Graduate Studies in Biomedical Technology and Medical Physics
University of Patras 2020

Physiology and Pathophysiology for Engineers and Physisists

part 2 - neurons

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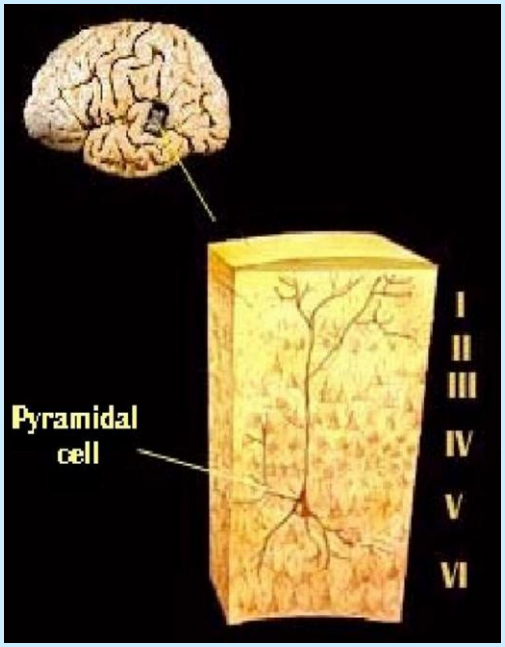
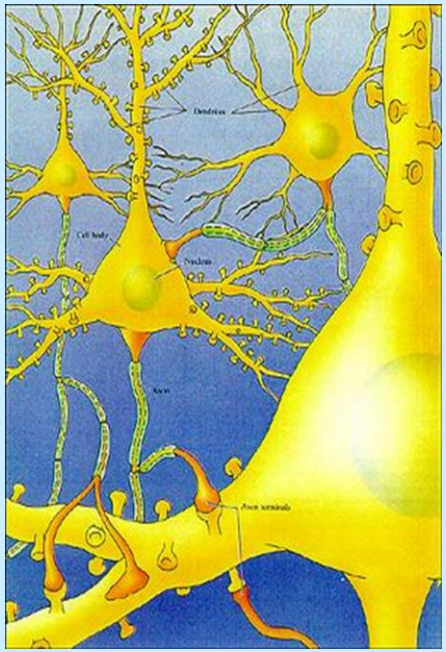
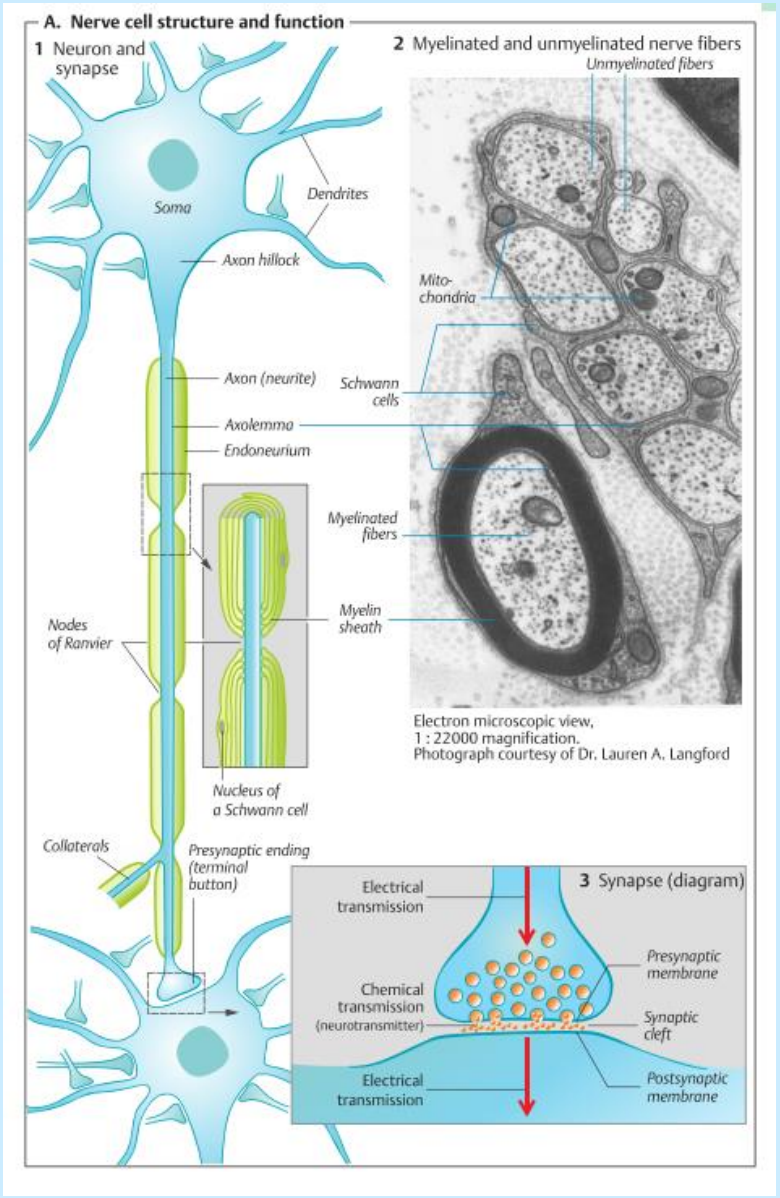
Cells of the Nervous System







Cells of the Nervous System: are of 2 kinds

- Over 100 billion nerve cells **(neuron**s)
- **Supporting cells** - - more numerous (**neuroglia)**

Neurons have 3 properties :

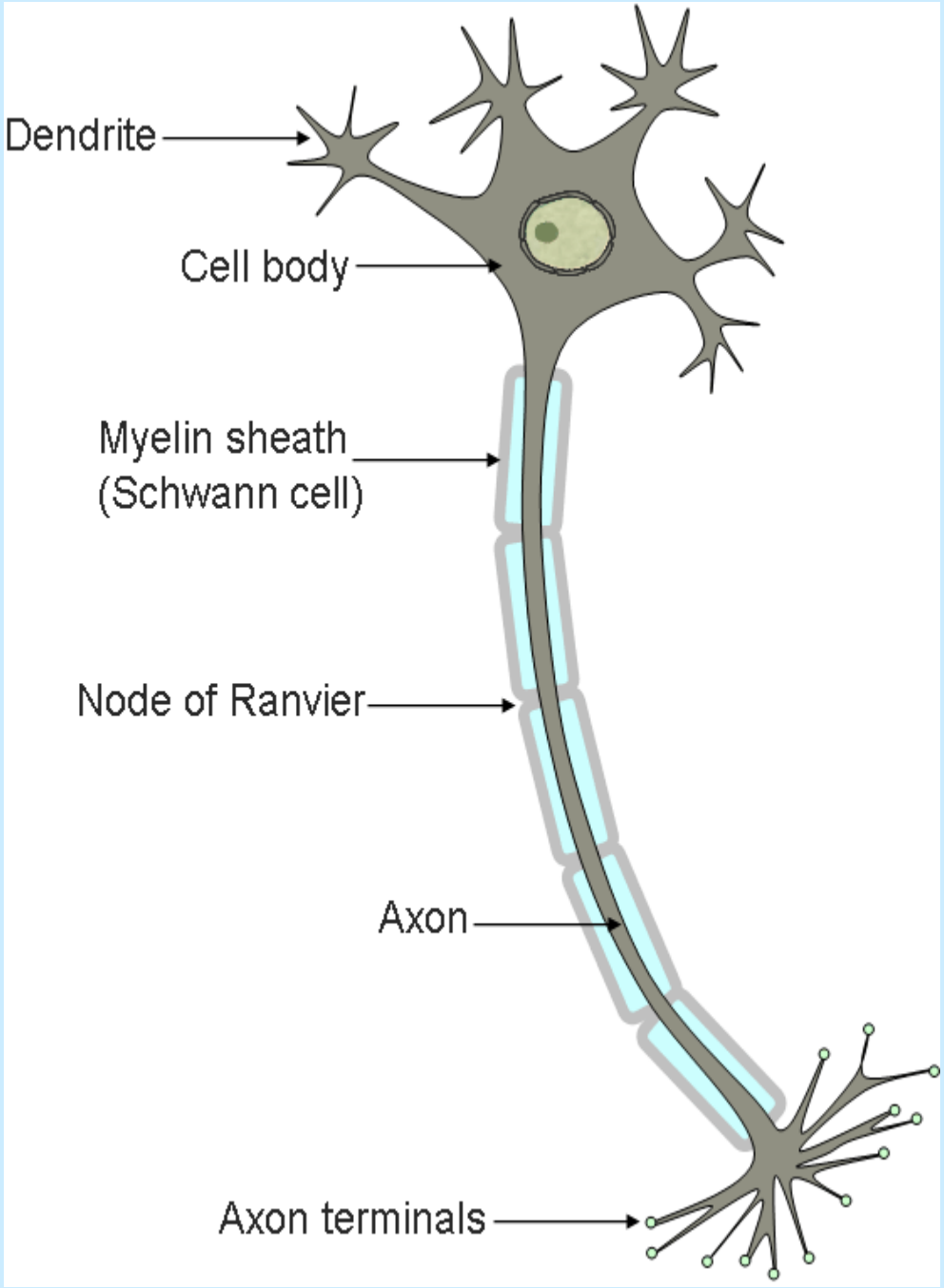
- **Excitability** - ability to respond to stimuli with action potentials.
- **Conductivity** - ability to transmit an action potential.
- **Synaptic transmission**

Nerve Processes

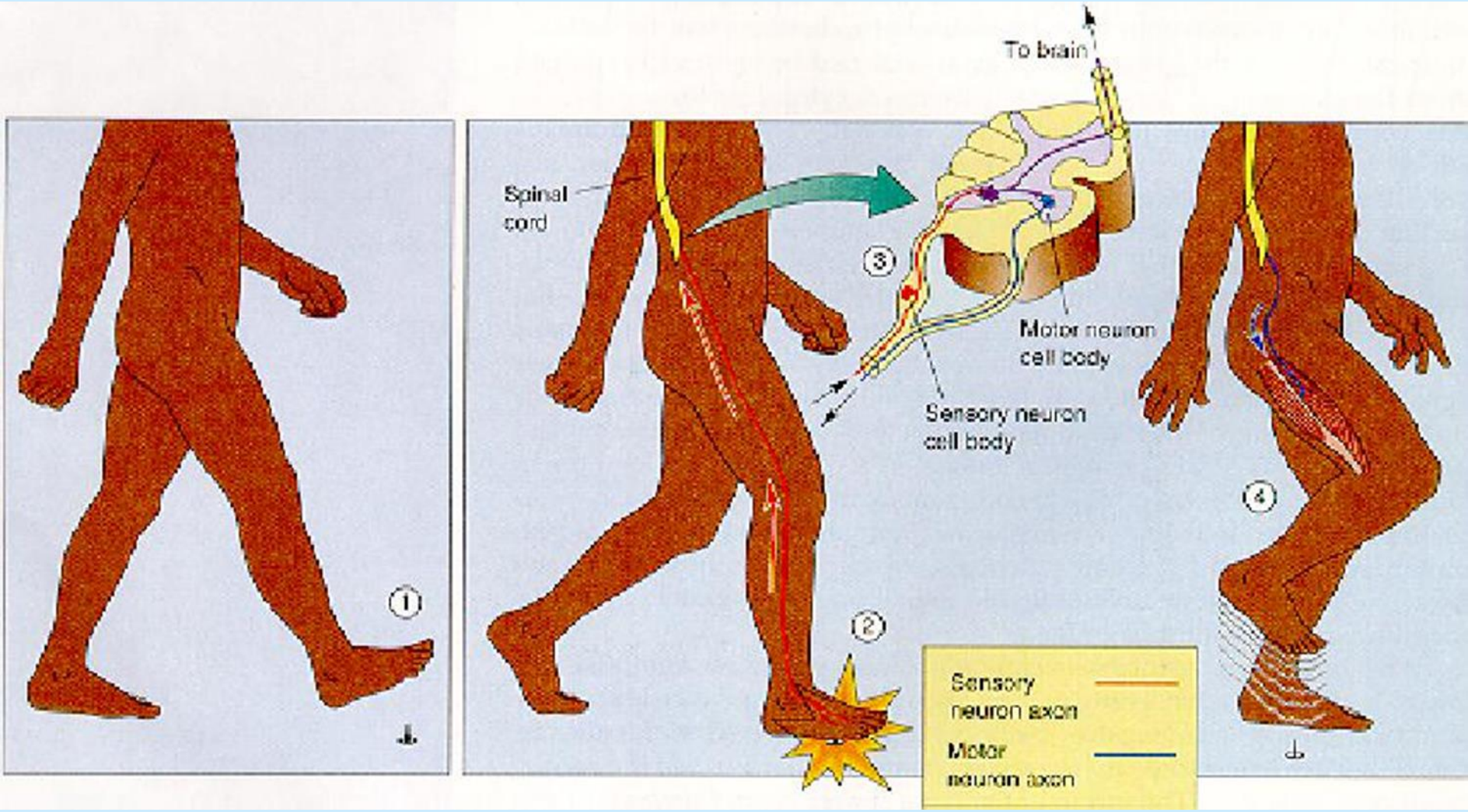
Two kinds - axons and dendrites - also called **nerve fiber**s.

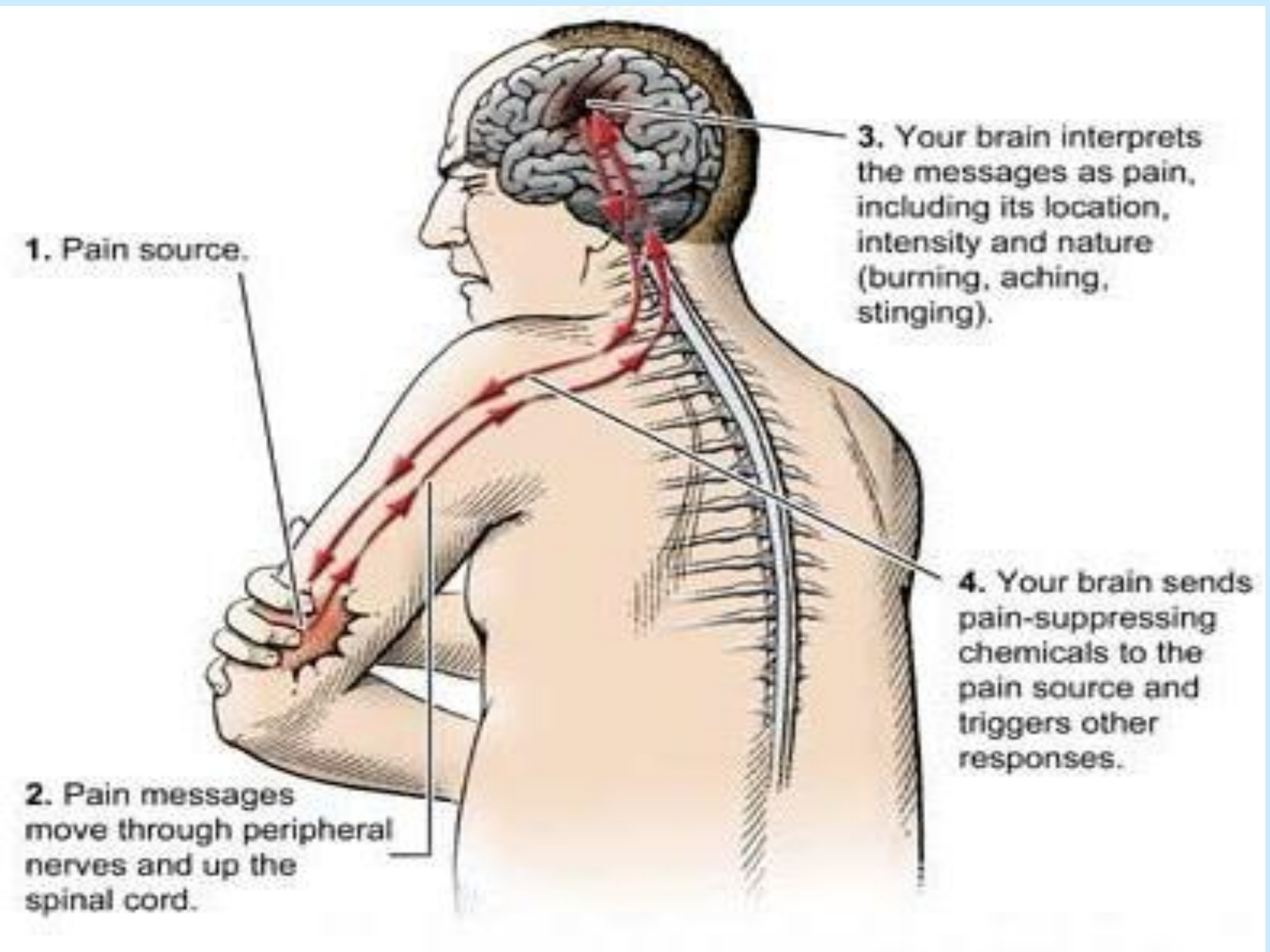
Dendrites - short, threadlike processes that are extensions of the cell body and conduct nerve impulses **toward** the cell body. Can have as many as 200 dendrites in one neuron.

Axon - slender process that extends from the cell body for from less than a millimeter (in the brain) to more than a meter (sciatic nerve). Carries nerve impulses **away** from the cell body. Generally just one.



The function of Neurons




1. Pain source.
2. Pain messages move through peripheral nerves and up the spinal cord.
3. Your brain interprets the messages as pain, including its location, intensity and nature (burning, aching, stinging).
4. Your brain sends pain-suppressing chemicals to the pain source and triggers other responses.

Types of PNS Neurons -

Based on direction in which they transmit nerve impulses.

- Afferent (sensory) neurons - convey information from sensory receptors in the skin, sense organs, muscles, joints, and viscera to the CNS. **Exteroceptors** (monitor external), **proprioceptors** (monitor position), **interoceptors** (monitor internal activities).

- **Efferent (motor) neurons -** convey nerve impulses away from the CNS to the effectors (muscles and glands).

- Interneurons - lie (1) between sensory and motor neurons in neural pathways and transmit signals through pathways of the CNS, where integration occurs, and (2) in autonomic ganglia. About 90% of the neurons of the body are interneurons.

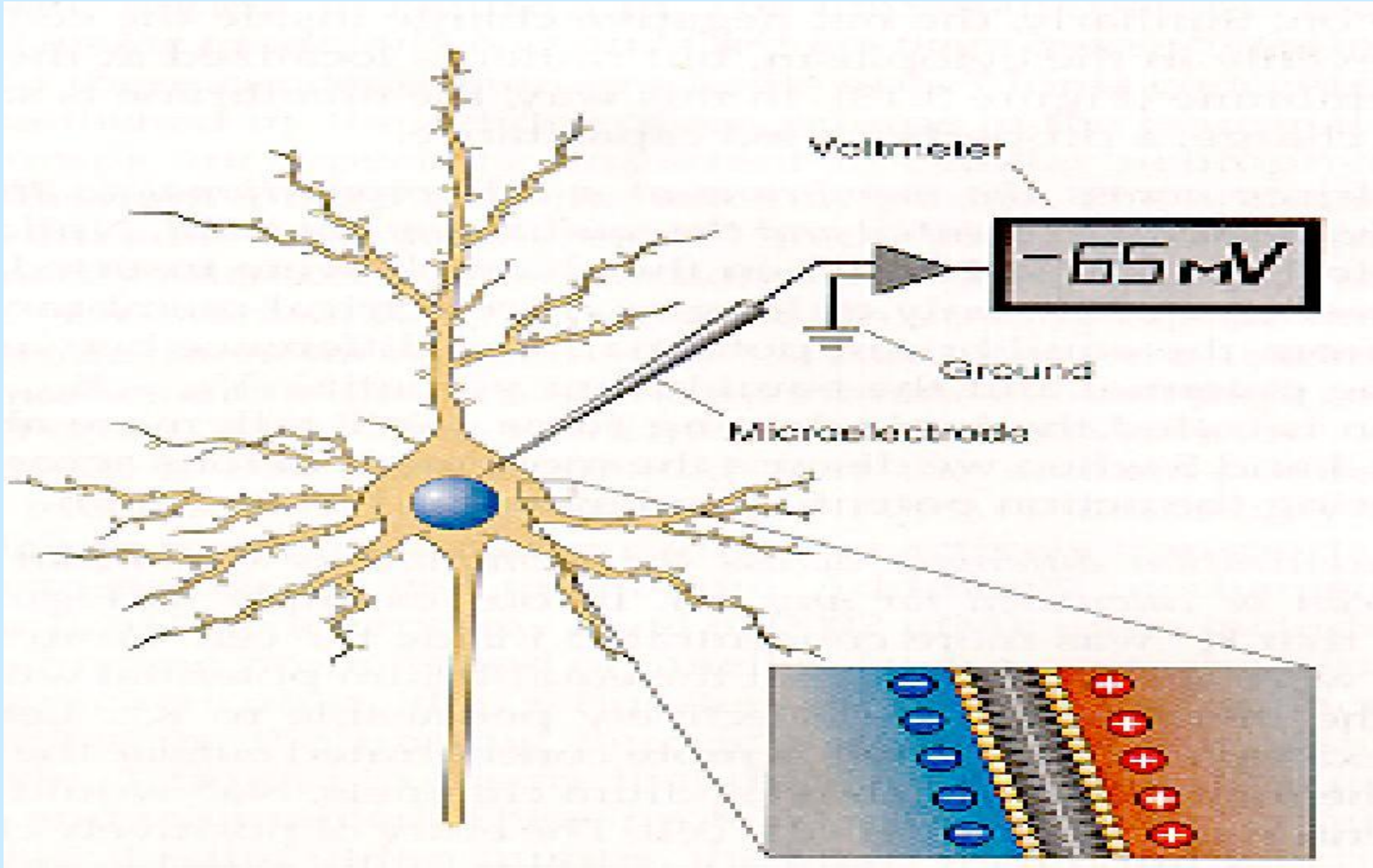
How do neurons accomplish this communication intracellularly and intercellulatly?

They use 3 unique mechanisms:

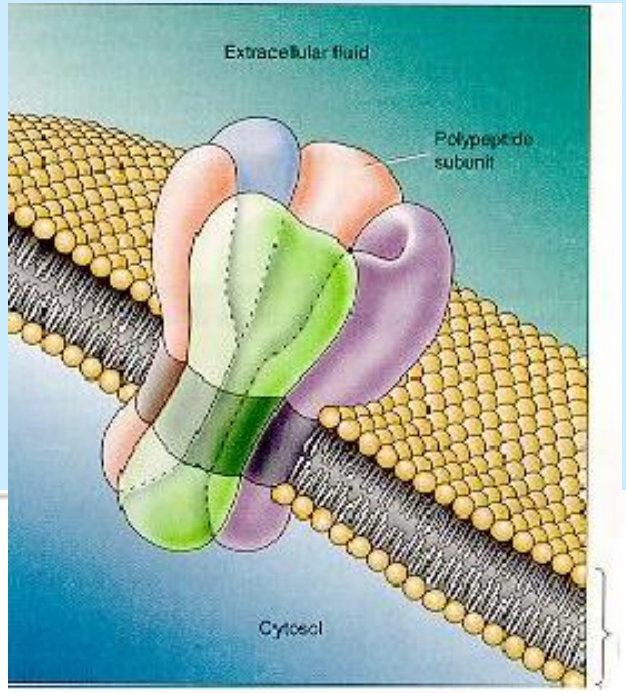
1. Excitability
2. Conductivity
3. Synaptic transmission

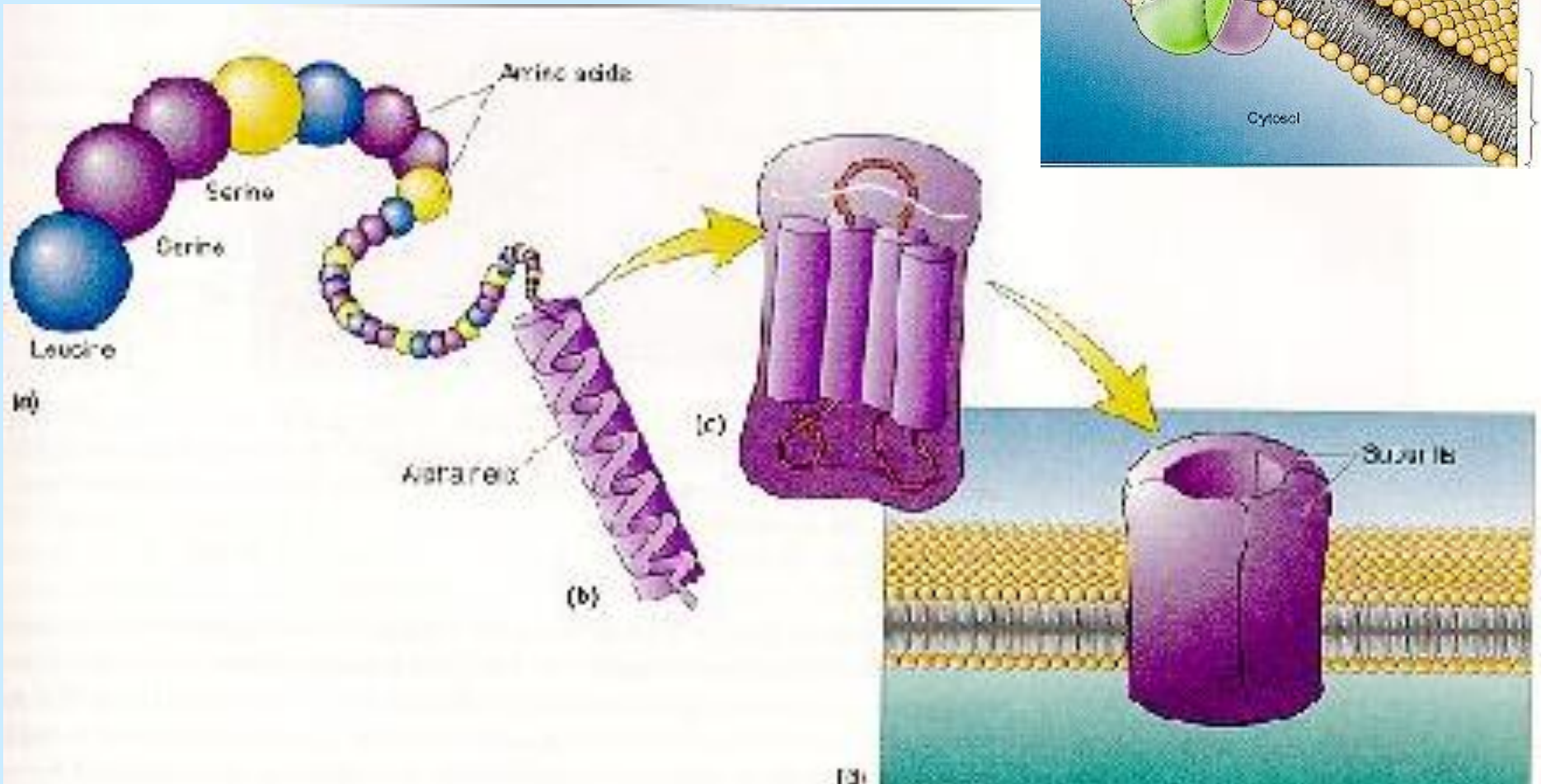
The membranes of **all** cells are electrically polarized, i.e. they have a resting membrane potential about 70 mV inside negative

The membranes of all cells are electrically polarized, i.e. they have a resting membrane potential (RMP)

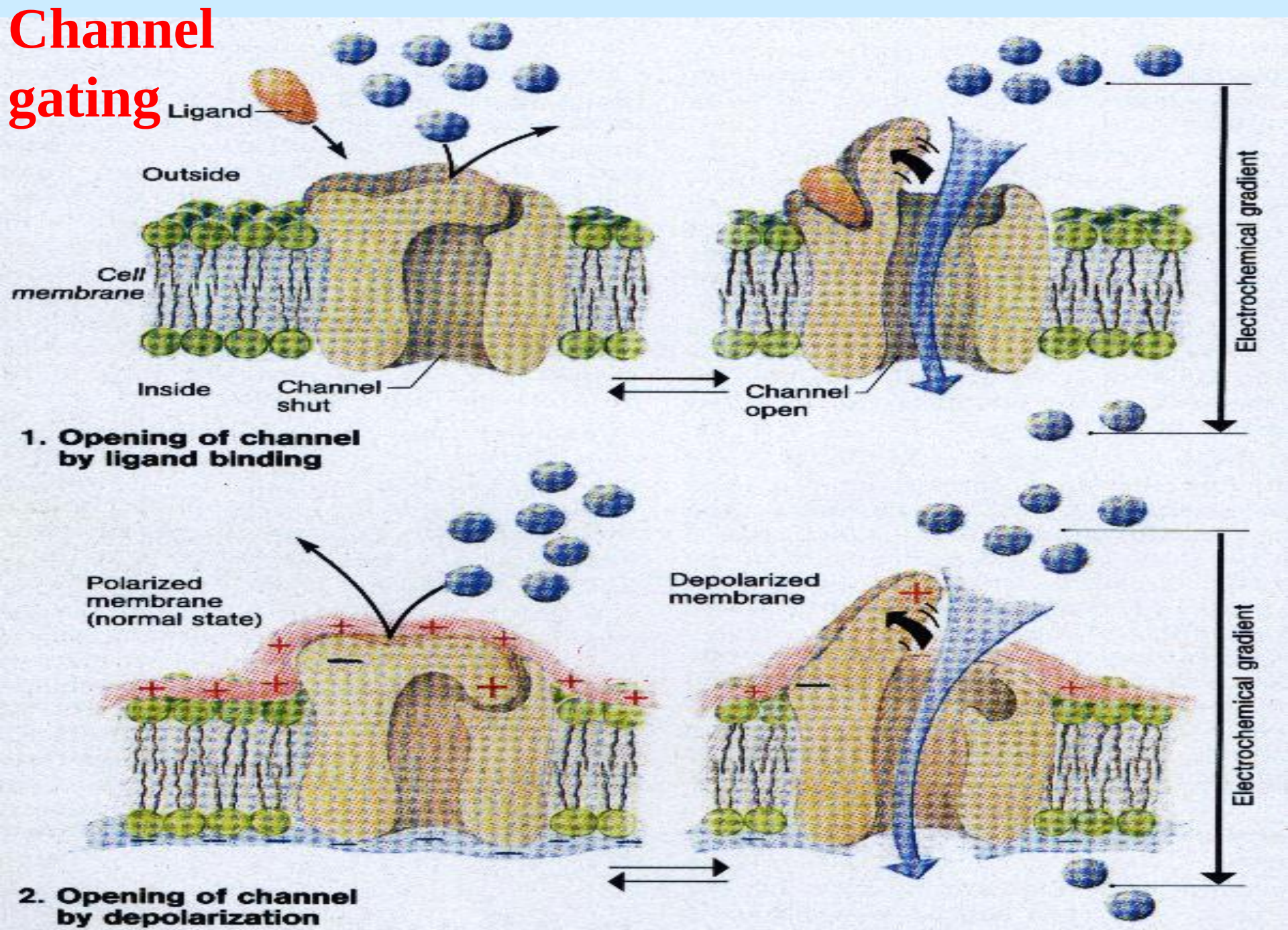


The RMP is created by gated **channels** and ionic **concentration gradients** across the membranes





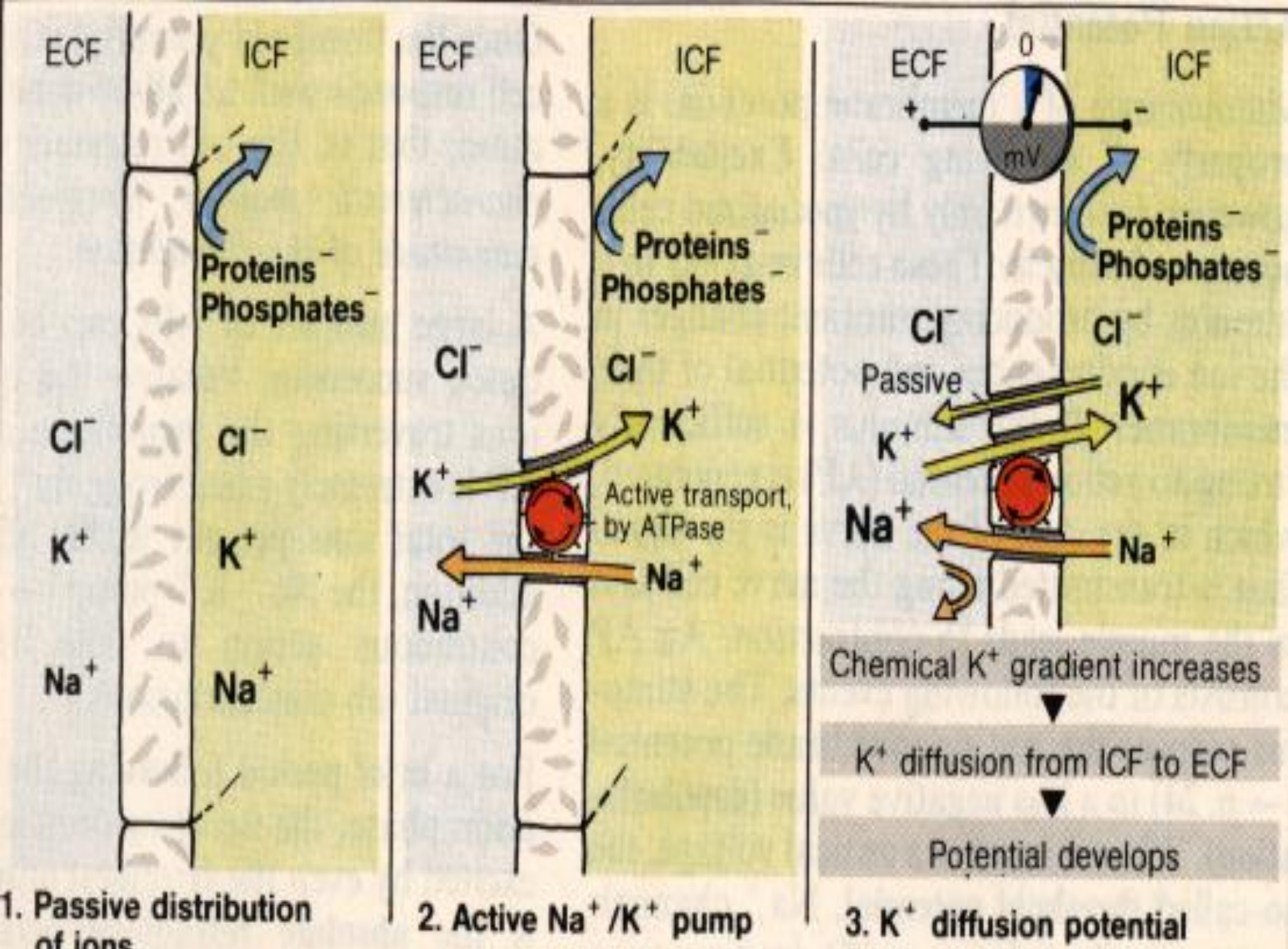
Channel gating



Ionic gradients: Extracellular space has more [Na+] and [Cl-], while intracellular space has more [K+]

	"Effective" concentration (mmol/kg H_2O)		Equilibrium potential
	Interstitium (ECF)	Cell (ICF)	
K^+	4.5	160	– 95 mV
Na^+	144	7	+ 80 mV
H^+	$4 \cdot 10^{-5}$ (pH 7.4)	10^{-4} (pH 7.0)	– 24 mV
Cl^-	114	7	– 80 mV
HCO_3^-	28	10	– 27 mV

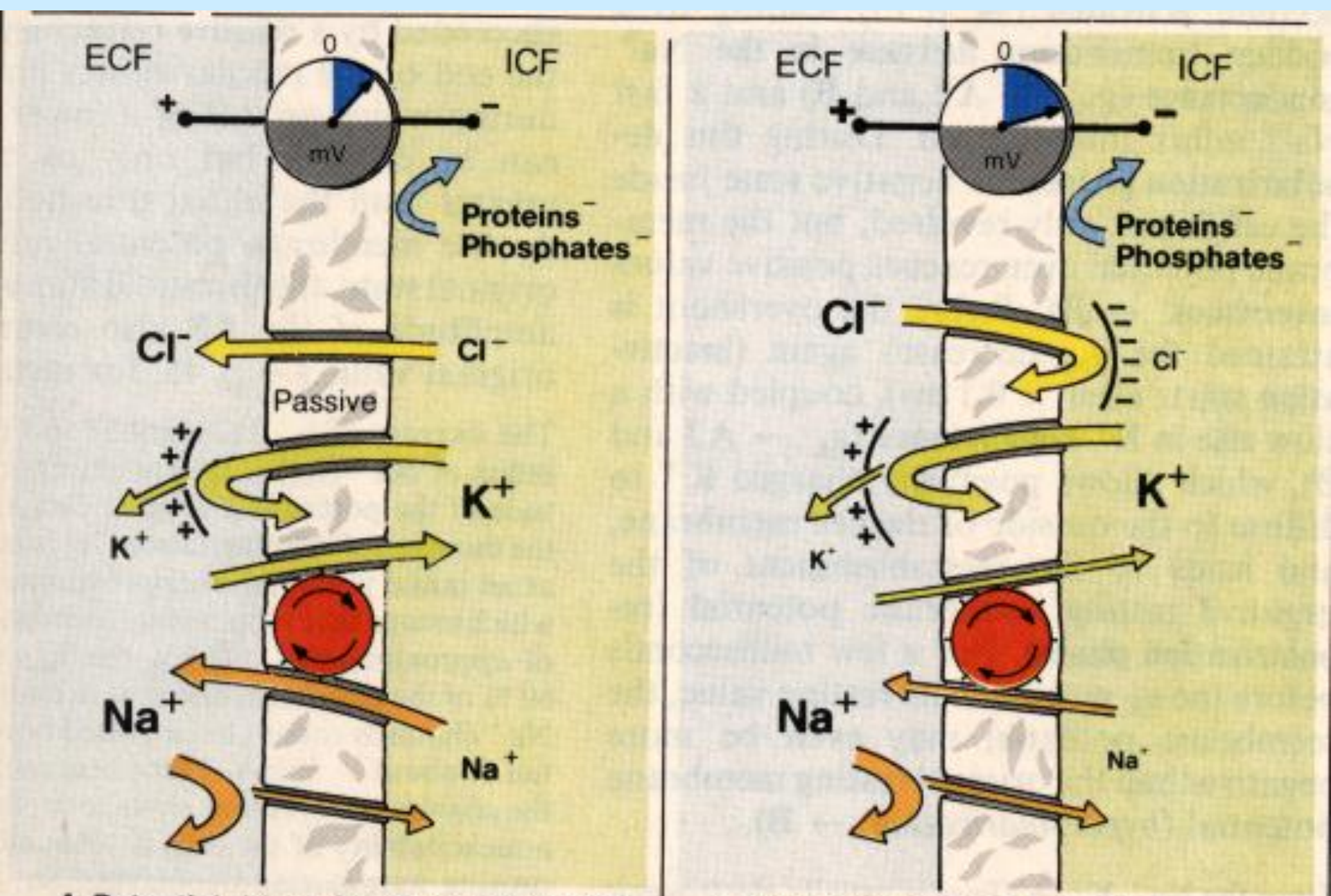
B. Typical "effective" concentrations and equilibrium potentials of important ions in skeletal muscle (37° C) (after Conway)



1. Passive distribution of ions

2. Active Na^+ /K^+ pump

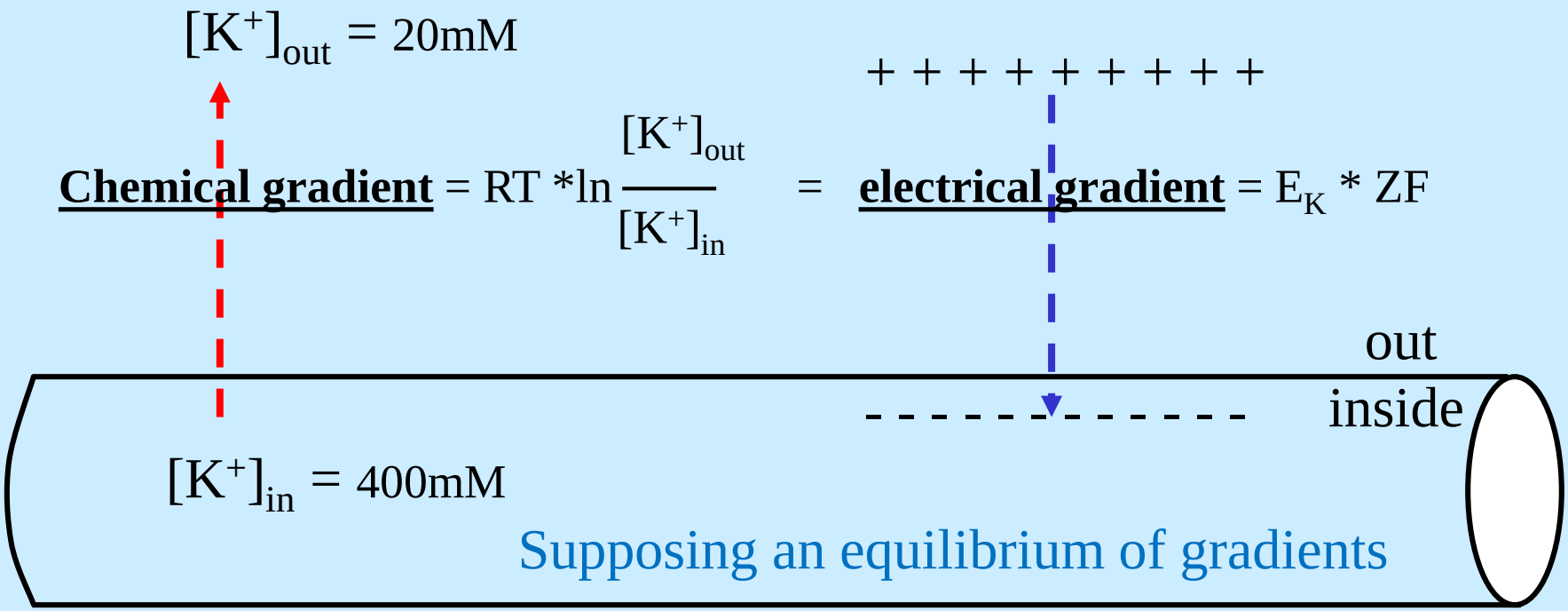
3. K^+ diffusion potential



4. Potential drives Cl^- from ICF to ECF

5. Final state: resting potential

A. Causes and consequences of the resting potential

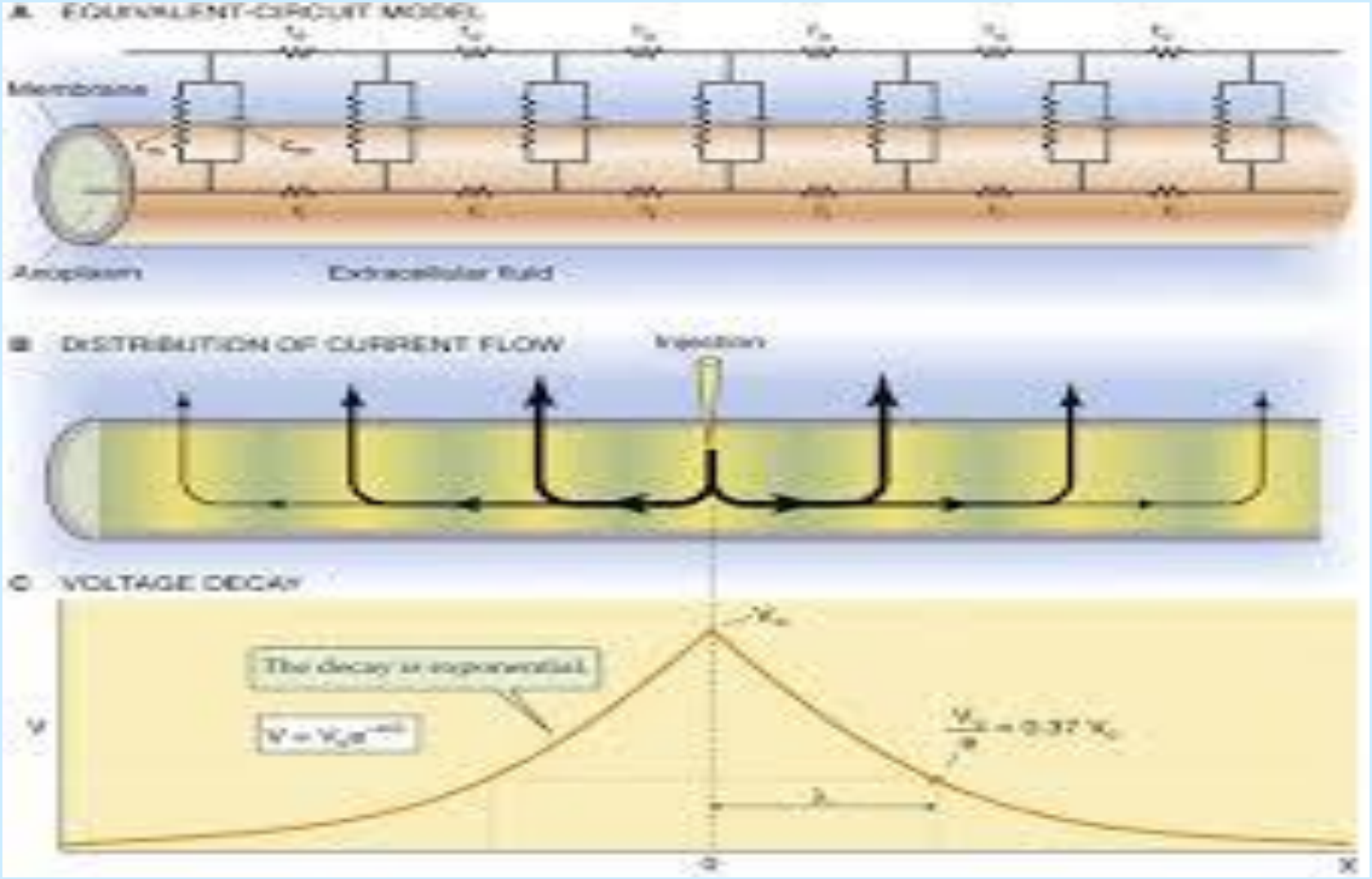


Using this thermodynamics relationship Nernst suggested an equation for measuring the equilibrium potential E_{ion} of an ion crossing a membrane

NERNST EQUATION: $E_{ion} = \frac{RT}{ZF} * \ln\frac{[K^+]_{out}}{[K^+]_{in}}$

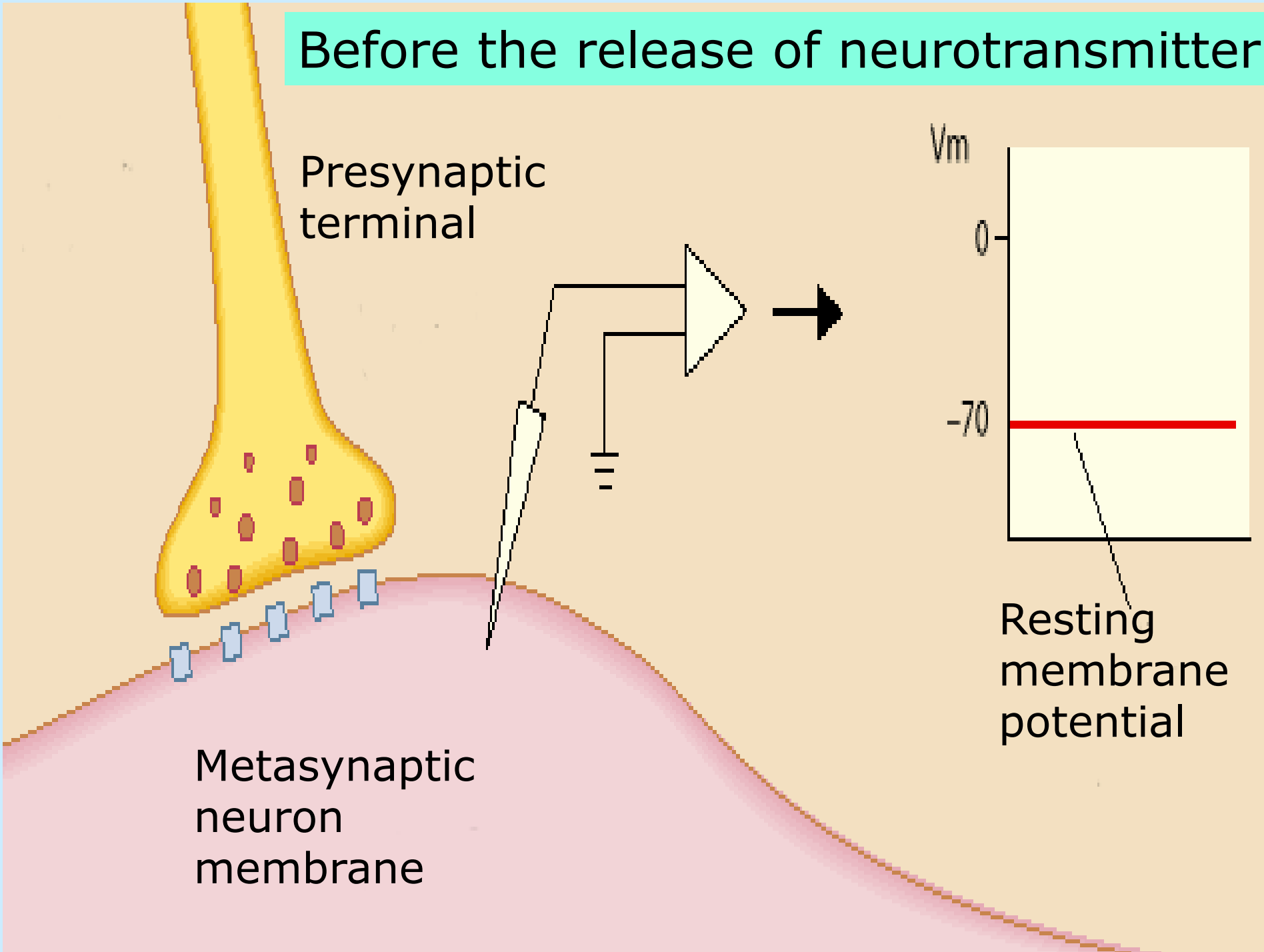
Where
R is the universal gas constant (8.314570 J K-1 mol-1)
T the temperature in Calvin
z the valence of the ion
F is the Faraday constant (96,485 Cmol-1)

The membrane potential depends on the **ionic gradients** and the membrane **permeability**

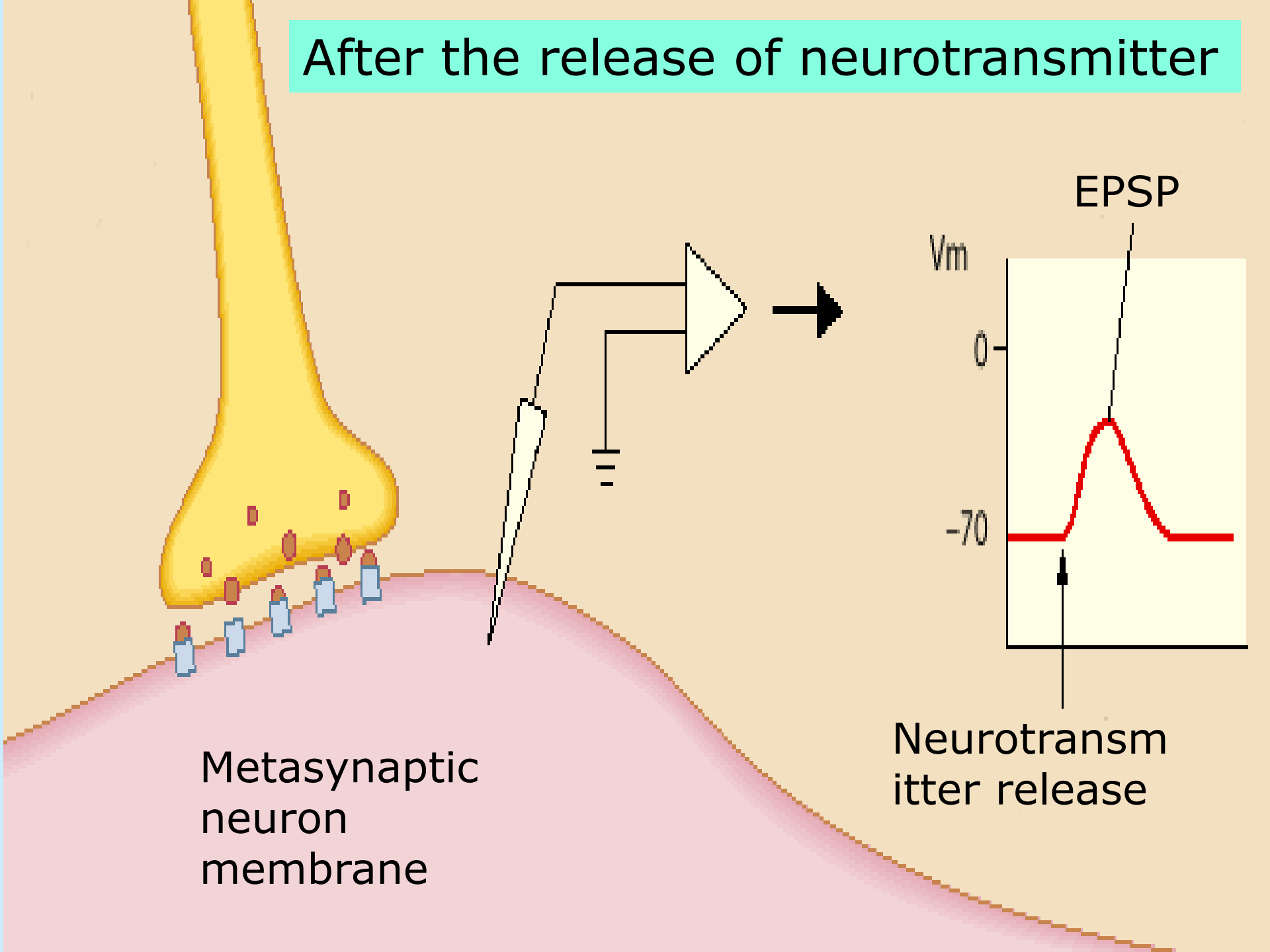


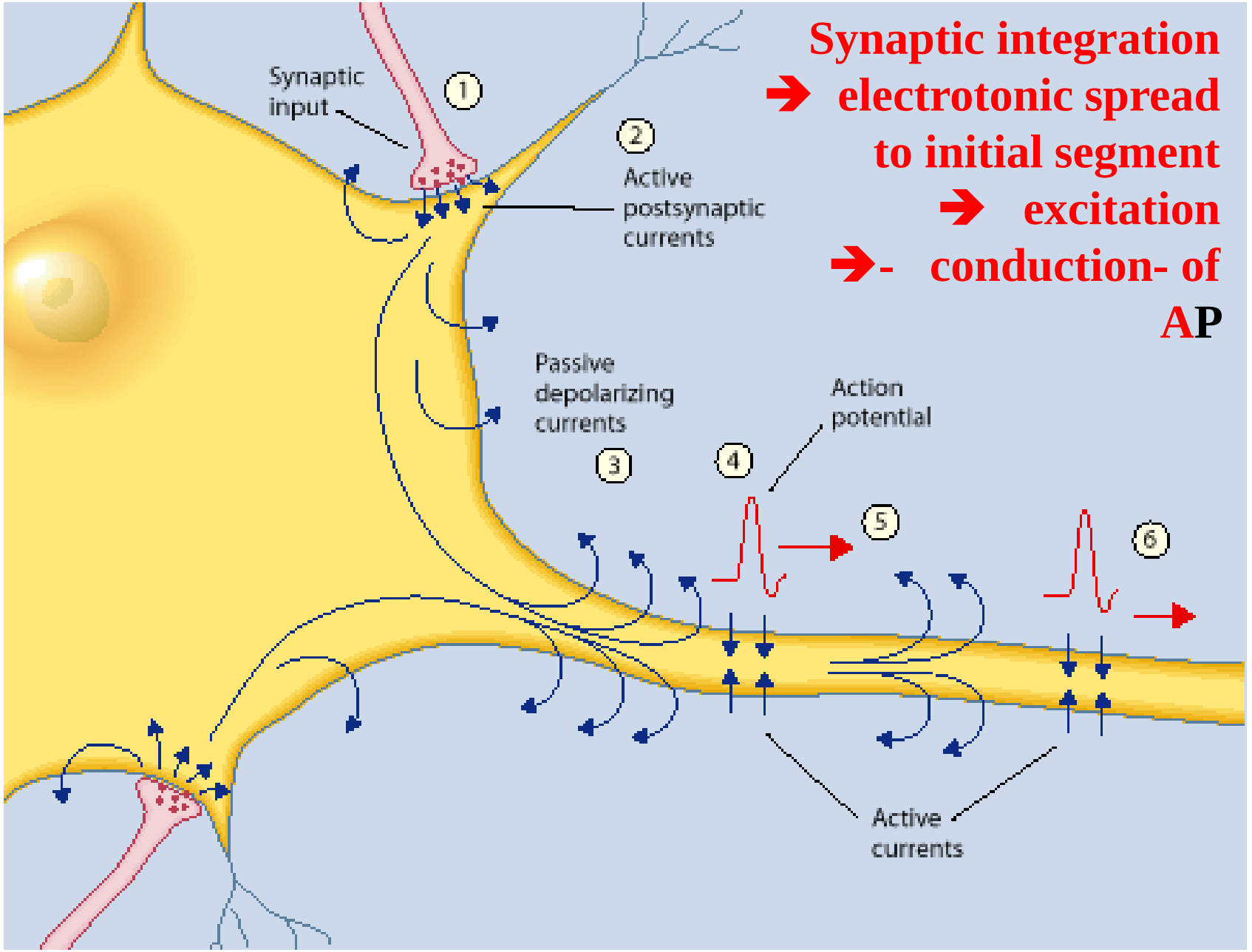
Changes of he membrane potential spread electrotonically with the potential gradually diminishing with distance from the point the change was made – **depending on what?**

Before the release of neurotransmitter



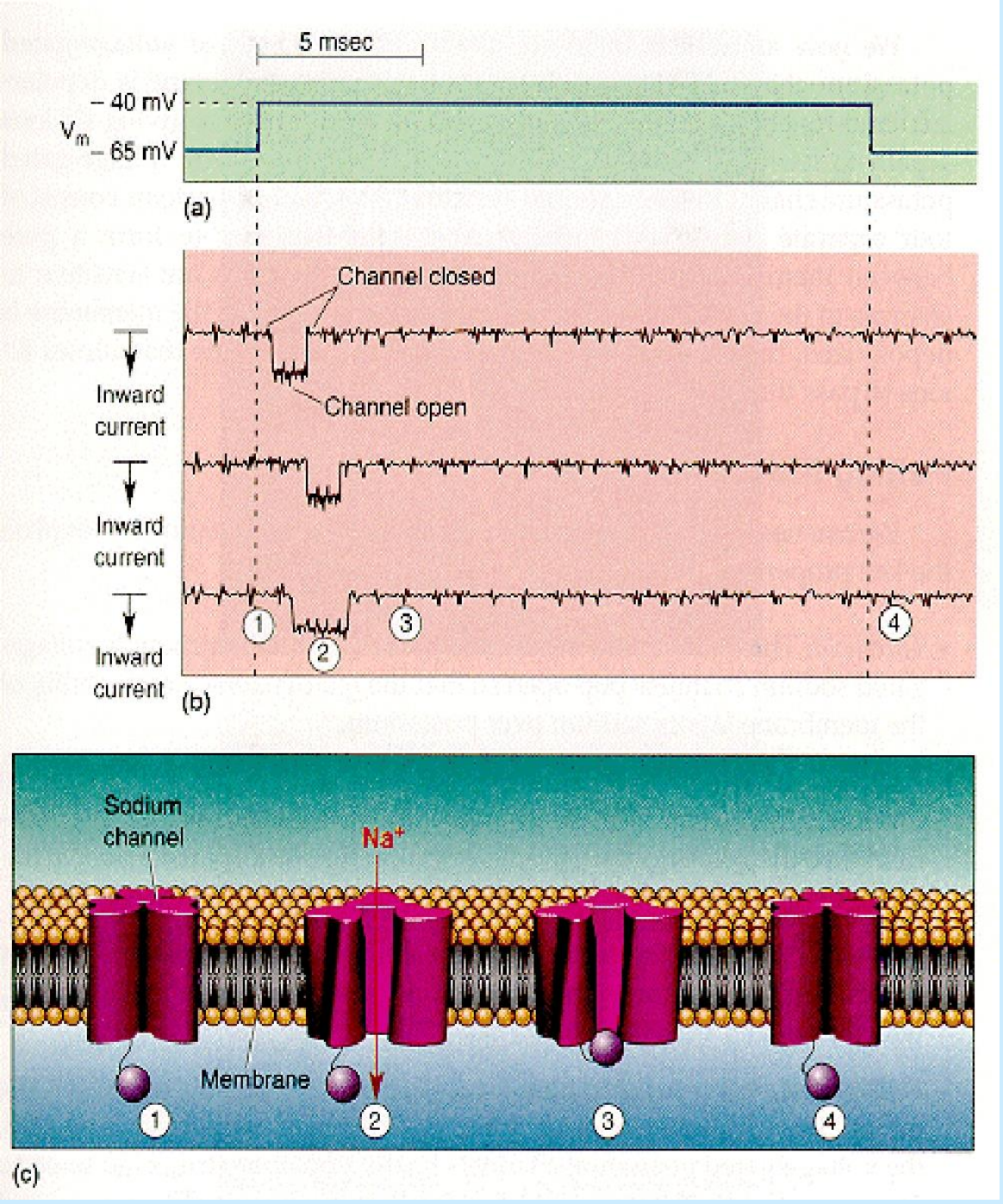
After the release of neurotransmitter

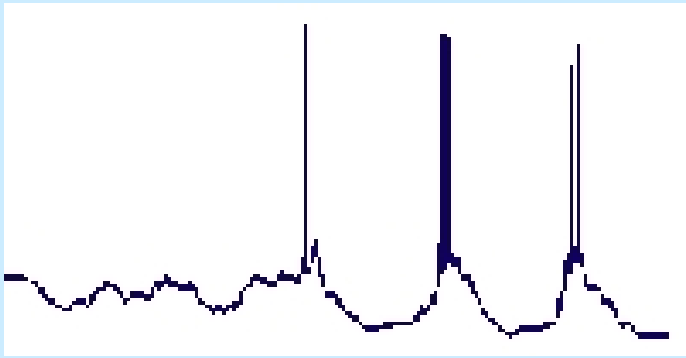


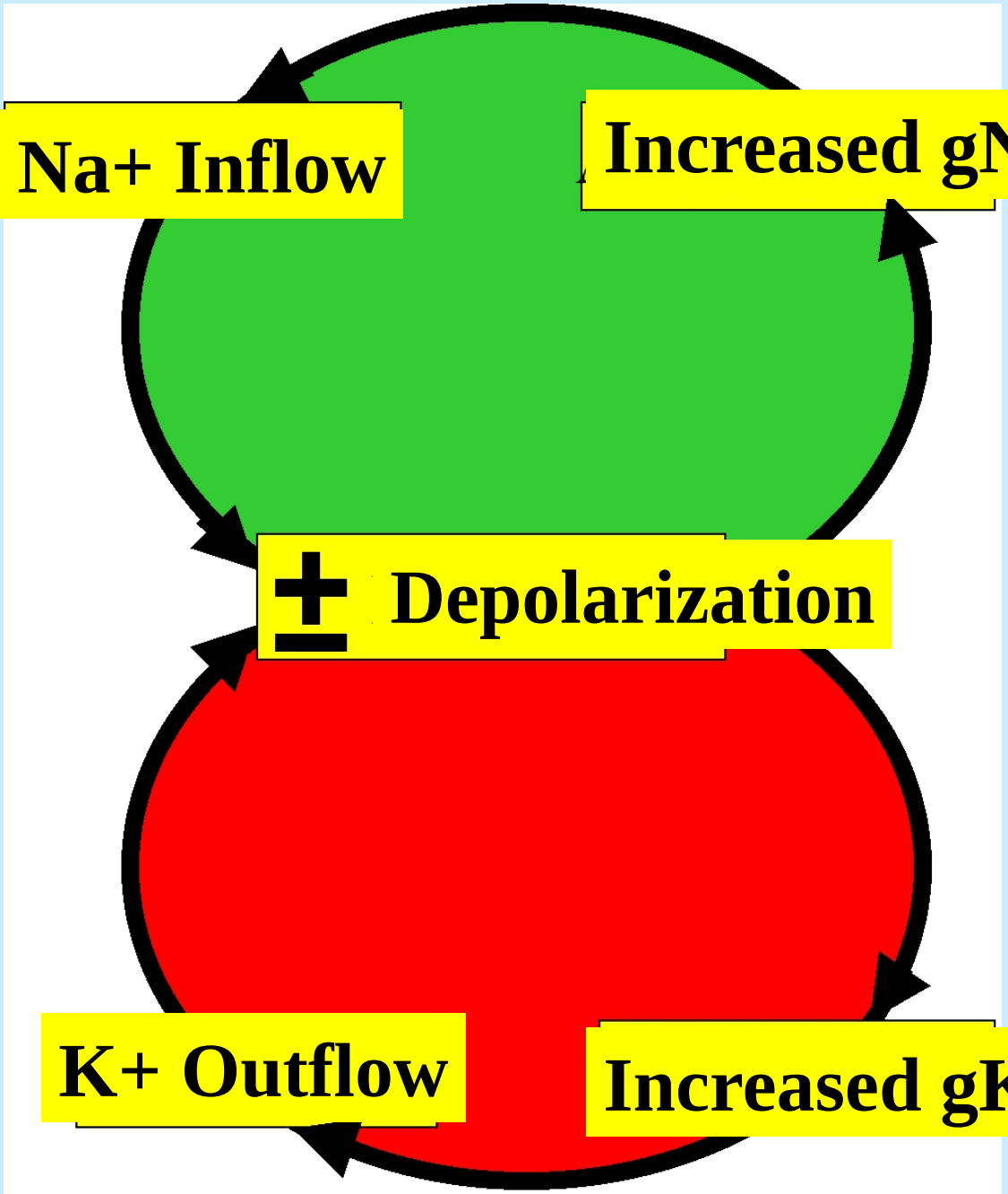

Synaptic integration
➔ electrotonic spread to initial segment
➔ excitation
➔- conduction- of AP
Synaptic input
1
2
Active postsynaptic currents
Passive depolarizing currents
3
4
Action potential
5
6
Active currents

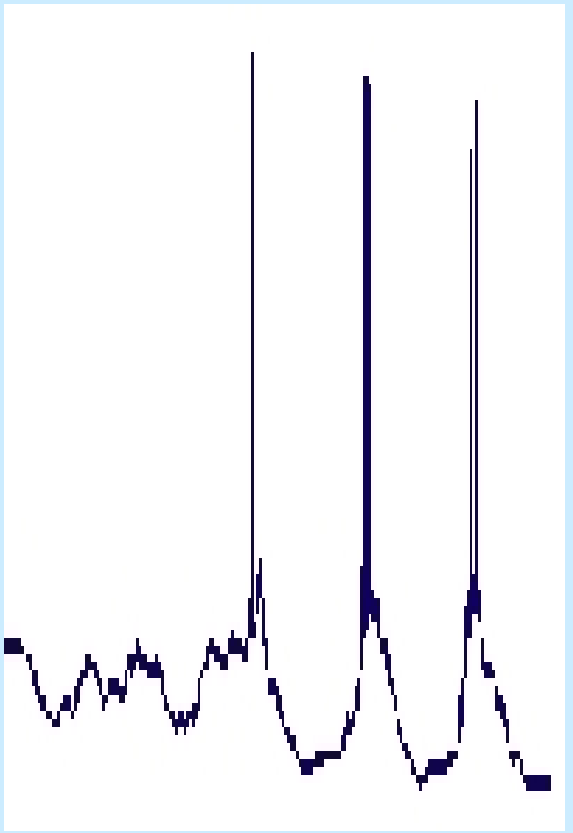
EXCITABILITY:

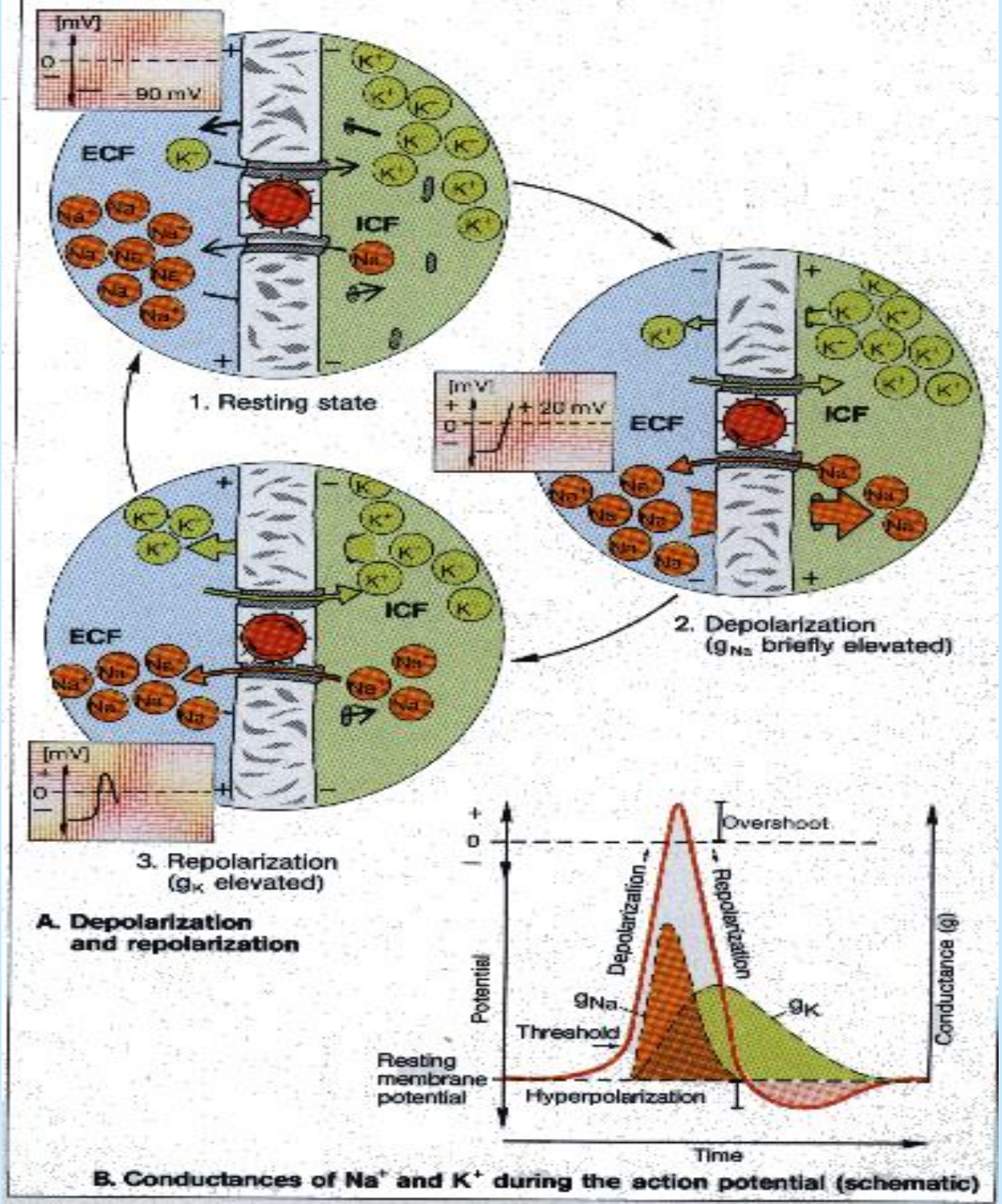
Upon sufficient depolarization from RMP, neurons can generate **action potentials**

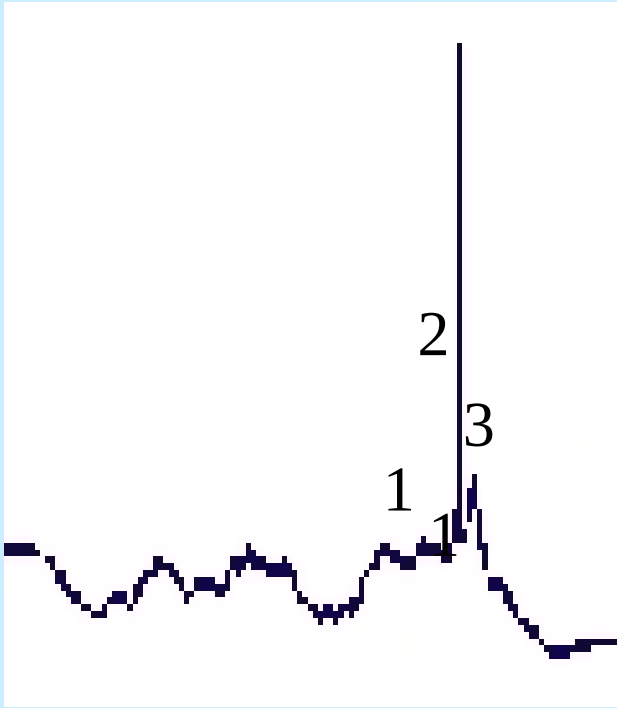

5 msec
– 40 mV
V_m
– 65 mV
(a)
Channel closed
Channel open
Inward current
Inward current
Inward current
1
2
3
4
(b)
Sodium channel
Na^+
Membrane
1
2
3
4
(c)

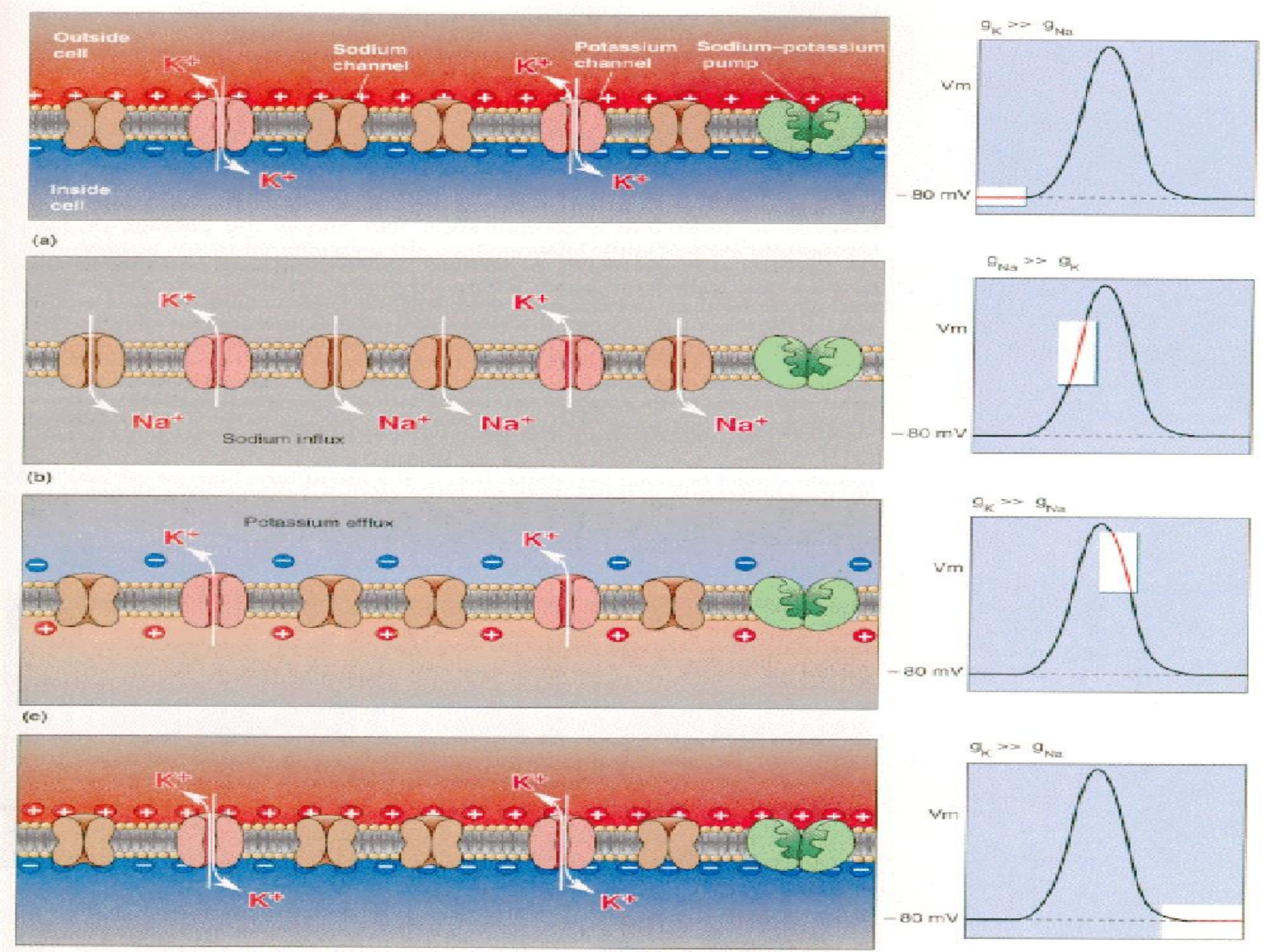


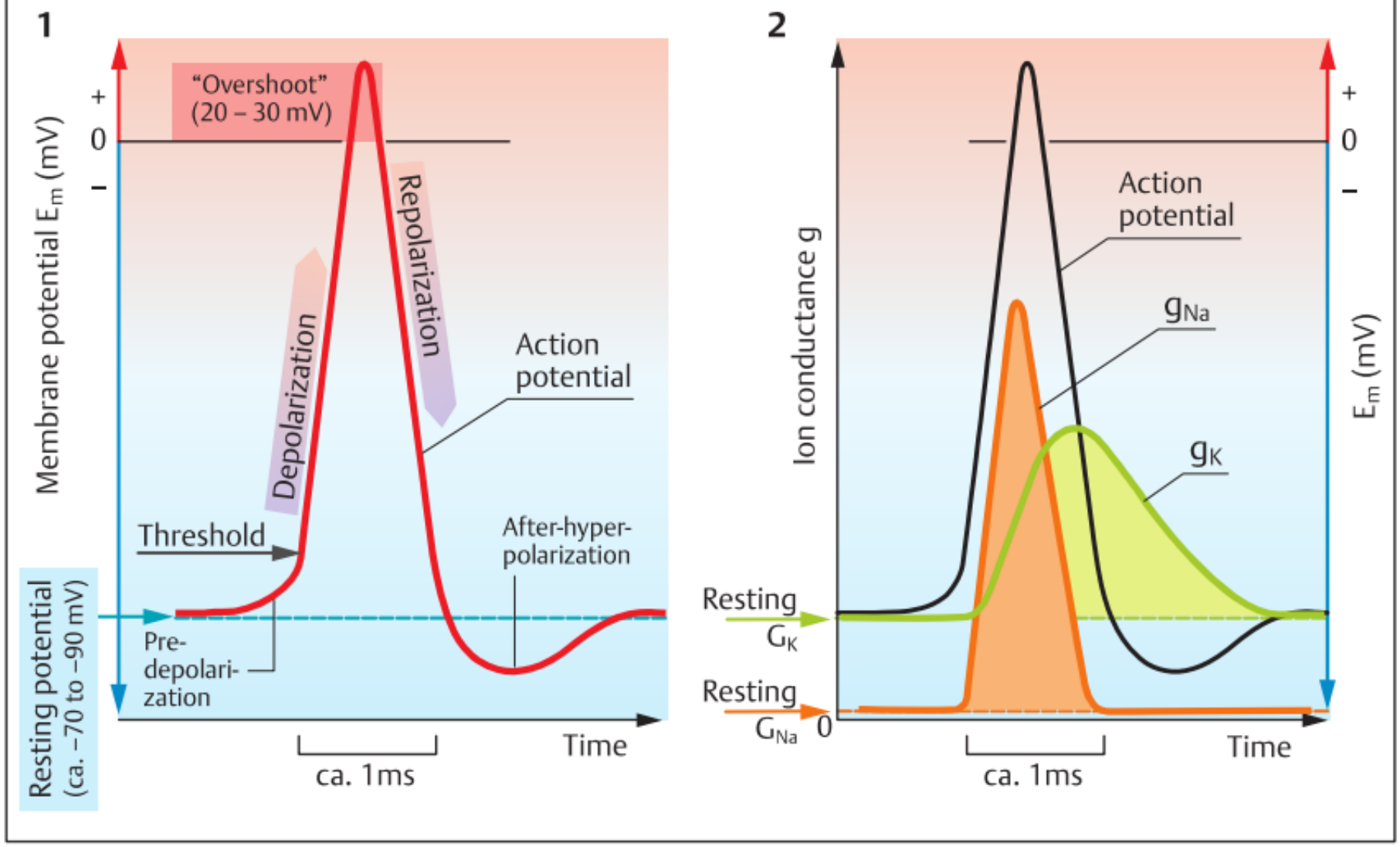

Na+ Inflow
Increased gNa+
± Depolarization
K+ Outflow
Increased gK+




[mV]
0
−90 mV
ECF
ICF
1. Resting state
[mV]
+ 20 mV
2. Depolarization
(g_{Na} briefly elevated)
3. Repolarization
(g_K elevated)
A. Depolarization and repolarization
Overshoot
Depolarization
Repolarization
Potential
g_{Na}
g_K
Threshold
Resting membrane potential
Hyperpolarization
Conductance (g)
Time
B. Conductances of Na^+ and K^+ during the action potential (schematic)


1
1
2
3


Outside cell
Sodium channel
Potassium channel
Sodium–potassium pump
Inside cell
K+
(a)
Na+
Sodium influx
(b)
Potassium efflux
(c)
Vm
−80 mV
gK >> gNa
gNa >> gK


A. Action potential (1) and ion conductivity (2) (nerve and skeletal muscle)
1
"Overshoot"
(20 – 30 mV)
+
0
–
Membrane potential E_m (mV)
Depolarization
Repolarization
Action potential
Threshold
After-hyper-polarization
Resting potential
(ca. –70 to –90 mV)
Pre-depolari-zation
Time
ca. 1ms
2
Ion conductance g
Action potential
g_{Na}
g_K
Resting G_K
Resting G_{Na}
0
+
0
–
E_m (mV)
Time
ca. 1ms

Action Potential

•Conducted change in the permeability of the cell membrane.

•**Threshold stimulus** - stimulus that is strong enough to initiate an impulse in a neuron.

•In response to a threshold stimulus, voltage-gated sodium ion channels open and **Na + rushes into** the cell.

•Influx of Na + results in reversal of the electrical charge at the point of stimulus to about 30 mV. Called **depolarizatio**n.

•Nerve is said to **fire** when stimulus is strong enough to depolarize the membrane to threshold level and generate a nerve impulse.

•Depolarizing a small area on the axon stimulates the adjacent area, which also contains voltage-gated sodium ion channels, to depolarize and an **action potential** is generated.

•**Nerve impulse** - train of action potentials.

Action Potential - Repolarization

•Shortly after depolarization, voltage-gated potassium ion channels open which accelerates the **outflow** of K + ions.
•Na + channels close and sodium ions are **pumped ou**t.
•Outflow of K+ may result in **hyperpolarization** to below -70 mV.
•Potassium ion channels eventually close and membrane is restored to resting potential.

Refractory Period

•Absolute: Brief period, 0.5 - 1 msec, after depolarization before an adequate stimulus can generate another action potential. Most nerve fibers are cable of generating about 300 impulses per second.
•Relative: several msec

All-or-None Principle

When the response is independent of stimulus size.

Minimum stimulus is necessary to initiate an action potential. Increase in the intensity of the stimulus does not increase the strength of the impulse. Like a gun. If don't pull the trigger hard enough, nothing happens. As soon as pull above the minimum amount, bullet will fire. Pulling the trigger harder will not make the gun fire harder. Applies primarily to action potentials in axons.

In contrast to: Graded response - occurs if only a small part of the membrane is affected. Not enough to cause action potential.

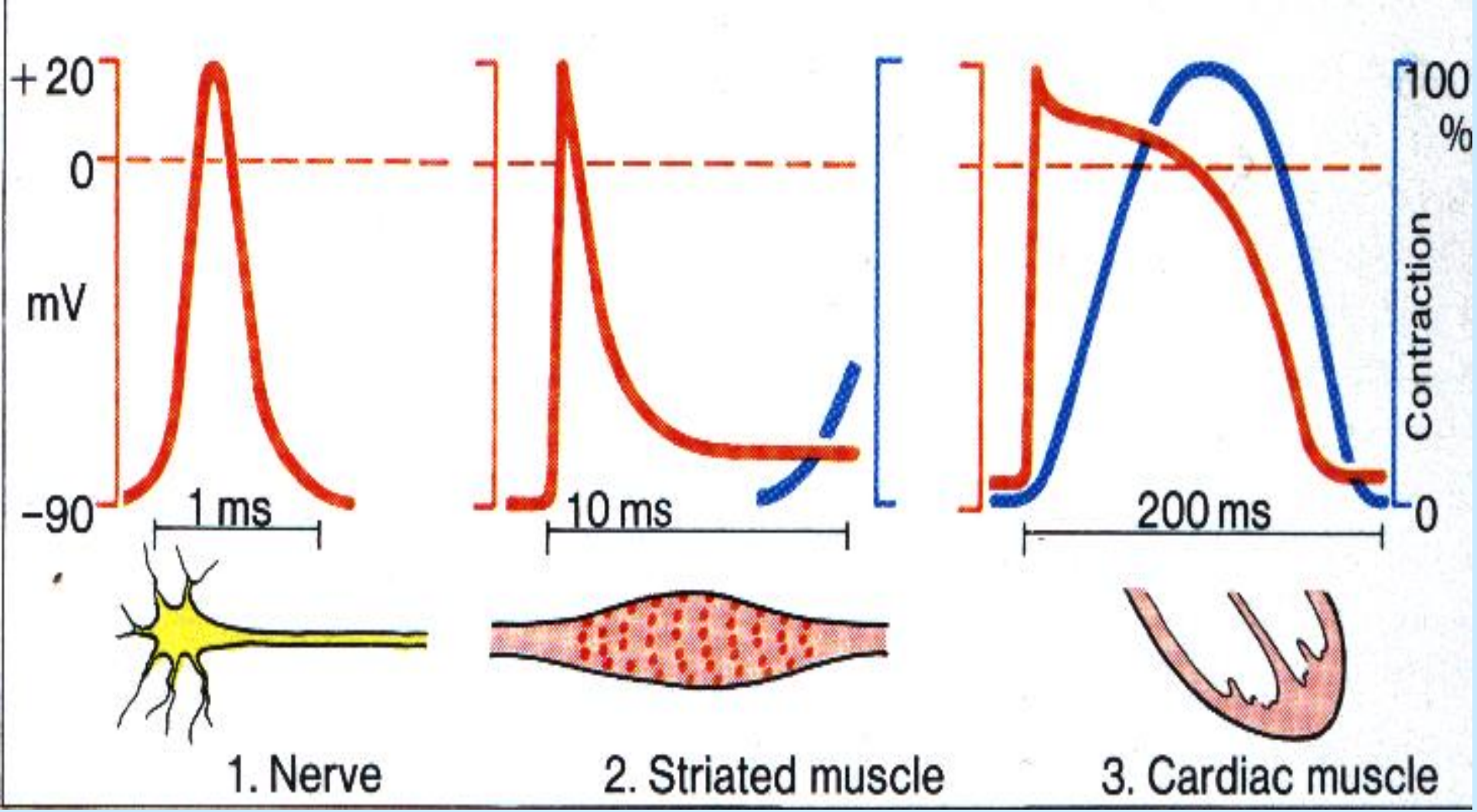
If all action potentials are alike….then how do we perceive Differences in Sensation?

i.e. Light touch versus strong shove or soft sound versus loud one.

Differences perceived when

.**Frequency** of the impulses (not their strength) is changed. Neurons can fire at different frequencies per second. The more frequent the impulses, the higher the level of excitation.

.**Number of neurons involved** - shove affects more neurons than does a light touch.



- **Excitability is the ability to sustain action potentials.**
- It differs in the 3 types of excitable cells. How?

PATHOPHYSIOLOGY OF THE NERVOUS SYSTEM

EXAMPLES OF MECHANISMS UNDERLYING SOME NEUROLOGICAL DISEASES

Pathophysiology is the physiology of abnormal states;

- it studies the functional changes that accompany a particular syndrome or disease;
- it describes the morphological and physiological changes occurring in disease and
- It tries to present the underlying mechanisms of disease.

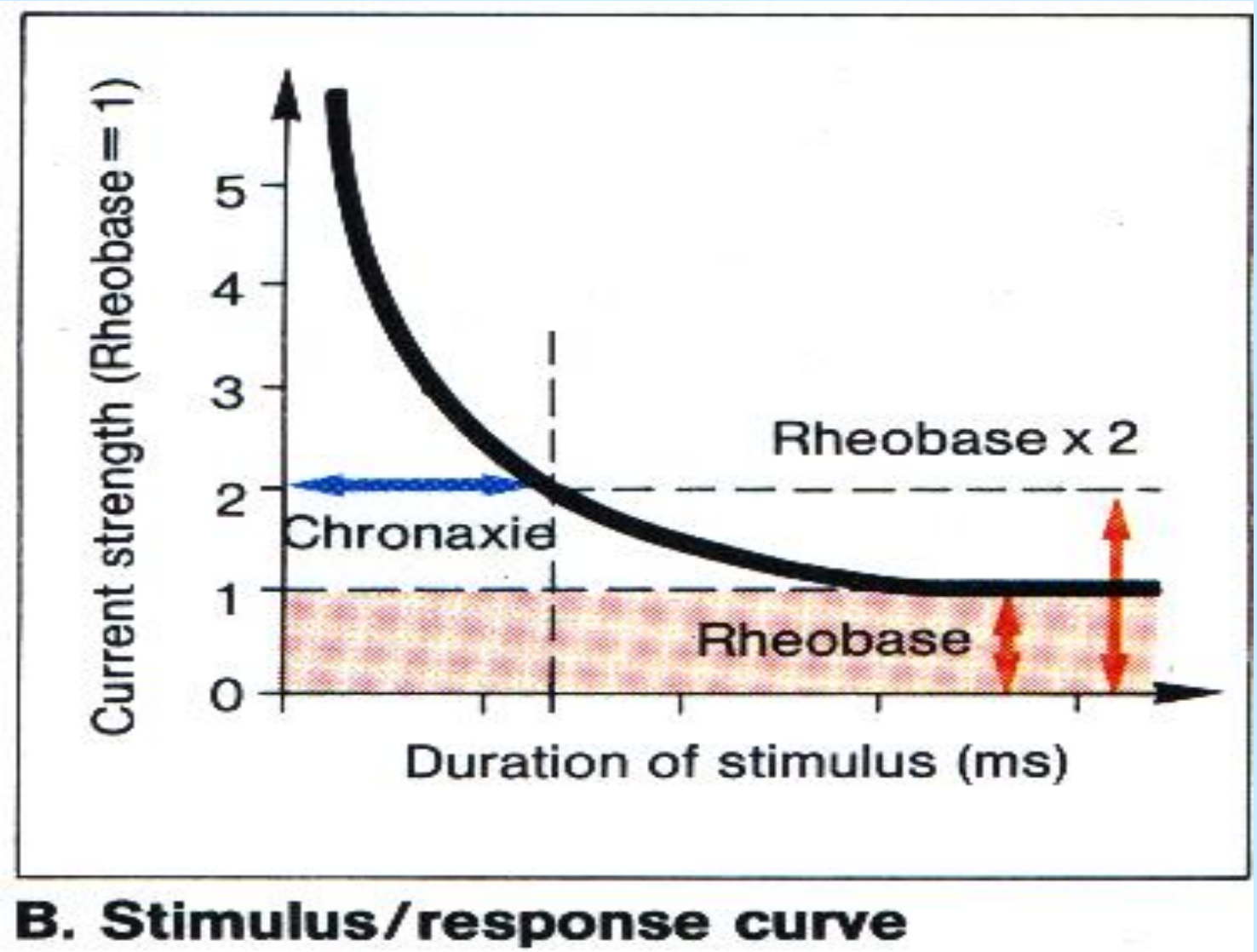
Speransky in 1934 had said: “Every disease is an exaggeration or a defect or a change of s specific physiological function”. A diagnosing physician therefore has first to identify which normal function has changed in each disease.

Examples will be given from diseases related to the specified normal functions as well as some examples of the related action of therapeutic drugs and poisons:

Neuronal and muscle excitability

- **Potassium** currents keep the membranes hyperpolarized at rest. Increase of extracellular [K+] as in renal failure or in Primary Hyperkalemic Paralysis decreases these currents and so causes **depolarization** of nerve and muscle membranes some of them going beyond excitation threshold (overdepolarization). As a result we see episodes of painful spontaneous contractures of muscle followed by paralysis. In heart the increase in ecitability has even more dramatic effects
- **Tetrodotoxin** is a specific blocker of voltage gated channels responsible for the action potential generation. It is contained in puffer fish and may therefore kill if this fish is not properly prepared

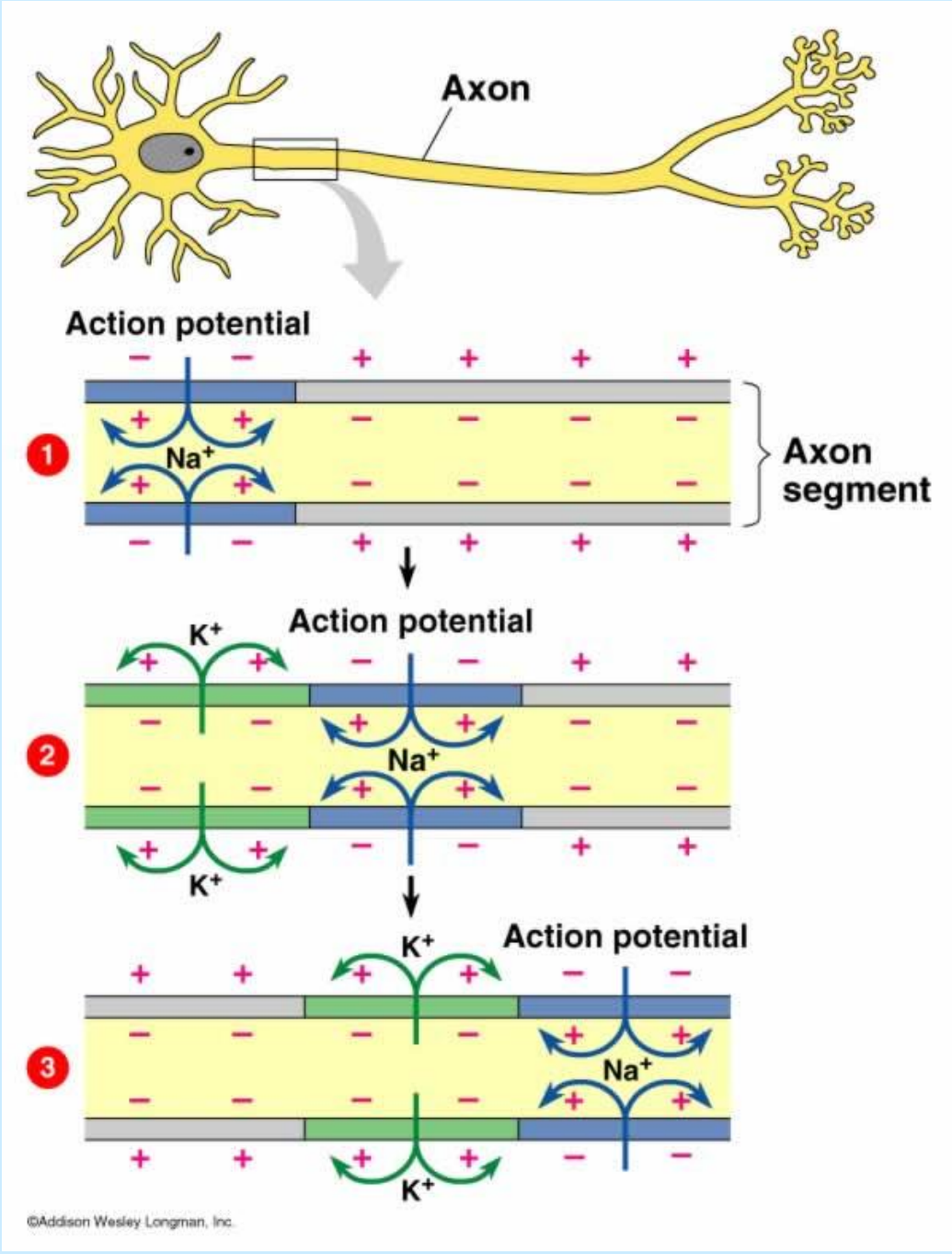
The excitability curve quantifies excitability for clinical evaluation



B. Stimulus/response curve

Axonal transport is important in pathology. Primary afferent neurons and motoneurons link the central nervous system with the periphery and thus form a protoplasmic bridge that crosses the blood-brain barrier. Certain viruses, such as the **rabies** and **polio viruses,** and toxins, such as **tetanus toxin,** can enter the central nervous system from the periphery if they are taken up and transported in the axons of these neurons.

Action potentials propagate on axons



Action potential propagation

Action potentials (to be useful as messages) have to **travel long distances with fidelity.**

Solution: AP propagation by **regeneration** on neighbouring parts of membrane after this is being electrotonically depolarized to threshold. → new AP. The power of an AP (100mV) ensures regeneration of identical AP in many small steps.

Second requirement: Message has to **travel fast**.

Solution: AP should depolarize more and further along the axon, so that fewer steps will be needed for the same distance. Given equal time for each AP, fewer steps make for higher speed.

This length of the step(how far the depolarization will still be above threshold) depends on

- **high r_m**
- **low C_m** and
- **low r_a**

This lengthening of the regeneration steps depends on

- **high r_m**
- **low C_m** and
- **low r_a**

Nature took two approaches:

(a)increase axon diameter, so that r_a decreases.

(b)when this solution reached space limits, it rapped axons with myelin so that r_m increased and on the same time C_m dropped. In this way we have saltatory propagation of AP from node to node.

Types of Conduction

Saltatory in minimal steps (therefore appearing as Continuous) - local current depolarizes adjacent portions of the membrane. When threshold is reached, action potential results. Process continues in a chain reaction. This happens in unmyelinated fibers.

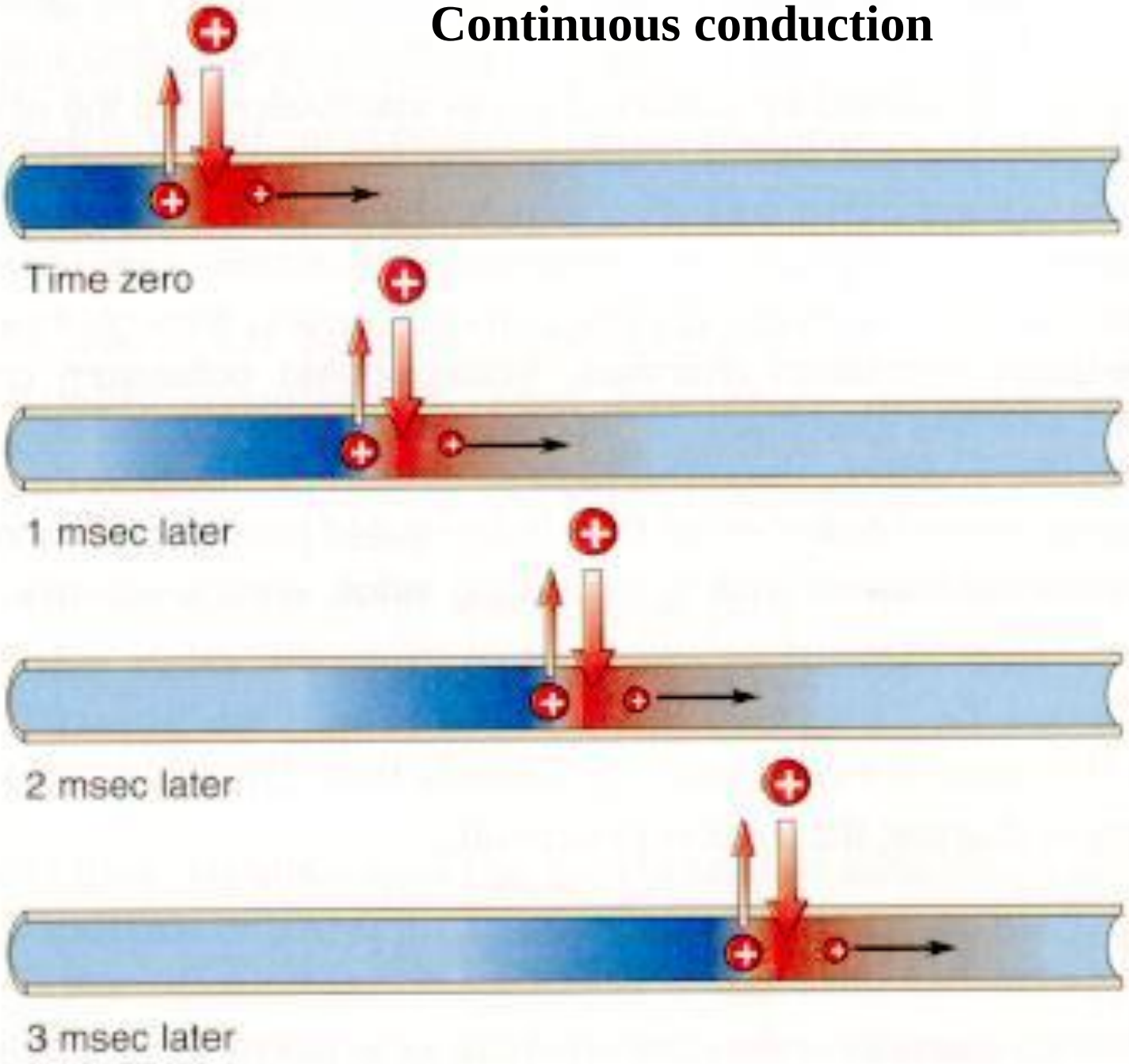
Saltatory in maximal steps- current loops are formed at Nodes of Ranvier due to insulation of myelin sheath. Action potential "jumps" from one node to the next where high concentration of voltage-gated channels are exposed to ECF. The longer the internode, the faster the speed of conduction. Requires less energy.

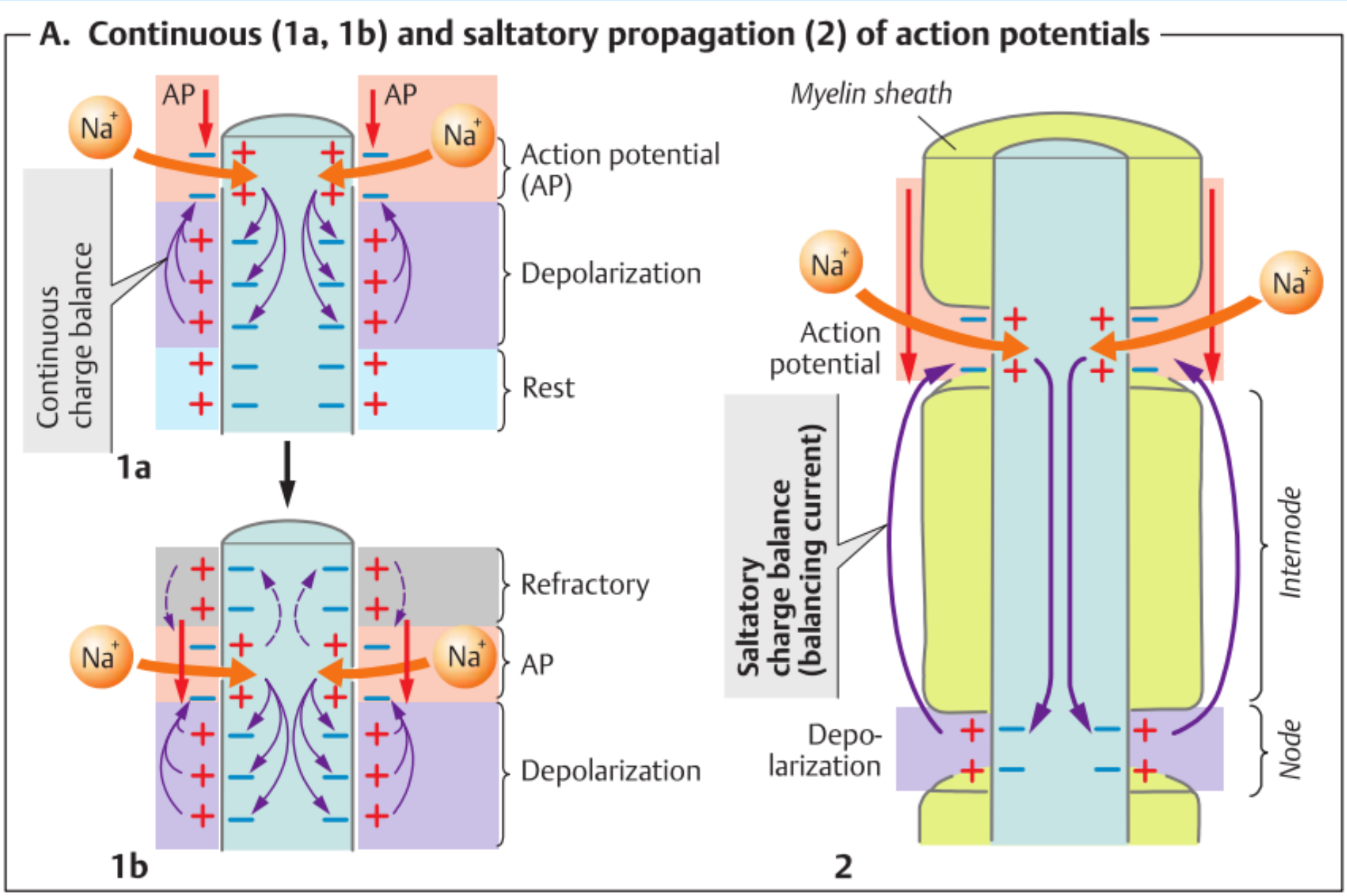
Speed of Impulse Conduction

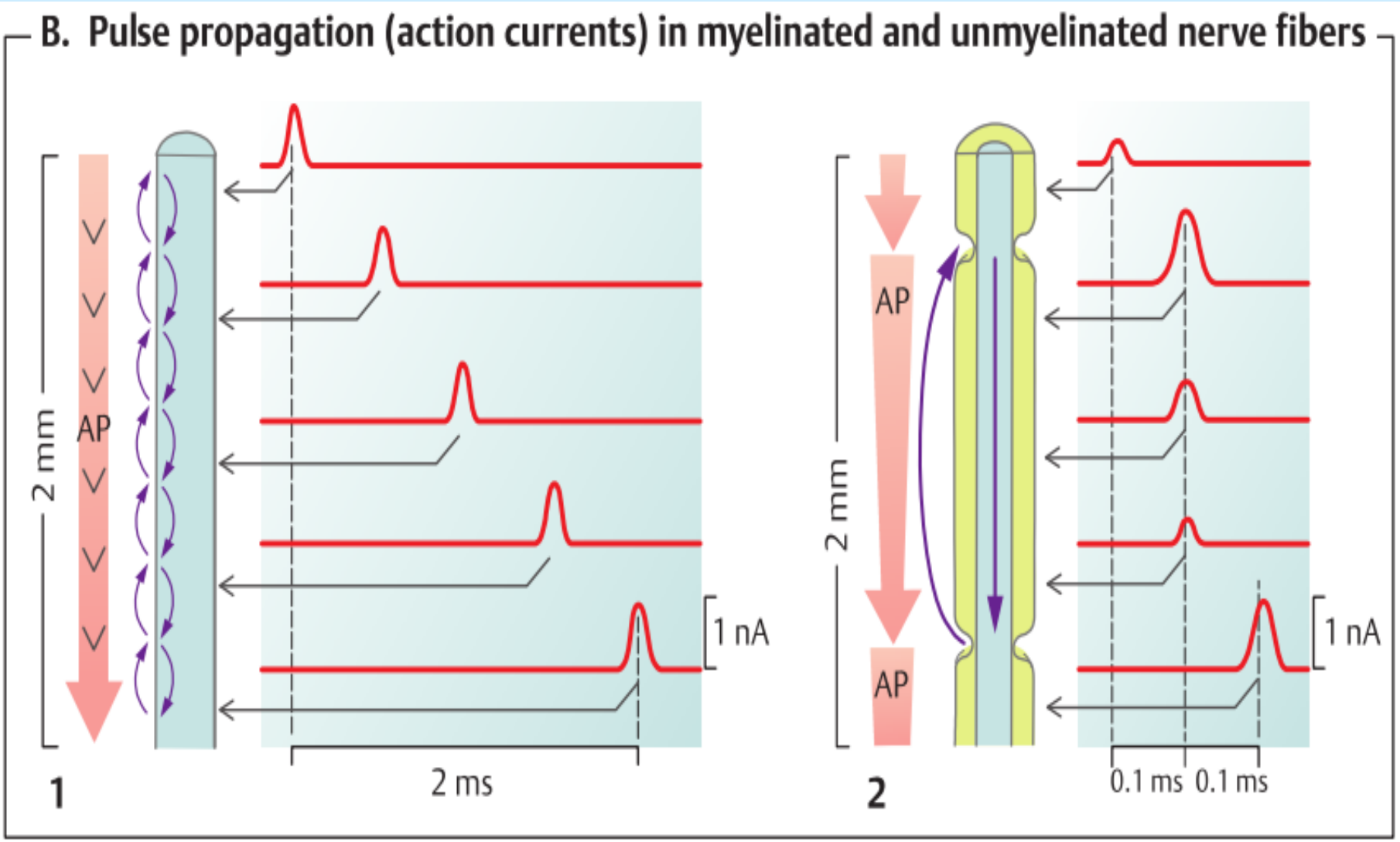
Large diameter fibers (5 to 20 μm) conduct impulses at speeds greater than smaller fibers.

Presence of myelin increases conduction velocity - up to 12 to 120 m/s versus 0.5 to 2 m/s for unmyelinated fibers.

Continuous conduction




A. Continuous (1a, 1b) and saltatory propagation (2) of action potentials
AP
AP
Na+
Na+
Action potential (AP)
Depolarization
Rest
Continuous charge balance
1a
Refractory
AP
Depolarization
1b
Myelin sheath
Action potential
Saltatory charge balance (balancing current)
Depo-larization
Internode
Node
2


B. Pulse propagation (action currents) in myelinated and unmyelinated nerve fibers
2 mm
AP
1 nA
2 ms
1
AP
AP
2 mm
1 nA
0.1 ms 0.1 ms
2

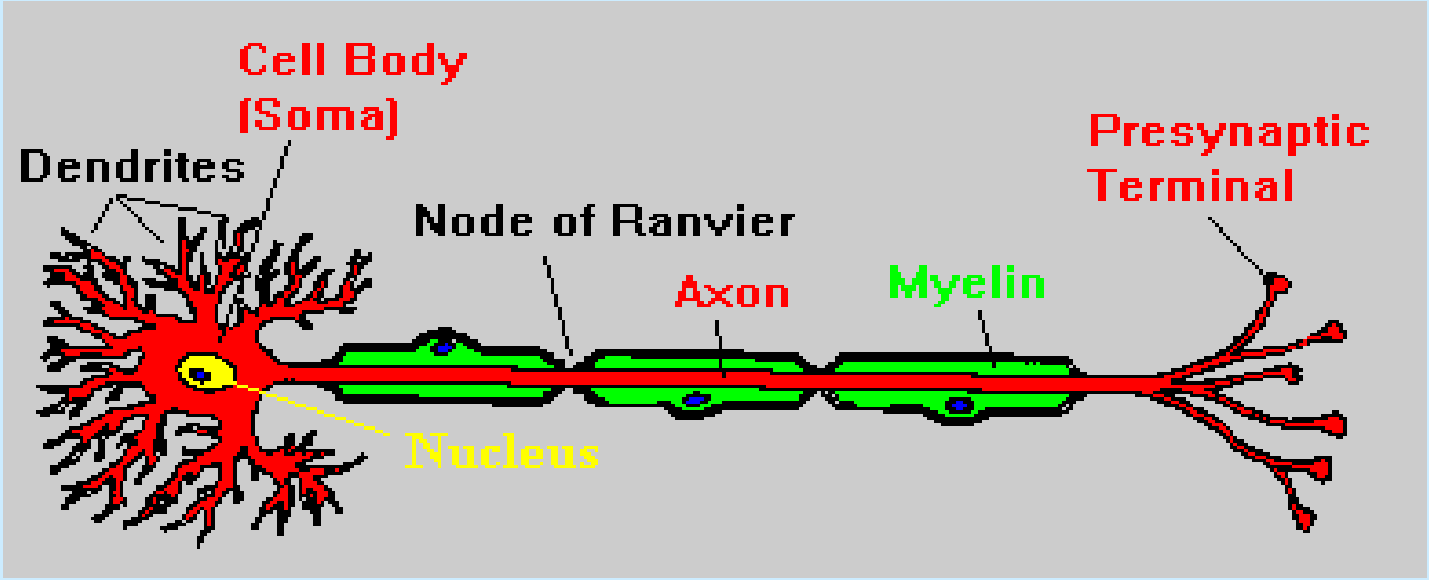
C. Classification of nerve fibers (in humans)

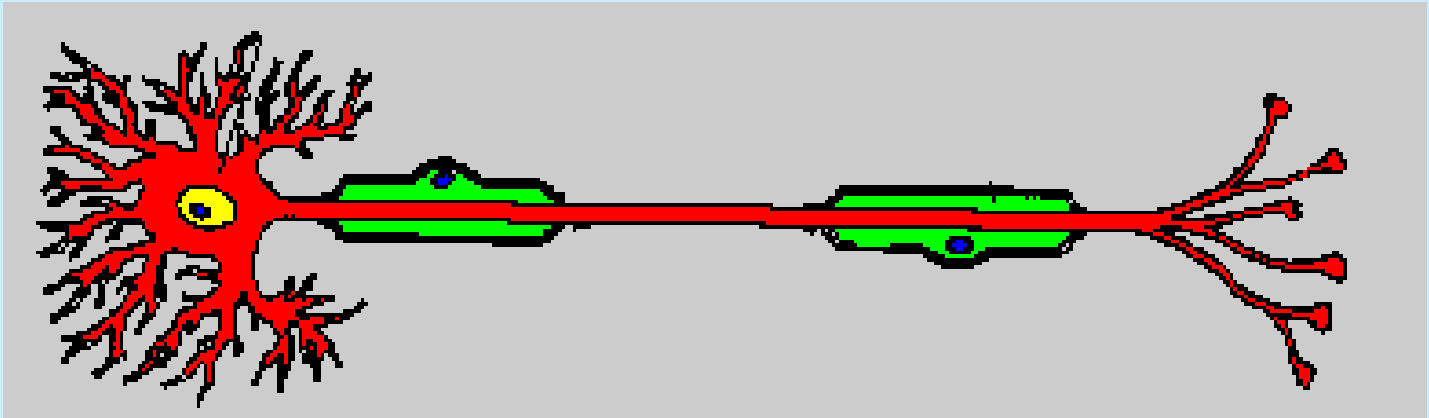
Fiber type	Function according to fiber type (Lloyd and Hunt types I – IV)	Diameter (µm)	Conduction rate (m/s)
Aα	Skeletal muscle efferent, afferents in muscle spindles (Ib) and tendon organs (Ib)	11 – 16	60 – 80
Aβ	Mechanoafferents of skin (II)	6 –11	30 – 60
Aγ	Muscle spindle efferents	1 – 6	2 – 30
Aδ	Skin afferents (temperature and "fast" pain) (III)		
B	Sympathetic preganglionic; visceral afferents	3	3 – 15
C	Skin afferents ("slow" pain) (IV); sympathetic postganglionic afferents	0.5 –1.5 (unmyelinated)	0.25 – 1.5

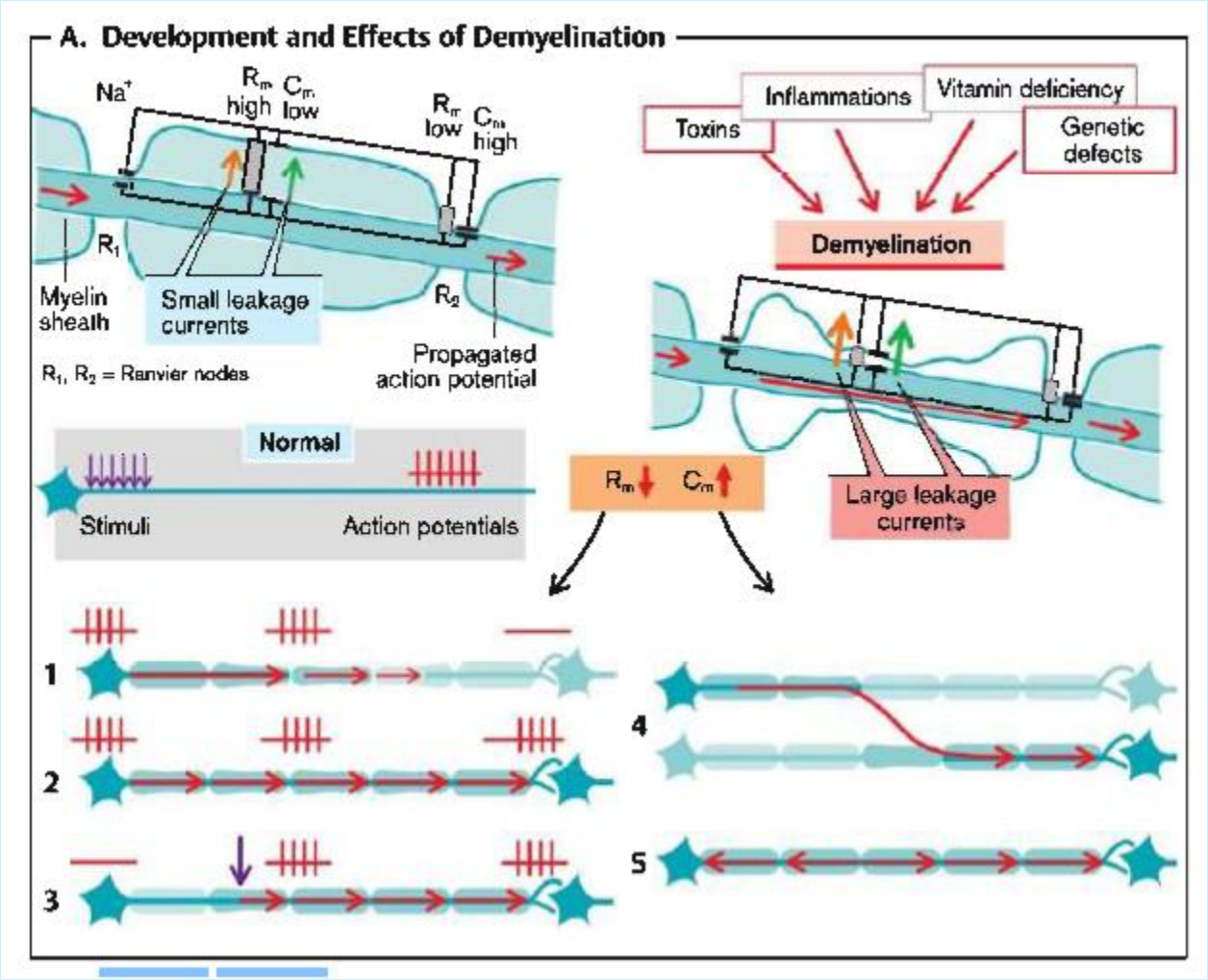
(After Erlanger and Gasser)

Note that the ratio between speed and diameter is about 6

Pathophysiology: In some diseases, known as **demyelinating disorders,** the myelin sheath deteriorates and may be lost over one or more inter-nodes of many axons without interruption of the axons. In such cases, conduction of nerve impulses may be slowed or blocked, and the function of the affected axons is therefore abnormal.






A. Development and Effects of Demyelination
Na+
Rm high Cm low
Rm low Cm high
R1
Myelin sheath
Small leakage currents
R2
Propagated action potential
R1, R2 = Ranvier nodes
Toxins
Inflammations
Vitamin deficiency
Genetic defects
Demyelination
Normal
Stimuli
Action potentials
Rm Cm
Large leakage currents
1
2
3
4
5

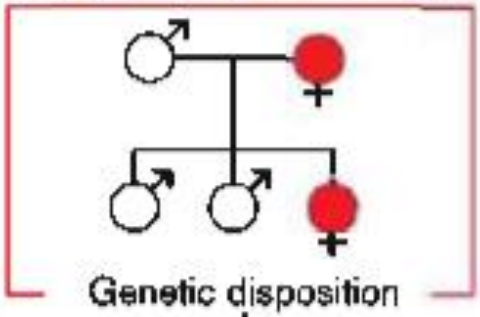
Pathophysiology -

Such demyelination occurs in the peripheral nervous system in the **Guillain-Barre syndrome** and in **diphtheria.** The neuropathy common in severe cases of **diabetes mellitus** is due to demyelination of peripheral axons.

When myelin is lost, the length constant, which is dramatically increased by myelination, becomes much shorter. Hence when the action potential is electrotonically conducted from one node of Ranvier to the next, it loses amplitude. If demyelination is sufficiently severe, the action potential may arrive at the next node of Ranvier with insufficient strength to fire an action potential. The axon will then fail to propagate action potentials.

An important demyelinating disease of the central nervous system is **multiple sclerosis,** where scattered progressive demyelination of axons in the CNS results in loss of motor control and sensory function.

B. Multiple Sclerosis



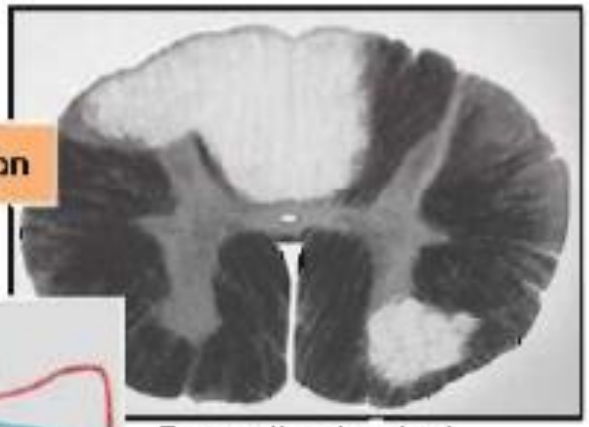
Genetic disposition

Autoimmune disease, possibly caused by viruses

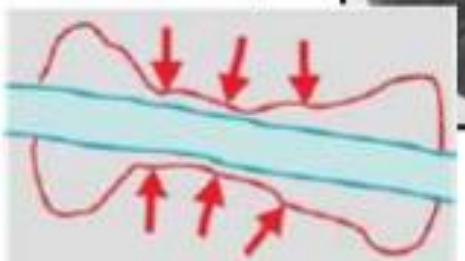
?

MHC
IL-2 rec.
IL-7 rec.

Inflammation



Demyelinating foci in spinal cord (after Netter)

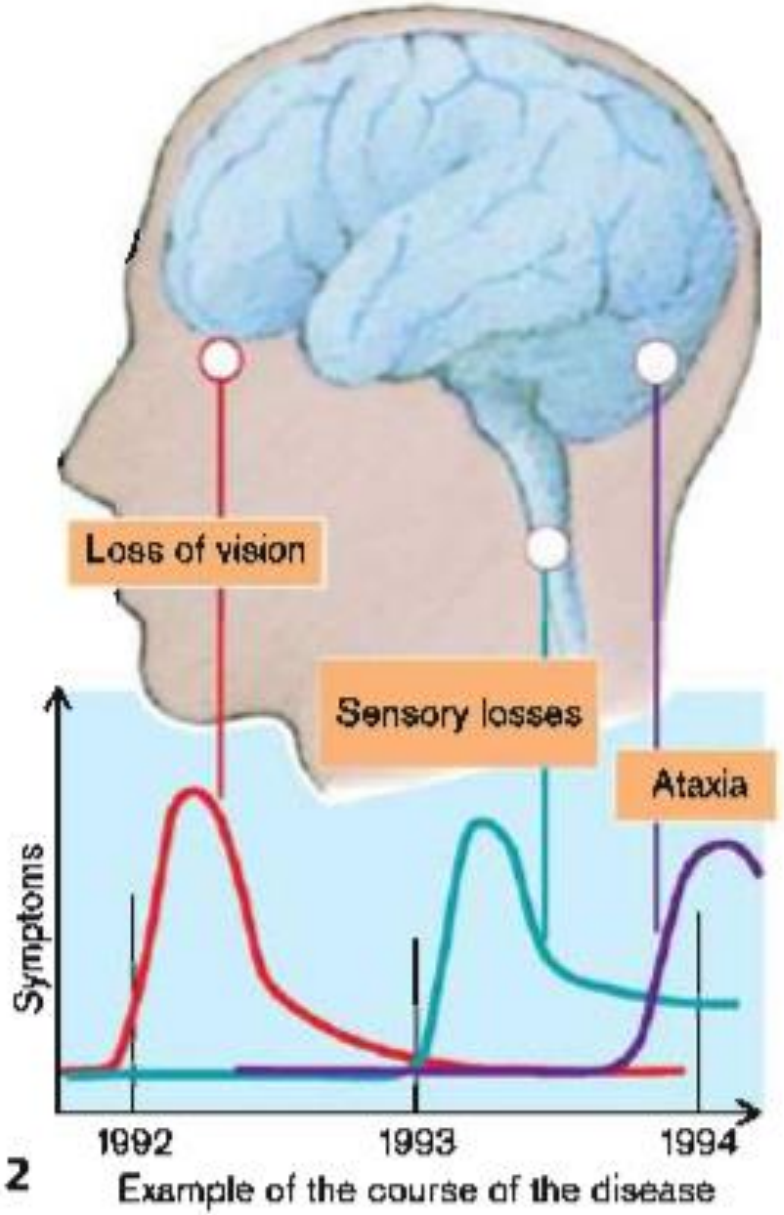


Demyelination in CNS

Multiple sclerosis

periodically recurrent neuronal losses

1

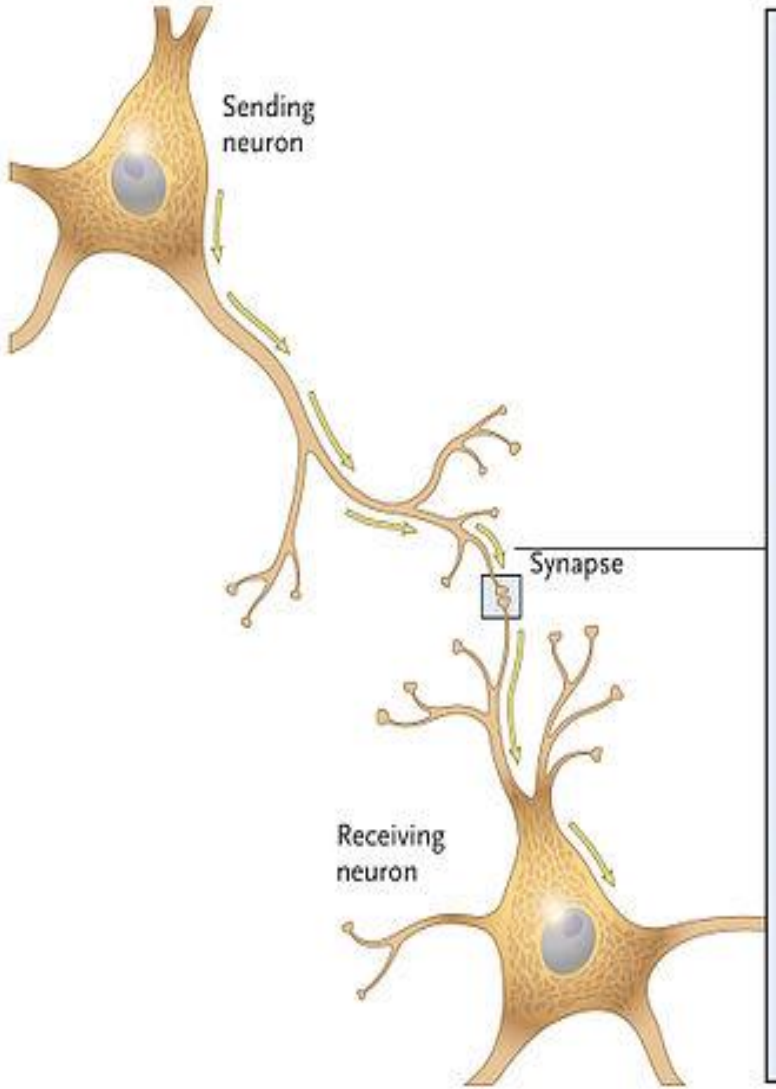


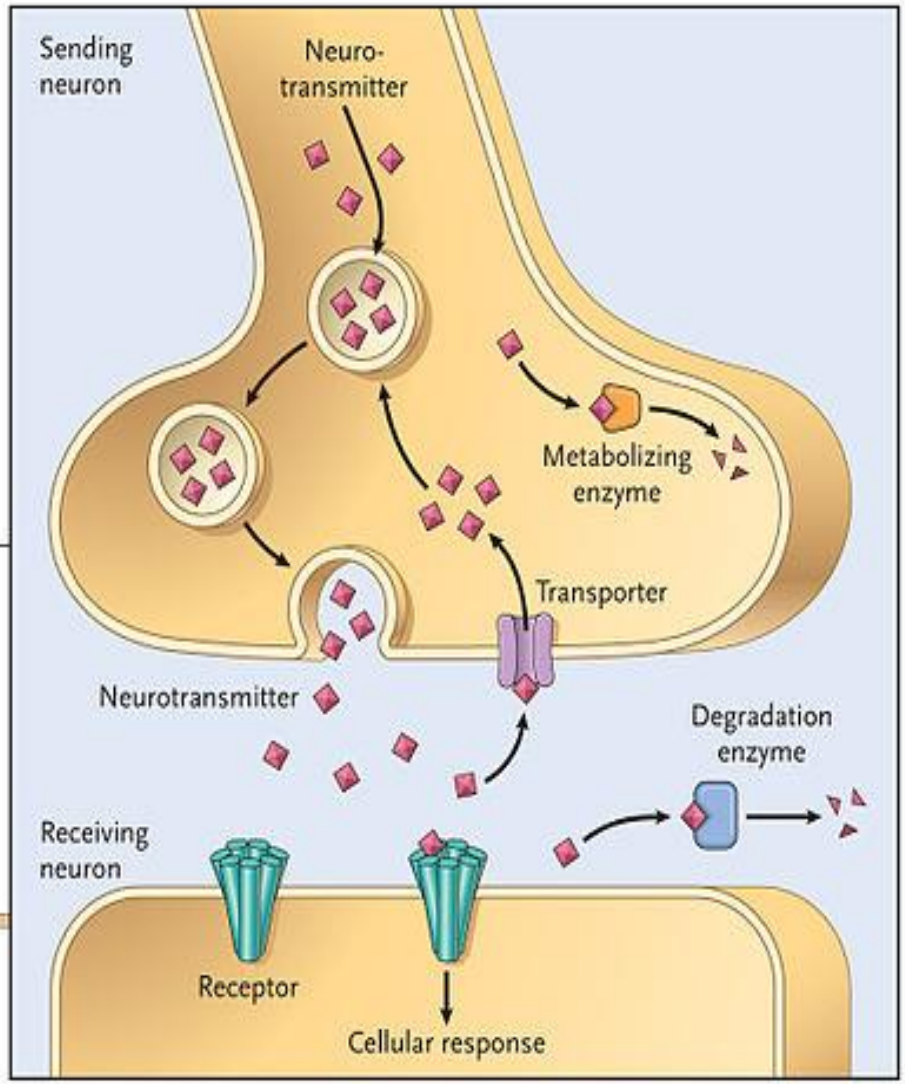
2 Example of the course of the disease

IN PRACTICE

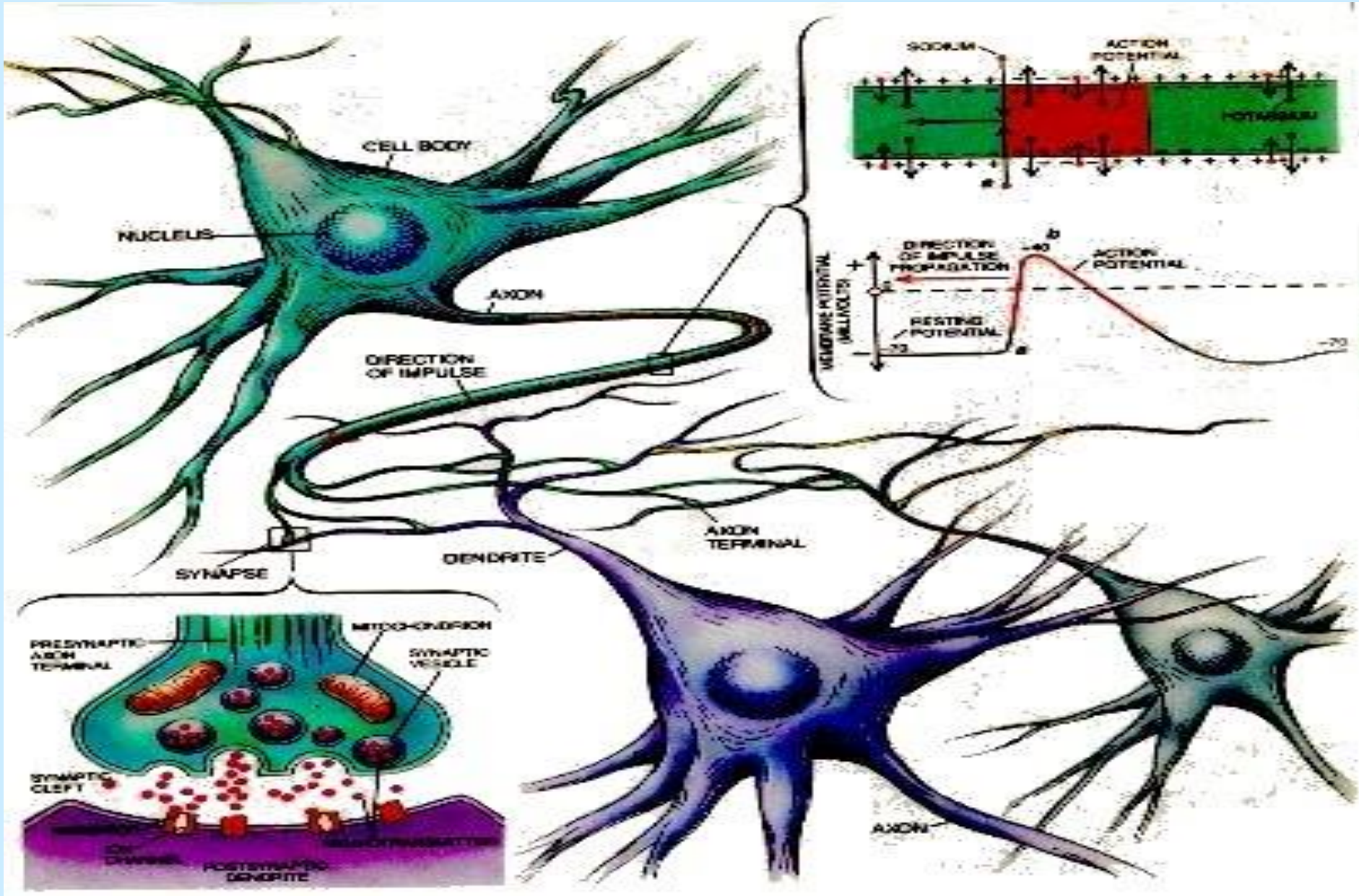
- How can we experimentally excite a neuron?
- How can we measure the conduction velocity of an axon or a nerve ?
- How fast can this be?
- What conditions may lead to accidental electrification? [low contact resistance with high voltage low frequency AC. ACDC only with stimulus ON and OFF.]
- What would be the main risk to our health? [ventricular fibrillation in heart]
- How does diathermy work? [with high frequency AC (>15 Hz)]

SYNAPTIC TRANSMISSION

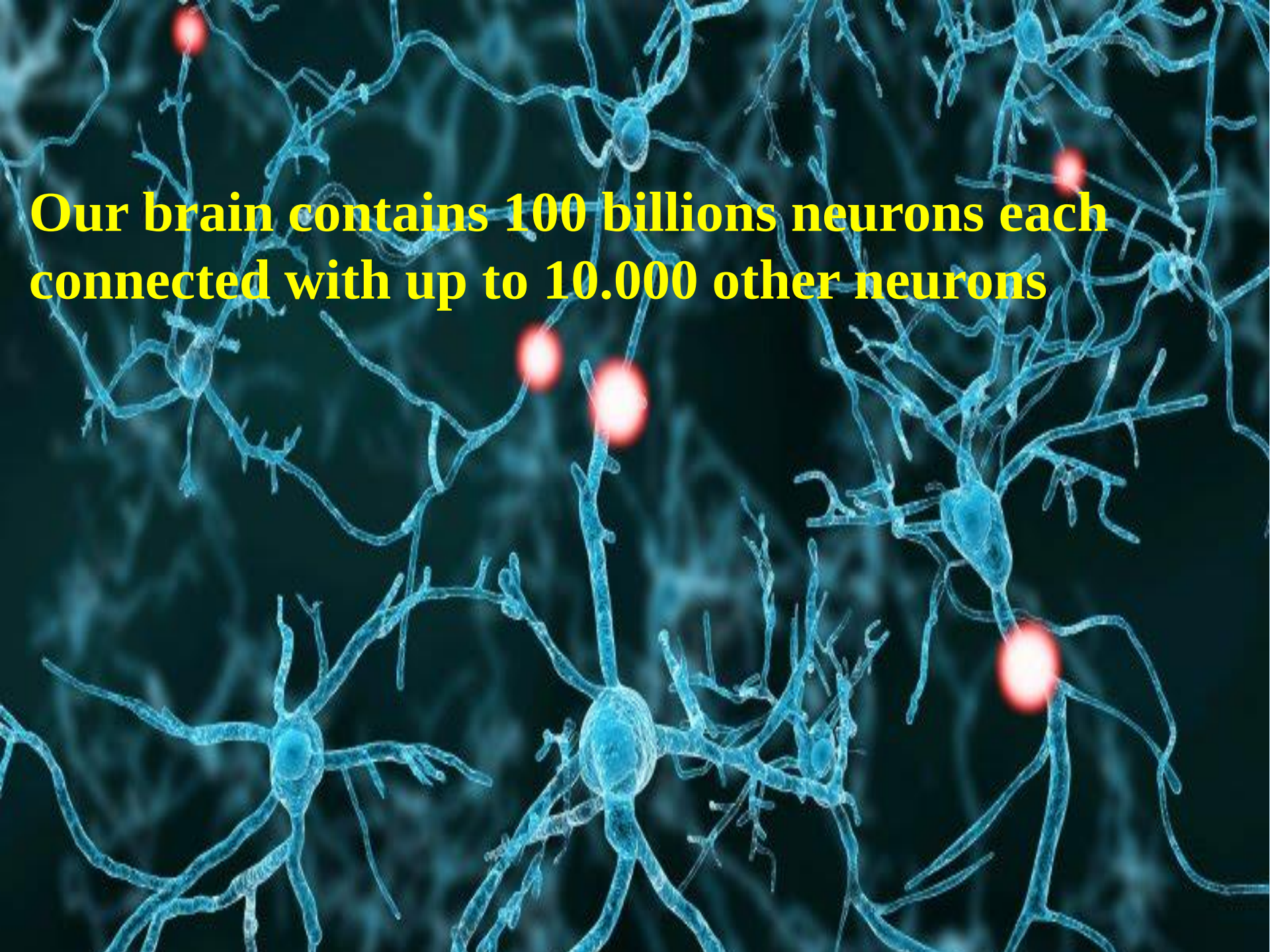




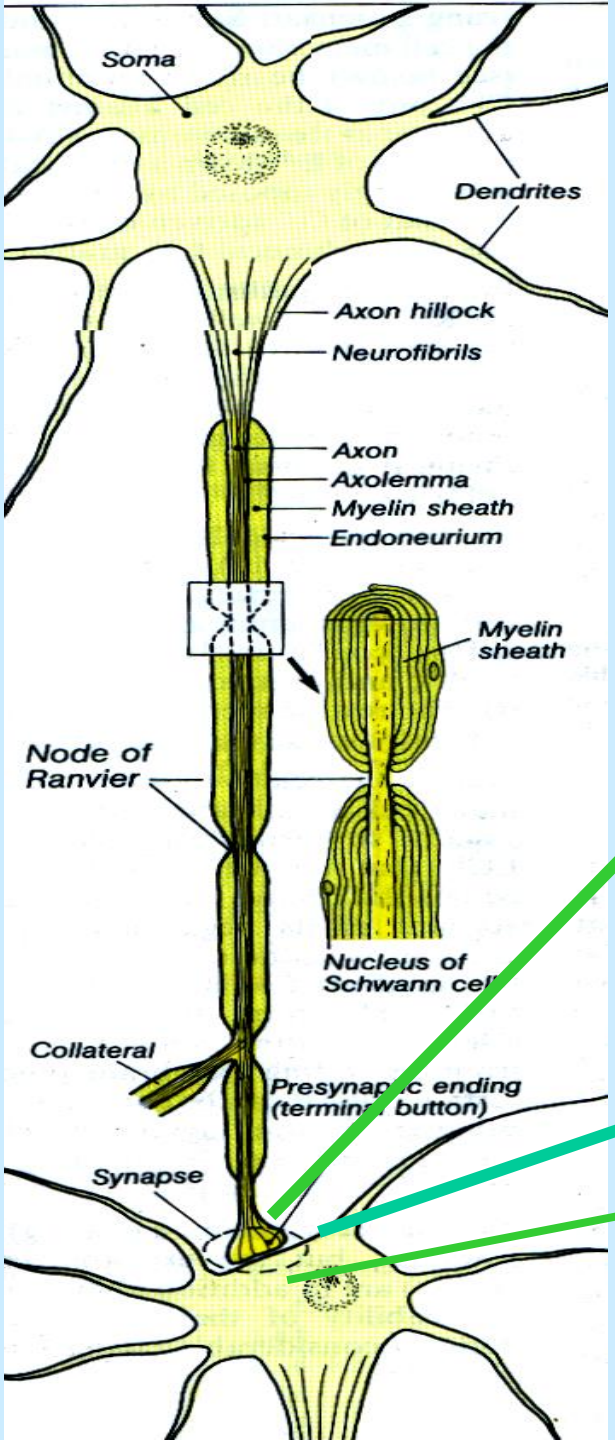
ACTION POTENTIAL CONDUCTION

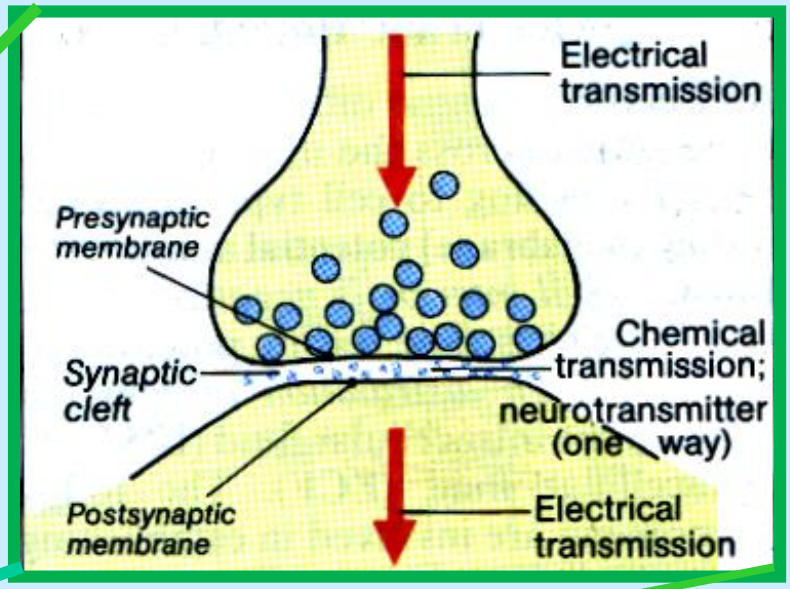


SYNAPTIC TRANSMISSION


Our brain contains 100 billions neurons each connected with up to 10.000 other neurons

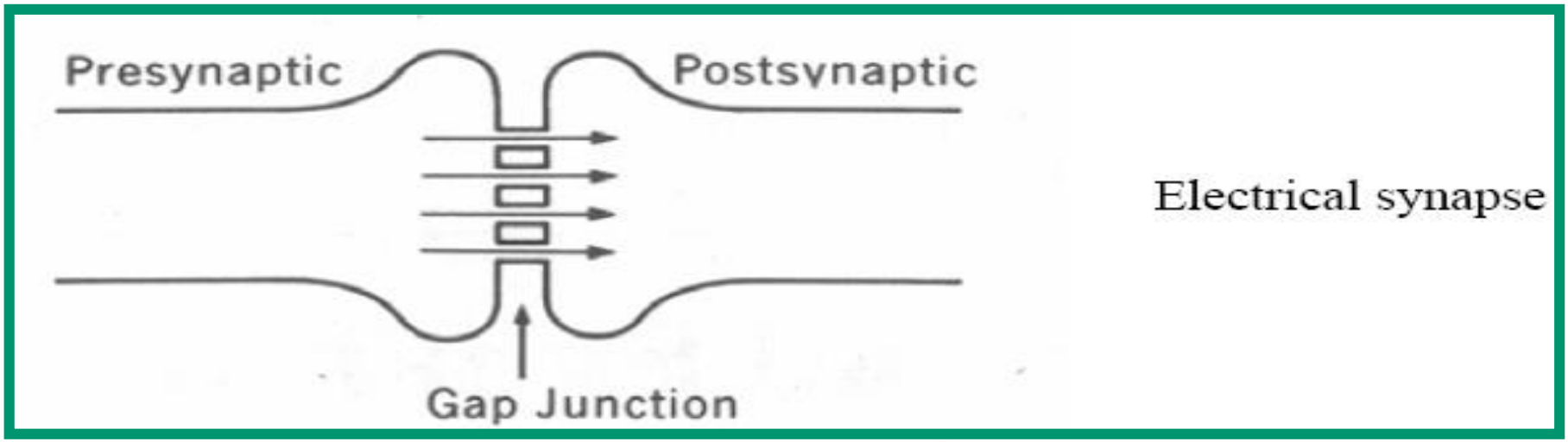
Synaptic transmission



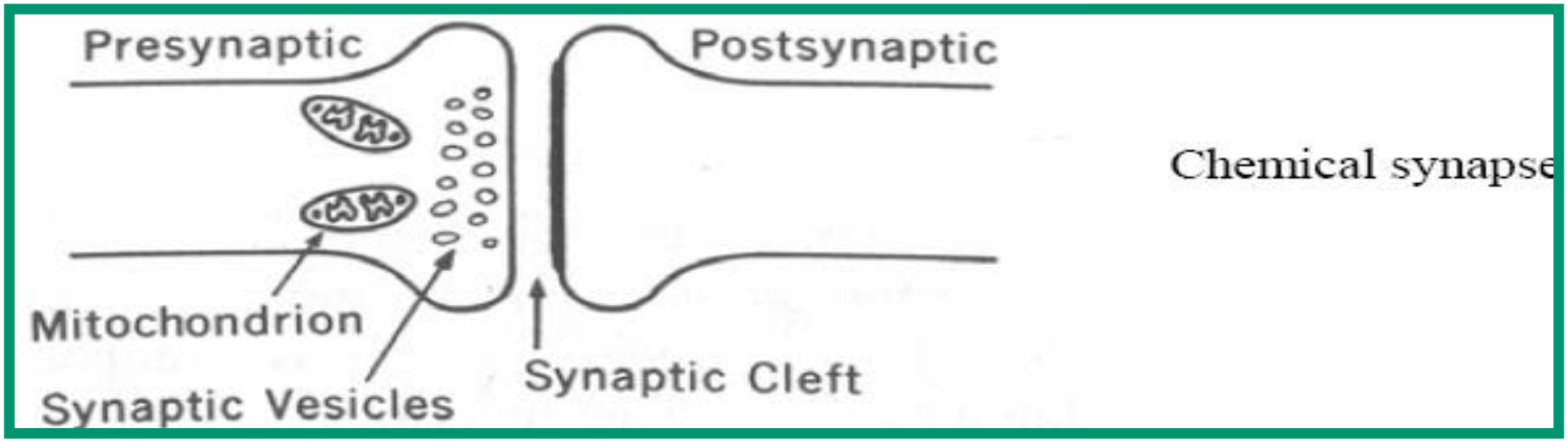


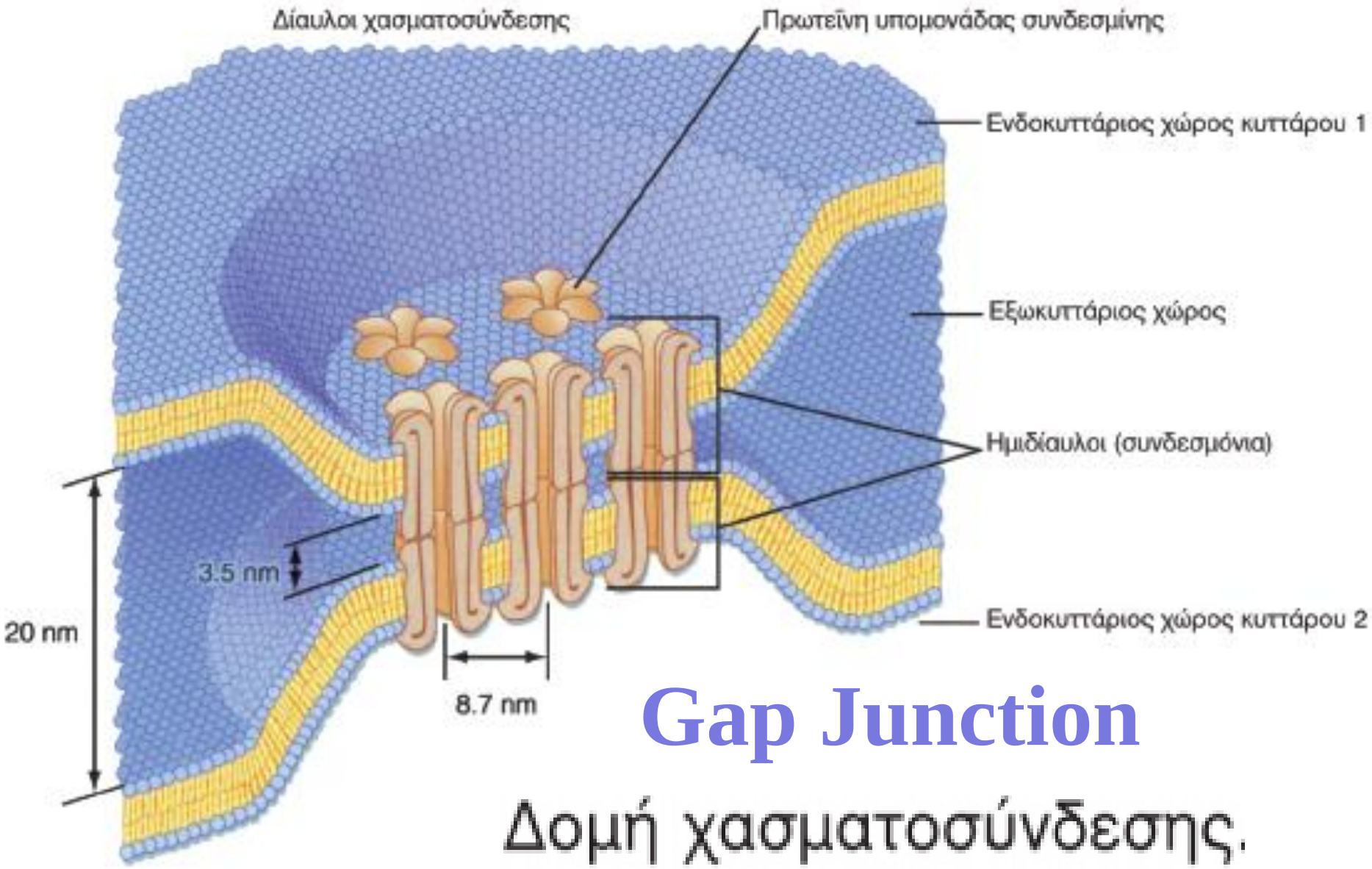
Synaptic transmission can be either electrical or (most often) chemical

A



B





Gap Junction

Δομή χασματοσύνδεσης.

Synaptic transmission – chemical ST

When action potential reaches the synaptic knob, it causes synaptic vesicles to release a **neurotransmitte**r.

Neurotransmitter diffuses across **synaptic cleft** (~25nm) at synapse **(neuroeffector junctio**n) and binds with receptors on post-synaptic membrane (another neuron, muscle cell, or gland cell).

Neurotransmitters are of 3 types:

- small molecules: amines and aminocids:

ACh - released at **cholinergic synapse**s. Common inside and outside CNS. Include neuromuscular junction.

Norepinephrine (NE) - important in brain and in portions of autonomic nervous system. Also called **noradrenalin**e. **Adrenergic synapse**s.

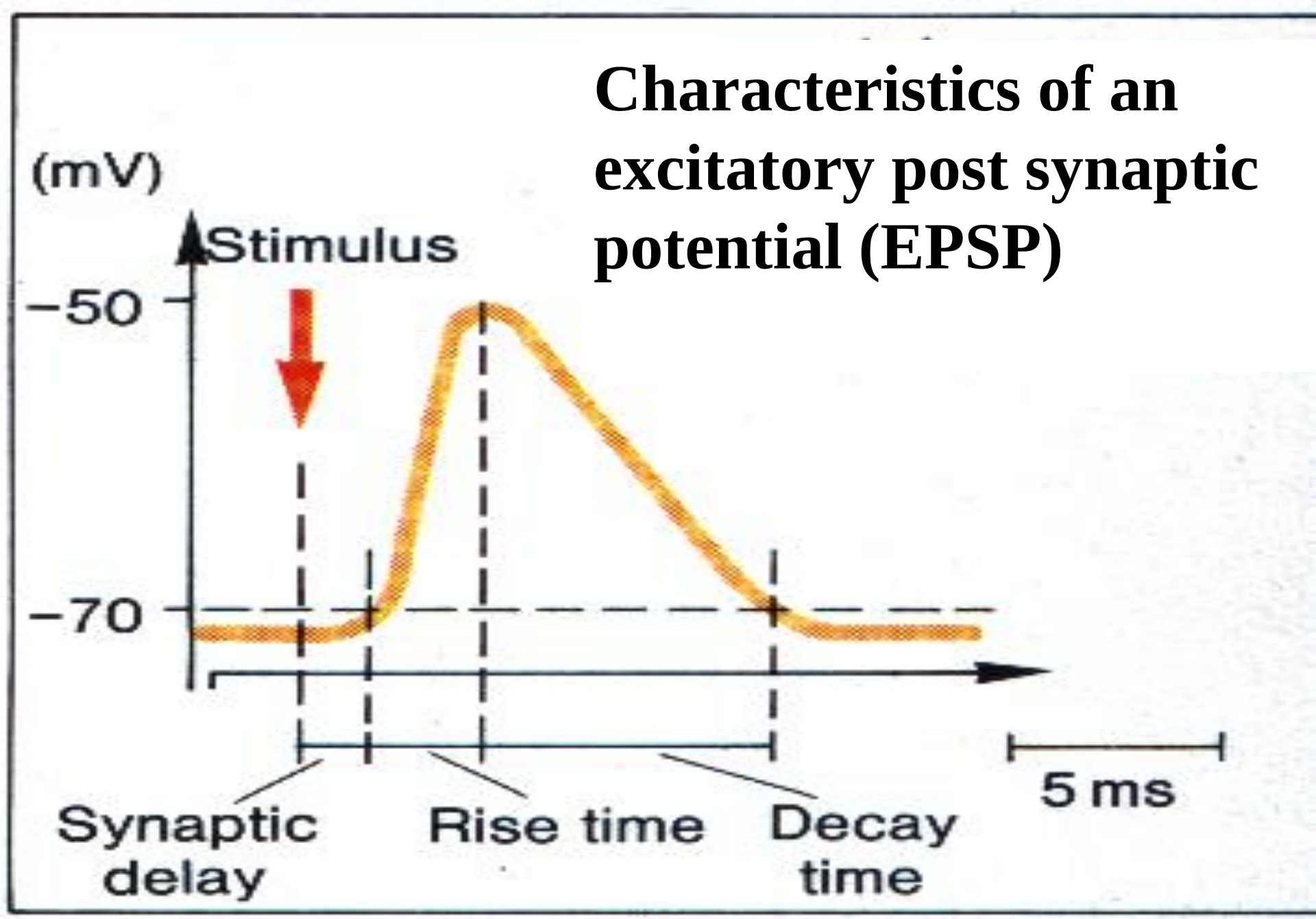
Others: **dopamin**e, **gamma aminobutyric acid (GABA**), **glycine** and **serotoni**n usually act as inhibitors. **Glutamate** and **aspartate** usually in excitatory synapses

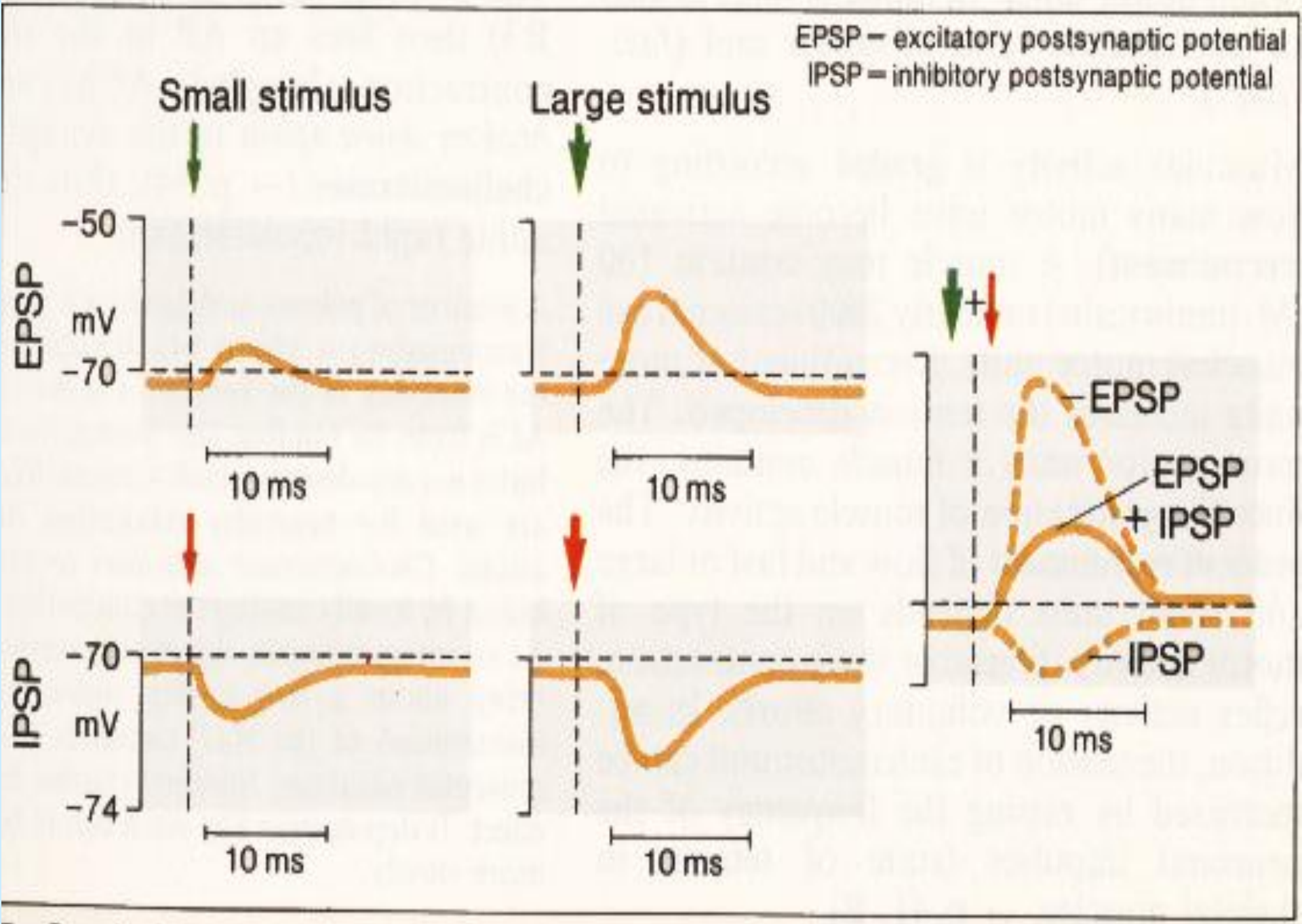
- Peptides
- Gases

3 types of neurotransmitter receptors:

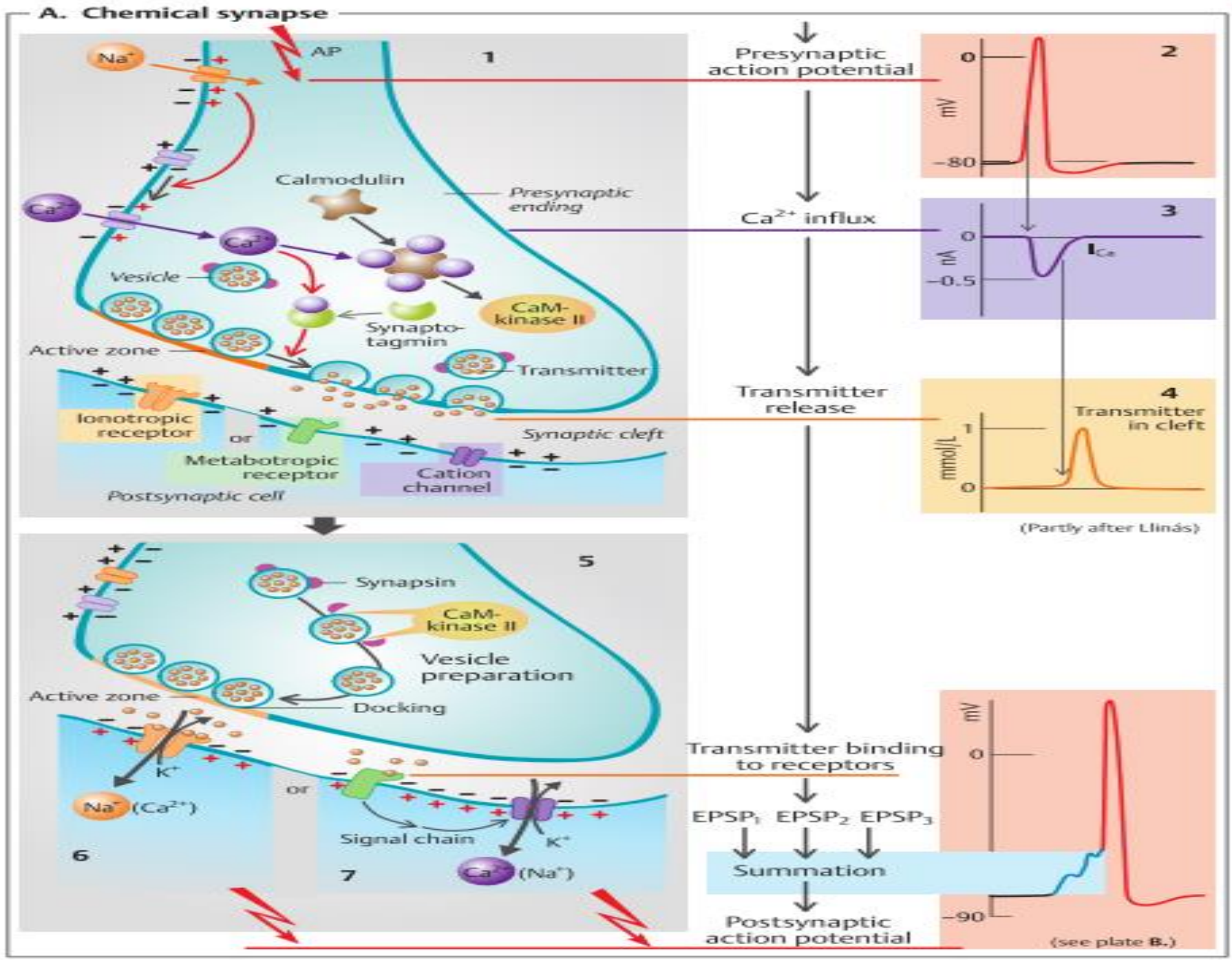
Ionotropic and metabolotropic

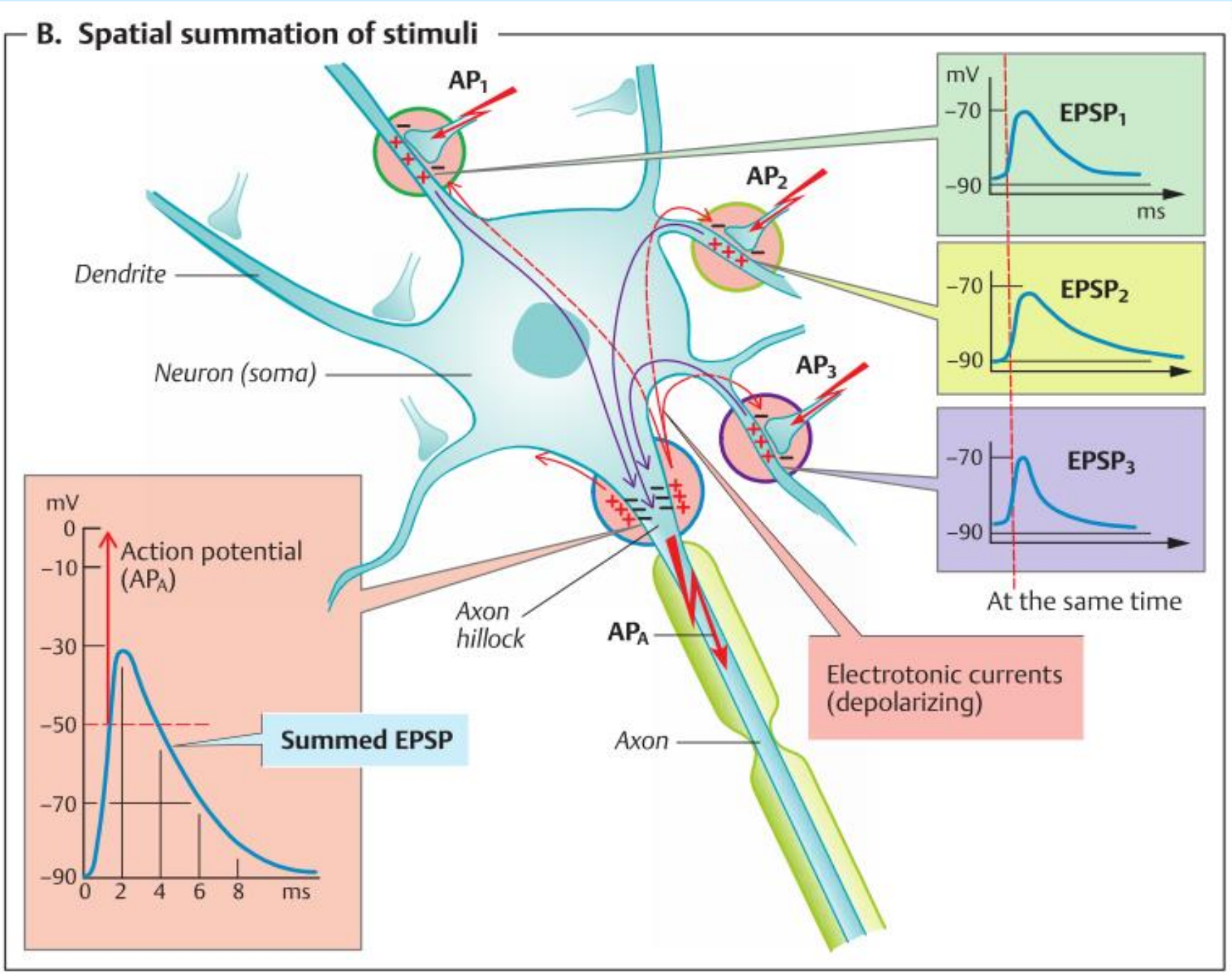
Characteristics of an excitatory post synaptic potential (EPSP)



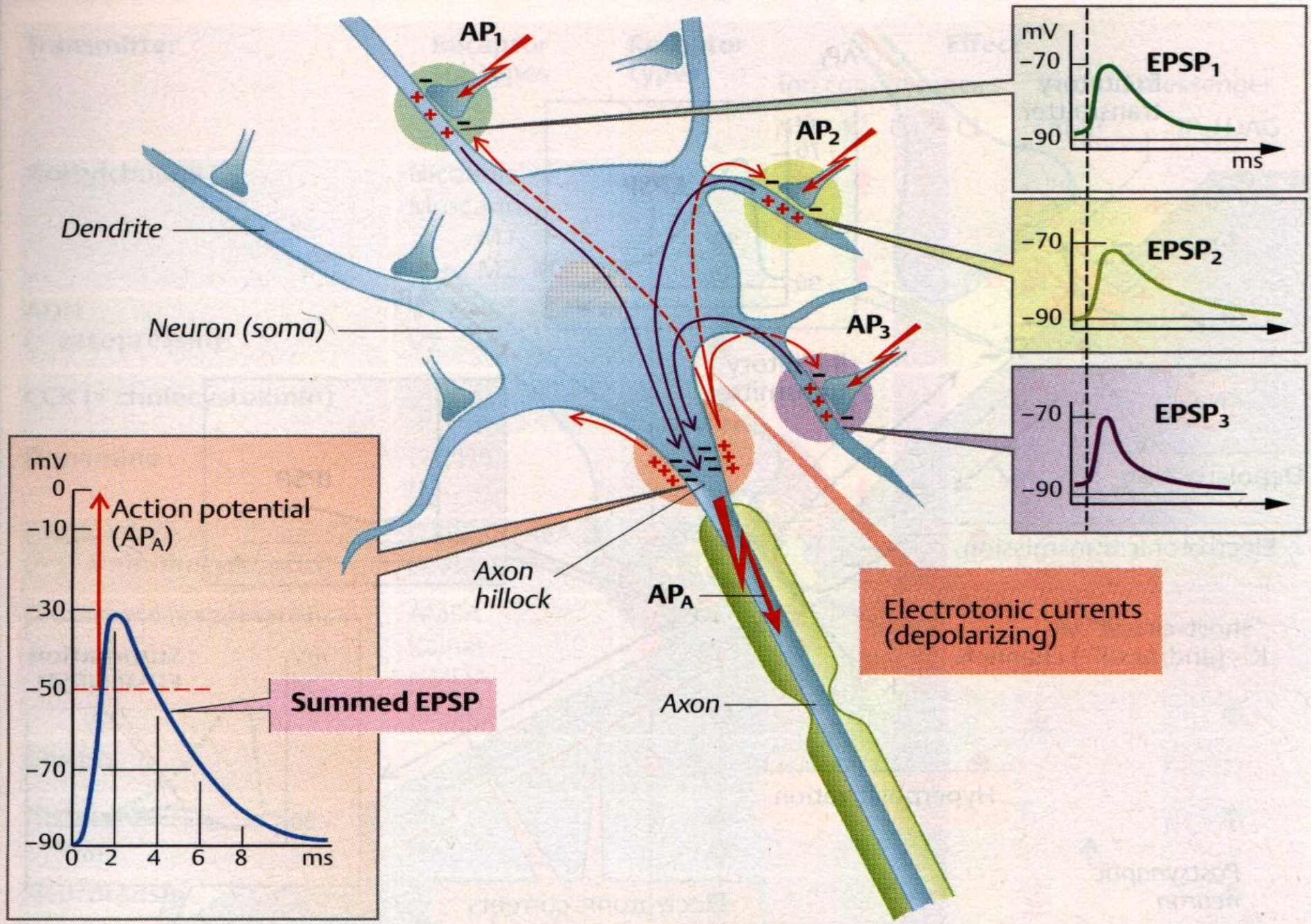


D. Graded response of EPSP and IPSP to stimuli

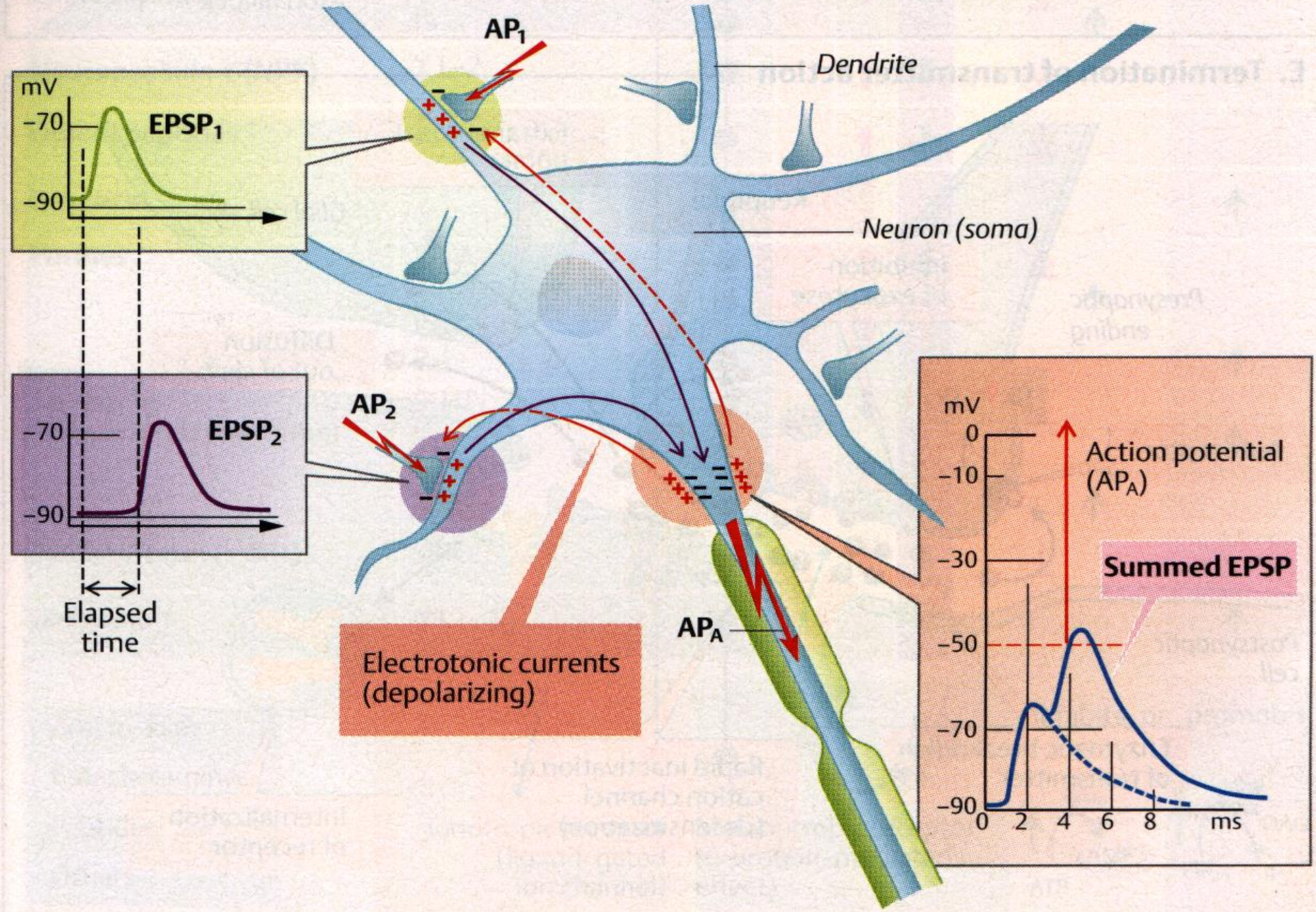

A. Chemical synapse
Na+
AP
1
Presynaptic action potential
2
0
mV
−80
Calmodulin
Presynaptic ending
Ca2+
Ca2+ influx
3
0
nA
−0.5
ICa
Vesicle
CaM-kinase II
Synapto-tagmin
Active zone
Transmitter
Transmitter release
4
Transmitter in cleft
mmol/L
1
0
Ionotropic receptor
or
Metabotropic receptor
Synaptic cleft
Cation channel
Postsynaptic cell
(Partly after Llinás)
5
Synapsin
CaM-kinase II
Vesicle preparation
Active zone
Docking
K+
Na+ (Ca2+)
or
Signal chain
K+
Ca2+ (Na+)
6
7
Transmitter binding to receptors
EPSP1 EPSP2 EPSP3
Summation
Postsynaptic action potential
mV
0
−90
(see plate B.)


B. Spatial summation of stimuli
AP1
AP2
AP3
Dendrite
Neuron (soma)
Axon hillock
APA
Axon
mV
-70
-90
ms
EPSP1
EPSP2
EPSP3
At the same time
Electrotonic currents (depolarizing)
mV
0
-10
-30
-50
-70
-90
0 2 4 6 8 ms
Action potential (APA)
Summed EPSP

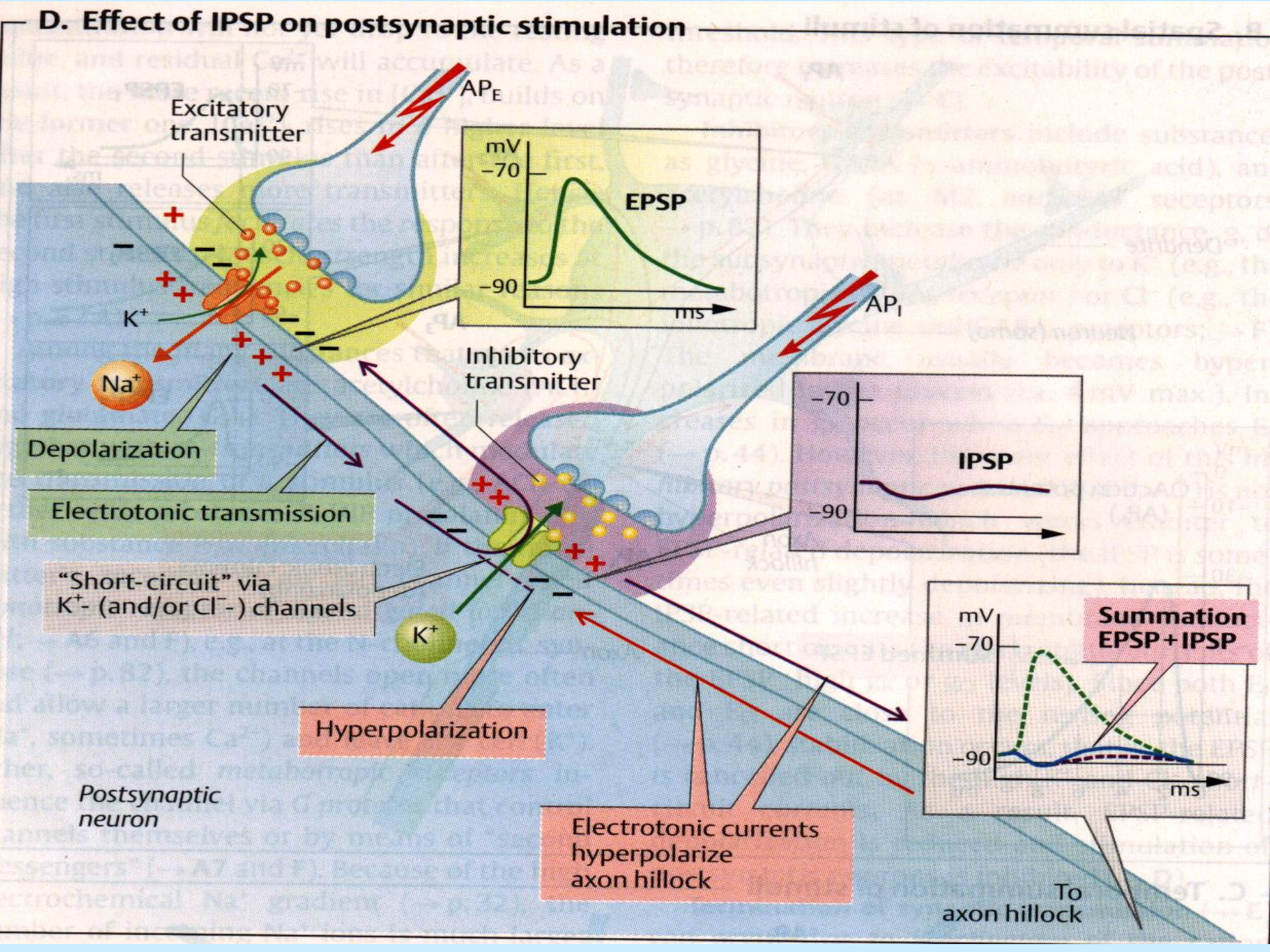
B. Spatial summation of stimuli



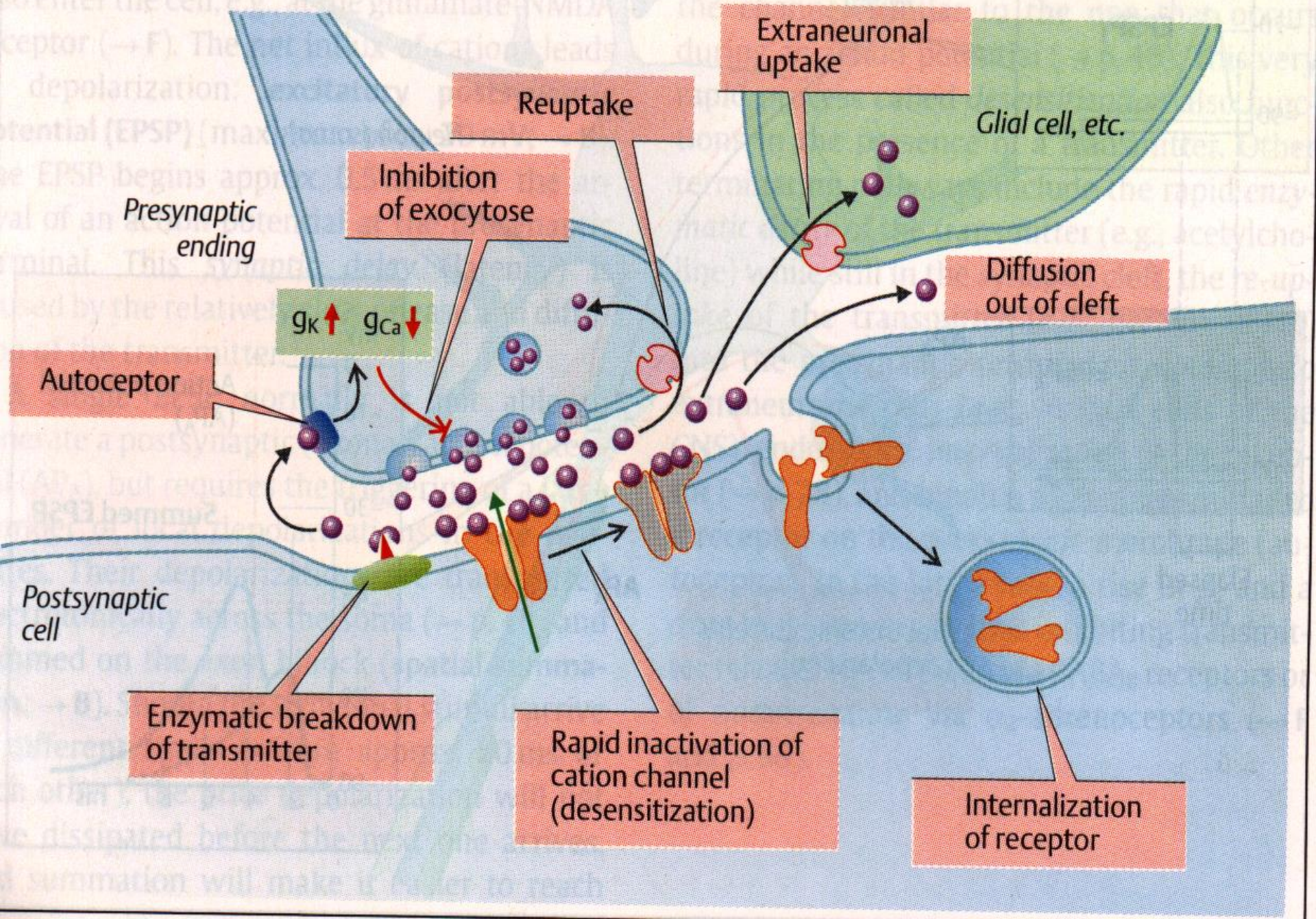
C. Temporal summation of stimuli

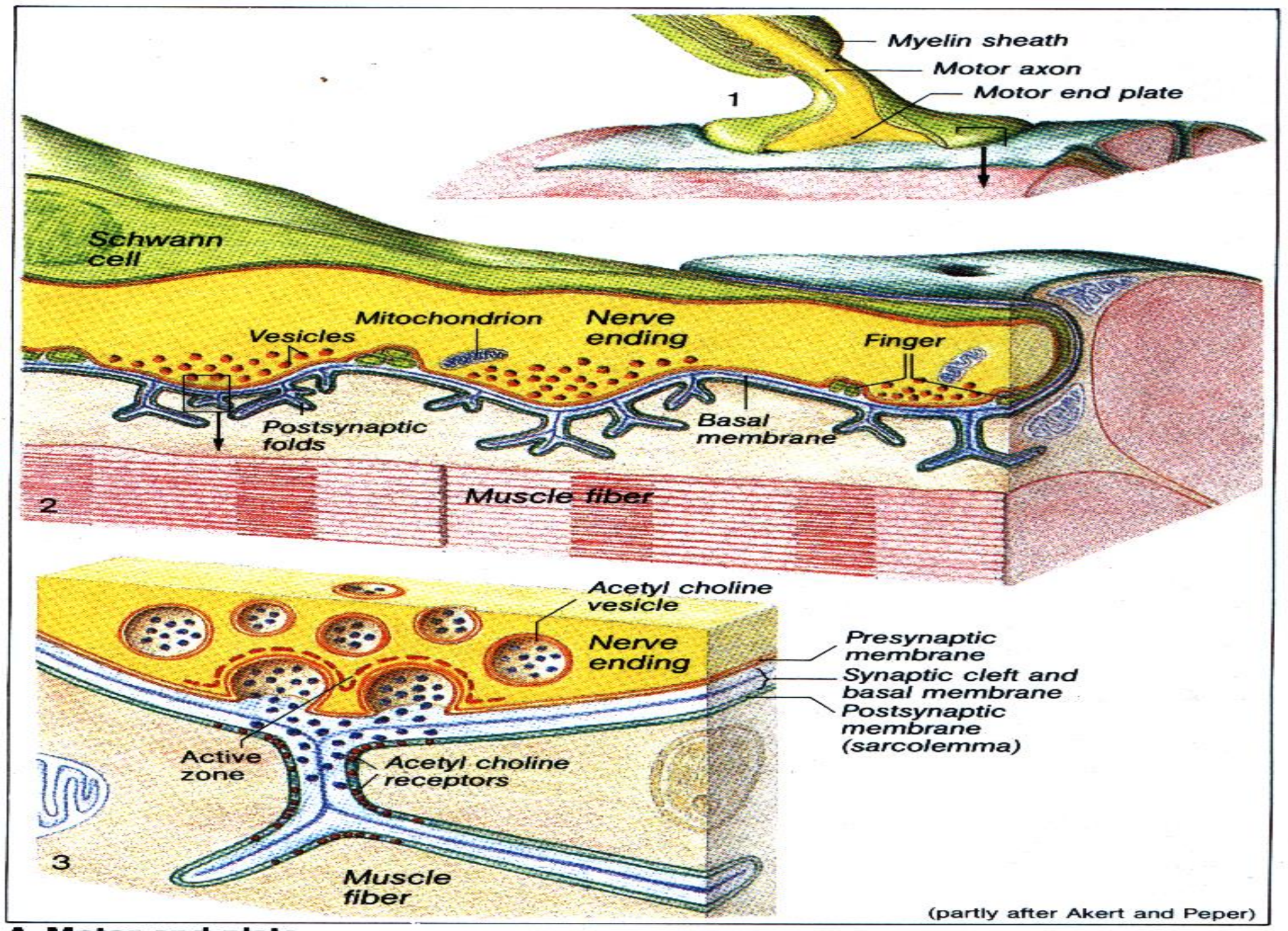


D. Effect of IPSP on postsynaptic stimulation



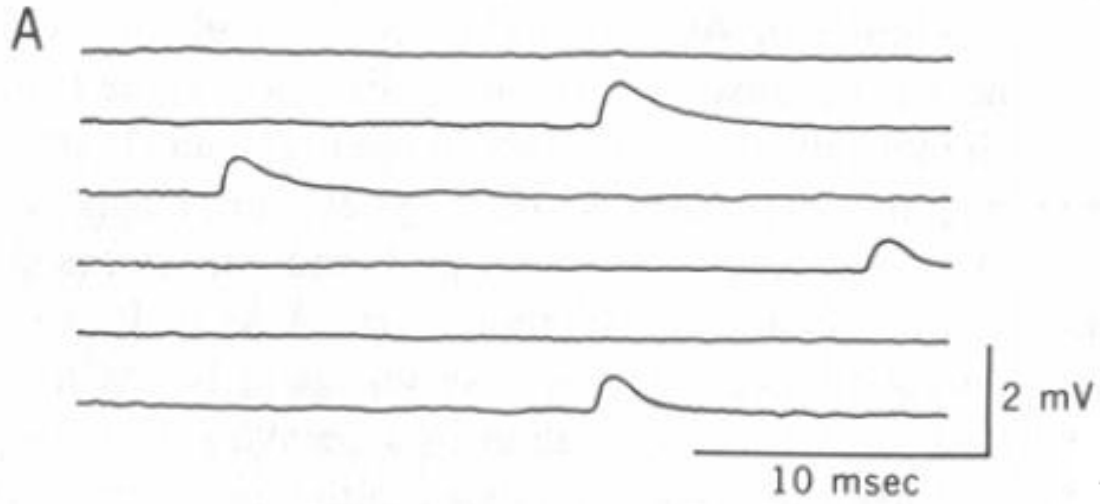
E. Termination of transmitter action





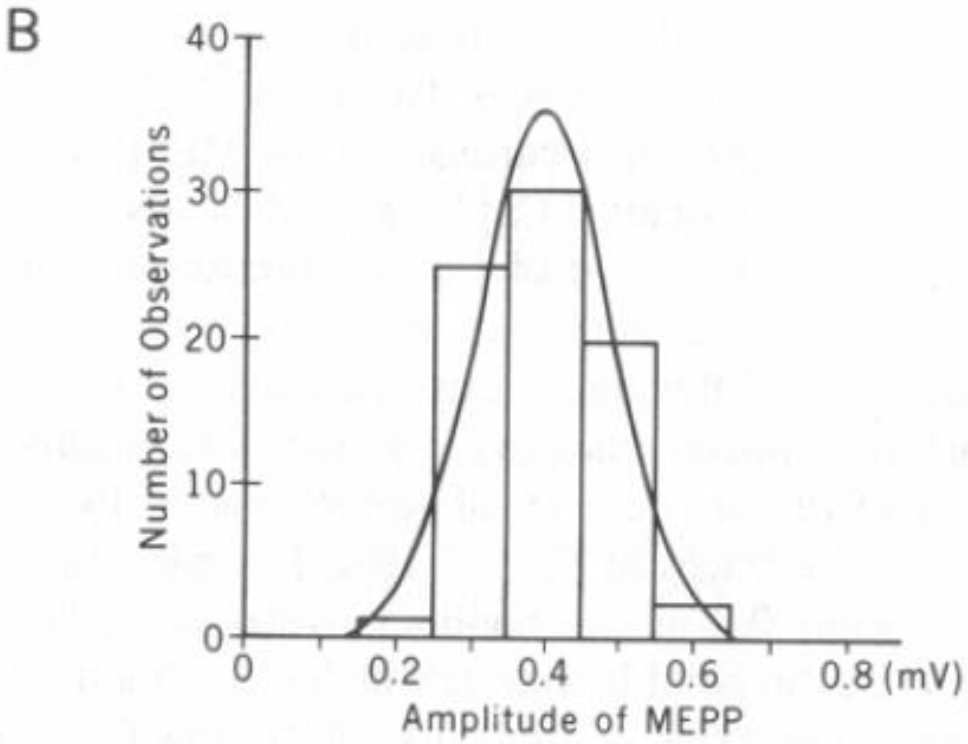
A. Motor end-plate

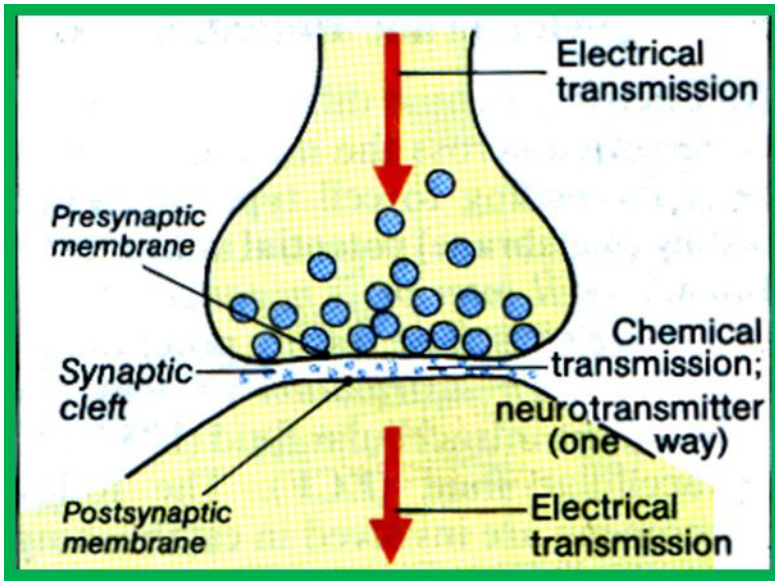
Quantal release of neurotransmitters



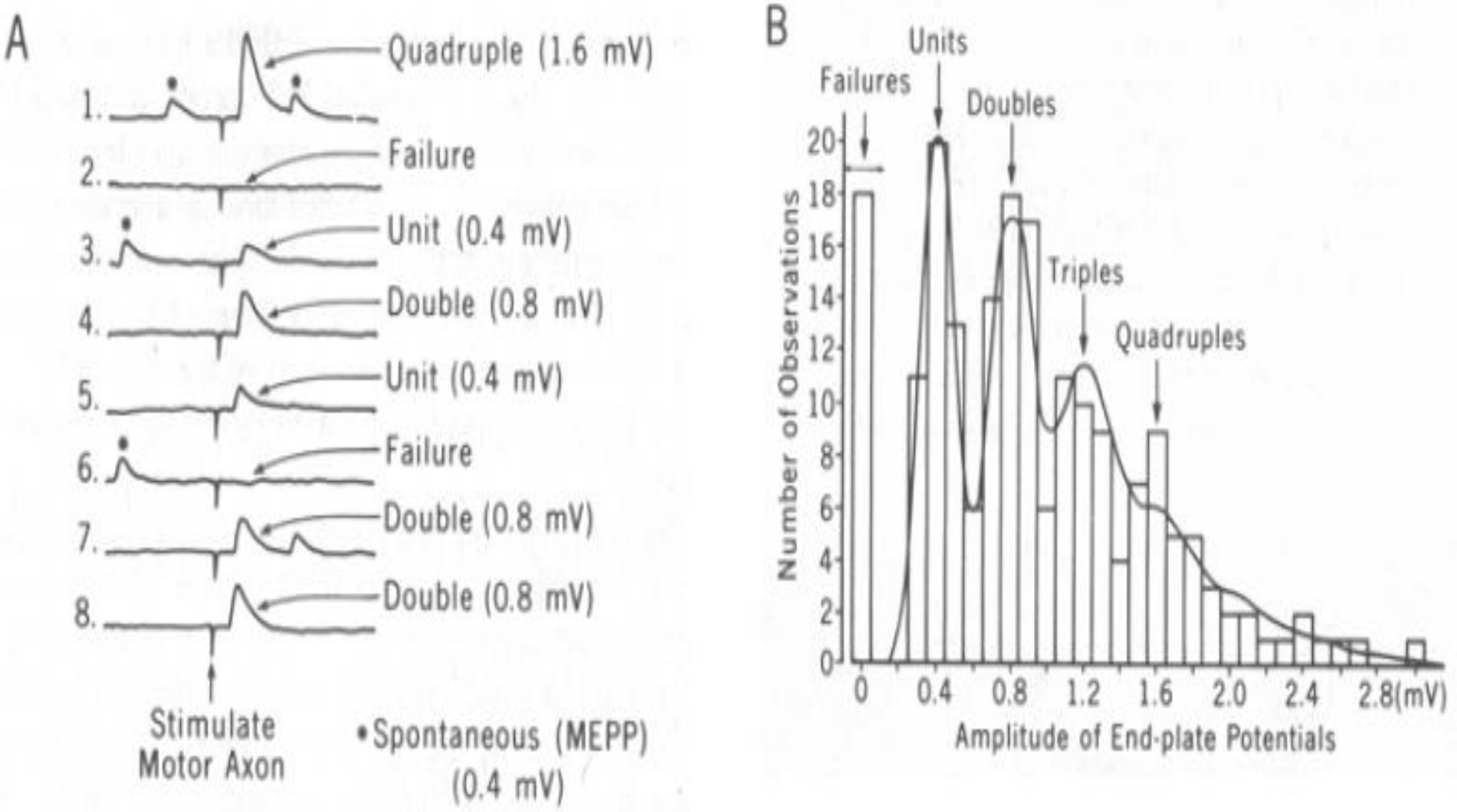
Spontaneous formation of miniature endplate potentials (MEPPs) due to spontaneous activity of nicotinic acetylcholine receptors (nAChR).

Average MEPP is 0.4mV and the result of a single exocytosis event.



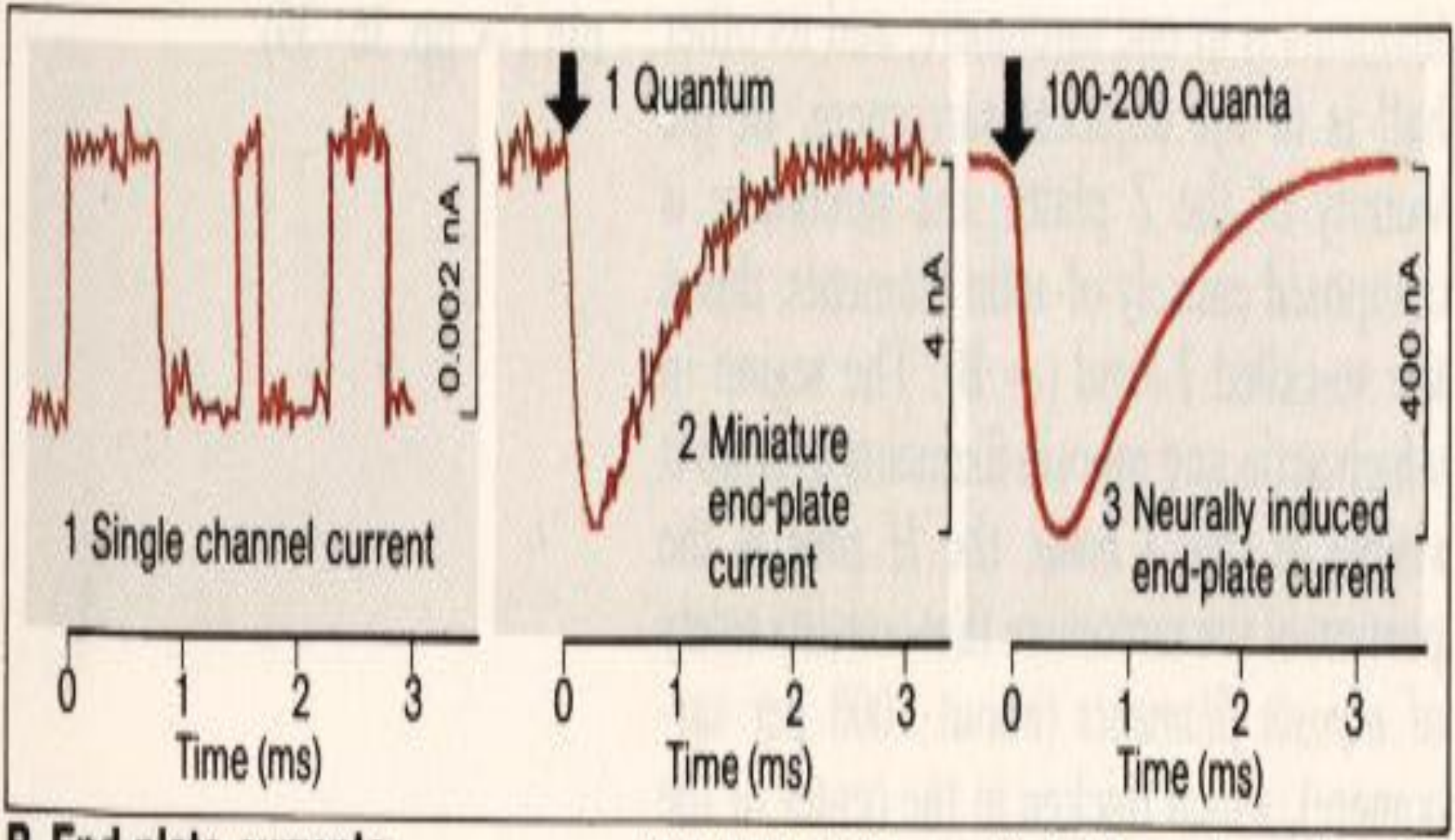


Quantal release of neurotransmitters



Induction

Reduction



B. End-plate currents

(after Neher and Sakmann(1), after Peper and co-workers (2))


ΤΈΛΟΣ