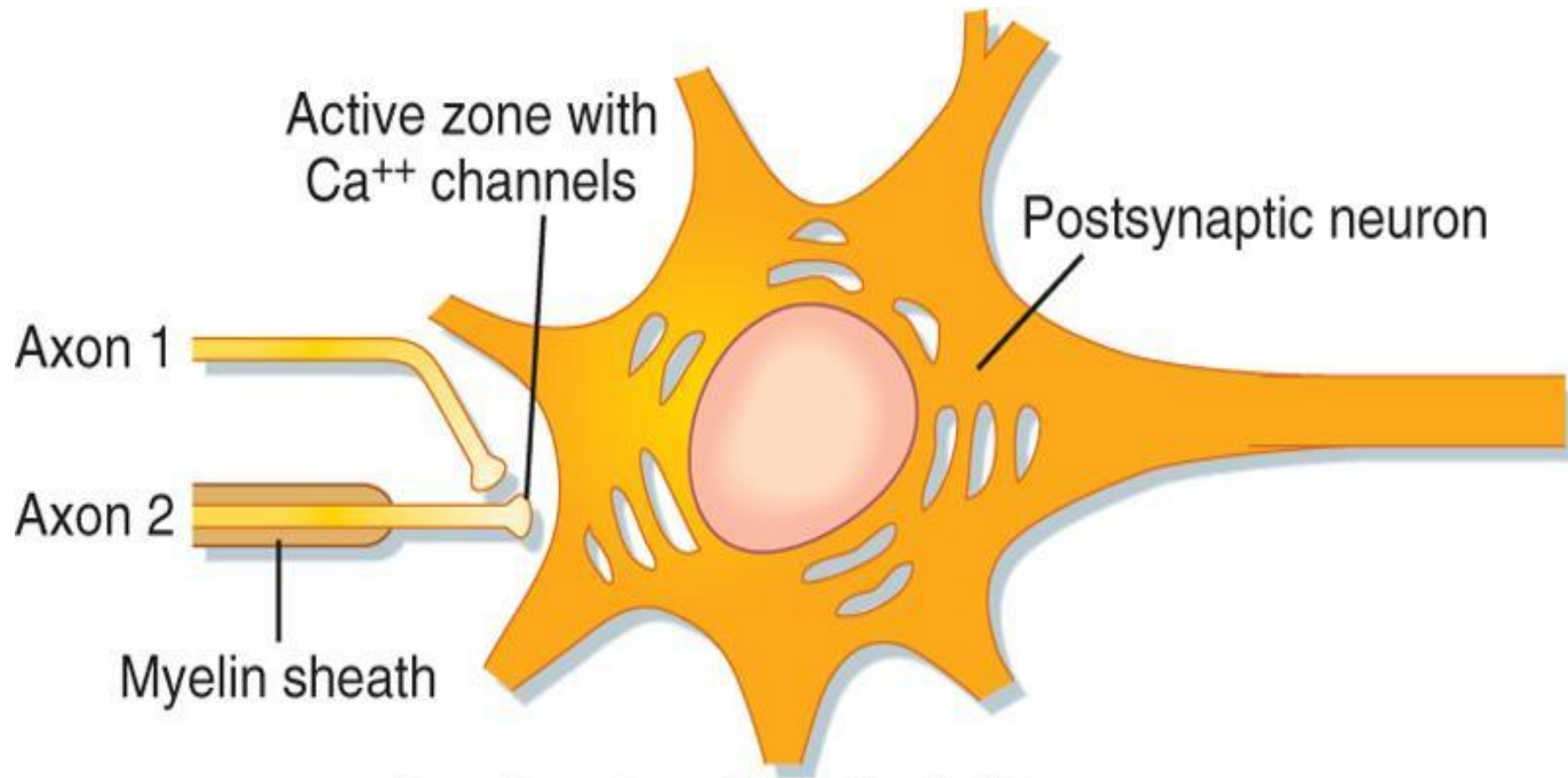
The amplitude of the EPSP that exceed the threshold is proportional to the firing rate induced.



An increase in firing rate can be obtained only by exciting the neurons during the relative refractory period (RRP).

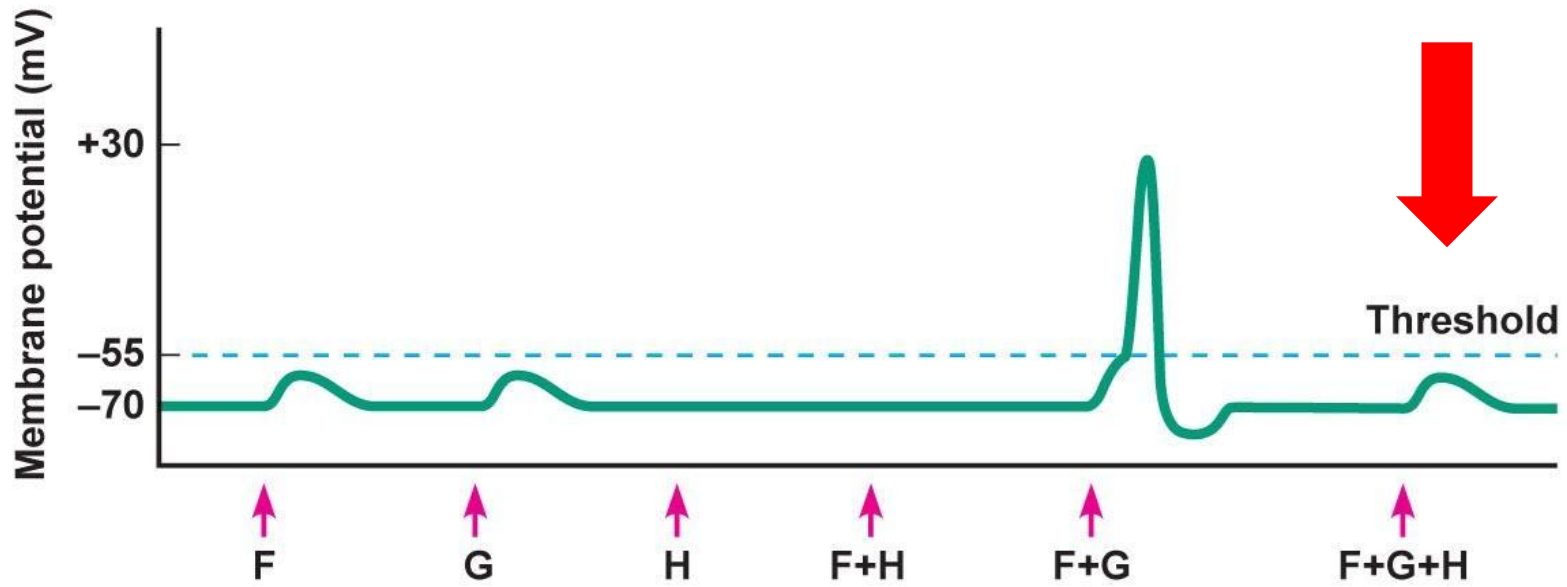
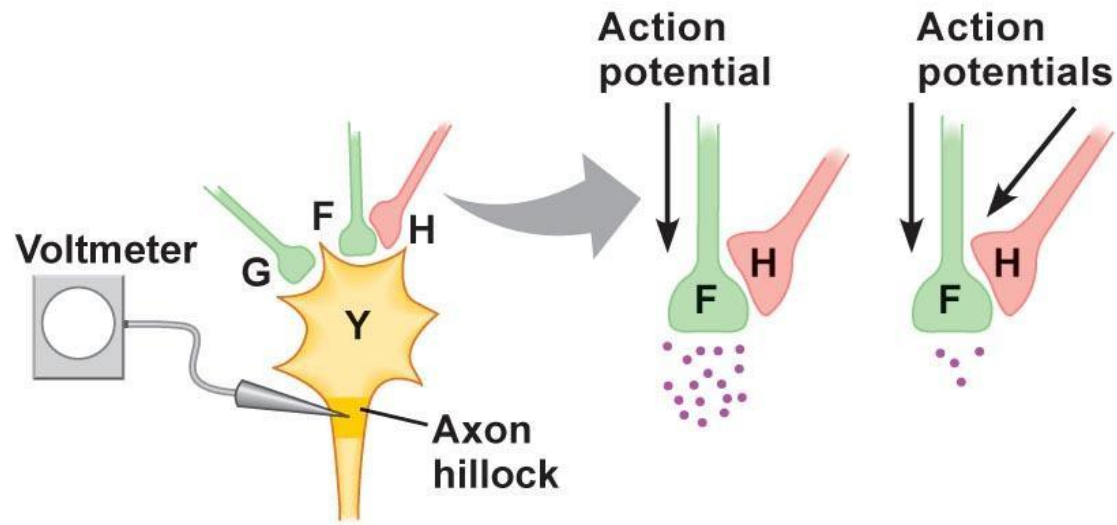
The RRP is characterized by a hyperpolarizing  $K^+$  outward current. To counteract that, a stronger depolarizing inward current.

The stronger is the depolarizing inward current, the more effective will be in counteracting the hyperpolarizing outward current, and the earlier a new action potential will be fired.

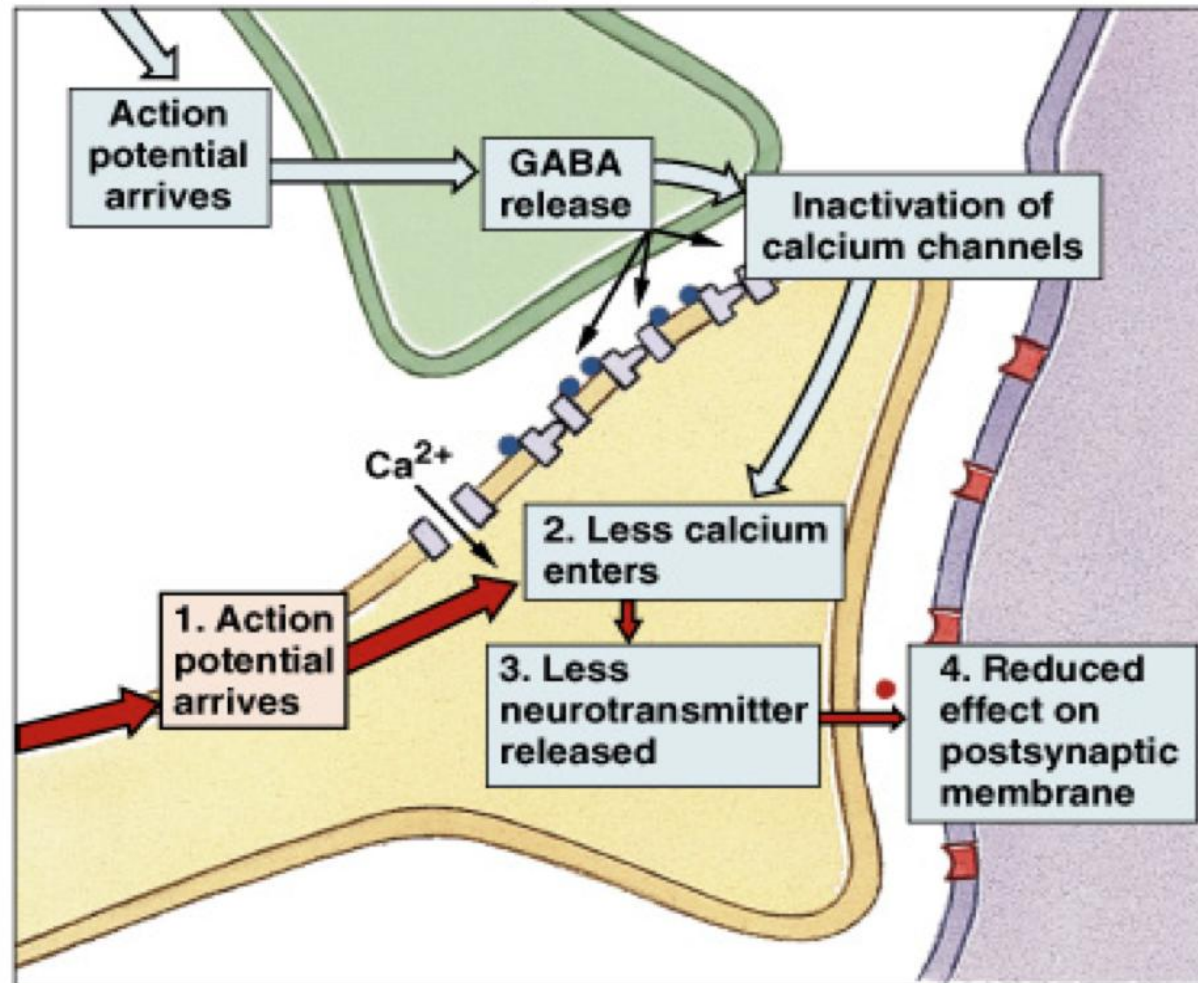


Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.  
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## Presynaptic inhibition



**Presynaptic inhibition**



**(a) Presynaptic inhibition**

**Presynaptic inhibition** can occur via both **ionotropic receptors** and **metabotropic receptors** on presynaptic terminals.

Well represented **ionotropic receptors** are GABA-A receptors, nicotinic AChRs and NMDA glutamate receptors.

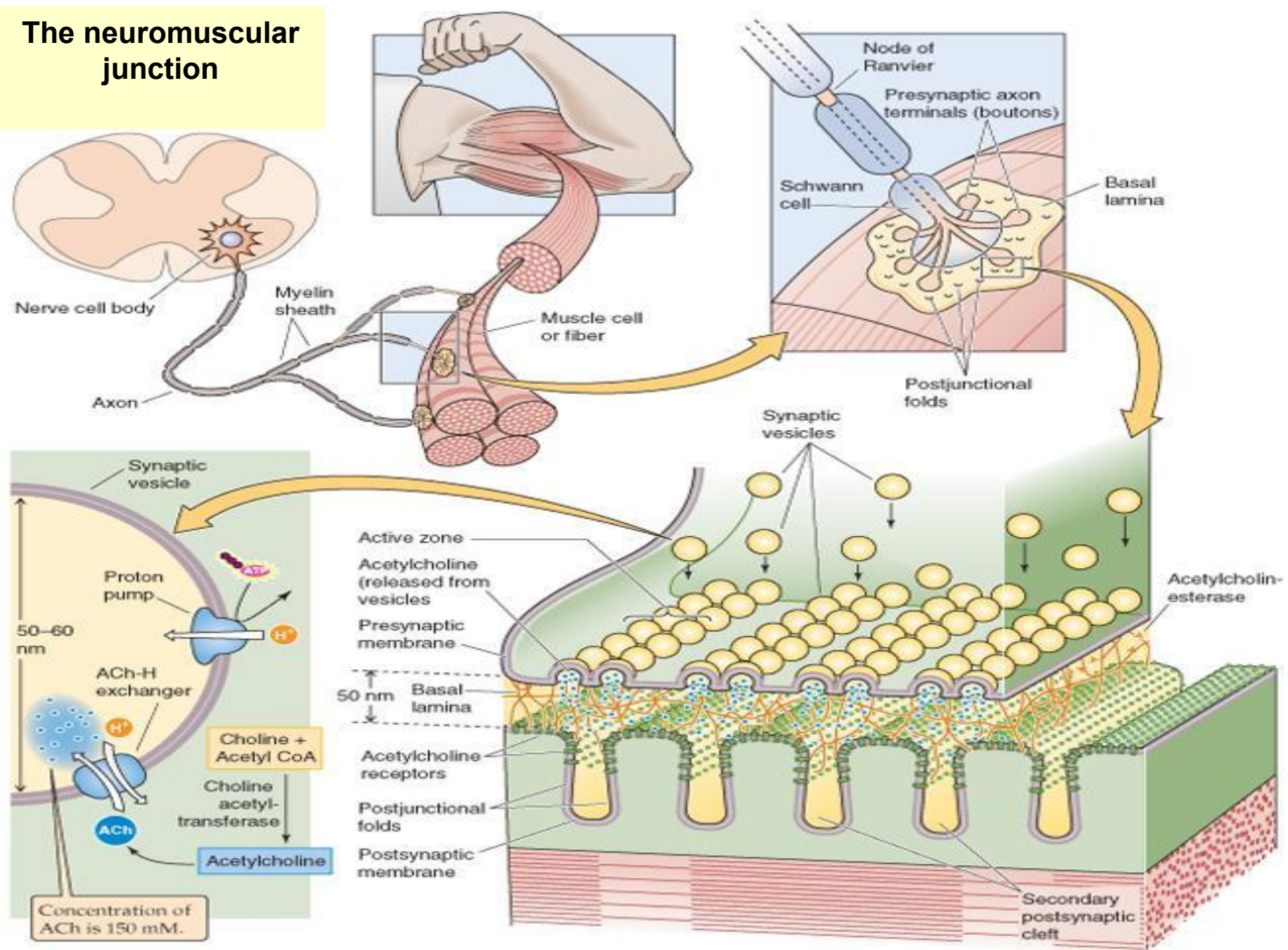
Well represented metabotropic receptors are GABA-B receptors, muscarinic AChRs and adenosine receptors.

**Ionotropic receptors** either hyperpolarize or depolarize the presynaptic membrane. It is thought that: i) a subthreshold depolarization of the presynaptic membrane may inactivate both  $\text{Na}^+$  and  $\text{Ca}^{2+}$  voltage-dependent channels, thus reducing the amplitude of the AP invading the terminal and the entrance of  $\text{Ca}^{2+}$ ; ii) a hyperpolarization may either block AP or reduce its amplitude.

As far as **metabotropic receptors** are concerned, the hypothesis is that they inhibit presynaptic  $\text{Ca}^{2+}$  channels through protein G subunits or phosphorylation by a second messenger activated protein kinase. As the presynaptic  $\text{Ca}^{2+}$  inflow is essential for the vesicular release of neurotransmitters, this reduces the efficacy of the excitatory synapses converging on a given postsynaptic neuron.

# **Neuromuscular junction**

# The neuromuscular junction



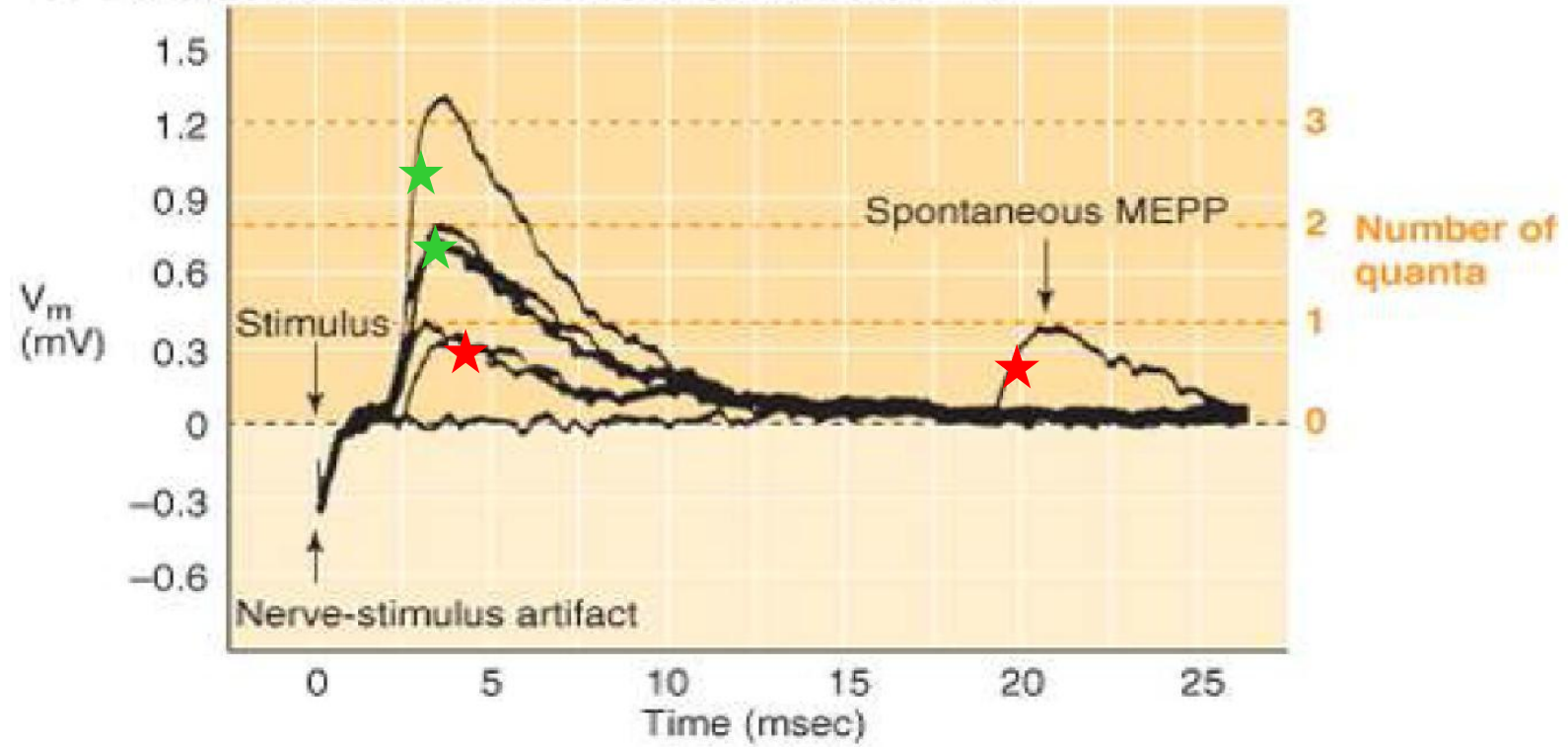
The nicotinic receptor for ACh is a cation channel. It is non-specific and through the channel both  $\text{Na}^+$  and  $\text{K}^+$  can flow. Since  $\text{Na}^+$  gradient is larger, that's the one prevailing. The endplate is therefore depolarized.

The endplate potential is always large enough to trigger an action potential in the portion of the membrane nearest to the endplate, where the  $\text{Na}^+$  voltage-gated channels are located.

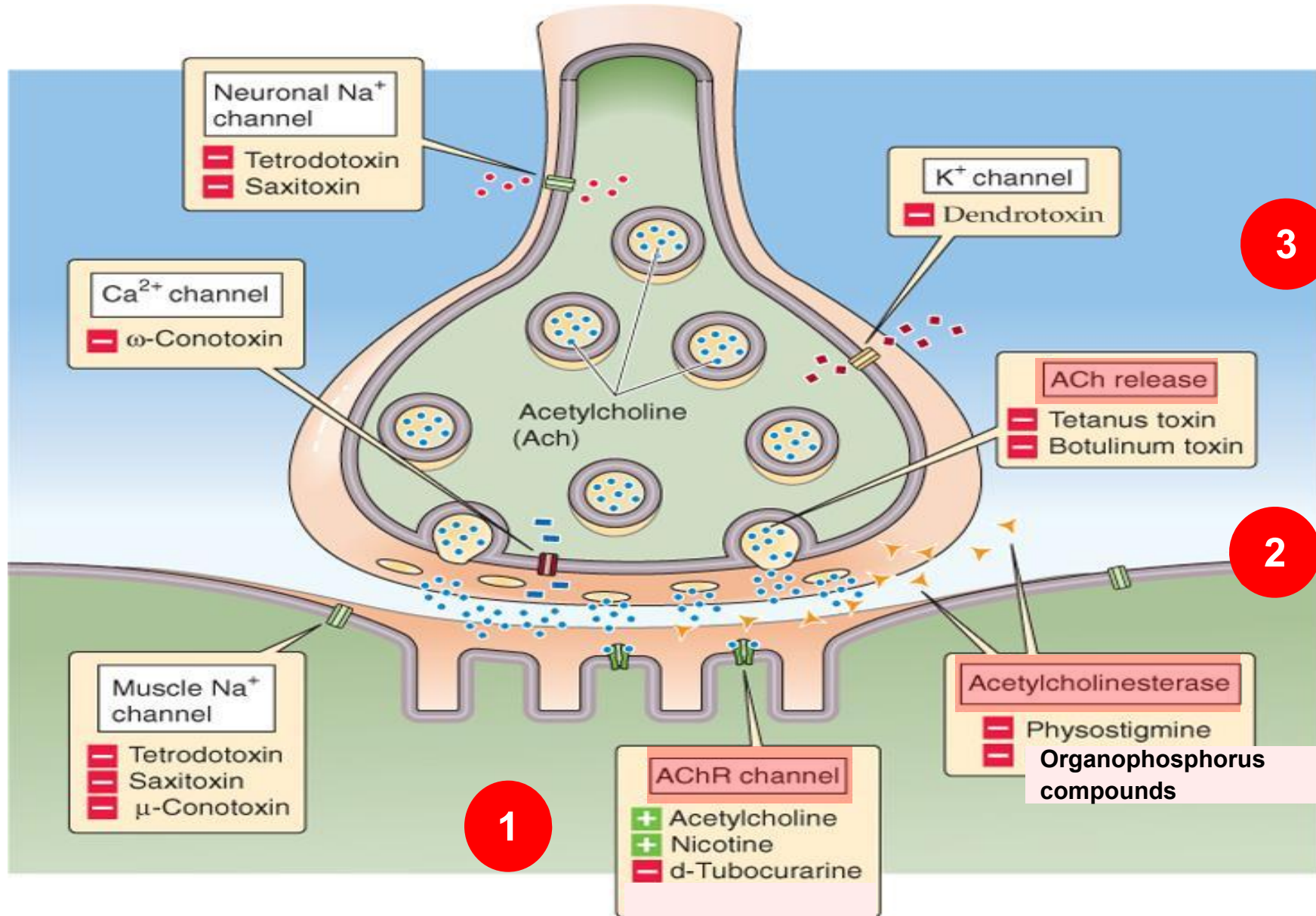
This is a rare example of 1:1 synapse because at every presynaptic AP correspond a postsynaptic AP.

ACh is degraded by the enzyme **acetylcholinesterase**. A tetrameric protein on the postsynaptic membrane.

**A** MINIATURE END-PLATE POTENTIALS (MEPPs)



# Synaptic interference



# Agonists and Antagonists

Agonists

Drugs that occupy receptors and activate them.

Antagonists

Drugs that occupy receptors but do not activate them. Antagonists block receptor activation by agonists.



Substances that bind to receptors are classified as agonists or antagonists.

**Agonists** activate their receptors, inducing a cell response.

**Antagonists** physically block the binding to the receptor by the natural agonists, preventing or reducing their influence on cell responses.

Many agonists of the nicotinic ACh receptor (**AChR**) have a structure similar to that of the natural neurotransmitter ACh. In general, such agonists activate the opening of AChR channels with the same unitary conductance as those activated by ACh, but with different kinetics of channel opening and closing.

The synthetic drugs **carbamylcholine** (**carbachol**) and **succinylcholine** contain the choline moiety of ACh that is required for receptor activation. Both agents are resistant to hydrolysis by muscle **acetylcholinesterase**. This property allows prolonged activation of muscular **AChRs**.

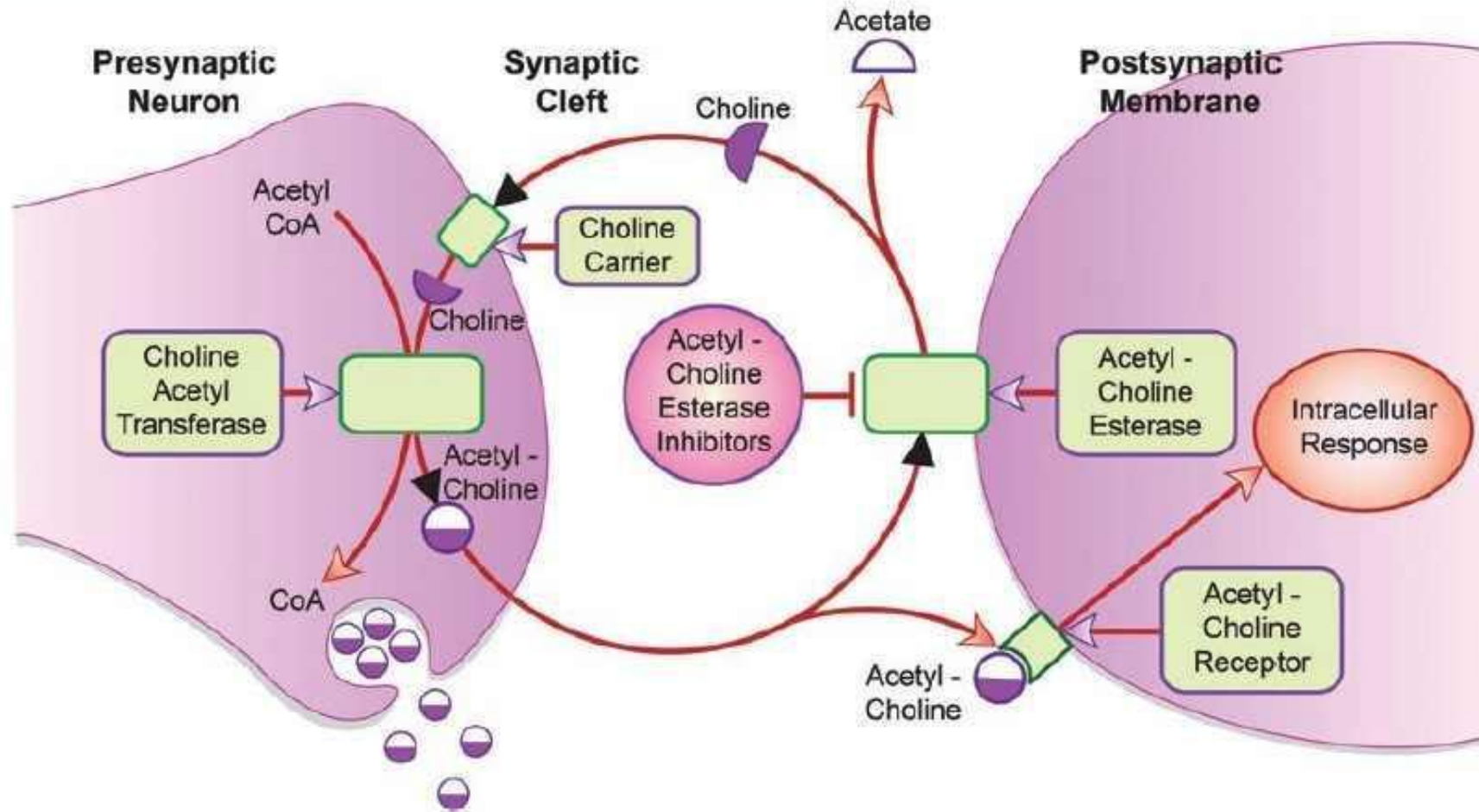
**Nicotine** is a natural constituent of tobacco that is responsible for the stimulant action and at least some of the addictive effects of smoking. Although **nicotine** is able to activate the **AChR** at the neuromuscular junction, the physiological effects of smoking are primarily manifested through the action of the substance on i) nicotinic **AChRs** in the CNS where it induces the liberation of neurotransmitters causing euphoria and a reduction in anxiety; ii) nicotinic **AChRs** in autonomic ganglia.

**1 - ENDPLATE INTERFERENCE**  
**depolarizing and non-depolarizing blockers**

**DURATION OF ACTION**

<b>SHORT-ACTING</b>	<b>INTERMEDIATE-ACTING</b>	<b>LONG-ACTING</b>
Mivacurium	Atracurium	Tubocurarine
	Cisatracurium	Metocurine
	Rocuronium	Pancuronium
	Vecuronium	Doxacurium
		Pipecuronium

## 2 - inhibitors of the acetylcholinesterase



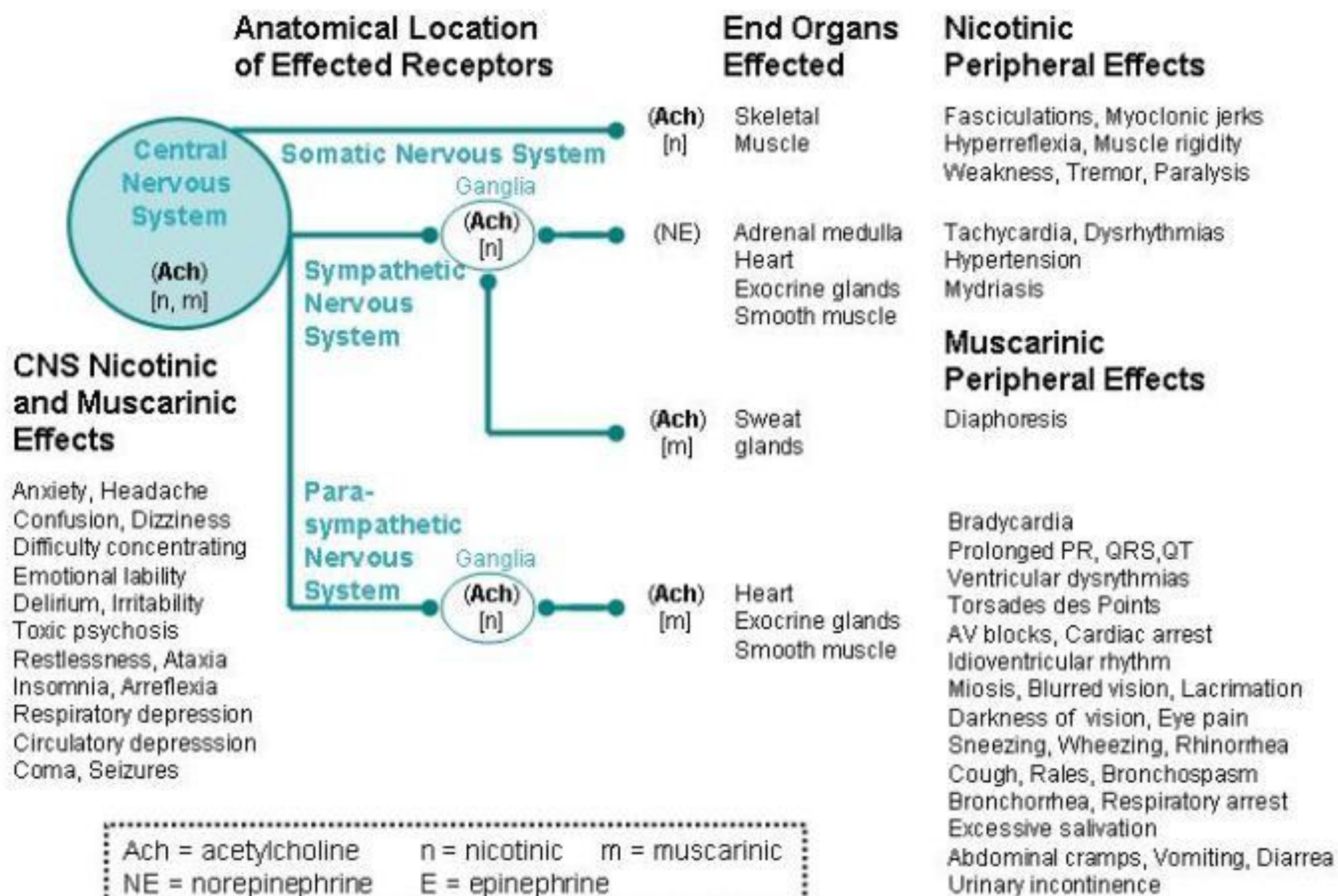
The **inhibition of acetylcholinesterase (AChE)** generally increases the amplitude and prolongs the duration of the postsynaptic response to ACh; thus, the enzyme plays an important role in limiting the excitatory action of ACh under normal physiological conditions.

The plant alkaloid **physostigmine** is the prototypic anticholinesterase, which acts also centrally since it crosses the **BBB**. **Neostigmine** is a synthetic inhibitor of **AChE**, analogous to **physostigmine**, which does not act on the **CNS** since it does not cross the **BBB**.

Another important class of synthetic **AChE** inhibitors consists of **organophosphorus compounds**. These compounds, that cross the **BBB**, react with a serine residue of **AChE** forming an essentially irreversible covalent modification of the enzyme. They are among the most potent and lethal of toxic chemicals, since their devastating effect is due to excessive enhancement of cholinergic neurotransmission, mediated by both **muscarinic** and **nicotinic** receptor.

Forms of these **organophosphorus compounds** are chemical warfare agents such as **nerve gases** and chemical agricultural aids **such as insecticides**. They are absorbed rapidly (seconds to minutes) by the respiratory system, quickly (30-90 minutes) through the gastrointestinal system, slowly (12-18 hours) through the skin.

# Nicotinic and Muscarinic Effects of Cholinesterase Inhibitors



### 3 - REDUCING THE ACh RELEASE

**Tetanus toxin** and **botulinum toxins** are **zinc-dependent protease** that interfere with the process of release of ACh. These toxins recognize gangliosides of the presynaptic membrane of motor neurons and enter nerve terminals by binding to the domain of synaptic proteins inside the vesicles that have opened during the exocytosis process releasing ACh .

**Tetanus toxin** and **botulinum toxins** specifically cleave three different proteins required for synaptic vesicle exocytosis:

**Tetanus toxin** and **botulinum toxins B, D, F and G** cleave **synaptobrevin**.

**Botulinum toxins C1 and A/E**, respectively, cleave **syntaxin** and **SNAP-25**.

1) **Tetanus toxin** inhibits the release of neurotransmitters by inhibitory interneurons of the spinal cord and causes a **spastic paralysis**.

2) **Botulinum toxins** inhibit the release of ACh by motor neurons causing a **flaccid paralysis**. **Botulinum toxin** has useful medical and cosmetic applications: i) Injection of a small amount of **botulinum toxin** into the eye muscles of a patient with strabismus (a condition in which both eyes cannot focus on the same object because of abnormal hyperactivity of particular eye muscles) is able to suppress aberrant muscle spasms and restore normal vision. ii) A commercial preparation of **botulinum toxin** known as Botox has also gained popularity for the temporary treatment of facial wrinkles that occur in human aging.