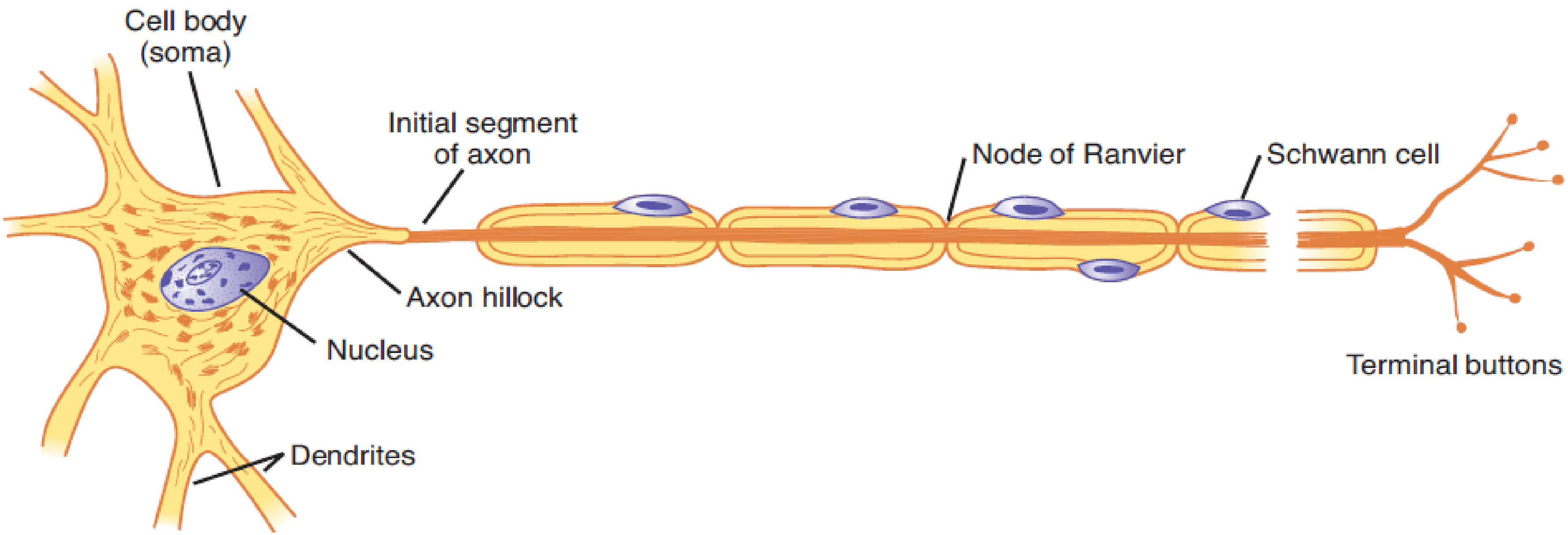
Neurophysiology
- basic principles -

Tutorial II_autumn

Most neurons share a group of traits:

- derive from ectoderm
- four morphological regions – dendrites, body, axon, synaptic terminals



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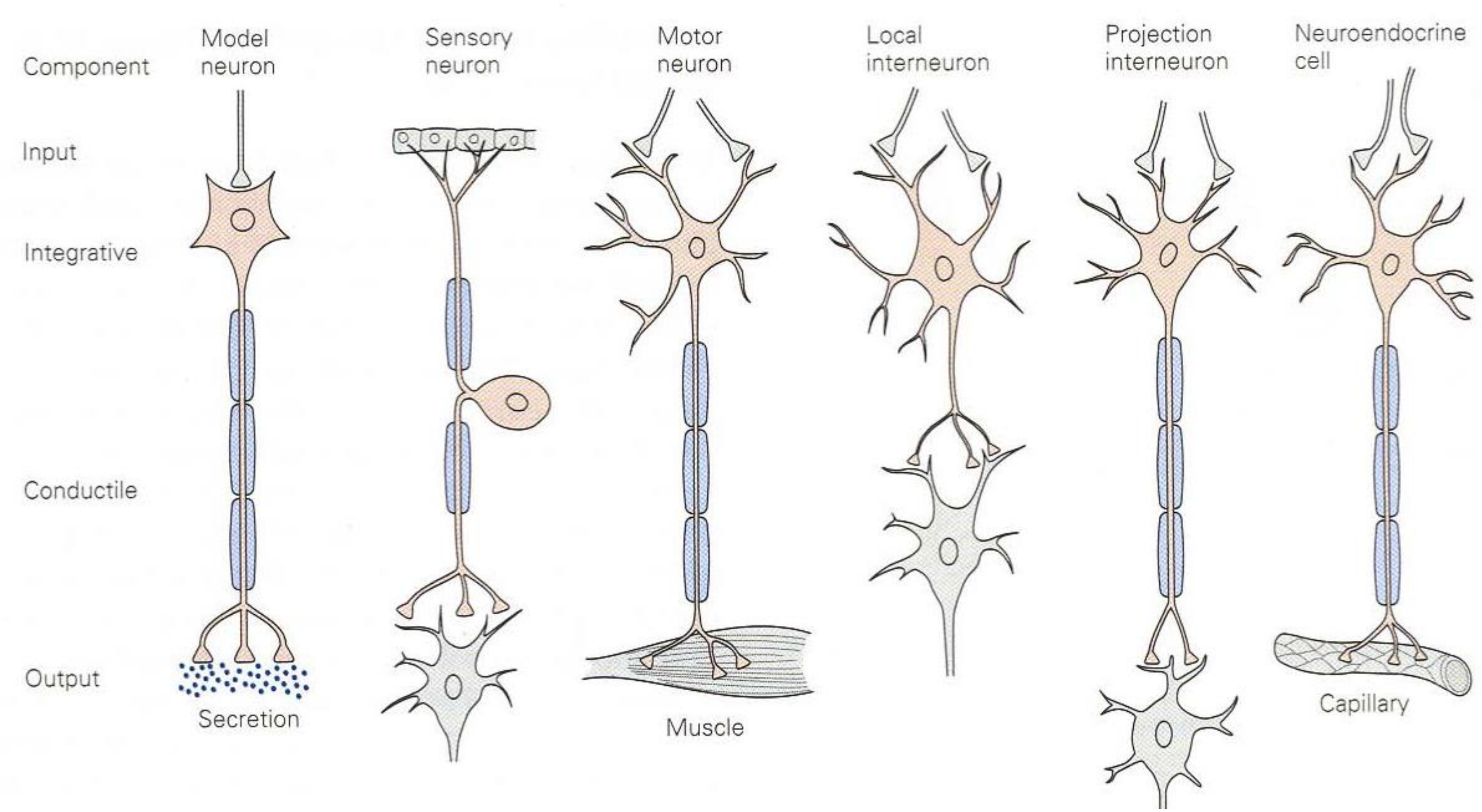
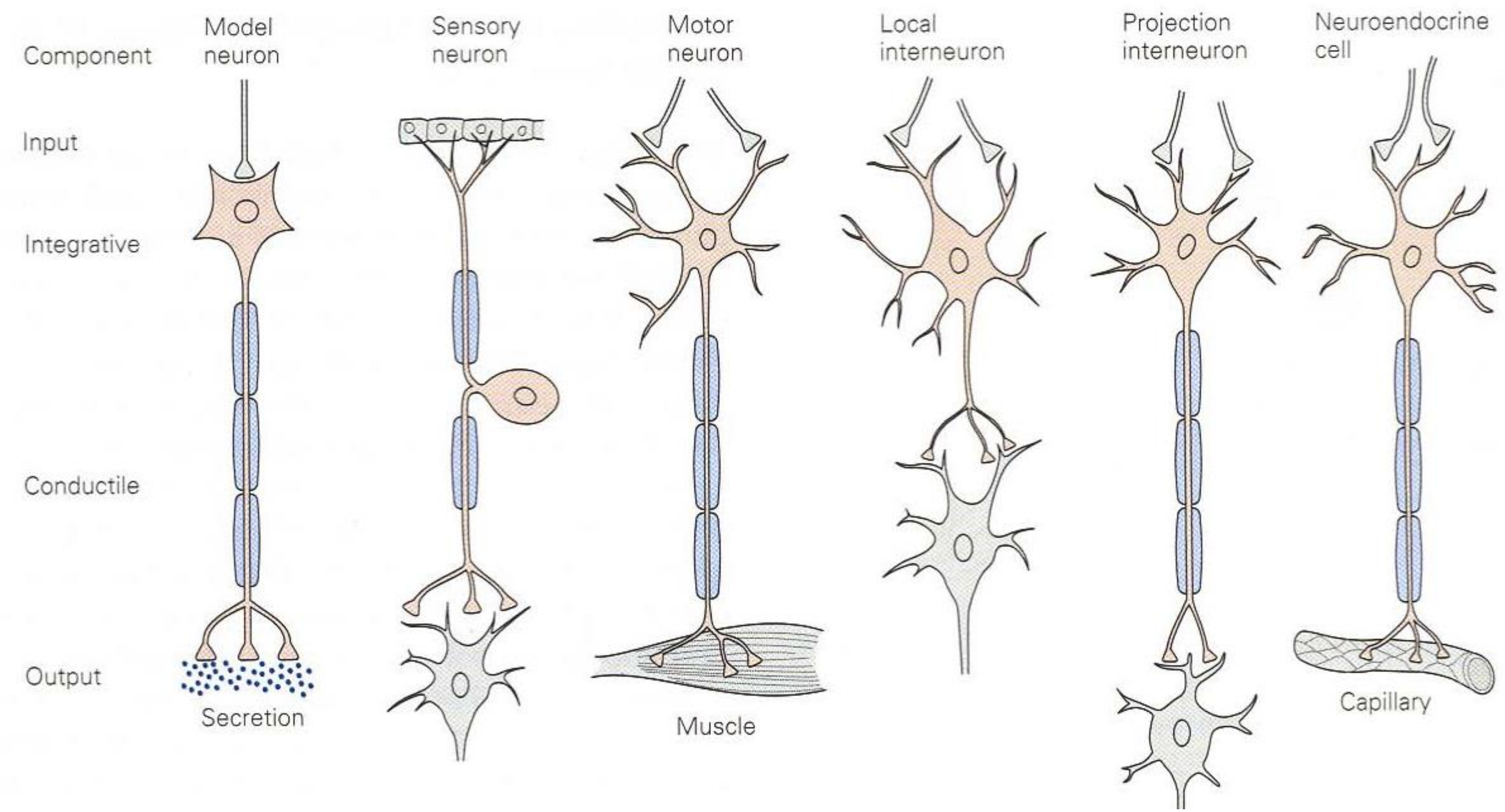


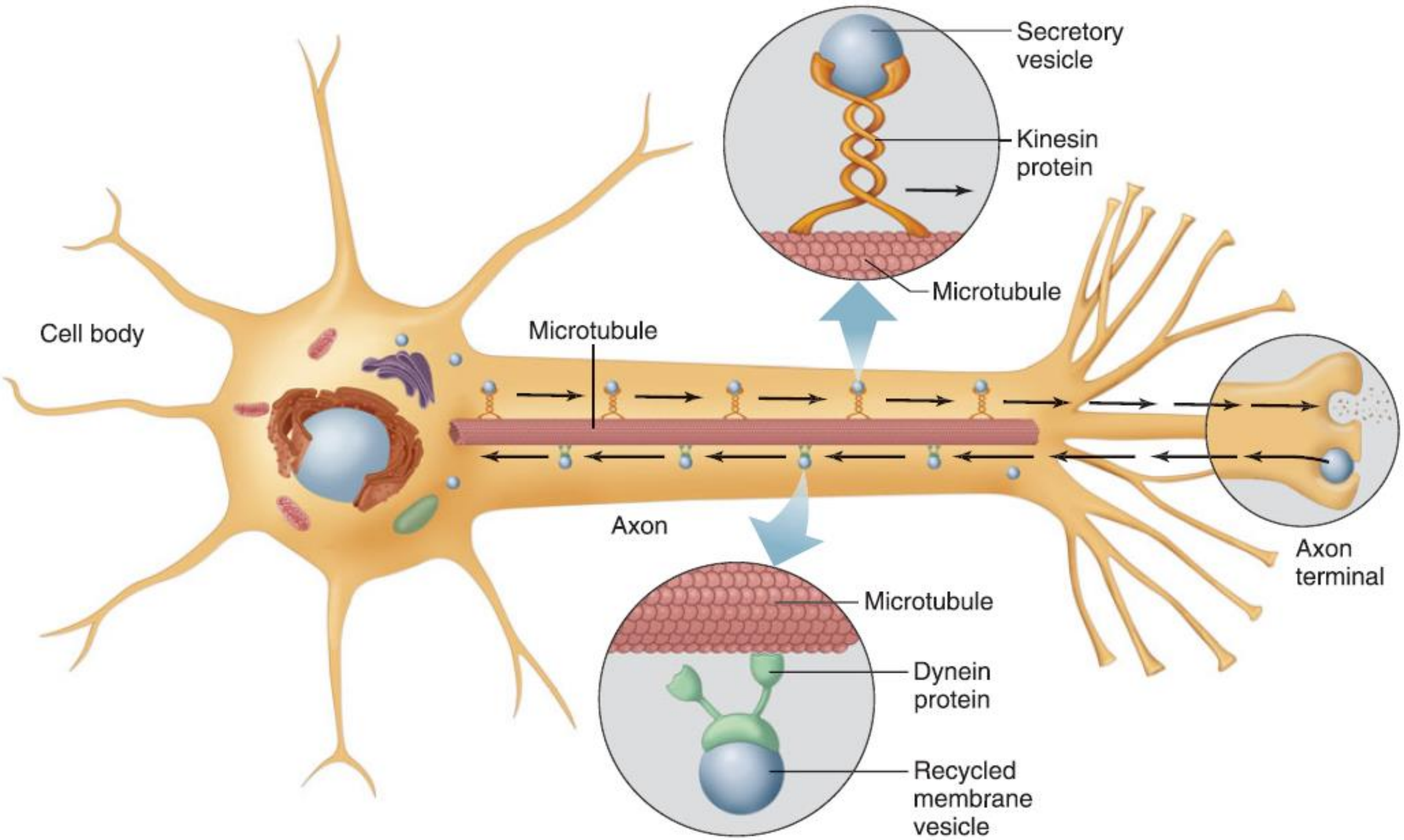
Most neurons share a group of traits:

- four functional components – input, integrative, conductive, output
- generate electrical potentials
- communication with another neurons



Axonal transport

- apparatus for the protein synthesis in the cell body
- orthograde/antegrade transport



Glial cells

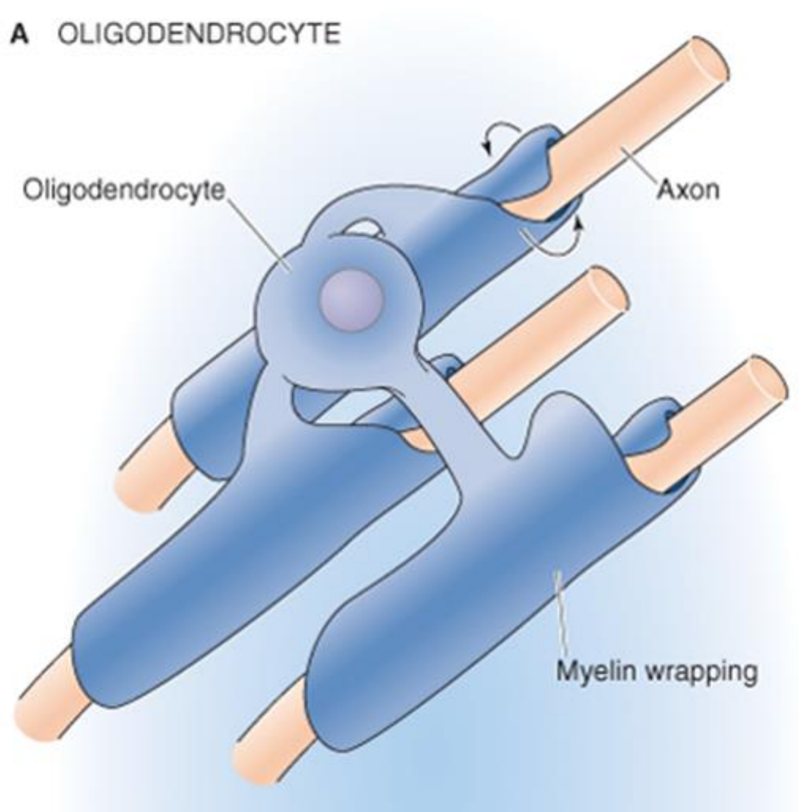
Microglial cells

- arise from macrophages
- scavenger cells (remove debris resulting from injury, infection, …)

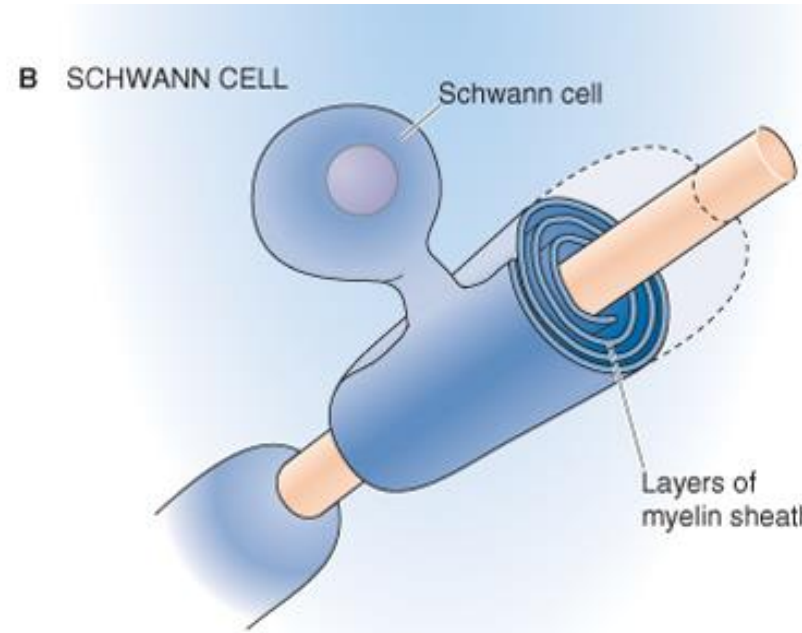
Macroglial cells

- Schwann cells (PNS), oligodendrocytes (CNS) - myelin

CNS


A OLIGODENDROCYTE
Oligodendrocyte
Axon
Myelin wrapping

PNS


B SCHWANN CELL
Schwann cell
Layers of
myelin sheath

Glial cells

Microglial cells

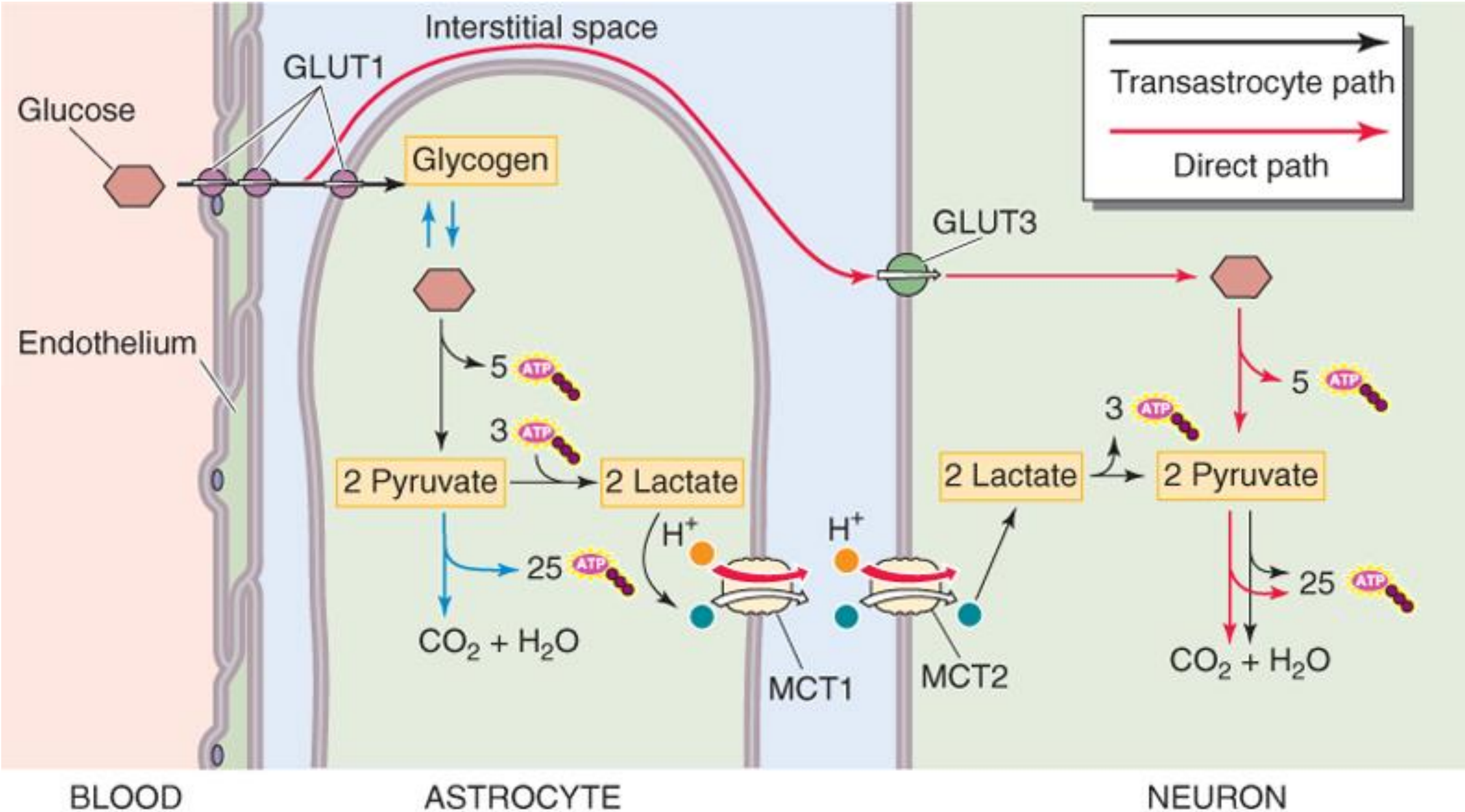
- arise from macrophages
- scavenger cells (remove debris resulting from injury, infection, …)

Macroglial cells

- Schwann cells (PNS), oligodendrocytes (CNS) - myelin
- astrocytes – send processes to:
  - blood vessels (tight junction formation → blood-brain barrier)
  - synapses and surface of nerve cells (produce tropic substances, maintain appropriate concentration of ions and neurotransmitters)

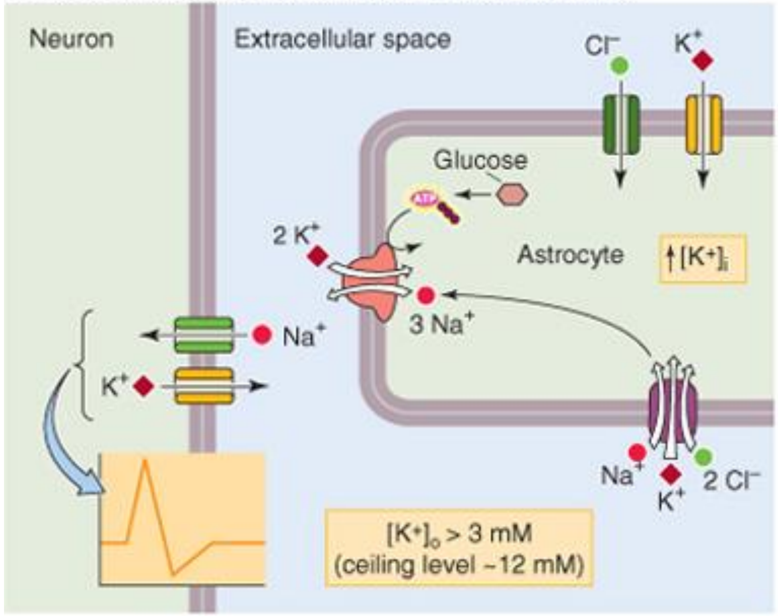
Astrocytes

- metabolic functions: K^+, pH, oxidative stress (GSH), energy storage (glycogen), glutamate-glutamin shuttle
- modulation of synaptic activity, tissue repair

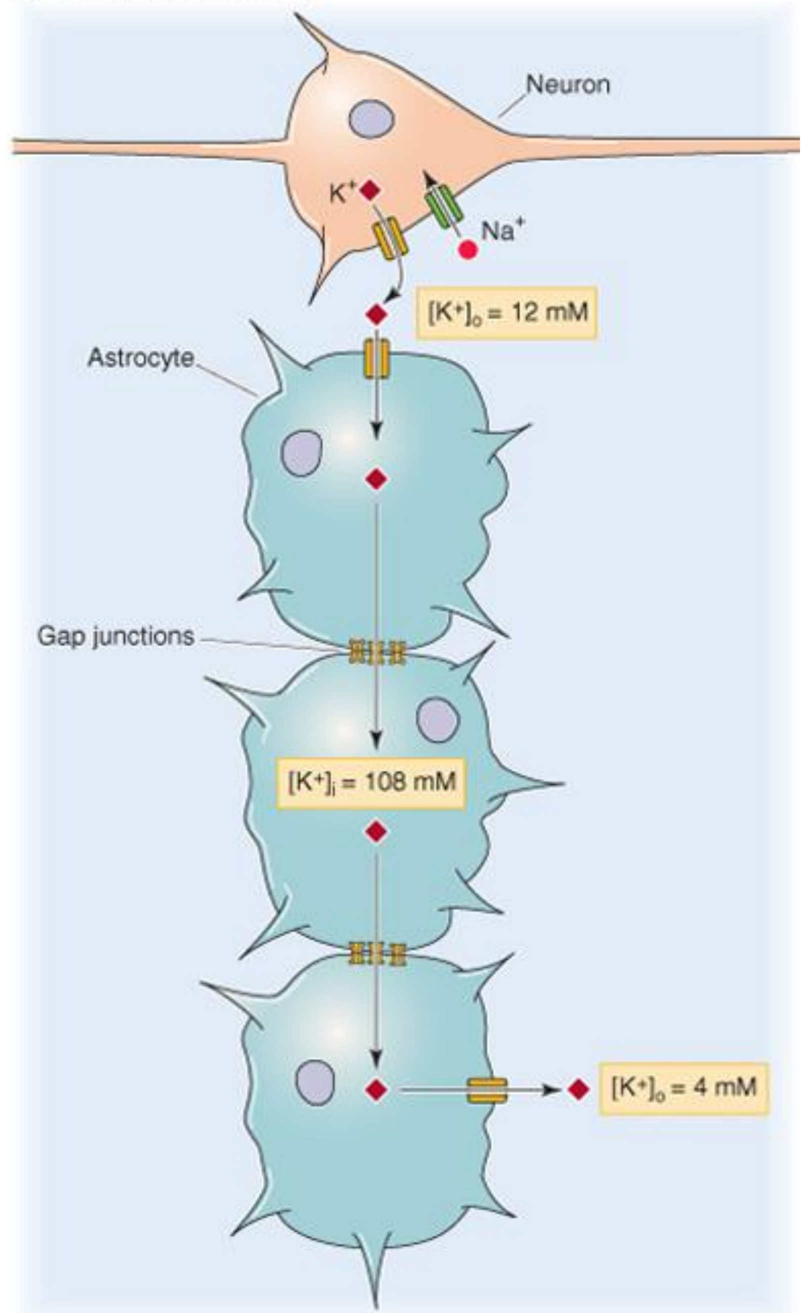


Boron & Boulpaep: Medical Physiology, 2nd Edition.

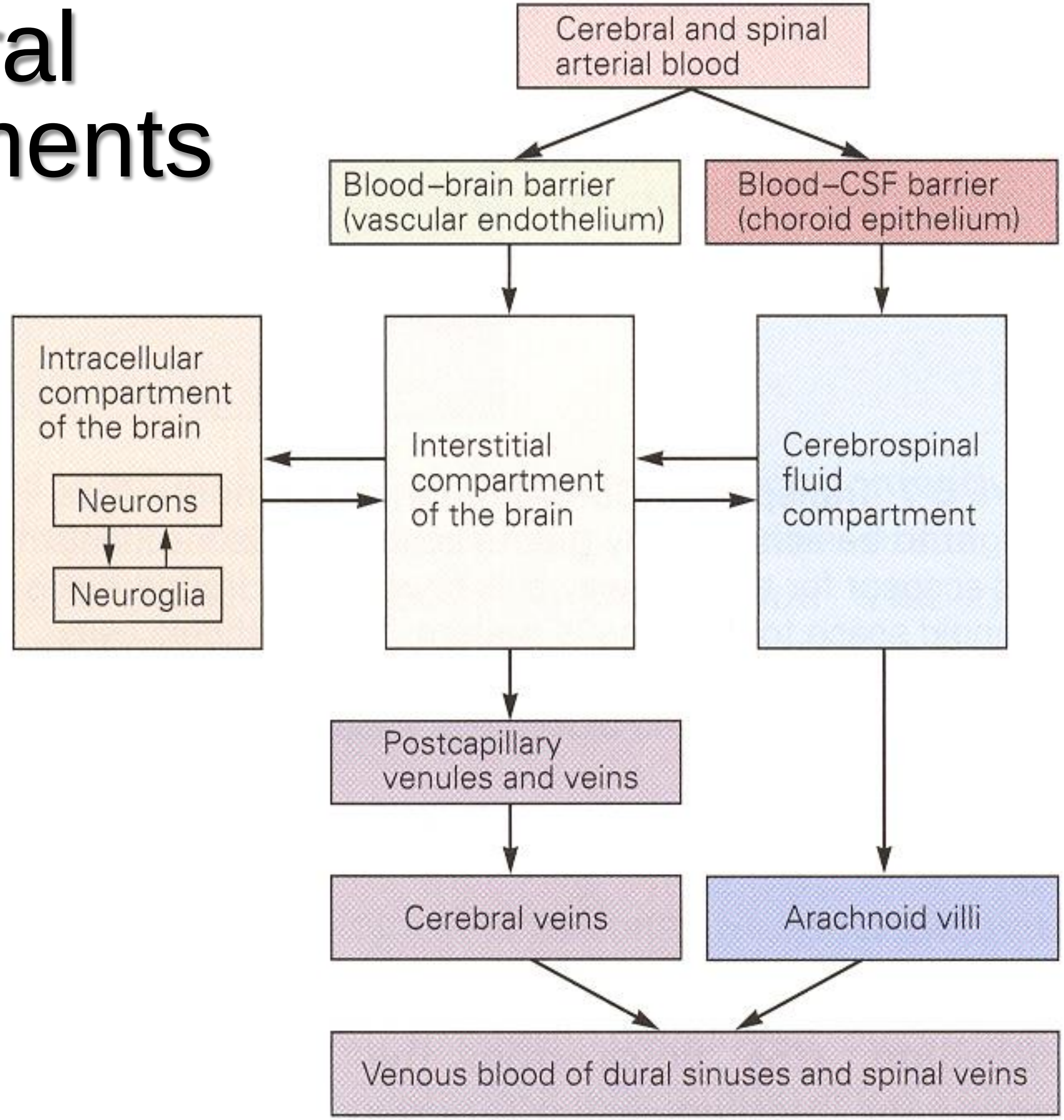
A MECHANISMS OF K^+ UPTAKE BY ASTROCYTES



B SPATIAL BUFFERING

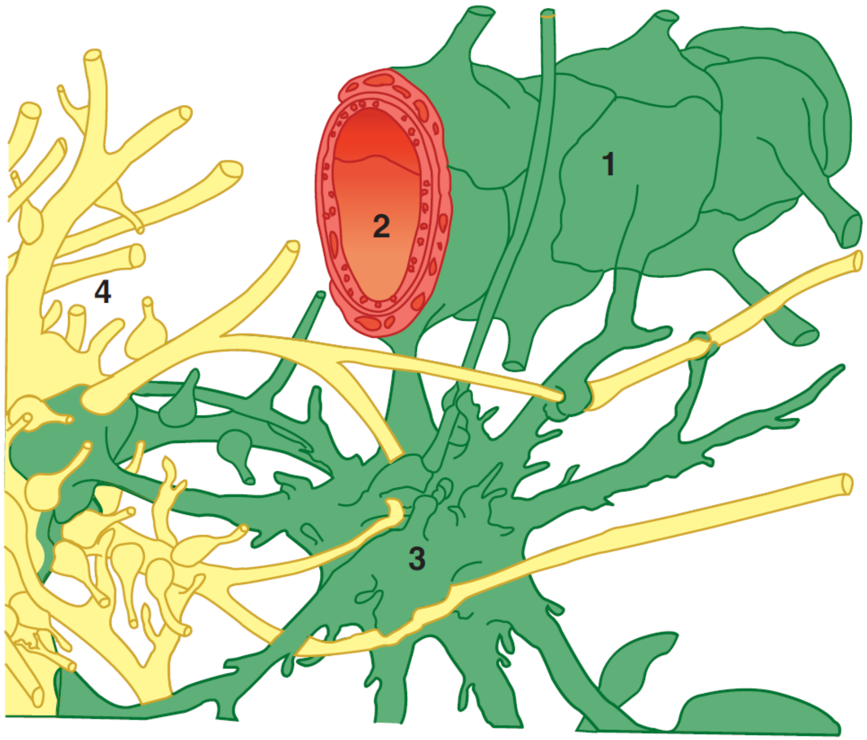


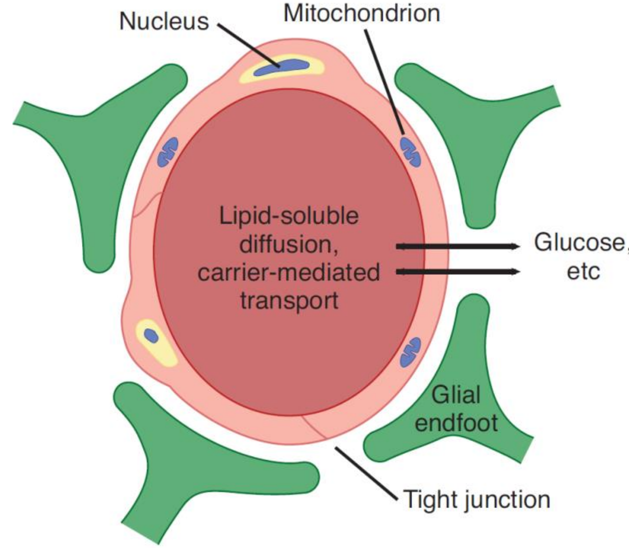
Cerebral Compartments



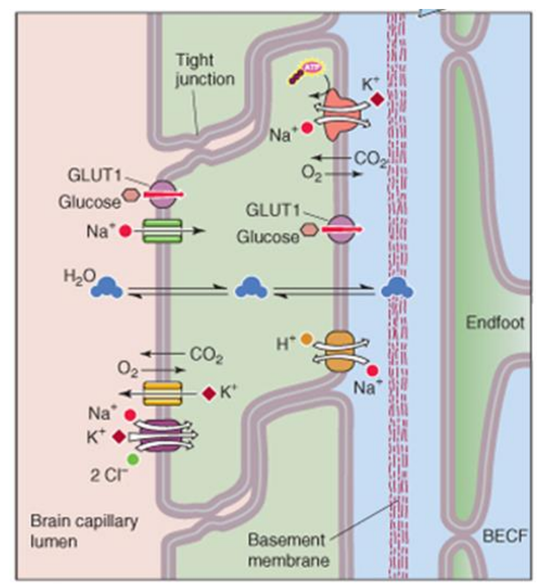
Blood-brain barrier

cerebral capillaries – tight inter-endothelial connections



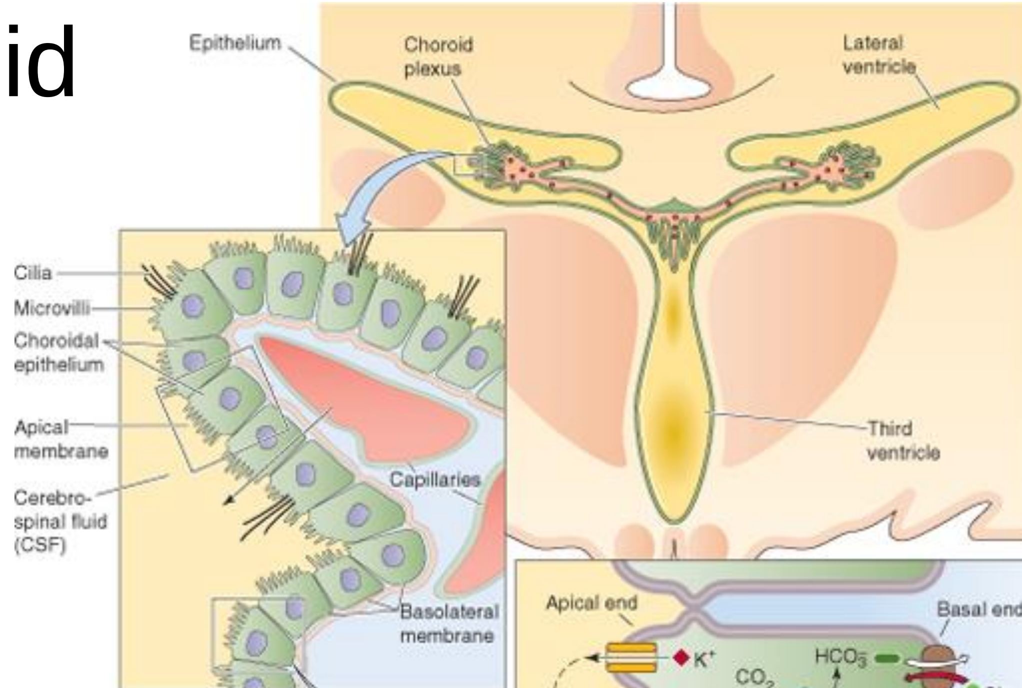


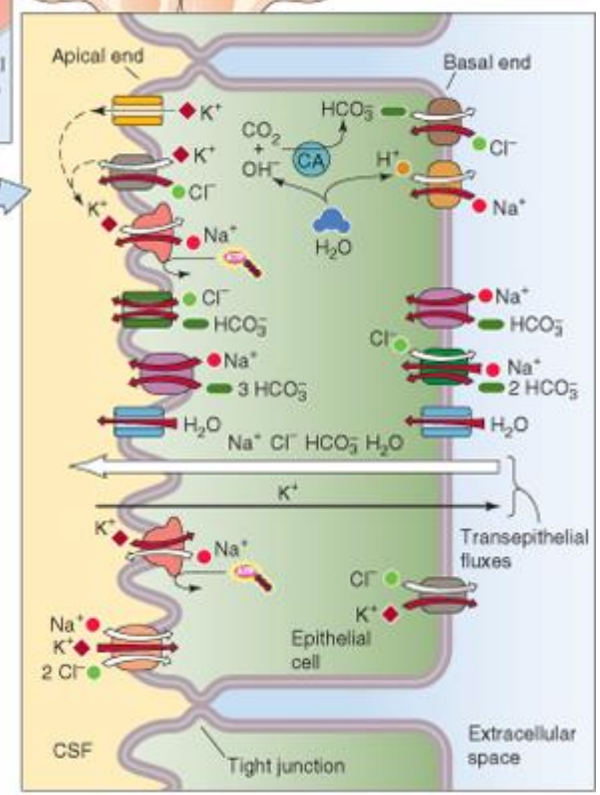
Ganong´s Review of Medical Physiology, 23rd edition



circumventricular organs

Cerebrospinal fluid
- production -





rate of production: 450-550 ml/day
(70 % come from plexus choriodei)
circulating volume: 130-150 ml

CSF pressure in supine position in lumbar region:
70-180 mmH_2O

Cerebrospinal fluid - composition -

Substance		CSF	Plasma	Ratio CSF/Plasma
Na^+	(meq/kg H_2O)	147.0	150.0	0.98
K^+	(meq/kg H_2O)	2.9	4.6	0.62
Mg^{2+}	(meq/kg H_2O)	2.2	1.6	1.39
Ca^{2+}	(meq/kg H_2O)	2.3	4.7	0.49
Cl^-	(meq/kg H_2O)	113.0	99.0	1.14
HCO_3^-	(meq/L)	25.1	24.8	1.01
P_{CO_2}	(mm Hg)	50.2	39.5	1.28
pH		7.33	7.40	. . .
Osmolality	(mosm/kg H_2O)	289.0	289.0	1.00
Protein	(mg/dL)	20.0	6000.0	0.003
Glucose	(mg/dL)	64.0	100.0	0.64
Inorganic P	(mg/dL)	3.4	4.7	0.73
Urea	(mg/dL)	12.0	15.0	0.80
Creatinine	(mg/dL)	1.5	1.2	1.25
Uric acid	(mg/dL)	1.5	5.0	0.30
Cholesterol	(mg/dL)	0.2	175.0	0.001

clear and colorless, up to 4 cells/µl, little amount of proteins

Cerebrospinal fluid: circulation

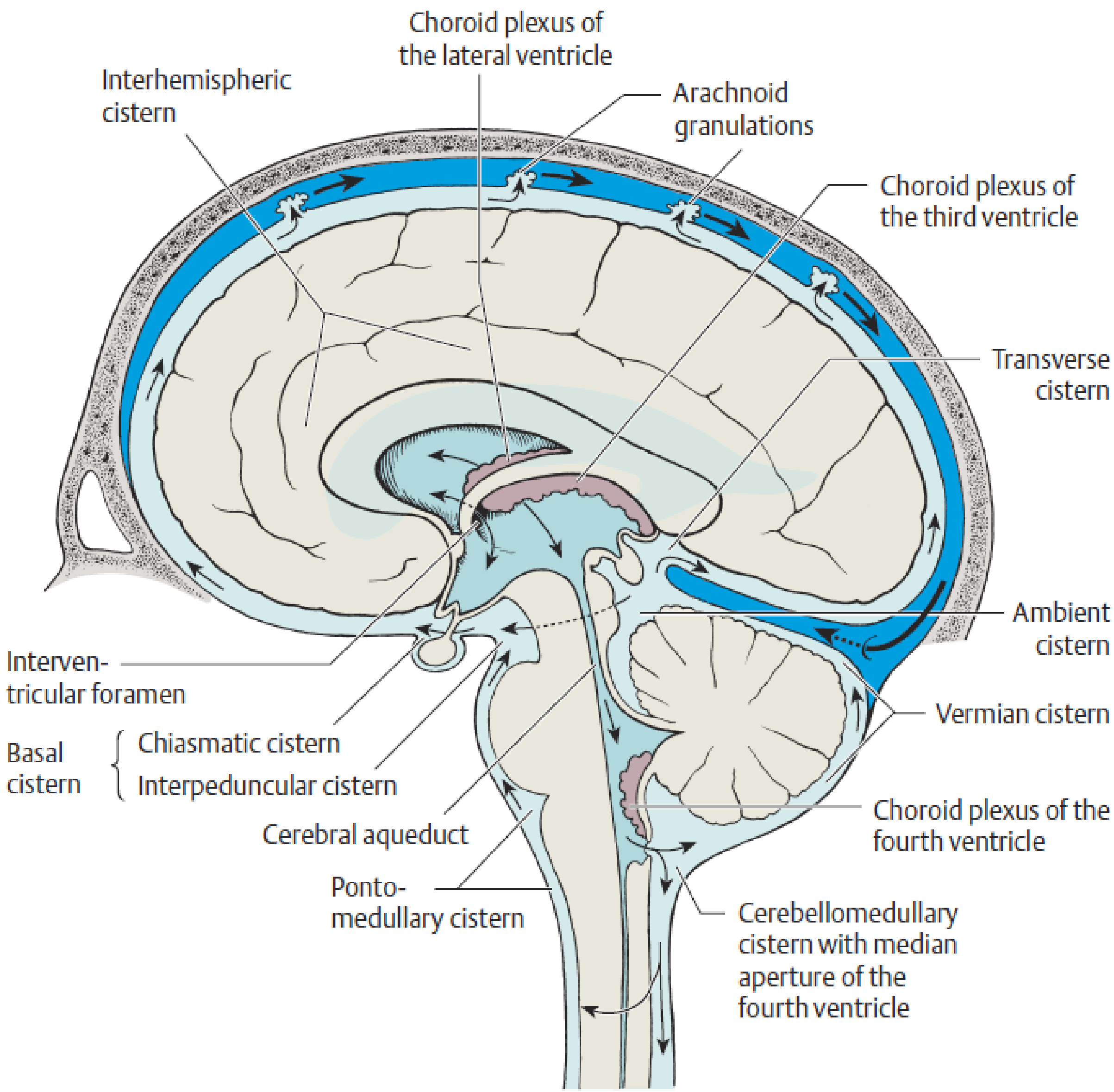
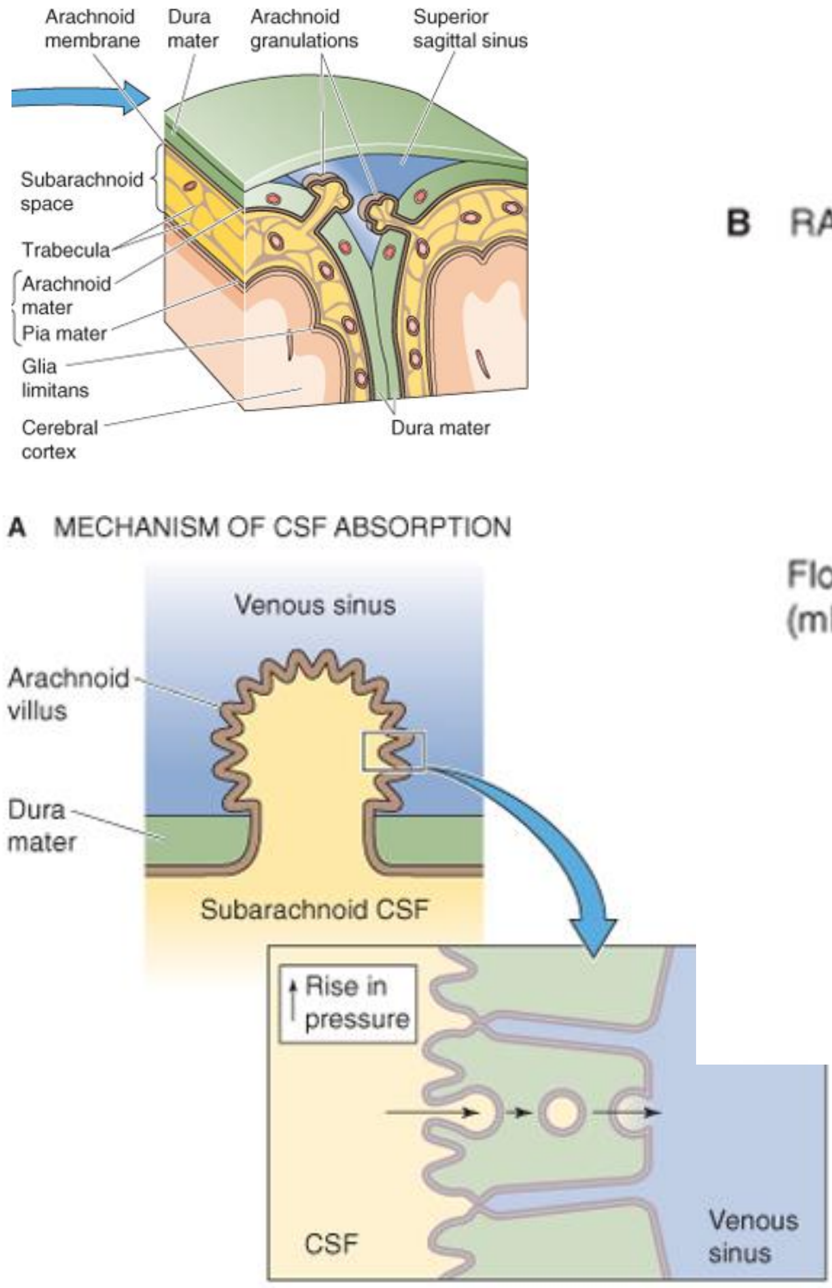
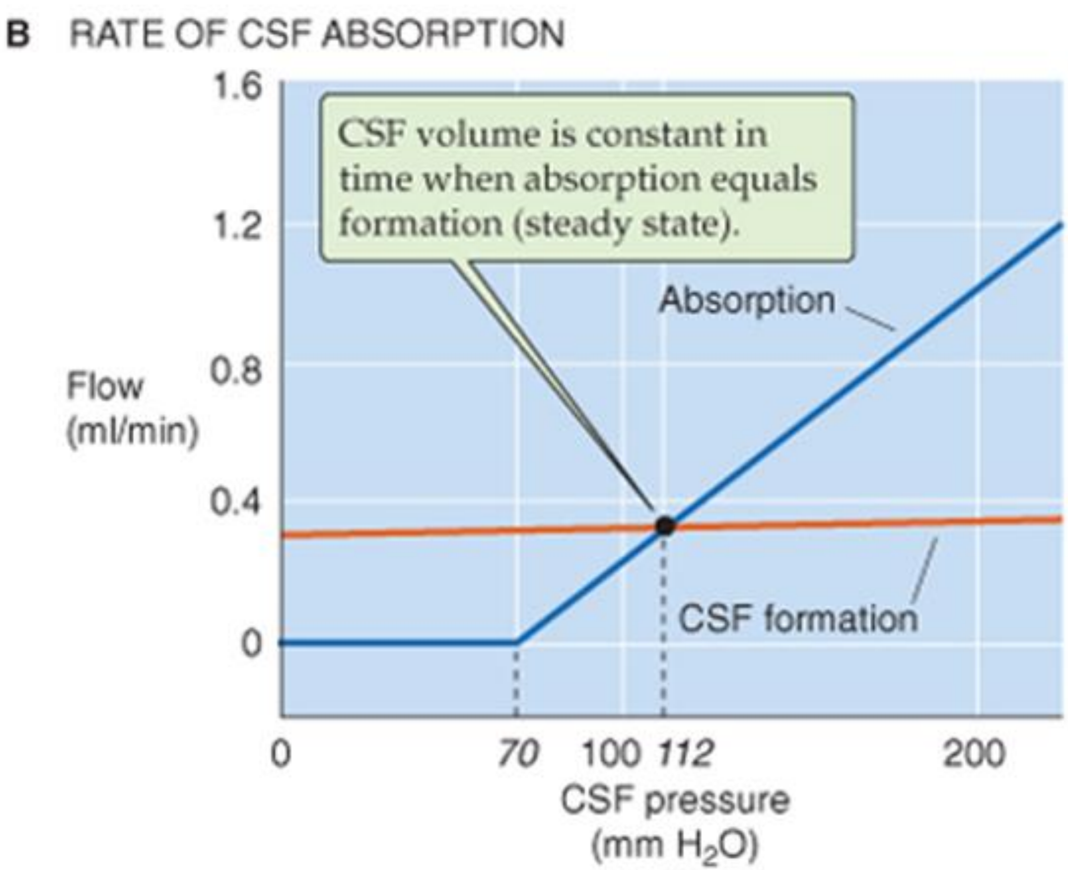


Fig. 10.4 **Circulation of the cerebrospinal fluid**

Cerebrospinal fluid: absorption





Resting membrane potential

A difference in the electrical potential (=voltage) across the plasma membrane of an unstimulated excitable cell.

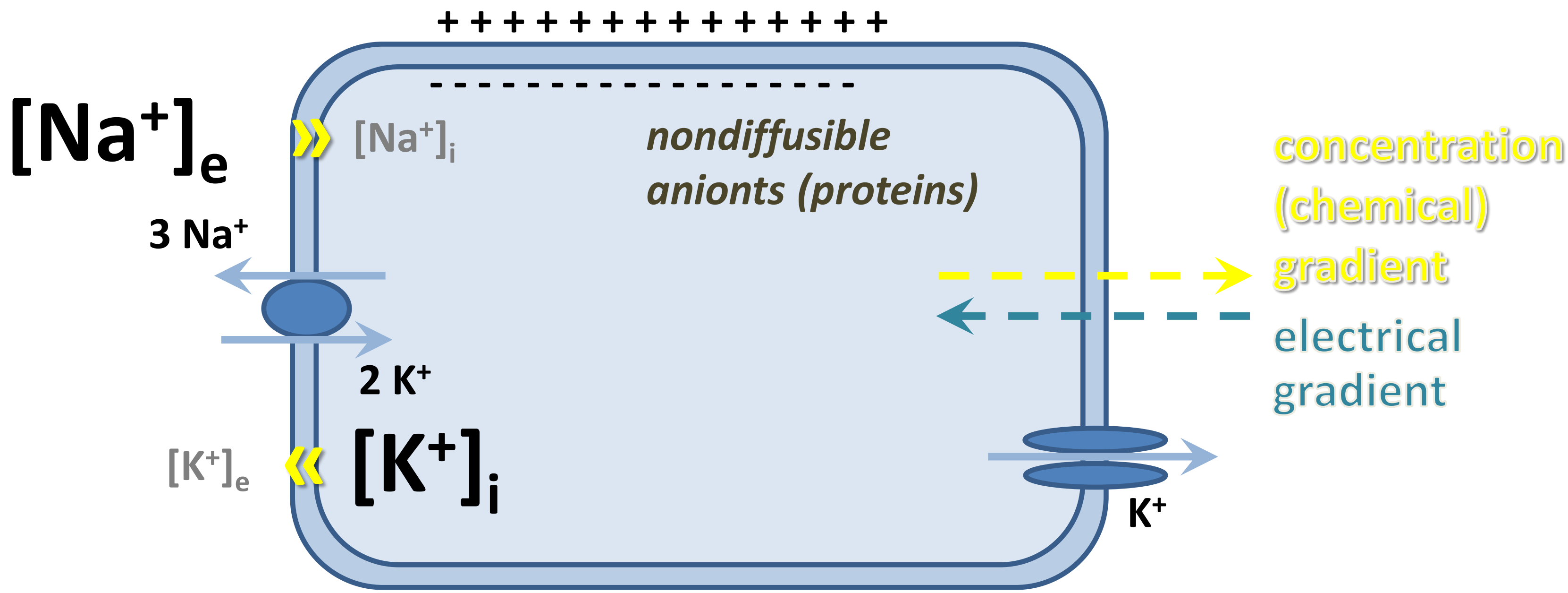
Resting membrane potential

the difference in electrical potential when the cell is at rest results from **two factors**:

(1) the unequal distribution of electrically charged ions, in particular, the positively charged **Na^+ and K^+ ions** and the negatively charged amino acids and proteins, on either side of the cell membrane, (*Na^+-K^+ pump)*

(2) the selective permeability of the membrane to K^+ *(ion channels).*

Resting membrane potential



Resting membrane potential

TABLE 2.1
Extracellular and Intracellular Ion Concentrations

	Concentration (mM)	
Ion	*Intracellular*	*Extracellular*
Mammalian neuron		
Potassium (K^+)	140	5
Sodium (Na^+)	5–15	145
Chloride (Cl^-)	4–30	110
Calcium (Ca^{2+})	0.0001	1–2

Resting membrane potential

- **Nernst equation**

  … to find out electrochemical balance of a concrete ion (equilibrium potential)

total work = electrical work + concentration work

electrical work = $z \cdot F \cdot E_r$

concentration work = $R \cdot T \cdot \ln \dfrac{[x]_i}{[x]_e}$

$$\text{total work} = z \cdot F \cdot E_r + R \cdot T \cdot \ln \frac{[x]_i}{[x]_e} = 0$$

in steady-state

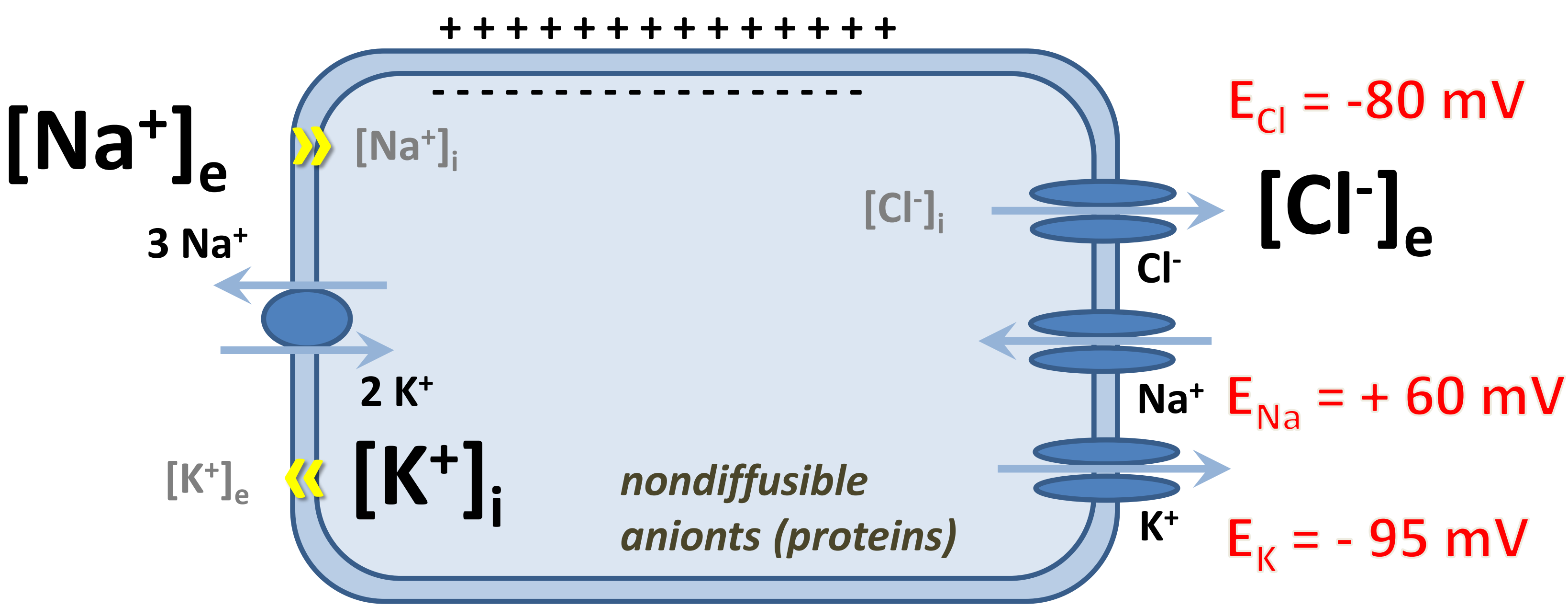
$$\boxed{E_r = -\frac{R \cdot T}{z \cdot F} \ln \frac{[x]_i}{[x]_e}}$$

E_K = - 95 mV

Resting membrane potential

- **Goldmann equation**

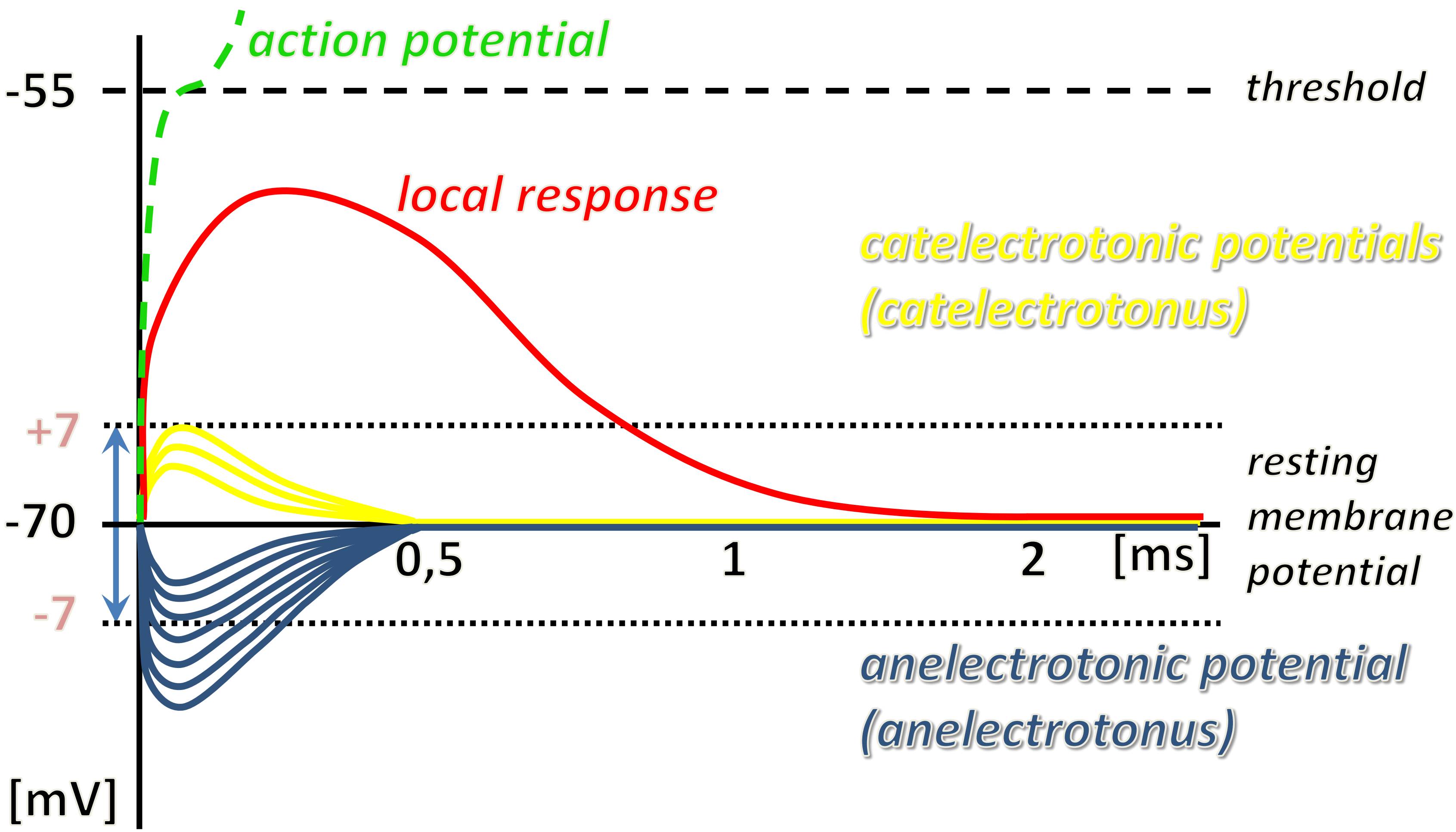
$$RMP = -\frac{R \cdot T}{F} \cdot \ln \frac{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_e}{P_K[K^+]_e + P_{Na}[Na^+]_e + P_{Cl}[Cl^-]_i}$$



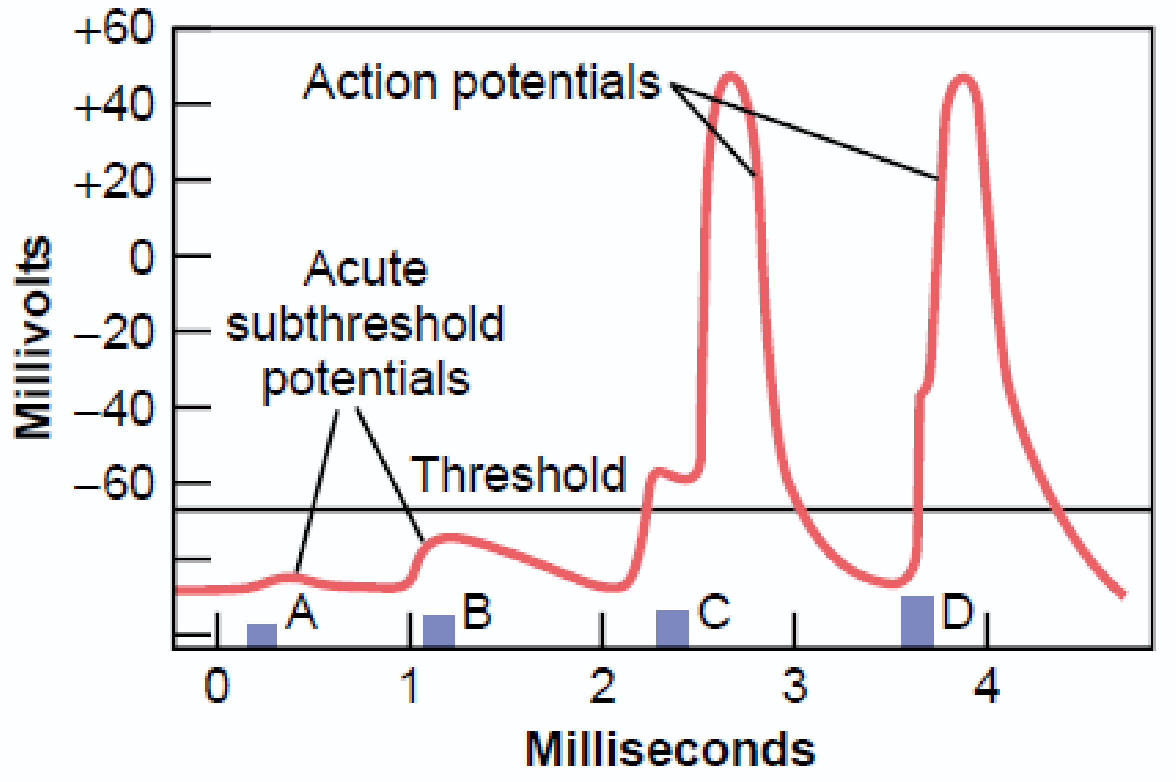
Electrotonic potentials, local response

... passive changes of membrane polarity caused by addition or removal of the charge by an electrode

Electrotonic potentials, local response



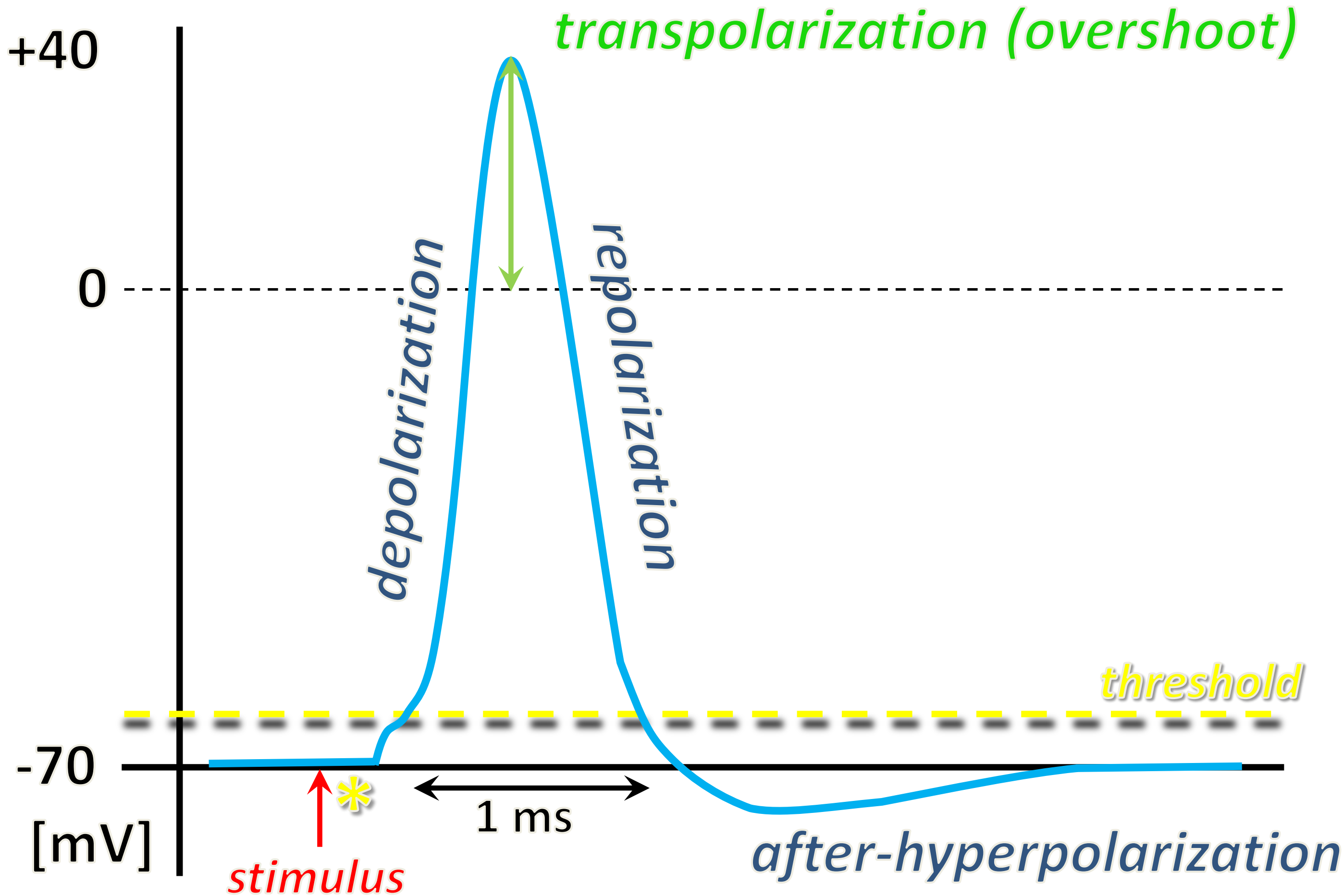
Action potential



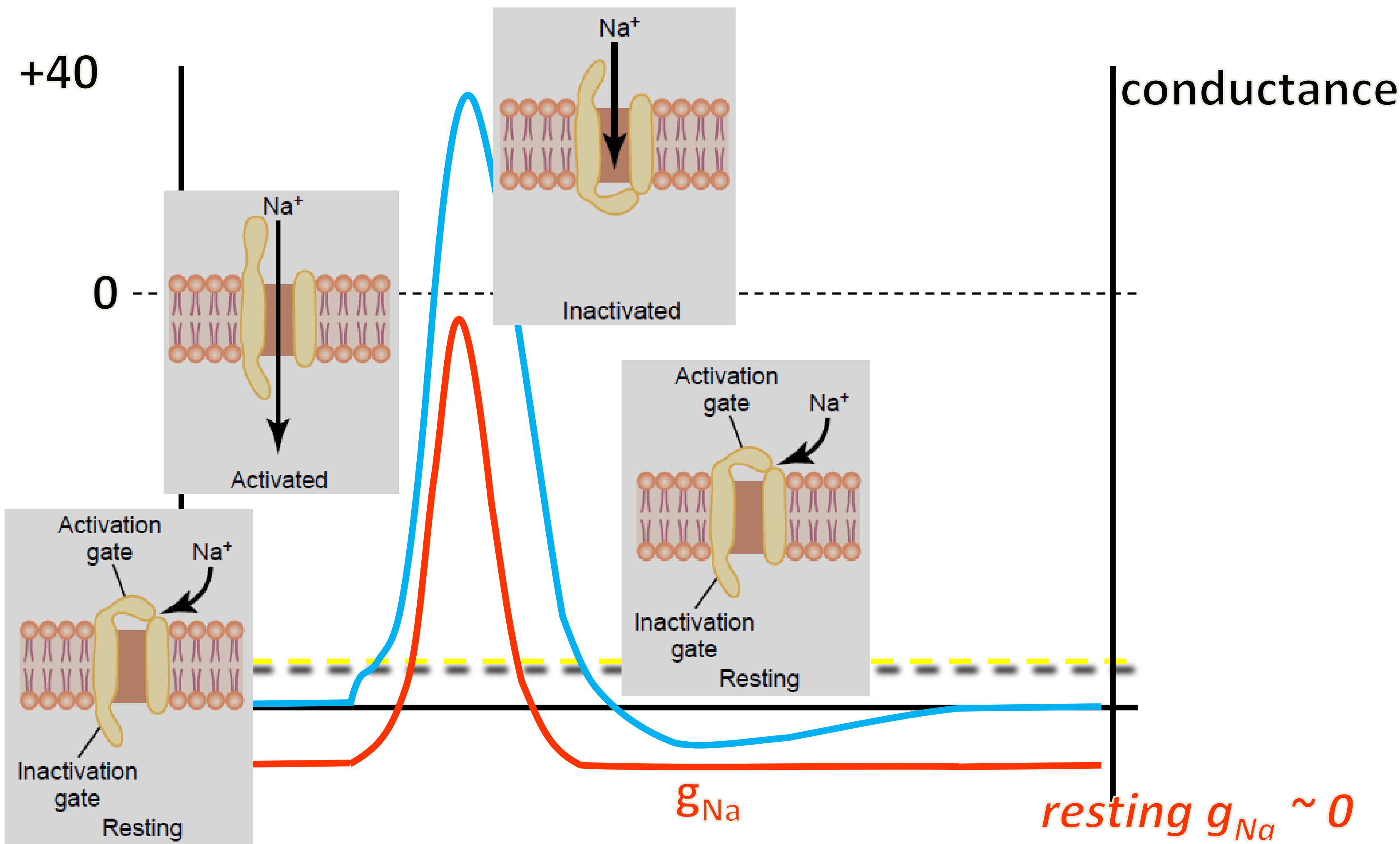
Guyton & Hall. Textbook of Medical Physiology

Action potential

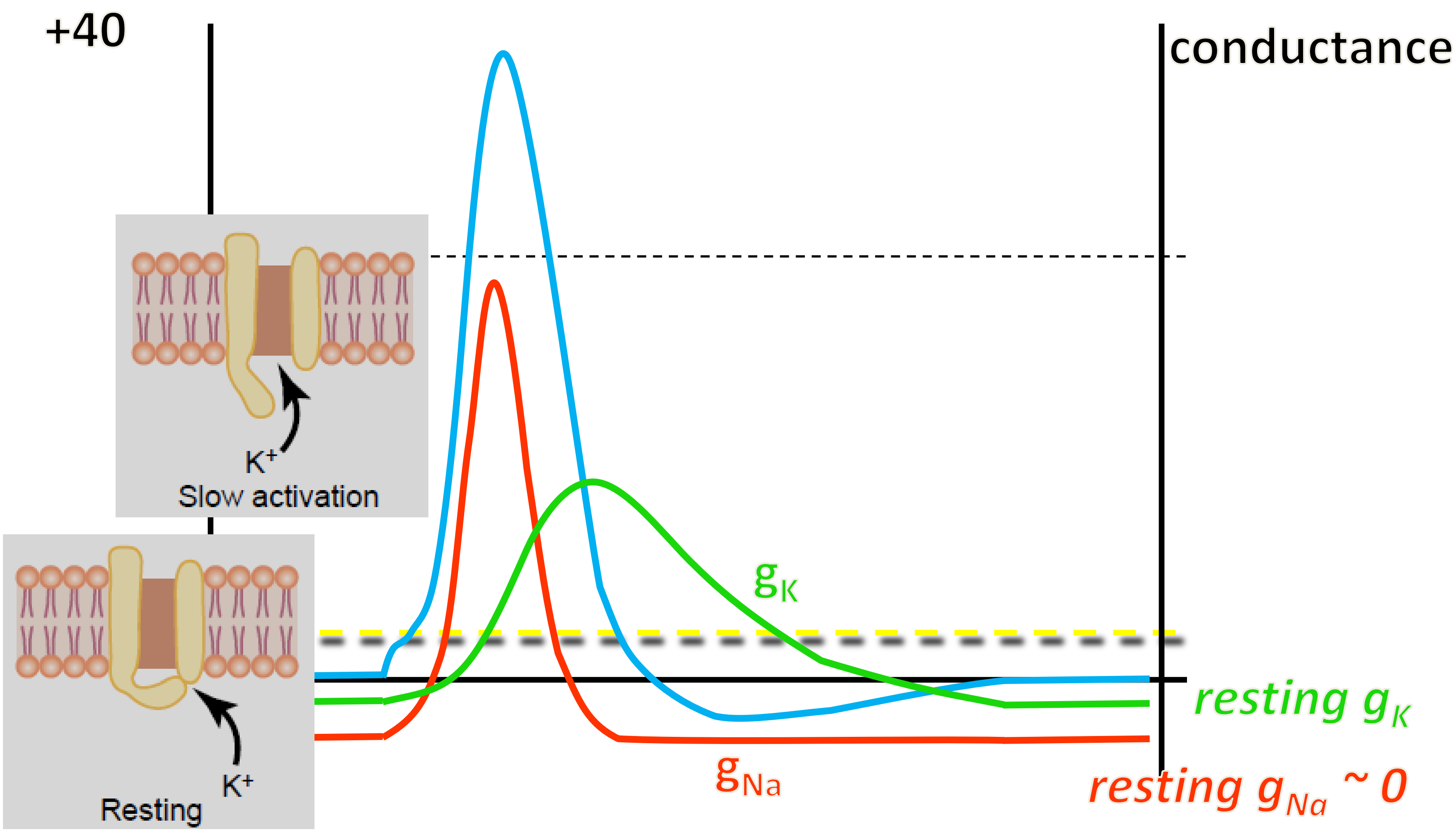
... propagated electrical response of a nerve fiber (or other excitable cells), all-or-non character



Action potential



Action potential



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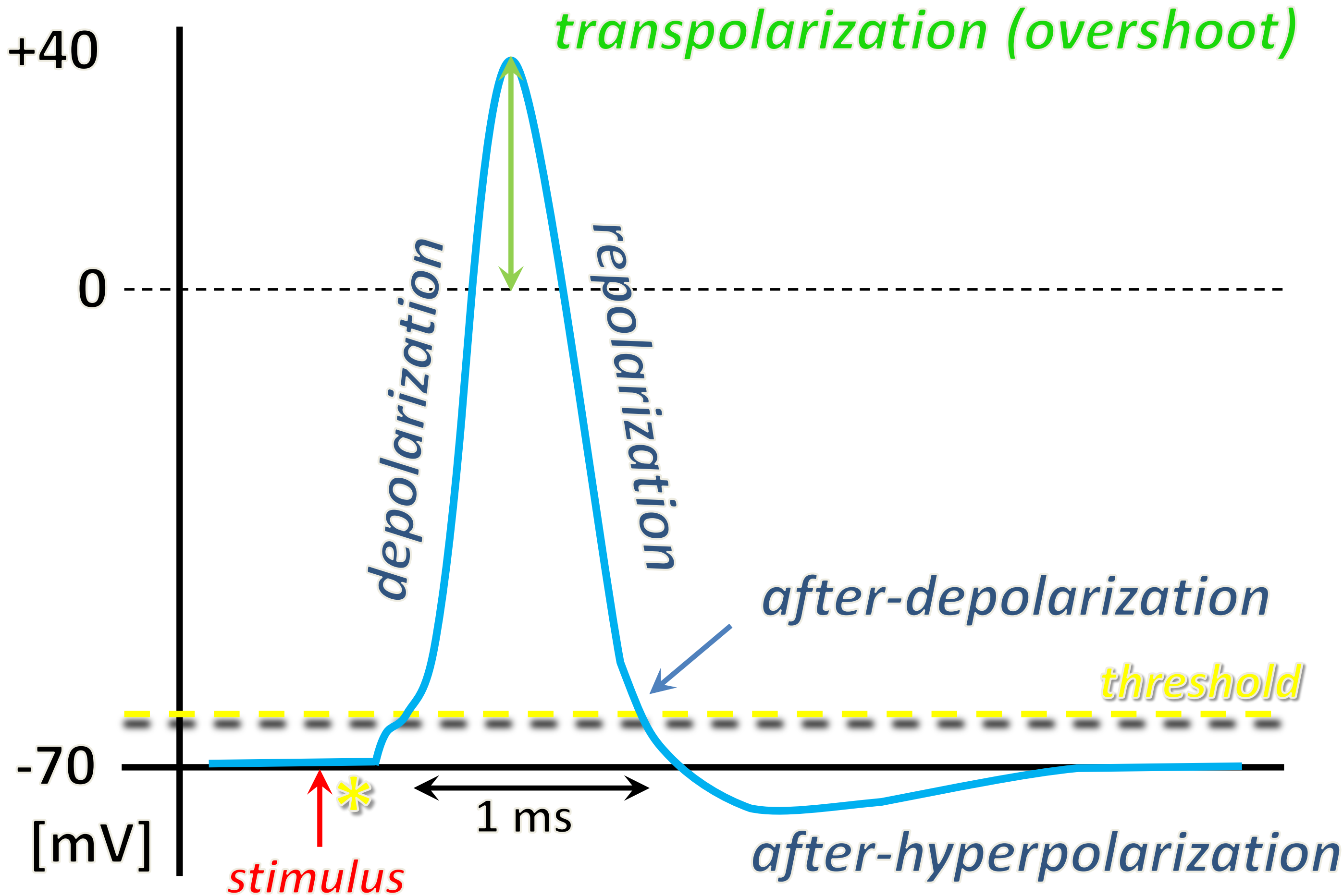
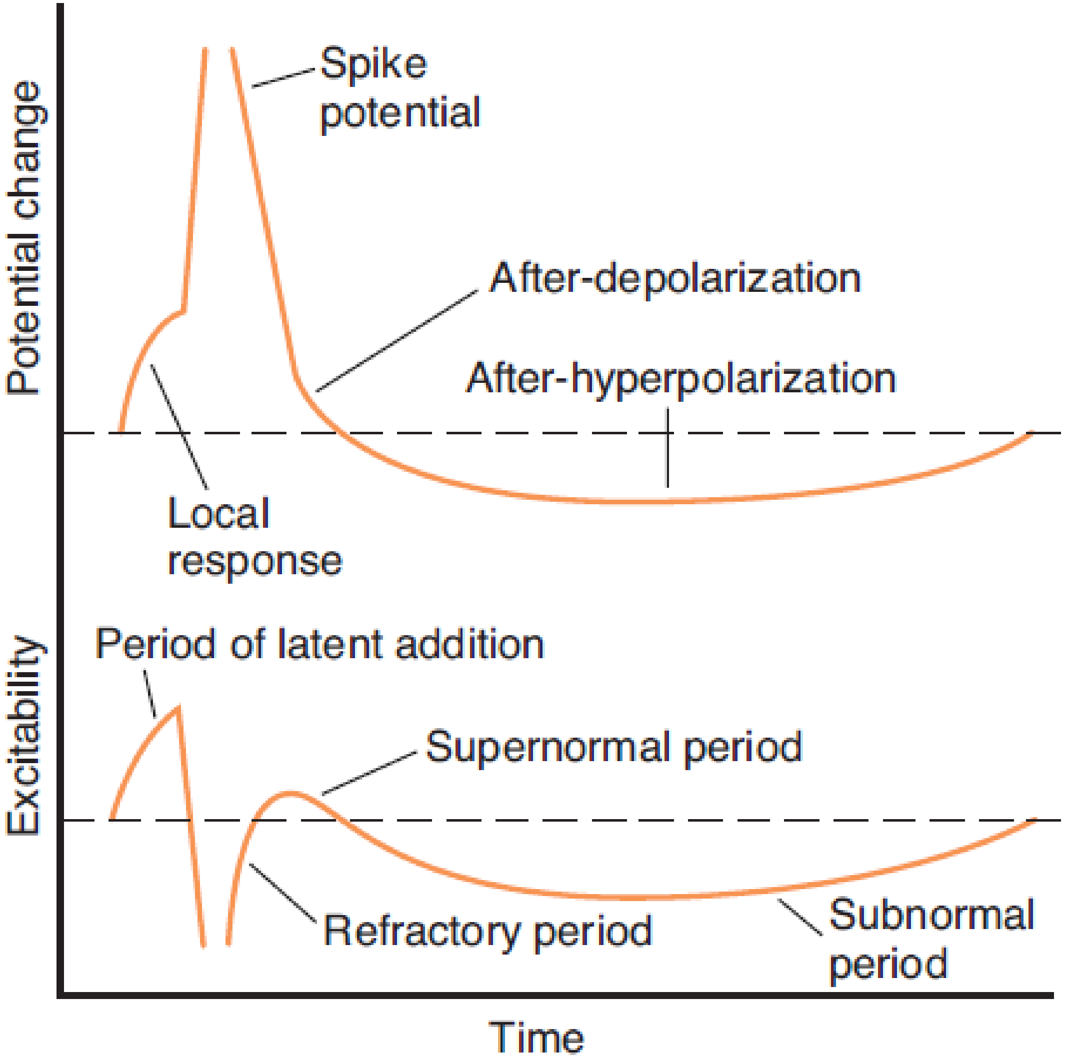
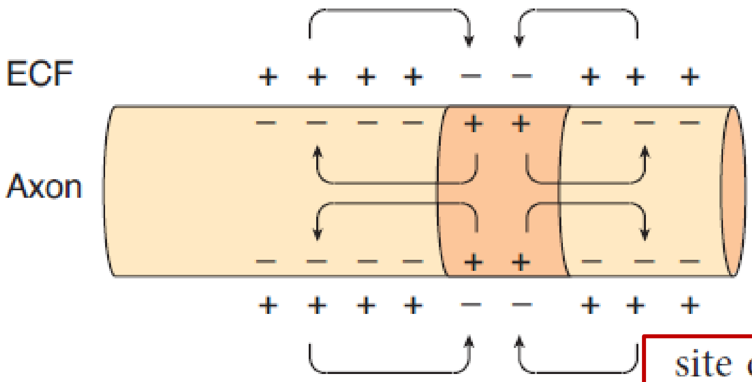


Action potential



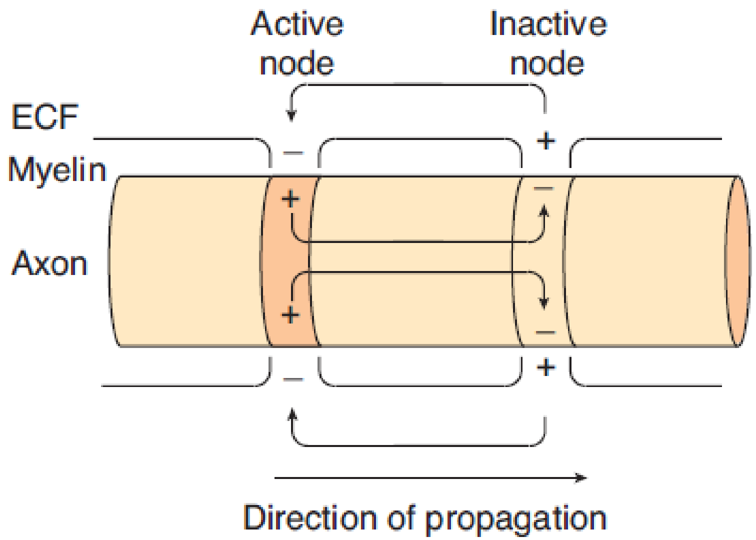
Conduction



orthodromic conduction

antidromic conduction

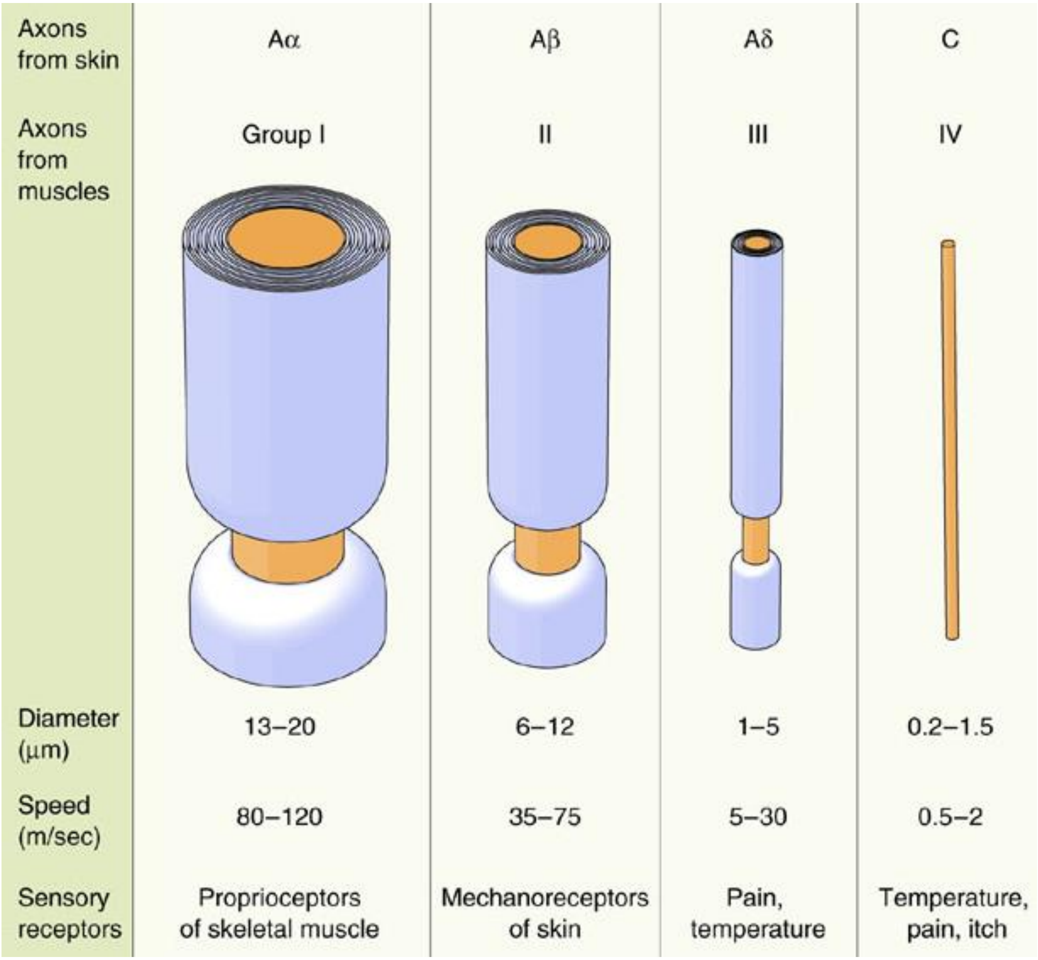
site direction is called **antidromic.** Because synapses, unlike axons, permit conduction in one direction only, an antidromic impulse will fail to pass the first synapse they encounter and die out at that point.



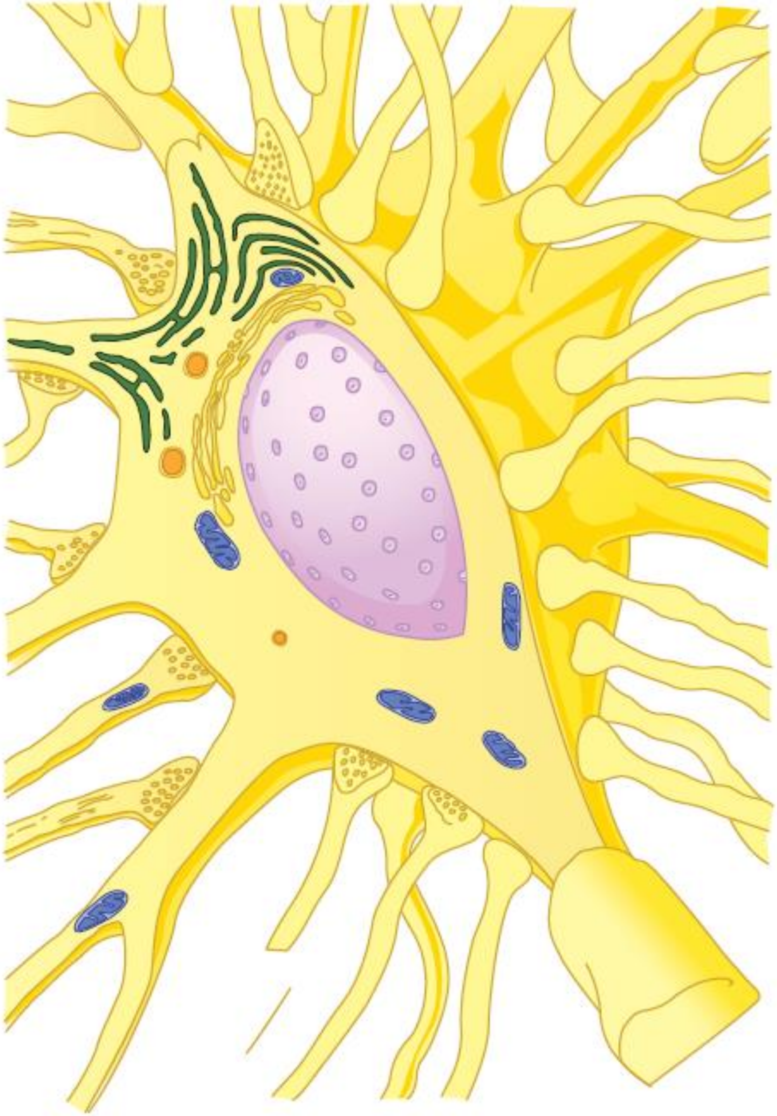
saltatory conduction

Nerve fibres

- … divided based on axonal diameter, conduction velocity, and function



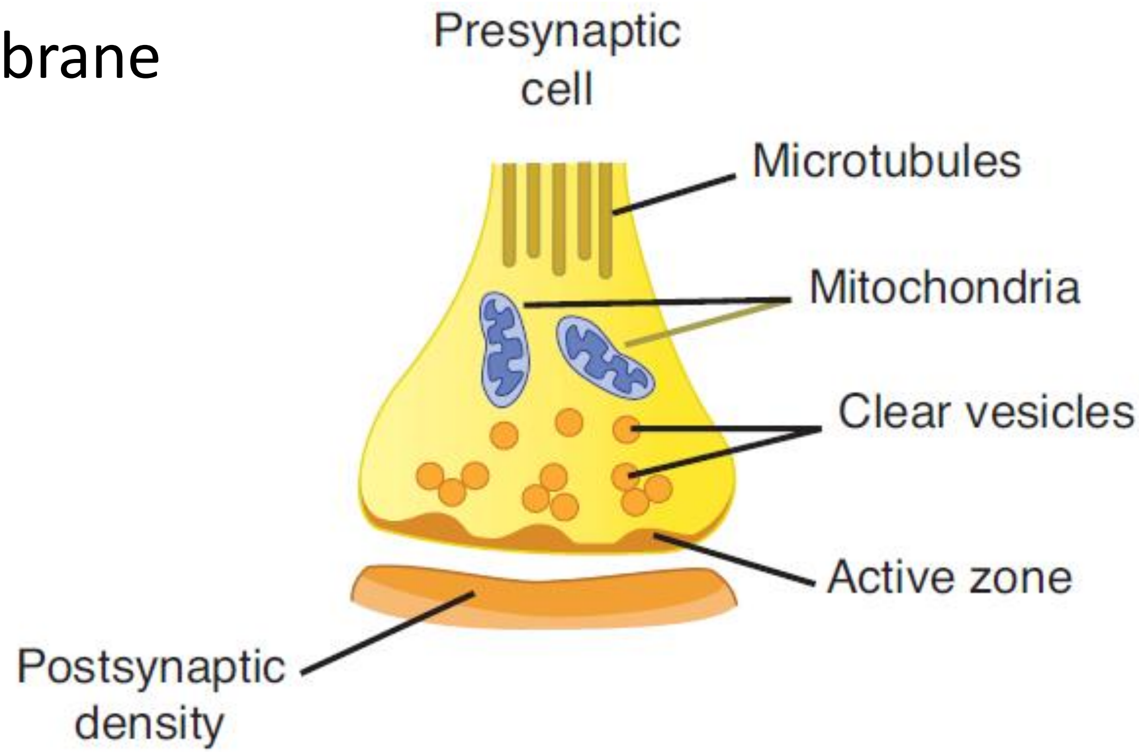
Synapses



Many different axons converge on the neuron, and their terminal boutons form axodendritic and axosomatic synapses.

Synapses - structure

presynaptic membrane
synaptic cleft
postsynaptic membrane

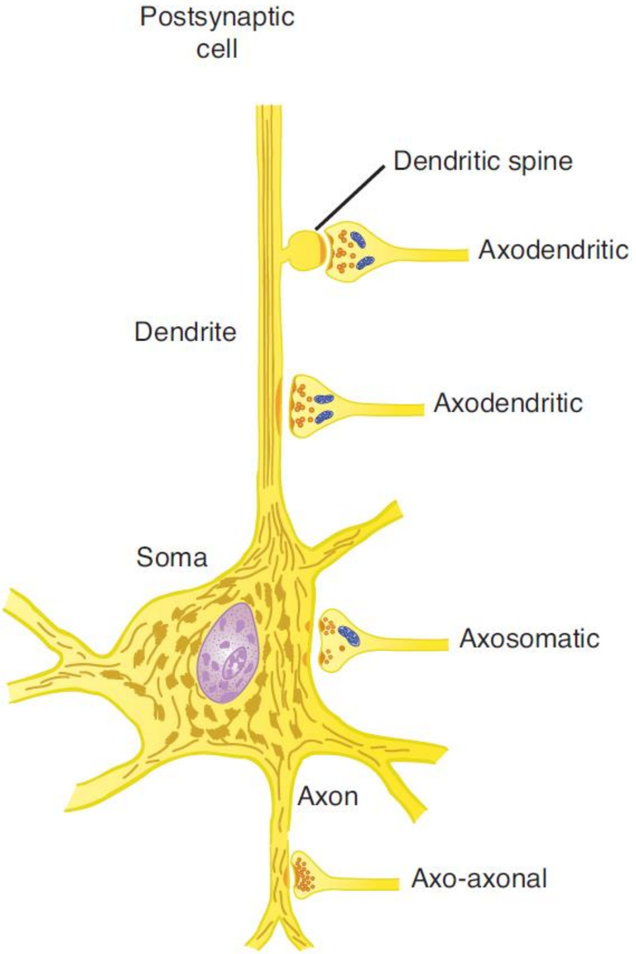


Synapses - types

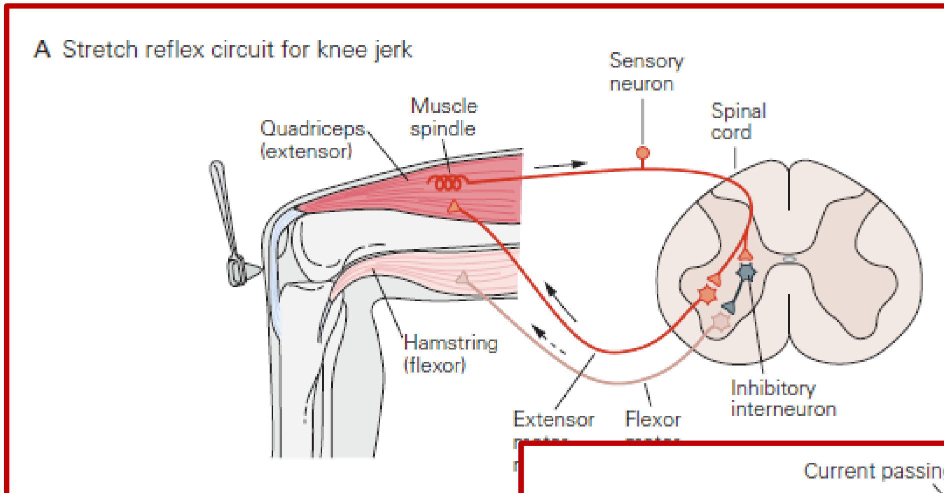
- axo-dendritic, axo-somatic, axo-axonal synapses

- electrical synapses
- chemical synapses

- excitatory synapses
- inhibitory synapses

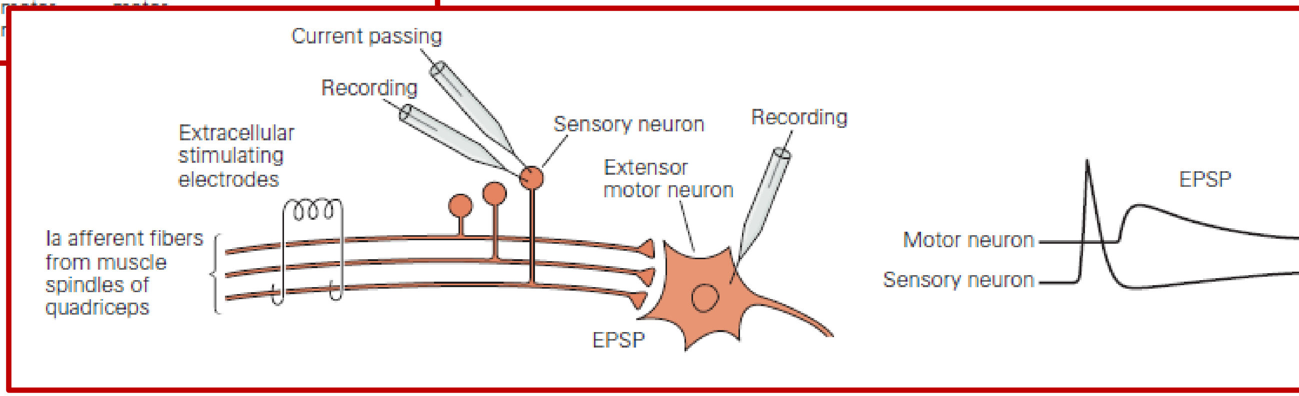


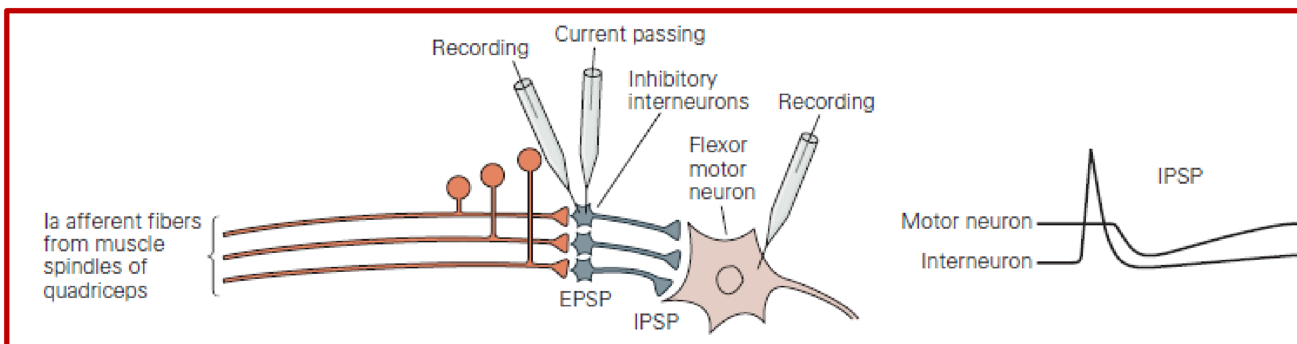
Synapses

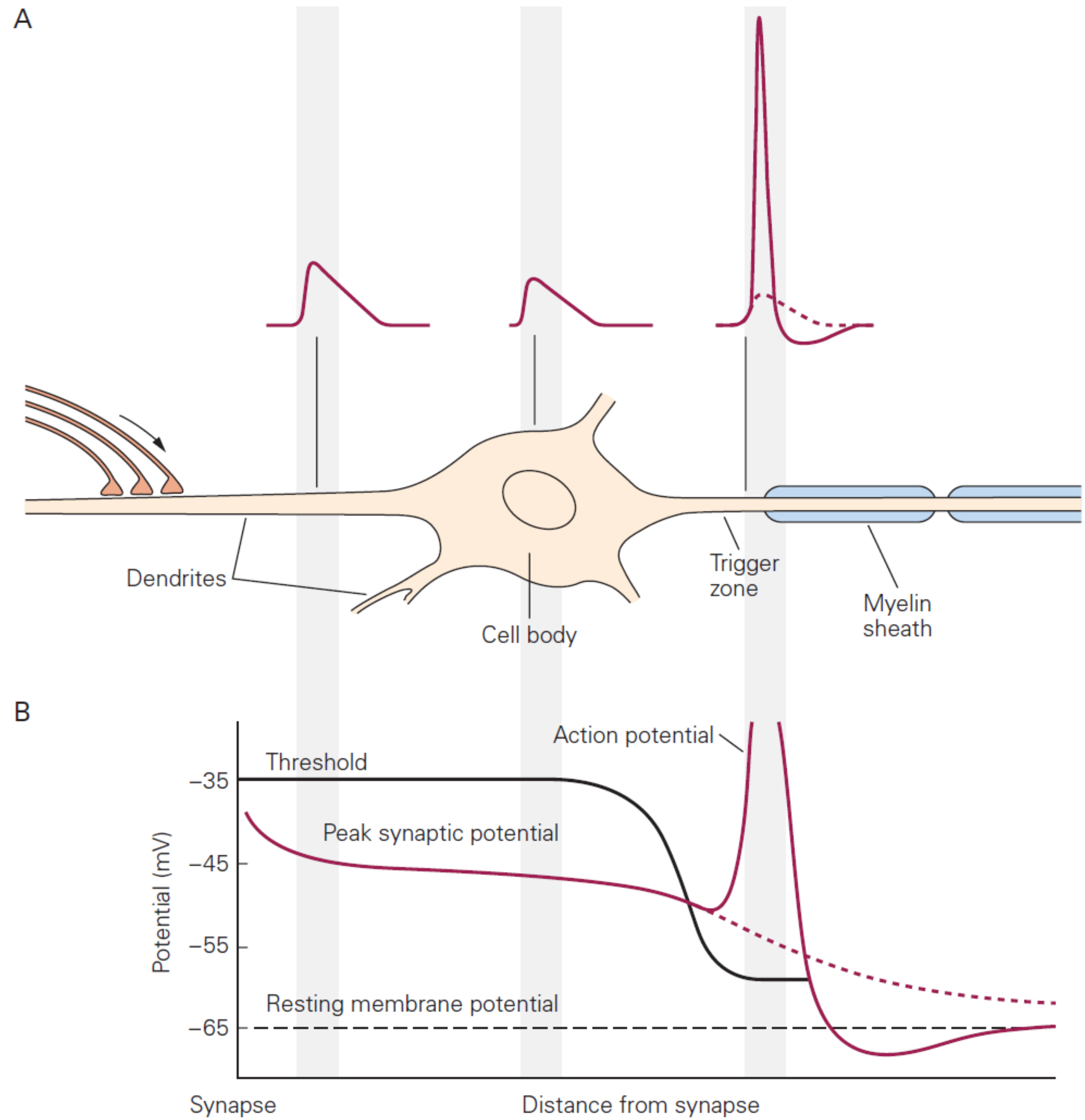


Excitatory postsynaptic potential (EPSP)

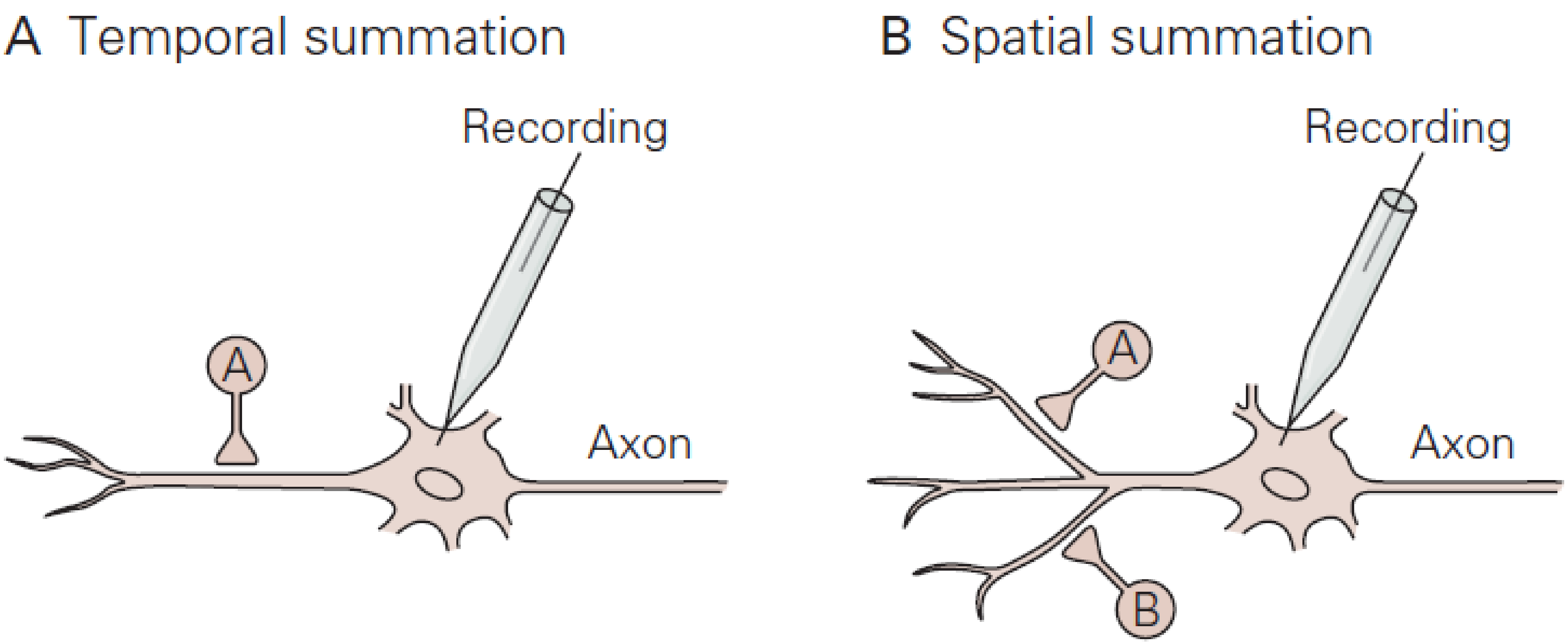
Inhibitory postsynaptic potential (IPSP)






A
Dendrites
Cell body
Trigger zone
Myelin sheath
B
Action potential
Threshold
Peak synaptic potential
Resting membrane potential
–35
–45
–55
–65
Potential (mV)
Synapse
Distance from synapse

Synapses


A Temporal summation
Recording
A
Axon
B Spatial summation
Recording
A
B
Axon

Synapses - neurotransmitters

Small molecule transmitters

- monoamines (acetylcholine, serotonin, histamine)
- catecholamines (dopamine, norepinephrine, epinephrine)
- amino acids (glutamate, GABA, glycine)

Large molecule transmitters

- large number of neuropeptides (substance P, enkephalin, vasopressin, etc.)

Synapses – neurotransmitters - receptors

- Each neurotransmitter (ligand) has **many subtypes of receptors** – effects differ in cells.

Transmitter	Receptor	Second Messenger	Net Channel Effects
Monoamines			
Acetylcholine	Nicotinic		↑Na^+, K^+
	M_1, M_3, M_5	↑IP_3, DAG	↑Ca^{2+}
	M_2, M_4	↓Cyclic AMP	↑K^+
Serotonin	$5HT_{1A}$	↓Cyclic AMP	↑K^+
	$5HT_{1B}$	↓Cyclic AMP	
	$5HT_{1D}$	↓Cyclic AMP	↓K^+
	$5HT_{2A}$	↑IP_3, DAG	↓K^+
	$5HT_{2C}$	↑IP_3, DAG	
	$5HT_3$		↑Na^+
	$5HT_4$	↑Cyclic AMP	
Catecholamines			
Dopamine	D_1, D_5	↑Cyclic AMP	
	D_2	↓Cyclic AMP	↑K^+, ↓Ca^{2+}
	D_3, D_4	↓Cyclic AMP	
Norepinephrine	α_1	↑IP_3, DAG	↓K^+
	α_2	↓Cyclic AMP	↑K^+, ↓Ca^{2+}
	β_1	↑Cyclic AMP	
	β_2	↑Cyclic AMP	
	β_3	↑Cyclic AMP	
Amino Acids			
Glutamate	Metabotropic[a]		
	Ionotropic		
	AMPA, Kainate		↑Na^+, K^+
	NMDA		↑Na^+, K^+, Ca^{2+}
GABA	$GABA_A$		↑Cl^-
	$GABA_B$	↑IP_3, DAG	↑K^+, ↓Ca^{2+}
Glycine	Glycine		↑Cl^-

[a]Eleven subtypes identified; all decrease cAMP or increase IP_3 and DAG, except one, which increases cAMP.

Synapses – neurotransmitters - receptors

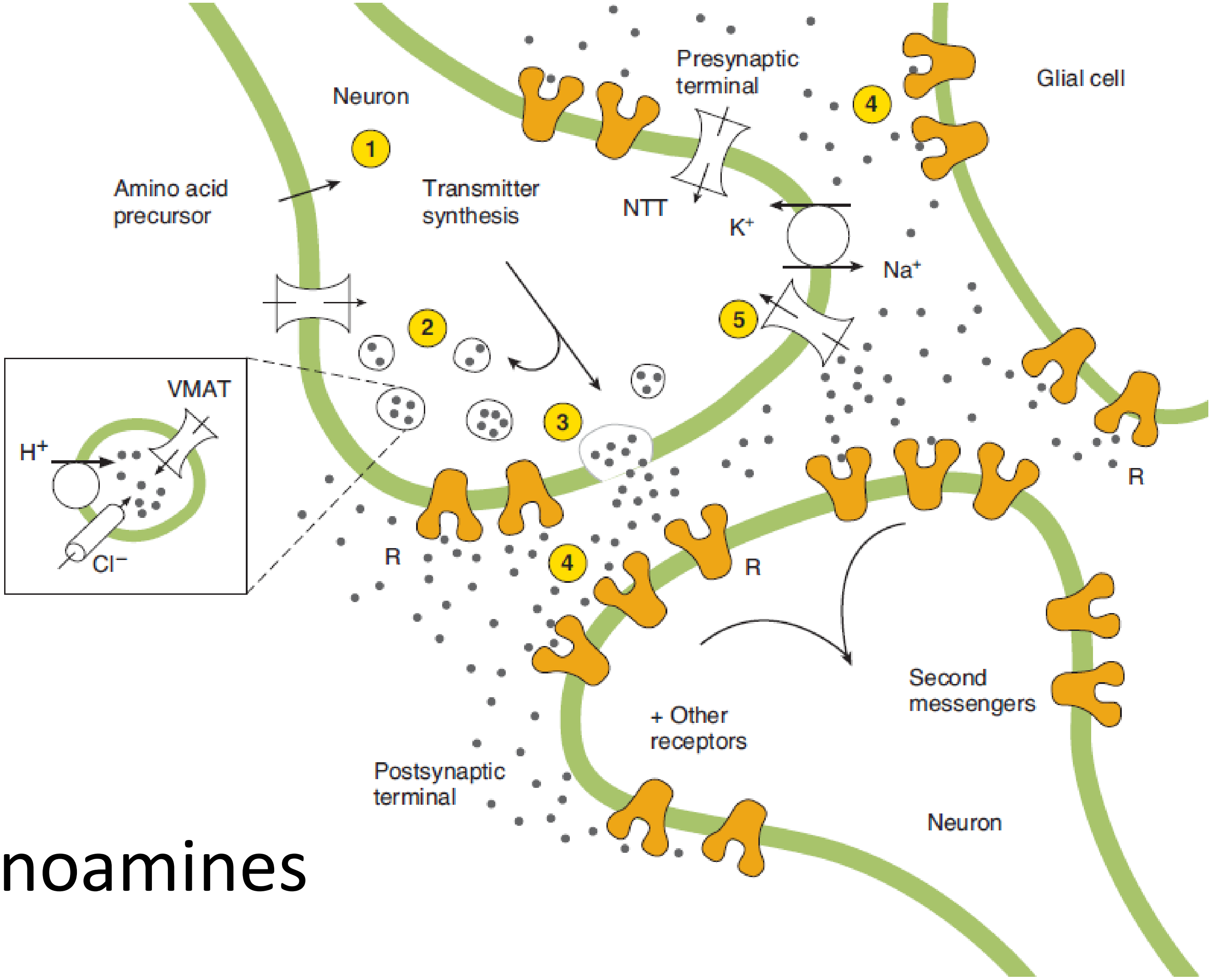
- Each neurotransmitter (ligand) has **many subtypes of receptors** – effects differ in cells.
- Receptors are also on presynaptic membrane (**autoreceptors**) – feeback control (negative, less often positive).
- Receptors **tend to group** in large families (structure and function) – <u>ionotropic</u> (ionic channel), <u>metabotropic</u> (G-proteins and proteinkinases)

Acetylcholine	Nicotinic		↑Na^+, K^+
	M_1, M_3, M_5	↑IP_3, DAG	↑Ca^{2+}
	M_2, M_4	↓Cyclic AMP	↑K^+

Synapses – neurotransmitters - receptors

- Each neurotransmitter (ligand) has **many subtypes of receptors** – effects differ in cells.
- Receptors are also on presynaptic membrane (**autoreceptors**) – feeback control (negative, less often positive).
- Receptors **tend to group** in large families (structure and function) – <u>ionotropic</u> (ionic channel), <u>metabotropic</u> (G-proteins and proteinkinases)
- Receptors are **concentrated in clusters** in postsynaptic membrane close to the place where the neurotransmitter is released.
- Prolonged exposure to ligands results in **desensitization of the receptors** – homologous and hereologous.

Synapses - neurotransmitters



Monoamines

Synapses – synaptic plasticity

- **Intrinsic signals** – *e.g.* rapid firing of the neuron
- **Extrinsic signals** – *e.g.* direct synaptic input from other neurons, or diffuse action of neuromodulators

- **Presynaptic modification** – alteration of the neurotransmitter release
- **Postsynaptic modification** – modulation of response to the neurotransmitter
- Both pre- and postsynaptic modification at the same time

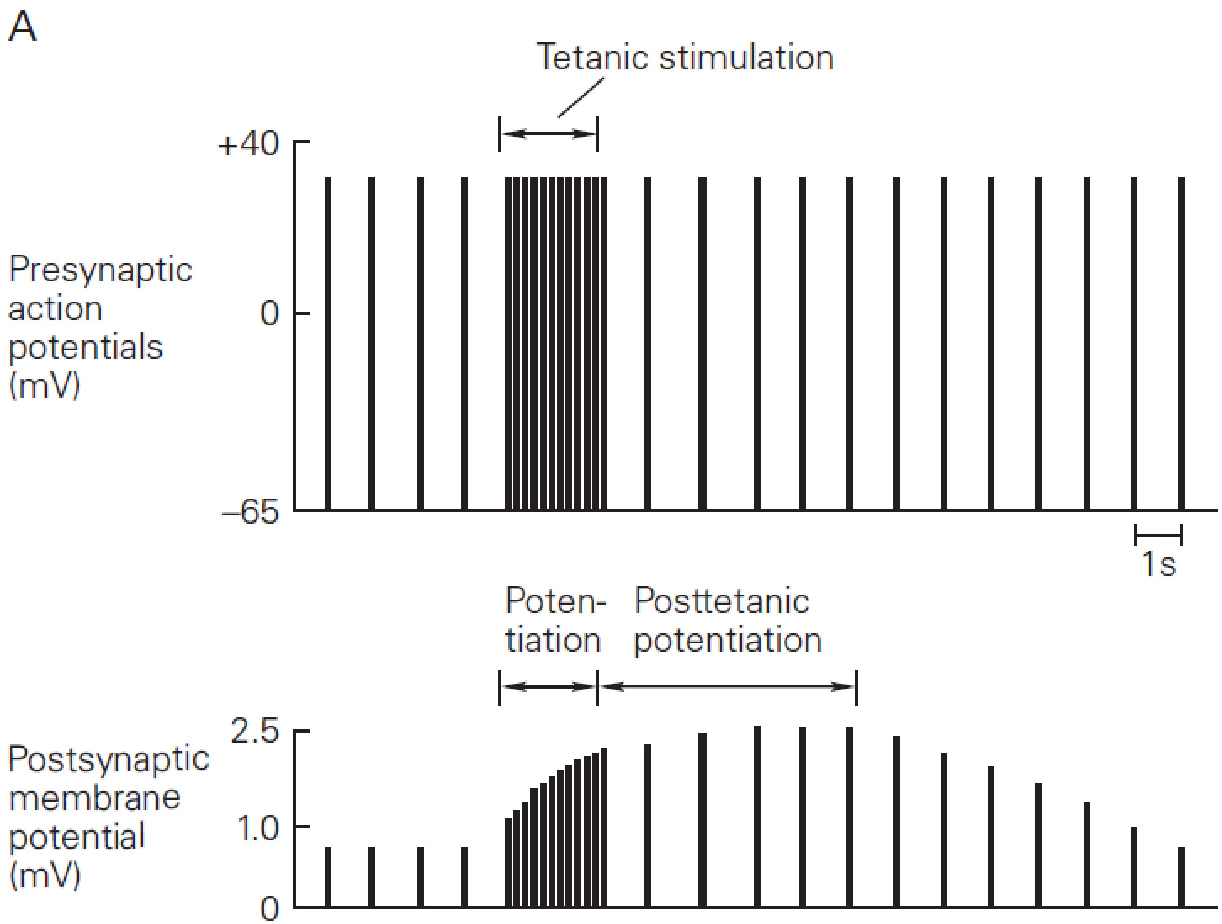
- **Short-term changes**
- **Long-term changes** – crucial to development and learning

Synapses – synaptic plasticity

- **Potentiation**
- **posttetanic potentiation** – increased size of EPSP during and after a repetitive (tetanic) stimulation of the presynaptic neuron (due to accumulation of Ca^{2+} and increased release of the transmitter)
- may be long-term → long-term potentiation (learning)

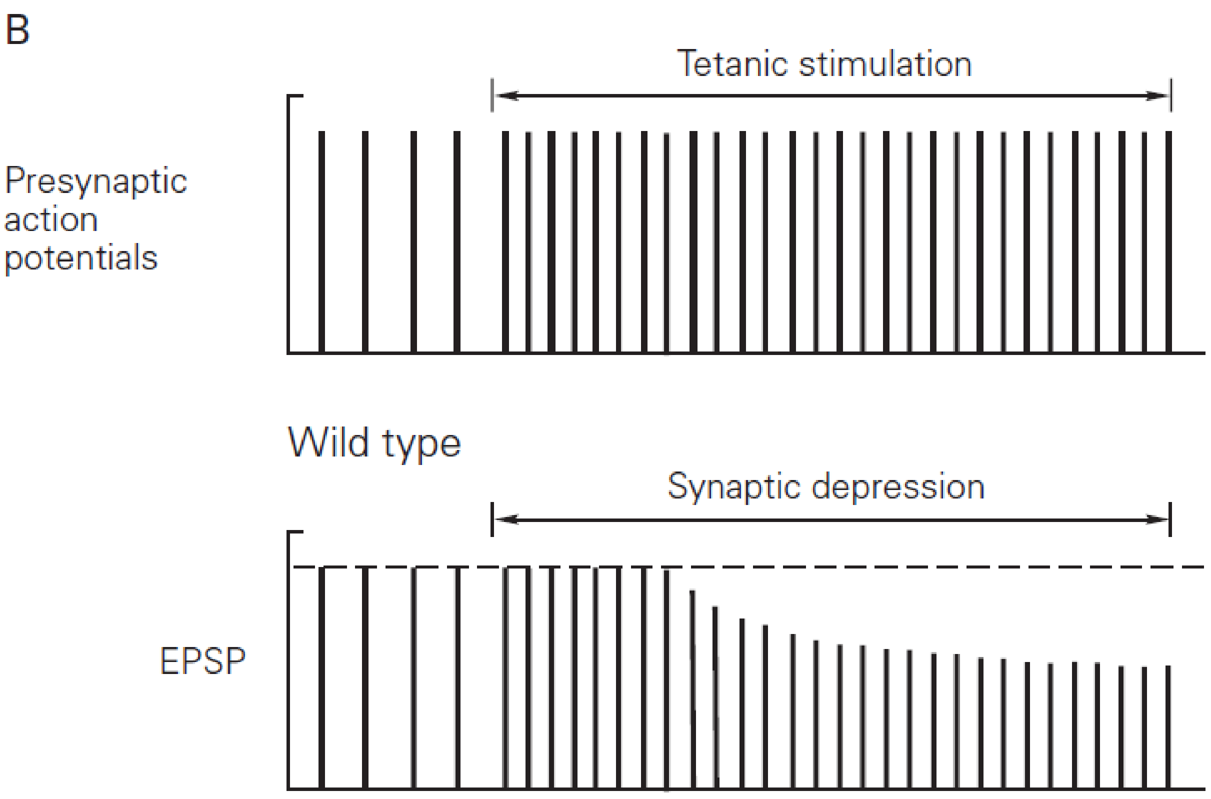
Synapses – synaptic plasticity

- **Potentiation**



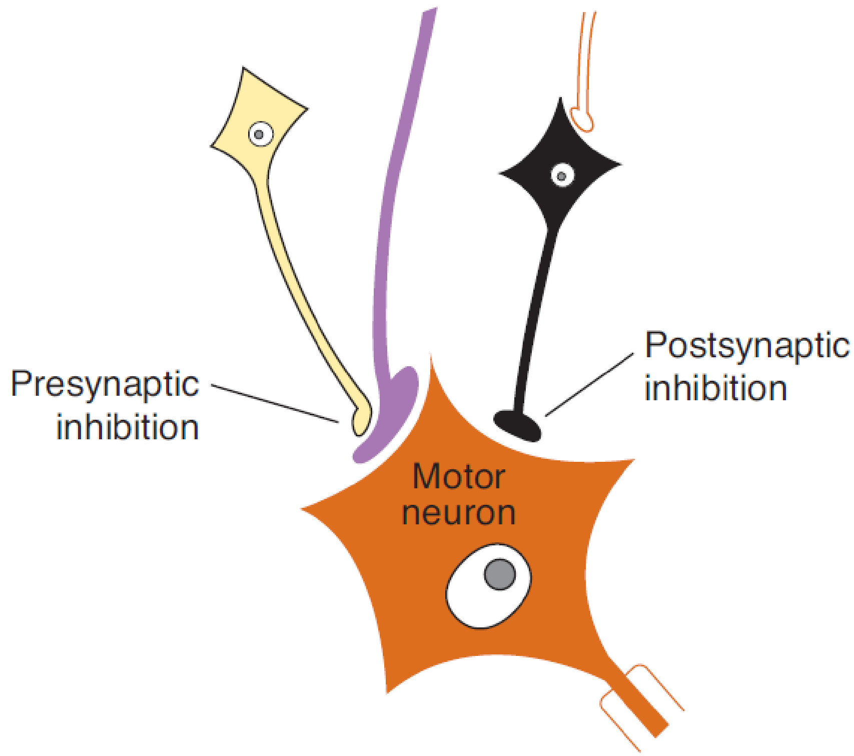
Synapses – synaptic plasticity

- **Synaptic depression**
- after a prolonged high-frequency stimulation - result from a temporary depletion of the store of releasable synaptic vesicles



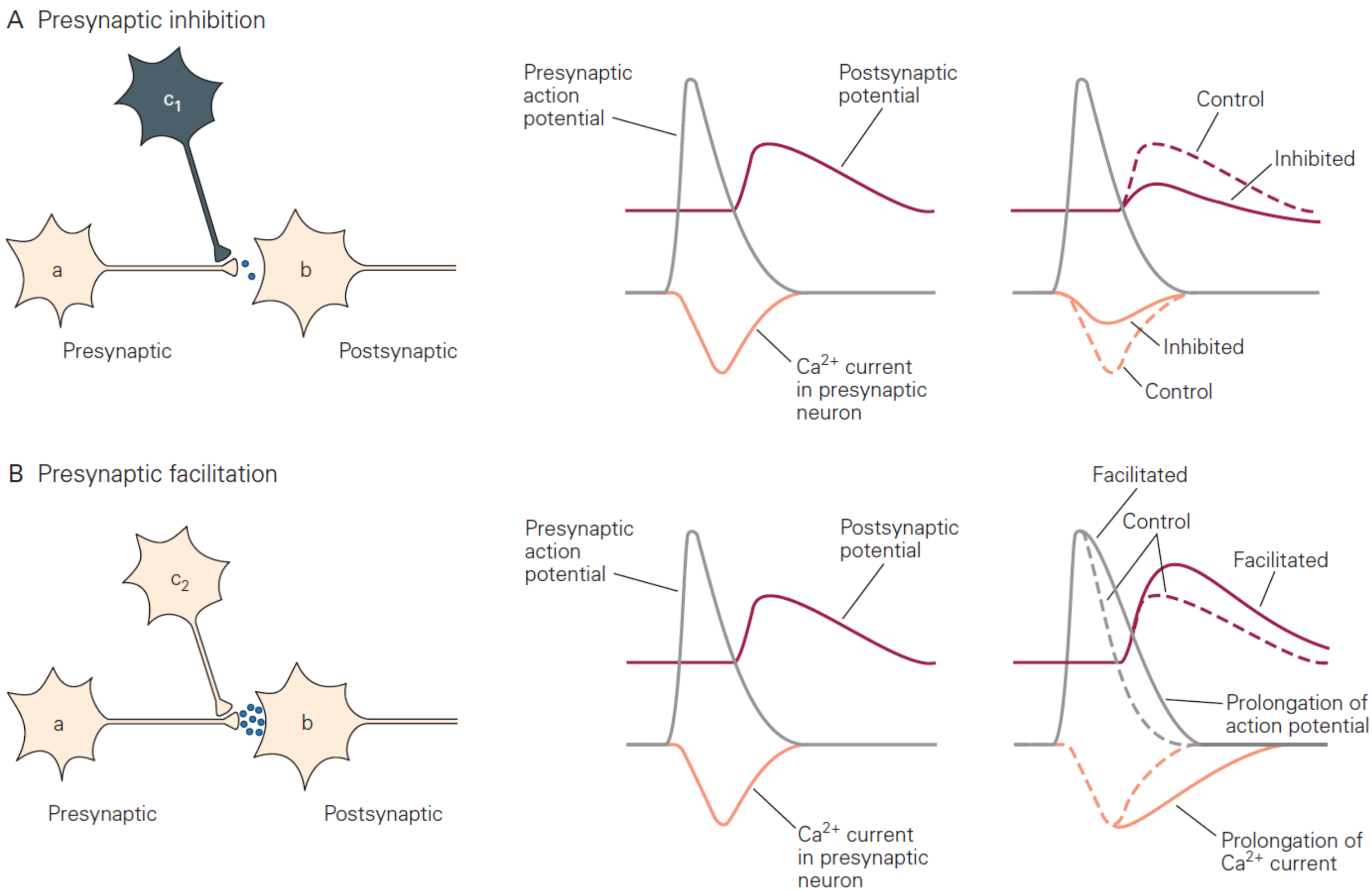
Synapses – synaptic plasticity

- **Postsynaptic inhibition/facilitation**
- release of excitatory/inhibitory neurotransmitter on the synapse $\rightarrow$ the probability of firing of the postsynaptic cell is increased/decreased



Synapses – synaptic plasticity

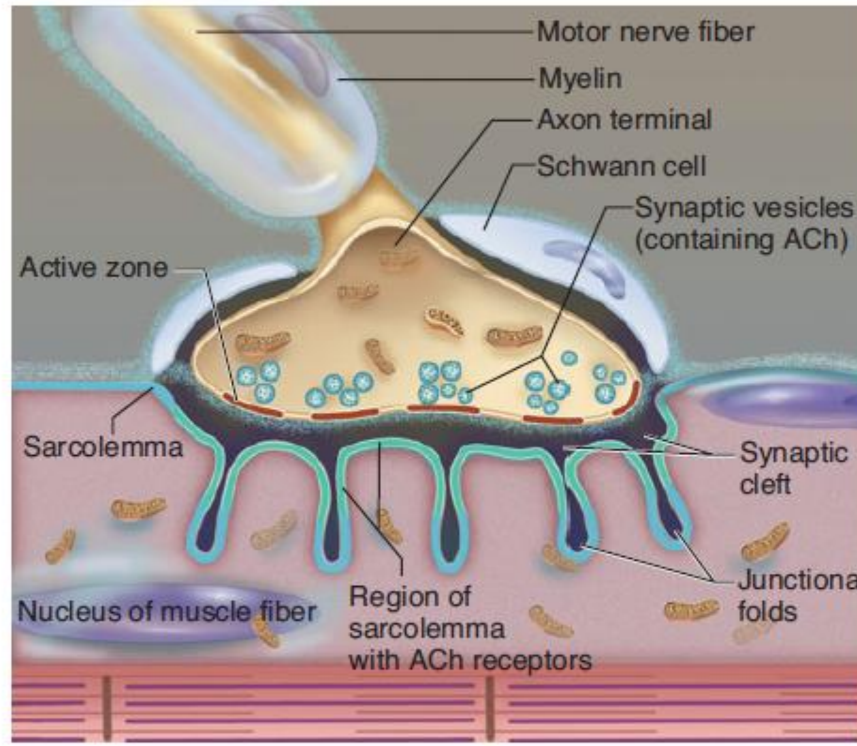
- **Presynaptic inhibition/facilitation** axo-axonal synapses



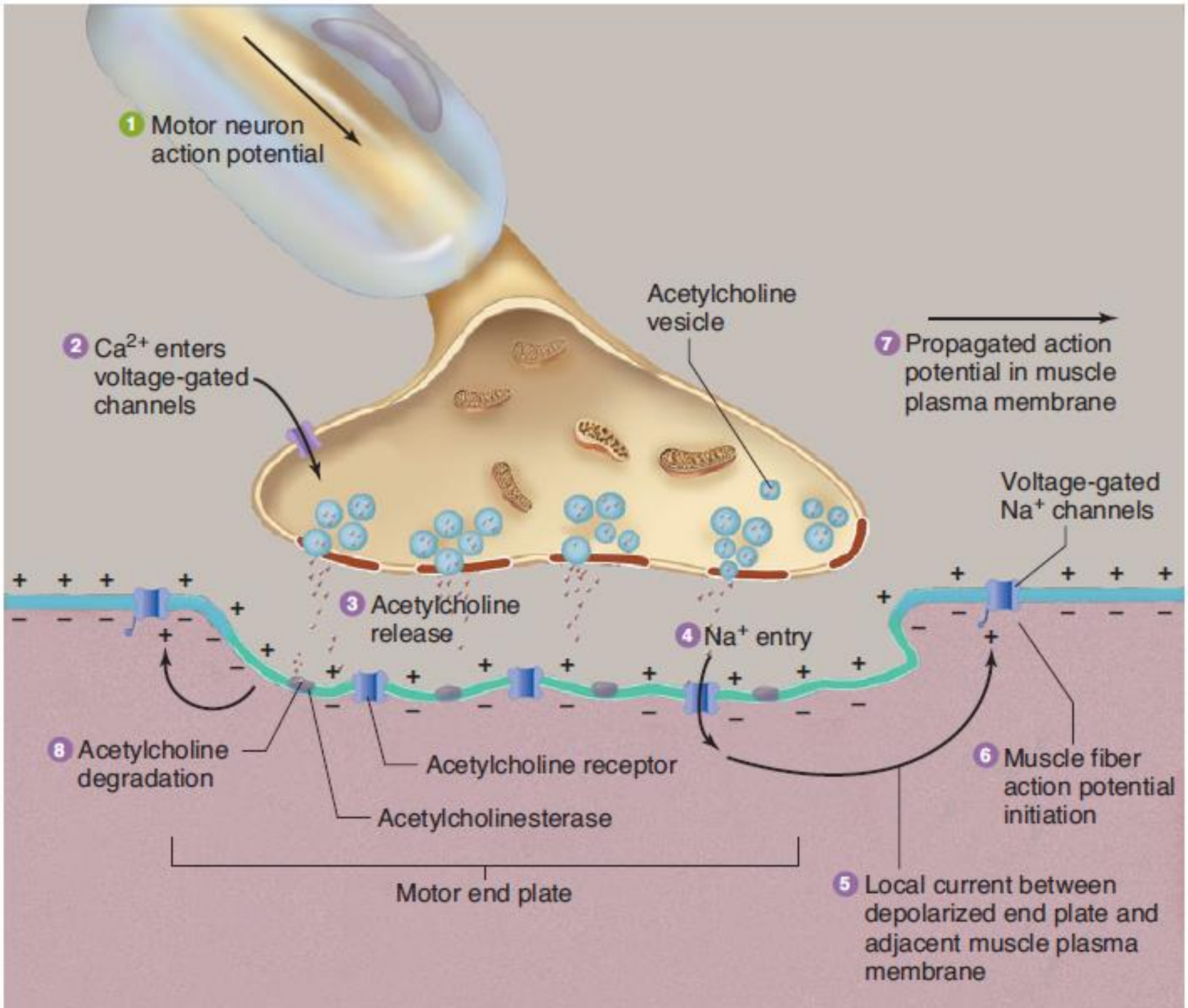
Neuromuscular junction

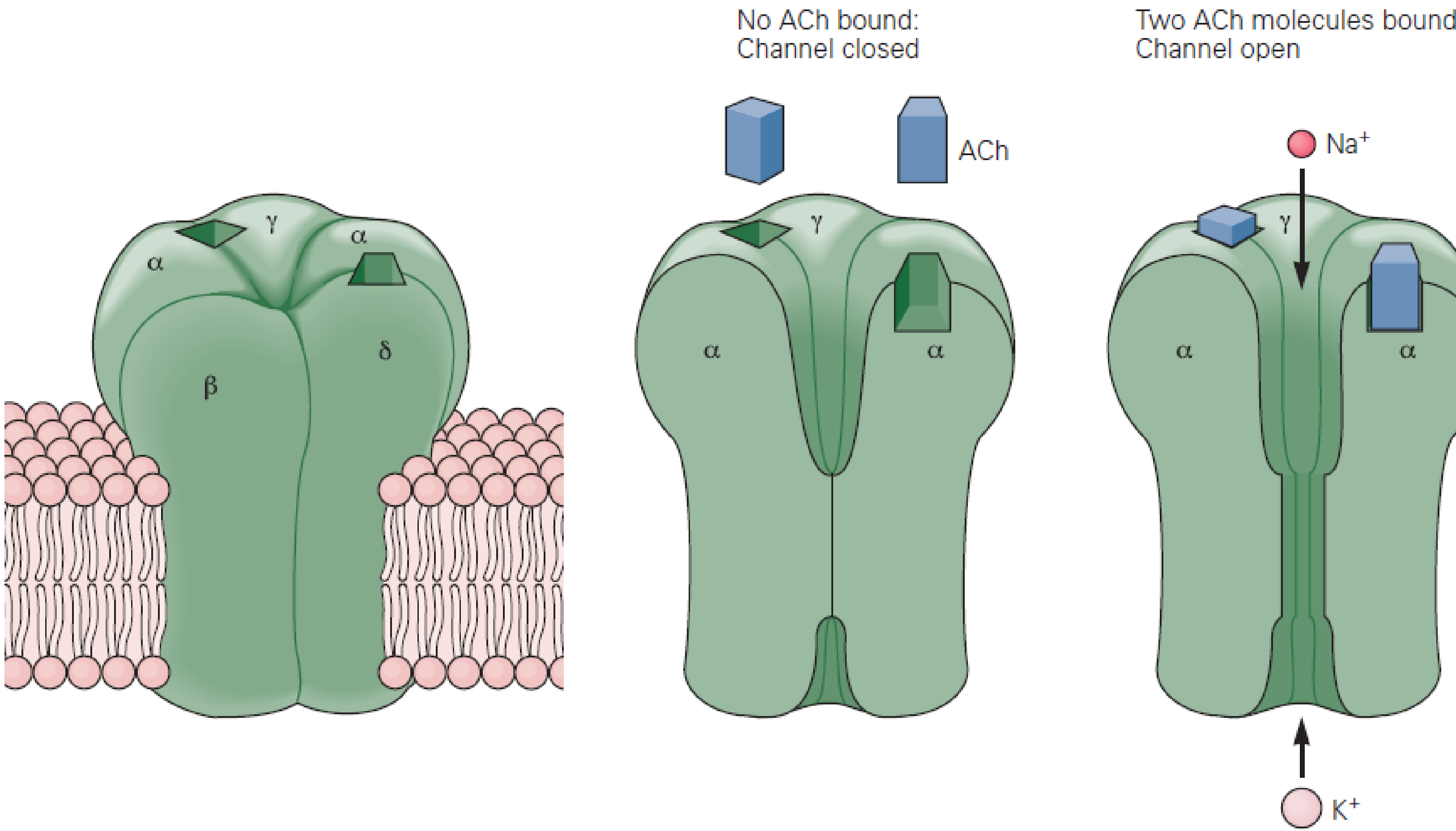
(a)

(b)



Neuromuscular junction





No ACh bound:
Channel closed
Two ACh molecules bound:
Channel open
ACh
Na+
K+
α
γ
α
β
δ
α
γ
α
α
γ
α

Neuromuscular junction

End-plate potential

- local depolarizing potential due to increased Na^+ conductance