Comunicarea în sistemul nervos: o scurtă prezentare generală (p II)

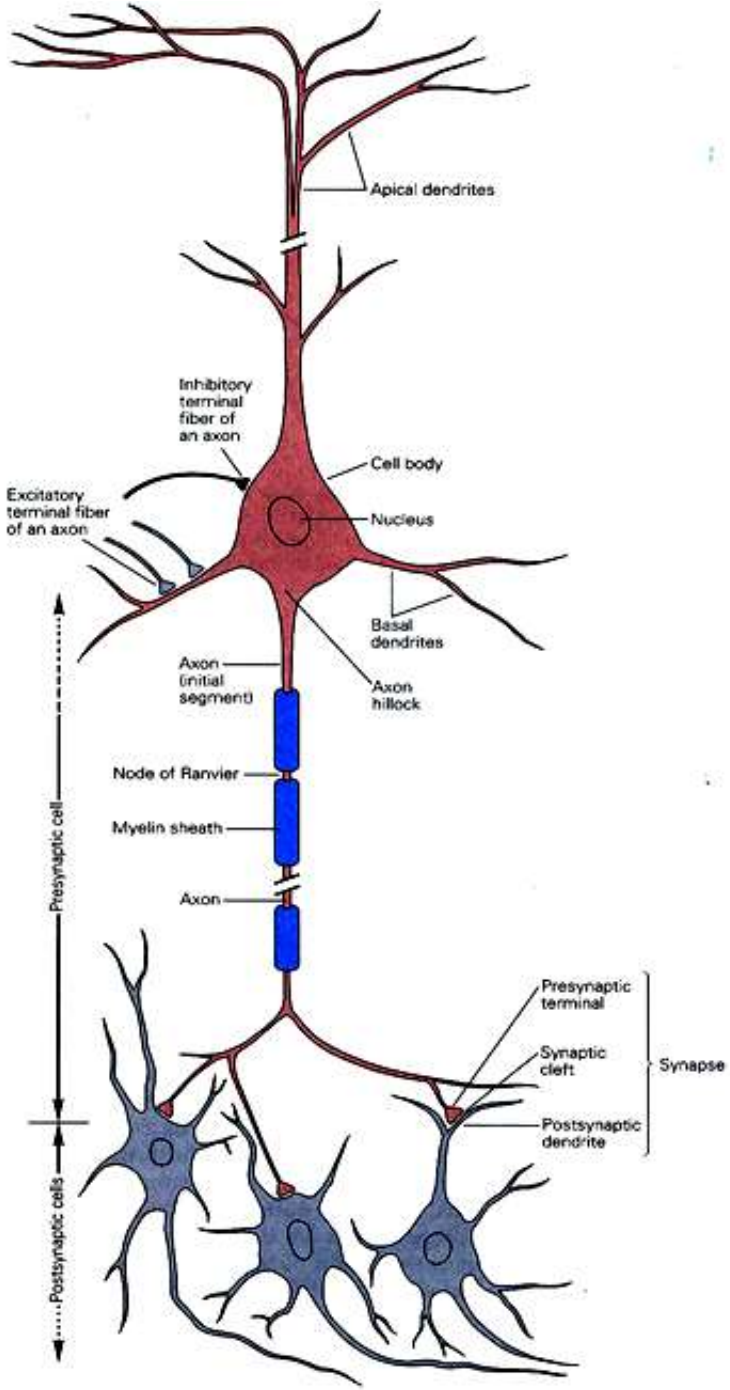
Nivel macro:

- Anatomia funcțională a sistemului nervos

Nivel Micro:

- Celulele
- Sinapse
- Neurotransmițători

Bazele Structurale ale unui Neuron Tipic



1) **Dendrites -** Processing Elements - generally no action potential is generated – electrical signaling is by passive conductance

2) **Soma –** Integration of input from dendrites and triggering of action potential. Also metabolic center – site of gene regulation (contains nucleus) and protein synthesis

3) **Axon –** Transmission of action potential – synaptic contact with target cell(s)

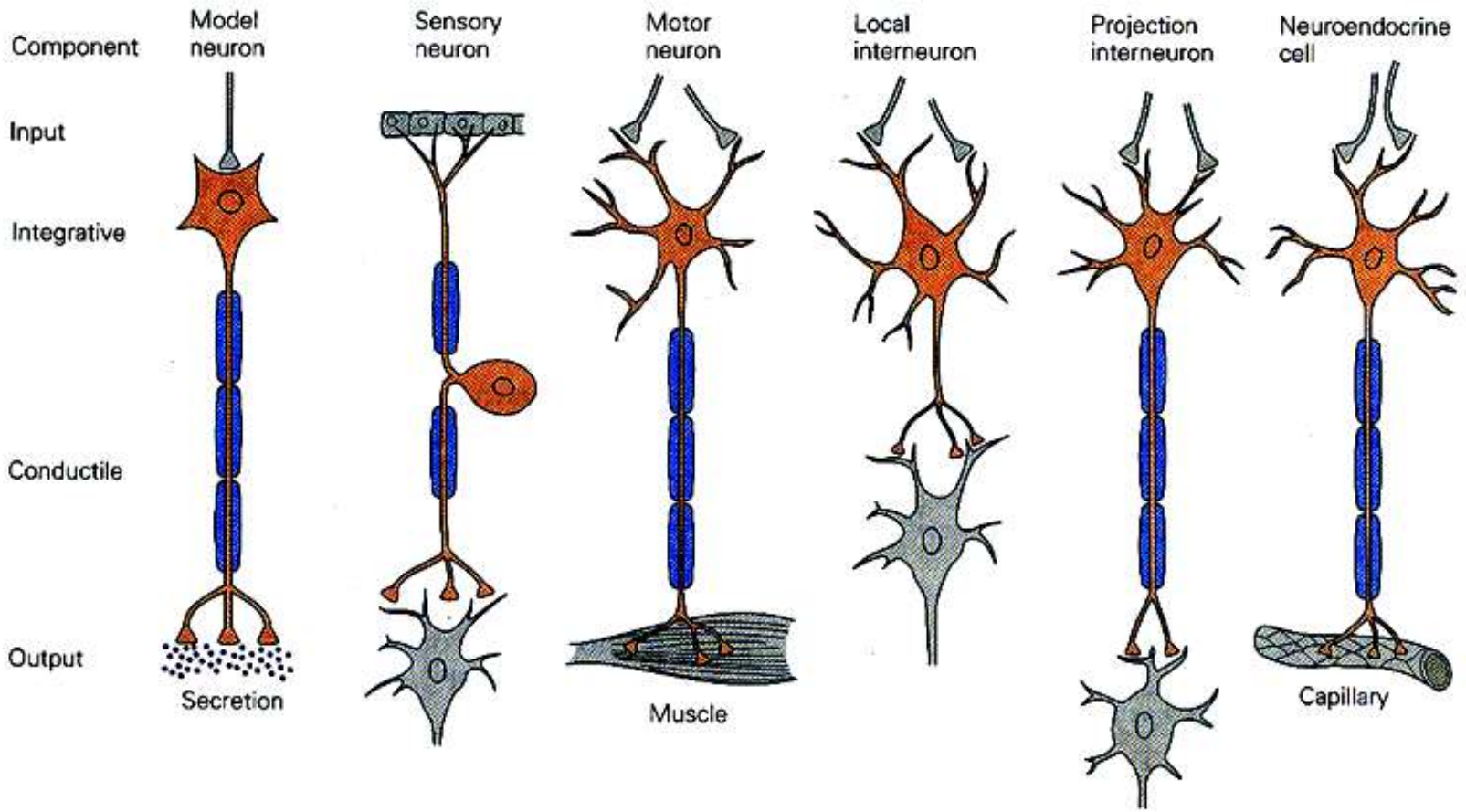
Bazele Structurale ale unui Neuron: 4 regiuni functionale

1) **Input (Receptive)** – Generally dendrites and soma

2) **Integrative** – Generally soma

3) **Conductive** – Generally axon

4) **Output** – Axon terminals

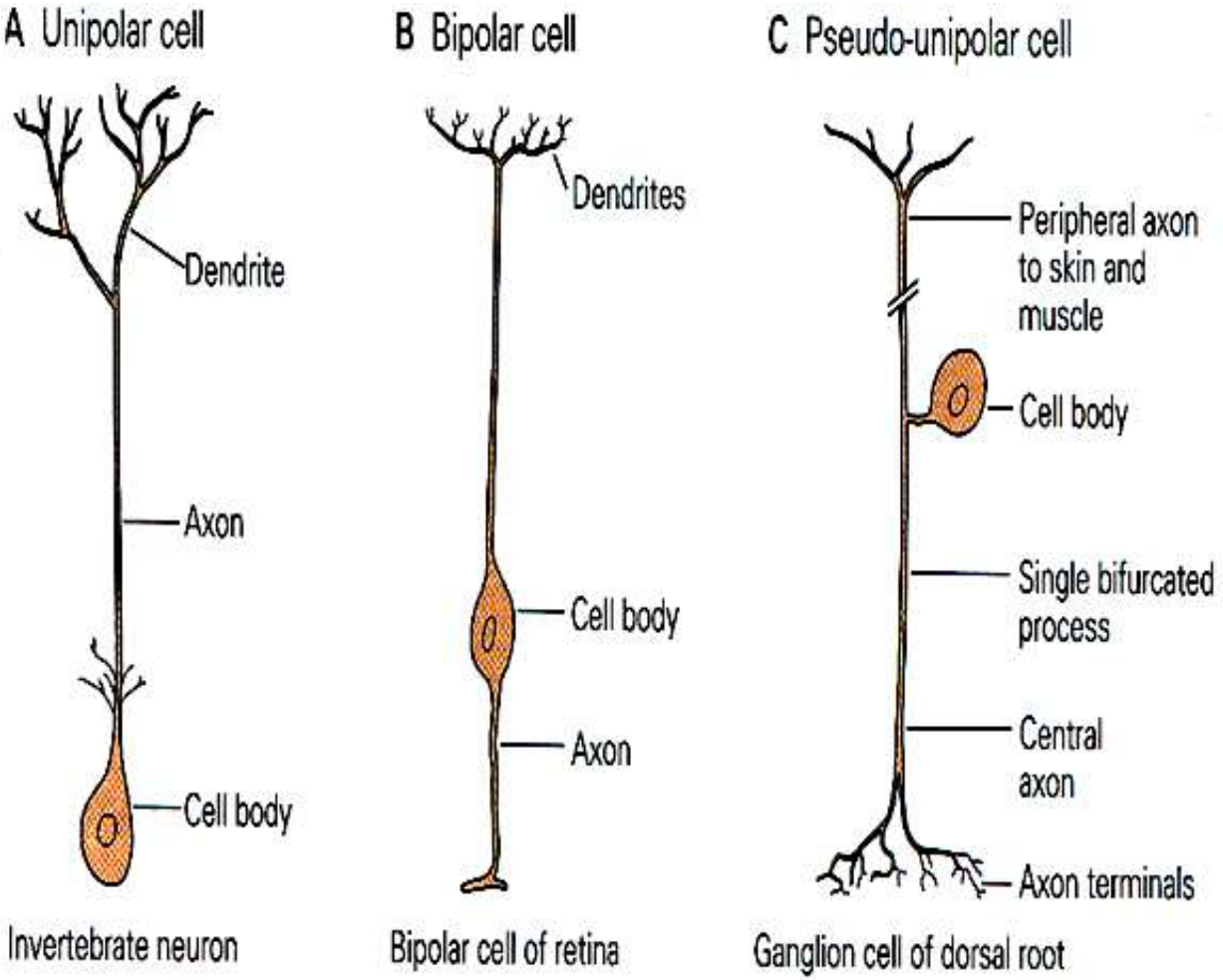


Clasificarea neuronilor pe baza numărului de procese care provin din corpul celulei

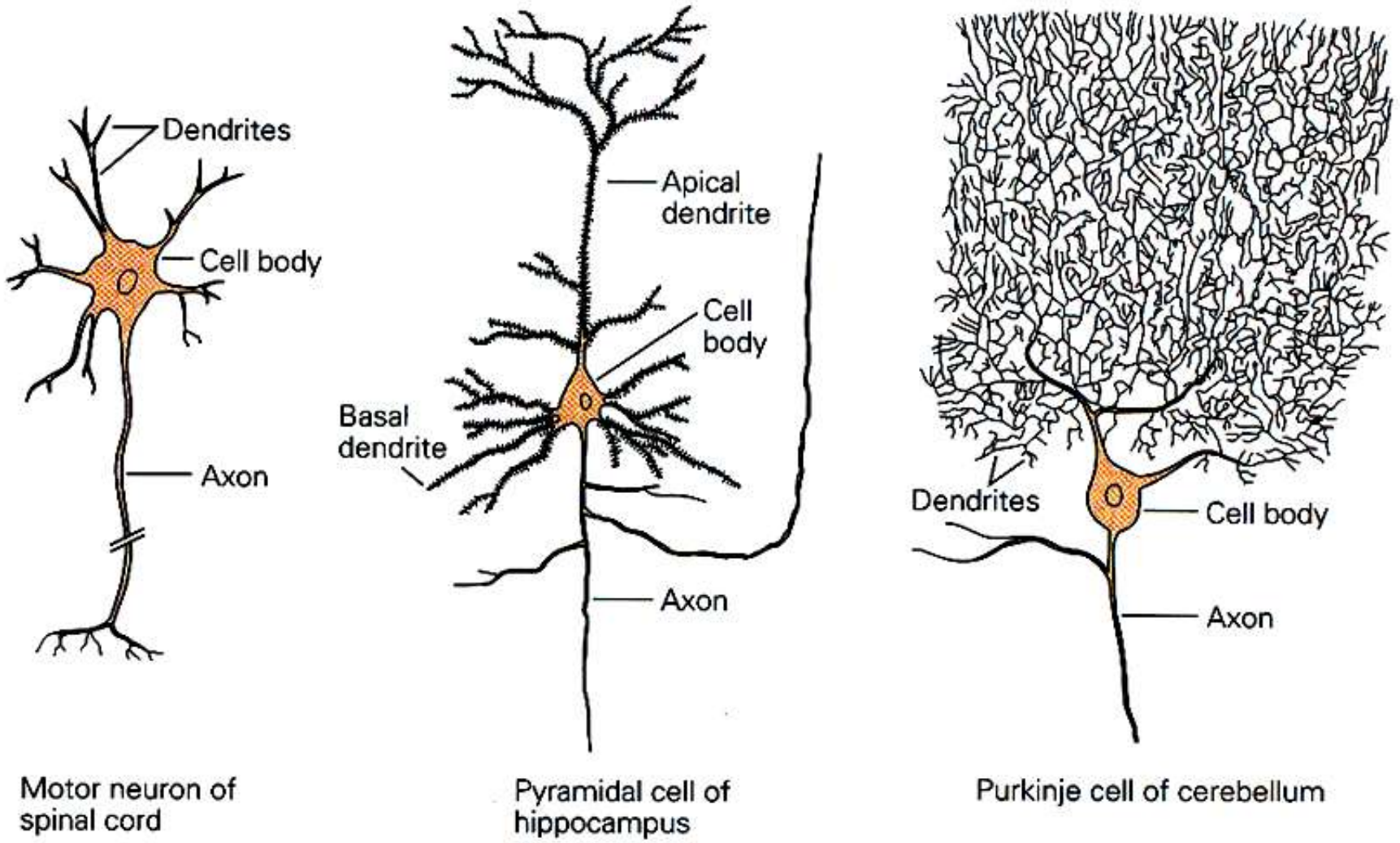
Unipolar - single process with different elements serving receptive vs transmission roles. Characteristic of invertebrate nervous system

Bipolar - two processes with distinct dendritic and axonal elements. Bipolar cell of retina

Pseudo-unipolar - single process that divides into receptive (dendritic) and transmission (axon) elements. Dorsal root ganglion



Neuron Multipolar - un axon, multiple dendrite.
Cel mai frecvent tip de celule din sistemul nervos al mamiferelor.



Potențialul de acțiune - bază pentru transmiterea semnalelor electrice între celule

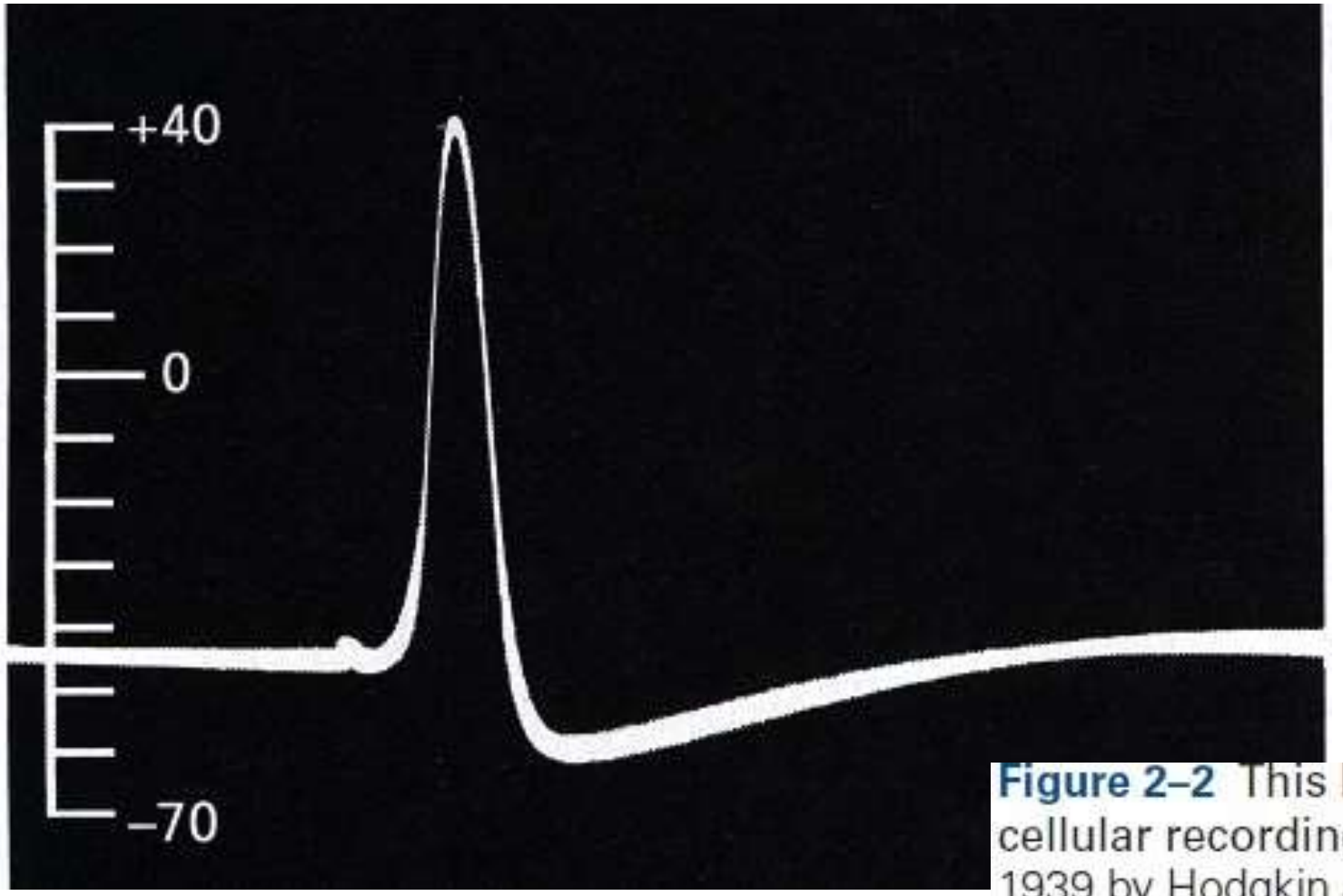
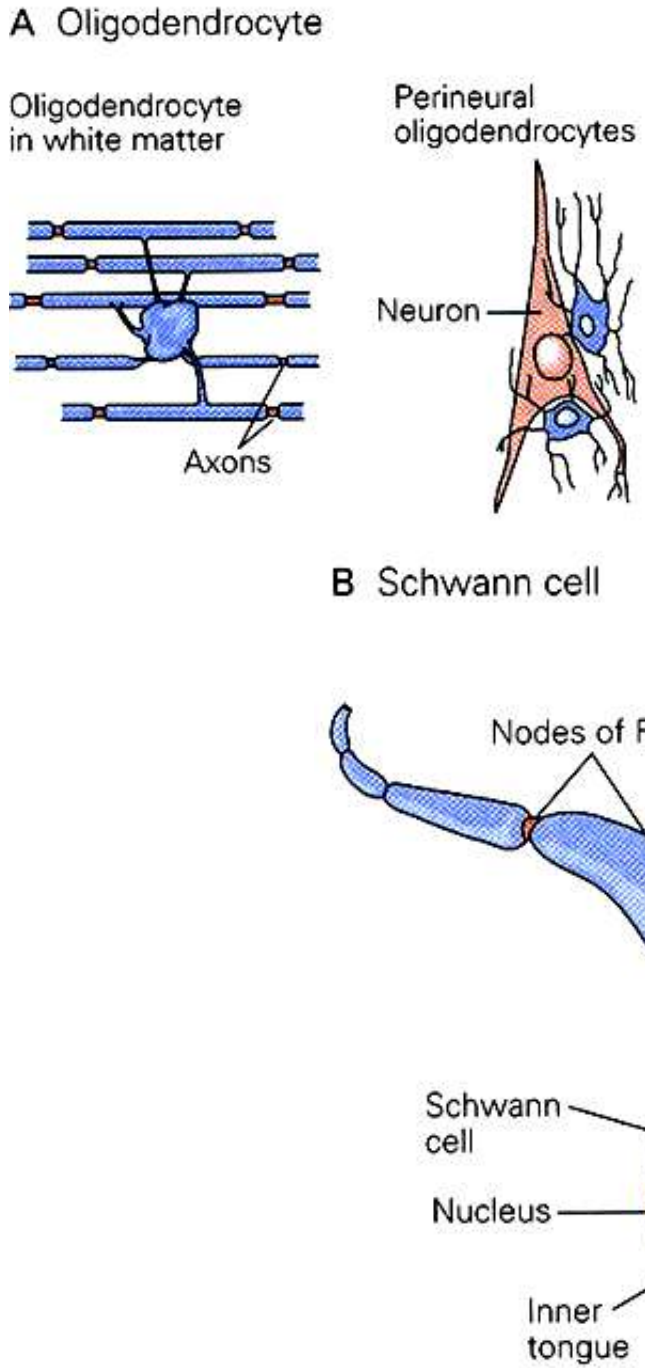
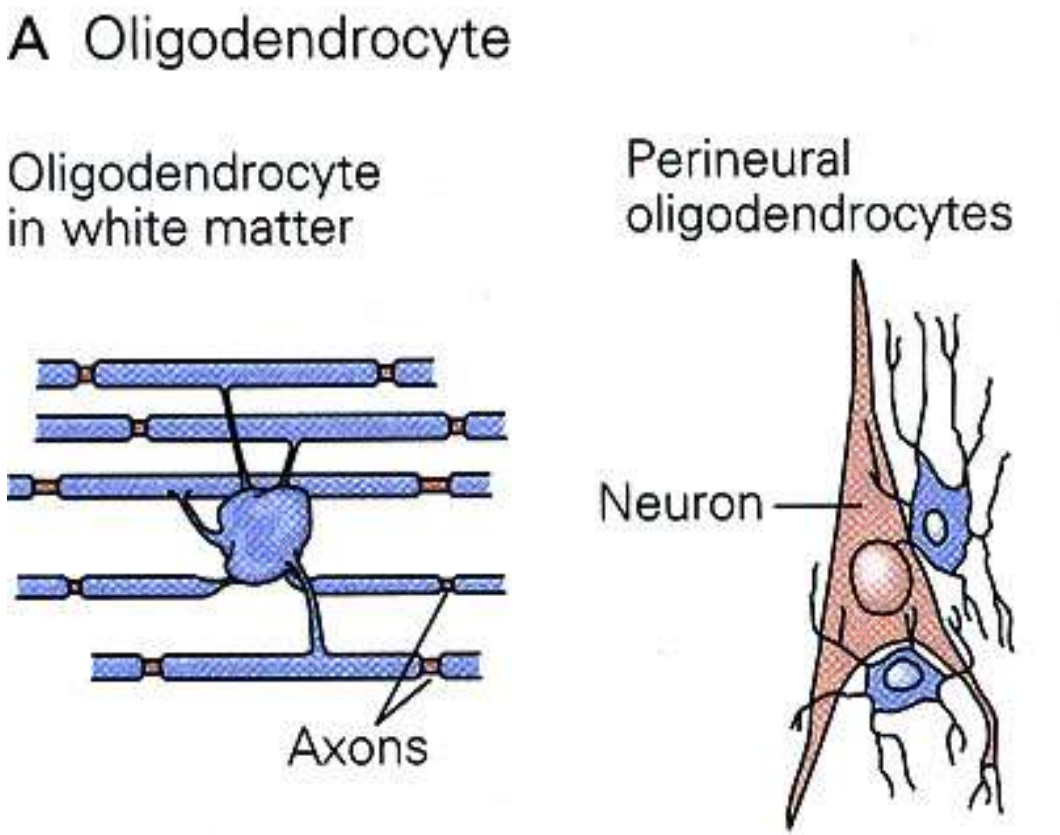


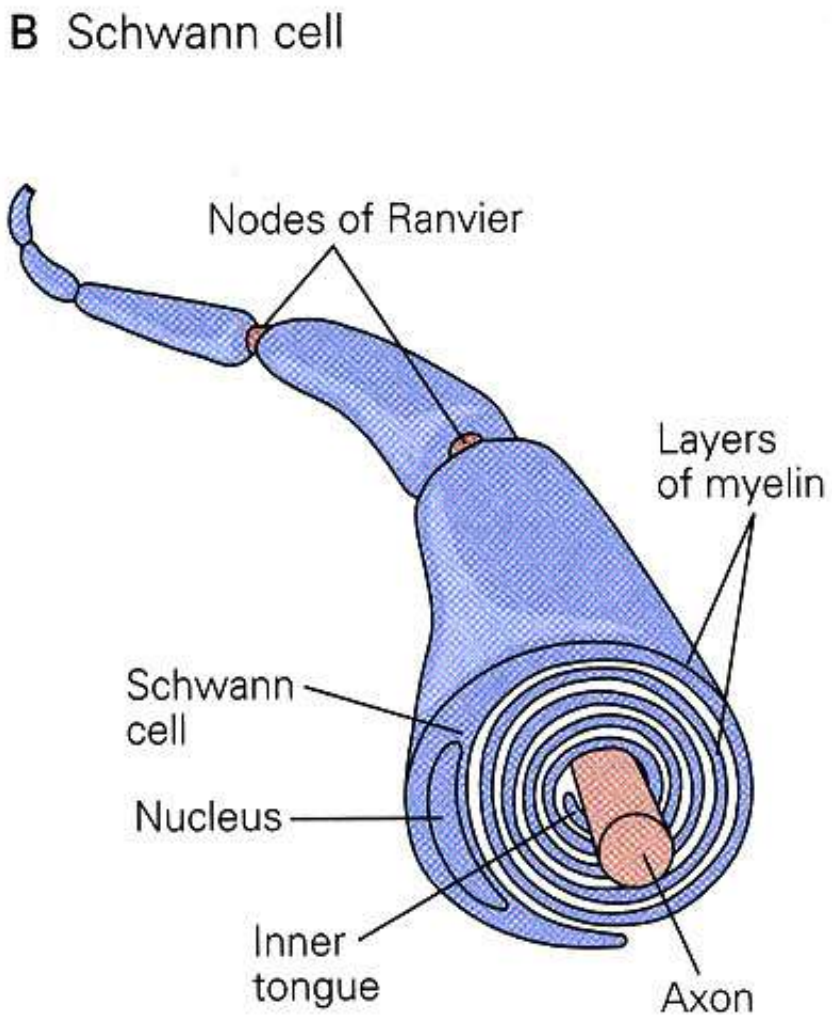
Figure 2–2 This historic tracing is the first published intracellular recording of an action potential. It was recorded in 1939 by Hodgkin and Huxley from a squid giant axon, using glass capillary electrodes filled with sea water. The timing pulses are separated by 2 ms. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as zero potential. (Reproduced, with per-

Celule Gliale

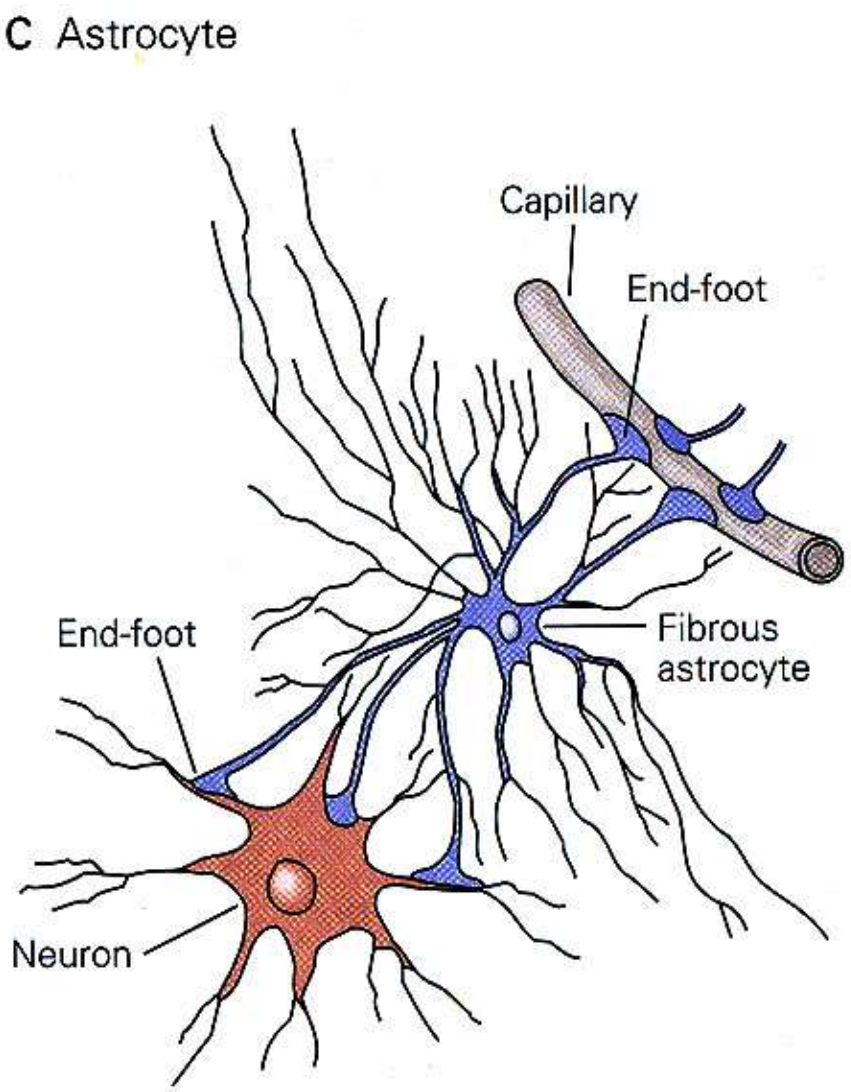




Oligodendrocytes – smaller cells with relatively fewer processes – provide myelin in white matter and in gray matter perineual oligodendrocytes surround and support neurons.

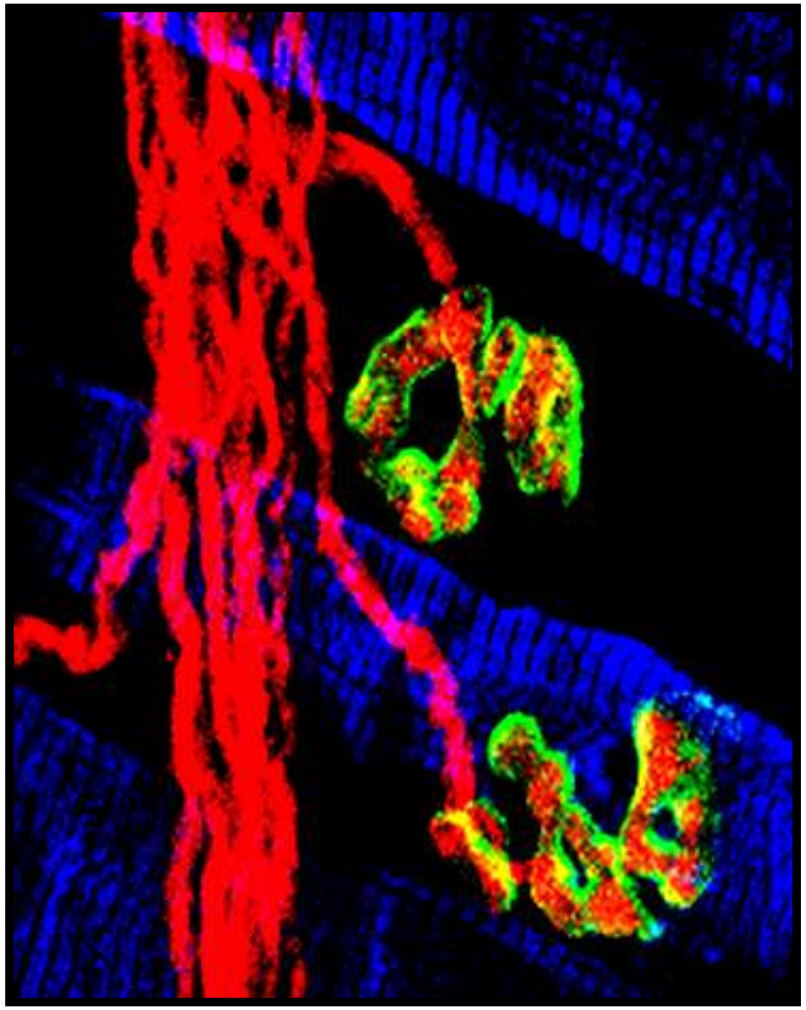


Schwann Cells – Provide myelin sheath surrounding peripheral axons. Several Schwann cells provide myelin sheath (~ 1 mm intervals) with intervening bare space (Nodes of Ranvier) – this is important in action potential propagation.

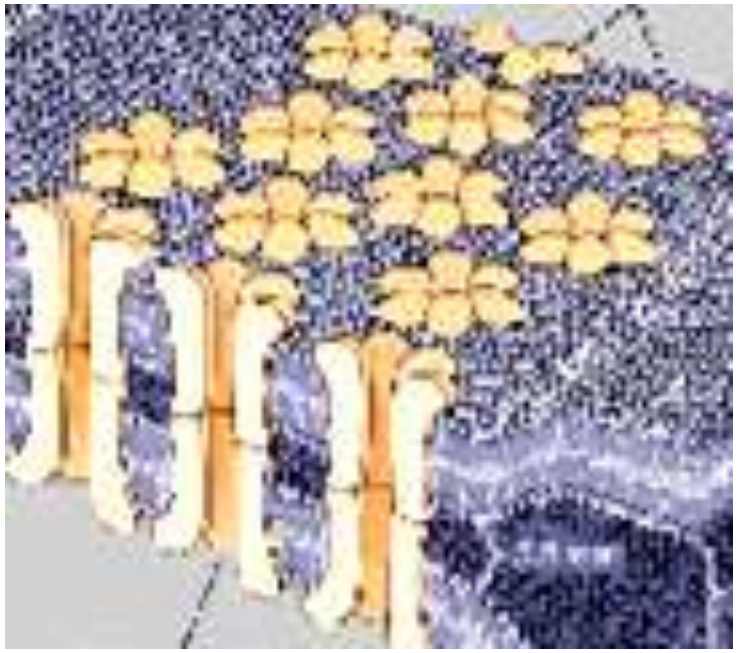


Astrocytes – Most numerous type of glial cells. Characterized by star-like shape and the broad end-feet processes that make contact with capillaries. Important role in forming the blood-brain barrier.

Sinapsa



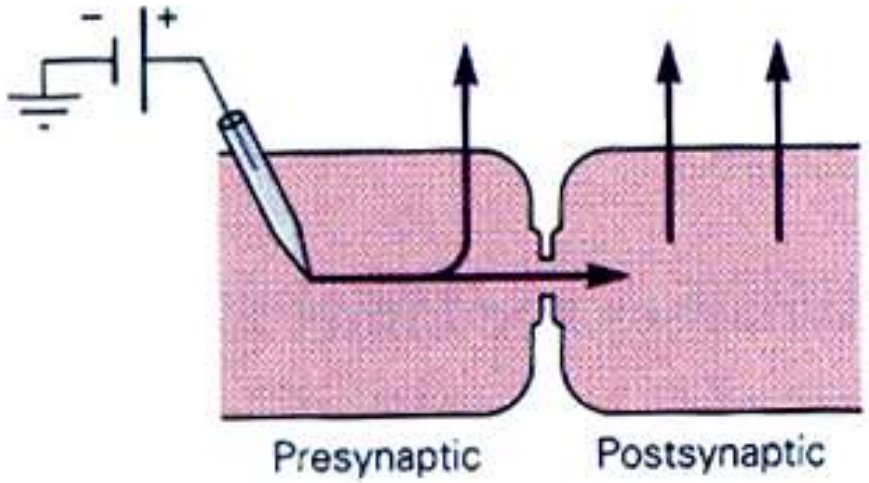
- Termen inventat de Charles Sherrington
- Zona specializată de contact între un neuron și celula țintă a acestuia.
- Electrice vs. chimice



Sinapse Electrice vs. Chimice

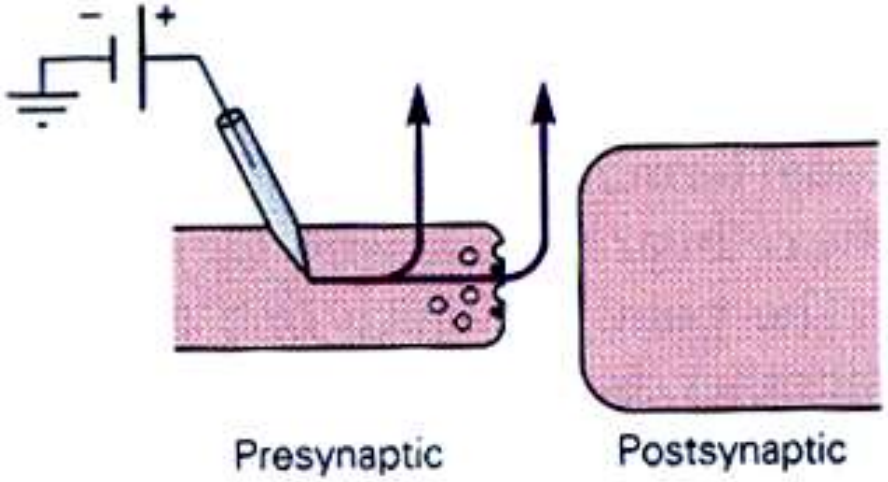
Type of synapse	Distance	Cytosolic Continuity	Components	Agent	Delay	Direction
Electrical	3.5 nm	Yes	Gap-junction	Current	Absent	Bidirectional
Chemical	20-40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Neurotransmitter	At least 0.3 ms, usually 1-5 ms	Unidirectional

Debitul de curent la sinapsele electrice și chimice

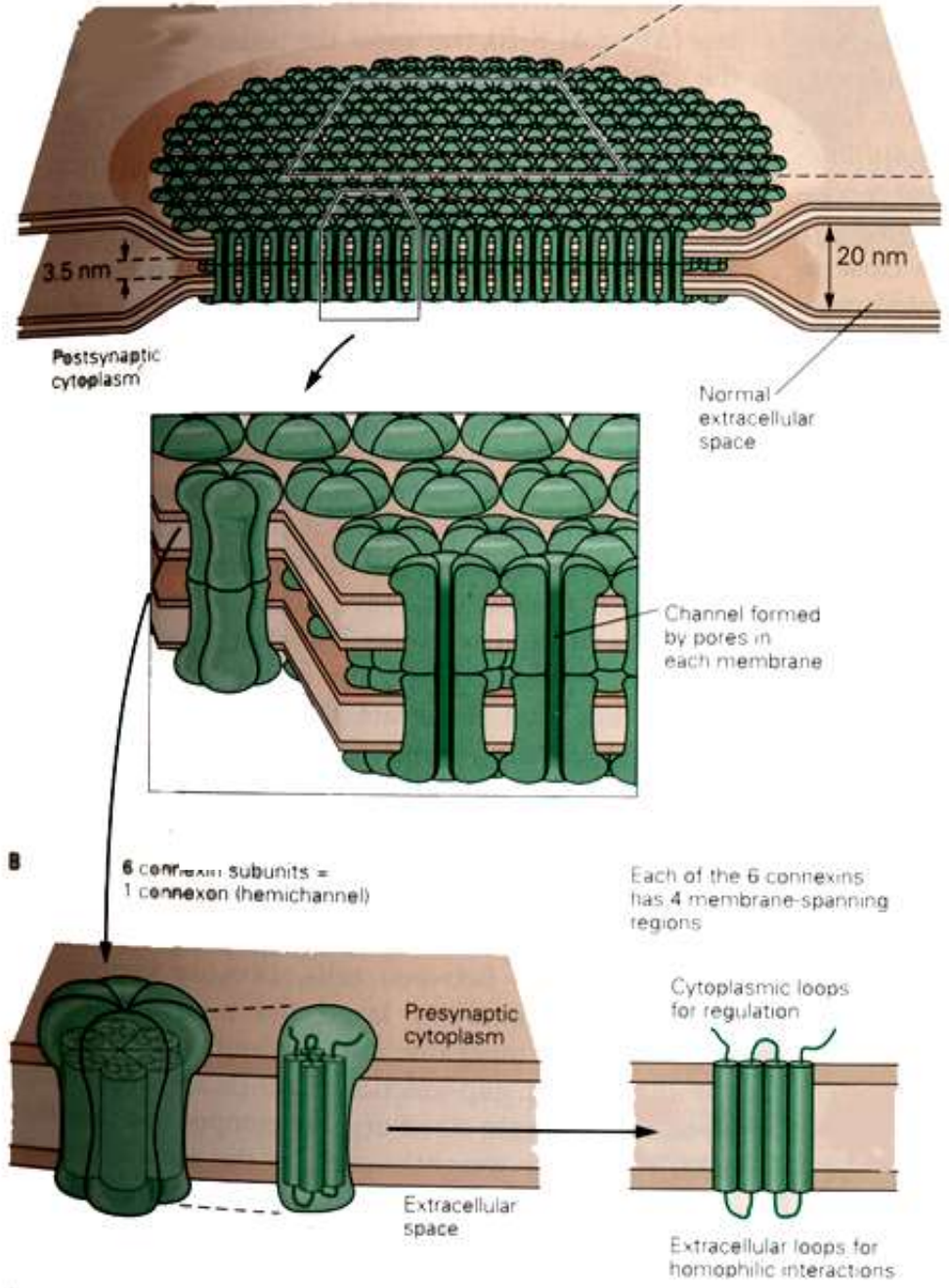


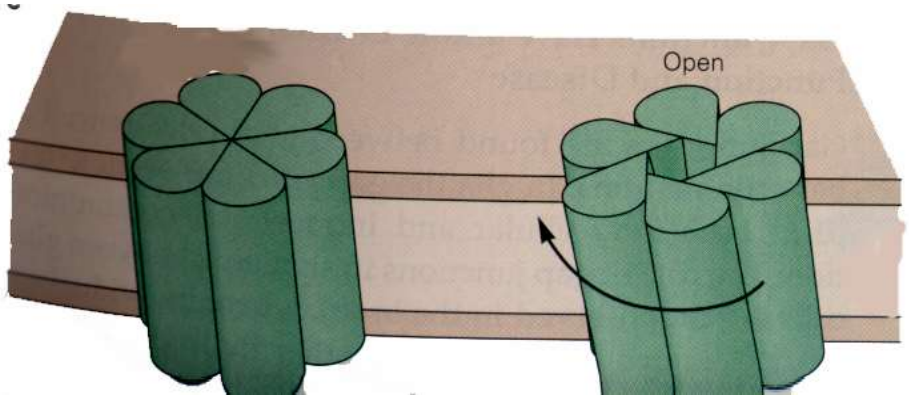
Sinapsa electrică: fluxul de curent se transmite direct de la neuron la celula țintă prin continuitate citosolică.

Sinapsă chimică: fluxul de curent limitat la neuron - nu se răspândește direct către celula țintă - nu există continuitate citosolică.



Gap Junctions (Jonctiuni “Gap” = Interval)

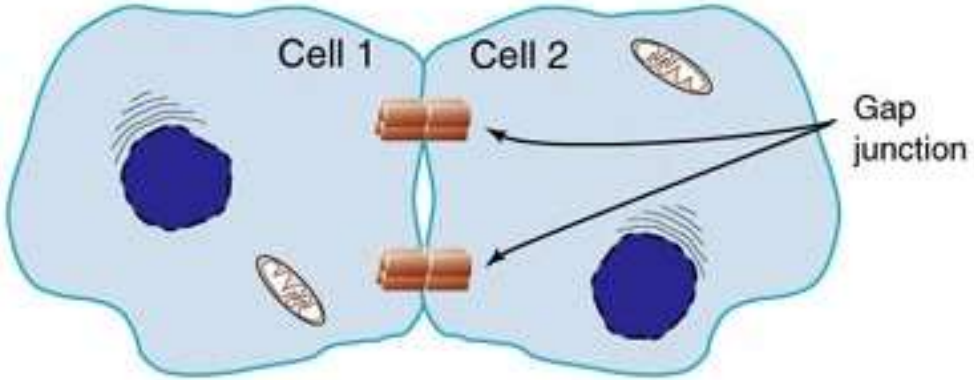


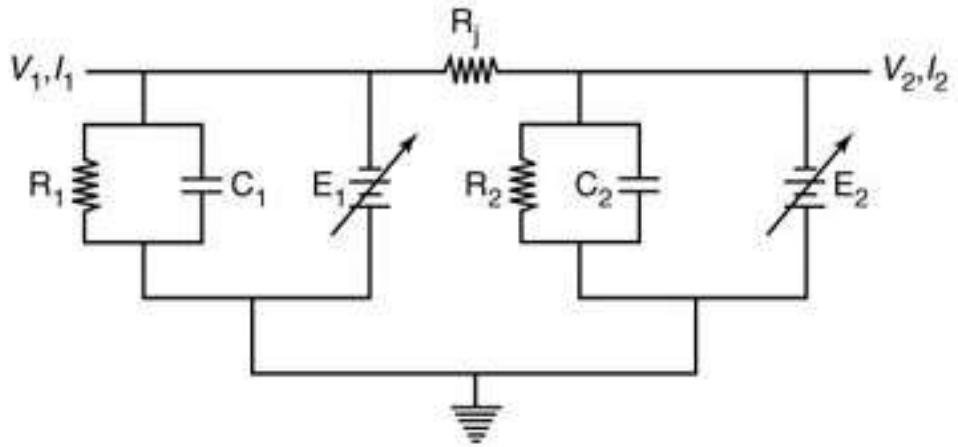


6 subunități de conexină fiecare cu 4 regiuni care traversează membrana

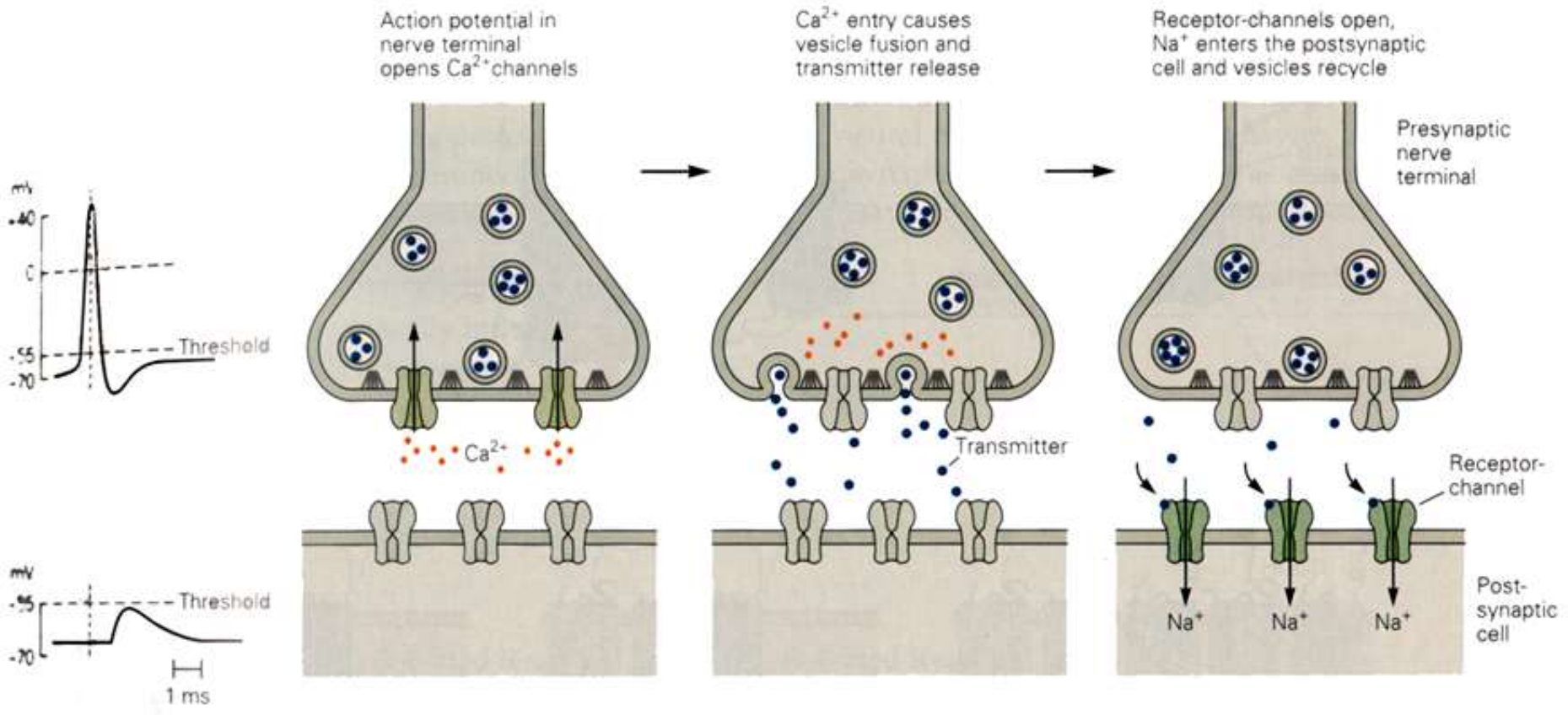
1 conexon hemi-canal – canalul este format prin deschiderea conexonilor pe fiecare membrană

Sinapse Electrice

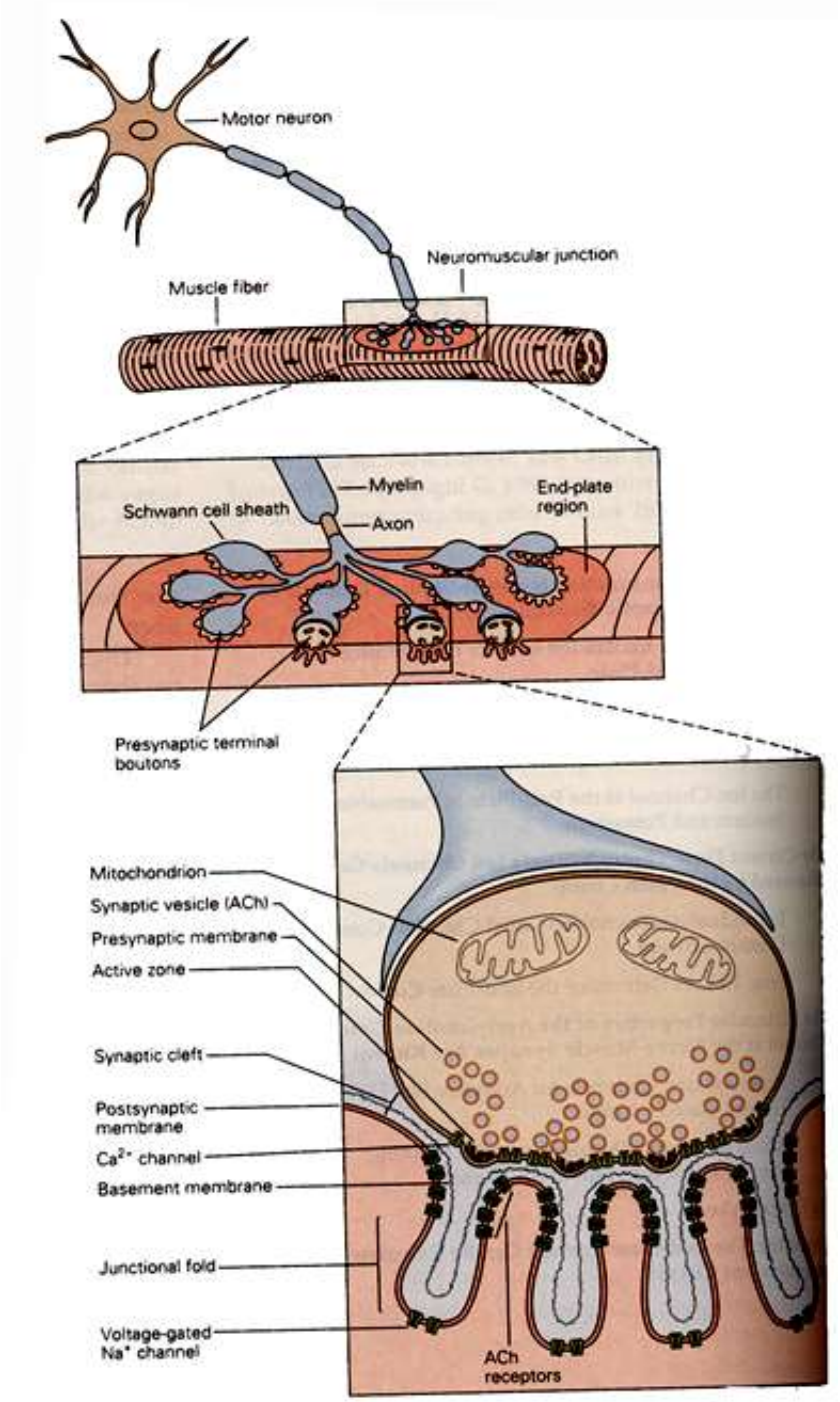




Transmisia sinaptică la sinapsele chimice



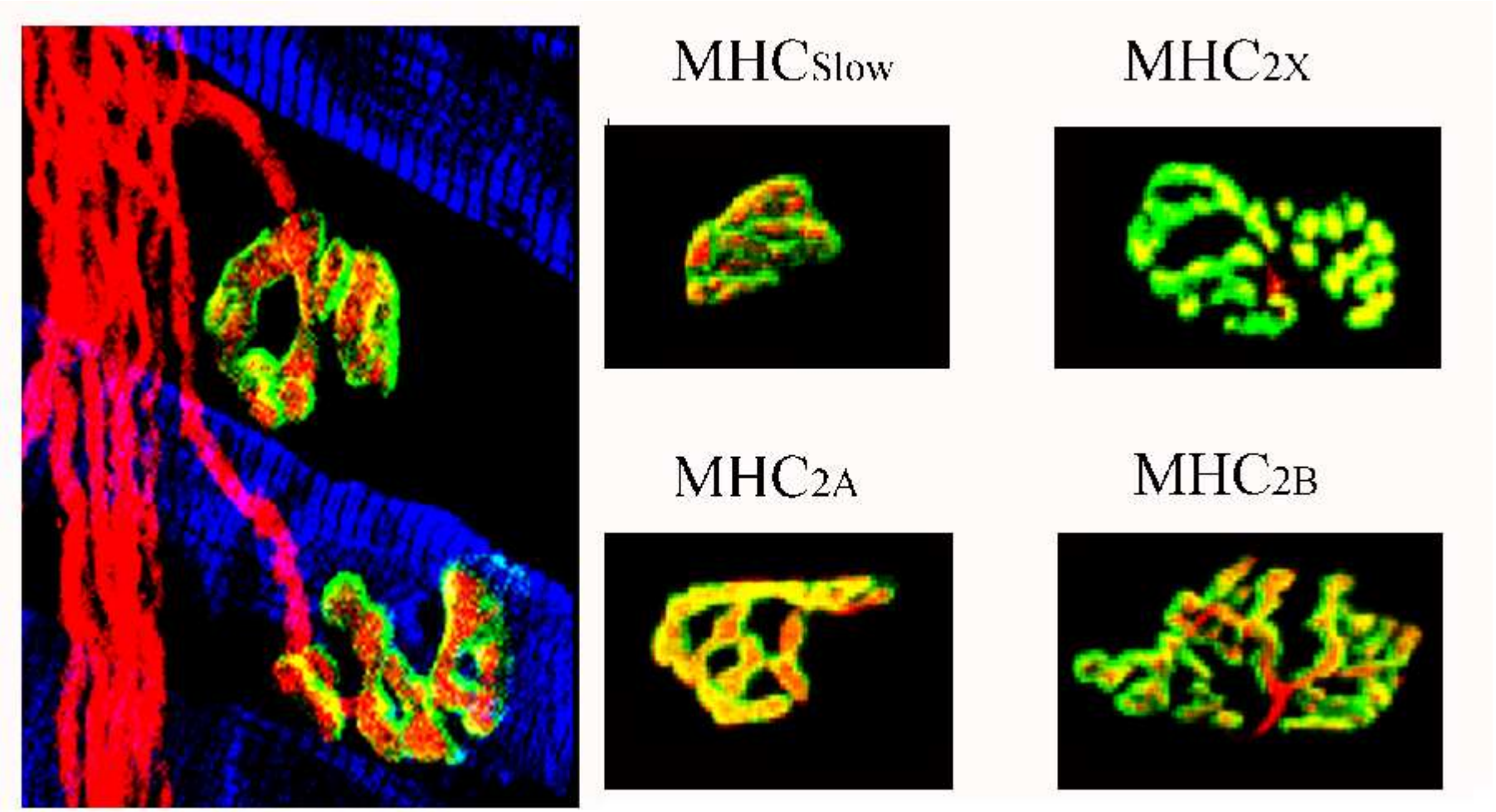
Joncțiuni neuromusculare



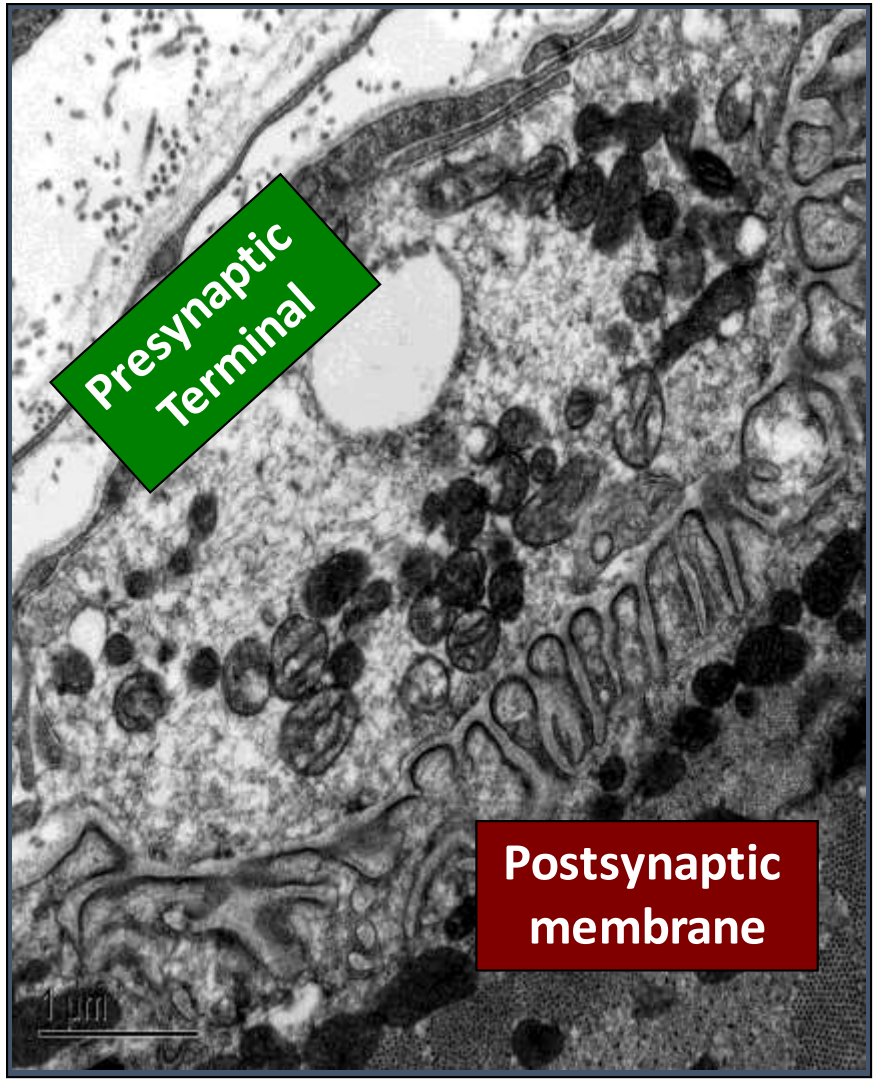
Neuronul motor - Potențialele de acțiune s-au propagat în axon până la terminalul presinaptic unde neurotransmițătorul (ACh) este eliberat din veziculele sinaptice

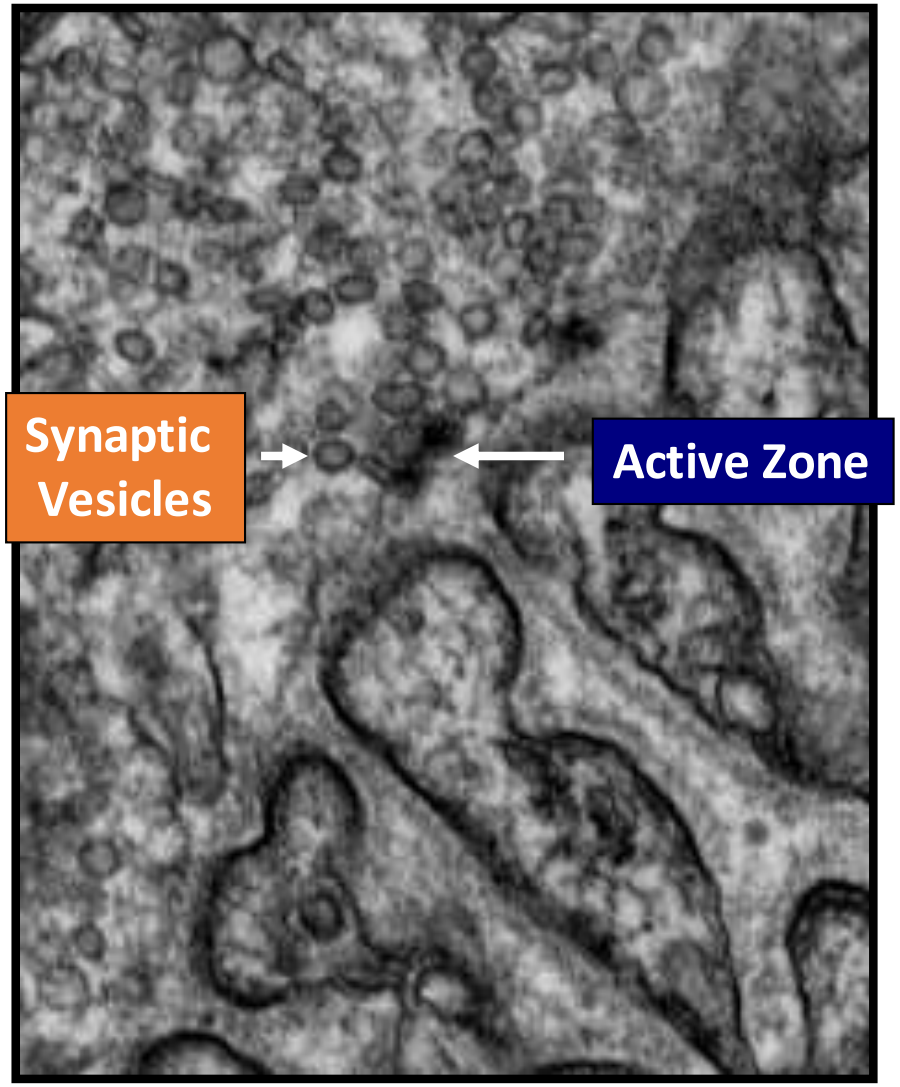
Fibra musculară - celulă țintă - localizarea receptorilor colinergici postsinaptici

Morfologia joncțiunii neuromusculare variază între tipurile de fibre musculare

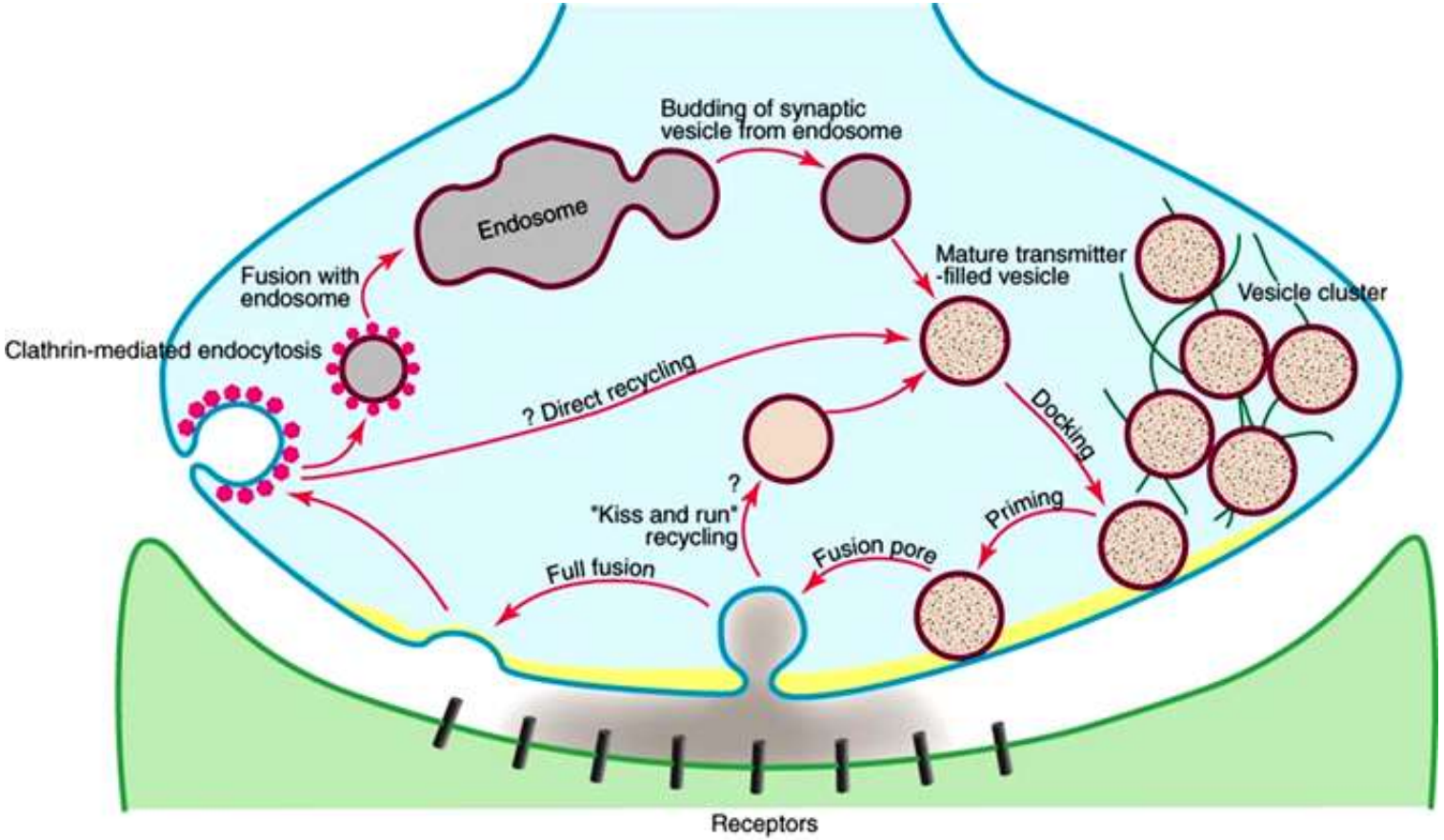


Densitatea veziculelor sinaptice la zonele active
(Rezervorul "gata de eliberat" de vezicule sinaptice)
(Readily-Releasable Pool of Synaptic Vesicles)

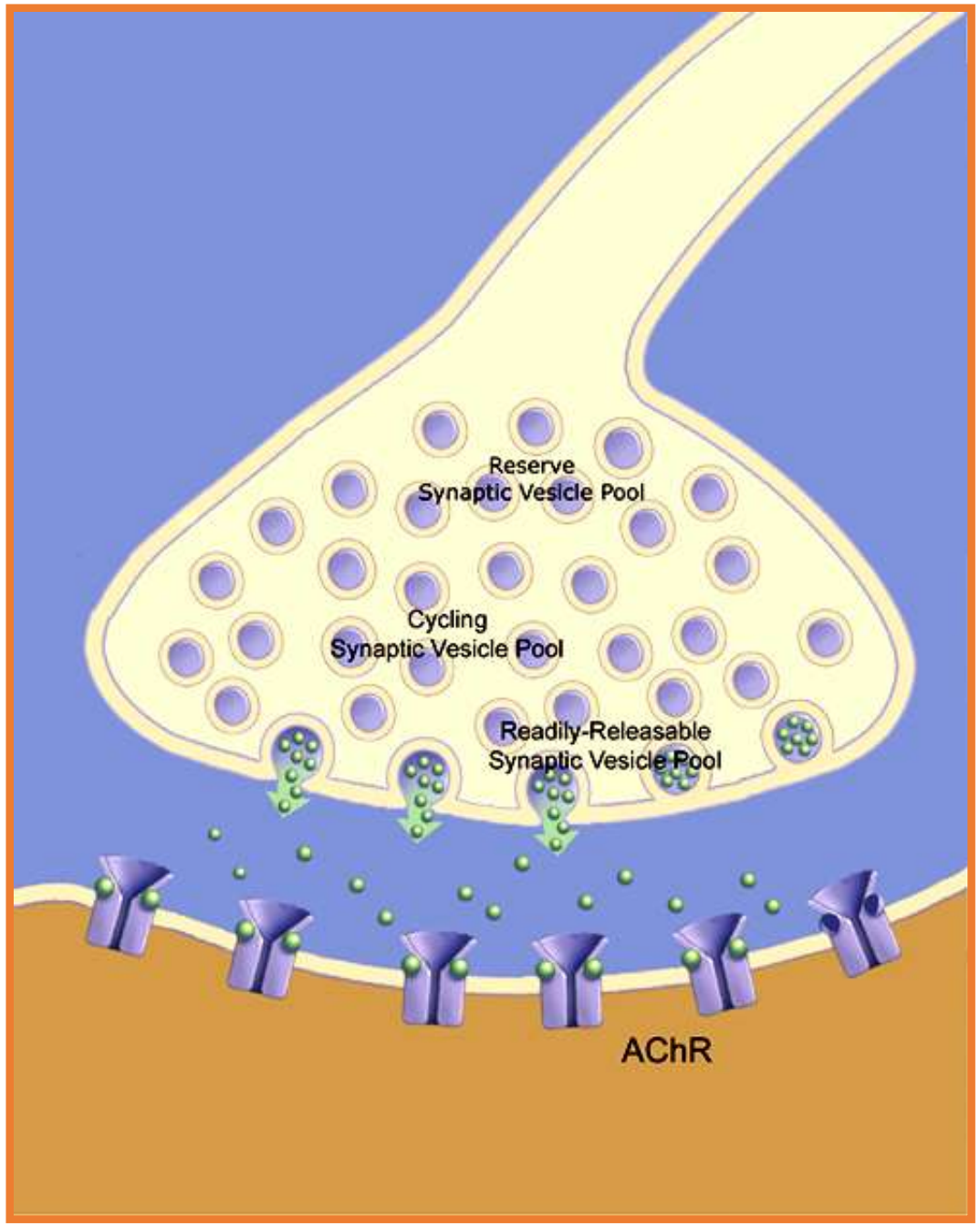




(Re)Ciclul(area) veziculei sinaptice



Veziculele umplute cu neurotransmițători se adună în apropierea zonelor active. Unele vezicule se îndreaptă spre siturile din zona activă și sunt pregătite pentru eliberare. În timpul unui potențial de acțiune, Ca2 + citosolic crește declanșând deschiderea unui por de fuziune și eliberarea neurotransmițătorului. Trei căi propuse pentru întoarcerea veziculelor în bazinul eliberabil: (1) printr-o reînchidere directă a porilor de fuziune și reformarea veziculei - „sărută și fugi” (“kiss an run”), (2) prin fuziune completă urmată de endocitoză mediată de clatrină și (3) prin fuziune completă și endocitoză ca mai sus, dar vezicula endocitată fuzionează mai întâi cu un endosom și veziculele mature se formează apoi prin înmugurirea din endosom.



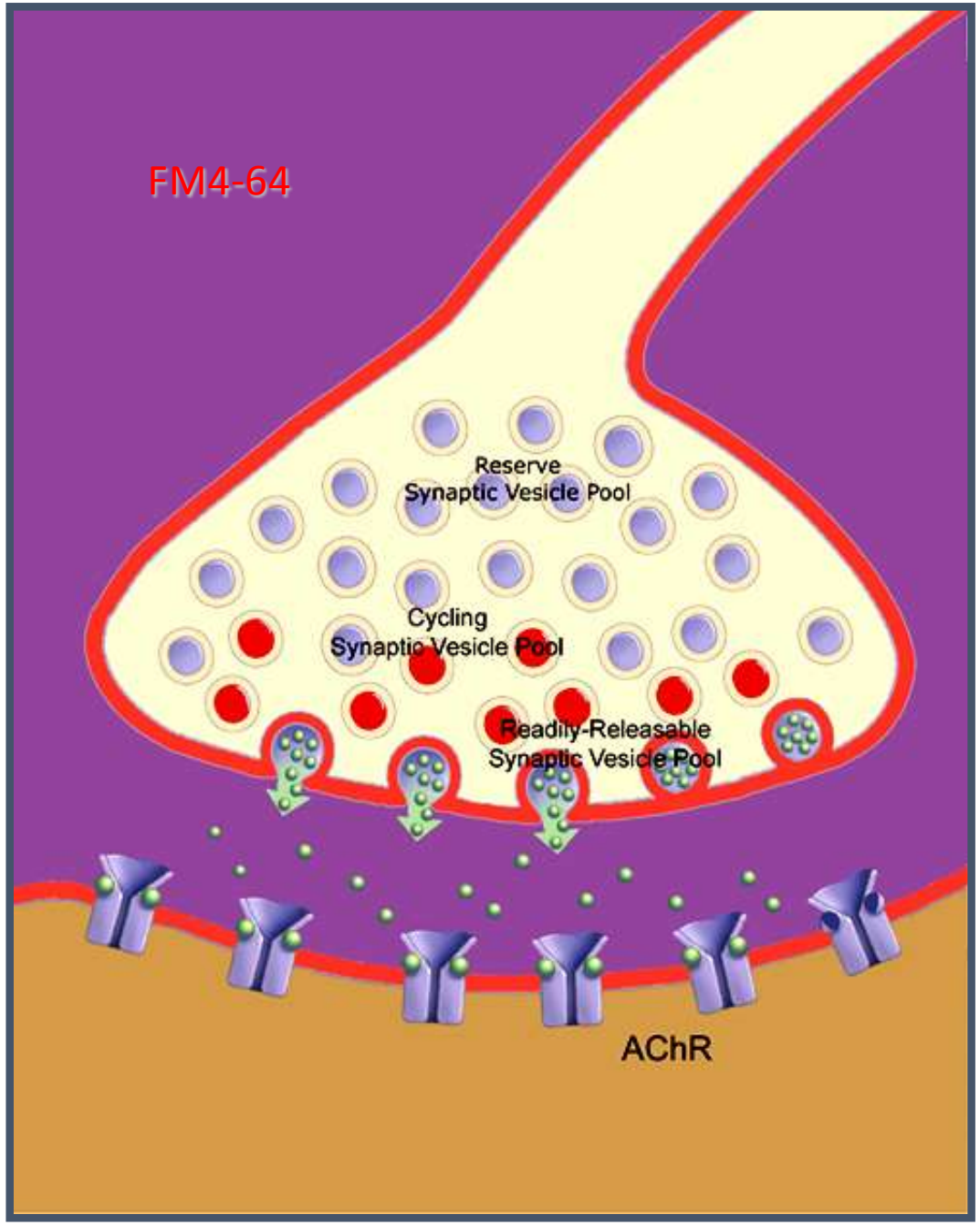
Synaptic Vesicle Pools

- Reserve Pool
- Cycling Pool

  Readily Releasable Pool

Bazine de vezicule sinaptice

- ❖ Bazinul de rezervă
- ❖ Bazinul de reciclare activă
- ❖ Bazinul “gata de eliberat”

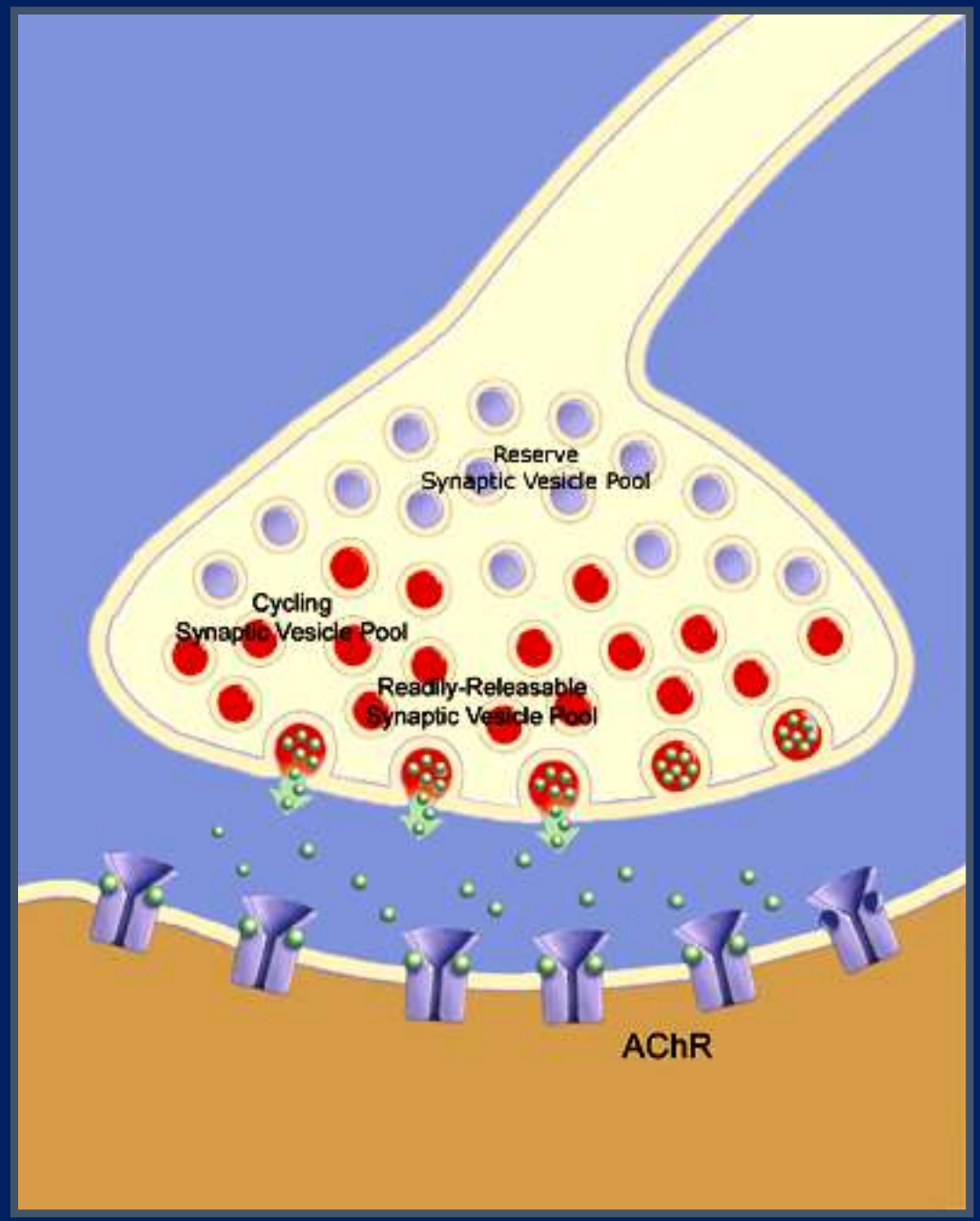


Synaptic Vesicle Pools

- Reserve Pool
- Cycling Pool
  - Readily Releasable Pool

Bazine de vezicule sinaptice

- ❖ Bazinul de rezervă
- ❖ Bazinul de reciclare activă
- ❖ **Bazinul "gata de eliberat"**



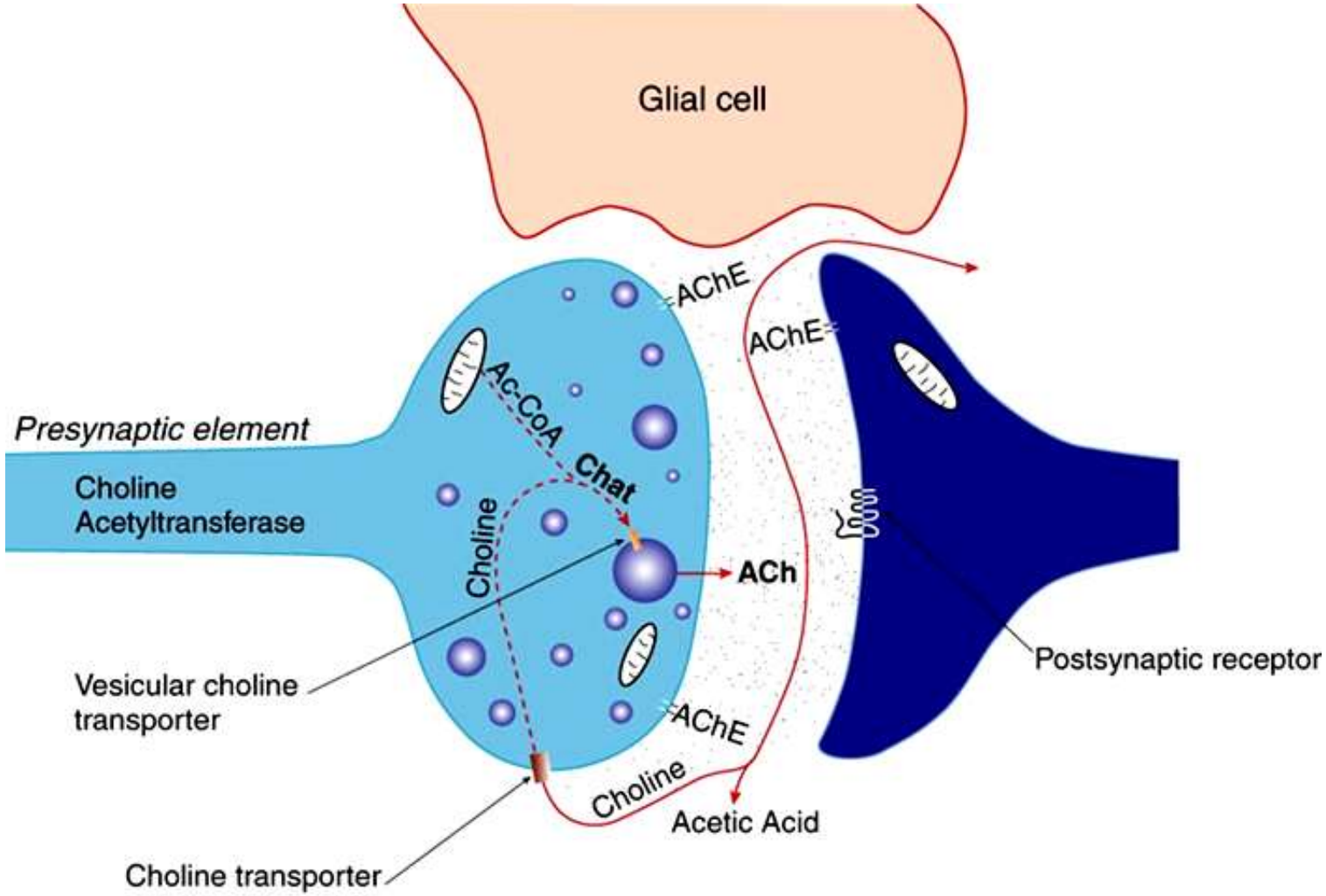
Synaptic Vesicle Pools

- Reserve Pool
- Cycling Pool
  - Readily Releasable Pool

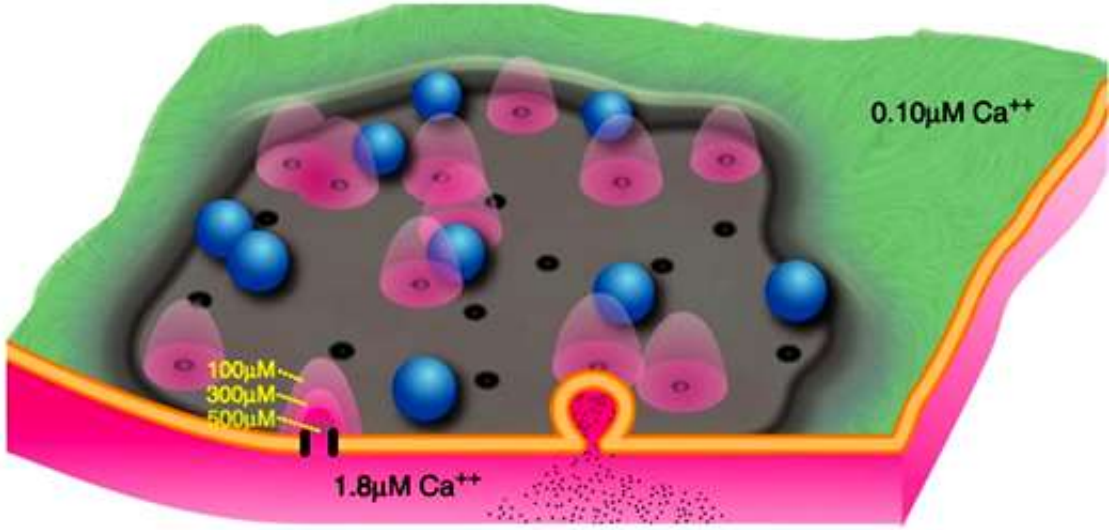
Bazine de vezicule sinaptice

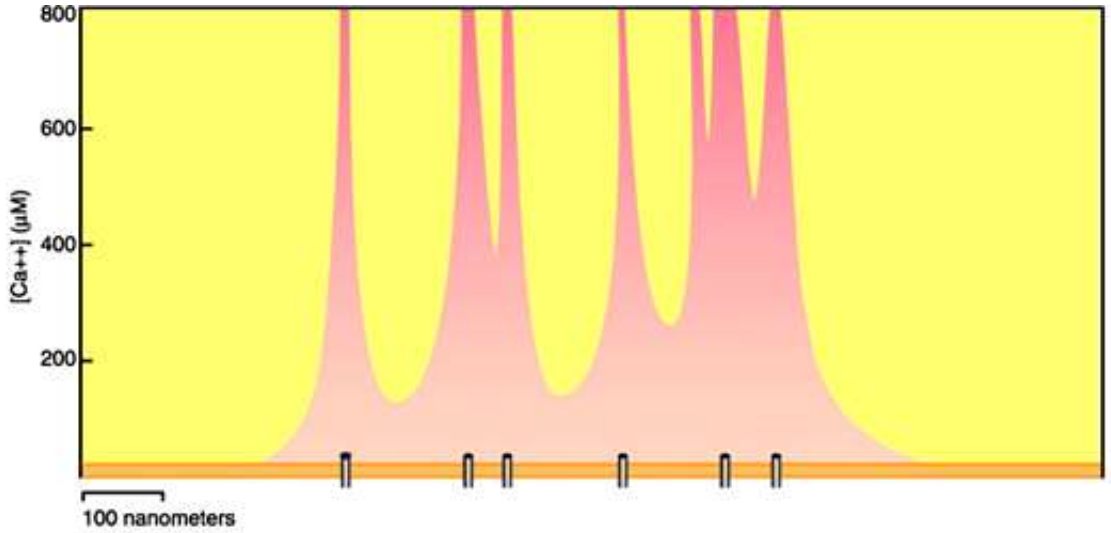
- ❖ Bazinul de rezervă
- ❖ **Bazinul de reciclare activă**
- ❖ Bazinul "gata de eliberat"

Sinteza acetilcolinei și eliberarea veziculelor sinaptice



Microdomenii de influx Ca2 + cu concentratii de [Ca2 +] i crescute



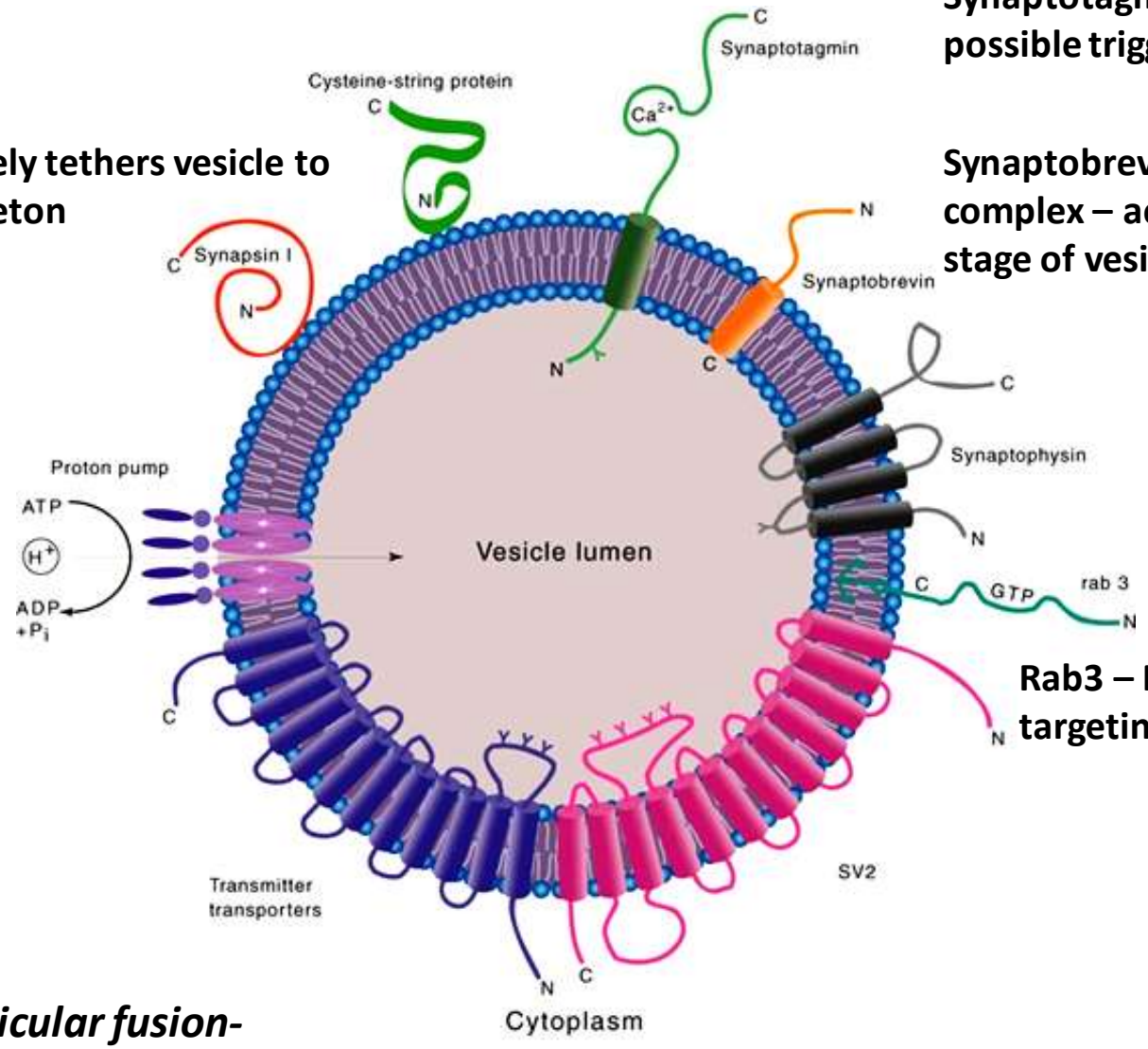


Proteinele veziculelor sinaptice

Synaptotagmin – Ca^{2+} binding – possible trigger for vesicle fusion

Synapsin – likely tethers vesicle to actin cytoskeleton

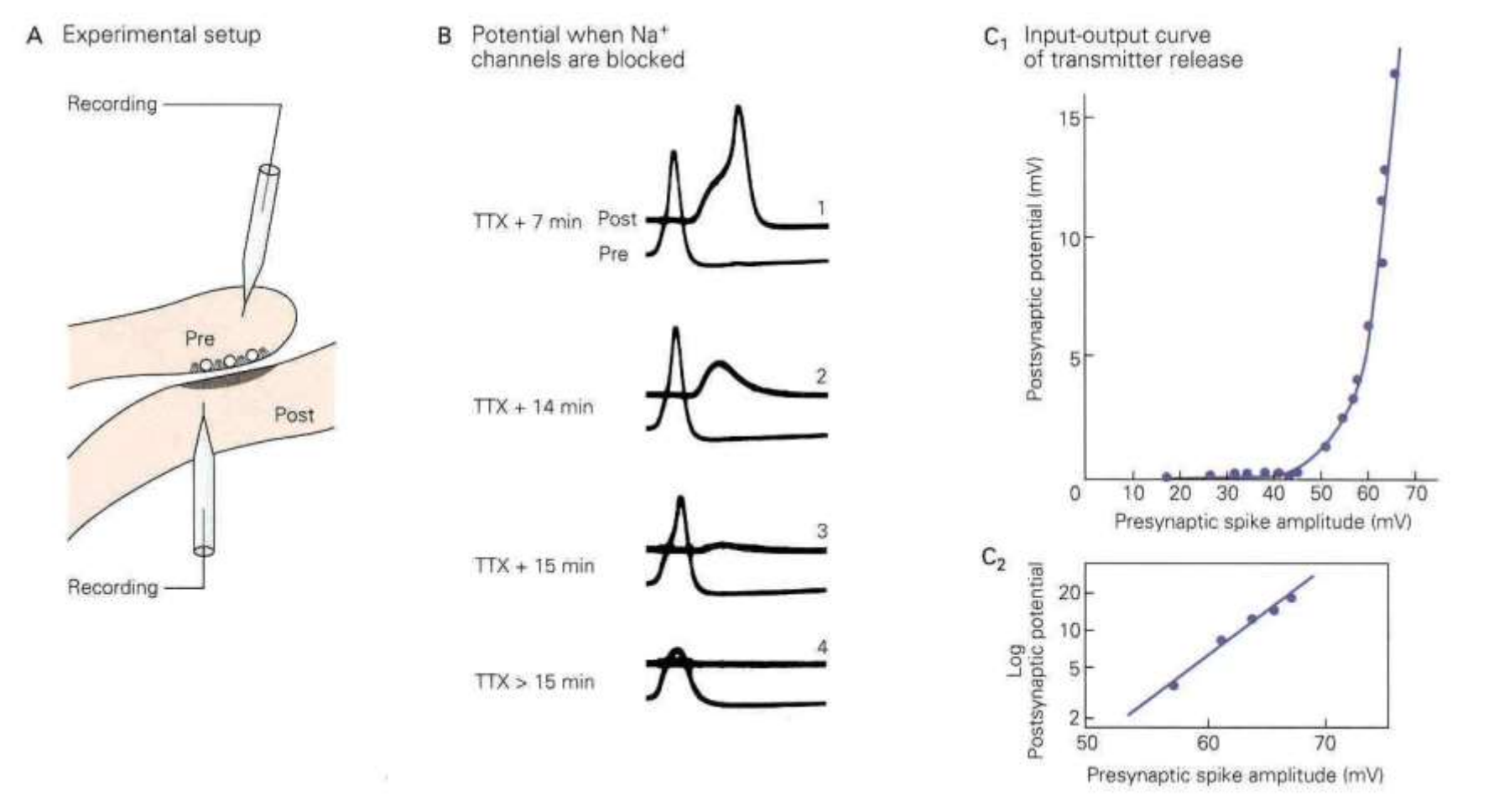
Synaptobrevin – Part of SNARE complex – acts in a late essential stage of vesicle fusion



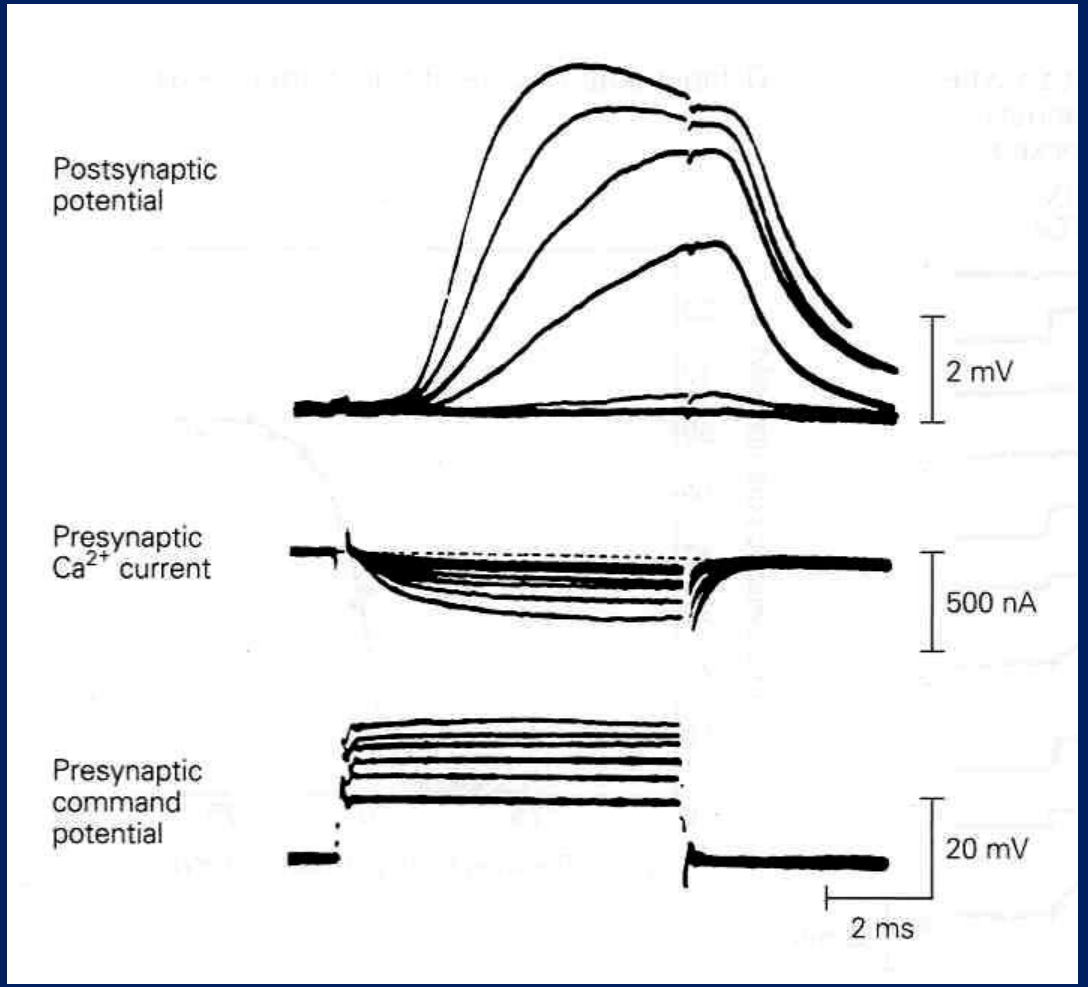
Rab3 – Possible role in vesicle targeting and availability

Transmitter uptake and vesicular fusion-
Captarea neurotransmițătorului și fuziunea veziculară

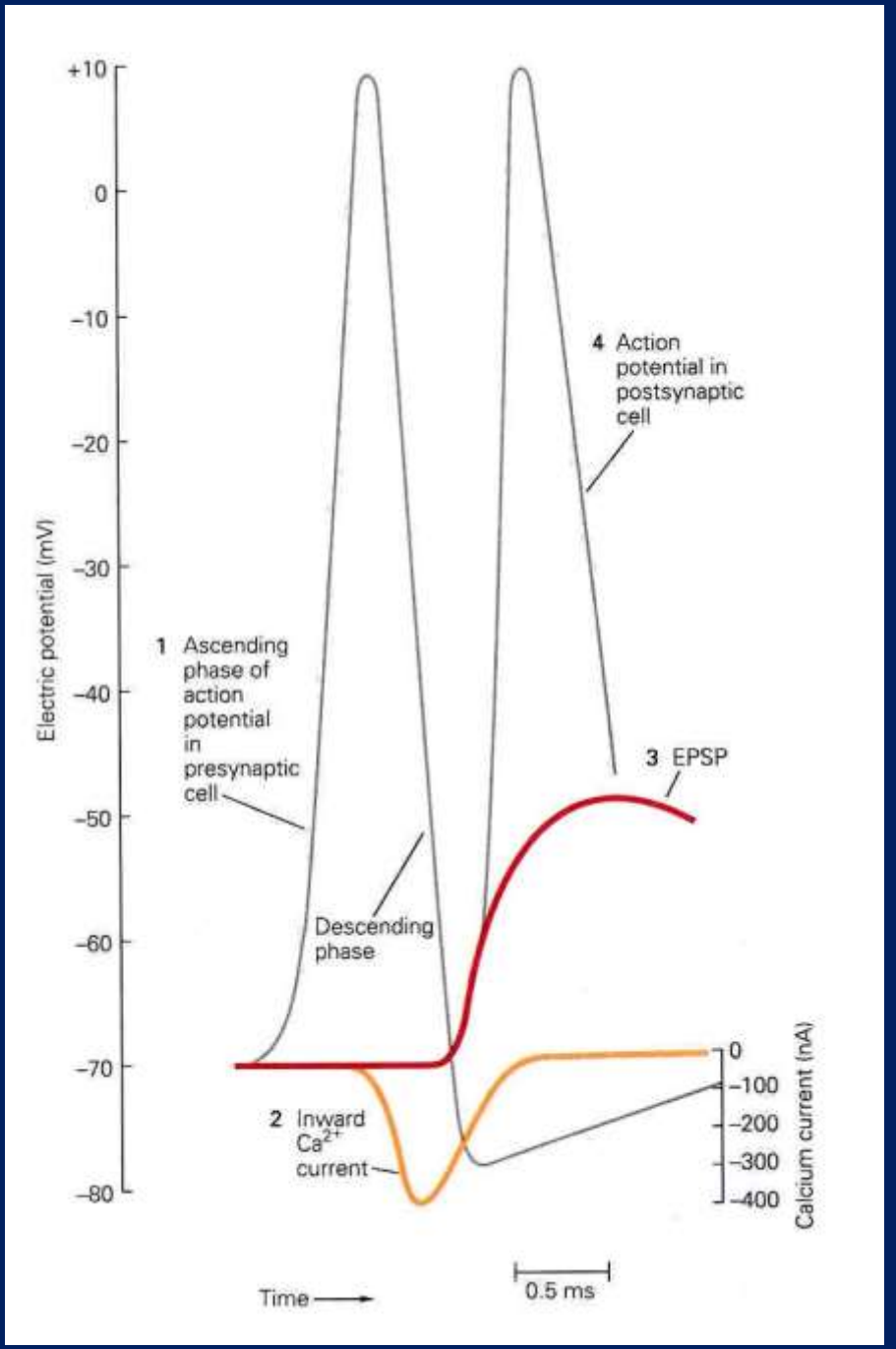
Eliberarea neuro-transmițătorului necesită depolarizarea terminalului presinaptic



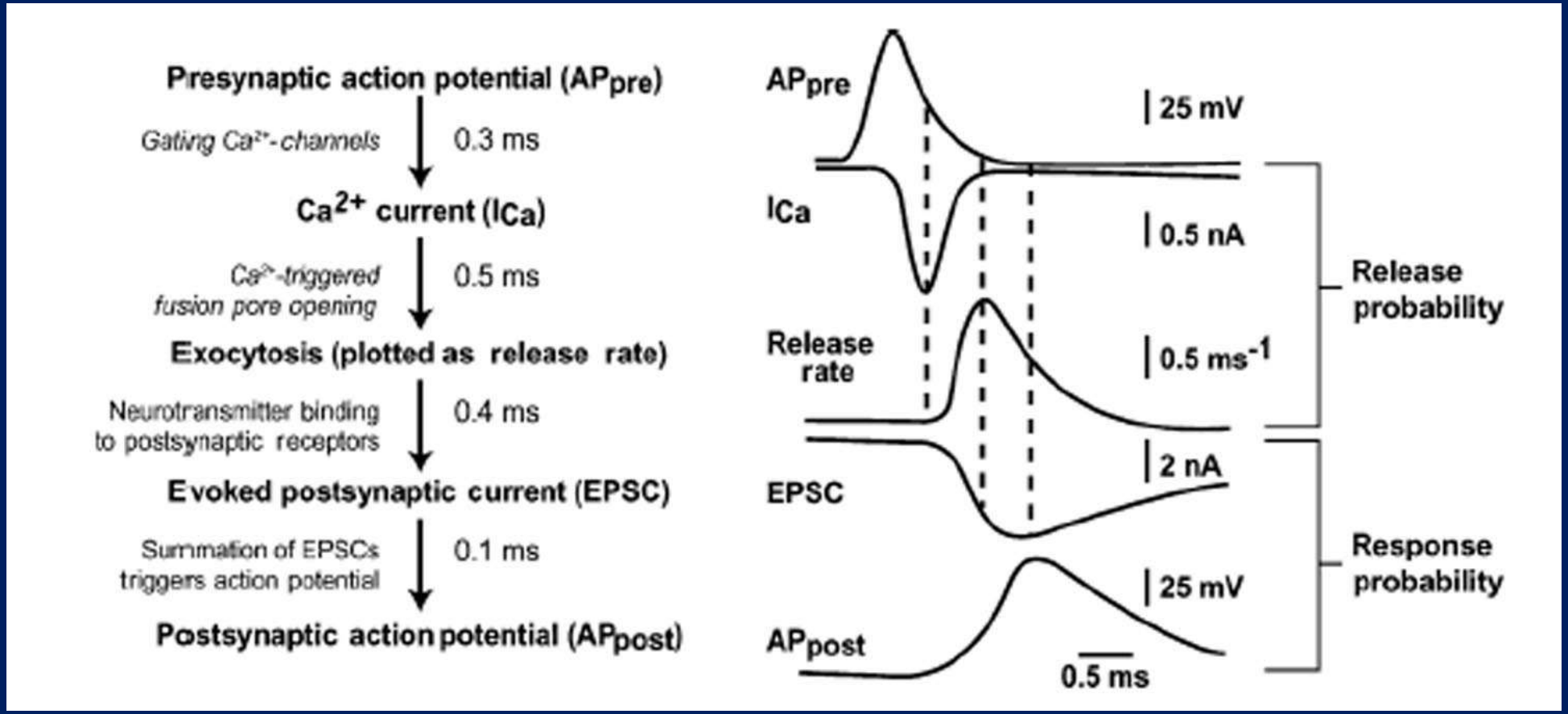
Eliberarea neuro-transmițătorului este o funcție a influxului Ca ++ în terminalul presinaptic



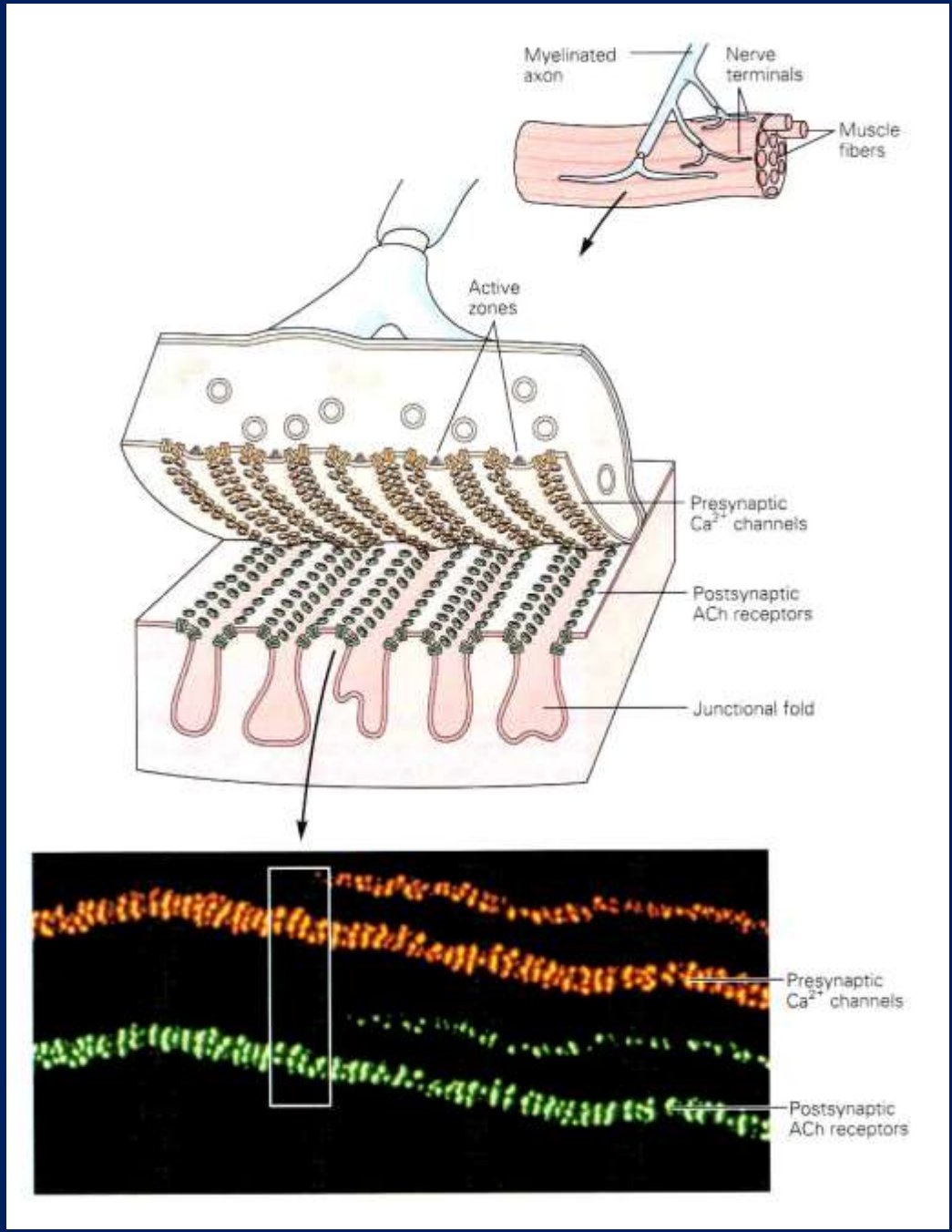
Timing-ul influxului de Ca ++ determină debutul transmisiei sinaptice



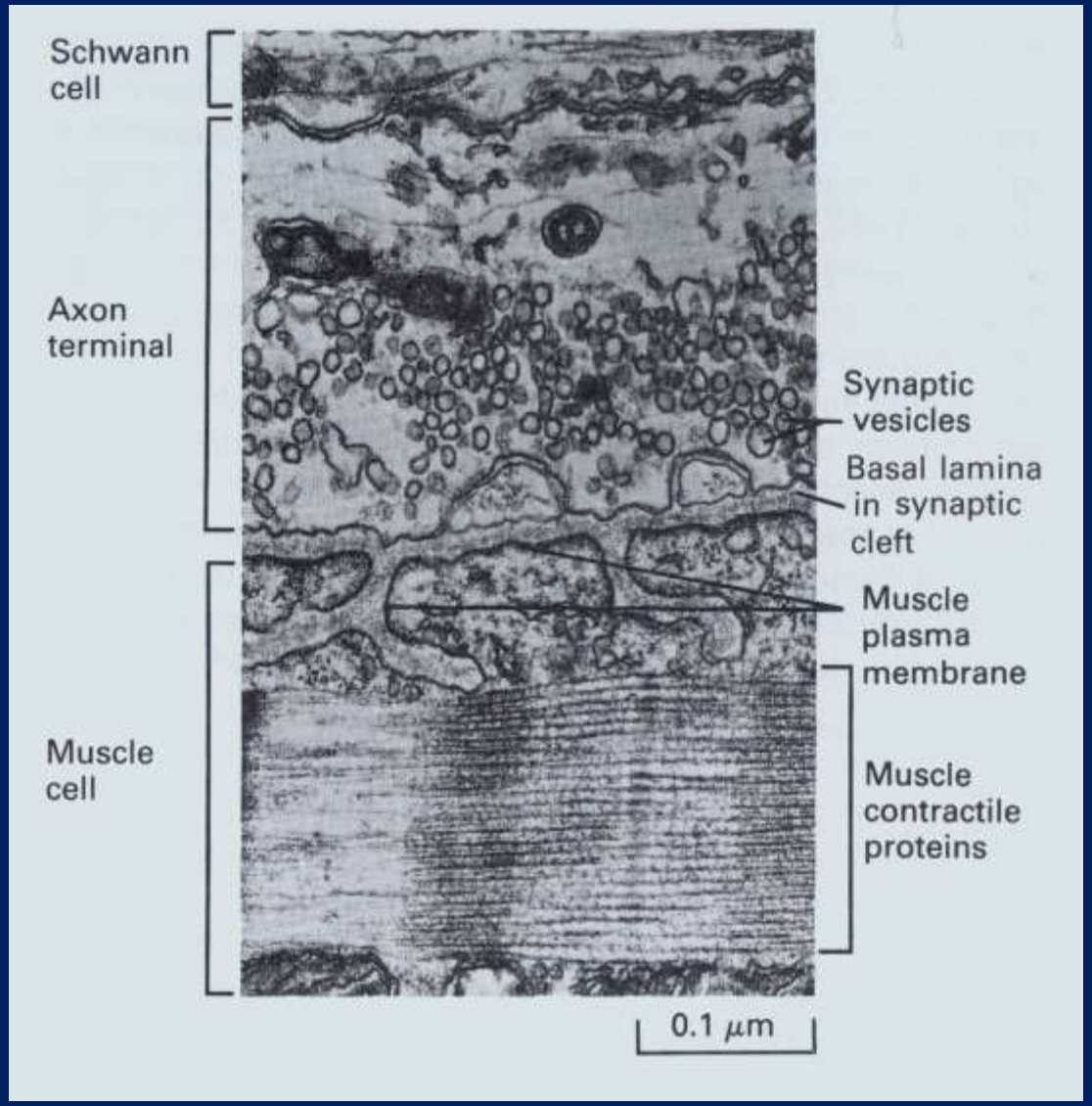
Secvența și sincronizarea transmisiei sinaptice



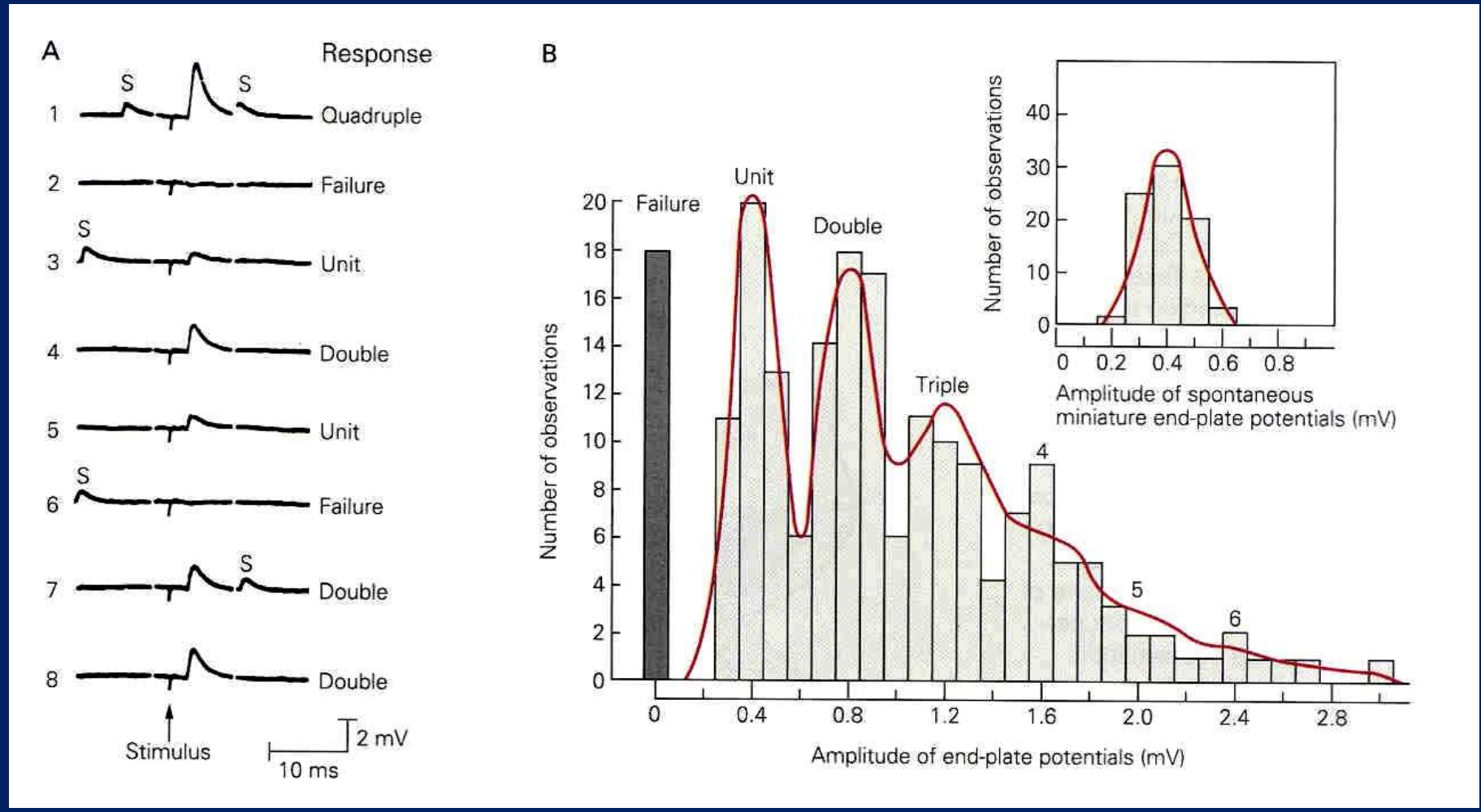
Localizarea canalelor Ca ++ și a receptorilor ACh la joncțiunea neuromusculară



Joncțiunea neuromusculară la vertebrate



Neurotransmițătorul este eliberat în Quante fixe

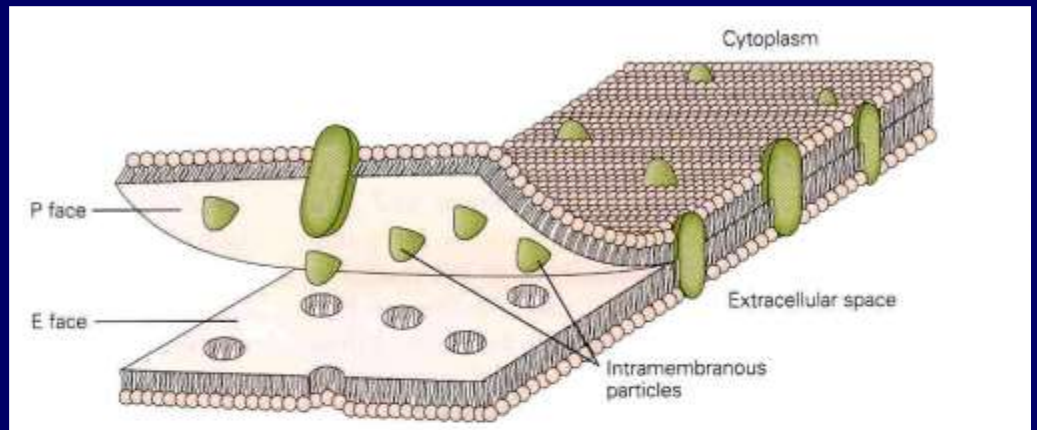


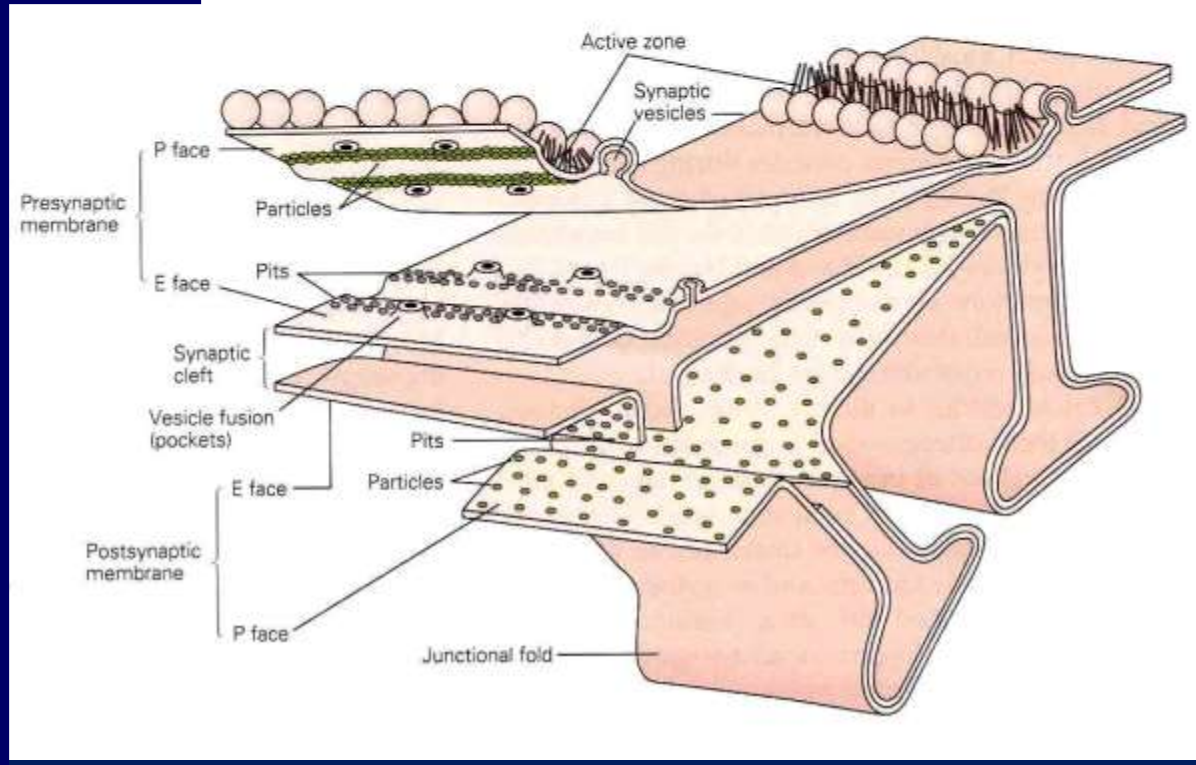
Mini EPP ~ 0.5 mV
Single AChRc ~ 0.3 μV

1 mini-Epp ~ 2000 AChRc
2 Ach/Rc = 4000 Ach/quanta

~ 150 quanta per 70 mV EPP

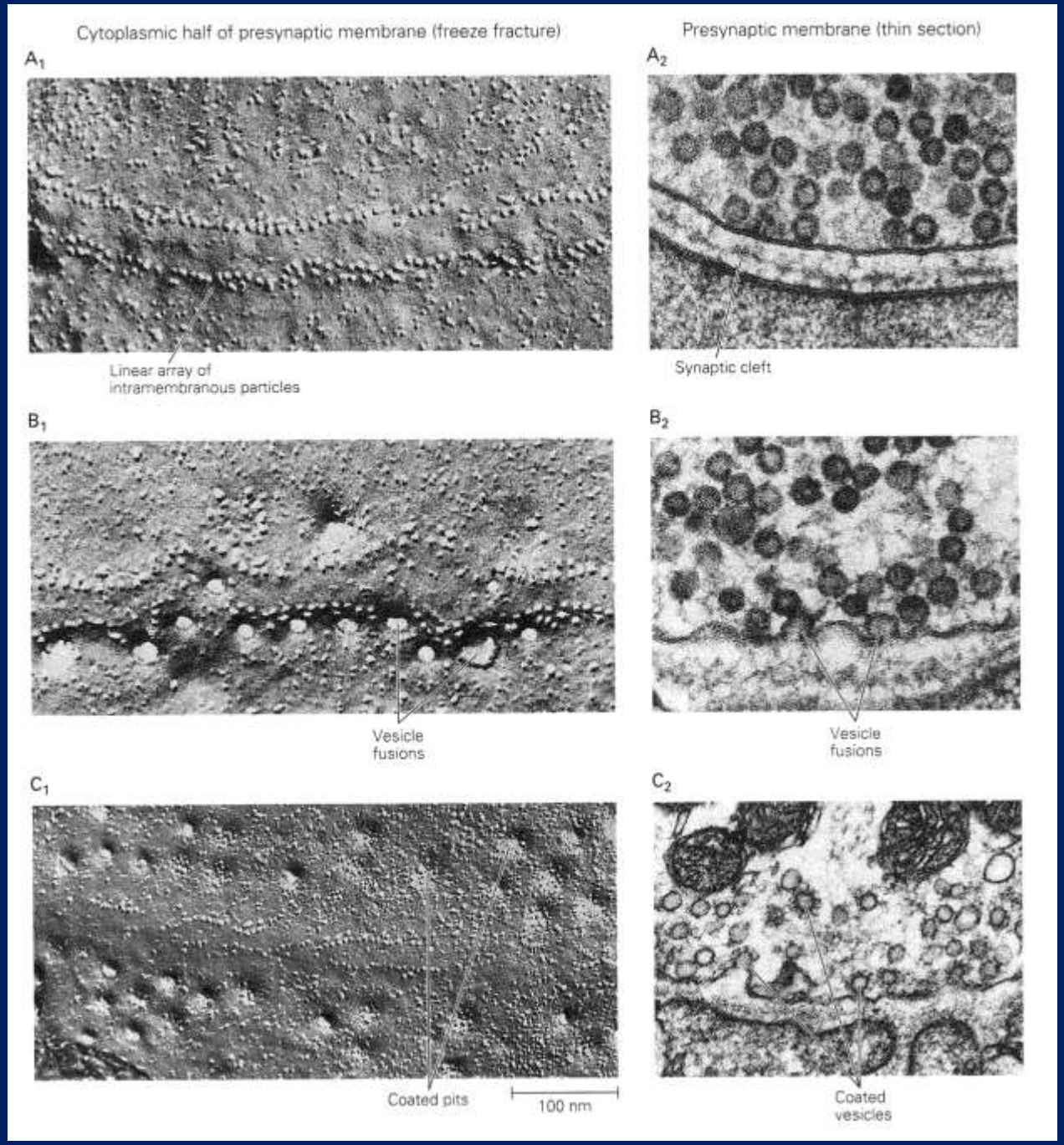
Freeze Fracture Techniques [Tehnici de “fractura înghețata”] pentru a vizualiza structura sinaptică



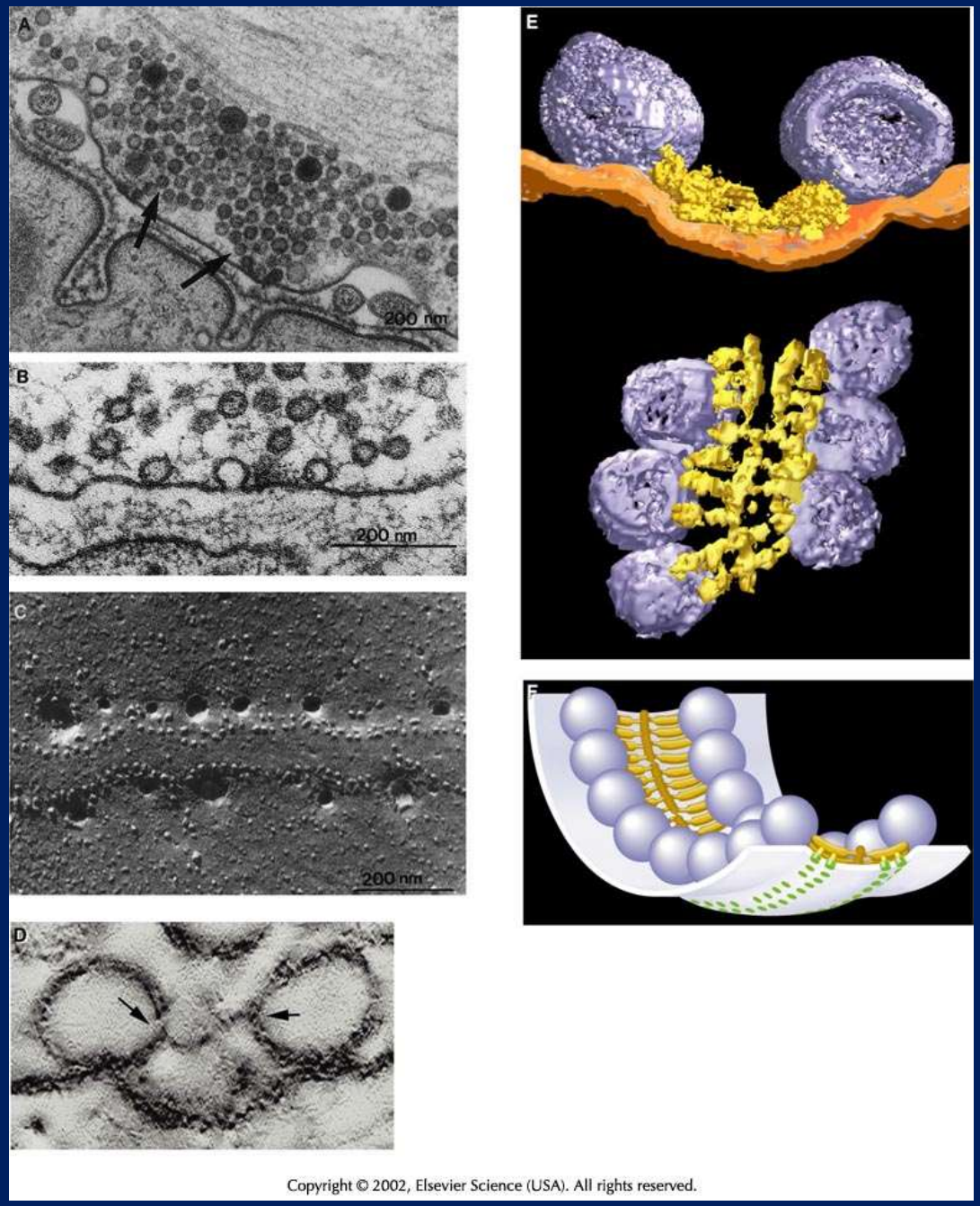


Vizualizarea EM a funcției sinaptice

A: t = 0 s
B: t = 5 ms
C: t = 10 s



Vizualizarea EM a funcției sinaptice



Mecanismele de fuziune și exocitoză a veziculelor

SNARE: N-ethylmaleimide-sensitive factor attachment protein receptor

SNAP: Synaptosomal associated protein

VAMP: Vesicle-associated membrane protein

NSF: N-ethylmaleimide-sensitive fusion protein

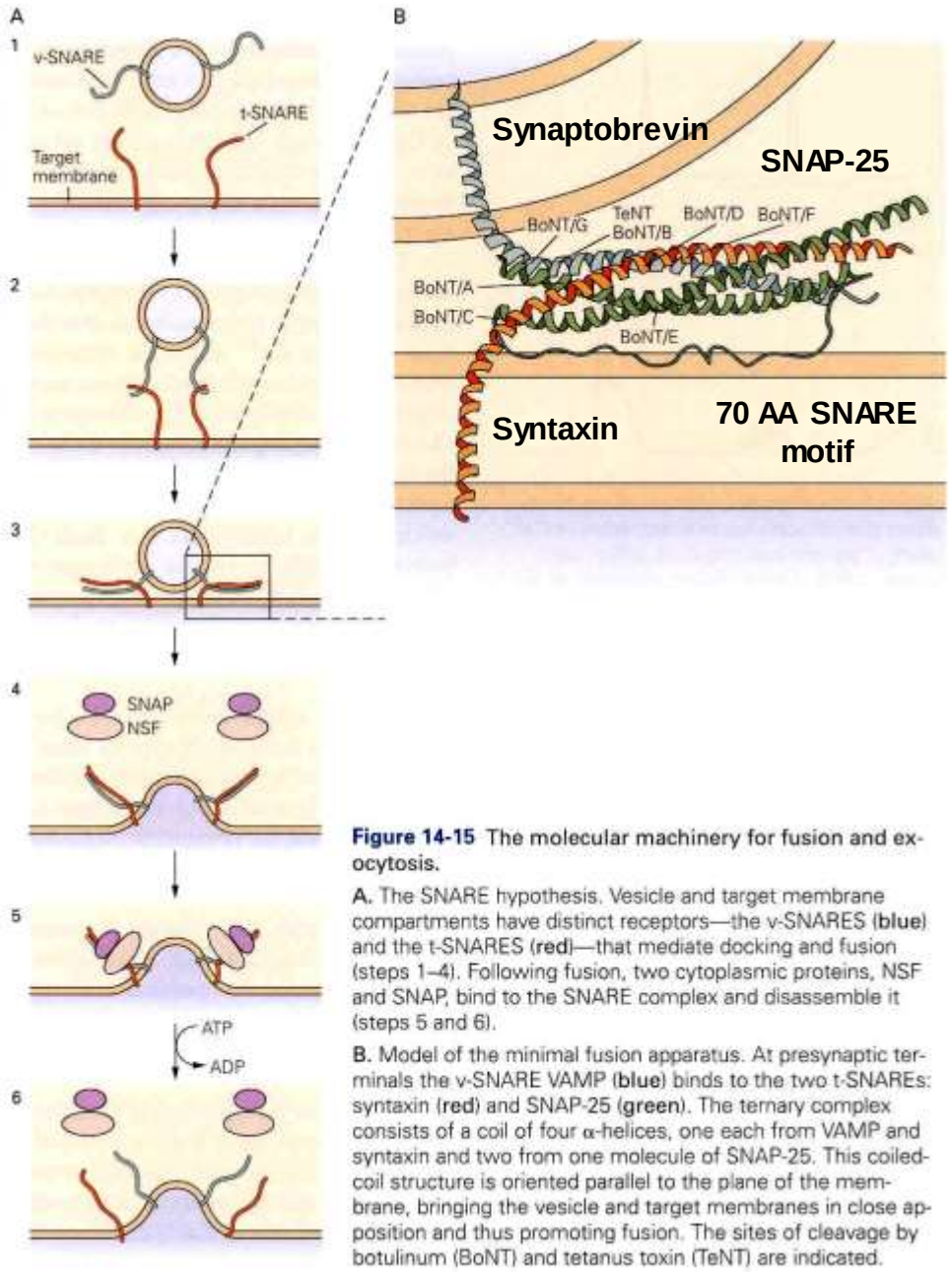
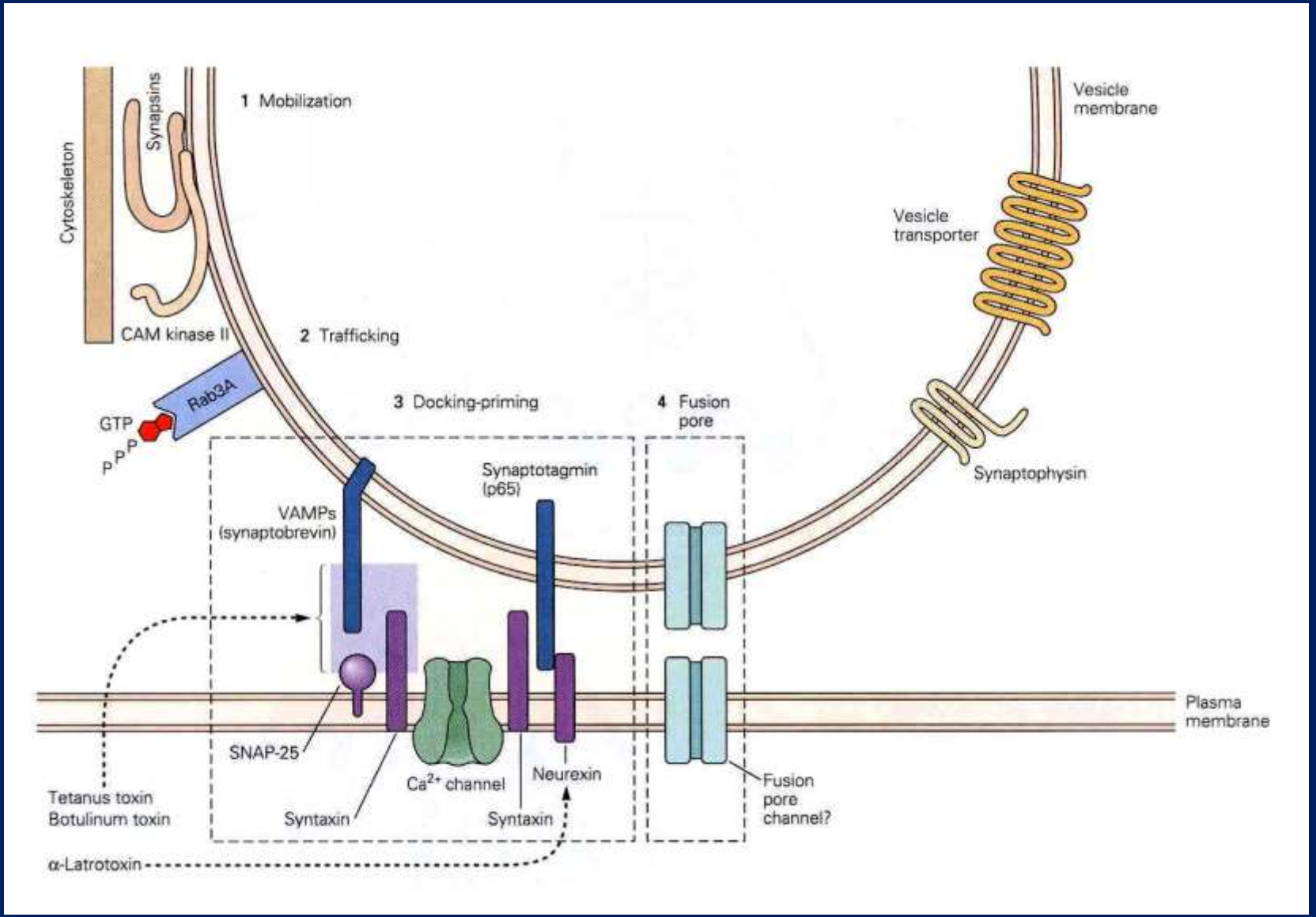


Figure 14-15 The molecular machinery for fusion and exocytosis.

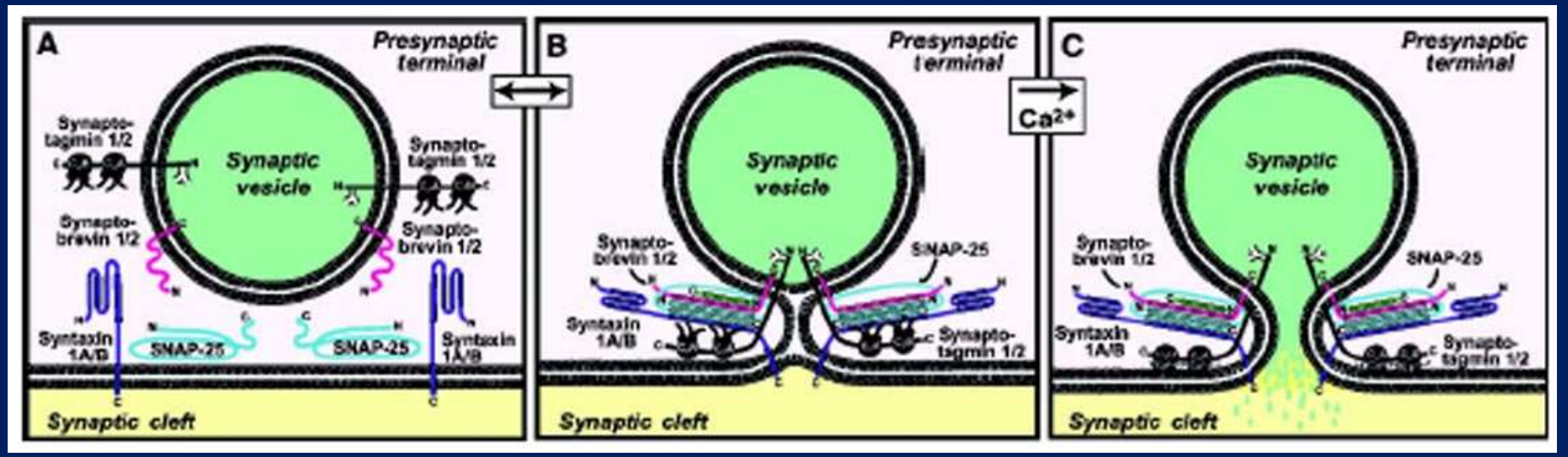
A. The SNARE hypothesis. Vesicle and target membrane compartments have distinct receptors—the v-SNARES (**blue**) and the t-SNARES (**red**)—that mediate docking and fusion (steps 1–4). Following fusion, two cytoplasmic proteins, NSF and SNAP, bind to the SNARE complex and disassemble it (steps 5 and 6).

B. Model of the minimal fusion apparatus. At presynaptic terminals the v-SNARE VAMP (**blue**) binds to the two t-SNAREs: syntaxin (**red**) and SNAP-25 (**green**). The ternary complex consists of a coil of four α-helices, one each from VAMP and syntaxin and two from one molecule of SNAP-25. This coiled-coil structure is oriented parallel to the plane of the membrane, bringing the vesicle and target membranes in close apposition and thus promoting fusion. The sites of cleavage by botulinum (BoNT) and tetanus toxin (TeNT) are indicated.

Mecanismele de fuziune și exocitoză a veziculelor



Mecanismele de fuziune și exocitoză a veziculelor



Docked —ATP→ **Primed** —Ca^{++}→ **NT Release**

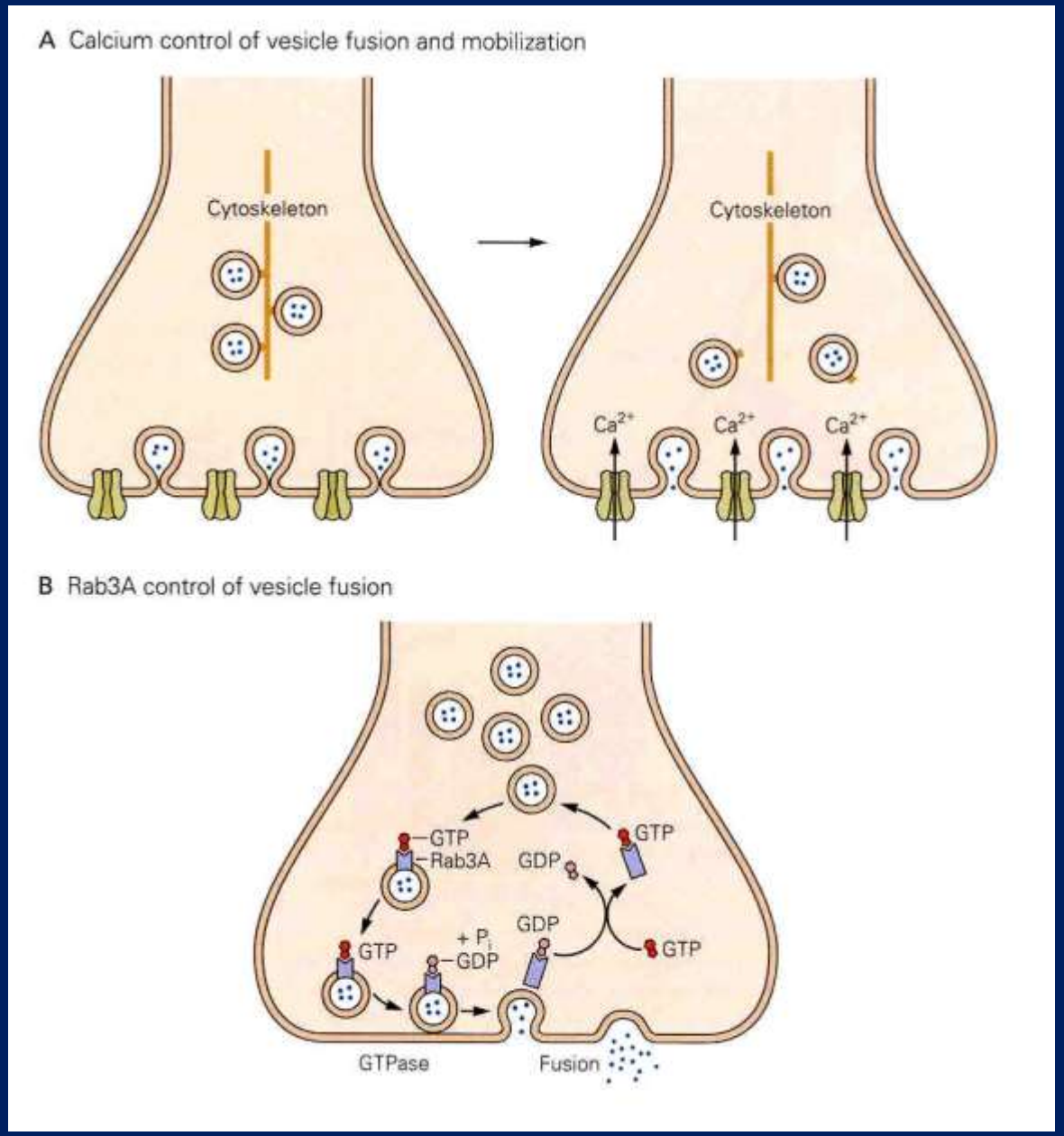
Synaptotagmin:

- Leagă Ca ++
- Leagă fosfolipidele în mod dependent de Ca ++
- Leagă SNARES
- Funcționează ca senzor Ca ++ pentru eliberarea NT

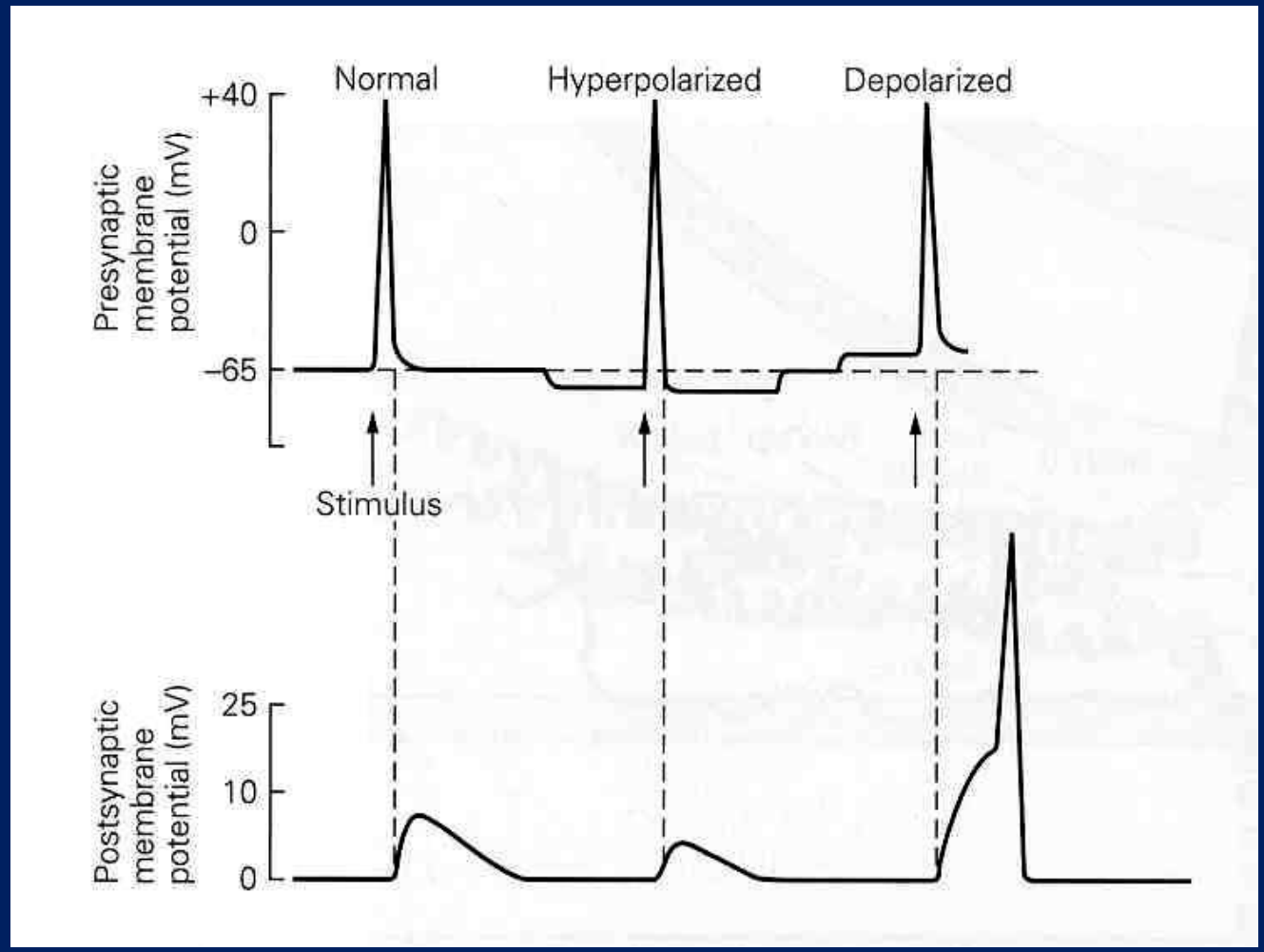
Controlul fuziunii veziculare de către Ca ++

Synapsins

Rab3

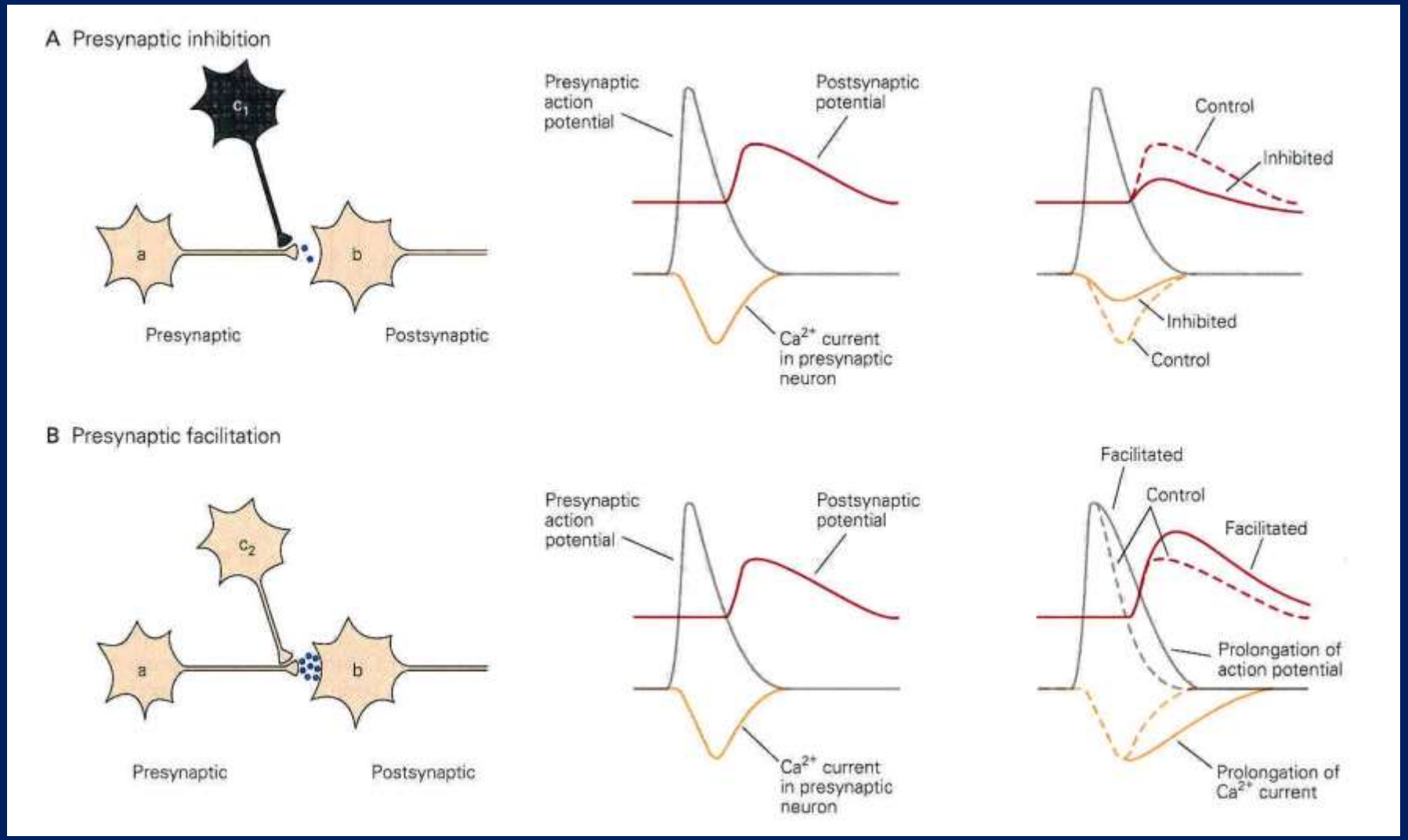


Modulare sinaptică:
Modularea presinaptică a eliberării neurotransmițătorului

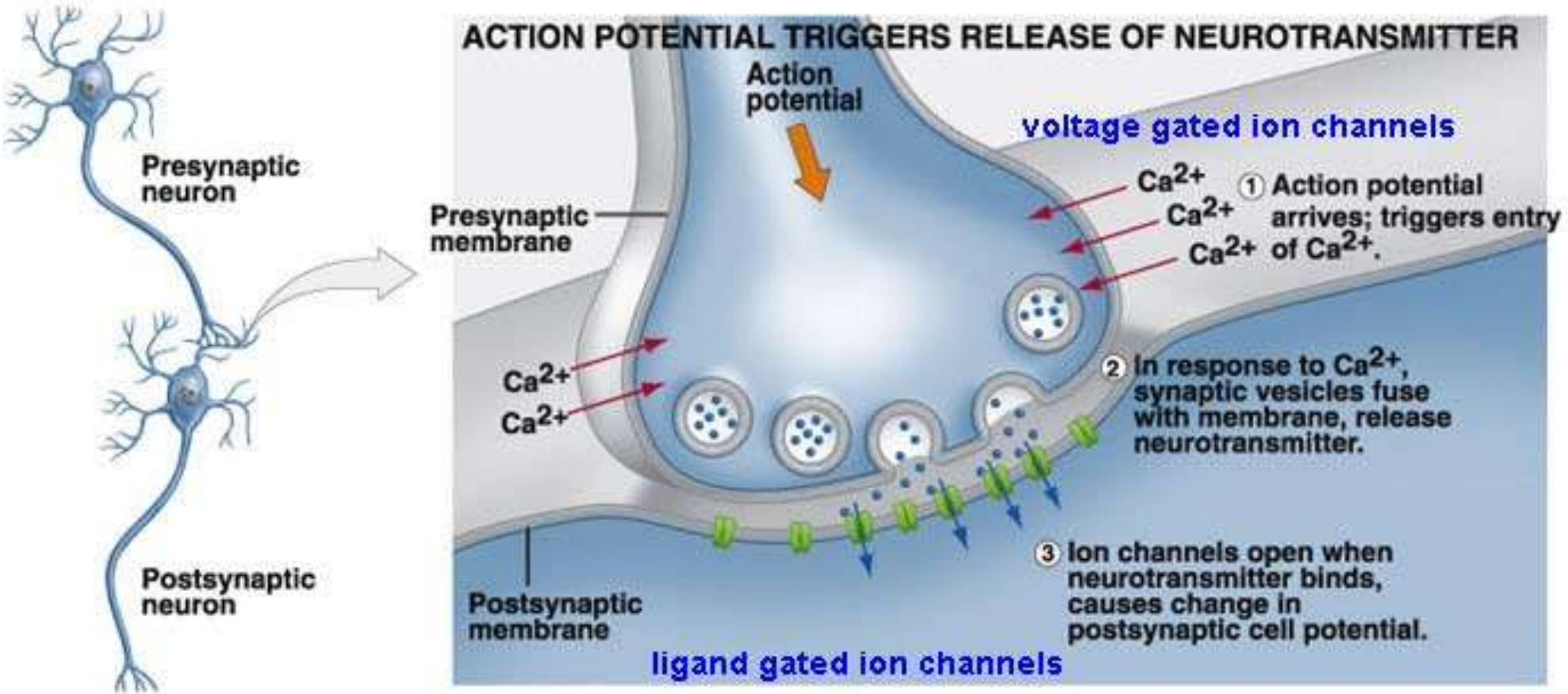


Modulare sinaptică:

Modularea Axo-axonică a eliberării neurotransmițătorului



Transmisia sinaptică (chimică) – mai simplu nu se poate ☺



Neurotransmițători

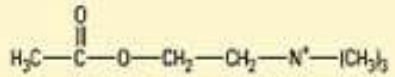
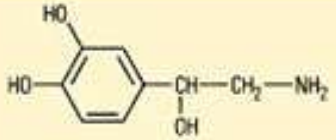
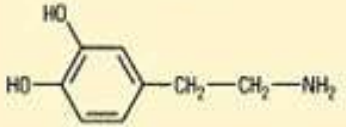
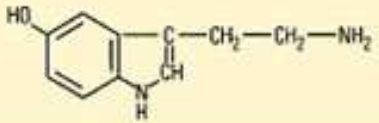
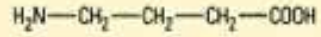
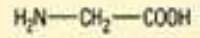
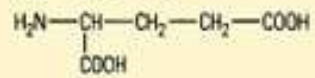
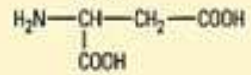
Definiția unui neurotransmițător

- Este sintetizat de neuroni.
- Este prezent în terminalul presinaptic și eliberat în cantități suficiente pentru a exercita o acțiune categorică asupra țintei postsinaptice.
- Când este administrat exogen, imită acțiunea transmițătorului endogen.
- Există un mecanism specific pentru eliminarea acestuia din locul său de acțiune.

Clase de neurotransmițători

- ✓ **Neurotransmițători cu molecule mici**
- ✓ **Neuropeptide**

Table 48.1 The Major Known Neurotransmitters

Neurotransmitter	Structure	Functional Class	Secretion Sites
Acetylcholine		Excitatory to vertebrate skeletal muscles; excitatory or inhibitory at other sites	CNS; PNS; vertebrate neuromuscular junction
Biogenic Amines			
Norepinephrine		Excitatory or inhibitory	CNS; PNS
Dopamine		Generally excitatory; may be inhibitory at some sites	CNS; PNS
Serotonin		Generally inhibitory	CNS
Amino Acids			
GABA (gamma aminobutyric acid)		Inhibitory	CNS; invertebrate neuromuscular junction
Glycine		Inhibitory	CNS
Glutamate		Excitatory	CNS; invertebrate neuromuscular junction
Aspartate		Excitatory	CNS
Neuropeptides			
Substance P	Arg—Pro—Lys—Pro—Gln—Gln—Phe—Phe—Gly—Leu—Met	Excitatory	CNS; PNS
Met-enkephalin (an endorphin)	Tyr—Gly—Gly—Phe—Met	Generally inhibitory	CNS

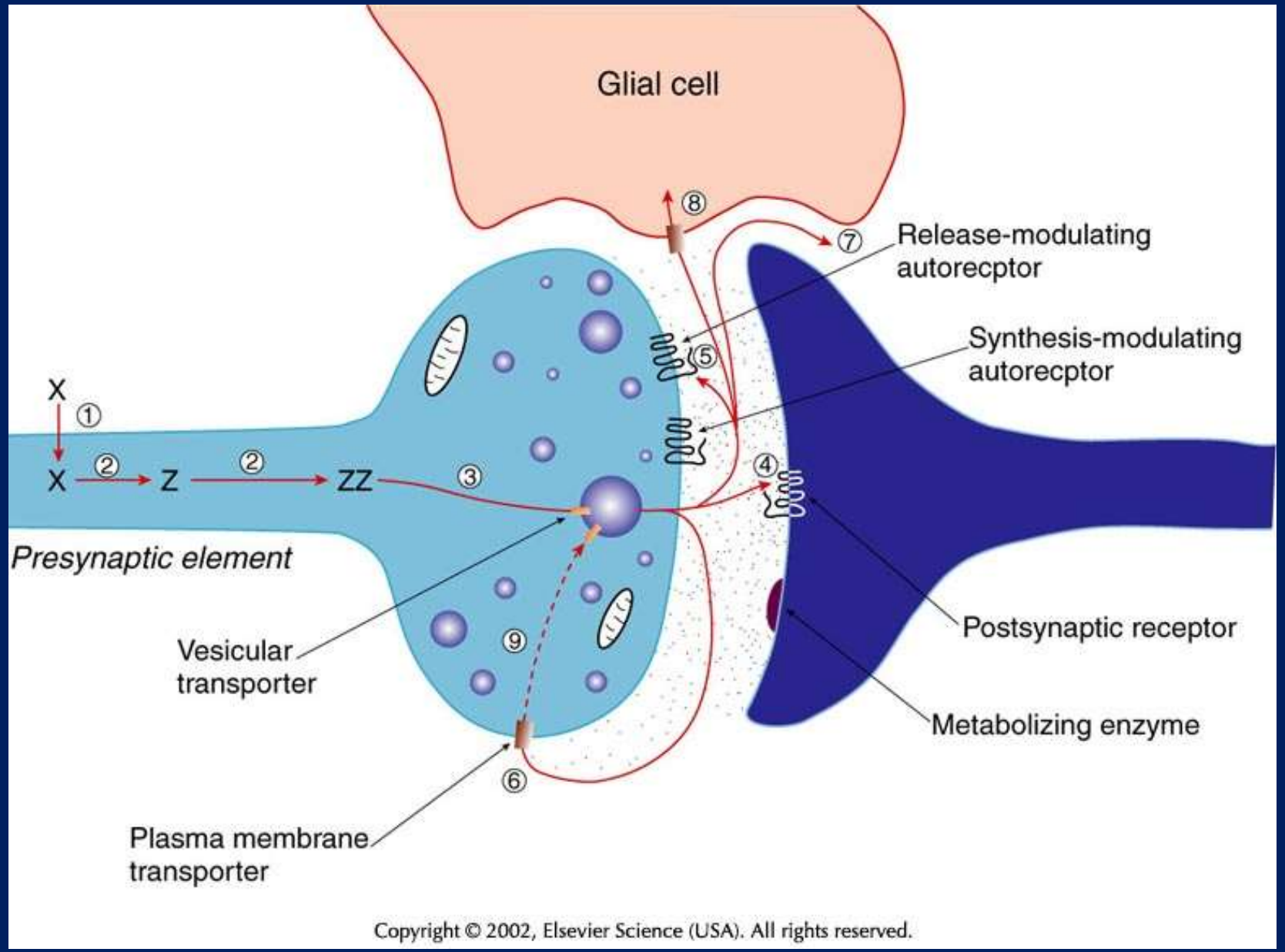
Epinephrine, Histamine, ATP, Adenosine

Familii de neurotransmițători peptidici

Table 15-3 Some Families of Neuroactive Peptides

Family	Peptide members
Opioids	Opiocortins, enkephalins, dynorphin, FMRFamide
Neurohypophyseal hormones	Vasopressin, oxytocin, neurophysins
Tachykinins	Substance P, physalaemin, kassinin, uperolein, eledoisin, bombesin, substance K
Secretins	Secretin, glucagon, vasoactive intestinal peptide, gastric inhibitory peptide, growth hormone–releasing factor, peptide histidine isoleucineamide
Insulins	Insulin, insulin-like growth factors I and II
Somatostatins	Somatostatins, pancreatic polypeptide
Gastrins	Gastrin, cholecystokinin

Ciclul de viață al unui neurotransmițător clasic

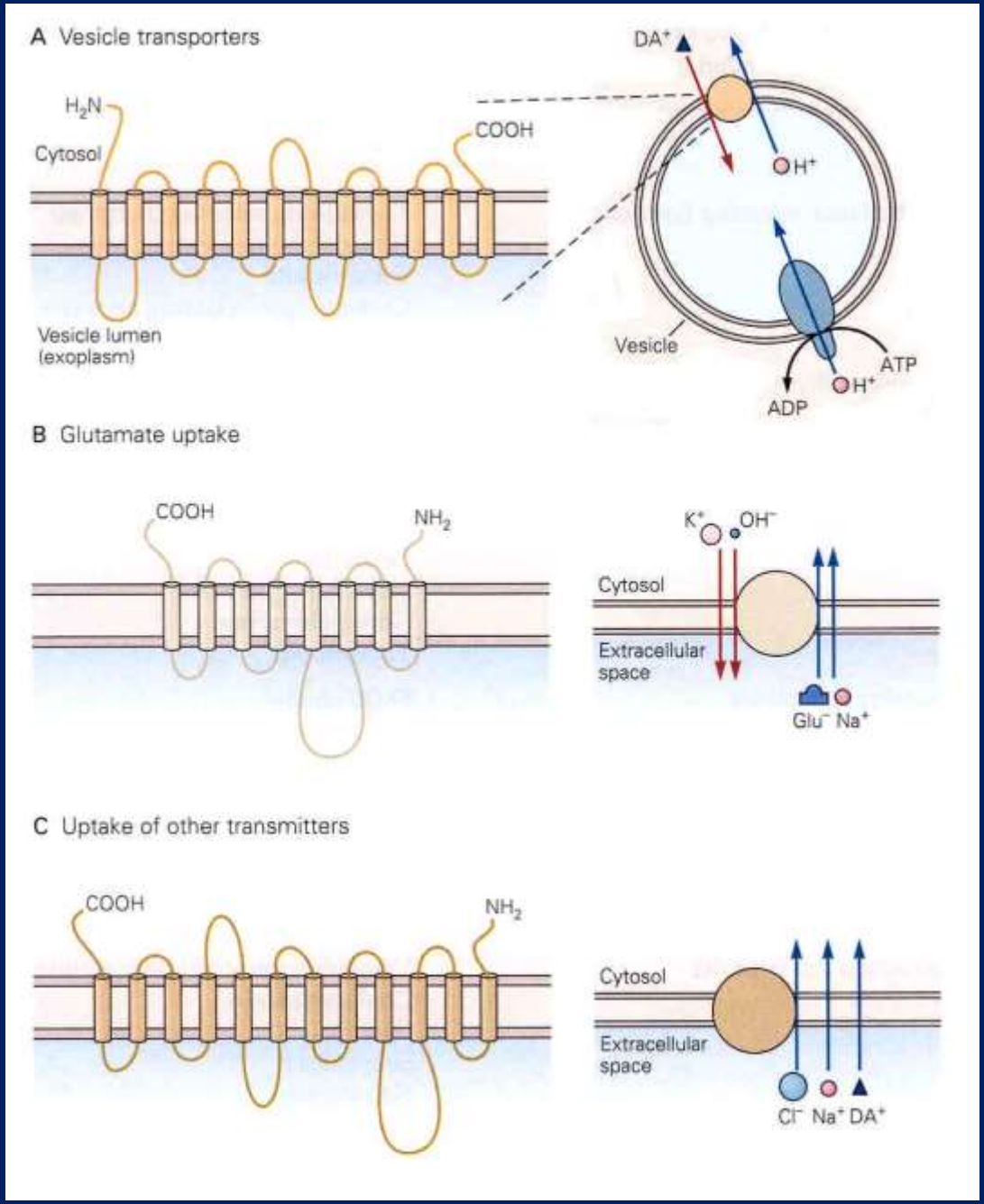


Transmitter Uptake and Packaging

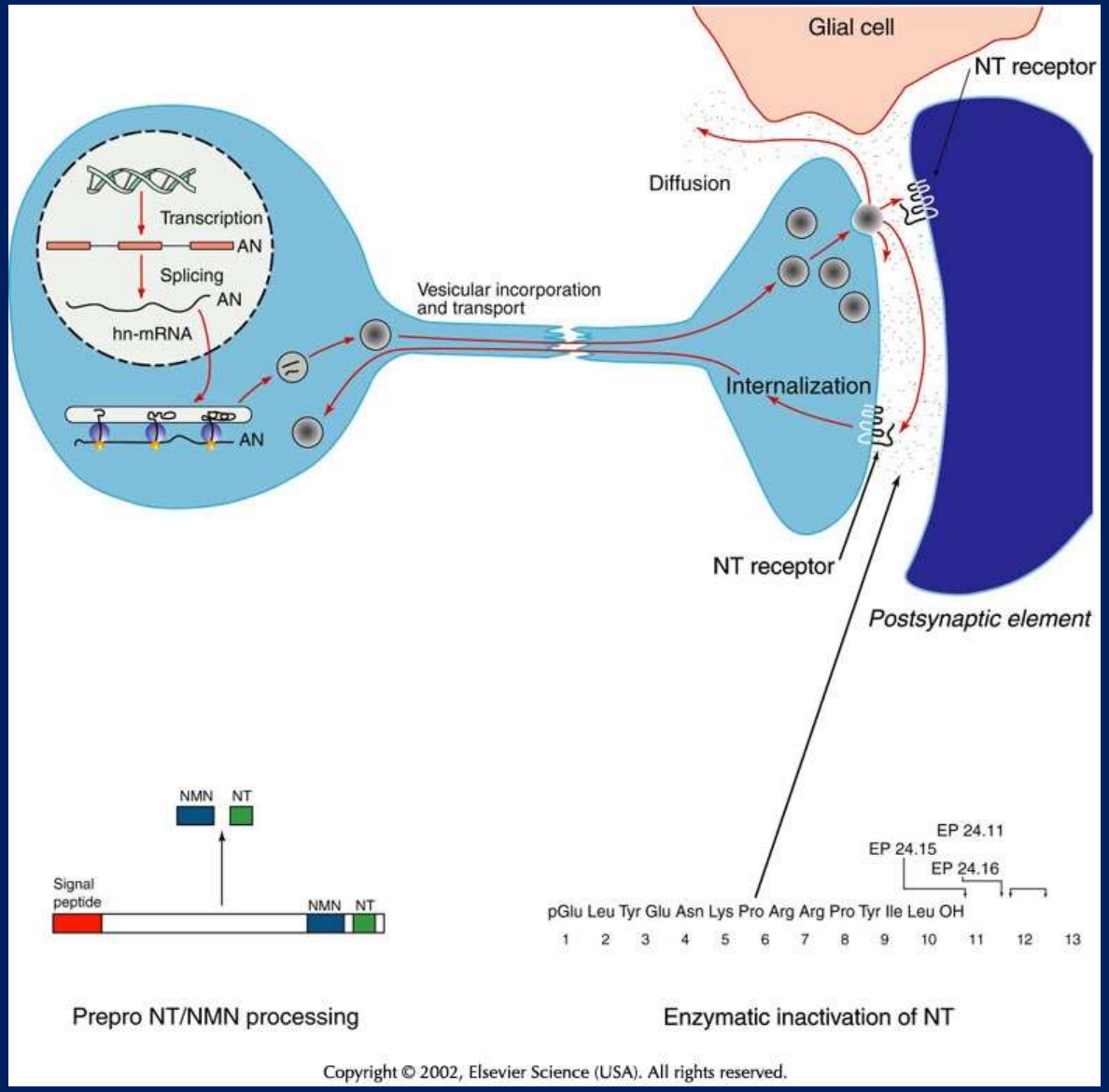
Captarea și impachetarea neurotransmițătorului

Transportoare veziculare:

- **Ach**
- **Amine Biogene**
- **Glutamat**
- **Glycine & GABA**



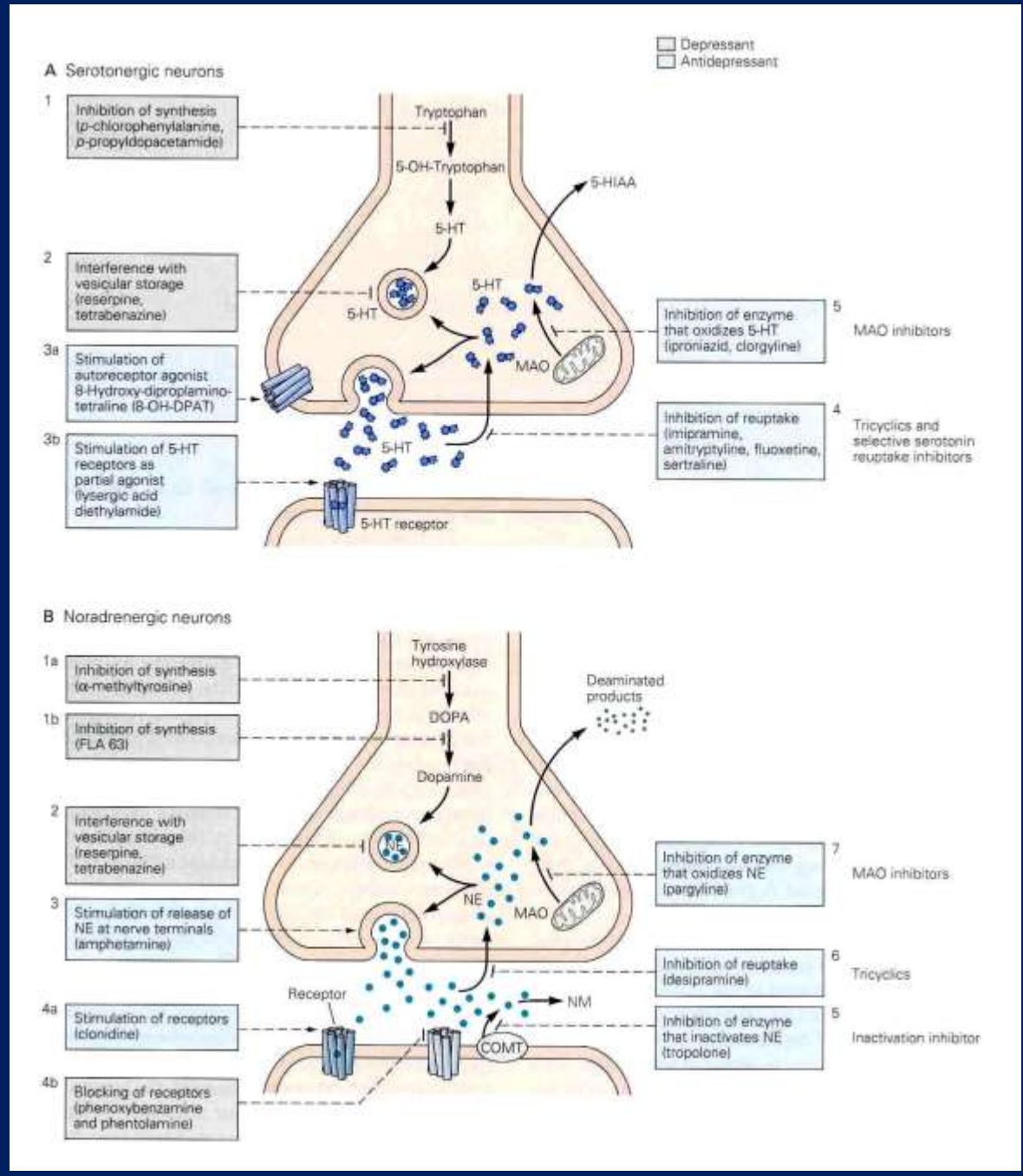
Sinteza, eliberarea și încetarea acțiunii unui neurotransmițător peptidic (neurotensină)



Mecanisme de îndepărtare a neurotransmițătorului

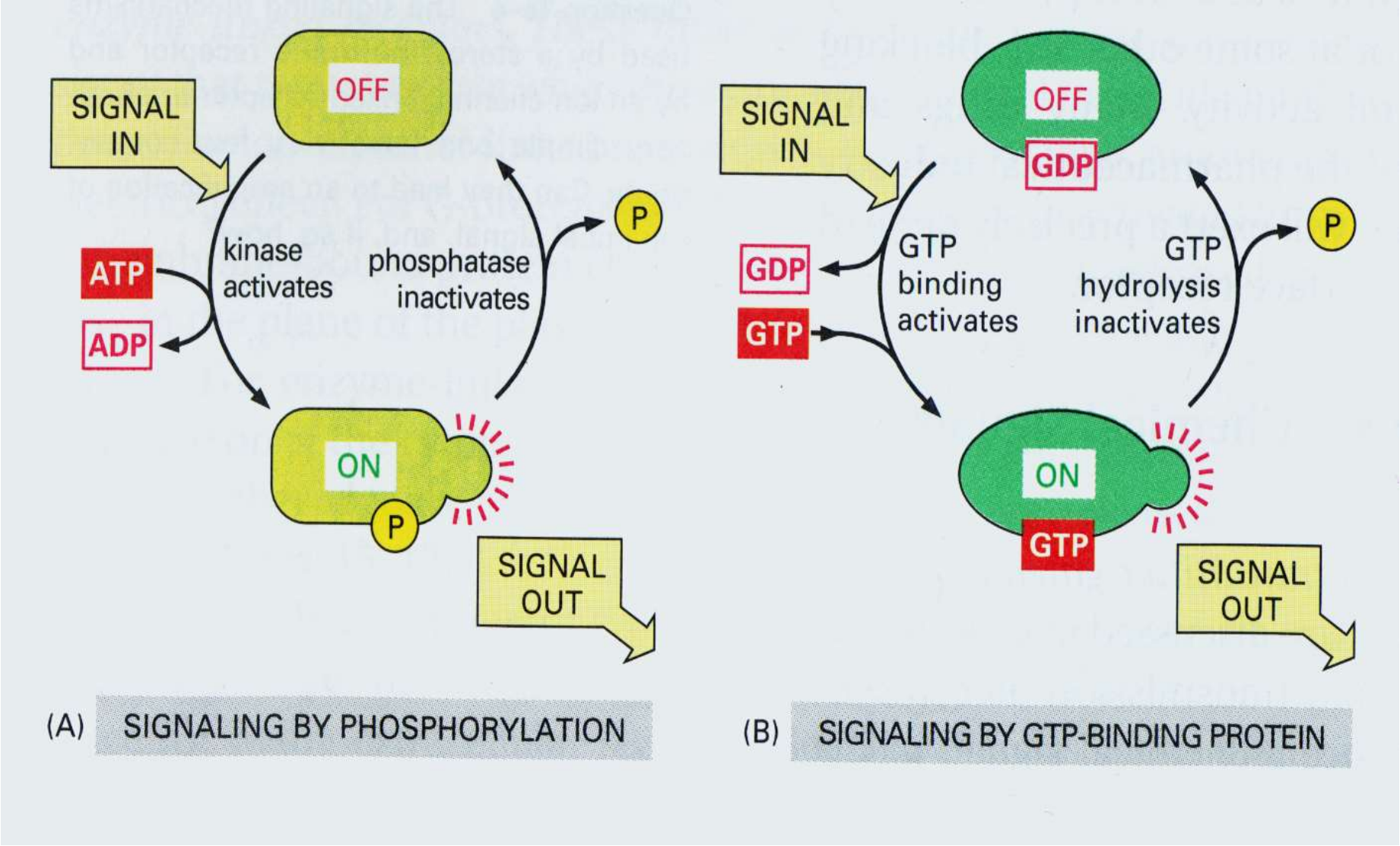
- Degradare (Ach)
- Recaptare *(Reuptake)* (NTs cu molecule mici)
- Difuzie (toate NT, neuropeptidele)

Transmisia sinaptică ca loc de intervenție farmacologică

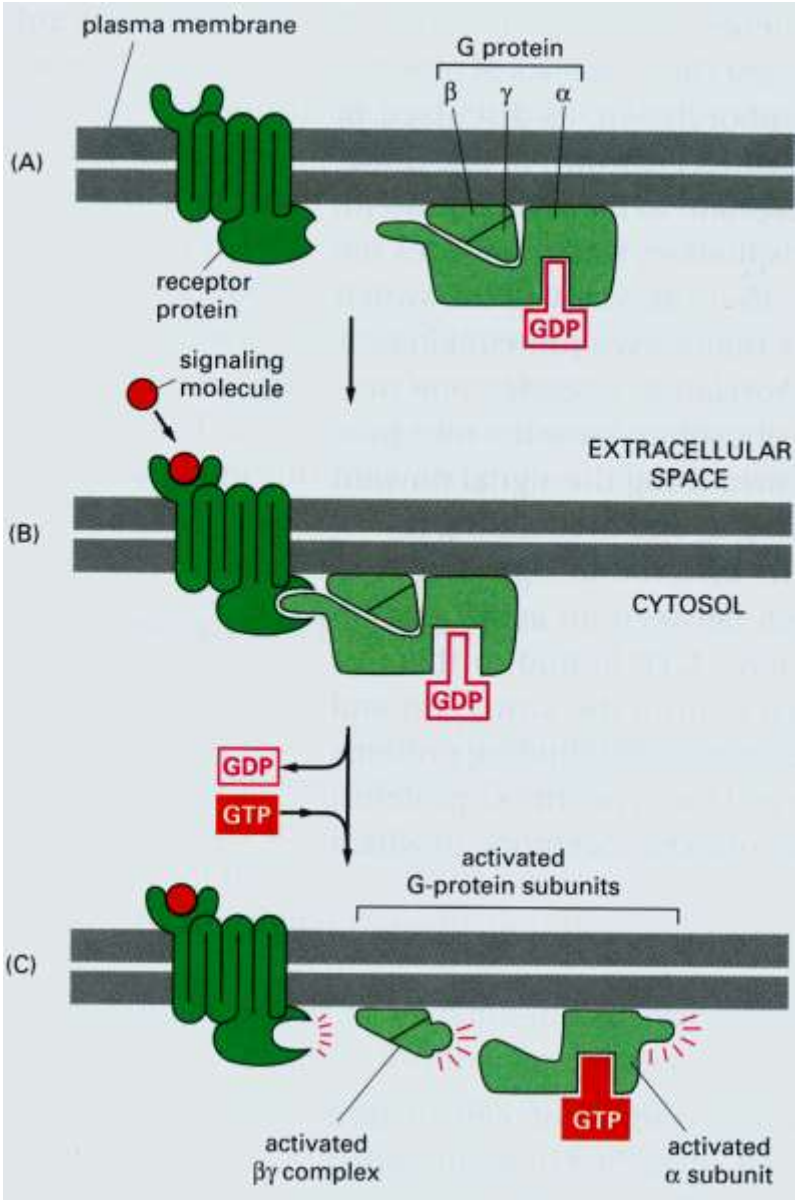


Semnalizarea Intracelulară
în Sistemul Nervos

Moleculele de semnalizare intracelulară acționează ca "întrerupătoare" moleculare



Proteinele G se dezasamblează în două subunități de semnalizare atunci când sunt activate



Subunitatea alpha a proteinei G se dezactiveaza prin hidrolizarea GTP-ului său legat

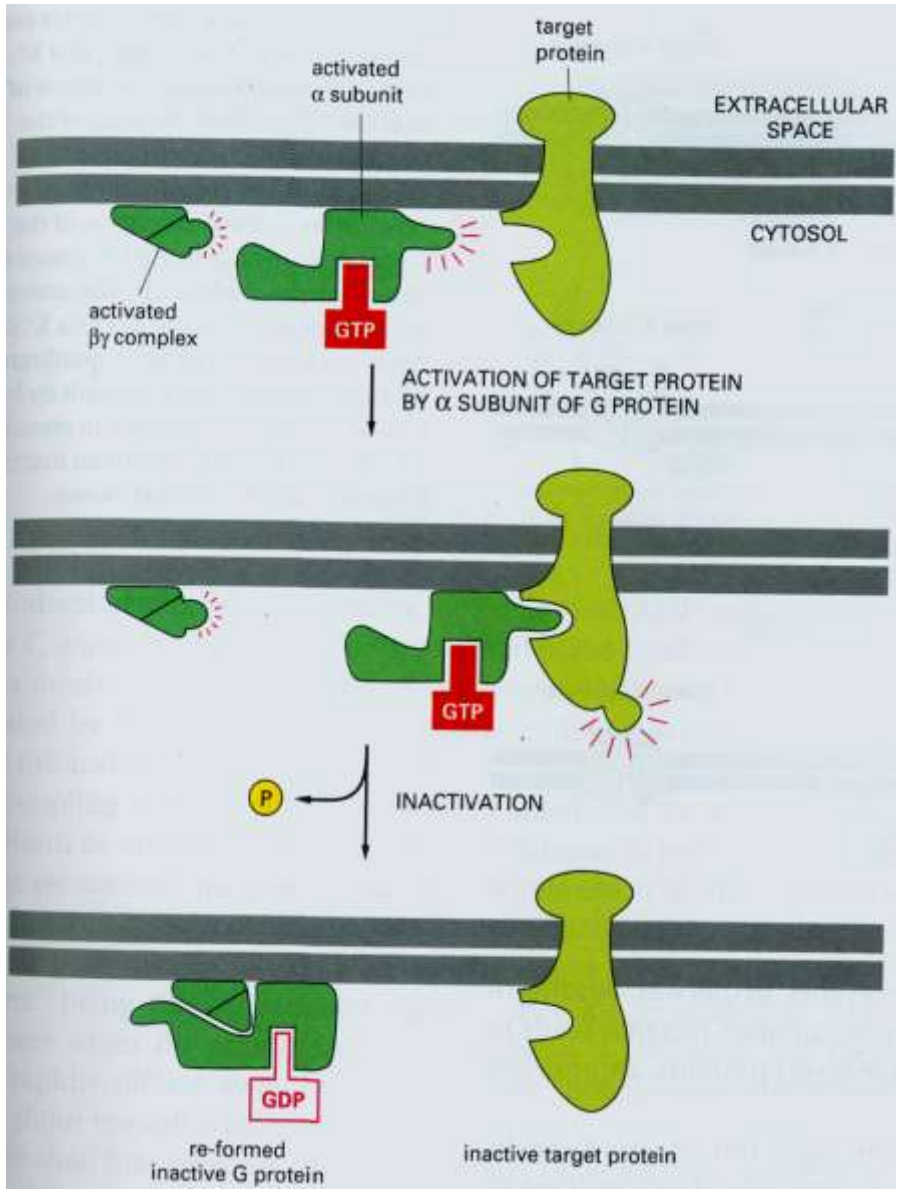
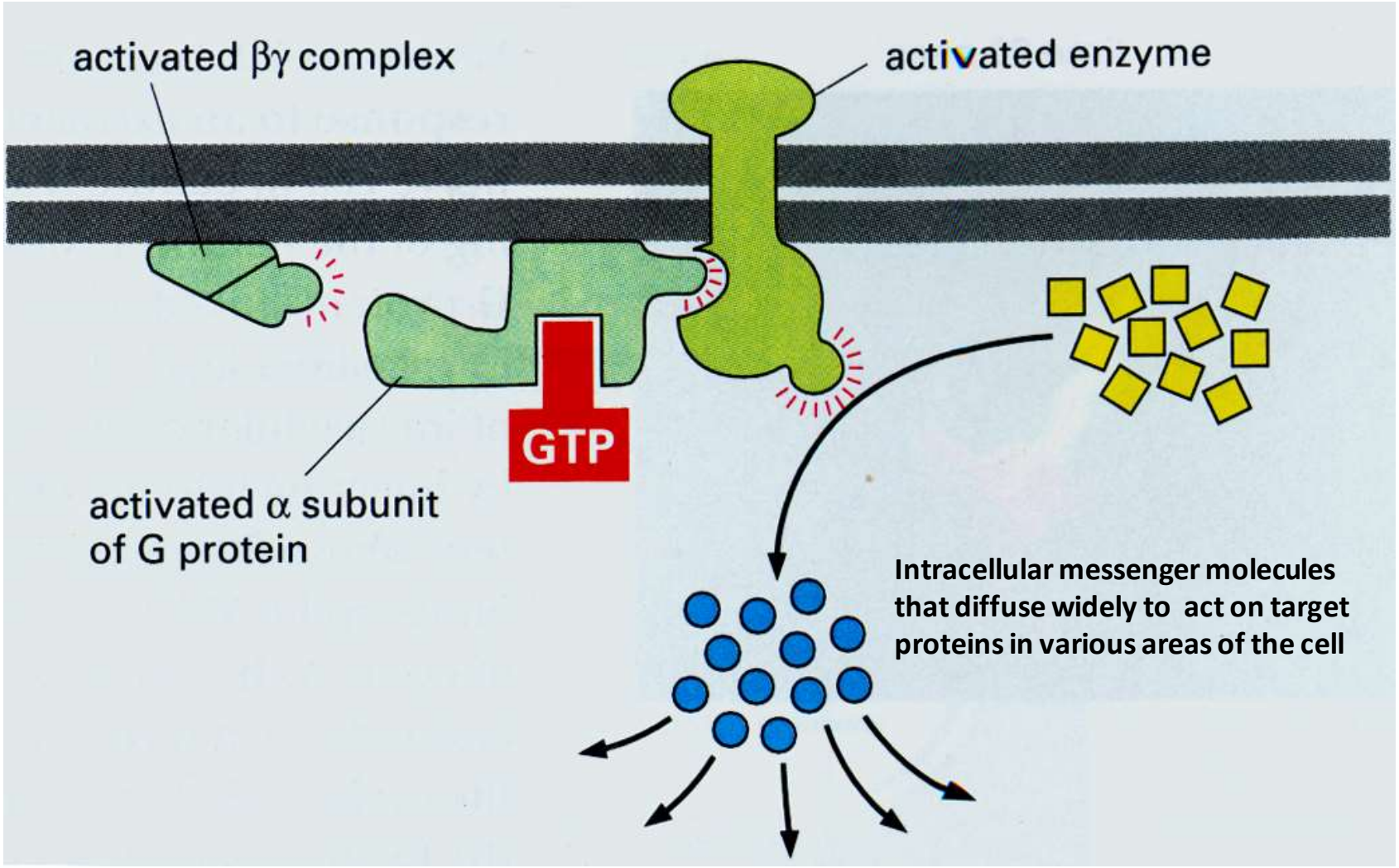


TABLE 21-2 Some Neurotransmitter Receptors That Are Coupled to G Proteins

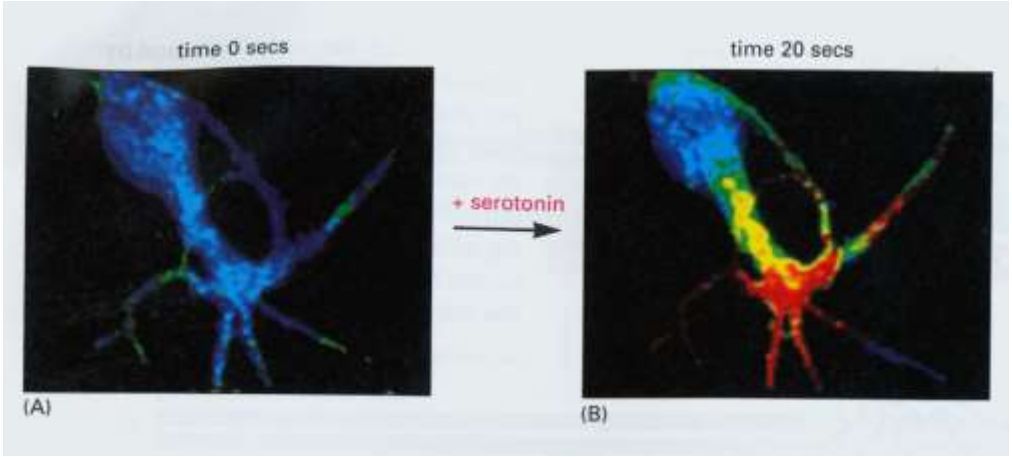
Receptor Class	Typical Ligands
Small neurotransmitters	Epinephrine, norepinephrine Dopamine
	Serotonin* (for $5HT_1$, $5HT_2$, $5HT_4$ class receptors)
	Histamine
	Acetylcholine* (for muscarinic receptors)
	GABA* (for B-class receptors)
	Glutamate*
	ATP
	Adenosine
Neuropeptides	Opiods (e.g. β-endorphin)
	Tachykinins (e.g. substance P)
	Bradykinin
	Luteinizing hormone–releasing hormone (LHRH)
	Thyrotropin-releasing hormone (TRH)
	Vasoactive intestinal peptide (VIP)
	Adrenocorticotropic hormone (ACTH)
	Cholcystokinin (CCK)
	Gastrin
	Endothelin
	Vasopressin
	Oxytocin
Environmental signals	Light (receptor is the visual pigment rhodopsin)
	Odorants (hundreds of different receptors)

Enzimele activate de proteinele G catalizează sinteza moleculelor-mesager intracelulare

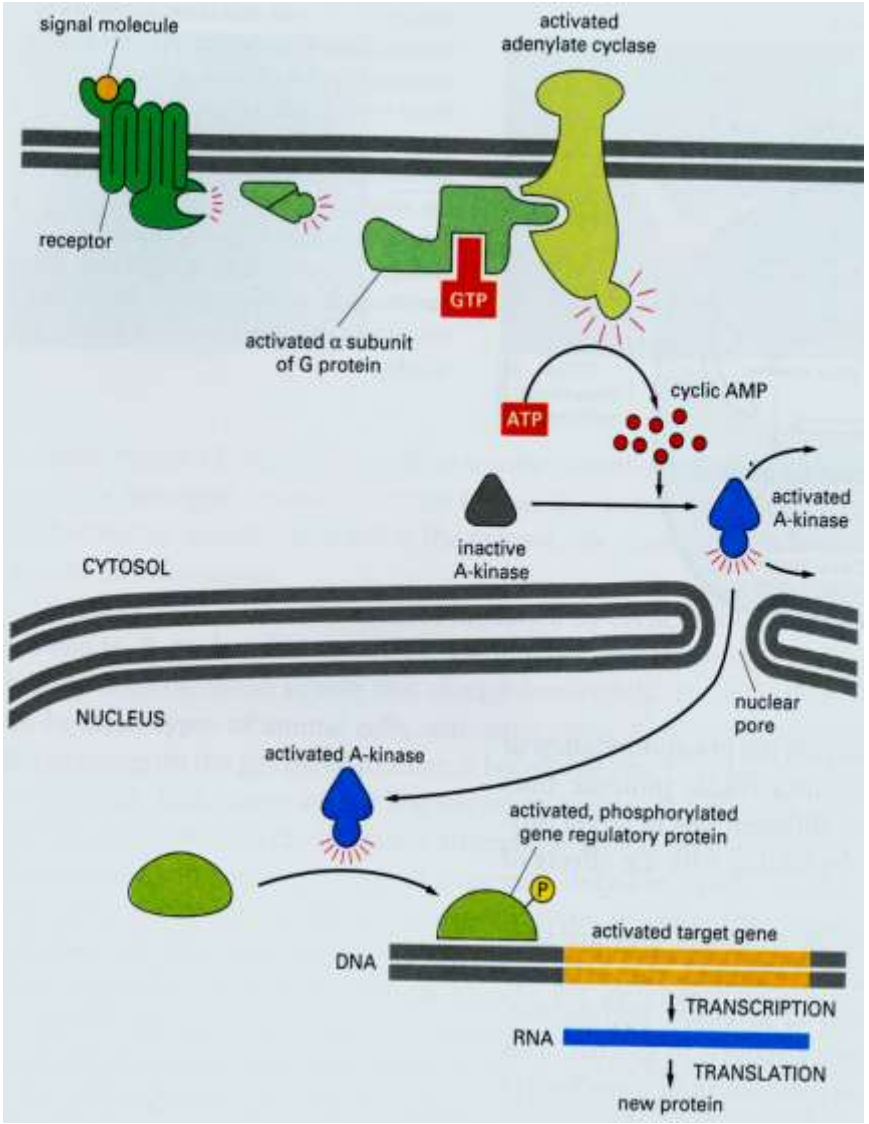


Mesageri secunzi: AMPc

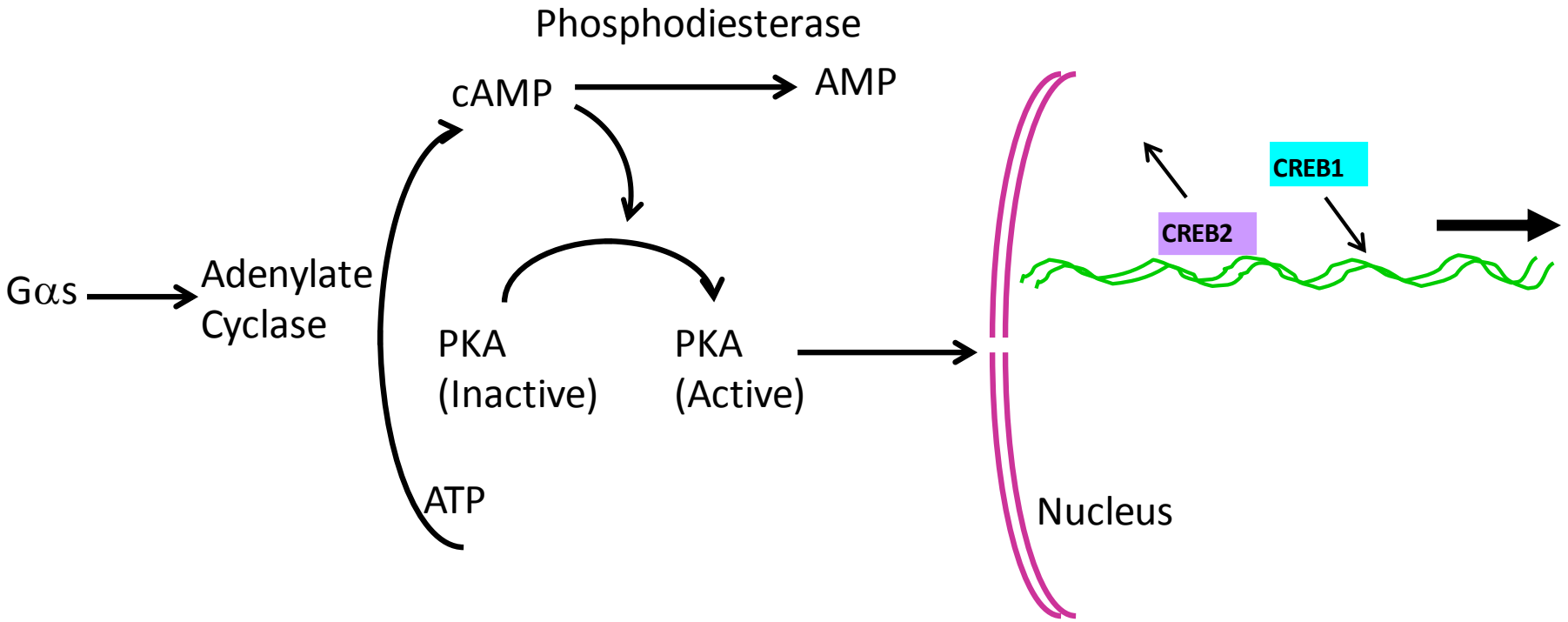
Creșterea AMPc ca răspuns la un semnal extracelular



Activarea transcripției genice de către creșterea AMPc



Metabolismul AMPc este crucial pentru funcțiile celulare

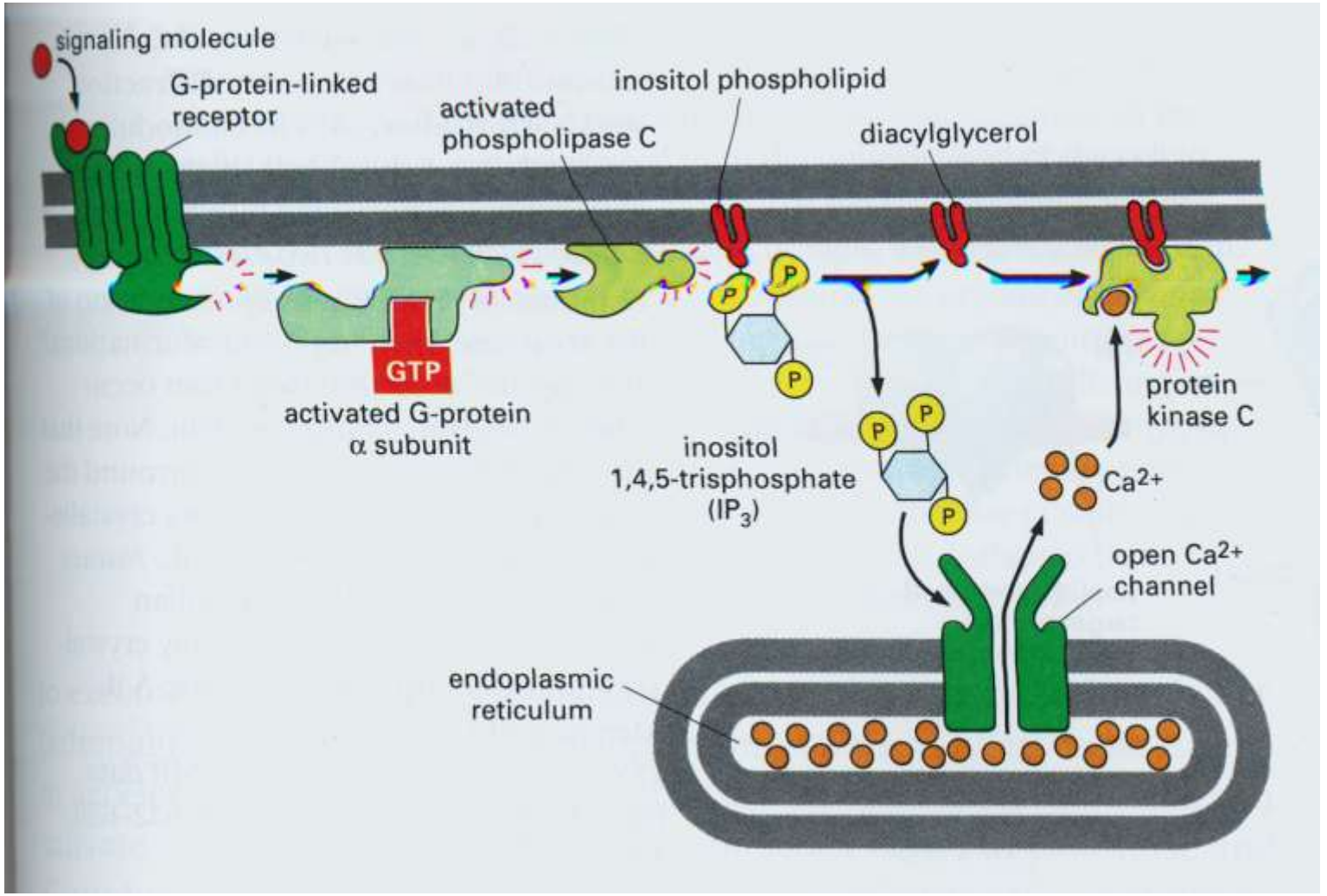


Drosophila Memory mutants:

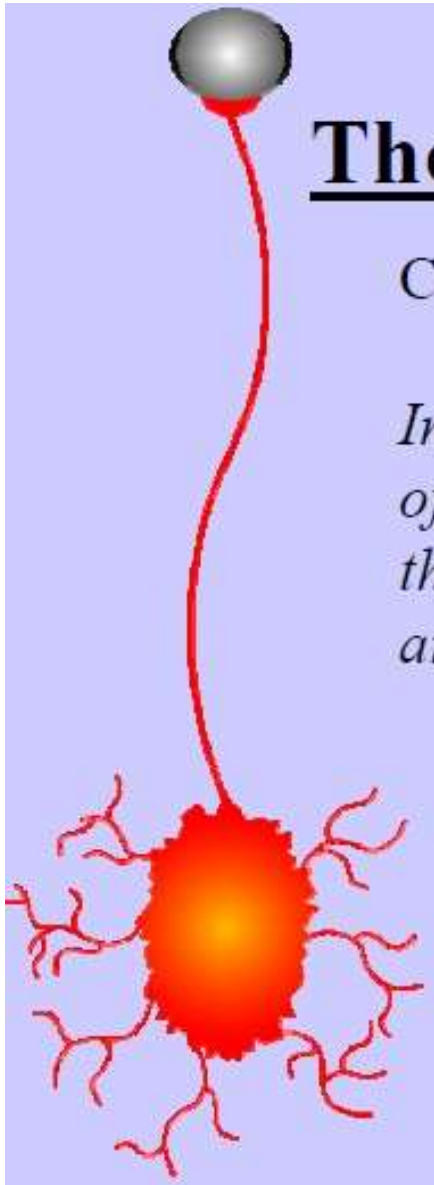
Dunce: Defective PDE- **cAMP** → **Loss of short-term memory**

Rutabaga: Defective AC- **cAMP** → **Loss of short-term memory**

Mesageri secunzi : PLC



Semnalizarea Intercelulară Retrogradă
în Sistemul Nervos



The Neurotrophic Factor Hypothesis

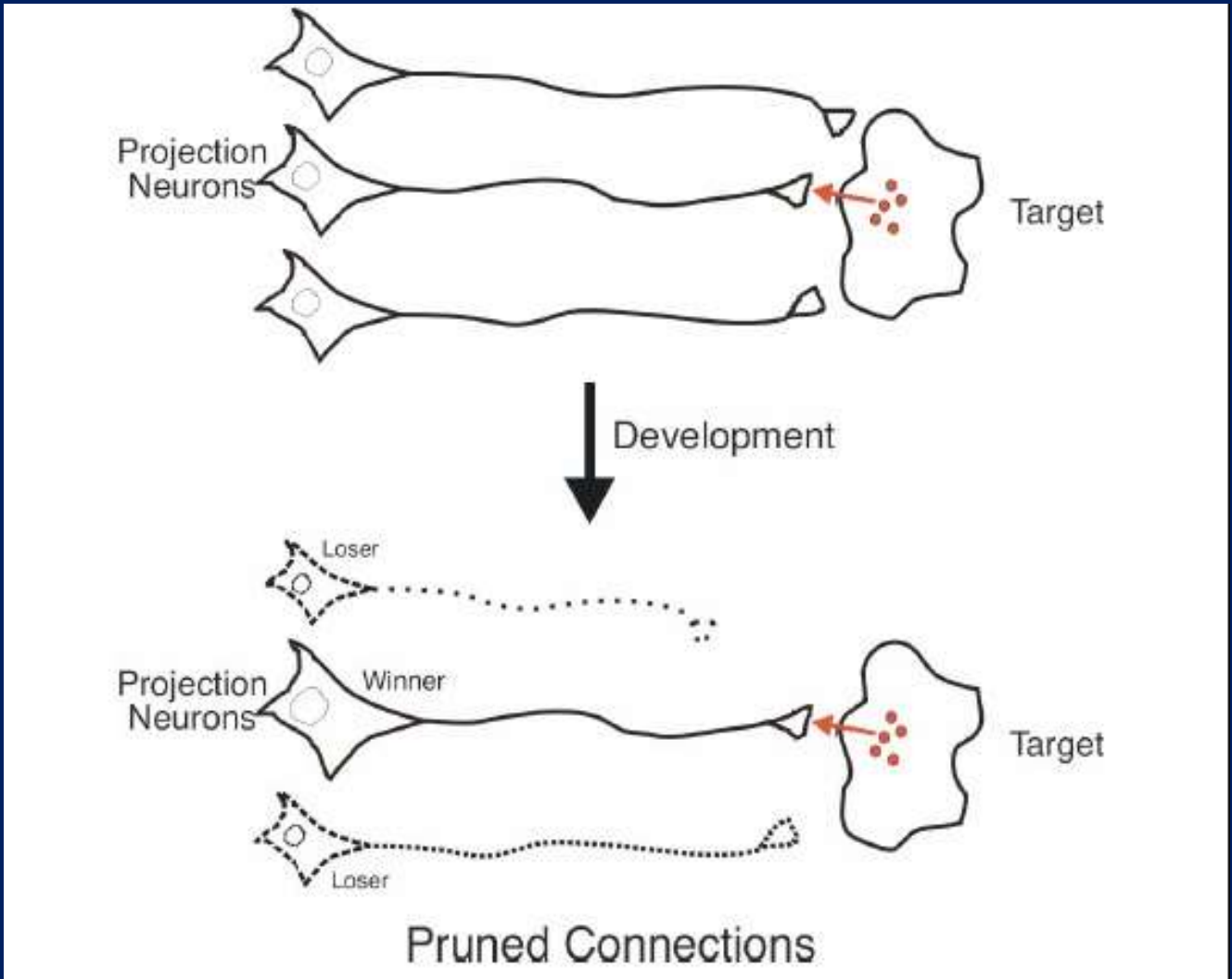
Concisely stated by Dale Purves in 1986:

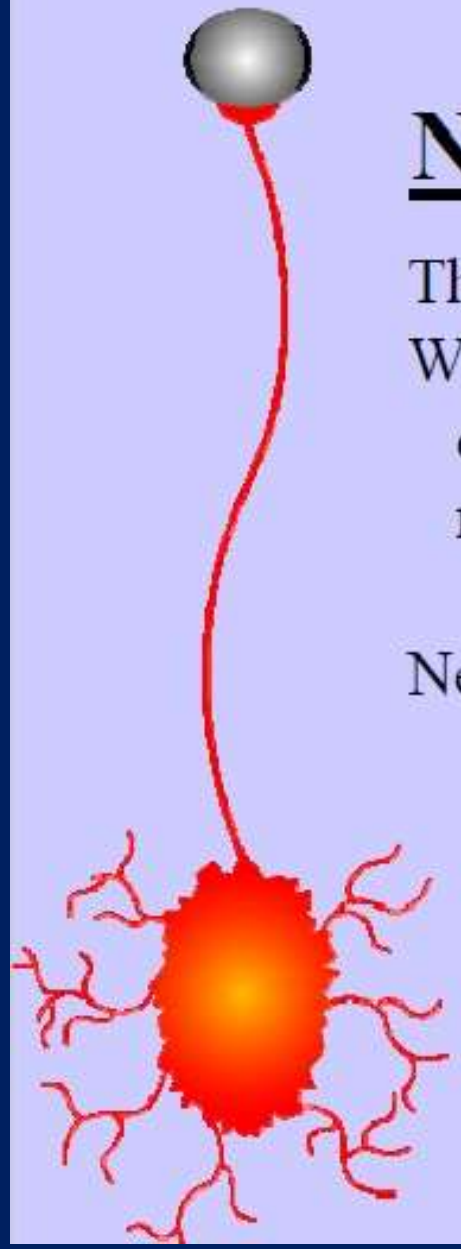
Innervating neurons compete for a limited supply of a target-derived trophic factor in order to match the density of innervation to the size of the target and to ensure the propriety of innervation.

Exuberant connectivity is pruned as the result of competition between axon terminals for a limiting supply of a trophic factor provided by the target.

“FROM EXUBERANT TO PRUNED CONNECTIONS”

DE LA LEGĂTURI EXUBERANTE LA CONEXIUNI SELECTIVE





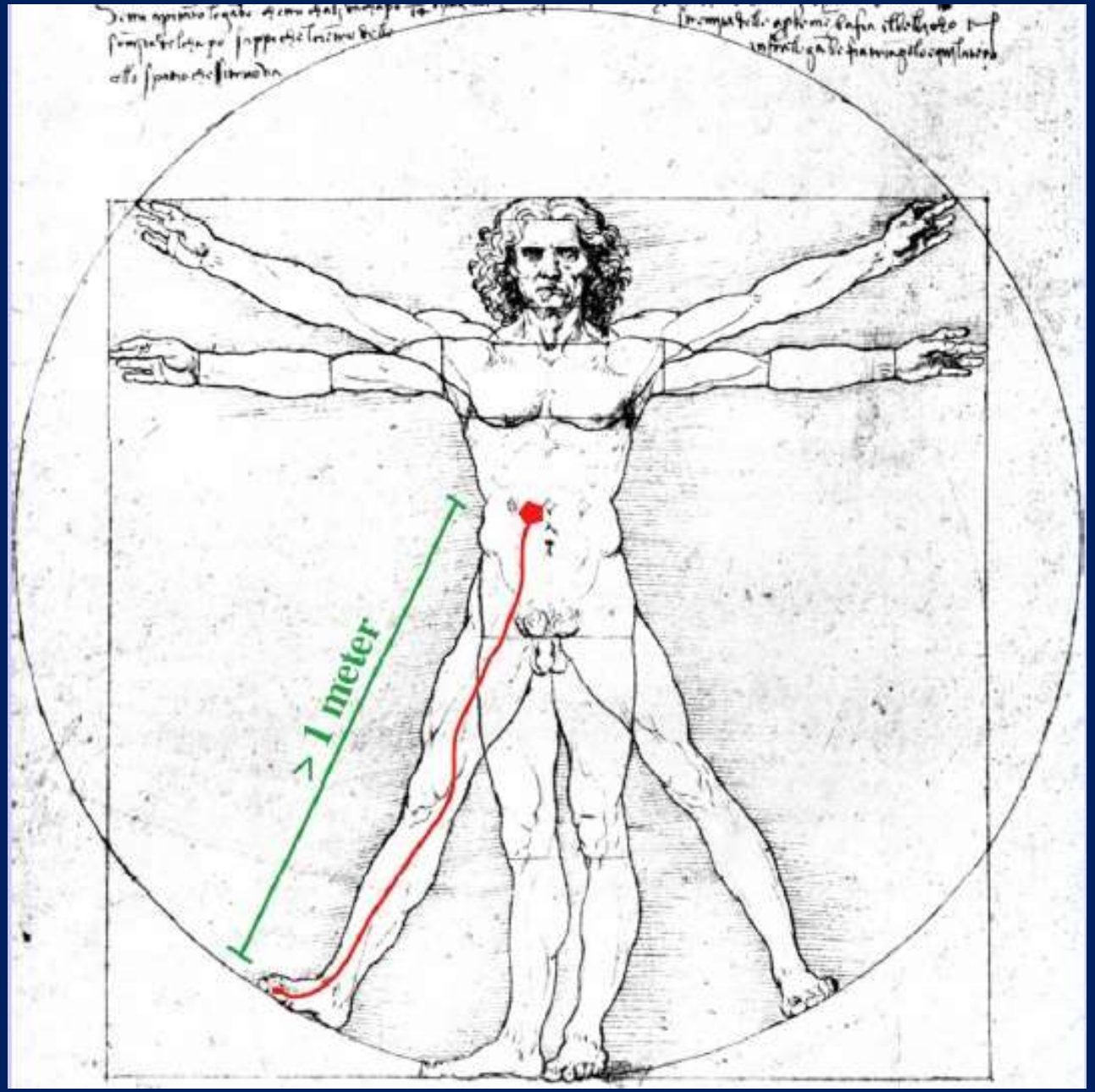
Neurotrophic NOT Neurotropic

The distinction is important.

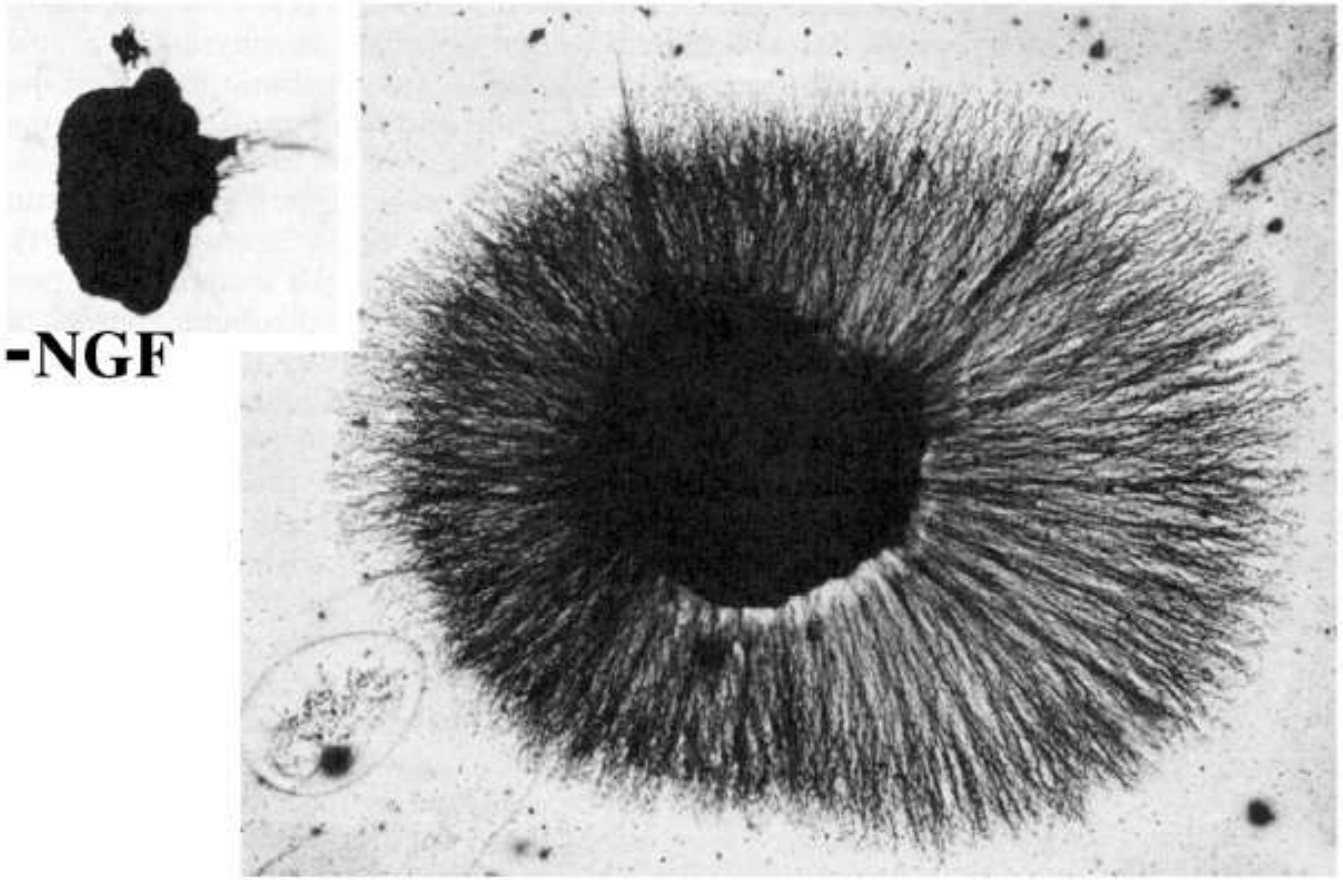
While neurotropism is certainly a critical factor in development of the nervous system, it is largely restricted to local action via gradients.

Neurotrophism, in contrast, is rooted in:

ACTION AT A DISTANCE.


> 1 meter

NGF Effects on Neurite Outgrowth



-NGF

+NGF

Cultured Chick DRG (24 hr)

From Levi-Montalcini and Hamburger 1953

Signals

What is the molecular basis of the Neurotrophic Factor Hypothesis?

NGF is released by the target and binds to receptors located on the presynaptic terminal of an innervating axon. These receptors in turn transduce a signal that is communicated from the distal axon terminal back to the cell body.

Neuron survival depends upon this retrograde signal.

So what is this signal?

Growth Factor Signaling Pathways:

MAPK = mitogen-activated protein kinase
- -ERK1/2 = extracellular signal regulated kinase
- -p38/HOG = high osmolarity glycerol-induced kinase
- -JNK/SAPK = c-jun N-terminal kinase/ stress-activated protein kinase

PI3K = phosphoinositide-3 kinase

JAK/STAT = Janus kinase/ signal transducer and activator of transcription

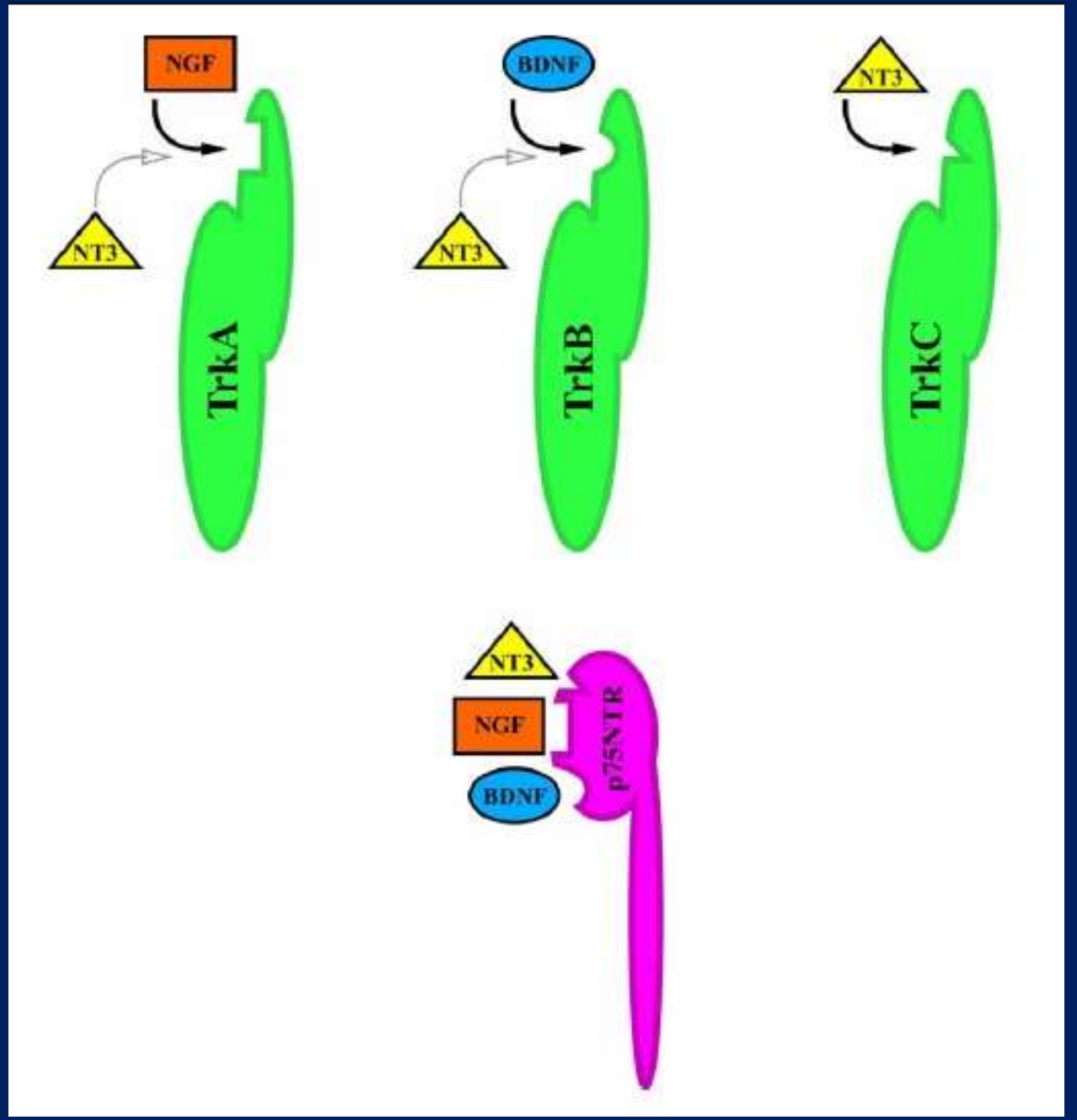
PLCγ and PKC = phospholipase C and protein kinase C

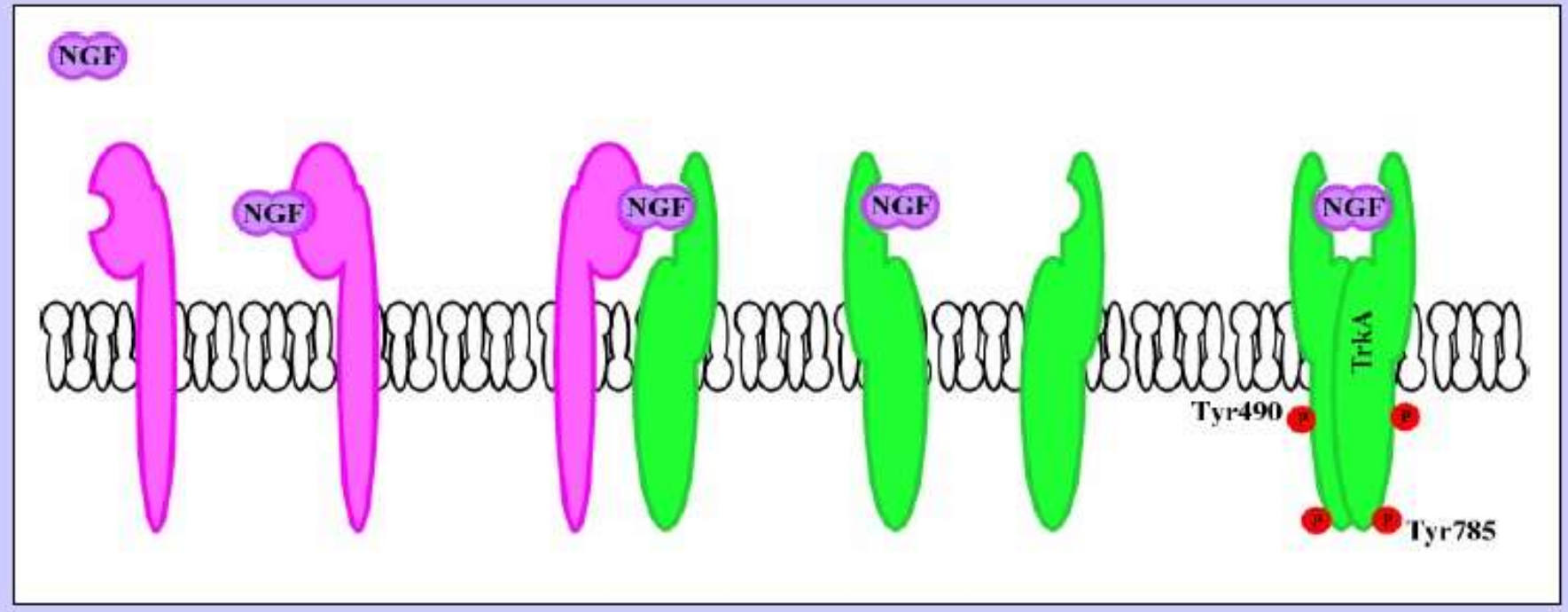
Exemple de factori neurotrofici și receptorii lor

NGF = Nerve Growth Factor
BDNF = Brain-Derived Neurotrophic Factor
NT-3 = Neurotrophin-3
NT-4/5 = Neurotrophin-4 and Neurotrophin-5

Receptor Tyrosine Kinases (RTK):
- TrkA
- TrkB
- TrkC

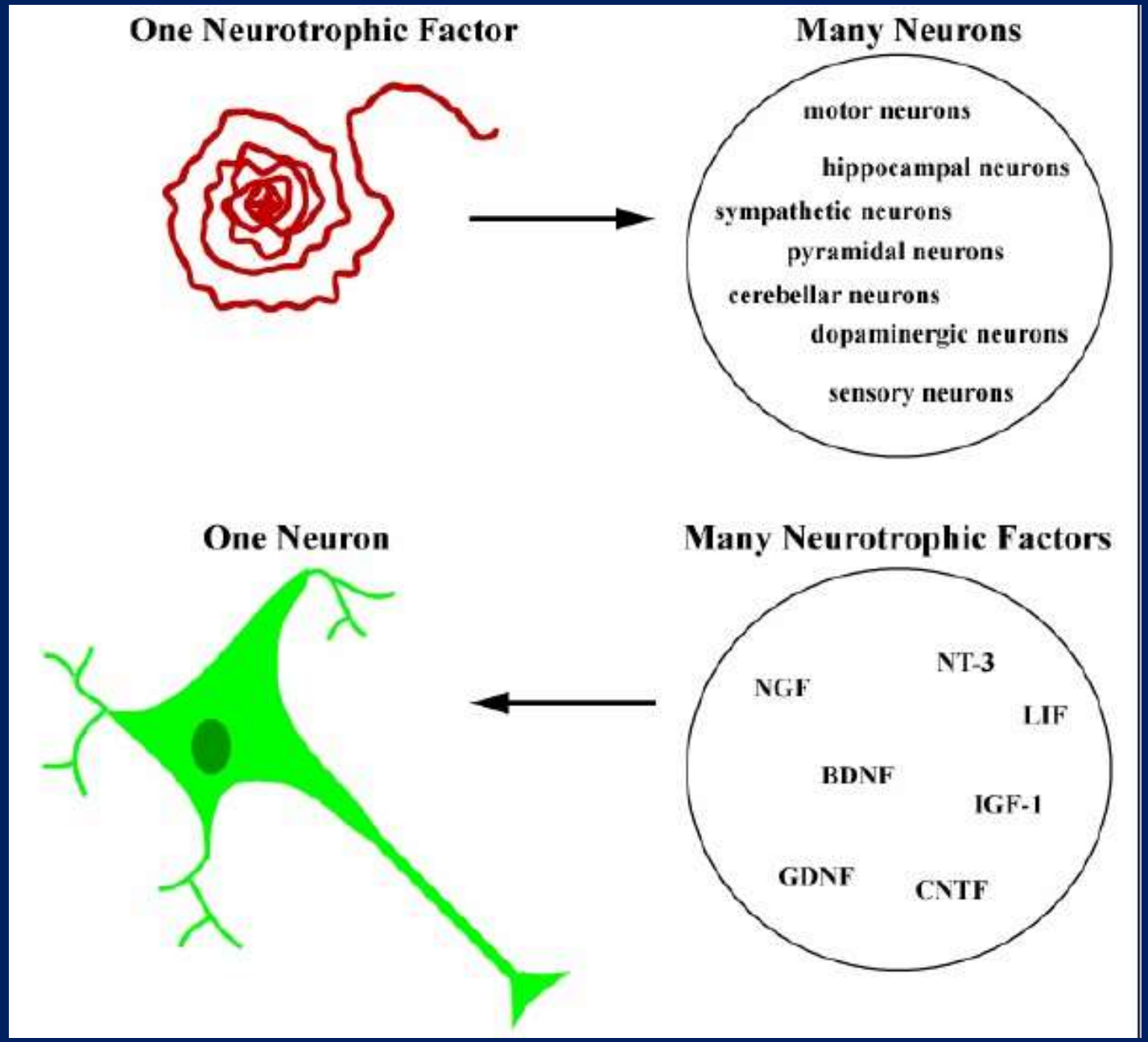
Common Neurotrophin Receptor:
- p75NTR


NGF
NT3
TrkA
BDNF
NT3
TrkB
NT3
TrkC
NT3
NGF
BDNF
p75NTR



p75NTR only = "low-affinity" binding
TrkA only = "low-affinity" binding

TrkA + p75NTR = "high affinity" binding and
full biological activity



BDNF:	Trigeminal Neurons Petrosal-Nodose Neurons Vestibular Neurons Cochlear Neurons Dorsal Root Ganglion (DRG) Neurons Cortical Neurons Hippocampal Neurons

DRG Neuron:	NGF BDNF NT-3 NT-4/5 GDNF Neurturin