

Tema 2

Neurotrofines, sinaptogènesi, supervivència i mort neuronal. Paper en el desenvolupament, la degeneració i en la neurotoxicitat

Esdeveniments clau després de posicionament final de neurones

- ✓ Creixement axònic
- ✓ Establiment de mapes topogràfics
- ✓ Connexions sinàptiques adients: dianes pre- i postsinàptiques
- ✓ Regulació de nombre de connexions

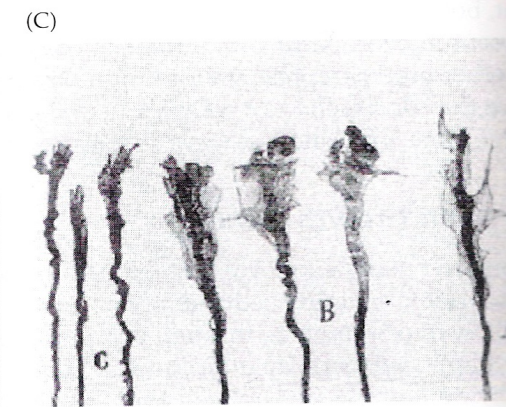
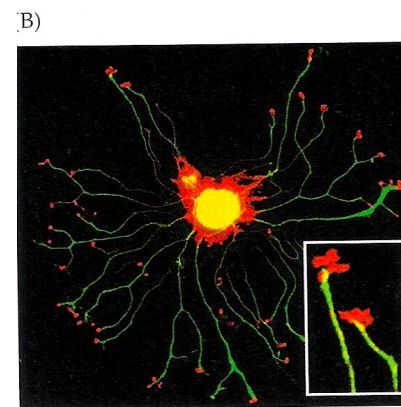
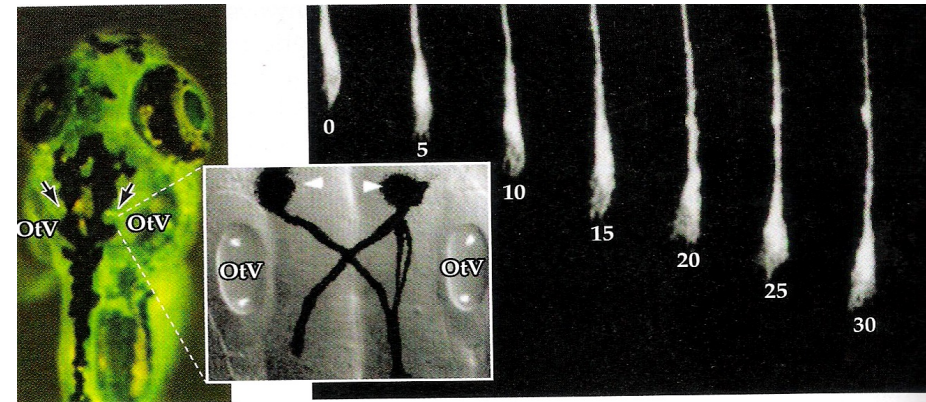
El con de creixement axònic

Migracions de mm o cm

Harrison, RG (1910)

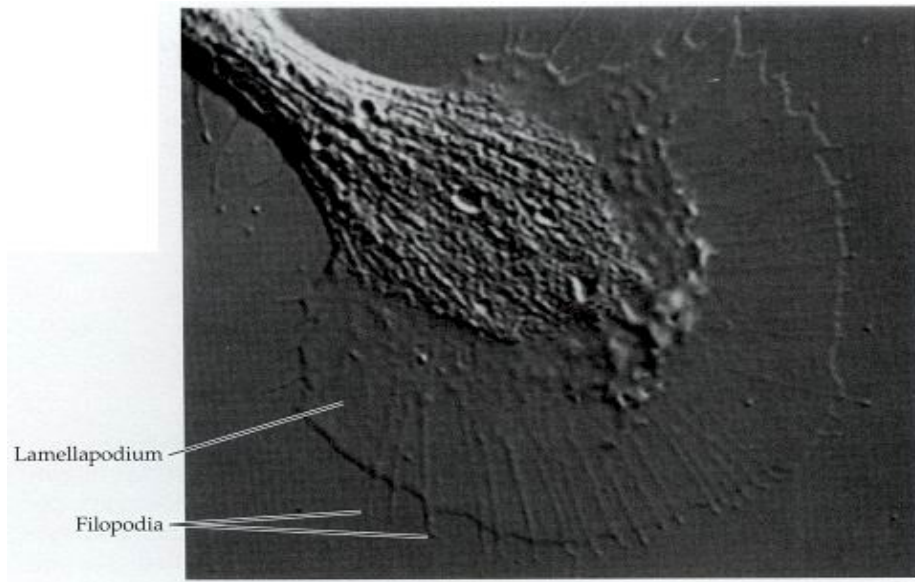
Extensió dendrítica

- Elevada motilitat
- Exploració medi extracel·lular
- Determinació de direcció de creixement
- Lamel·lipodis i filopodis
- Canvis de direcció a “punts de decisió”

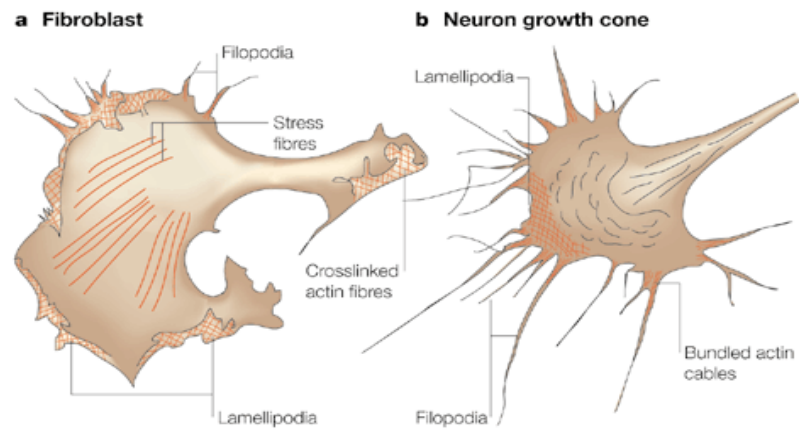


Neuroscience, Purves et al., 4 ed.

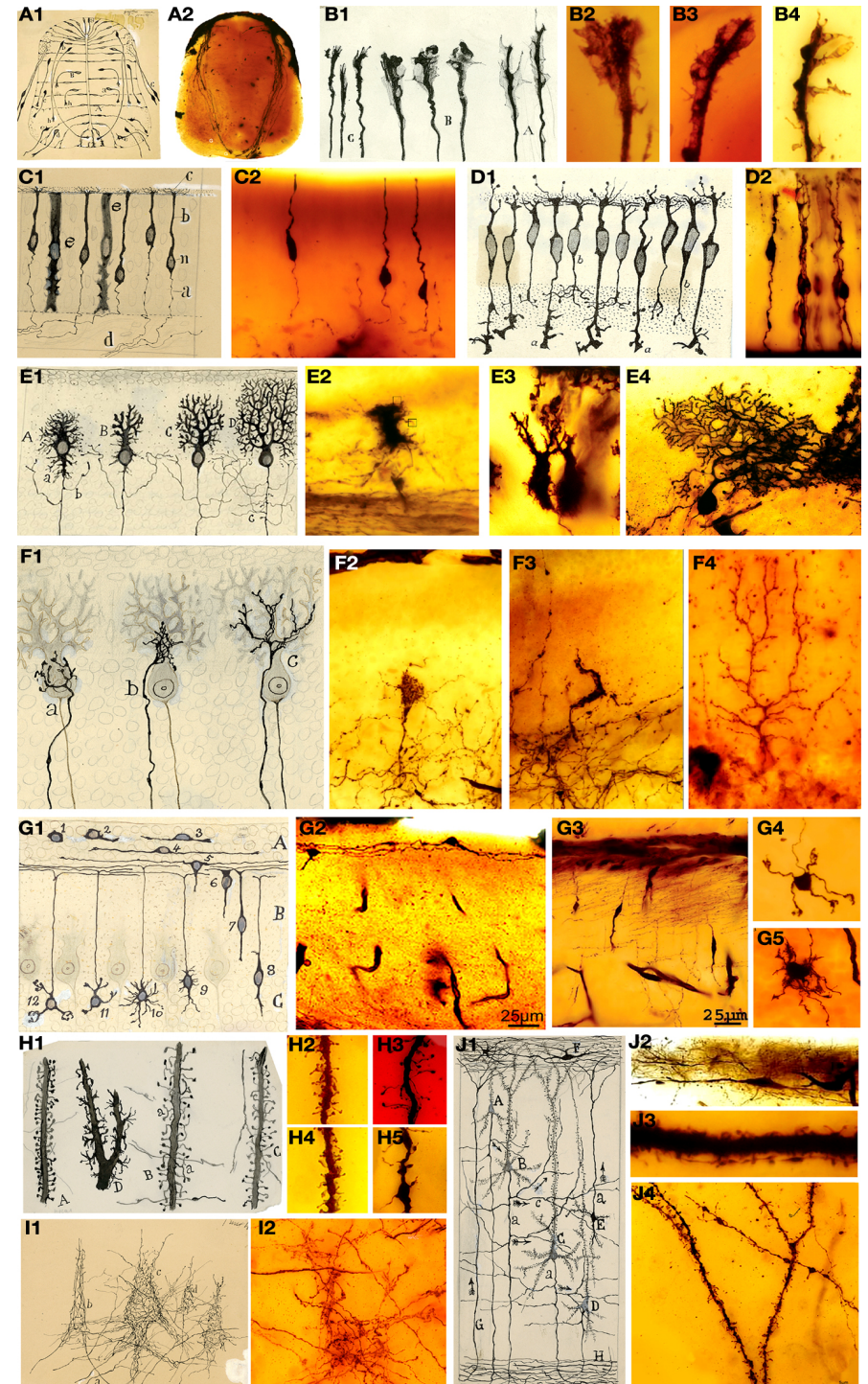
Tema 2



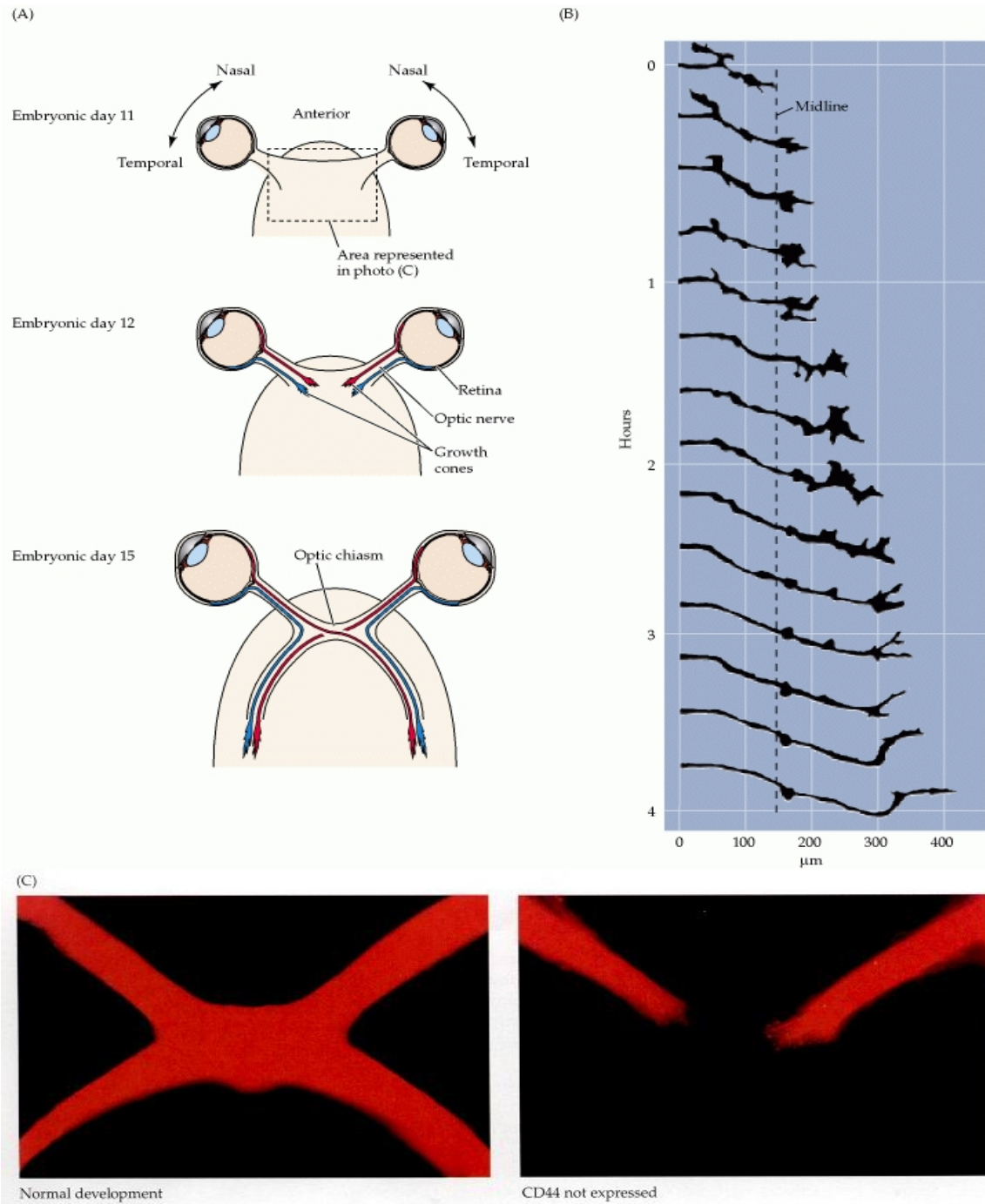
Neuroscience, Purves et al., 3 ed.



Nature Reviews | Neuroscience



Tema 2

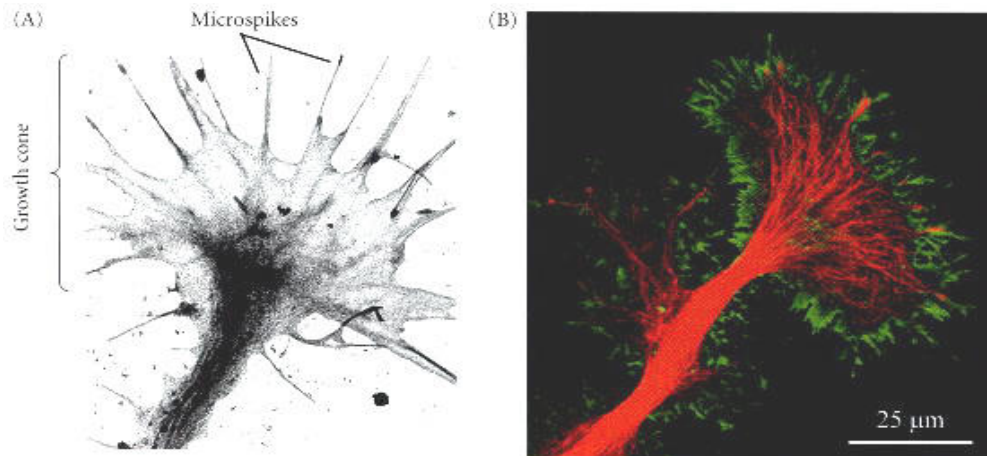


Tema 2

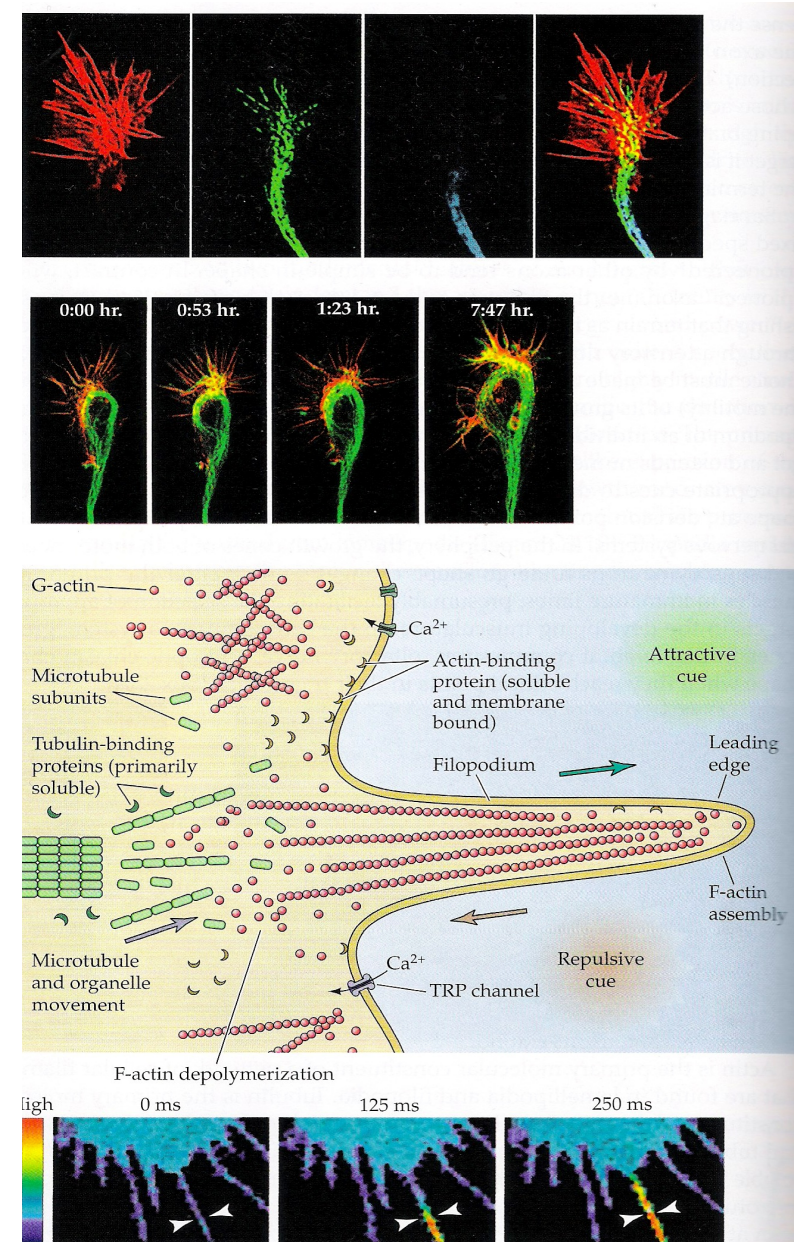
Bases moleculars de motilitat de con de creixement axònic

- ✓ Microfilaments: lamel·lipodis i filopodis
- ✓ Microtúbuls: elongació

<http://www.sinauer.com/neuroscience4e/animations23.1.html>



Developmental Biology, Gilbert et al., 6 ed.



Neuroscience, Purves et al., 4 ed.

Tema 2

Participació de senyals no difusibles en guia axònica

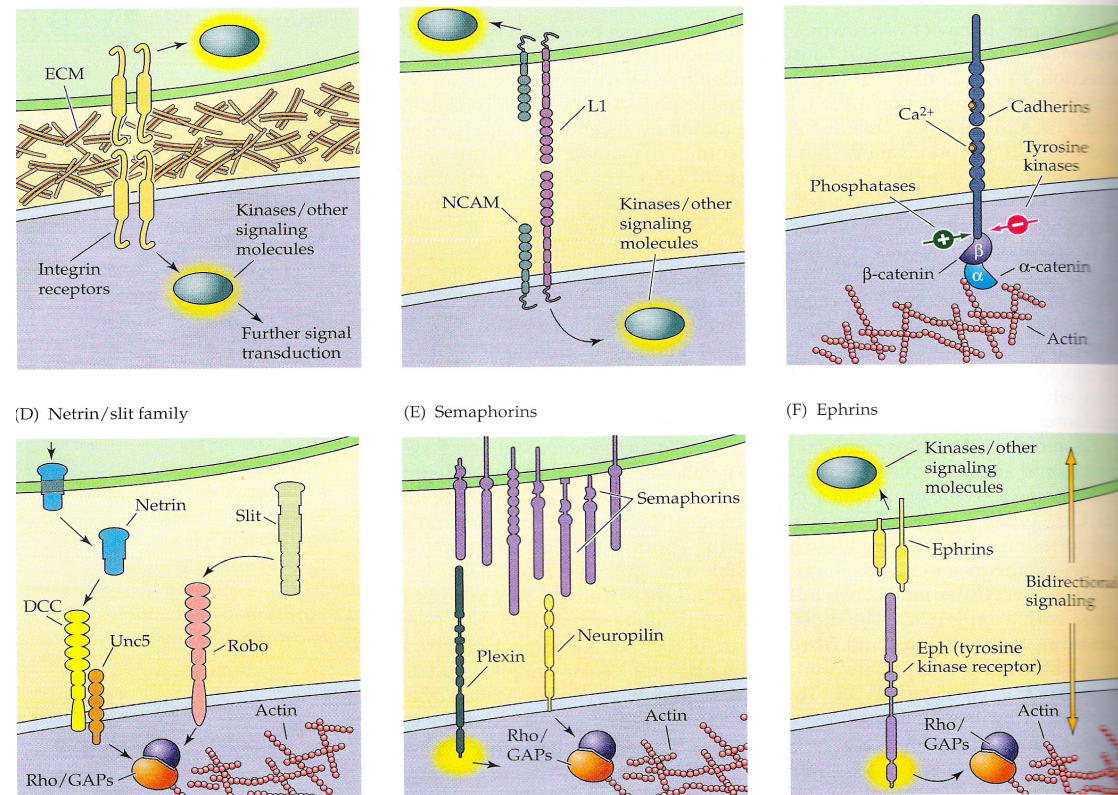
- ✓ Pistes per a guia
- ✓ Receptors i mecanismes de transducció de senyal que responguen a pistes
- Inici de cascades intracel·lulars → canvis en actina/tubulina
- ✓ Molècules relacionades amb adhesió cel·lular i reconeixement cèl·lula-cèl·lula
 - * ECM i els seus receptors d'integrines
 - * CAMs\$ no dependents de Ca²⁺, cadherines

Molècules d'ECM

Laminina, col·làgena, fibronectina

Paper més clar en SNP

CAMs\$ no dep\$ Ca²⁺, cadherines
relacionades amb desordres de neurodesenvolupament (ex. : agènesi de cos callós)



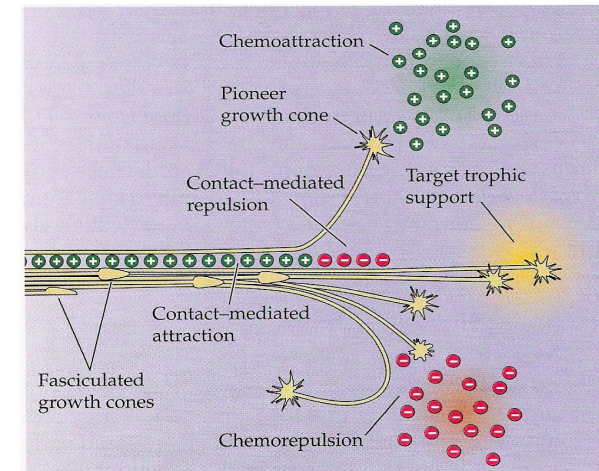
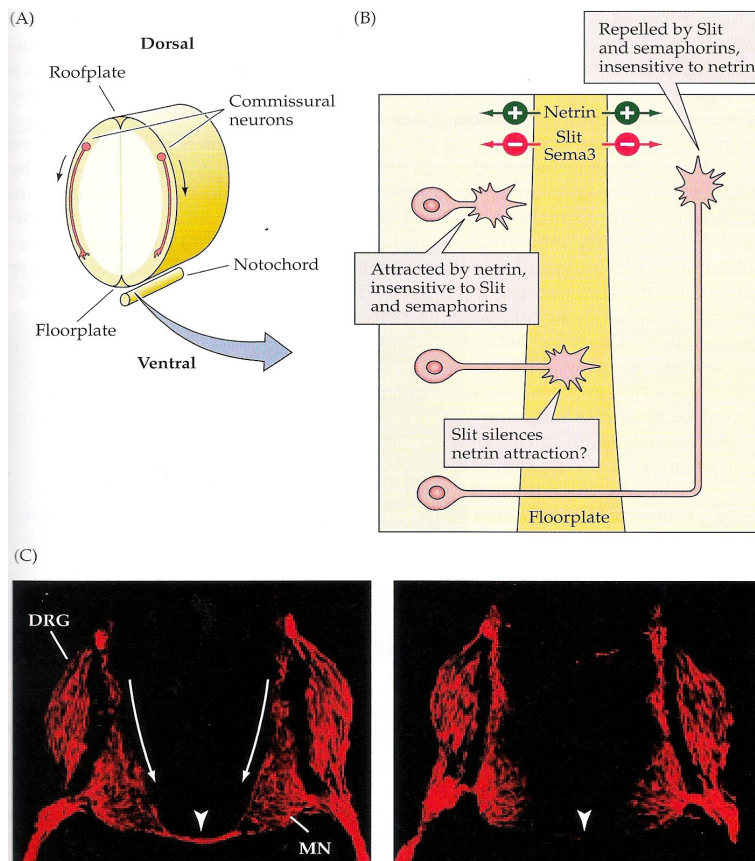
Tema 2

Participació de senyals difusibles en guia axònica. Senyals canònics

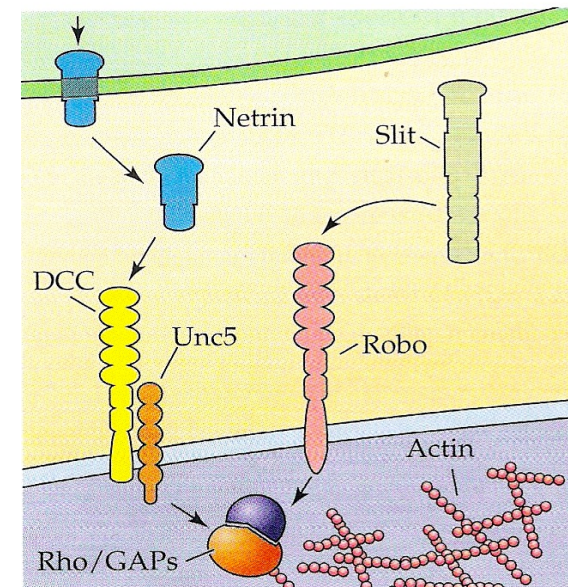
- Cajal
- Quimioatracció i quimiorepulsió
- Molècules tròpiques i tròfiques

LA FAMILIA NETRINES/SLIT

Placa basal



(D) Netrin/slit family



Tema 2

Participació de senyals difusibles en guia axònica. Senyals canònics

SEMAFORINES

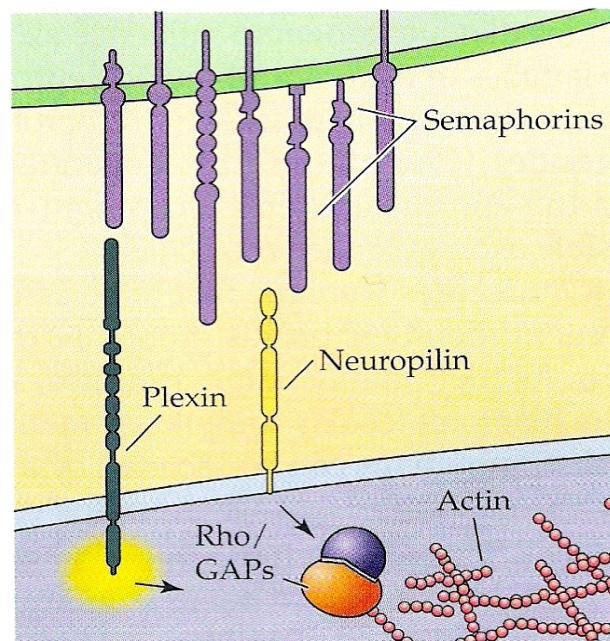
On cal no anar!

Repel·lents junt a Slit/Robo

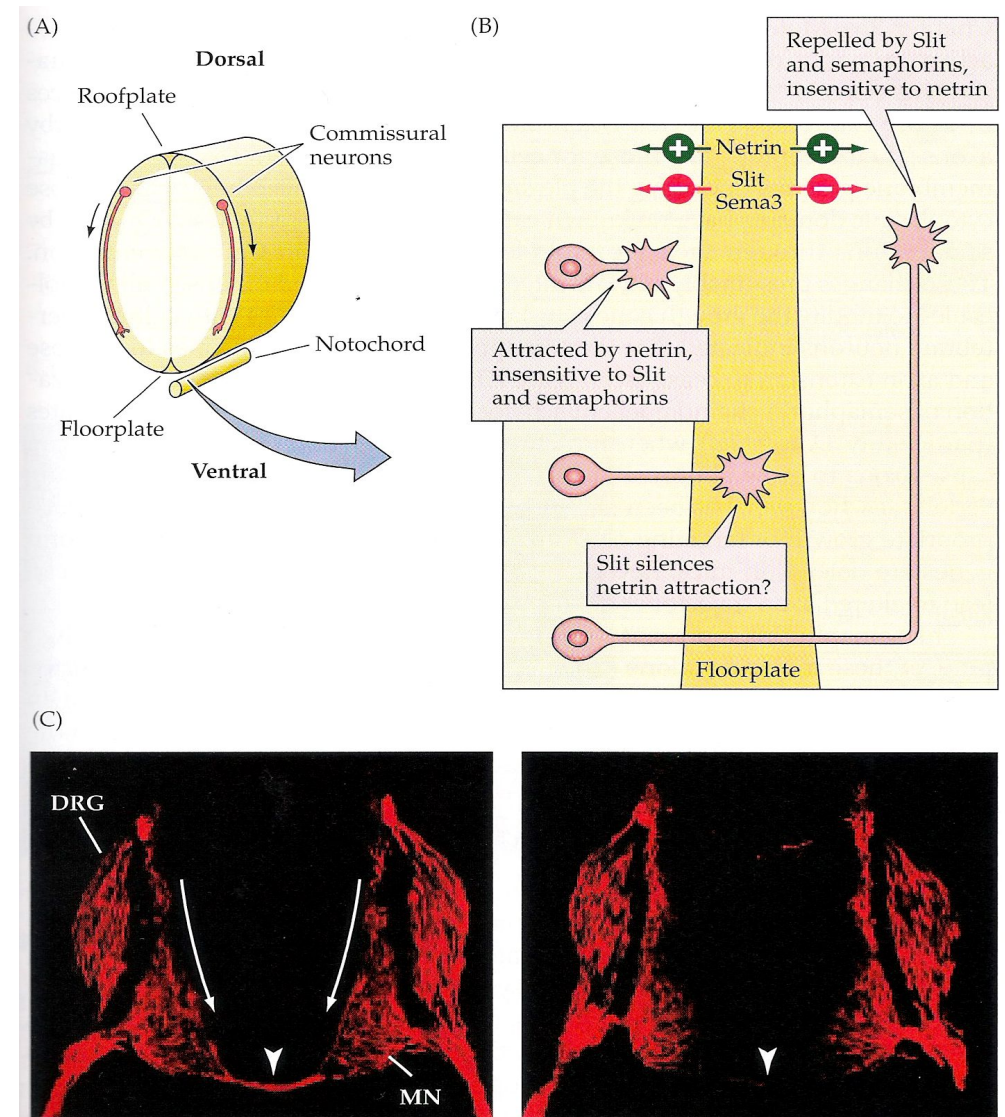
- NogoA (mielina, regeneració axònica)
- Semaforines

Localització en cèl·lules o ECM

(E) Semaphorins



Neuroscience, Purves et al., 3 ed.



Tema 2

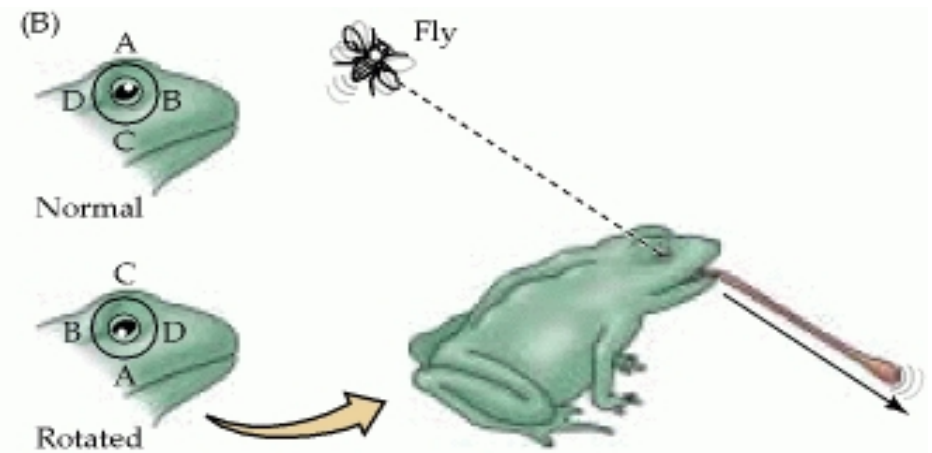
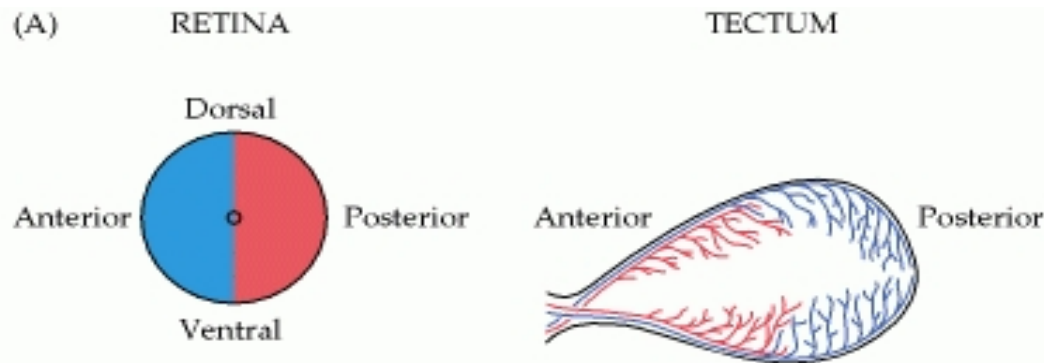
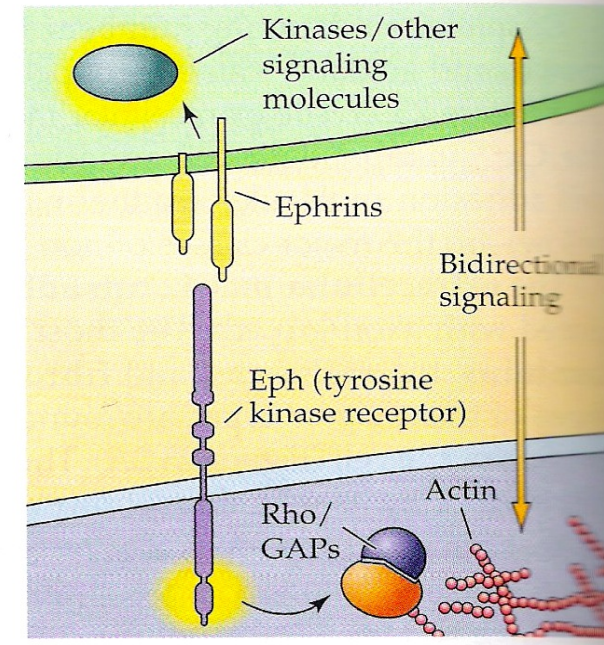
Participació de senyals difusibles en guia axònica. Senyals canònics

EFRINES

No difusibles

Formació de mapes topogràfics

(F) Ephrins



Neuroscience, Purves et al., 3 ed.

Tema 2

Participació de senyals difusibles en guia axònica. Senyals canònics

Morfògens i factors de creixement

MORFÒGENS: Proteïnes que especifiquen destinació cel·lular

També implicades en guia axònica

- Hh
- BMP
- Wnt

FACTORS DE CREIXEMENT O TRÒFICS

Implicació en supervivència neuronal

També implicats en guia axònica

- HGF
- FGF
- GDNF
- BDNF + NT3

Alguns relacionats amb fasciculació axònica

Tema 2

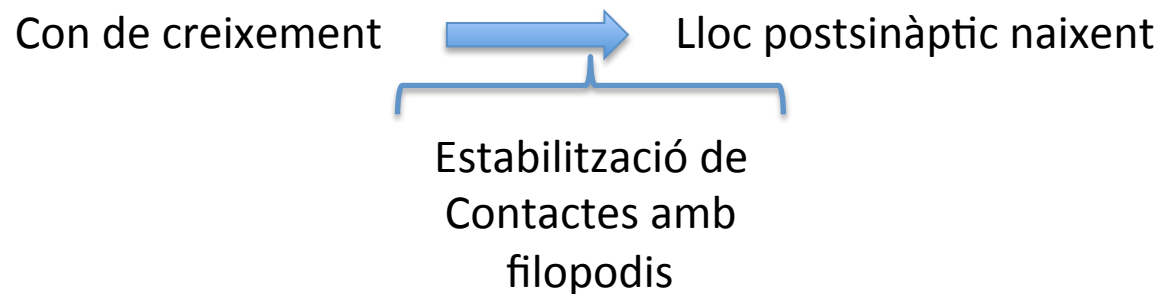
Formació selectiva de sinapsi

Arribada d'axó a regió/cèl·lula diana → DECISIONS:

- ✓ Estabilització de contactes sinàptics
- ✓ Retracció i innervació d'una altra cèl·lula
- ✓ Errada en la formació de sinapsi = degeneració, PCD

Molècules relacionades amb guia axònica també contribueixen a identificació i estabilització de sinapsi.

- Cadherines importants per a reconeixement de lloc sinàptic a dendrita, soma, múscul...



- * Agrupament (*clustering*) de vesícules sinàptiques
* Construcció de PSD

Tema 2

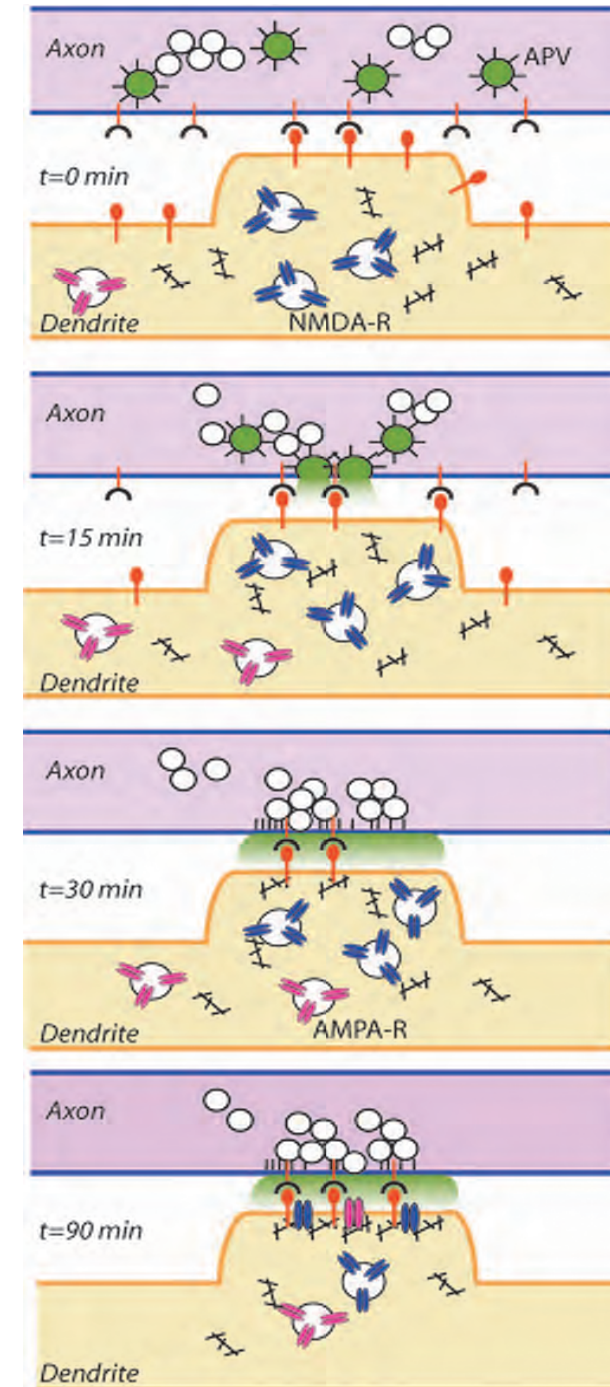
Formació selectiva de sinapsi

Participació de neurexines i neuroligines

- ✓ Promoció d'adhesió
 - ✓ Domini intracitoplàsmic de neuroligina localitza vesícules sinàptiques i les proteïnes d'ancoratge (*docking*) i molècules relacionades amb fusió.
 - ✓ Neuroligina funció similar a element postsinàptic
- Agrupament (*clustering*) de receptors i canals

Com generar diversitat de sinapsis amb poques molècules?

"If you can't be with the one you love, love the one you are with"



Tema 2

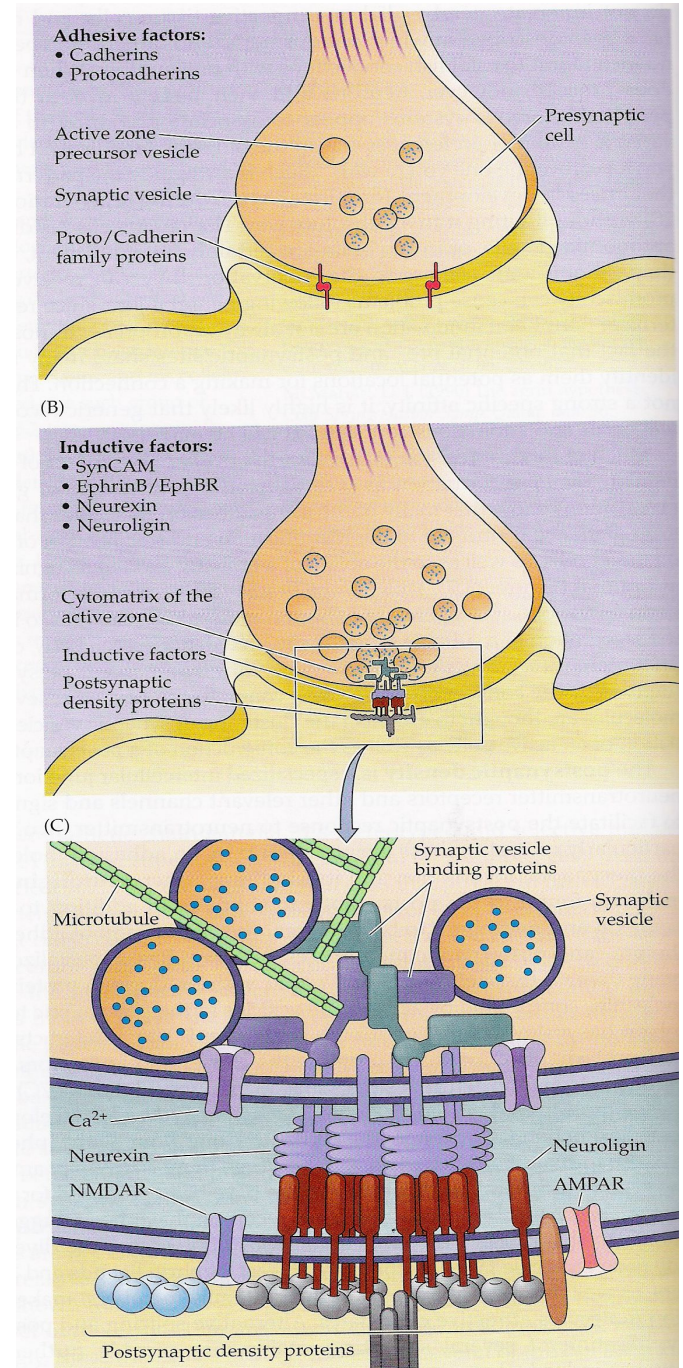
Formació selectiva de sinapsi

Participació de neurexines i neuroligines

- ✓ Promoció d'adhesió
 - ✓ Domini intracitoplàsmic de neurexina localitza vesícules sinàptiques i les proteïnes d'ancoratge (*docking*) i molècules relacionades amb fusió.
 - ✓ Neuroligina funció similar a element postsinàptic
- Agrupament (*clustering*) de receptors i canals

Com generar diversitat de sinapsi amb poques molècules?

"If you can't be with the one you love, love the one you are with"

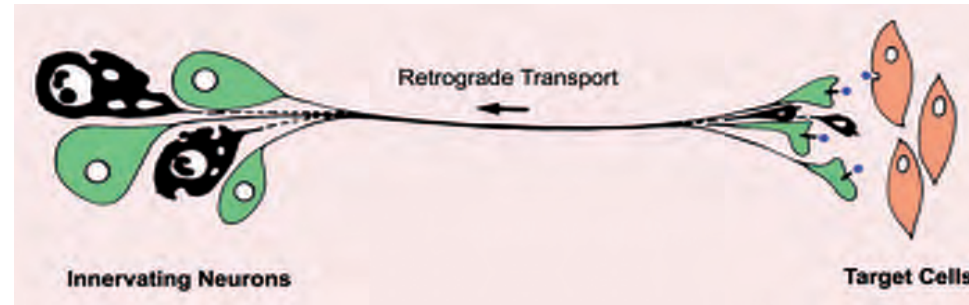


Tema 2

Interaccions tròfiques

Dependència a llarg termini de cèl·lules postsinàptiques

= Interacció tròfica



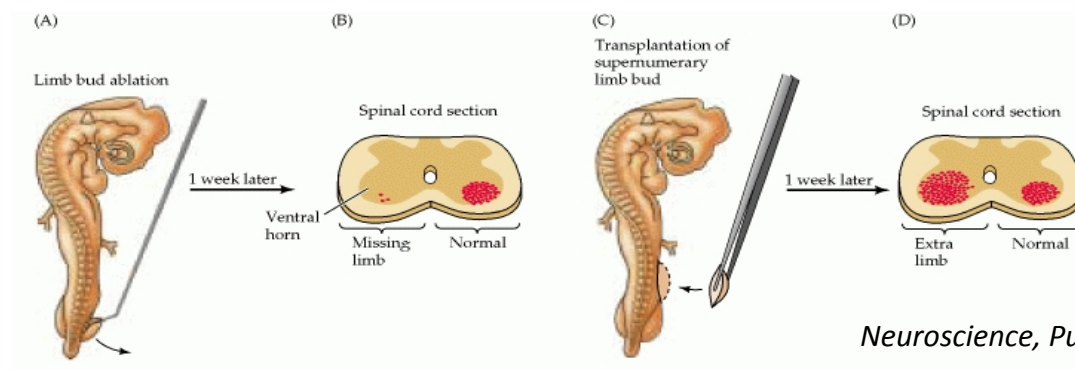
Factors neurotròfics o neurotrofines

Fundamental Neuroscience Squire et al. 3 ed.

- Derivats de cel. diana
- Regulen diferenciació, creixement i supervivència en cèl·lules veïnes

Per què les neurones depenen tant de les seues cèl·lules diana?

- Escala de SN canviant durant desenvolupament
 - Necessitat de fer coincidir el nombre de neurones amb nre. de cèl·lules diana
- Producció d'un excés (2-3) de neurones → Eliminació, PCD, regulada per neurotrofines



Neuroscience, Purves et al., 3 ed.

TABLE 19.2 Some Possible Functions of Developmental PCD in the Nervous System*

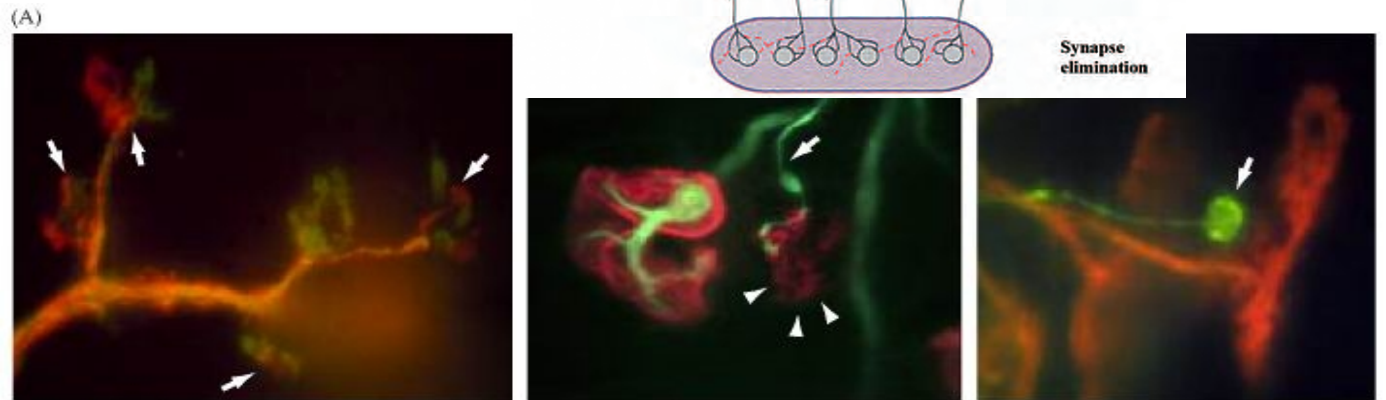
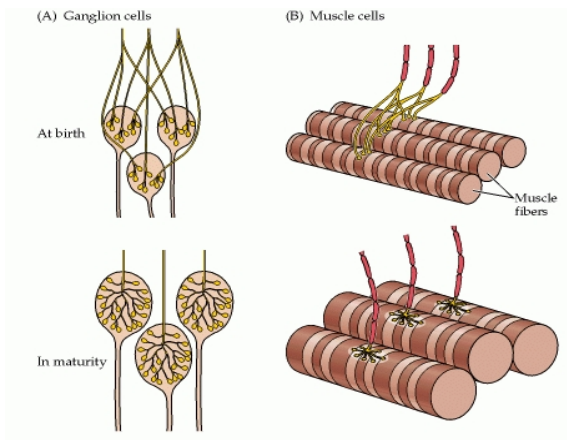
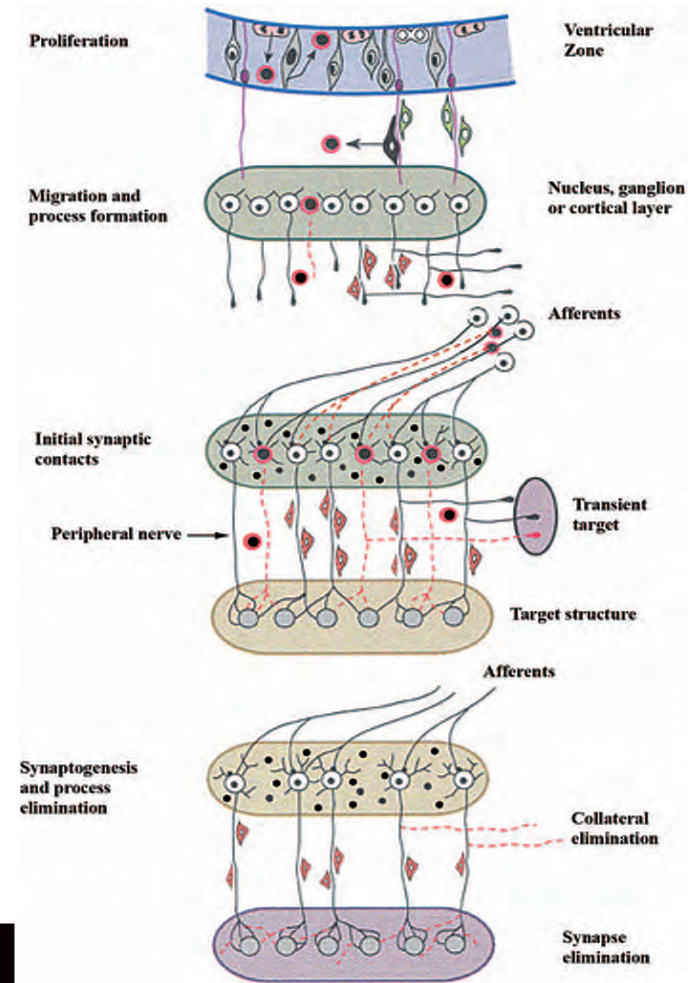
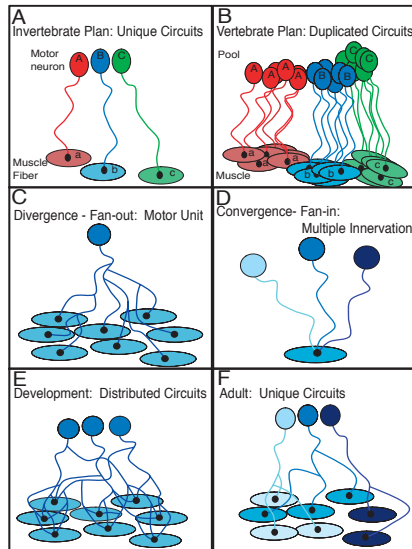
-
1. Differential removal of cells in males and females (sexually dimorphic spinal motor nucleus in many mammals).
 2. Deletion of some of the progeny of a specific sublineage that are not needed (loss of specific progeny of the AB blastomere that is involved in generating ring ganglia in *C. elegans*).
 3. Negative selection of cells of an inappropriate phenotype (ligand/receptor-induced cell death in the early chick embryo retina?).
 4. Pattern formation and morphogenesis (neurulation/neural tube closure; differential thickness of cortical layers).
 5. Deletion of cells that act as transient targets or that provide transient guidance cues for axon projections (death of pioneer neurons/glia in insects).
 6. Removal of cells and tissues that serve a transient physiological or behavioral function (loss of Roh-Beard sensory neurons during metamorphosis in frogs).
 7. "Systems"-matching by creating optimal quantitative innervation between interconnected groups of neurons and between neurons and their targets (see text and Fig. 19.4).
 8. Systems-matching between neurons and their glial partners by regulated glial PCD (Schwann cells and peripheral axons; see Figs. 19.5 and 19.15).
 9. Error correction by the removal of ectopically positioned neurons or of neurons with misguided axons or inappropriate synaptic connections (loss of ipsilaterally projecting retinal ganglion cells).
 10. Removal of damaged or harmful cells (death of cells with DNA damage).
 11. Regulation of the size of mitotically active neural progenitor populations (see text and Fig. 19.4).
 12. The production of excess neurons may serve as an ontogenetic buffer for accommodating mutations that require changes in neuronal numbers in order to be evolutionary adaptive (evolutionary increases in limb size may require increased sensory and motoneuron survival).
 13. Regulated survival of subpopulations of adult-generated neurons as a means of experience-dependent plasticity (see text and Fig. 19.18).
-

*For references see Buss *et al.*, 2006; Oppenheim *et al.*, 2001.

Tema 2

Refinament de connexions sinàptiques

- ✓ Innervació polineuronal
- ✓ Eliminació sinàptica
- ✓ Convergència i divergència



Neuroscience, Purves et al., 3 ed.

- <http://www.sinauer.com/neuroscience4e/animations23.2.html>

Tema 2

Bases moleculars d'interaccions tròfiques

- ✓ Les neurones depenen d'un mínim de factor tròfic per a sobreviure → conseqüències per a nombre apropiat de connexions
- ✓ Les cèl·lules diana sintetitzen i secreten factors tròfics apropiats per a neurones en desenvolupament
- ✓ La producció de factors tròfics es fa en quantitats limitades, per la qual cosa la supervivència, persistència i diferenciació de neurones depèn de competència neural.

NGF

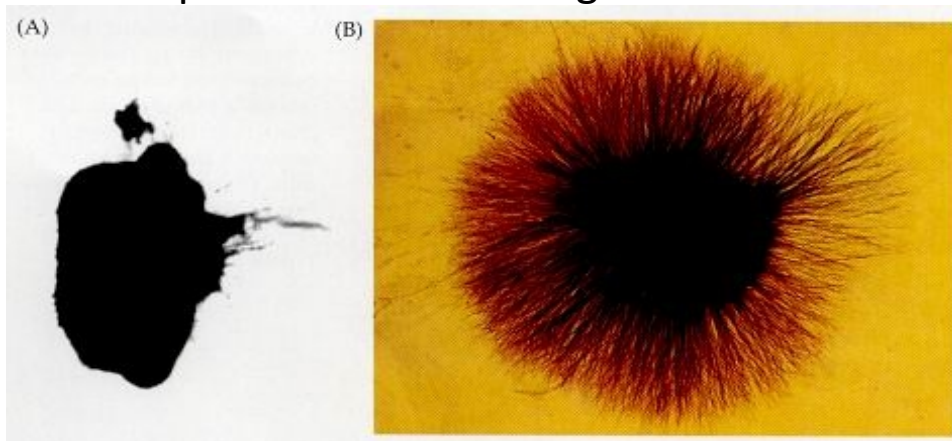
Factor de creixement nerviós.

Cerca de molècula promotora de supervivència

Transplantament de sarcoma

Glàndules salivals de ratolí mascle

Efectes pràcticament restringits a SNP



Neuroscience, Purves et al., 3 ed.



Rita Levi-Montalcini & Viktor Hamburger

Tema 2

Bases moleculars d'interaccions tròfiques

NEUROTROFINES

Yves Barde & Hans Thoenen

Purificat de SNC

1⁶ purificació necessària

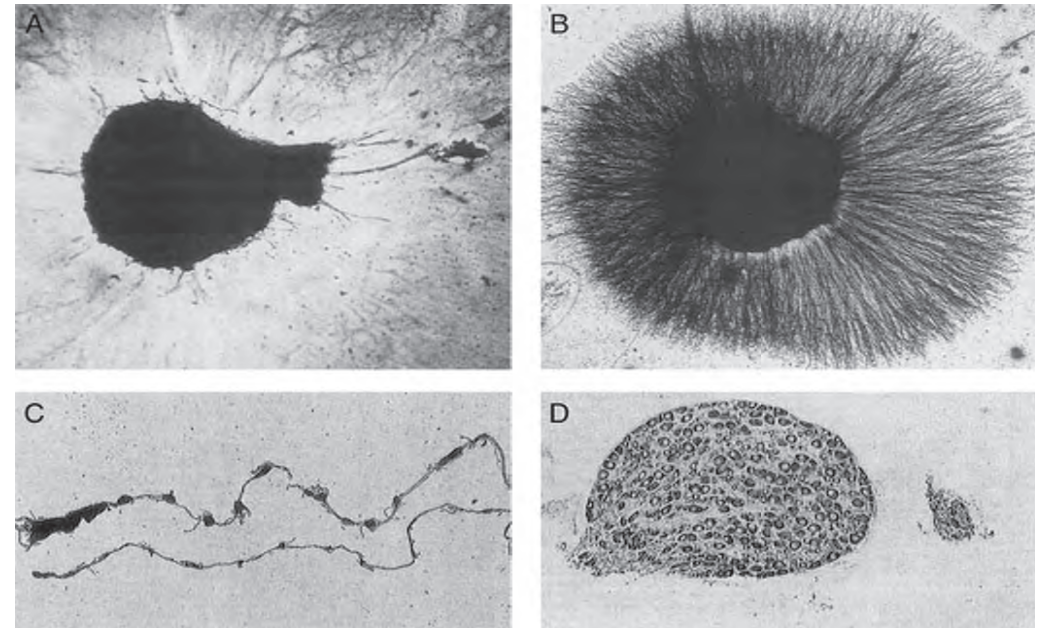
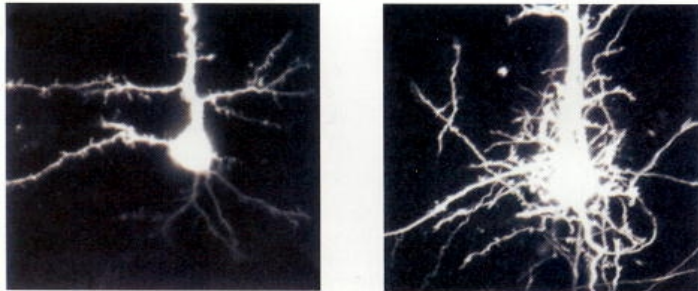
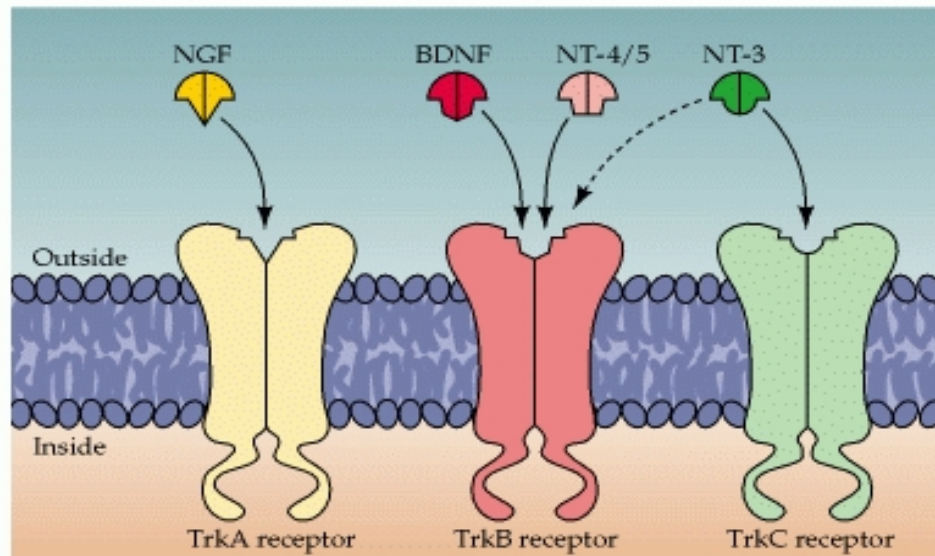


FIGURE 19.2 Biological activity of nerve growth factor (NGF). Explanted sensory and sympathetic ganglia or dissociated neurons were used in bioassays detecting neurotrophic activity. (A) Control ganglion 24h in culture without NGF and (B) experimental ganglion 24h after NGF treatment. Treatment with NGF (100 ng/ml) causes the formation of a "halo" of axonal growth from sensory neurons in the ganglion. Why the factor was named NGF is obvious. Reprinted with permission from Levi-Montalcini. (C and D) Experimental immunosympathectomy. Antibodies that selectively block NGF activity were administered to newborn mice to deprive the developing animals of endogenous factor. Sympathetic ganglia were examined several weeks after the treatment. Note the marked atrophy of the entire sympathetic chain ganglia (lower in C) and the almost complete loss of sympathetic neurons in a histological section of a single ganglion (right side in D) after antibody treatment. Controls are in the upper part of C and on the left in D. Photographs kindly provided by Viktor Hamburger and Rita Levi-Montalcini.



Neuroscience, Purves et al., 3 ed.

TABLE 19.3 Percentage of Neurons Lost in Neurotrophic Factor or Receptor Deficient Mice*

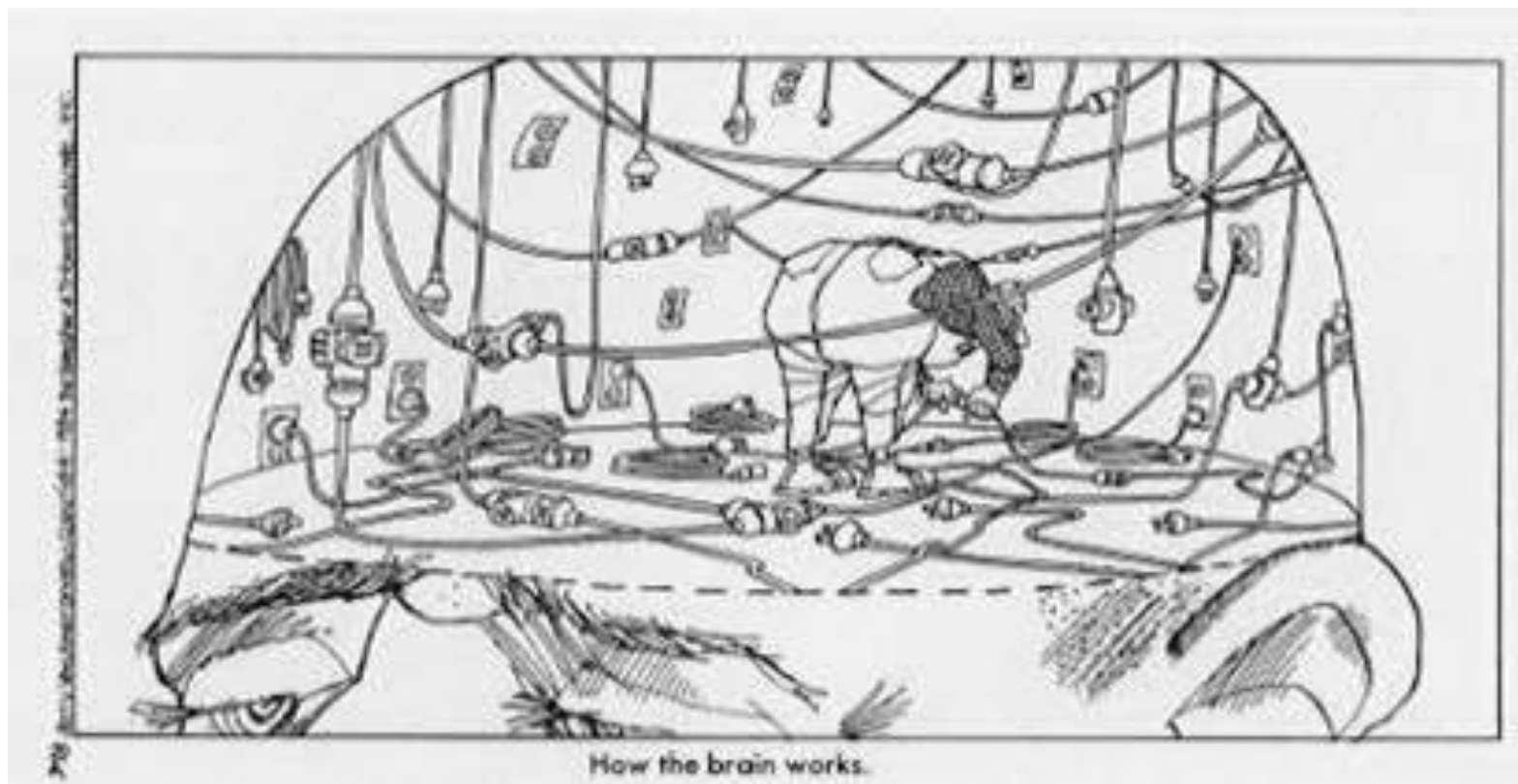
Neurotrophic factor/receptor null mutation	Viability	Losses in PNS ganglia						Losses in CNS nuclei	
		Dorsal root ganglia	Trigeminal ganglia	Nodose petrosal ganglia	Vestibular ganglia	Cochlear ganglia	Superior cervical ganglia	Spinal moto neurons	Facial moto neurons
TrkA	Poor	-70-90%	-70-82%	?	-0%?	-0%?	-95%	-0%?	?
NGF	Poor	-70%	-75%	-0-15%	?	-0%	-82-95%	-0%?	?
TrkB	Very poor	-0-41%	-39-60%	-90-94%	-56-85%	-15-20%	-0%	-0%**	-0%**
BDNF	Moderate	-0-44%	-0-45%	-39-66%	-82-87%	-7%	-0%	-0%	-0-3%
NT-4	Good	-0-14%	-0-5%	-40-59%	-0-21%	?	-0%	-0%	-0-8%
BDNF/NT-4	Good	-0%	-9-34%	-79-90%	-82-90%	?	-0%	-0%	-0-11%
TrkC	Moderate	-17-38%	-21-48%	-14-18%	-15-29%	-50-85%	-0%	-0%	-0%
NT-3	Very poor	-36-79%	-61-68%	-30-47%	-15-34%	-85%	-48-53%	?	-0%
TrkB/TrkC	Very poor	-41%	?	-95%	-58-100%	-61-100%	-0-4%	-0-5%	-0-5%
BDNF/NT-3	Very poor	-84%	-74%	-62%	-99%	-100%	?	?	?
BDNF/NT-4/NT-3	Very poor	-92%	-88%	-96%	-100%	?	-47%	-20%	-22%
gp130 (IL receptor)	Very poor	-21%						-41%	-31%
CNTRF α	Very poor	-0%	-0%	?	?	?	-0%	?	-40%
LIFR	Very poor	?	?	?	?	?	?	-40%	-35%
c-ret	Very poor	-0%	?	?	?	?	-100%	-50%	-30%
GFR α 1	Very poor	-0%	-0%	-15%	-0%	-0%	-0%	-24%	-0%
GFR α 2	Poor	-0%	-0%	-0%	-0%	-0%	-0%	-24%	?
GFR α 3	Good	-0%	-0%	?	?	?	-50-95%	?	?
GDNF	Very Poor	-0-23%	?	-0-40%	-0%	?	-35%	-22-37%	-18%
Neurturin	Good	-0%	?	-0%	?	?	-0%	-0%	?

*For references to original studies, see Huang and Reichardt, 2001; Airaksinen and Saarma, 2002; von Bartheld and Fritzsche, 2006.

**Losses reported by Klein *et al.*, 1993 (*Cell* 75, 113-122) could not be replicated.

Tema 2

Plasticitat neuronal

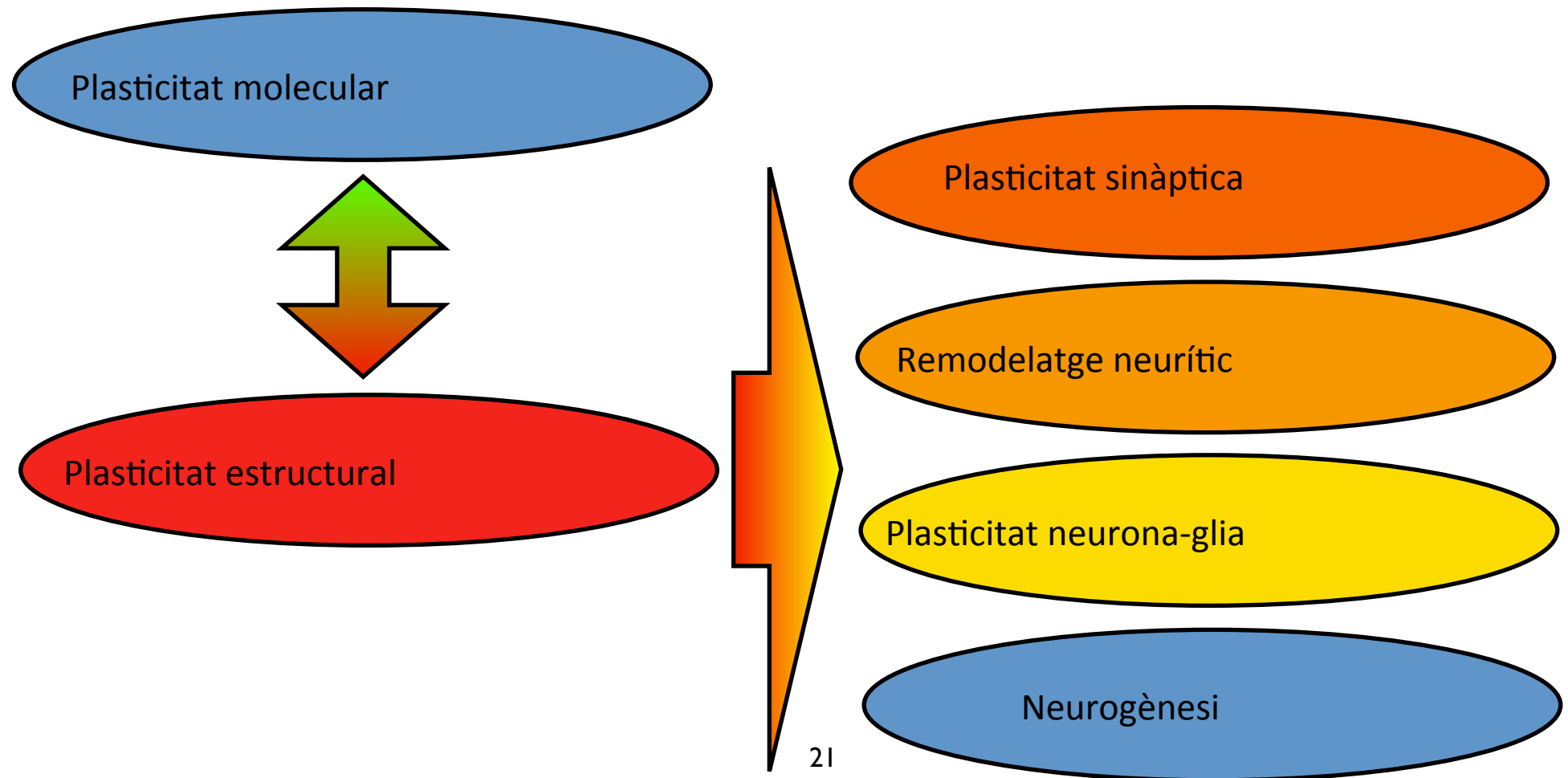


Tema 2

Refinament de connexions sinàptiques

“Neuronal plasticity can be defined as the ability of neurons to react with adaptive changes to intrinsic or extrinsic inputs”

Persistència de plasticitat en desenvolupament postnatal i vida adulta



Plasticitat molecular

Dinàmica molecular sinàptica

✓ Dinàmica de proteïnes relacionades amb la síntesi, empaquetatge, alliberament i recaptació de neurotransmissors

✓ Dinàmica de receptors de neurotransmissors, canals i bombes iòniques

✓ Relació de receptors amb proteïnes de la bastida sinàptica

✓ Modificació per factors tròfics, hormones, citocines

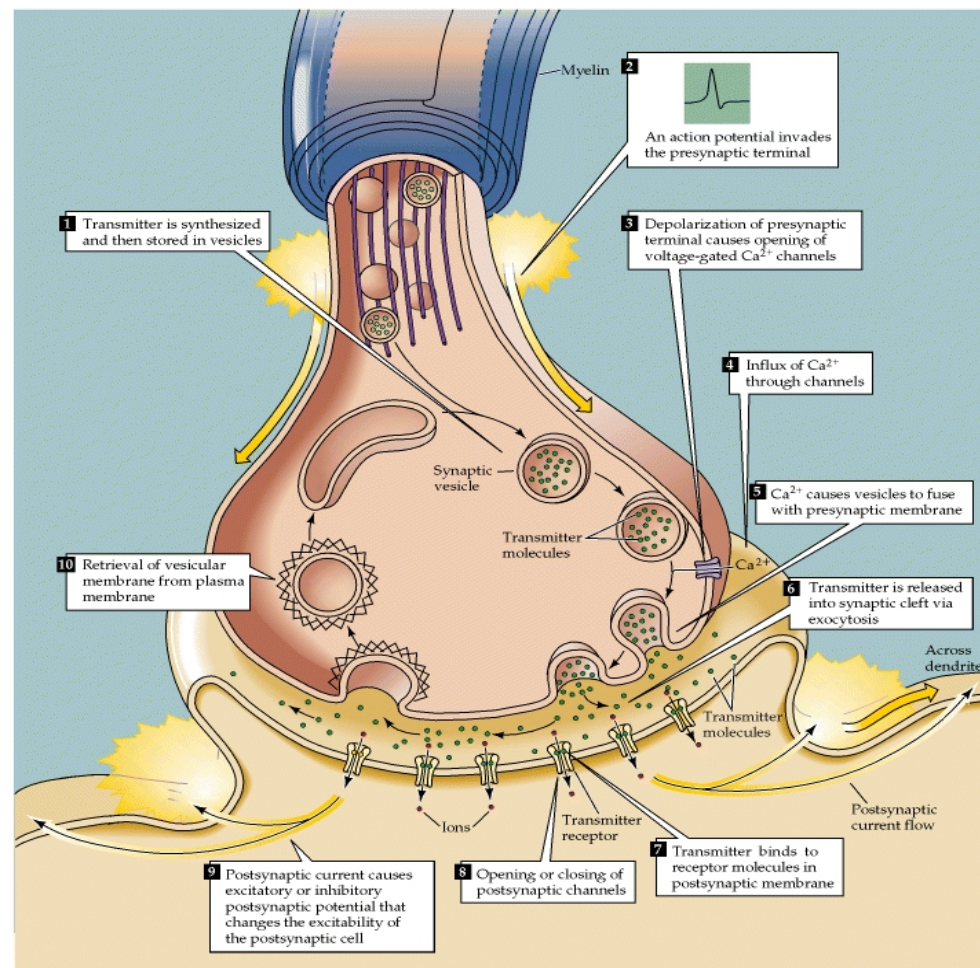
★ Entrada de Ca^{2+} amb despolarització:

Canvis bioquímics

Inici de programes transcripcionals dependents d'activitat



Canvis estructurals

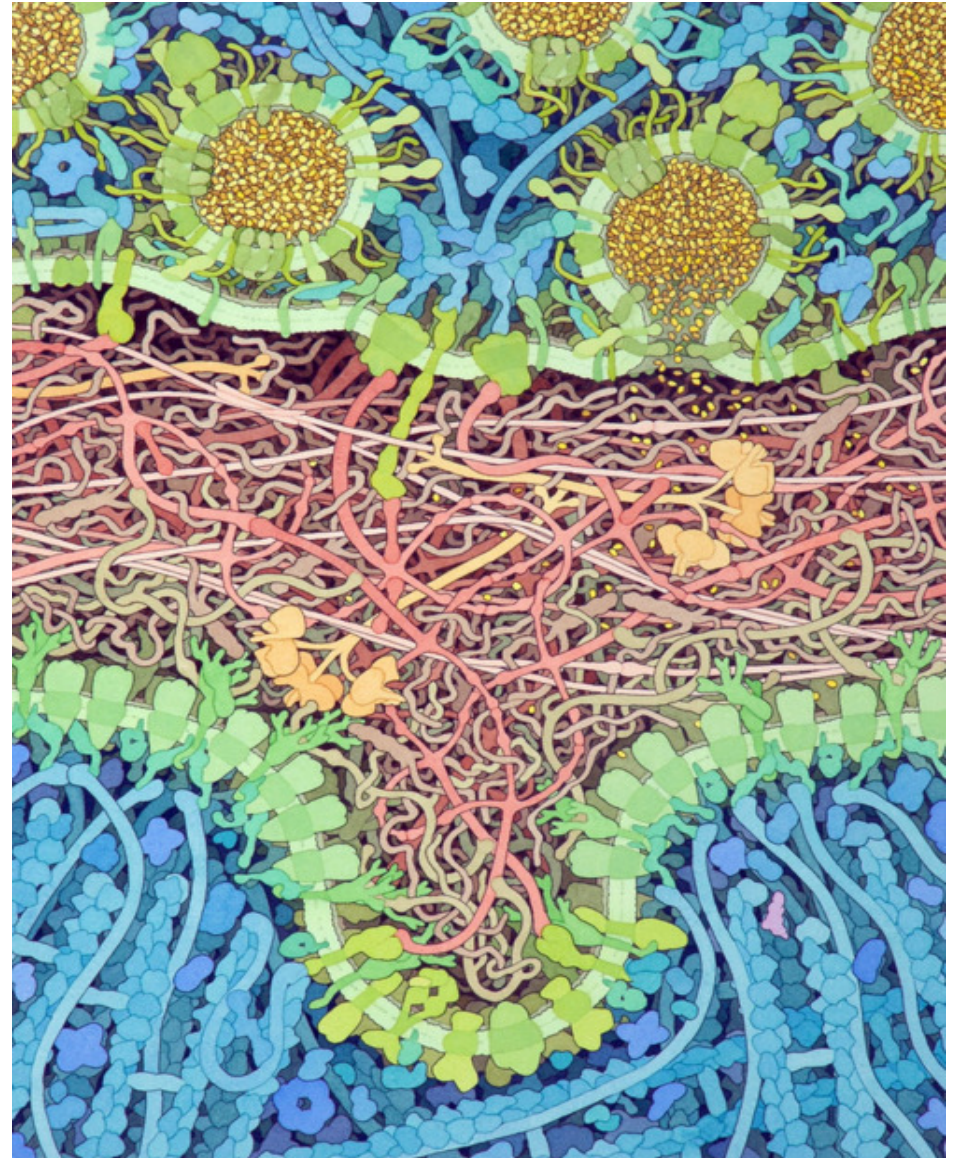


Fundamental Neuroscience Squire et al. 3 ed.

Plasticitat molecular

Plasticitat molecular subjacent al remodelatge neuronal

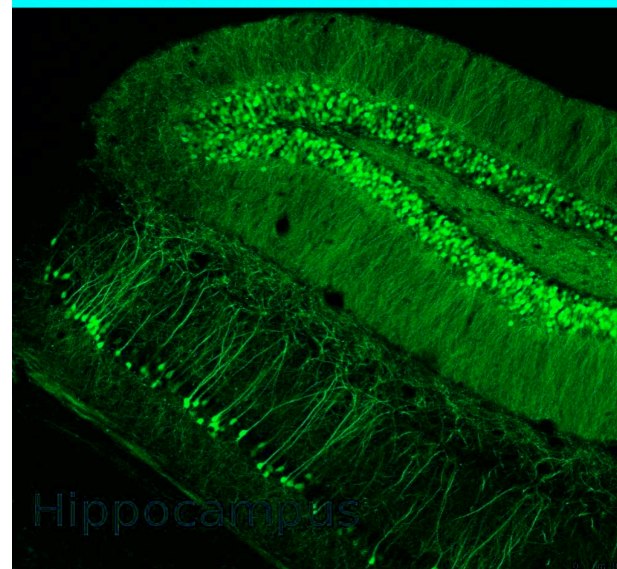
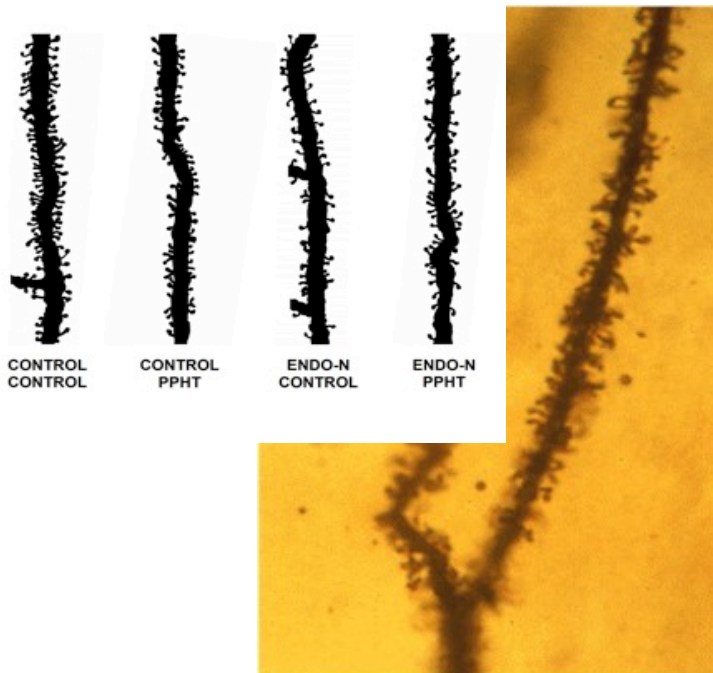
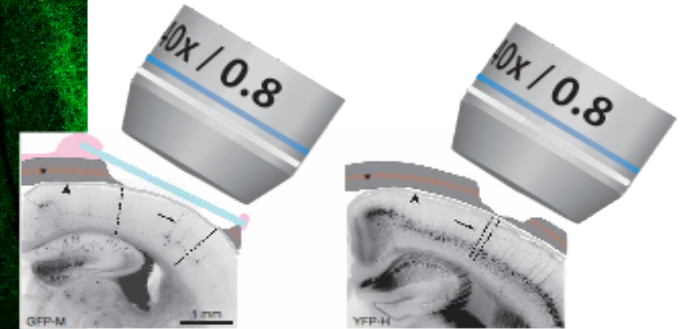
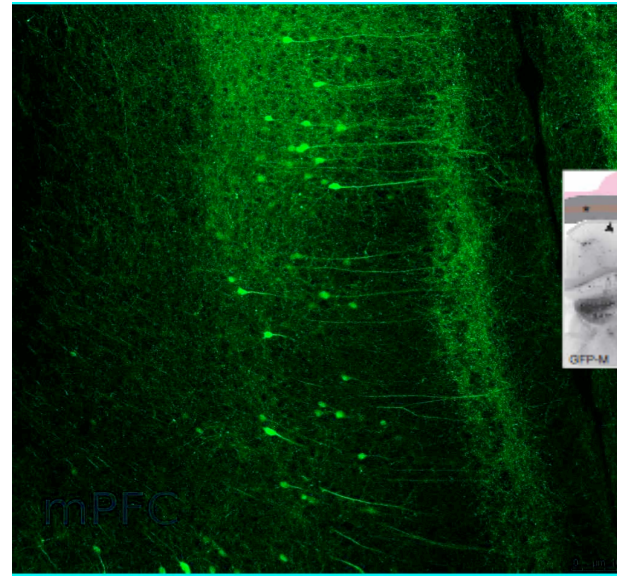
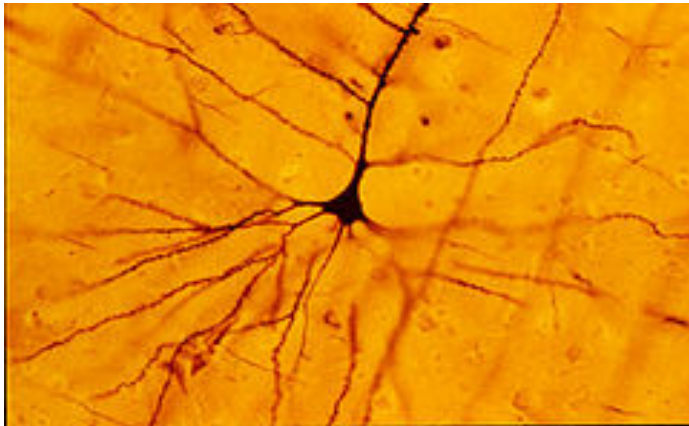
- Regulació de l'expressió de proteïnes de citoesquelet
- Regulació de l'expressió de proteïnes implicades en adhesió cèl·lula-cèl·lula i cèl·lula-matriu extracel·lular



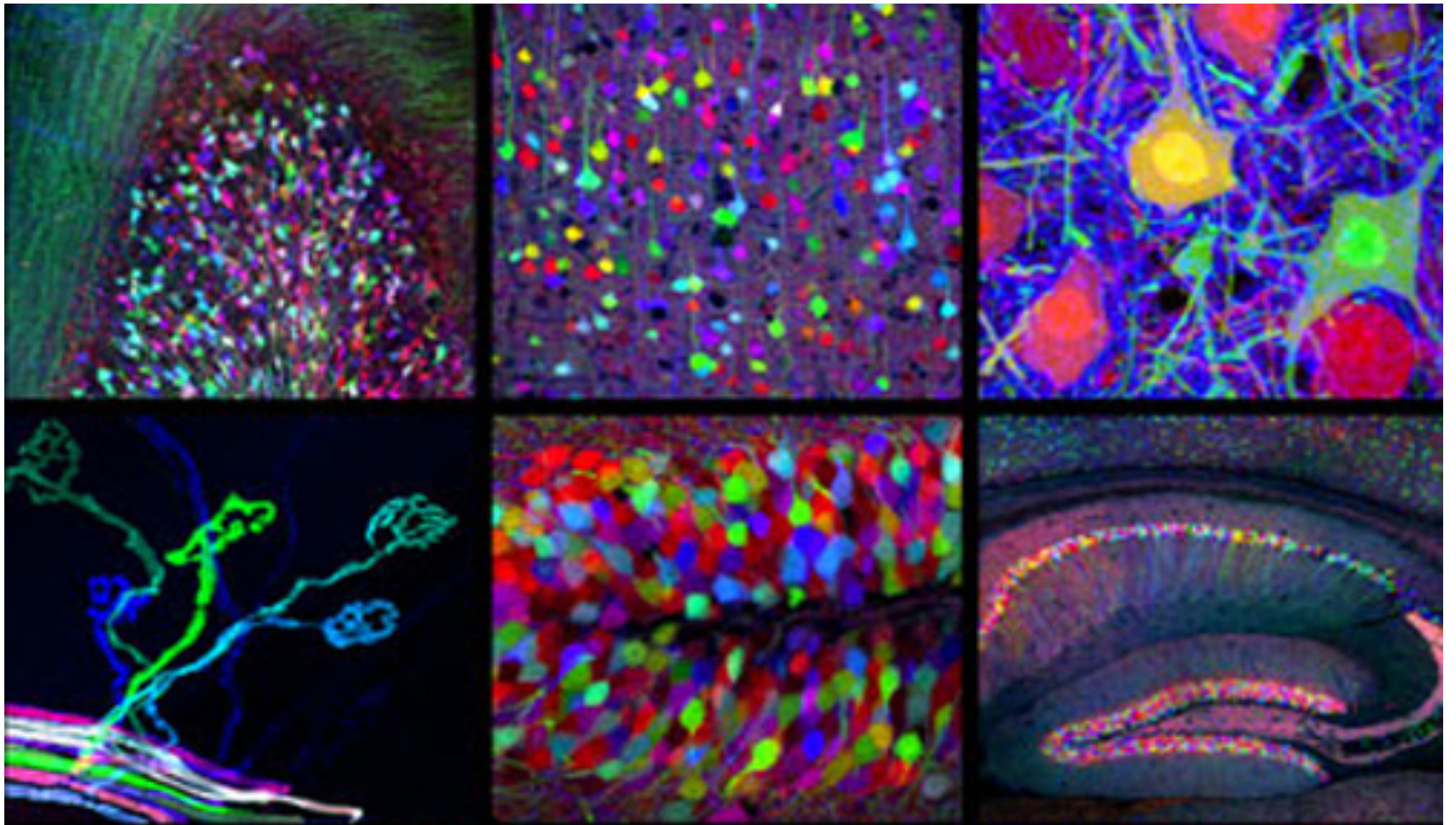
Tècniques d'estudi de la plasticitat estructural neuronal

Anàlisi d'estructura neuronal:

Tècniques de Golgi/transgènics amb proteïnes fluorescents



<http://www.youtube.com/watch?v=HWvyd1fYdOI&NR=1>



Plasticitat en experiències primerenques i períodes crítics

- Períodes curts i moments molt concrets de desenvolupament postnatal/posteclosió

Tasques sensoriomotores i comportaments més complexos: períodes més llargs

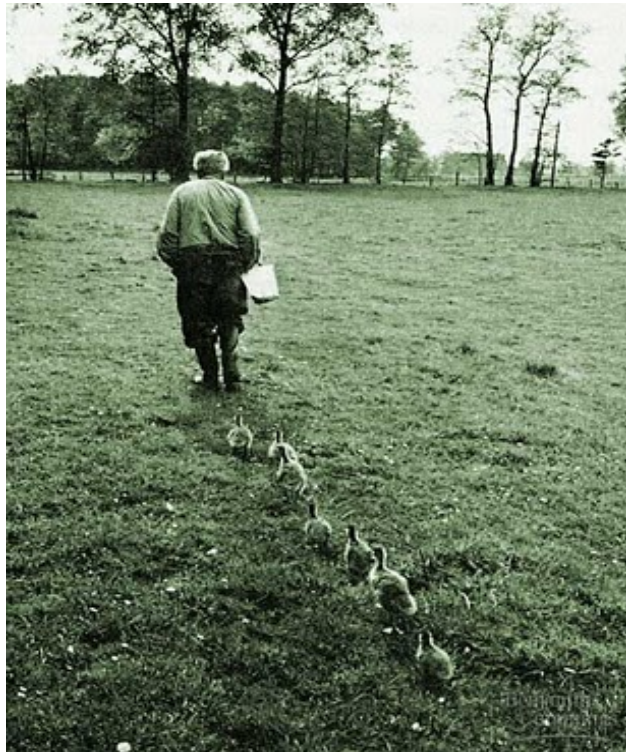


TABLE 1 Known critical periods and molecular mechanisms across systems (see text for references)

System	Age	Confirmed regulators	Delay ^a	Species ^b
Neuromuscular junction	<P12	ACh	+	mouse
Climbing fibers (CBL)	P15–16	NMDA, mGluR1, G _q , PLC β , PKC γ	nd	mouse
LGN layers	<P10	Retinal ACh, cAMP; MAO-A, NO, MHC-I, CREB	nd	mouse, ferret, cat
Ocular dominance	P3 weeks-months	GABA, NMDA, PKA, ERK, CaMKII, CREB, BDNF, tPA, protein synthesis, NE, ACh	+	cat, rat, mouse, ferret
Orientation bias	<P28	NR1, NR2A, PSD95	+	cat, mouse
Whisker-barrel map formation	<P7	NR1, MAOA, 5HT _{1B} , cAMP, mGluR5, PLC β , FGF8	nd	mouse
Whisker RF tuning	P14–16		nd	rat
Tonotopic map (cortex)	P16–50	ACh	+	rat
Absolute pitch	<7 years		nd	human
Taste/olfaction	none	GABA, mGluR2, NO, neurogenesis	+	mouse
Imprinting	14–42 hrs	Catecholamines	+	chick
Stress/anxiety	<P21	Hormones, 5HT _{1A}	nd	rat, mouse
Slow-wave sleep	P40–60	NMDA	+	cat, mouse
Sound localization	<P200	GABA, NMDA	+	barn owl
Birdsong	<P100	GABA, hormones, neurogenesis	+	zebrafinch
Human language	0–12 years		nd	human

^aPotential for critical period delay by altered experience. +, yes; nd, not determined.

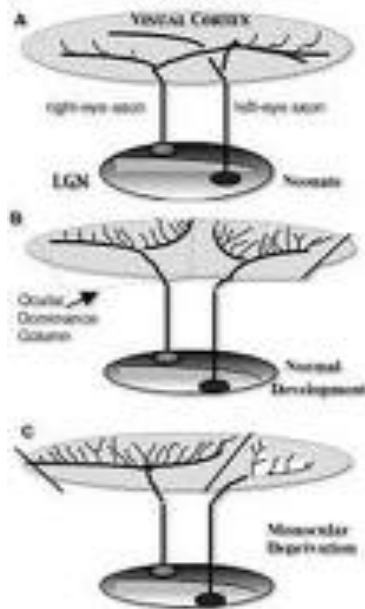
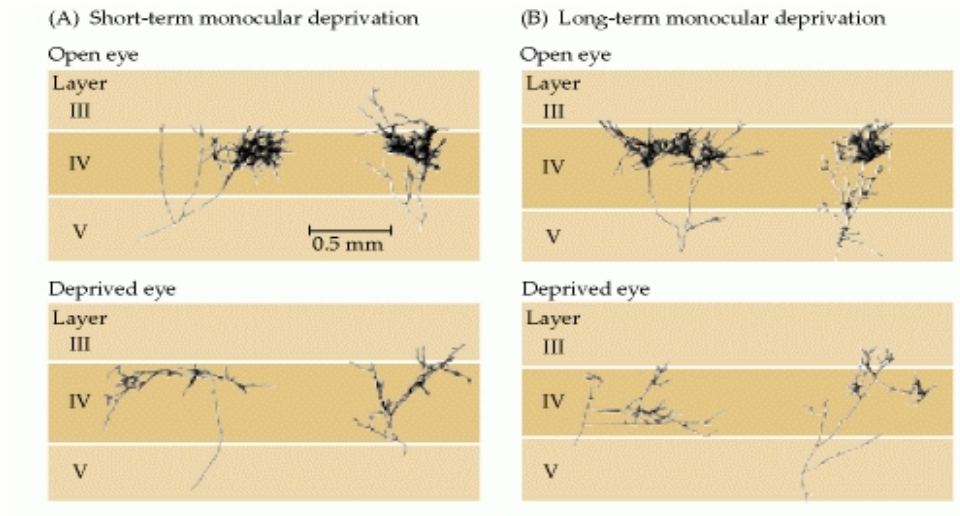
^bPrimary species for elucidation of molecular mechanism.

Períodes crítics en desenvolupament visual

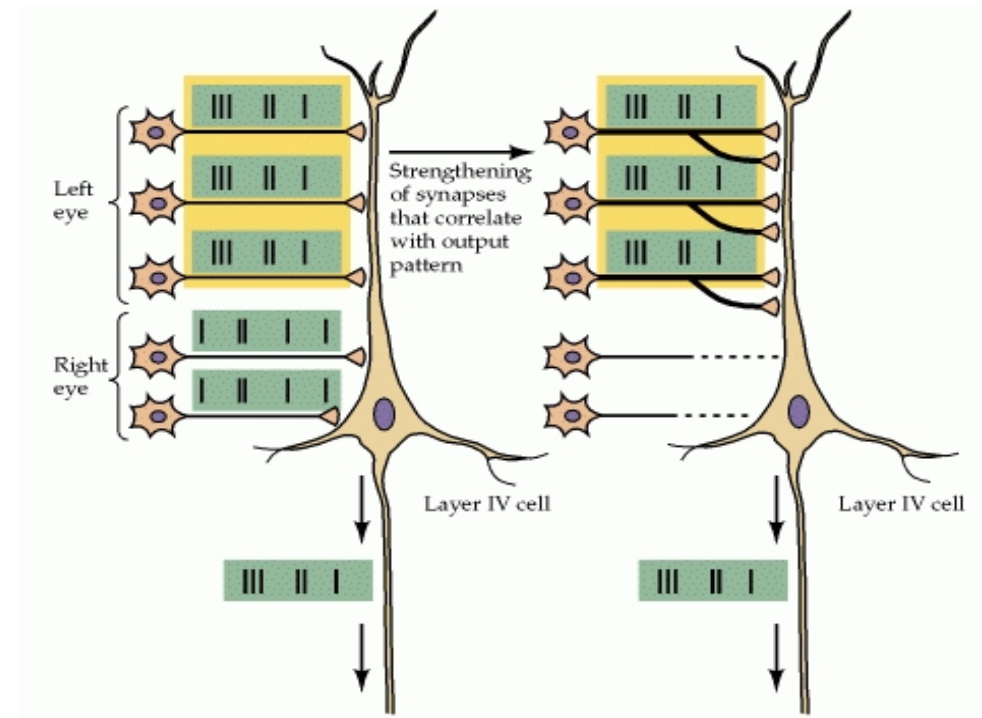
Sols ambliopia si privació en 3 primers mesos de vida en gats.

3-4 dies al voltant de període crític són suficients.

- Primats: més prolongat 6 mesos.

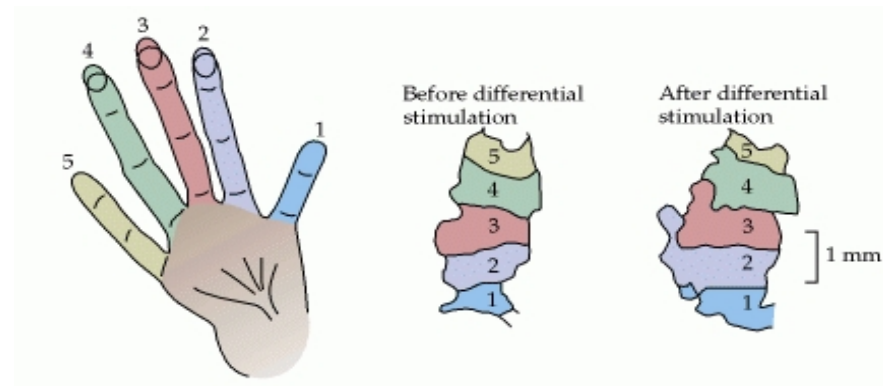
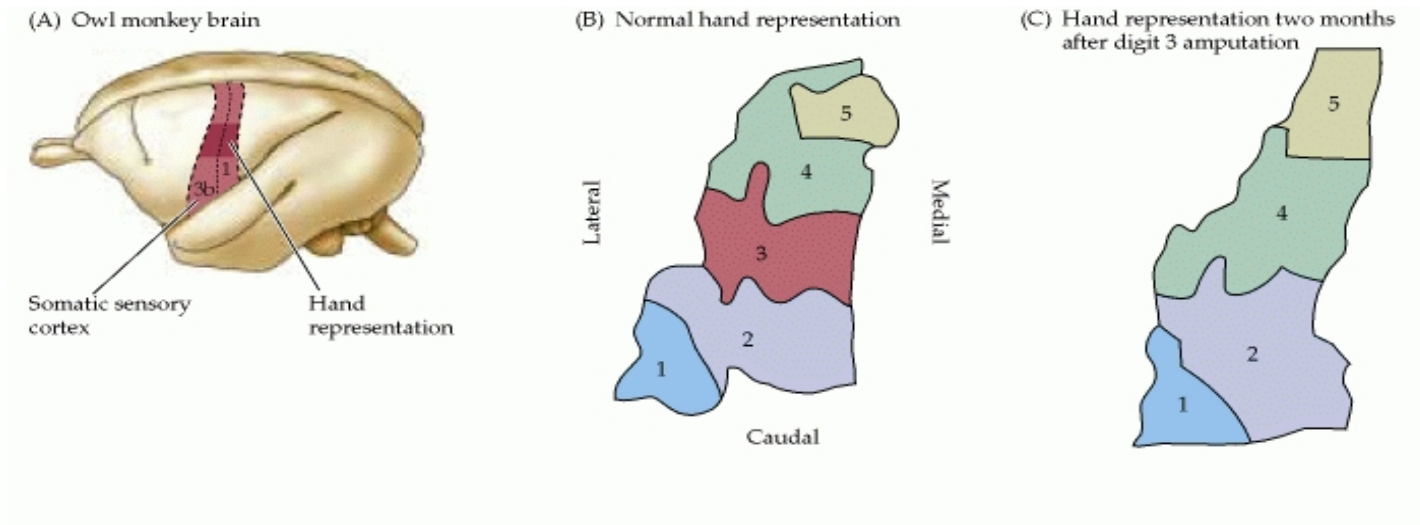


Postulat de Hebb



Neuroscience, Purves et al., 3 ed.

Plasticitat funcional de l'escorça cerebral adulta



Neuroscience, Purves et al., 3 ed.

Tema 2

Reparació i regeneració del sistema nerviós

1. Creixement d'axons de ganglis perifèrics o de neurones del SNC, que projecten fora de SNC

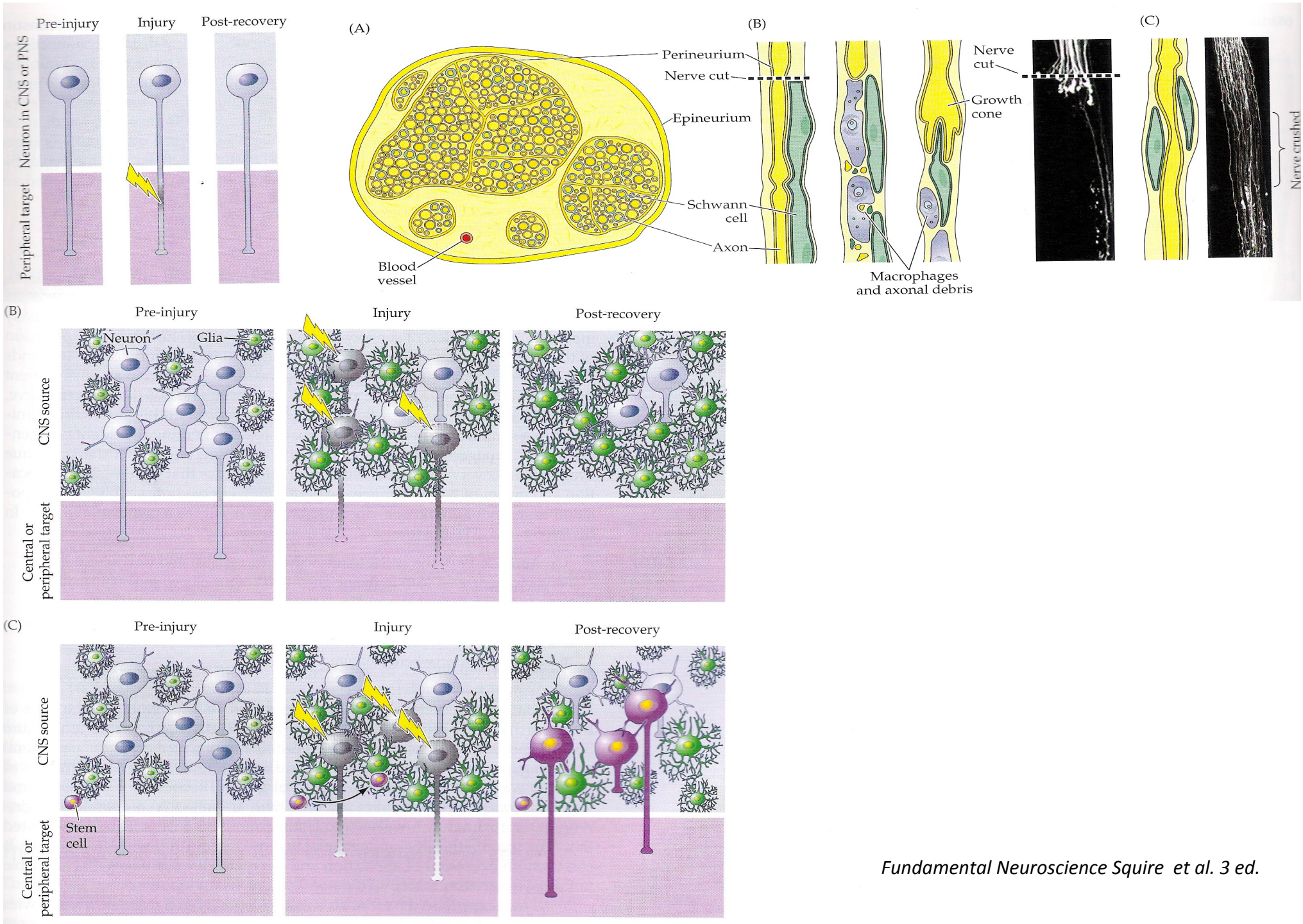
Recapitulació de desenvolupament

2. Restauració de neurones de SNC afectades que sobreviuen

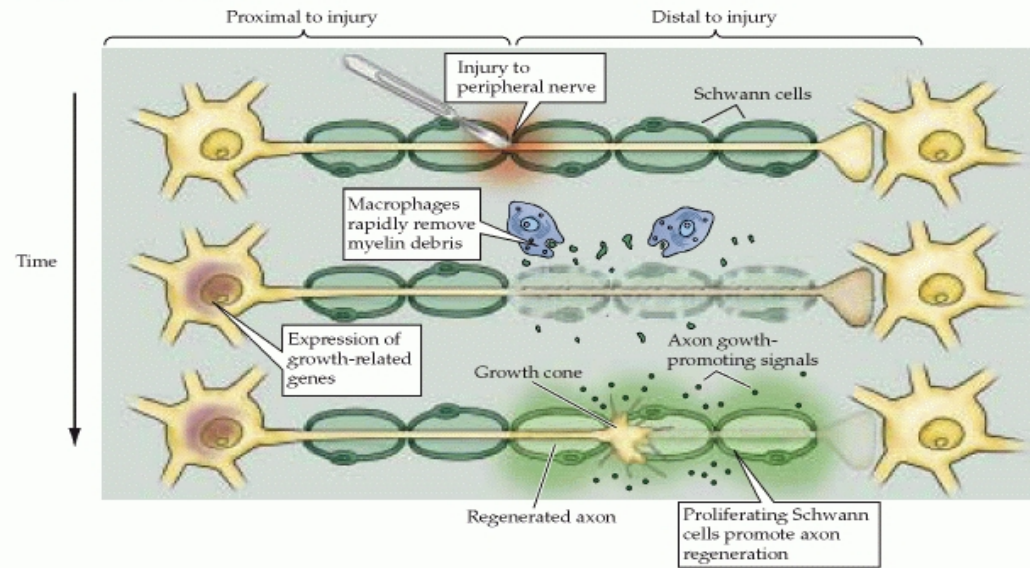
Requereix el creixement cooperatiu d'altres estructures en un medi molt complex

Reparació molt complicada en mamífers adults

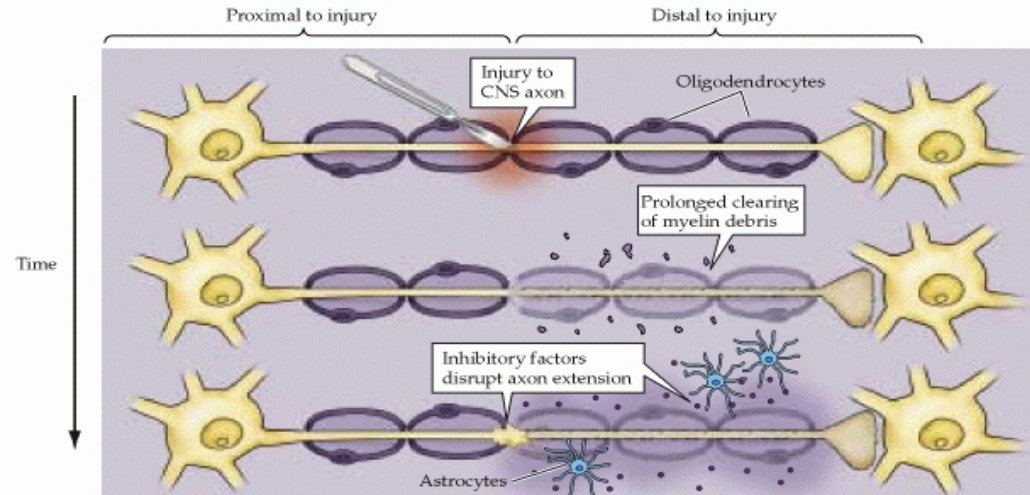
Neurogènesi adulta i trasplantament neural



(A) Peripheral nervous system



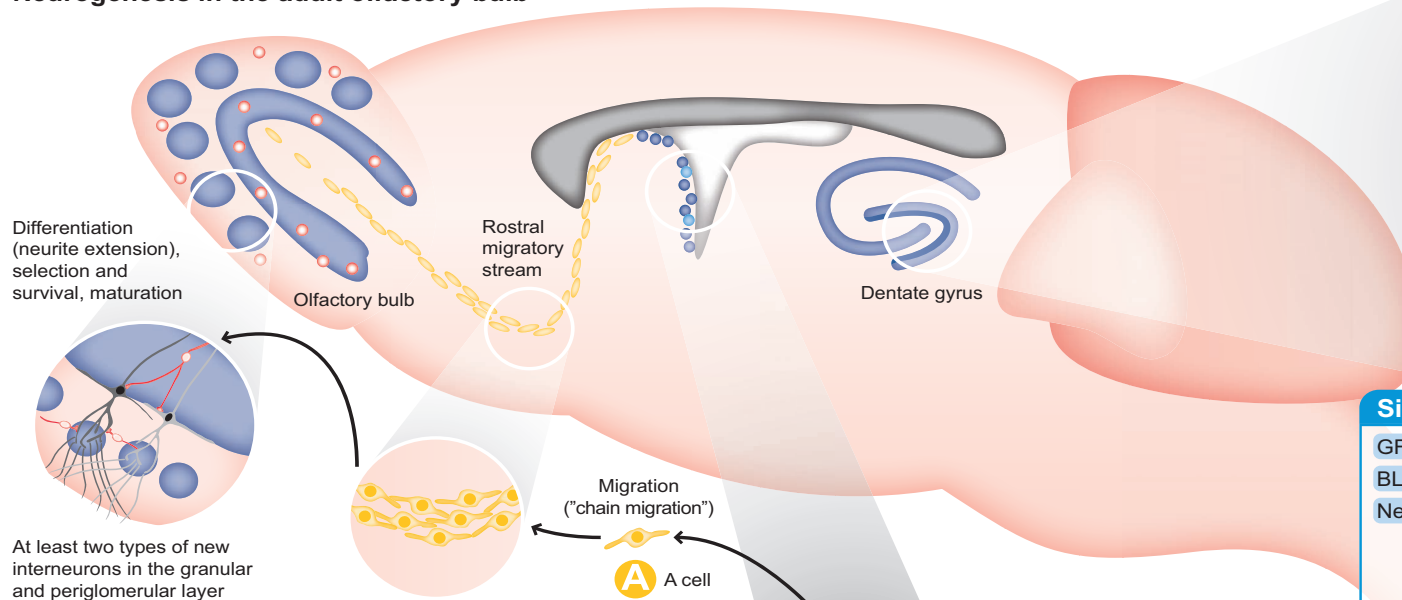
(B) Central nervous system



Adult neurogenesis

By Gerd Kempermann* and Abcam

Neurogenesis in the adult olfactory bulb



At least two types of new interneurons in the granular and periglomerular layer

Simplified sequence of marker expression

B → **C** → **A** **New neuron**

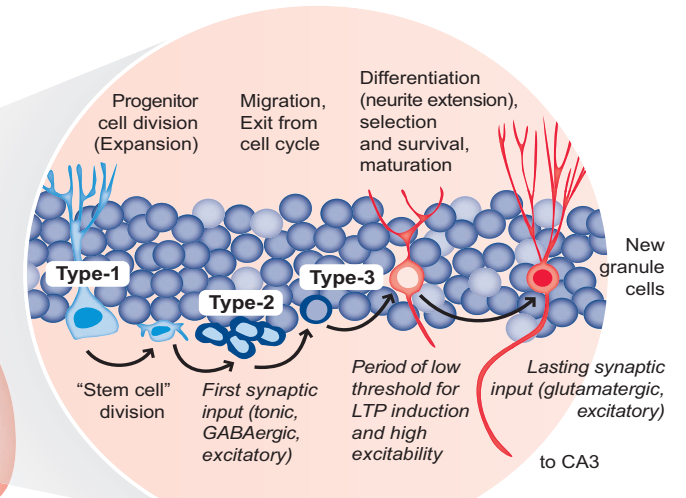
GFAP	EGFR, Dix	
BLBP, (Pax6)	DCX, PSA-NCAM, Ascl1	Calretinin, (TH)
Nestin, Sox2		NeuN

Note: not all marker combinations are present in all cells.

Oligodendrocytic lineage

PDGFR α	Olig2
----------------	-------

Neurogenesis in the adult hippocampus



Simplified sequence of marker expression

GFAP		
BLBP		
Nestin, Sox2		
	DCX, PSA-NCAM	
		Calretinin, Tuc4
		Calbindin
		NeuN

Suggested readings (recent Review articles only):

Duan X, Kang E, Liu CY, Ming GL, Song H. Development of neural stem cell in the adult brain. *Curr Opin Neurobiol.* 2008 Feb;18(1):108-15. Epub 2008 May 29. Review. PMID: 18514504

Ehninger D, Kempermann G. Neurogenesis in the adult hippocampus. *Cell Tissue Res.* 2008; 331(1):243-50. PMID: 17938969

Eisch AJ, Cameron HA, Encinas JM, Meltzer LA, Ming GL, Overstreet-Wadiche LS. Adult neurogenesis, mental health, and mental illness: hope or hype? *J Neurosci.* 2008 12; 28(46):11785-91. PMID: 19005040

Fabel K, Kempermann G. Physical activity and the regulation of neurogenesis in the adult and aging brain. *Neurochemical Med.* 2008; 11(2):59-66. PMID: 18286387

Gould E. How widespread is adult neurogenesis in mammals? *Nat Rev Neurosci.* 2007; 9(6):481-8. PMID: 17514200

Ihrle RA, Alvarez-Buylla A. Cells in the astroglial lineage are neural stem cells. *Cell Tissue Res.* 2008; 331(1):179-91. PMID: 17786483

Kempermann G. The neurogenic reserve hypothesis: what is adult hippocampal neurogenesis good for? *Trends Neurosci.* 2008; 31(4):163-9. PMID: 18329110

Lledo PM, Merkle FT, Alvarez-Buylla A. Origin and function of olfactory bulb interneuron diversity. *Trends Neurosci.* 2008; 31(8):392-400. PMID: 18603310

Lledo PM, Alonso M, Grubb MS. Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Rev Neurosci.* 2006; 7(3):179-93. PMID: 16495940

Parent JM, Murphy GG. Mechanisms and functional significance of aberrant seizure-induced hippocampal neurogenesis. *Epilepsia.* 2008;49 Suppl 5:19-25. PMID: 18522597

Sahay A, Hen R. Adult hippocampal neurogenesis in depression. *Nat Neurosci.* 2007; 10(9):1110-5. PMID: 17726477

Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell.* 2008; 132(4):645-60. PMID: 18295581

Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi. Transmissió sinàptica, neurotransmissors i receptors: caracterització farmacològica. Generació de potencials postsinàptics excitatoris (exemples de receptors del glutamat) i inhibitoris (exemples de receptors de GABA). Amines biogèniques, ATP, neurotransmissors peptídics. Neurotransmissors no convencionals: òxid nítric i endocannabinoides. Producció, degradació i recaptació dels neurotransmissors: potencial farmacològic. Les dues cares dels fàrmacs neuroactius: mòrfics, analgèsia i addicció

Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Soma neuronal (z. Recept.)

- Nucli
- Pericari

Ramificacions

- Dendrites (z. recept.)

Soma --->

Es ramifiquen i es fan més primes

- Axó

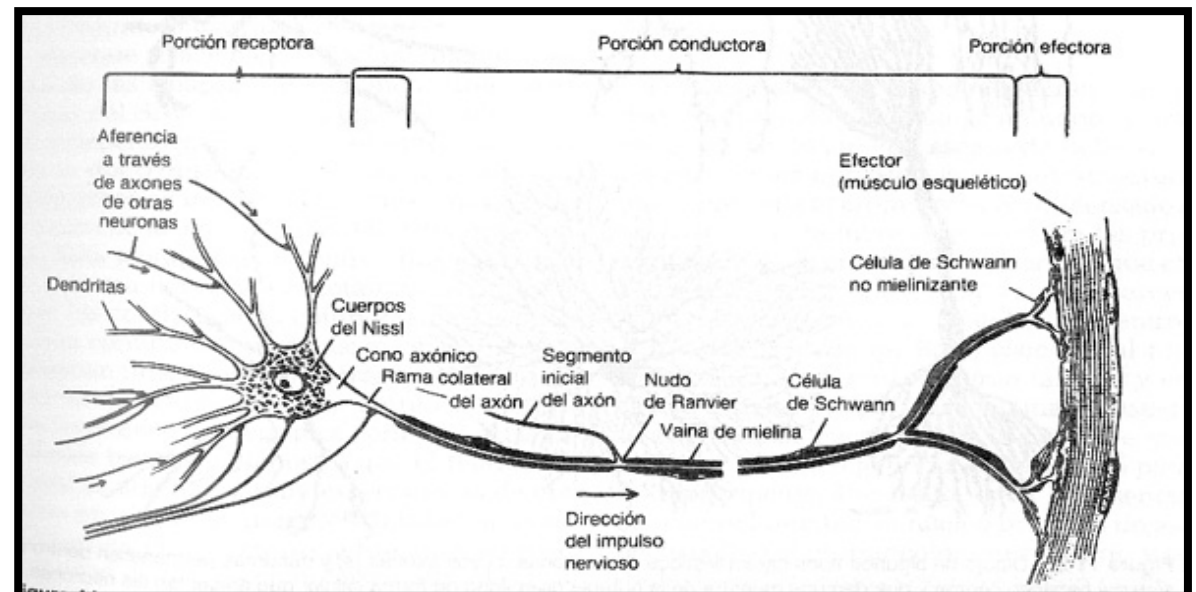
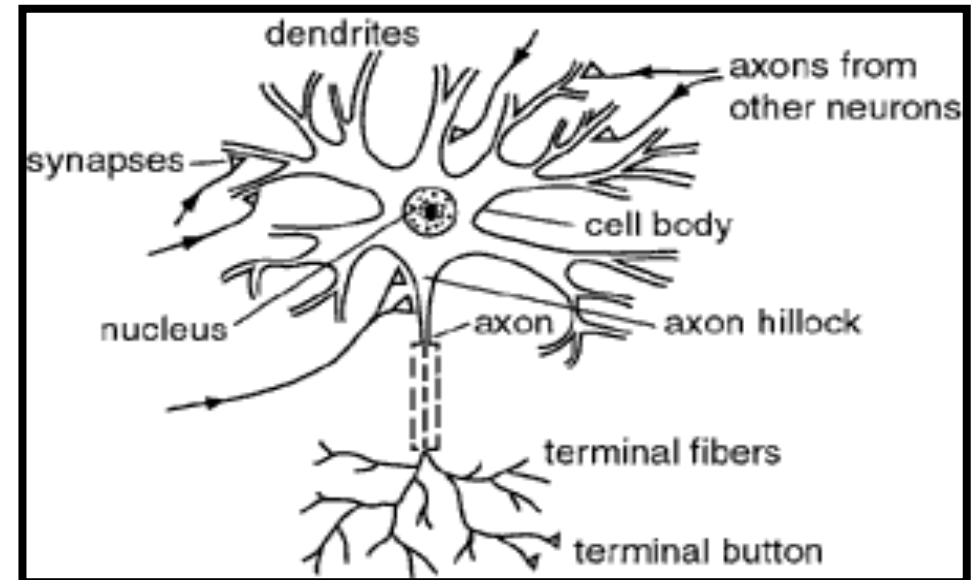
Soma ---> (o dendr.)

Segment inicial = con axònic -->

branca principal -->

col·laterals axòniques -->

sinapsi



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Morfologia neuronal

Criteris de classificació

1) Morfologia de l'arbre dendrític i nombre de dendrites que ixen del soma

- * Unipolars
- * Pseudounipolars
- * Bipolars
- * Multipolars

2) Presència d'espines dendrít.

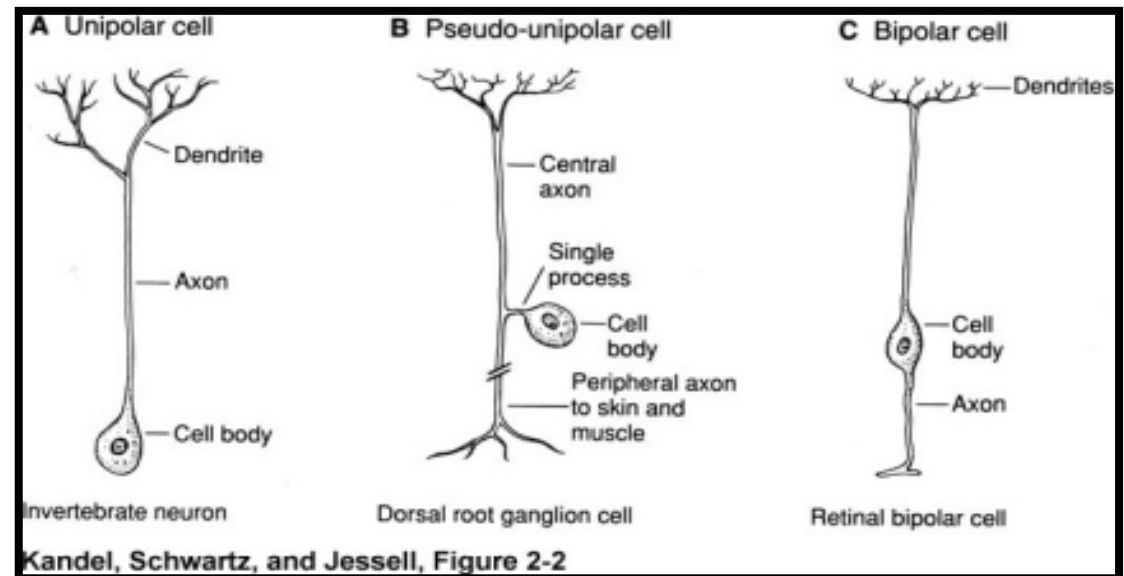
- * Espinoses
- * No espinoses
- * Poc espinoses

3) Longitud de l'axó

- * Golgi I (llarg)
- * Golgi II (curt)

4) Morfologia de l'axó i zona de contacte amb cèl·lula postsinàptica

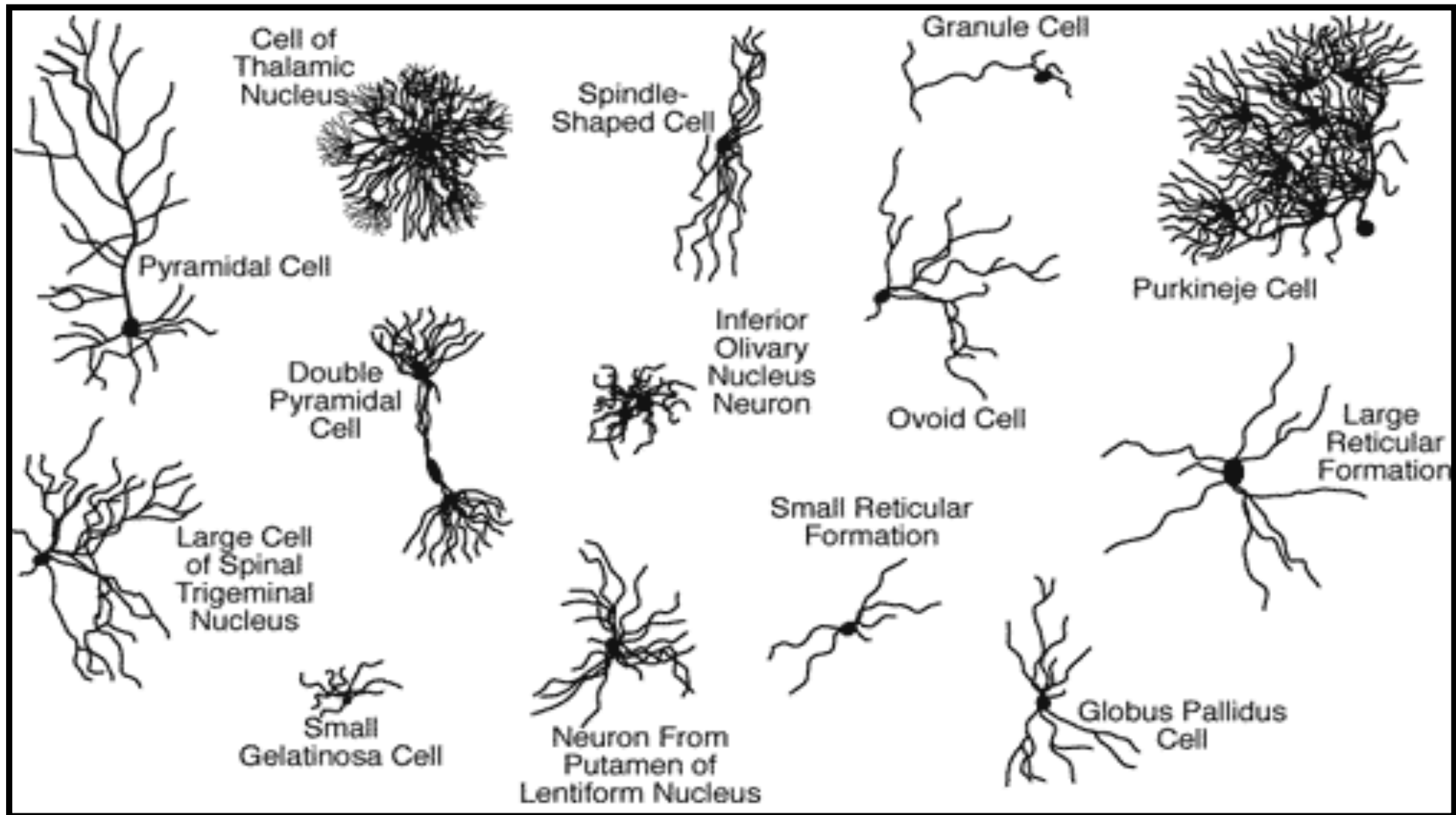
- * Neurones dels cistells (*basket cells*)
- * Neurones canelobre (segment inic. d'axó)



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

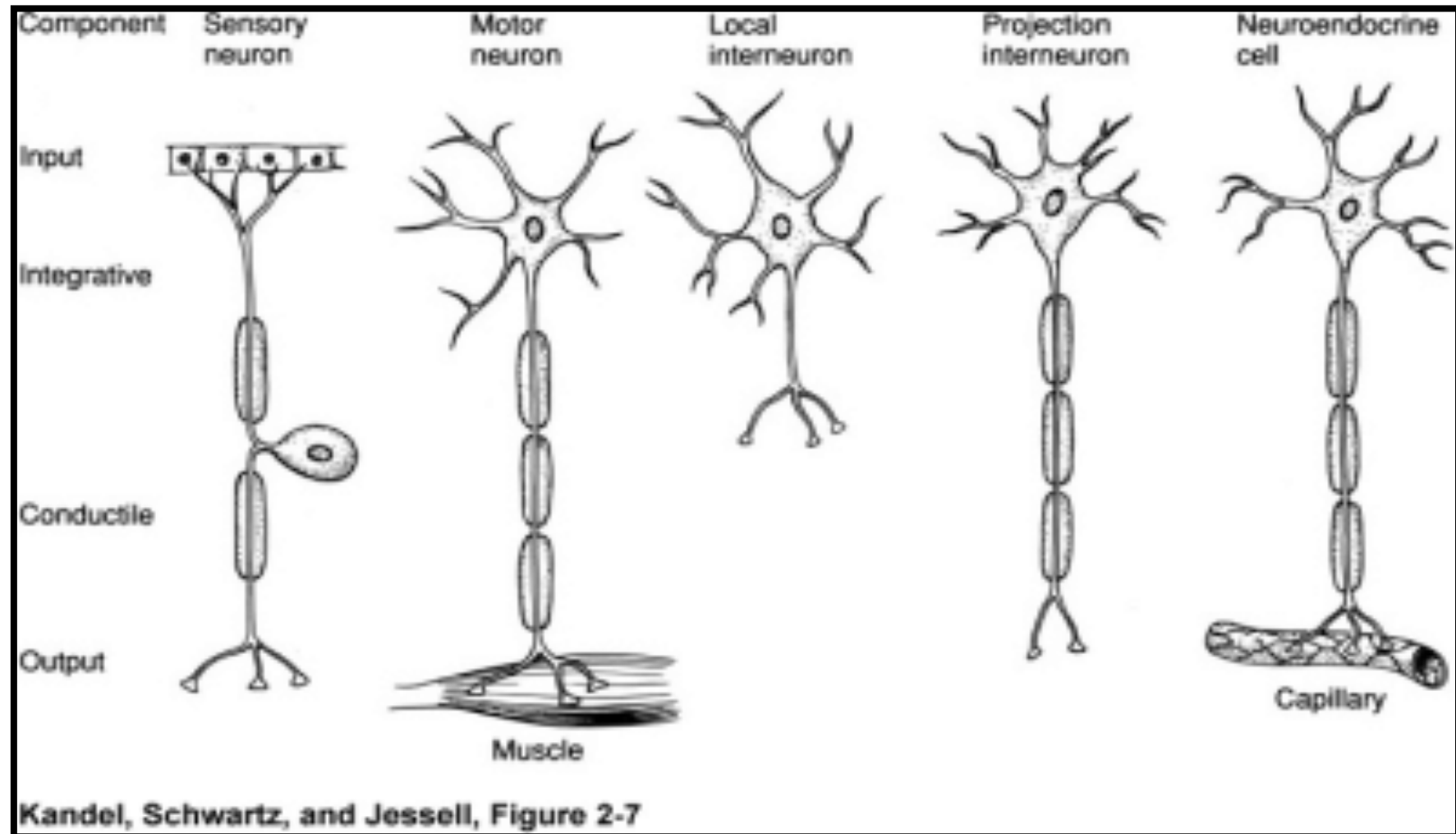
Morfologia neuronal



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Morfologia neuronal



Tema 3

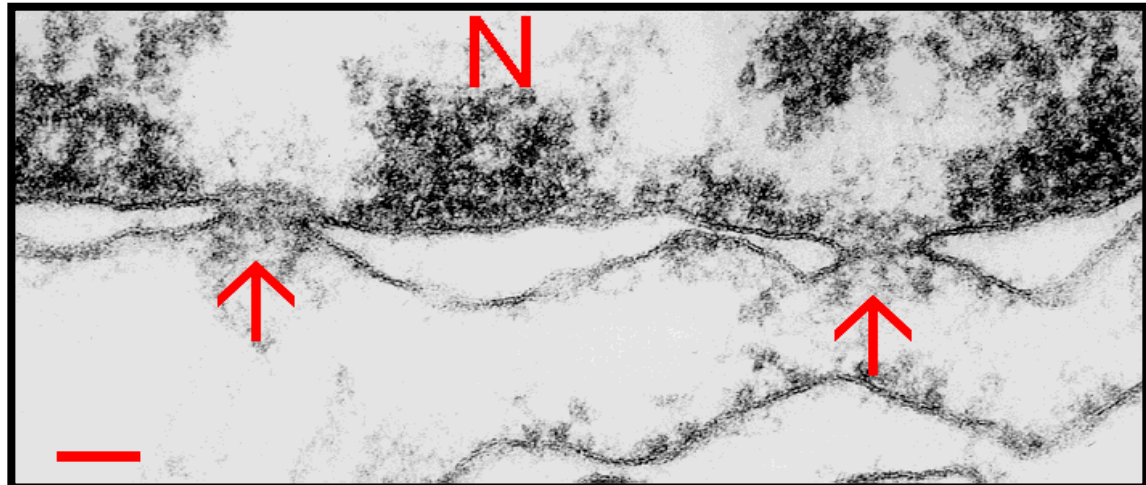
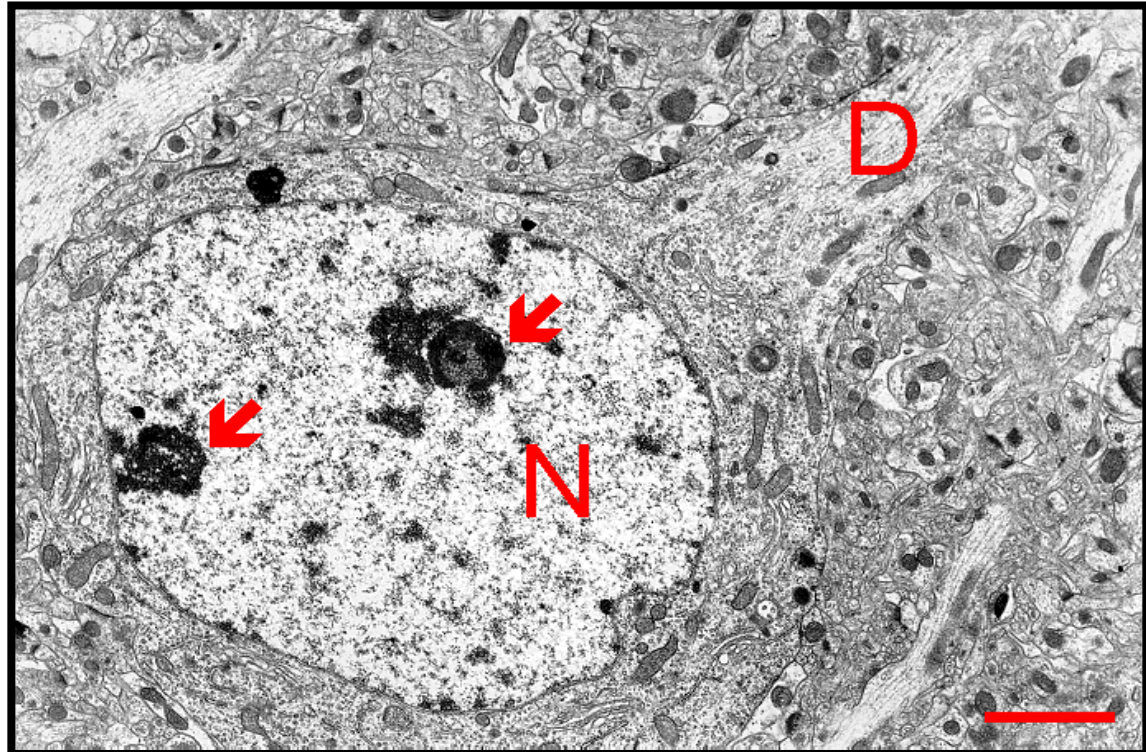
Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Soma

Nucli

- * Gran, esfèric o ovoide
- * Eucromatina ↑↑↑
- * Nuclèol (s) ↑
- * M nucl.: ↑ porus N.



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Soma

Citoplasma

* RER ↑↑

--> Grànuls de Nissl

* Rib. lliures

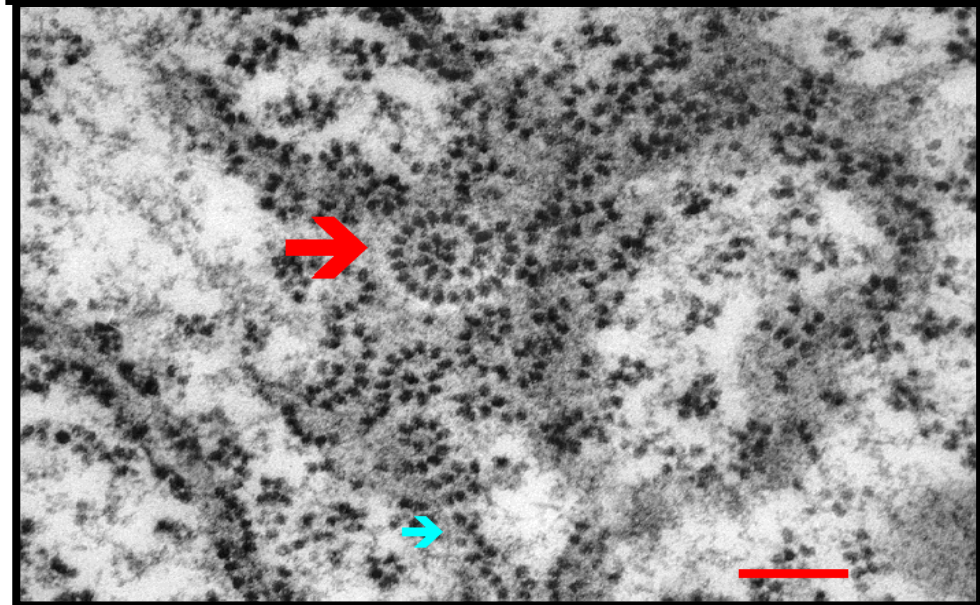
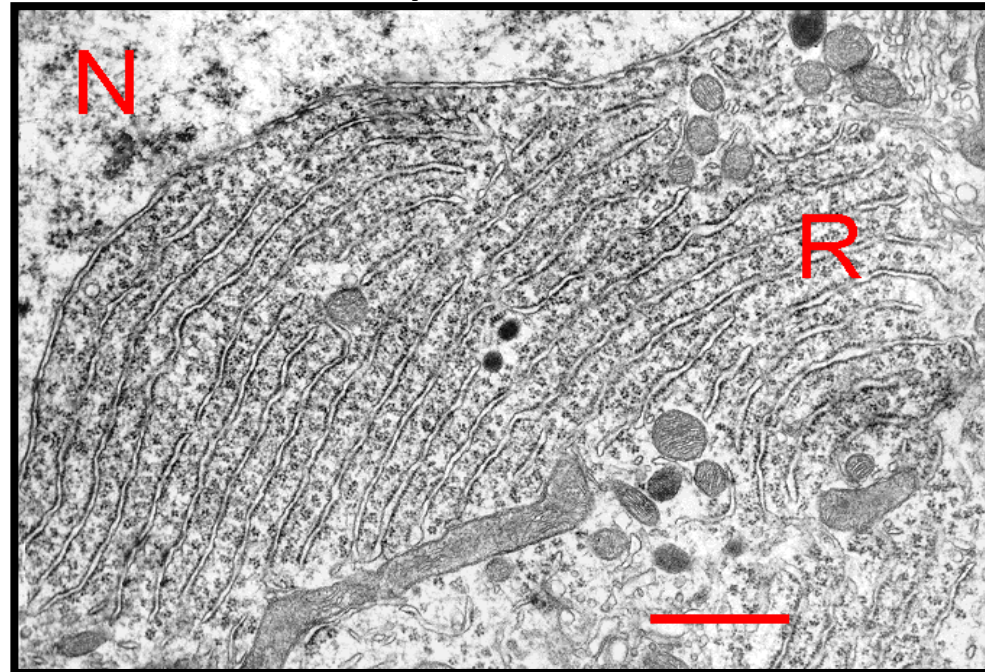
* Golgi ↑↑ Proper a nucl.

De vegades en dendr. secundàries

* Mitoc. ↑↑

* Lisosomes, cossos multivesiculars, lipofuscina

* Microtúb., microfilam. i neurofilam. (f. intermedis)



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Soma

Citoplasma

* RER ↑↑

--> Grànuls de Nissl

* Rib. lliures

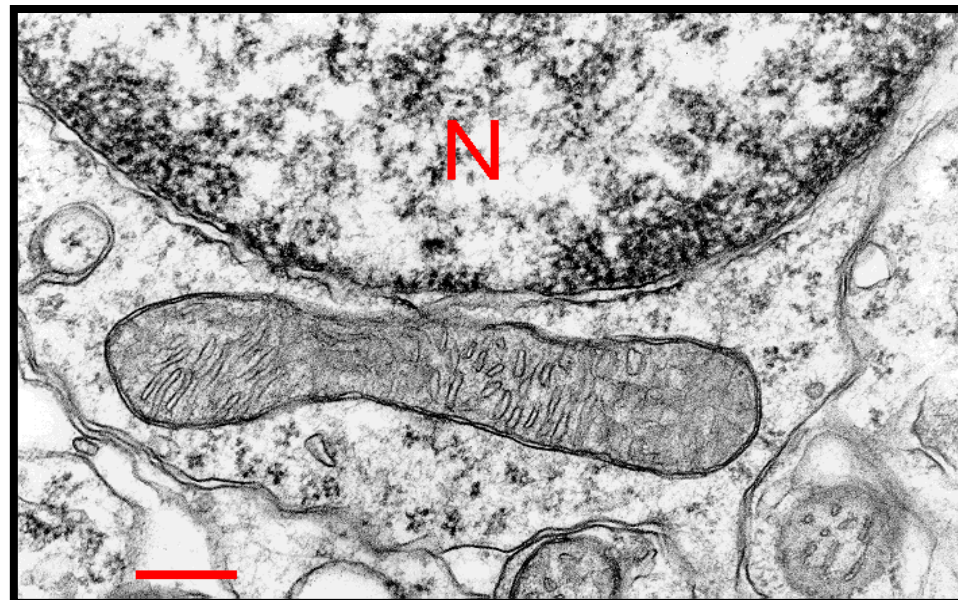
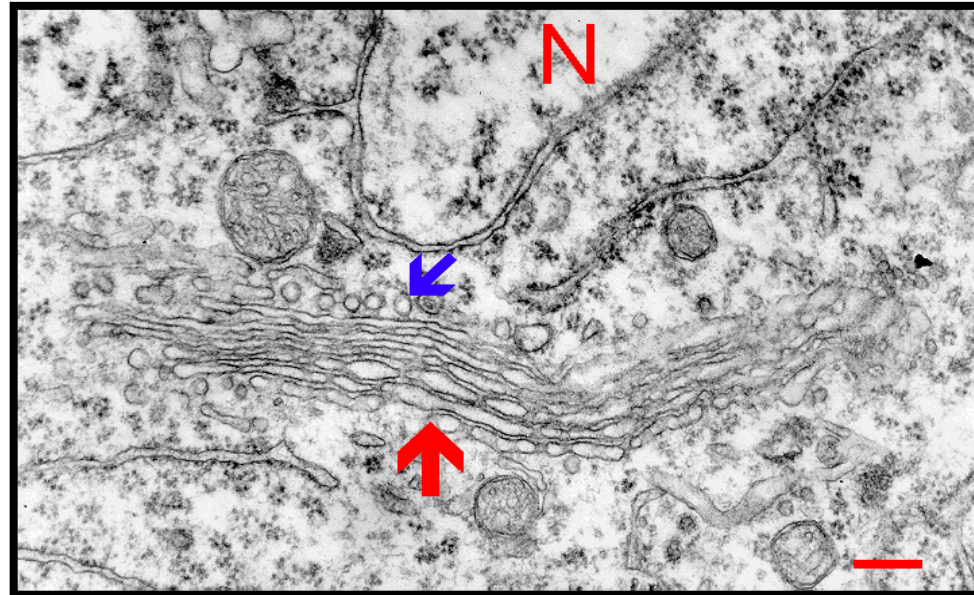
* Golgi ↑↑ Proper a nucl.

De vegades en dendr. secundàries

* Mitoc. ↑↑

* Lisosomes, cossos multivesiculars, lipofuscina

* Microtúb., microfilam. i neurofilam. (f. intermedis)



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Soma

Citoplasma

* RER ↑↑

--> Grànuls de Nissl

* Rib. lliures

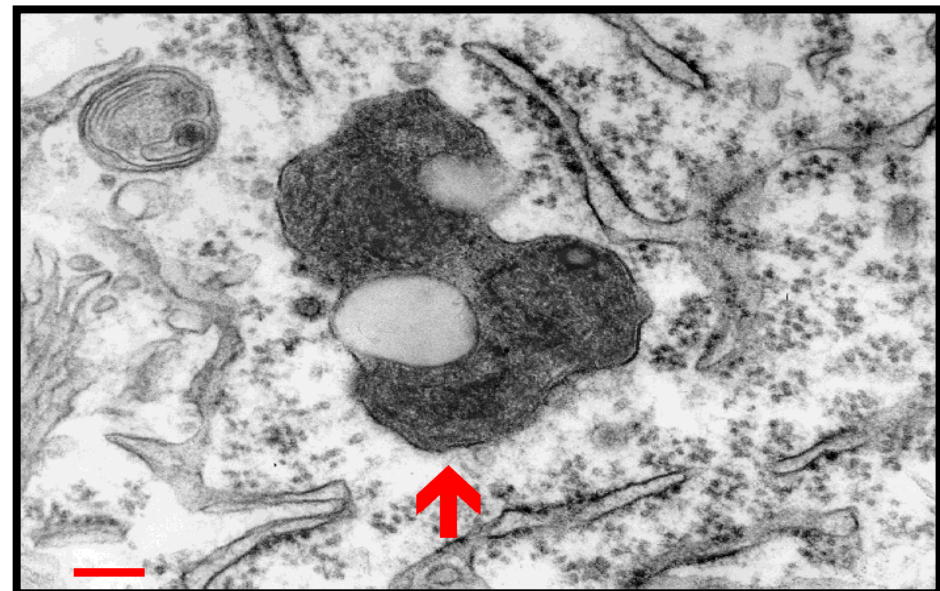
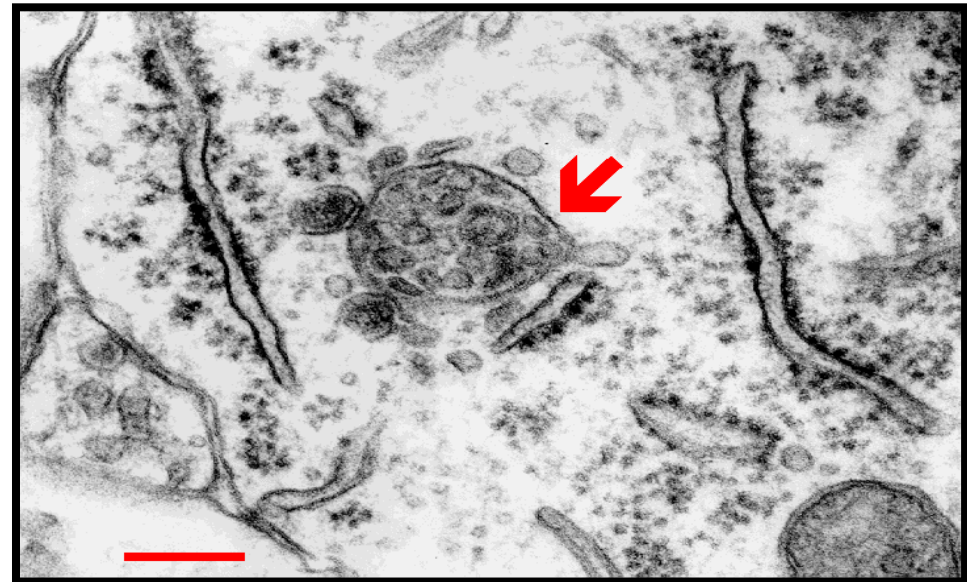
* Golgi ↑↑ Proper a nucl.

De vegades en dendr. secundàries

* Mitoc. ↑↑

* Lisosomes, cossos multivesiculars, lipofuscina

* Microtúb., microfilam. i neurofilam. (f. intermedis)



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Soma

Citoplasma

* RER ↑↑

--> Grànuls de Nissl

* Rib. lliures

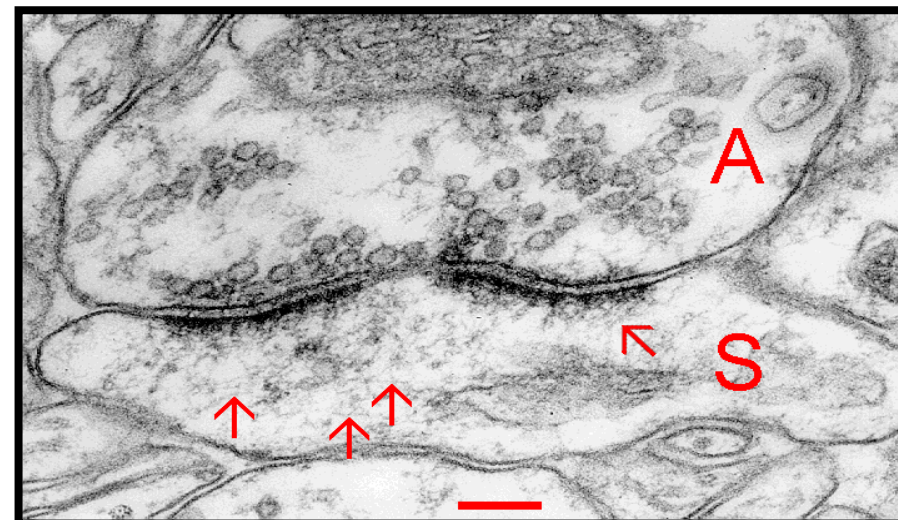
* Golgi ↑↑ Proper a nucl.

De vegades en dendr. secundàries

* Mitoc. ↑↑

* Lisosomes, cossos multivesiculars, lipofuscina

* Microtúb., microfilam. i neurofilam. (f. intermedis)



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Dendrites

Espines dendrítiques

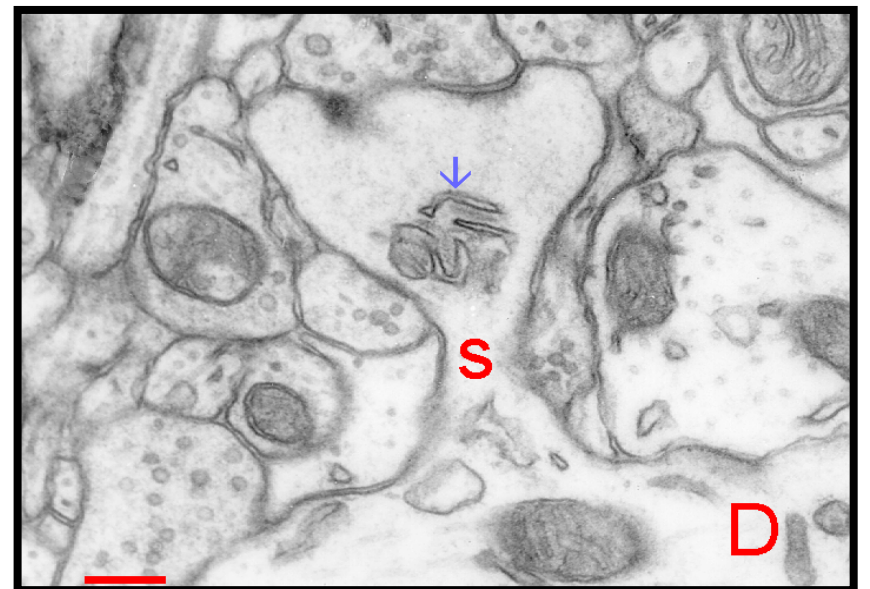
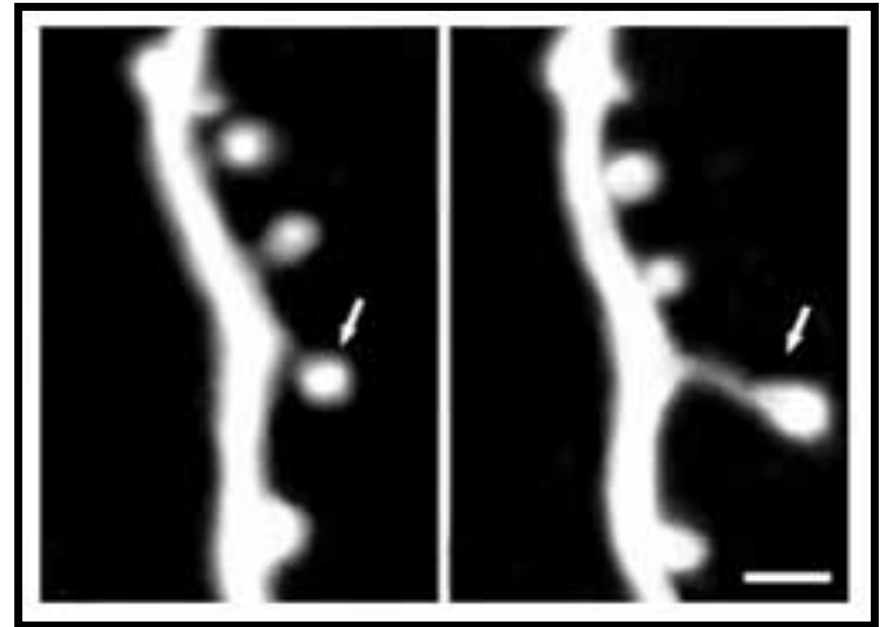
- * Cap + coll
- * Neurones espinoses / no esp.

- * Majoria d'espines: 1 contacte
- * Xarxa d'actina en cap (forma)

- * *Cisternes membranoses*
= aparell de l'espina:
REL: acumulació de Ca^{2+} ??

- * Cossos multivesiculats
i vesícules cobertes
(reciclatge de receptors de MP)

- * Ribosomes --> sint. prot. *in situ*



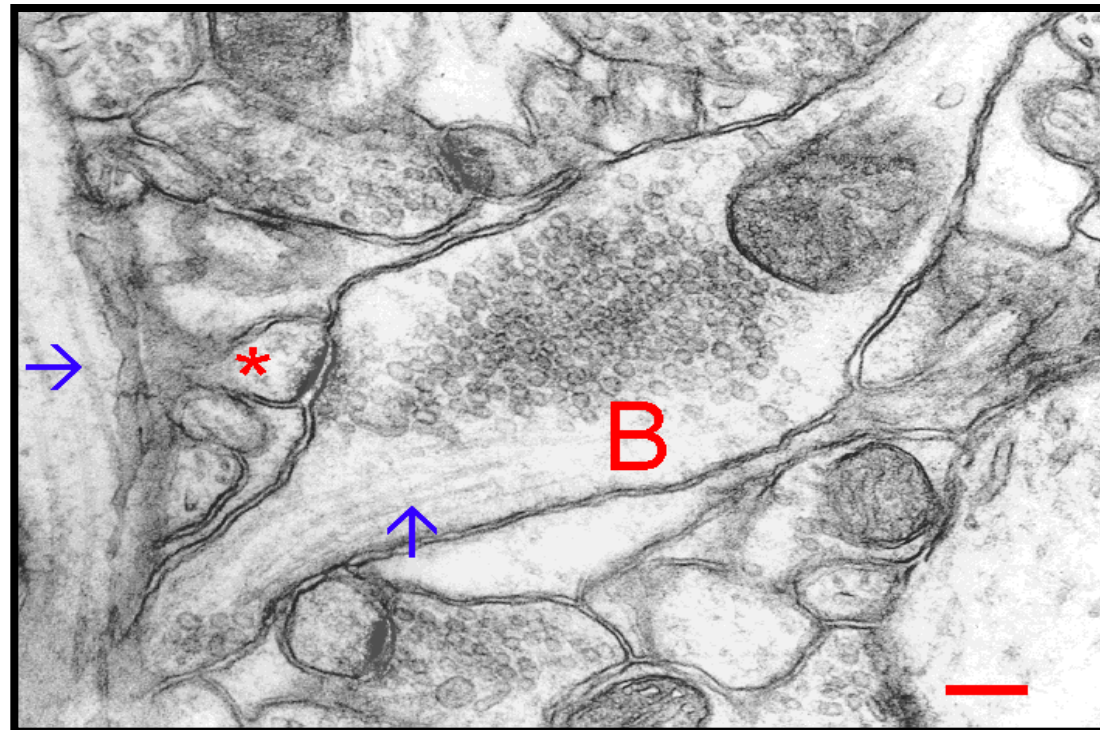
Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Axó

- * No hi ha ribosomes
- * Citosquelet: microtub. extrem + al soma, extrem menys al terminal axònic.
- * Cisternes membranoses.
- * Mitocondris



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Axó 3 parts

Segment inicial

- * ∃ Rib. ni Golgi
- * Microtub. i neurofilam.
- * Mitoc.
- * Làmina submembranosa
/ Beina de mielina

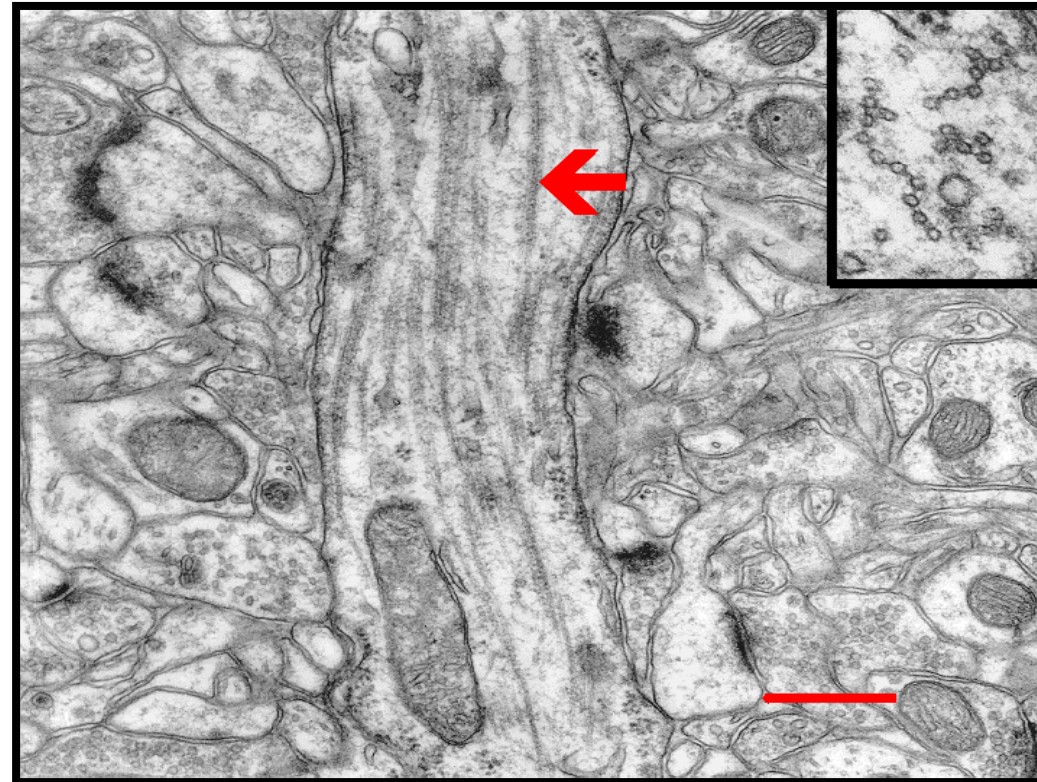
- * Contactes sinàptics
(axoaxònics: n. canelobre)

Segment intermedi

- * Sovint mielinitzat
- * Mitoc. (crestes longitudinals)
- * REL
- * Cossos multivesiculats
- * Feixos de neurofilam. i microtub.

Segment distal

- * No ∃ mielina
- * Vesícules sinàptiques
- * Vesíc. recobertes (endocitosi: reciclatge)
- * Ramificacions (botons presinàptics)
- * *Zones actives* --> exocitosi de vesíc.



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Sinapsi

* Unió funcional: 2 neurones / 1 neur.: 1 cèl·l. muscul.

Químiques

- Element presinàptic (vesíc.)

- Element postsinàptic

- Fenedura

* Tipus

- Axodendrítica

- Axosomàt.

- Axoaxò.

- - Dendrodendrít.

- Somatodendrít.

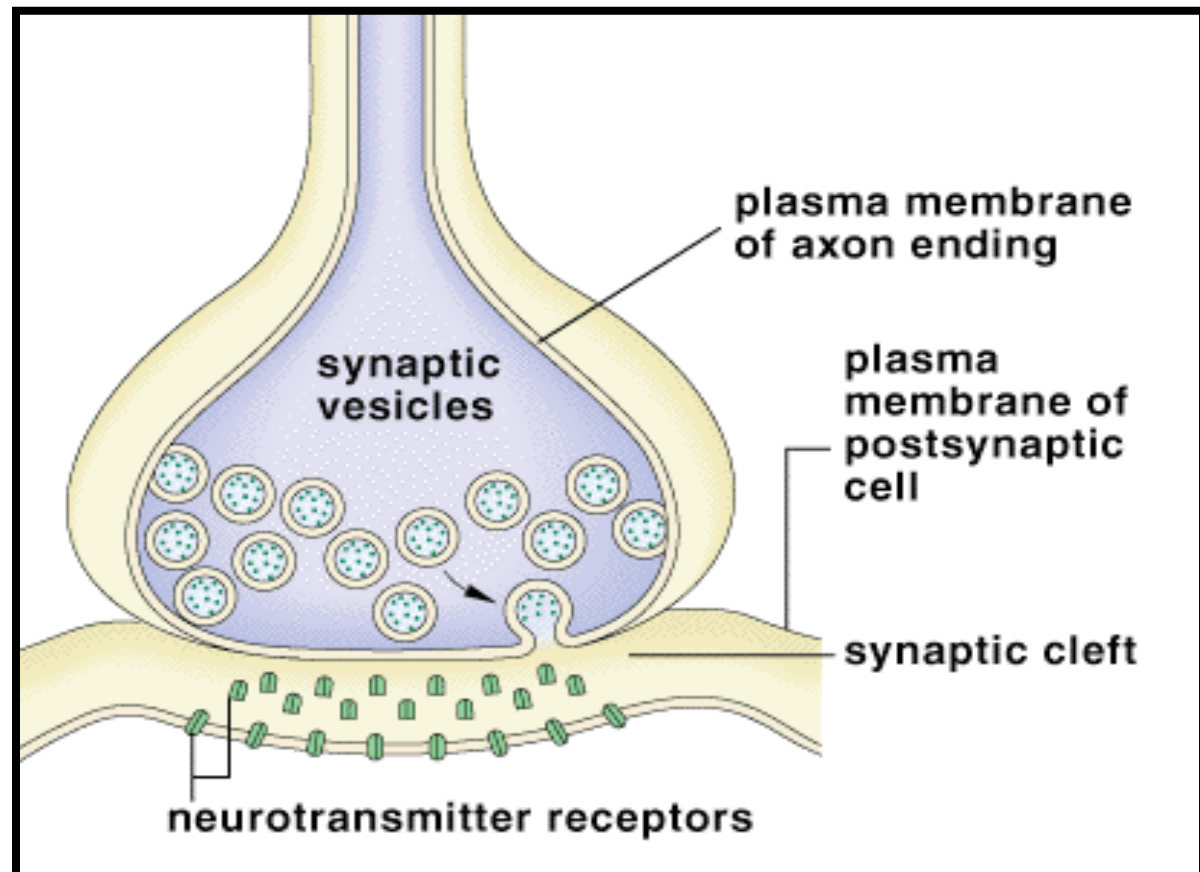
- Somatoaxò.

- Dendrosomàt.

- Somatosomàt.

Elèctriques

* Unions en GAP.



Tema 3

Estructura i funció neuronal. Estructura de la neurona i la sinapsi

Ultraestructura neuronal

Contactes sinàptics

Per morfologia:

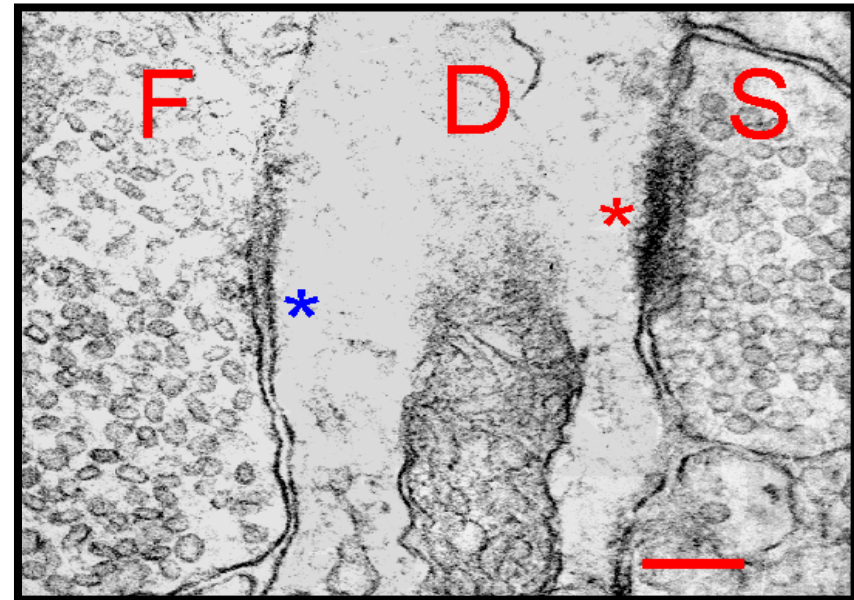
* Tipus 1 --> asimètriques:
densitat en elt. postsinàptic

Axoespínosa

* Tipus 2 --> simètriques:

No dens. sinàpt.

Axosomàt.



Vesícules sinàptiques

a) Centre clar

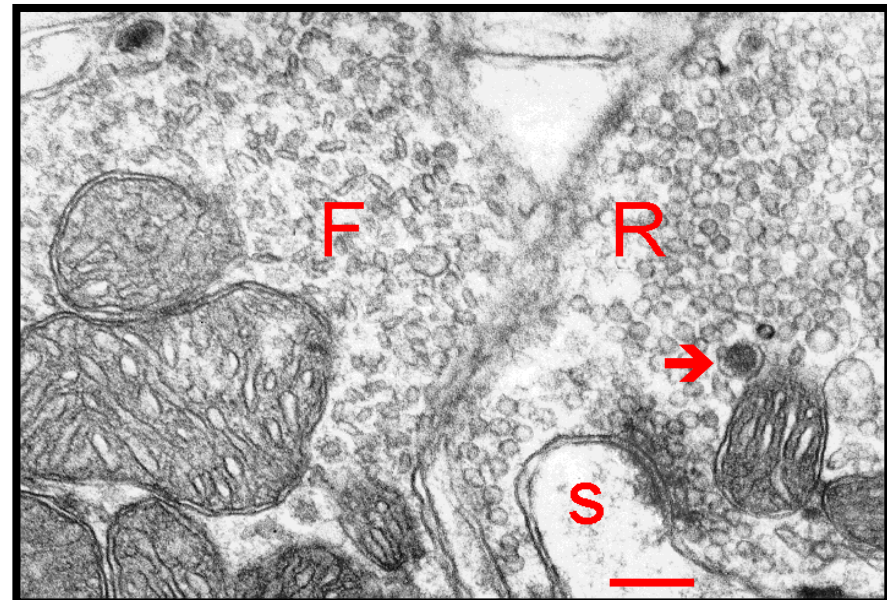
* Esfèriques grans (ACh, Glu) +

* Esfèriques menudes (GABA, Gly) -

* Ovals]

b) Granulars

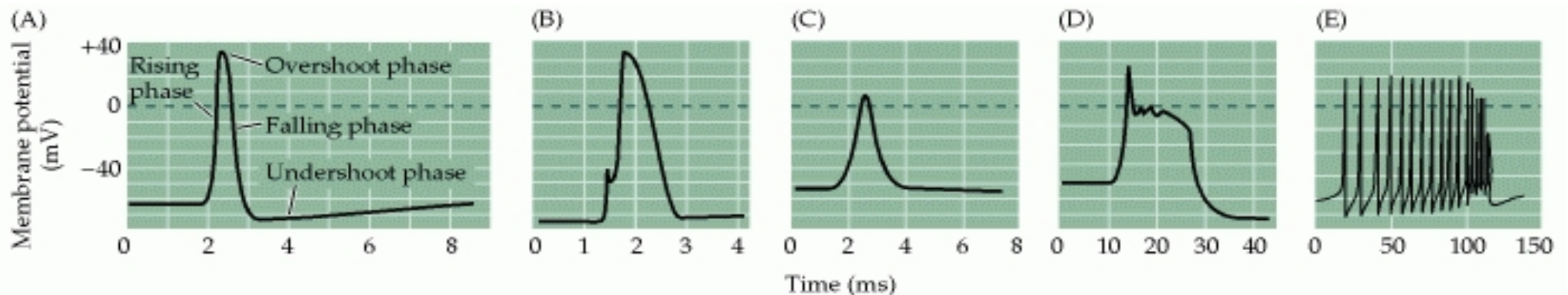
* Nucli dens (pèpt. i catecolamines)



Tema 3

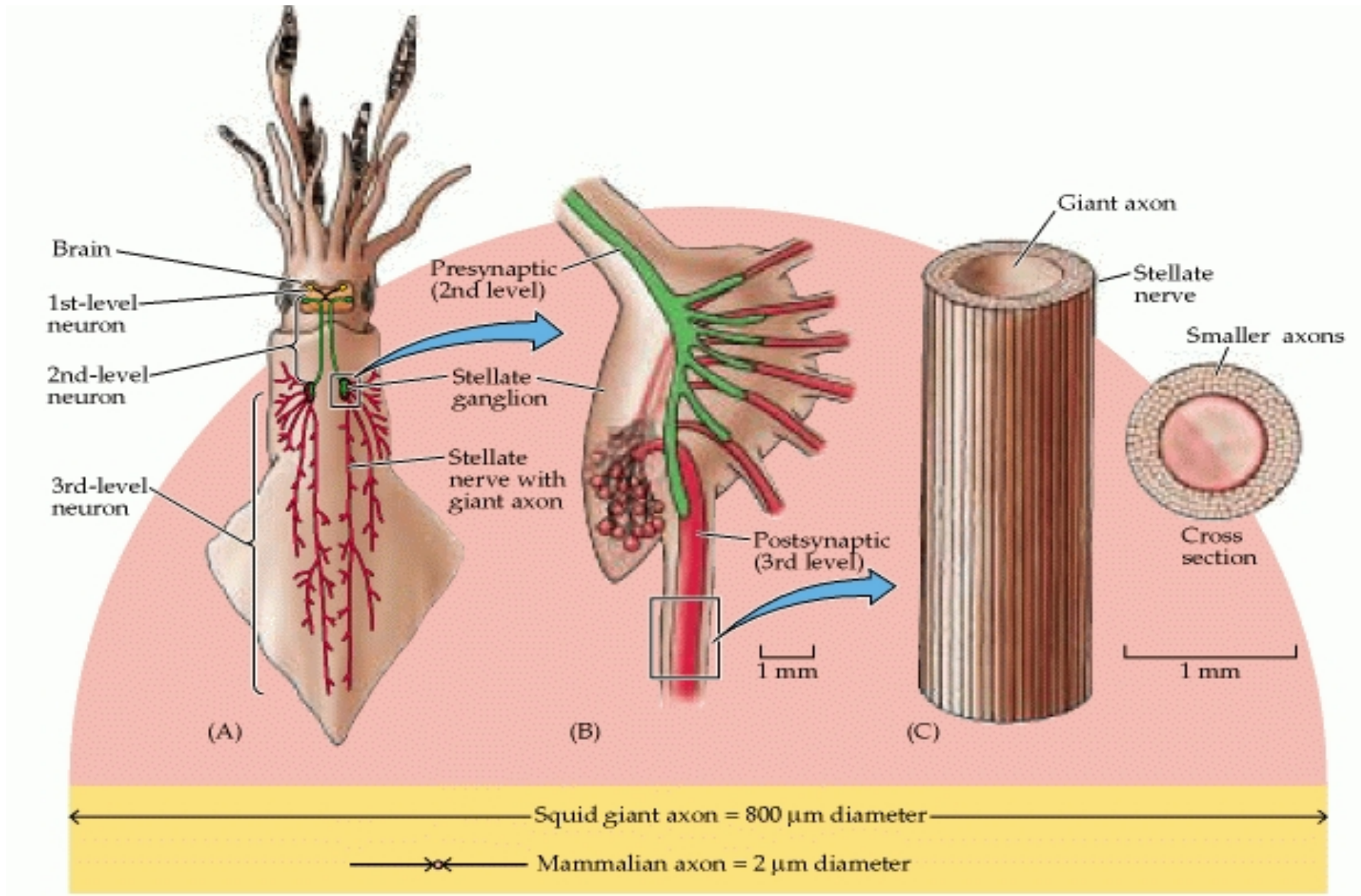
Transmissió sinàptica, neurotransmissors i receptors: caracterització farmacològica. Generació de potencials postsinàptics excitatoris (exemples de receptors del glutamat) i inhibitoris (exemples de receptors de GABA)

- Galè: “Els humors viatgen des del cervell fins als músculs a través dels nervis buits”
- El descobriment de l'electricitat va ser necessari per a entendre la transmissió nerviosa:
 - ✓ Aplicació d'estímuls elèctrics a nervis i músculs
 - ✓ La conducció d'informació a través de l'axó era deguda a la generació activa d'un canvi de potencial denominat potencial d'acció.
 - ✓ Quina era la natura d'aquest potencial d'acció?
 - ✓ Axó gegant del calamar: 0.55 mm diàmetre (Hodgkin i Huxley, 1939).
 - ✓ Els axons en repòs estan polaritzats: Pot en repòs -60 mV int. vs ext.
 - ✓ Quan existeix un potencial d'acció, el potencial de repòs es perd-> >0 mV
 - ✓ Potencial de repòs en neurones normals semblant al d'axó gegant



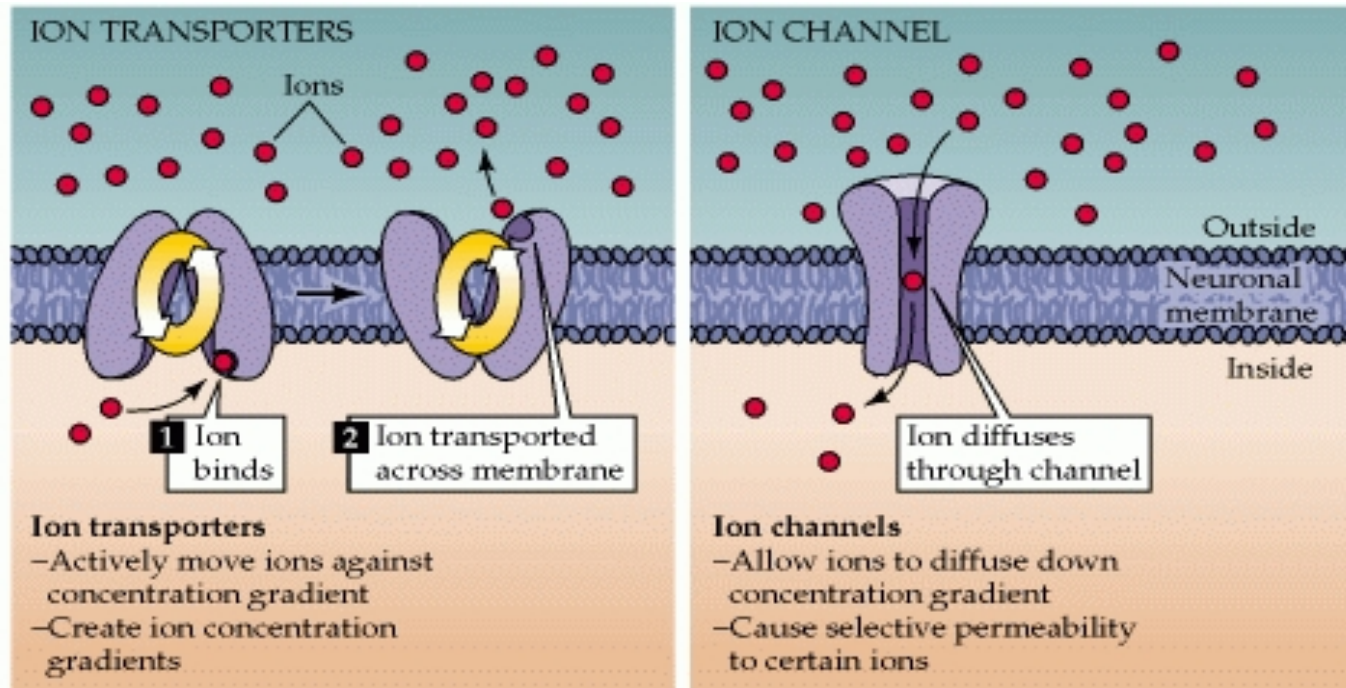
A) The phases of an [action potential](#) of the squid giant [axon](#). (B) [Action potential](#) recorded from a [myelinated axon](#) of a frog [motor neuron](#). (C) [Action potential](#) recorded from the cell body of a frog [motor neuron](#). The [action potential](#) is smaller and the [undershoot](#) prolonged in comparison to the [action potential](#) recorded from the [axon](#) of this same [neuron](#) (B). (D) [Action potential](#) recorded from the cell [body of a neuron](#) from the inferior olive of a [guinea pig](#). This [action potential](#) has a pronounced [plateau](#) during its falling phase. (E) [Action potential](#) recorded from the cell body of a Purkinje [neuron](#) in the [cerebellum of a guinea pig](#).

Purves *et al.* *Neuroscience*, 4 ed.



EL POTENCIAL DE MEMBRANA

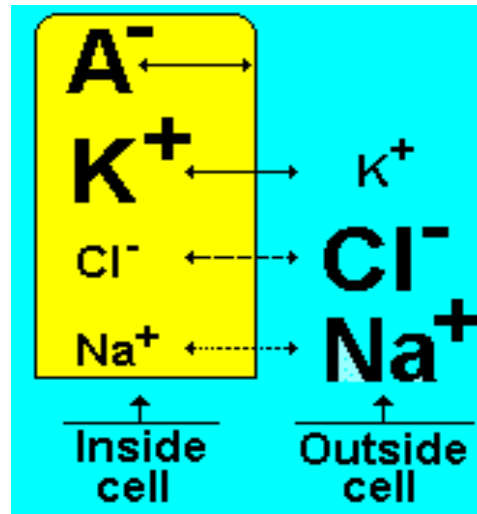
- El potencial de membrana és generat per la distribució diferencial d'ions
- ♦ A través de bombes iòniques i mecanismes de tamponament d'ions
- ♦ K^+ activament concentrat a la cèl·lula
- ♦ Na^+ , Cl^- , i Ca^{2+} activament alliberats a l'exterior
- ♦ Però osmolaritat semblant a la de l'exterior



	Concentr. (mM)	
Ion	Intracel.	Extracel.
Squid neuron		
Potassium (K^+)	400	20
Sodium (Na^+)	50	440
Chloride (Cl^-)	40–150	560
Calcium (Ca^{2+})	1	10
Mammal. neuron		
Potassium (K^+)	140	5
Sodium (Na^+)	5–15	145
Chloride (Cl^-)	4–30	110
Calcium (Ca^{2+})	1	1–2

EL POTENCIAL DE MEMBRANA

- Forces elèctriques i termodinàmiques determinen la distribució passiva d'ions
- El moviment d'ions pot causar hiperpolarització o despolarització



- Potencial d'equilibri a neurones de mamífers:

- ◆+56mV per a Na^+
- ◆-76mV per a Cl^-
- ◆+125mV per a Ca^{2+}

Si aquests canals s'obrin, la membrana tendeix a arribar a aqueixos valors de potencial de M.

EL POTENCIAL DE MEMBRANA

- Na⁺, K⁺, y Cl⁻ contribueixen a la determinació del potencial de M en repòs

Si la M sols fóra permeable a un ió i no existiren bombes iòniques, el pot. de M seria necessàriament el potencial d'equilibri d'aqueix ió.

Ex.: A l'axó gegant, la M és permeable en repòs a K⁺, Cl⁻ i Na⁺ (existeixen canals oberts en repòs). Per tant, el pot. en repòs està entre el que defineixen els tres ions. --> Equació de Goldman, Hodgkin, Katz.

The GHK voltage equation for N monovalent positive ionic species and M negative:

$$E_m = \frac{RT}{F} \ln \left(\frac{\sum_i^N P_{M_i^+} [M_i^+]_{\text{out}} + \sum_j^M P_{A_j^-} [A_j^-]_{\text{in}}}{\sum_i^N P_{M_i^+} [M_i^+]_{\text{in}} + \sum_j^M P_{A_j^-} [A_j^-]_{\text{out}}} \right)$$

This results in the following if we consider a membrane separating two K_xNa_{1-x}Cl-solutions:

$$E_{m, K_x Na_{1-x} Cl} = \frac{RT}{F} \ln \left(\frac{P_{Na^+} [Na^+]_{\text{out}} + P_{K^+} [K^+]_{\text{out}} + P_{Cl^-} [Cl^-]_{\text{in}}}{P_{Na^+} [Na^+]_{\text{in}} + P_{K^+} [K^+]_{\text{in}} + P_{Cl^-} [Cl^-]_{\text{out}}} \right)$$

It is "[Nernst-like](#)" but has a term for each permeant ion. The [Nernst equation can be](#) considered a special case of the Goldman equation for only one ion:

$$E_{m, Na} = \frac{RT}{F} \ln \left(\frac{P_{Na^+} [Na^+]_{\text{out}}}{P_{Na^+} [Na^+]_{\text{in}}} \right) = \frac{RT}{F} \ln \left(\frac{[Na^+]_{\text{out}}}{[Na^+]_{\text{in}}} \right)$$

■ E_m = The membrane potential (in [volts](#), equivalent to [joules](#) per [coulomb](#))

■ P_{ion} = [the permeability for that ion](#) (in meters per second)

■ [ion]_{out} = the extracellular concentration of that ion (in [moles](#) per cubic meter, to match the other [SI](#) units)

■ [ion]_{in} = the intracellular concentration of that ion (in moles per cubic meter)

■ R = The [ideal gas constant](#) (joules per [kelvin](#) per mole)

■ T = [The temperature](#) in kelvins

■ F = [Faraday's constant](#) (coulombs per mole)

The first term, before the [parenthesis, can be reduced](#) to 61.5 mV for calculations at human body temperature (37 °C)

EL POTENCIAL DE MEMBRANA

- Diferents tipus neuronals tenen diferents potencials de repòs
- Alguns no en tenen; constantment estan disparant potencials d'acció.
Ex.: Cons i bastonets Pot. repòs -40mV i s'hiperpolaritzen per llum.
Ex.: Neurones piramidals d'escorça visual Pot. repòs -75mV

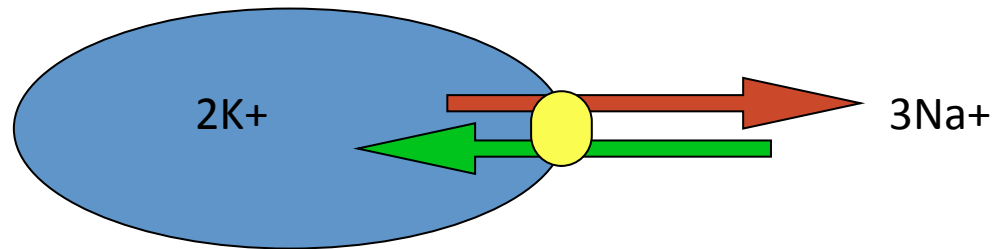
Aquests potencials de repòs estan ben regulats i són molt importants per al funcionament de neurones.

- Les bombes iòniques mantenen activament gradients iònics

★ K^+

La bomba Na^+/K^+ està estimulada per l'elevada $[\text{Na}^+]$ intracel·lular.

Necessita ATP per al seu funcionament.



Per tant, és hiperpolaritzant = electrògena

★Ca²⁺

Existeixen mecanismes intracel. de tamponament (CaBP)

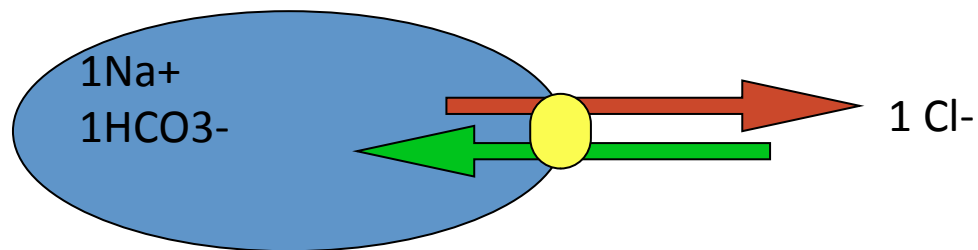
Bomba Ca²⁺/Mg²⁺ treu Ca²⁺ de cèl·lula

Bomba Na⁺/Ca²⁺ treu Ca²⁺ de cèl·lula

Dependents de gradient de Ca²⁺

★Cl⁻

bomba Cl⁻/HCO₃⁻

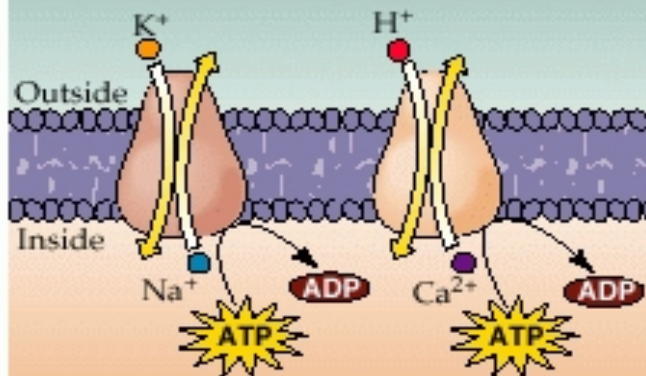


★ El pH també es troba regulat por bombes Na⁺/H⁺

ATPase PUMPS

(A) Na⁺/K⁺ pump

(B) Ca²⁺ pump



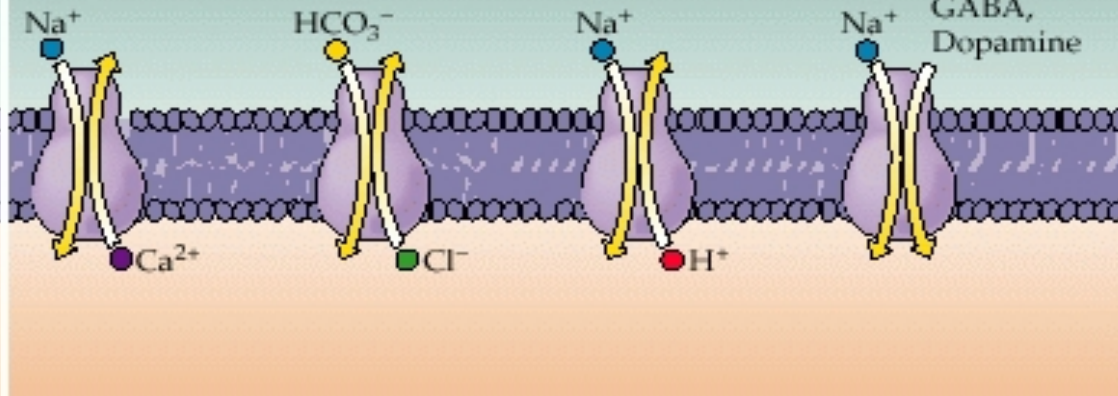
ION EXCHANGERS

(C) Na⁺/Ca²⁺ exchanger

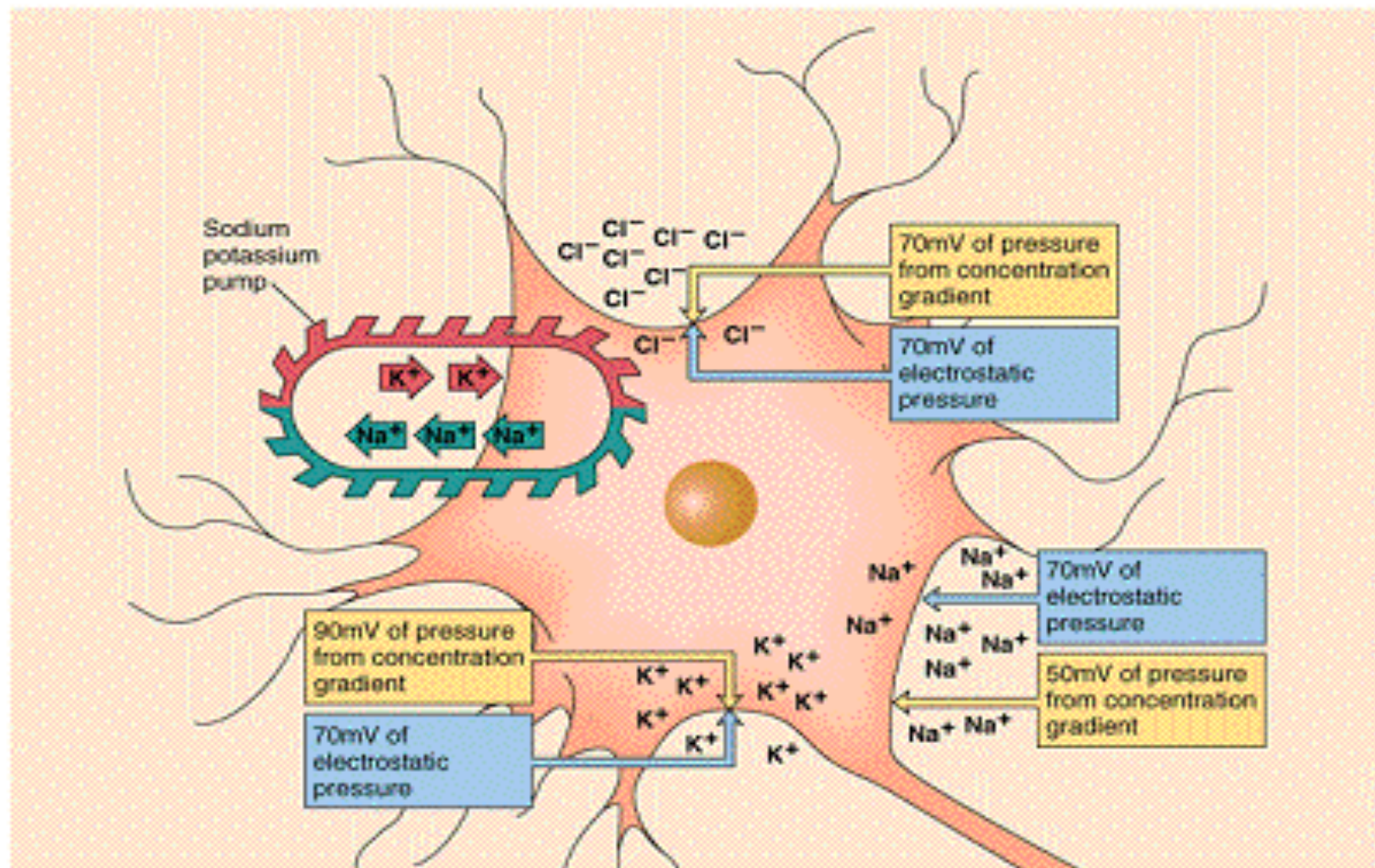
(D) Cl⁻/HCO₃⁻ exchanger

(E) Na⁺/H⁺ exchanger

(F) Na⁺/neurotransmitter exchanger

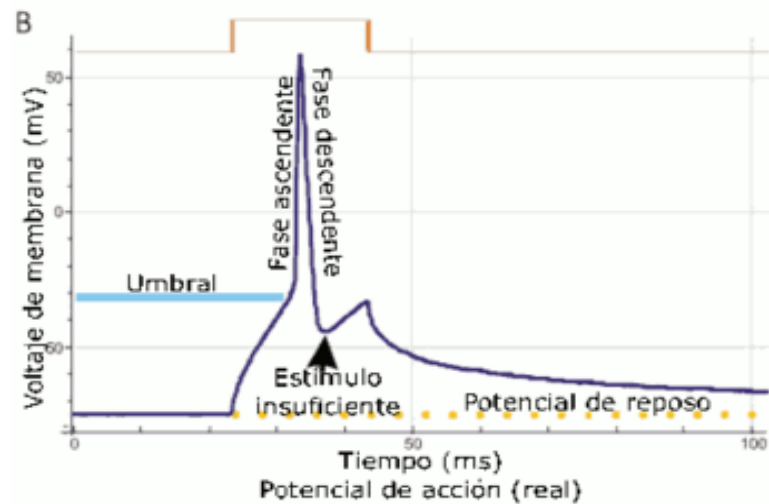
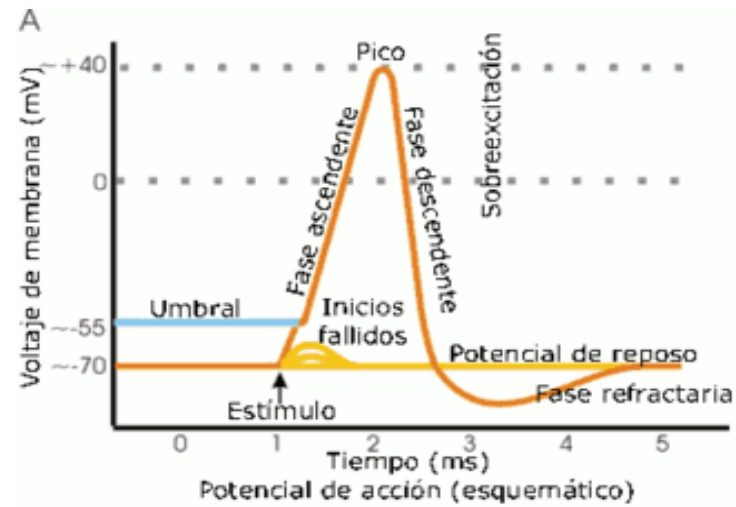


► Ion Distribution Across the Neural Membrane



EL POTENCIAL D'ACCIÓ

Un increment en les conductàncies de Na^+ i K^+ genera els potencials d'acció.

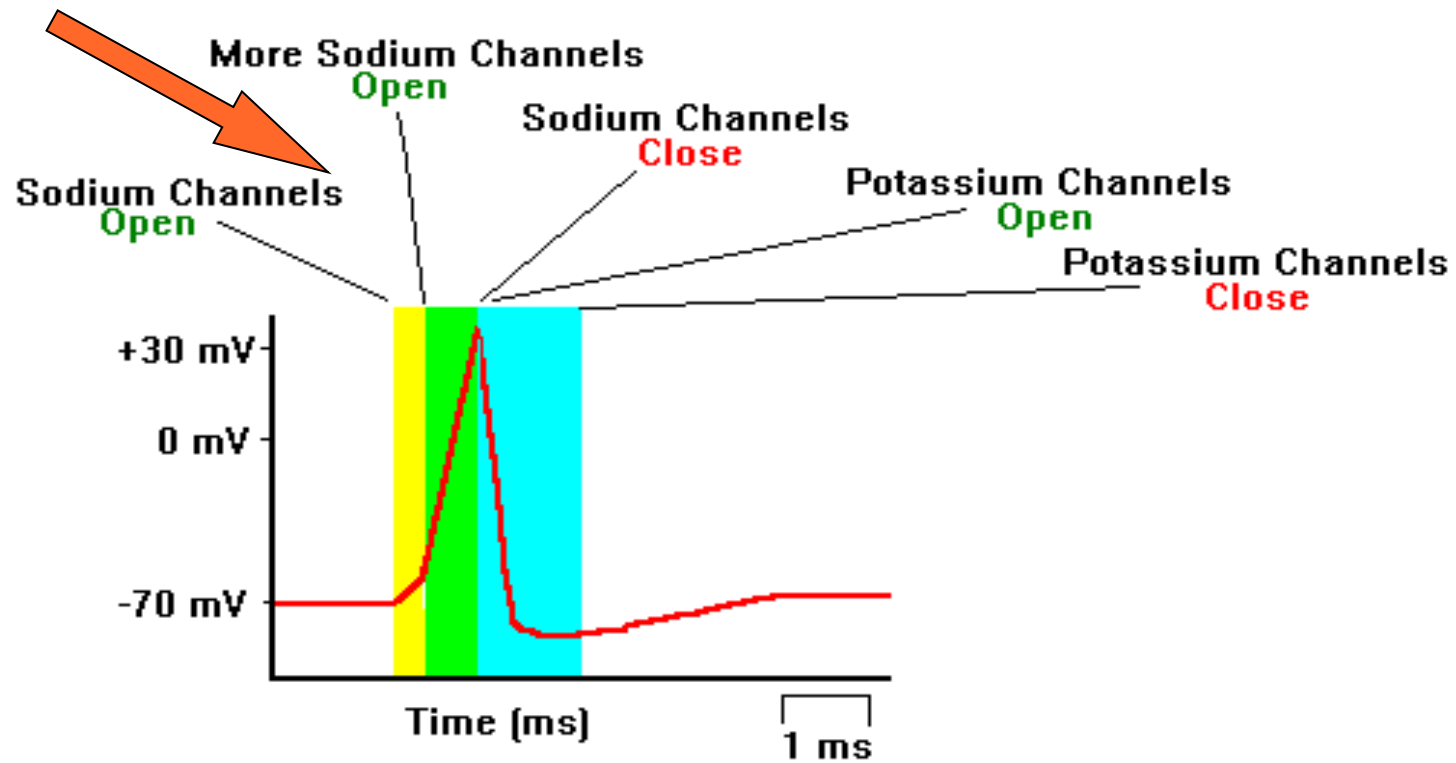


◆ <http://www.sinauer.com/neuroscience4e/animations2.3.html>

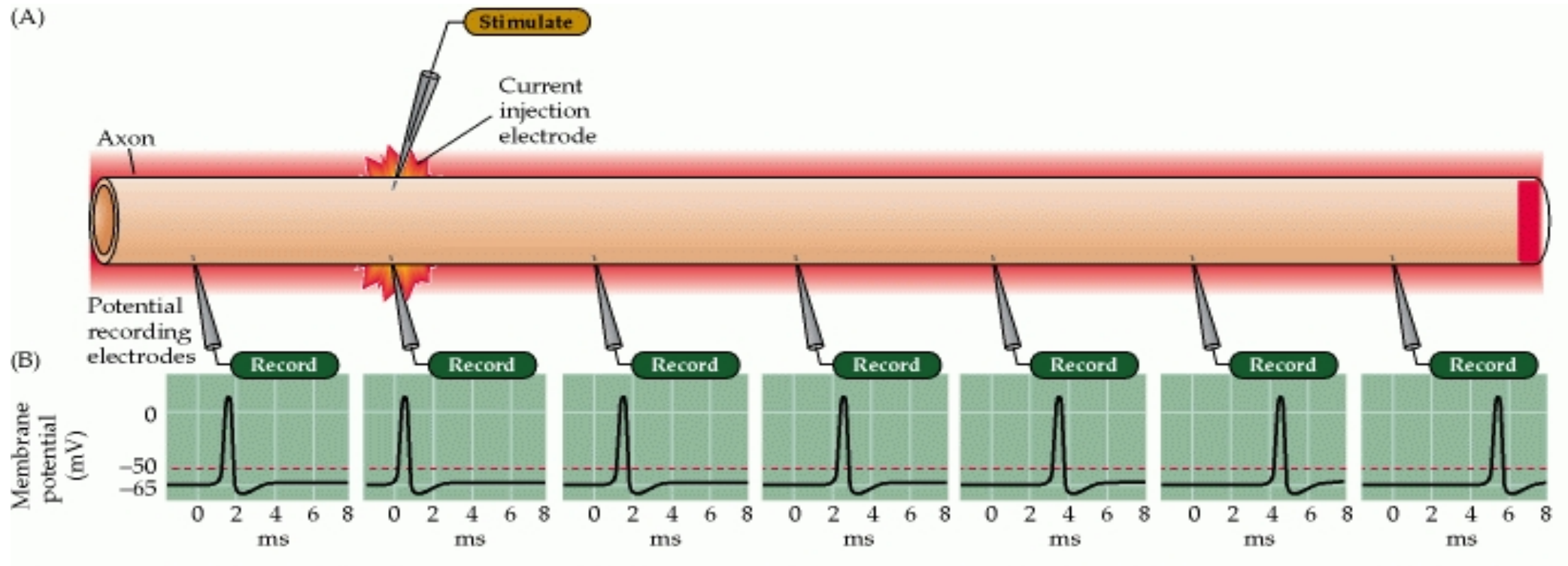
EL POTENCIAL D'ACCIÓ

Un increment en les conductàncies de Na^+ i K^+ genera els potencials d'acció.

TTX

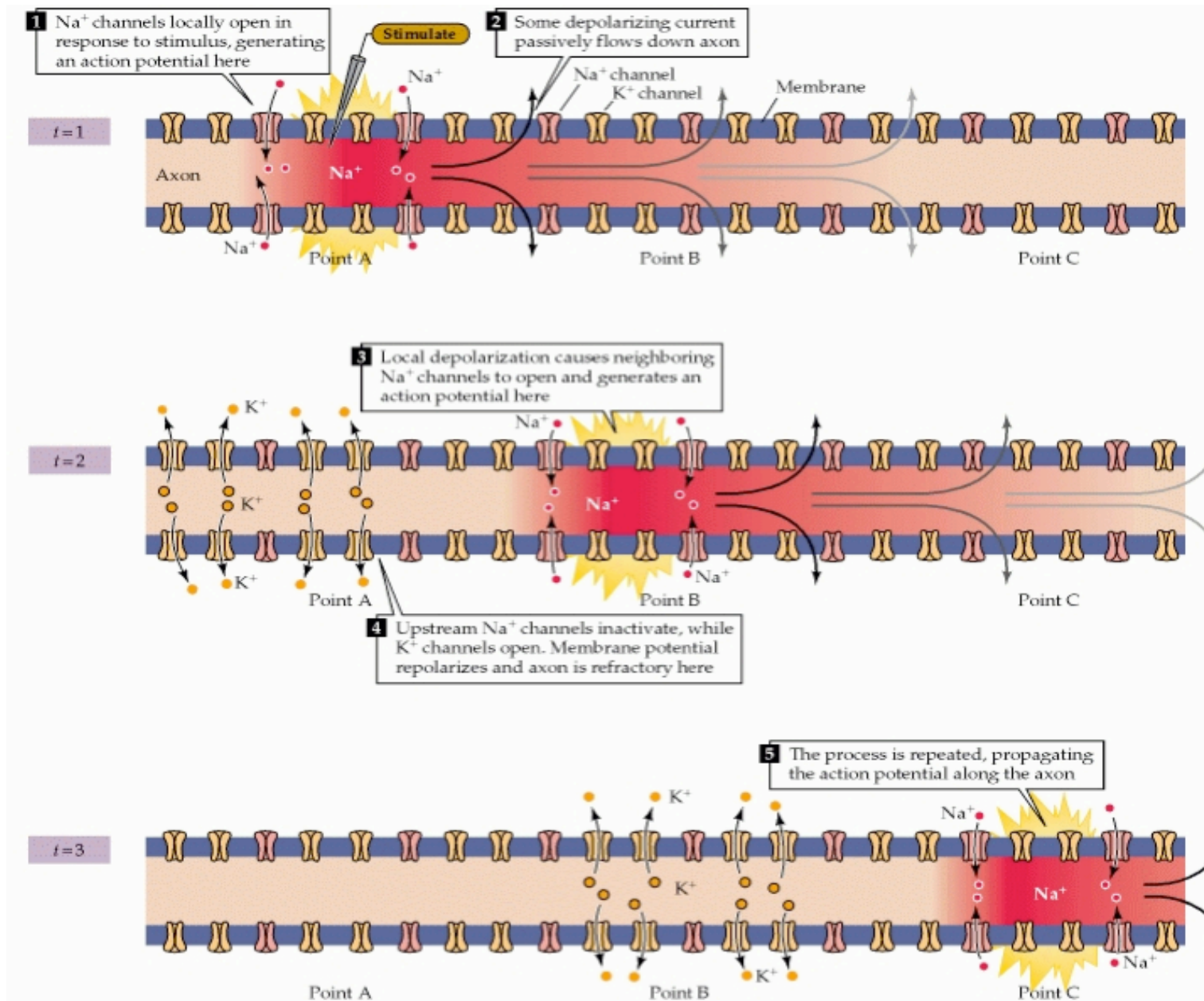


EL POTENCIAL D'ACCIÓ



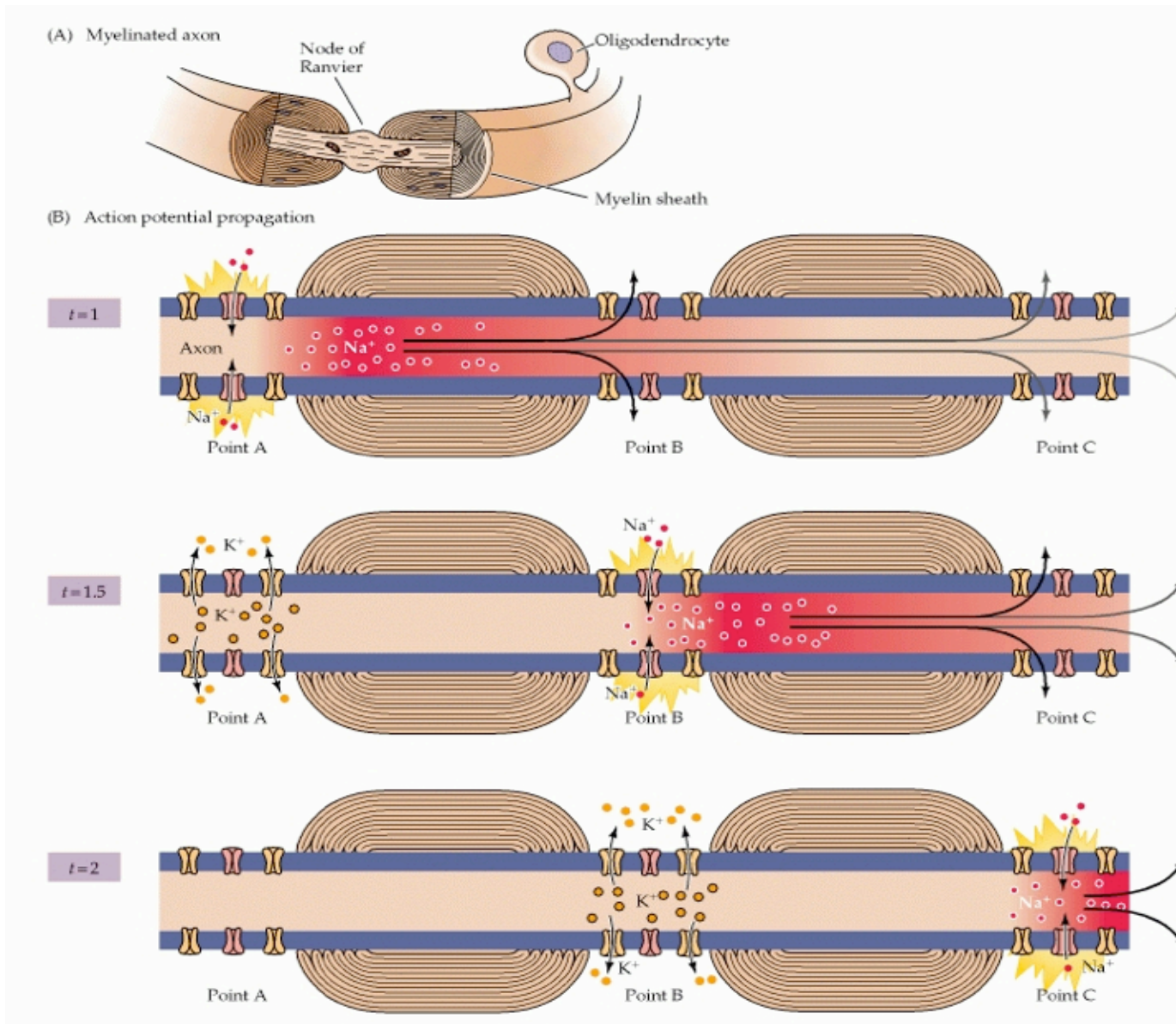
Purves et al. Neuroscience, 4 ed.

EL POTENCIAL D'ACCIÓ



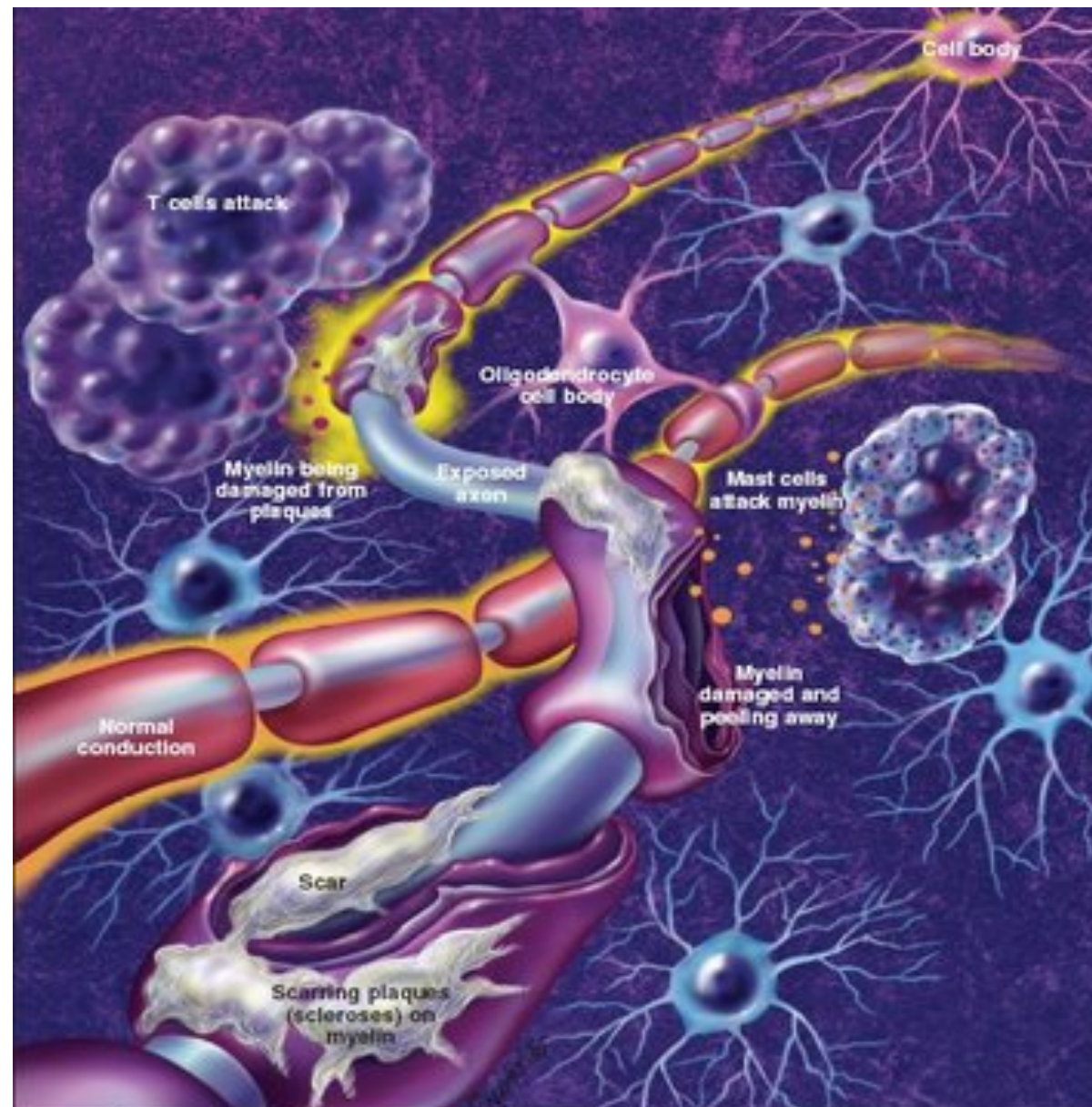
EL POTENCIAL D'ACCIÓ

★ Conducció saltatòria



EL POTENCIAL D'ACCIÓ

★ Conducció saltatòria / Esclerosi múltiple

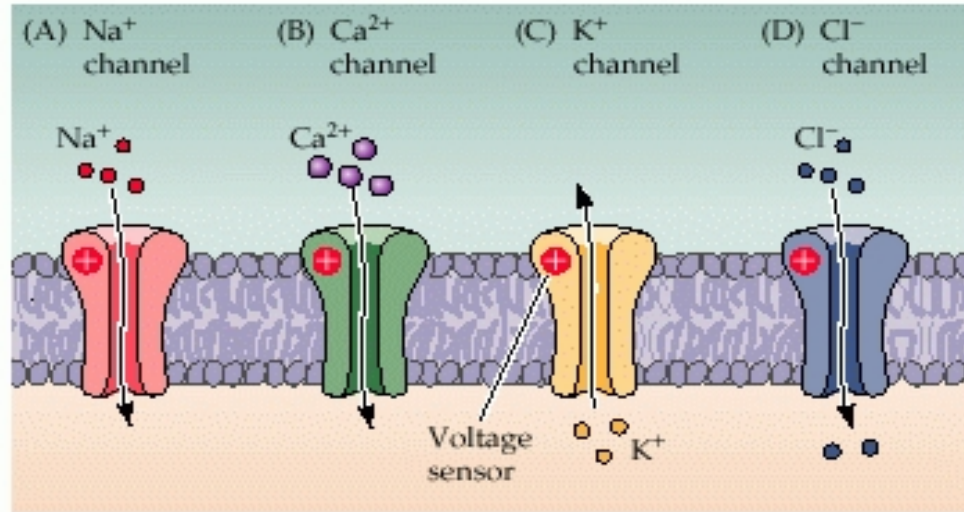


Inflammation, loss of myelin, scarring, and axonal damage represent the neurological insults that characterize MS.

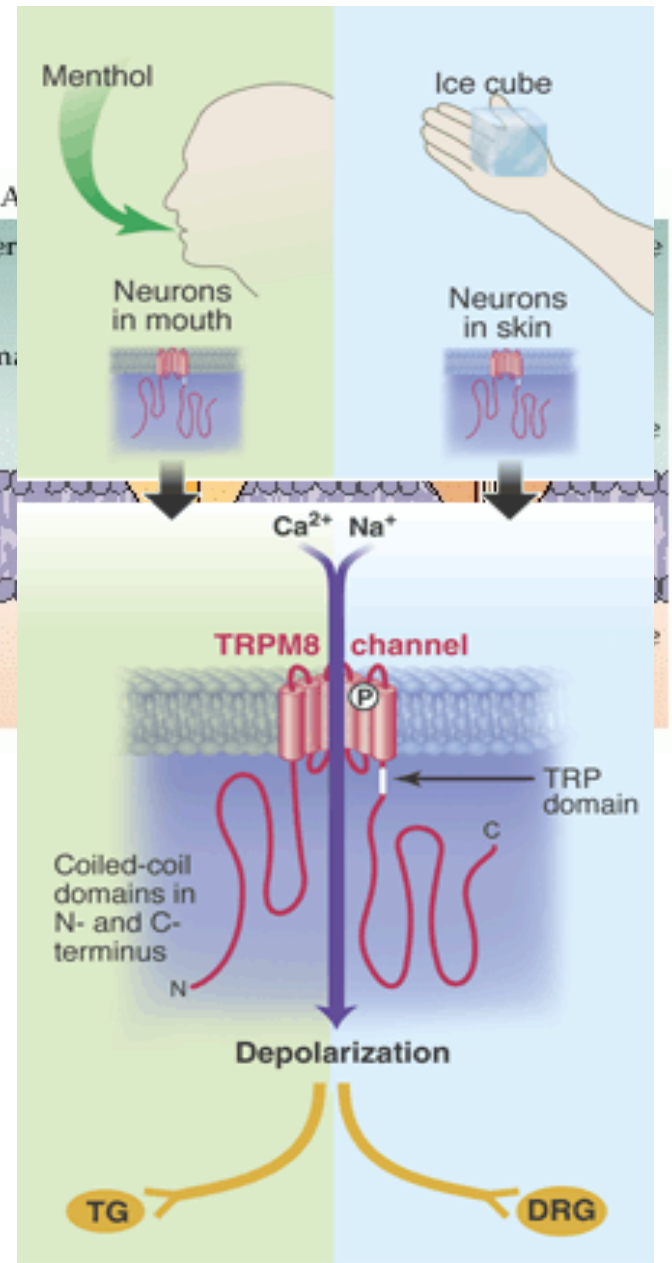
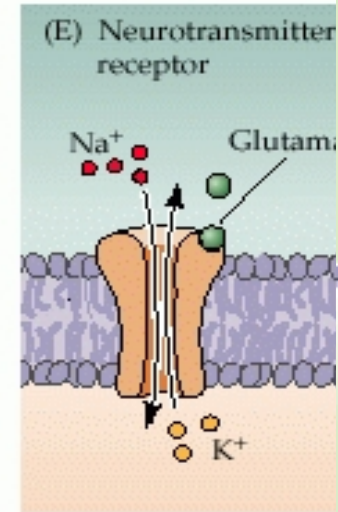
EL POTENCIAL D'ACCIÓ

Canals iònics

VOLTAGE-GATED CHANNELS

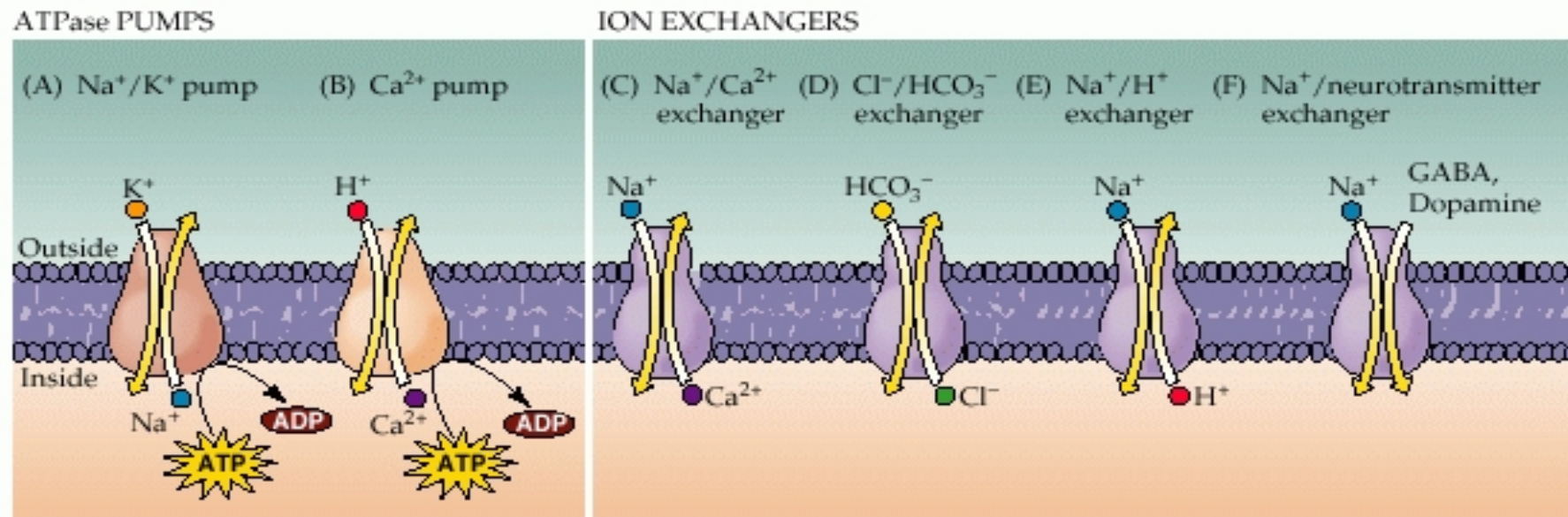


LIGAND-GATED CHANNEL



EL POTENCIAL D'ACCIÓ

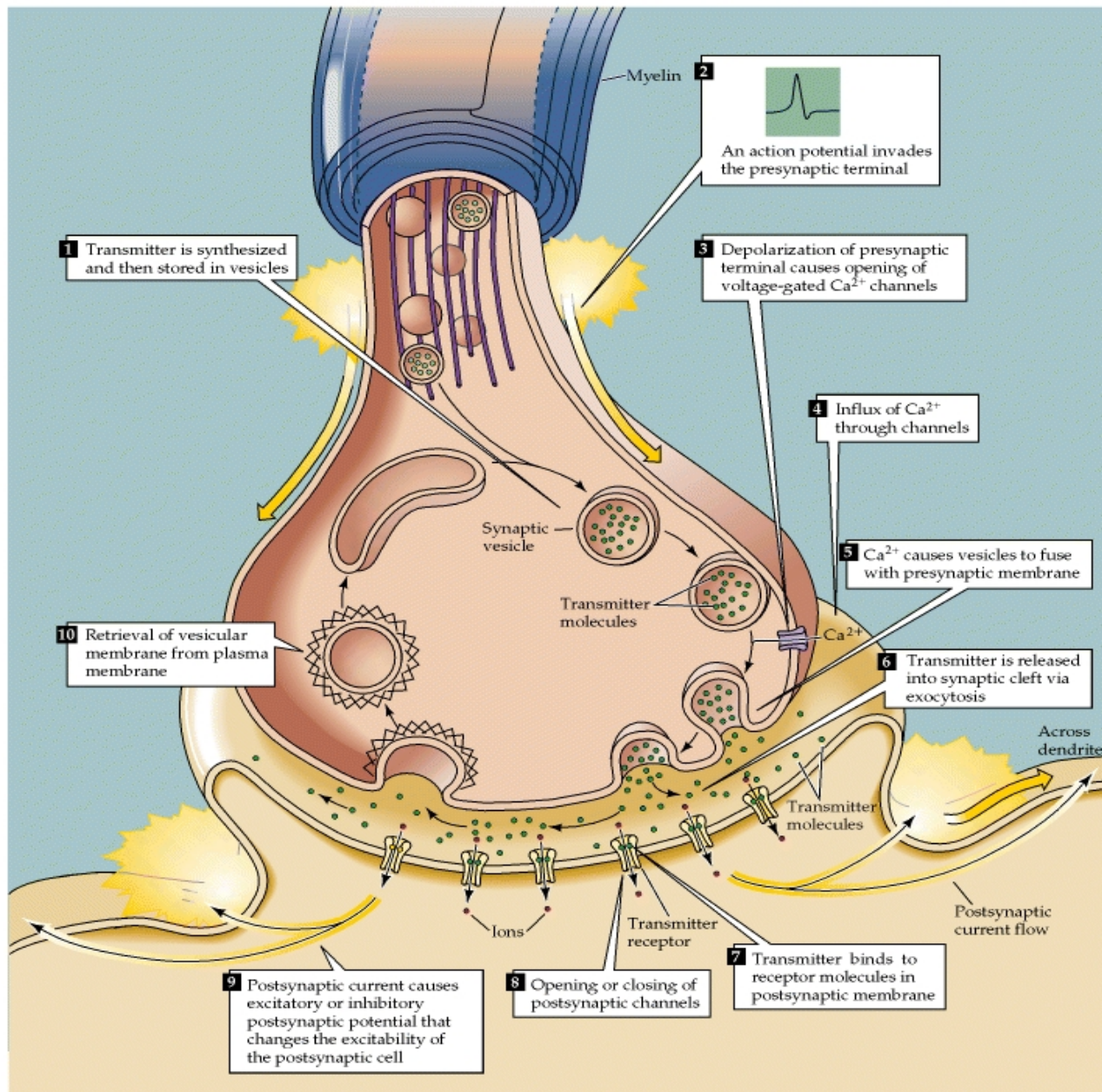
★ Canals iònics / transportadors actius



Purves et al. Neuroscience, 4 ed.

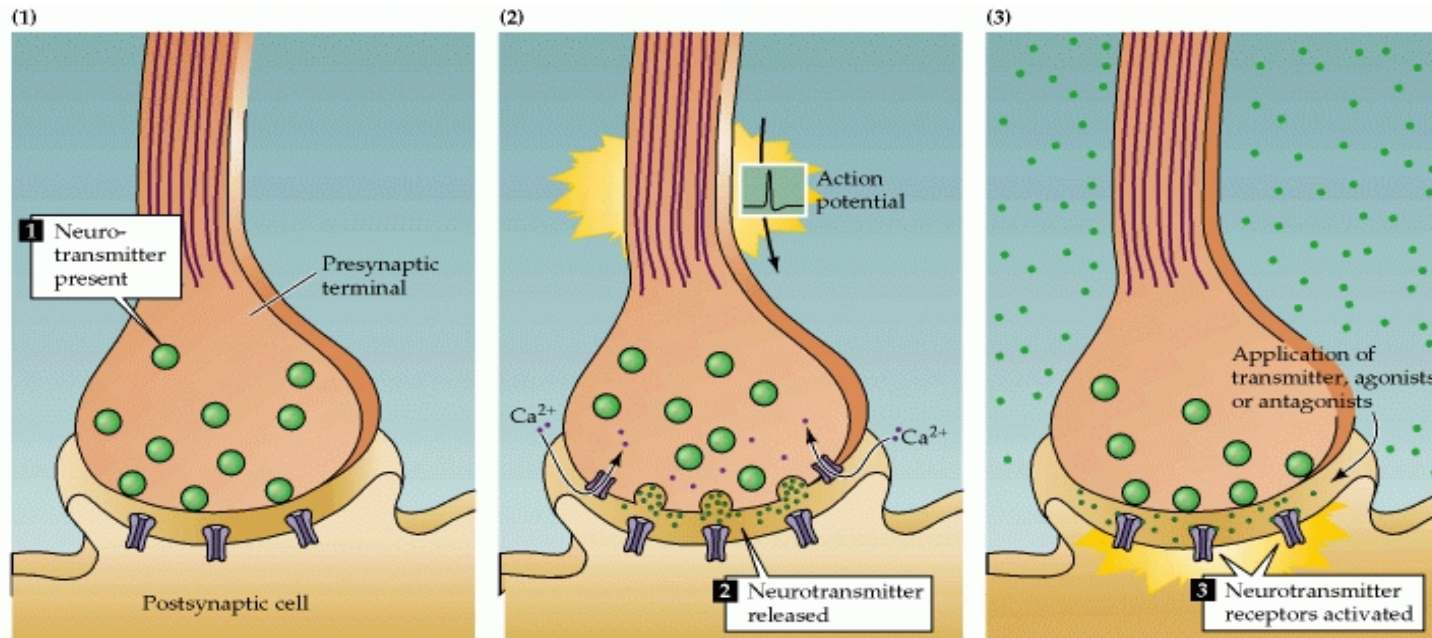
<http://www.sinauer.com/neuroscience4e/animations4.2.html>

Transmissió de senyal a sinapsis químiques



Neurotransmissors

Criteria que defineixen un neurotransmissor



+ de 100 neurotransmissors

- ✓ Molècules: efecte ràpid, activitat poc freqüent
- ✓ Neuropeptids: efecte lent = neuromodulador, activitat molt freqüent
- ✓ 1 neurona més d'1 neurotransmissor, cotransmissors

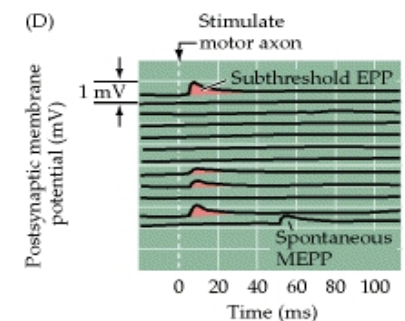
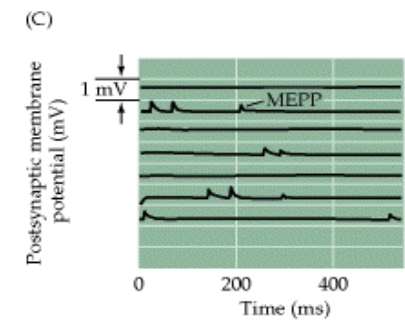
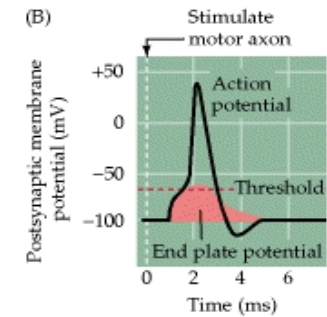
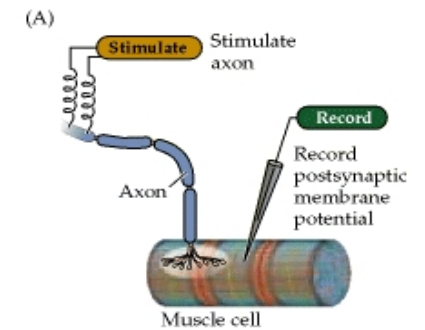
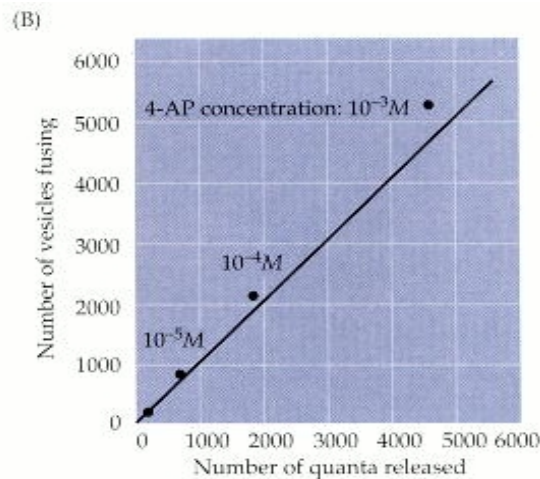
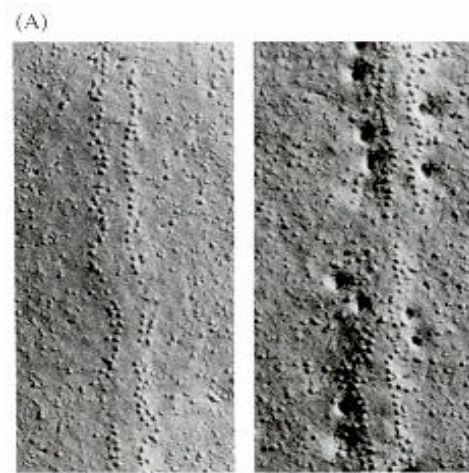
Control de concentració de neurotransmissor a la fenedura sinàptica

Regulació de:

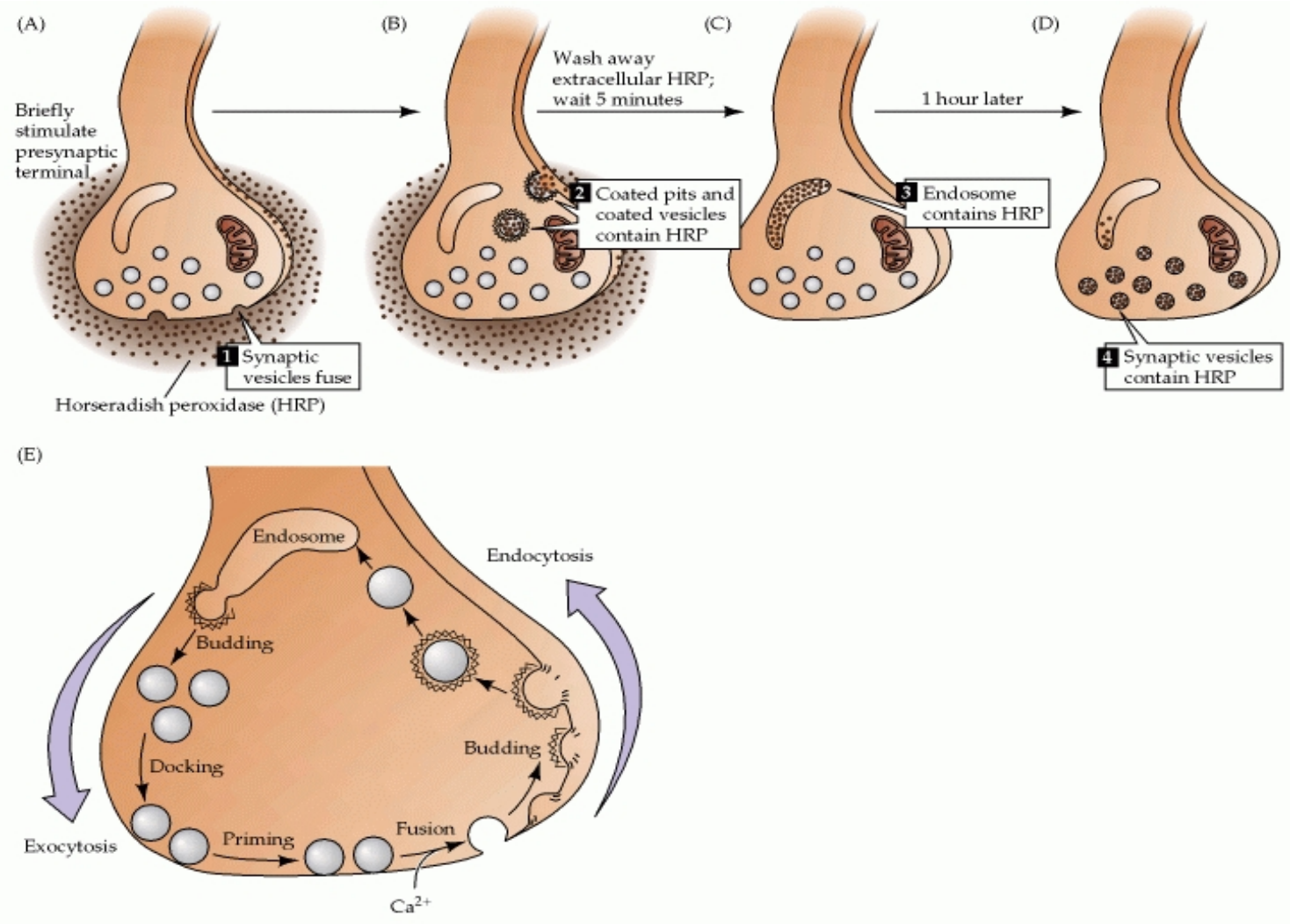
- ✓ Síntesi
- ✓ Empaquetament
- ✓ Alliberament
- ✓ Degradació/neteja
- ✓ Recaptació

Ej. 5HT

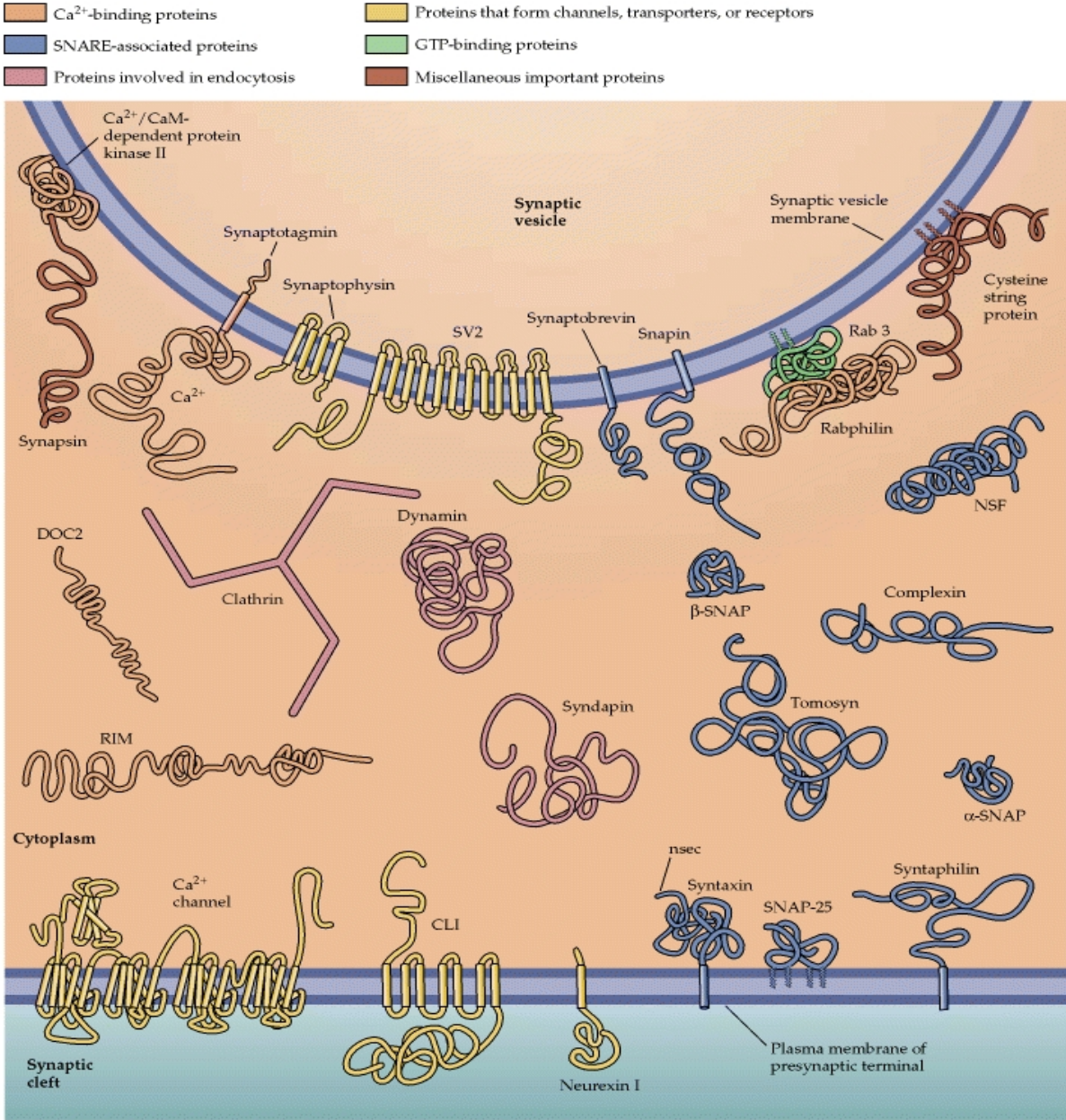
Potencial de acció indueix l'alliberament quàntic de neurotransmissor a través de la fusió de vesícules sinàptiques



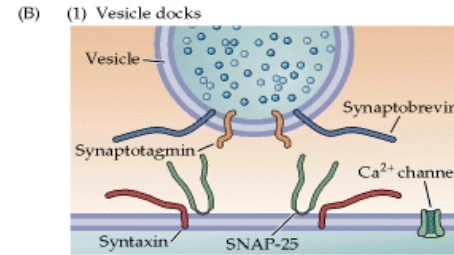
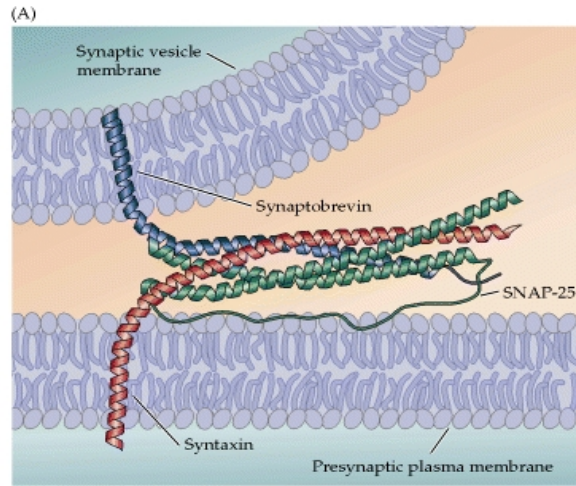
Reciclatge local de neurotransmissors



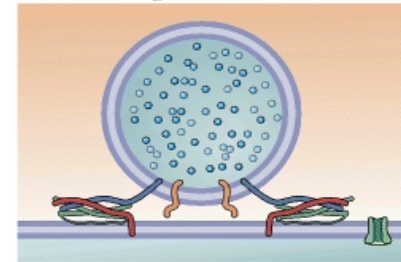
Mecanismes moleculars de la secreció de neurotransmissors



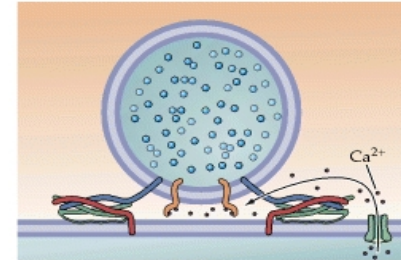
Mecanismes moleculars de la secreció de neurotransissors



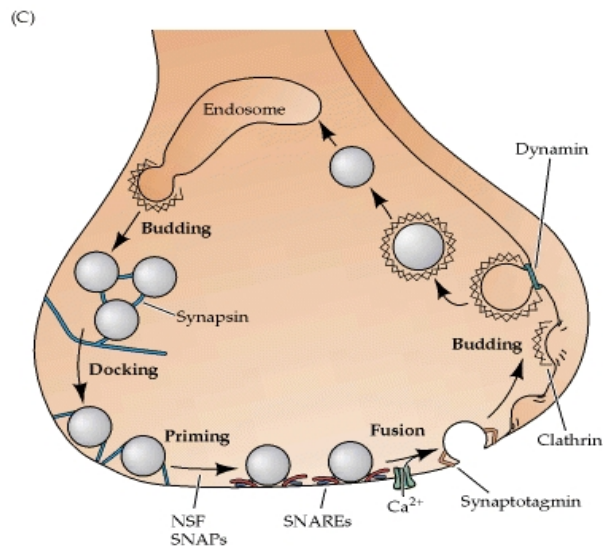
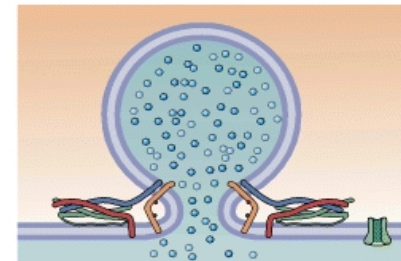
(2) SNARE complexes form to pull membranes together



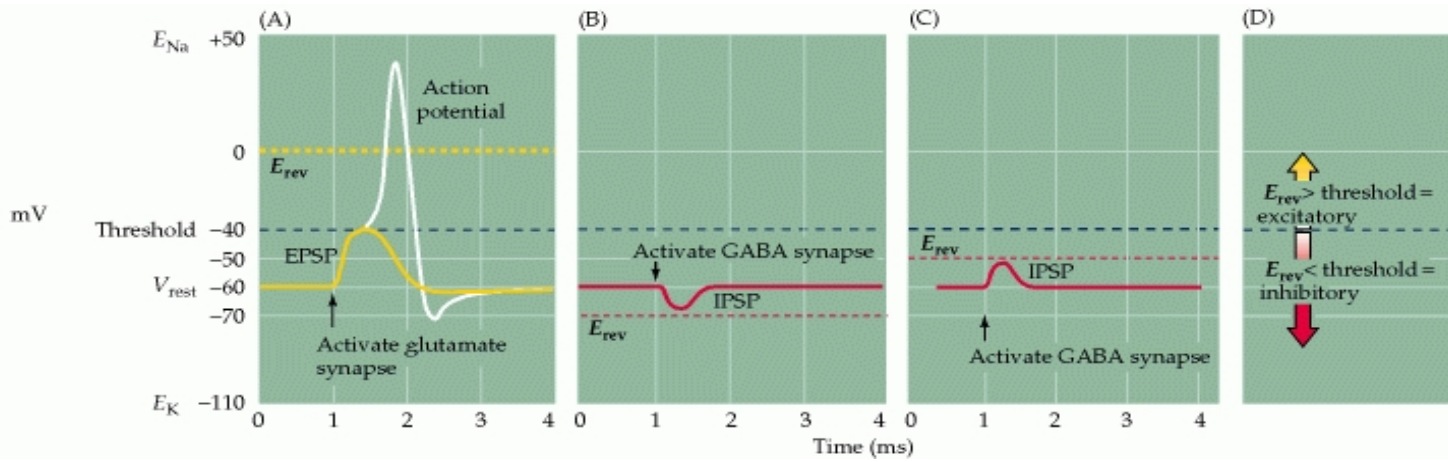
(3) Entering Ca²⁺ binds to synaptotagmin



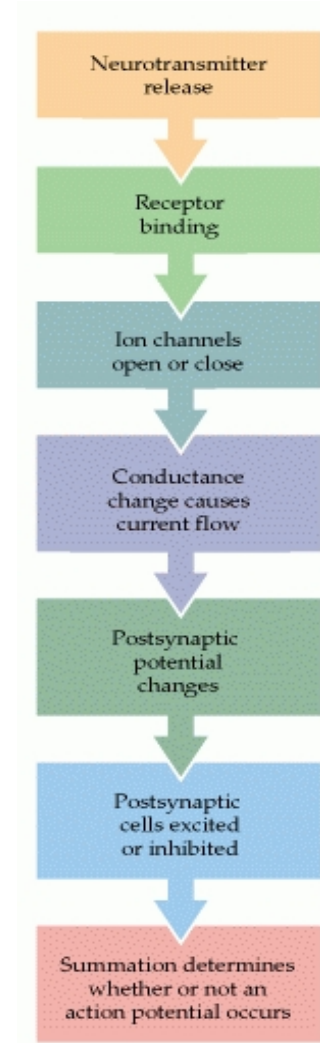
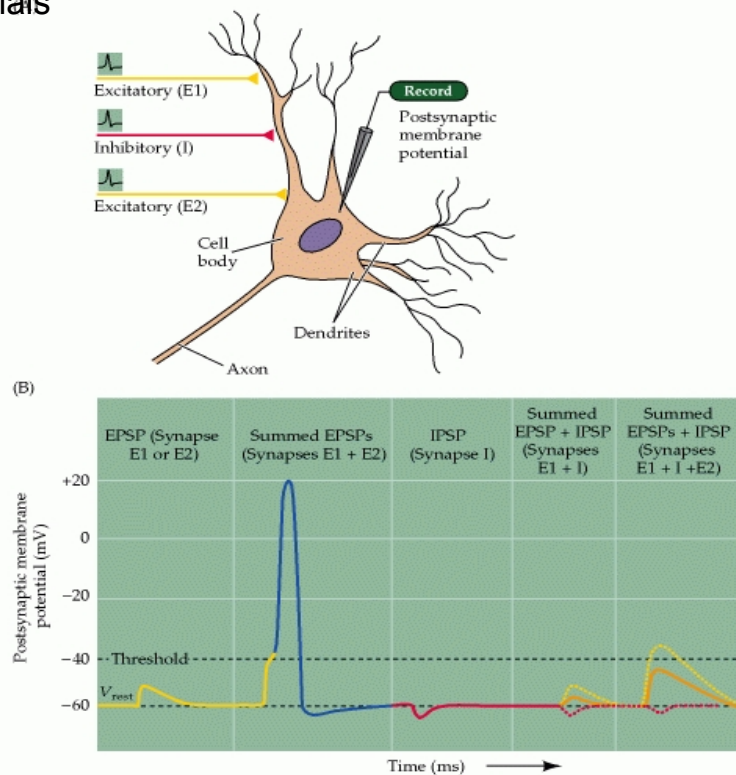
(4) Ca²⁺-bound synaptotagmin catalyzes membrane fusion



Potentials postsinàptics inhibidors i excitadors EPSP i IPSP



Suma de potencials



Purves et al. Neuroscience, 4 ed.

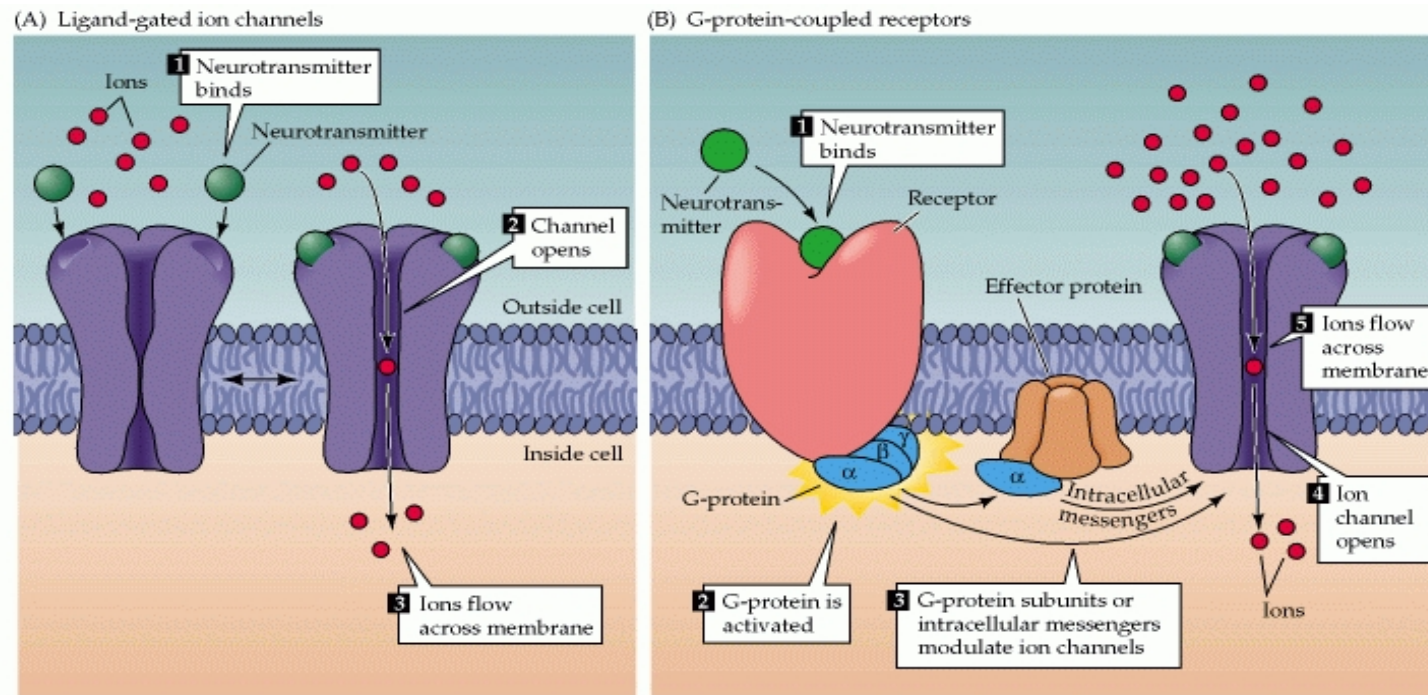
Receptors postsinàptics

✓ Ionotròpics: canals dependents de lligam

Efectes ràpids: msec (Ex. ACh a unió neuromuscular)

✓ Receptors acoblats a proteïnes G: metabotròpics

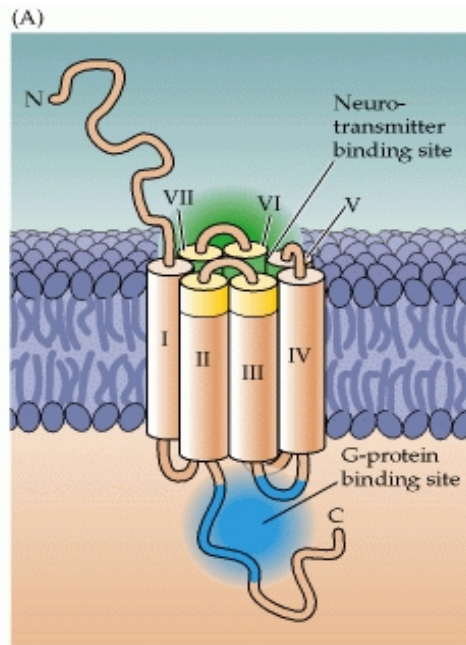
Efectes lents: centenars de msec-min



Purves et al. *Neuroscience*, 4 ed.

Els neurotransmissors i els seus receptors

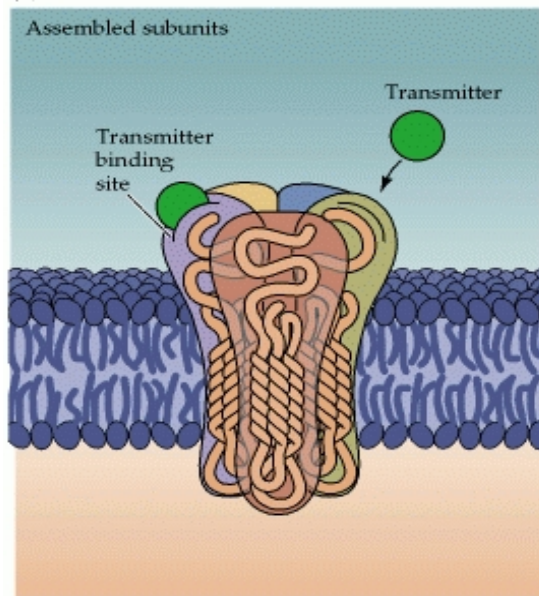
Neurotransmitter	Postsynaptic effect ^a	Precursor(s)	Rate-limiting step in synthesis	Removal mechanism	Type of vesicle
ACh	Excitatory	Choline + acetyl CoA	CAT	AChEase	Small, clear
Glutamate	Excitatory	Glutamine	Glutaminase	Transporters	Small, clear
GABA	Inhibitory	Glutamate	GAD	Transporters	Small, clear
Glycine	Inhibitory	Serine	Phosphoserine	Transporters	Small, clear
Catecholamines (epinephrine, norepinephrine, dopamine)	Excitatory	Tyrosine	Tyrosine hydroxylase	Transporters, MAO, COMT	Small dense-core, or large irregular dense- core
Serotonin (5-HT)	Excitatory	Tryptophan	Tryptophan hydroxylase	Transporters, MAO	Large, dense-core
Histamine	Excitatory	Histidine	Histidine decarboxylase	Transporters	Large, dense-core
ATP	Excitatory	ADP	Mitochondrial oxidative phosphorylation; glycolysis	Hydrolysis to AMP and adenosine	Small, clear
Neuropeptides	Excitatory and inhibitory	Amino acids (protein synthesis)	Synthesis and transport	Proteases	Large, dense-core
Endocannabinoids	Inhibit inhibition	Membrane lipids	Enzymatic modification of lipids	Hydrolysis by FAAH	None
Nitric Oxide	Excitatory and inhibitory	Arginine	Nitric oxid synthase	Spontaneous oxidation	None



(B)

Receptor class	Glutamate	GABA _B	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	GABA _B R1	D1 _A	α1	H1	5-HT 1	A type	M1
	mGlu R1	GABA _B R2	D1 _B	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

(B)

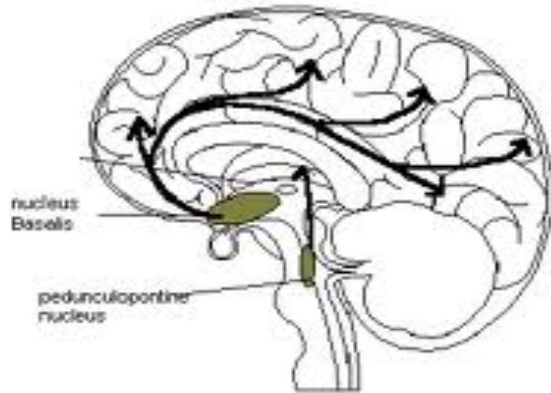


(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α ₁₋₇	α1	α ₂₋₉	5-HT ₃	P _{2X1}
	Glu R2	NR2A	Glu R6	β ₁₋₄	α2	β ₁₋₄		P _{2X2}
	Glu R3	NR2B	Glu R7	γ ₁₋₄	α3	γ		P _{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P _{2X4}
		NR2D	KA2	ε	β			P _{2X5}
				ρ ₁₋₃				P _{2X6}
								P _{2X7}

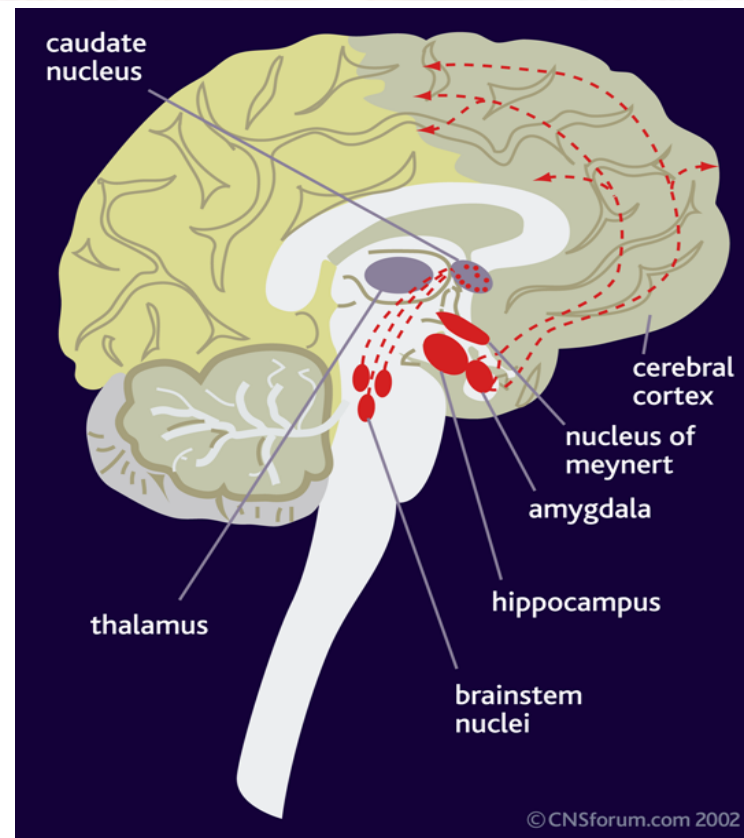
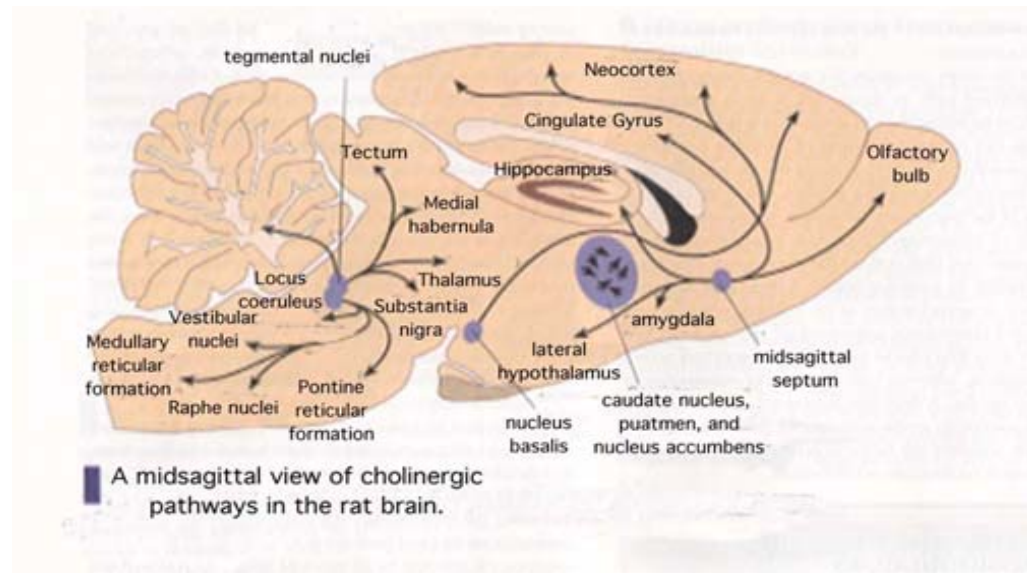
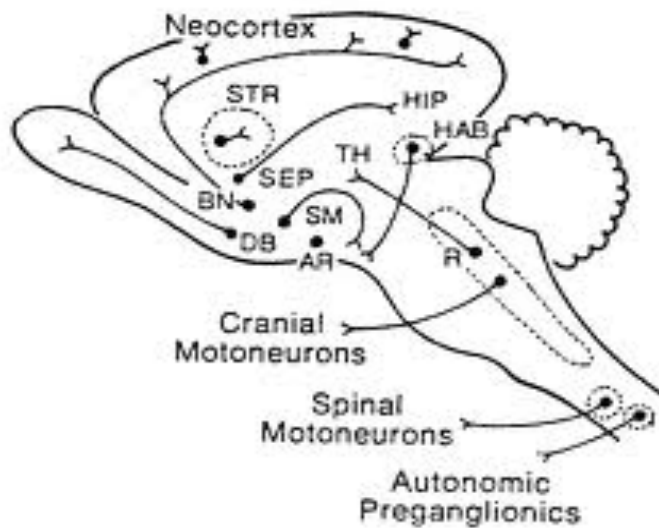
Acetilcolina Distribució

major cholinergic projections

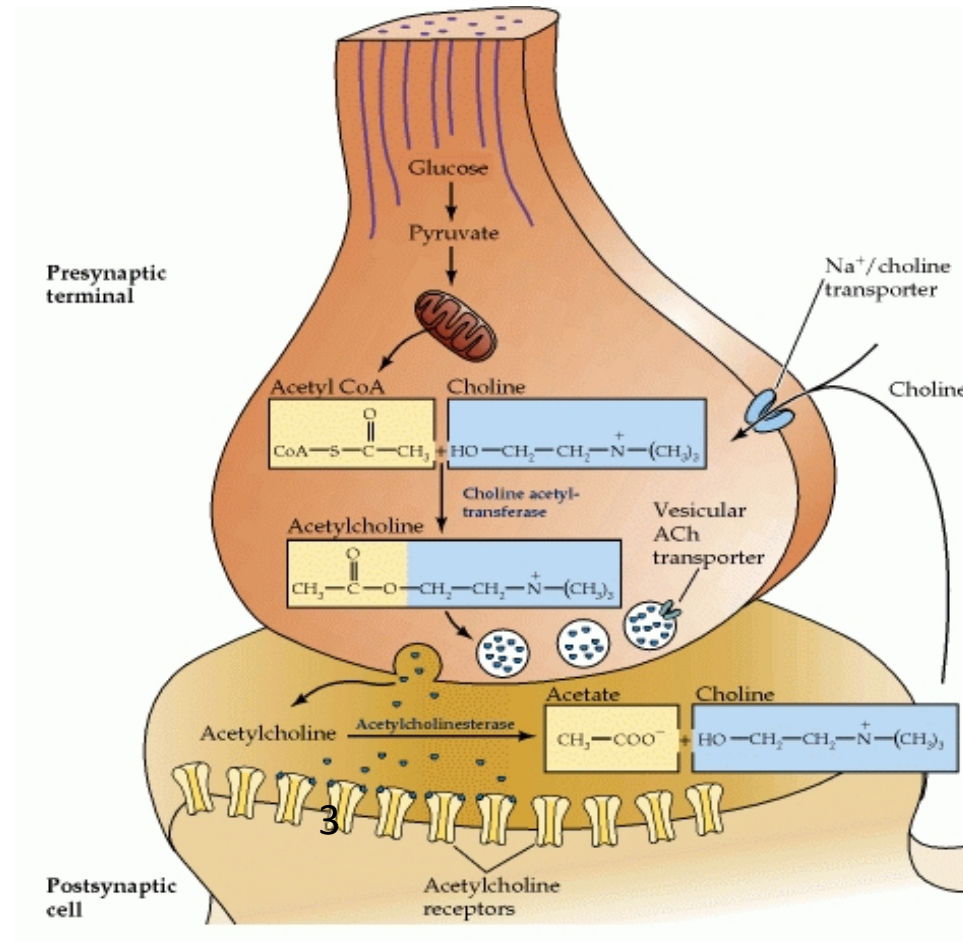


Nucleus basalis projects to the neocortex
PPN projects to the thalamus

ACETYLCHOLINE



Acetilcolina Síntesi

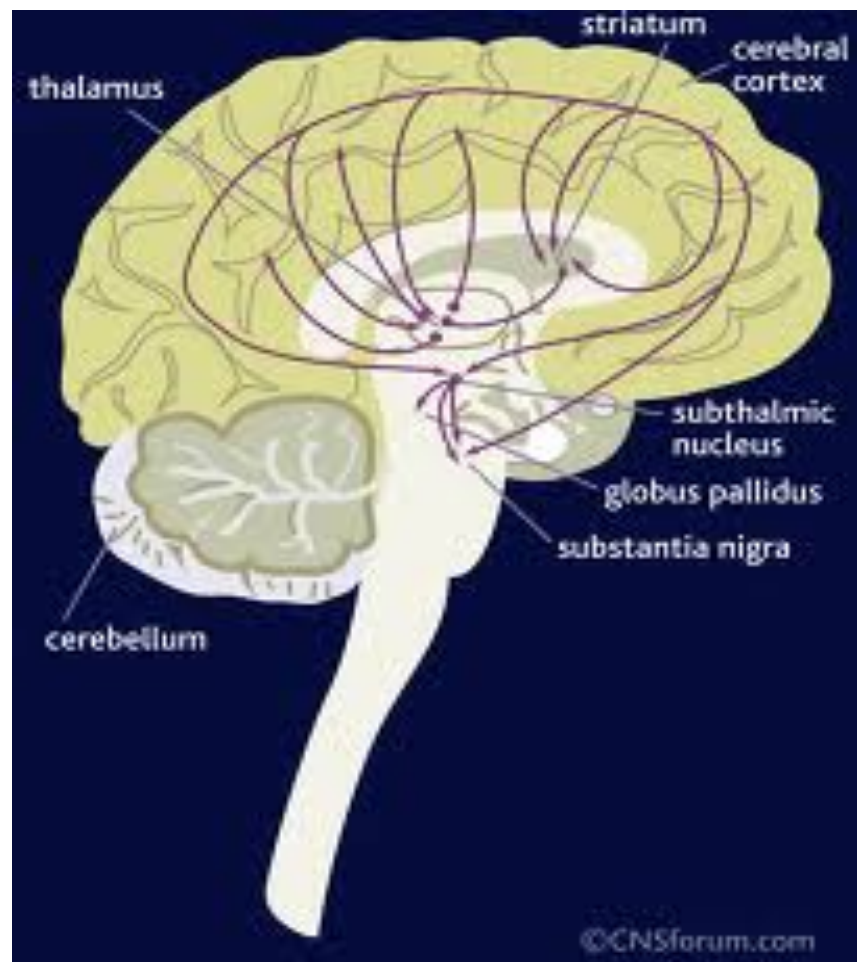


Purves et al. *Neuroscience*, 4 ed.

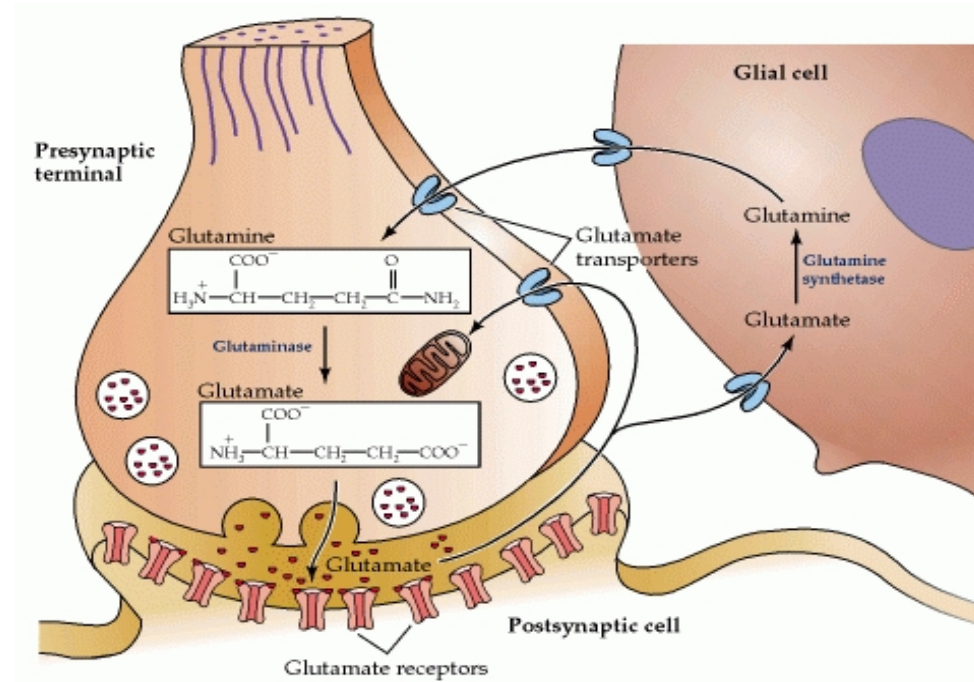
Farmacologia

<http://www.sinauer.com/neuroscience4e/animations6.1.html>

Glutamat Distribució



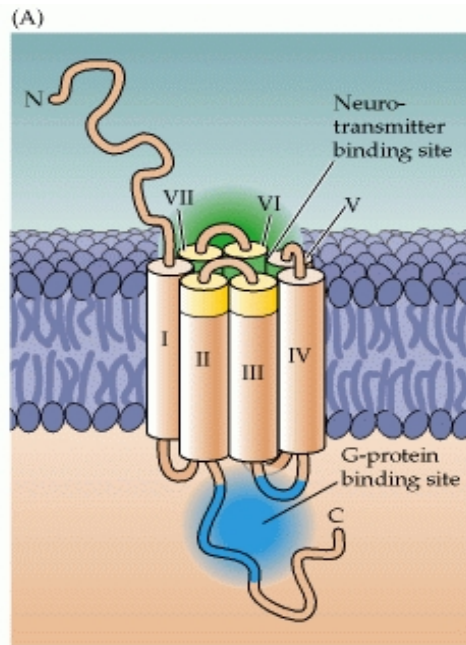
Glutamat Síntesi



Purves et al. *Neuroscience*, 4 ed.

Farmacologia

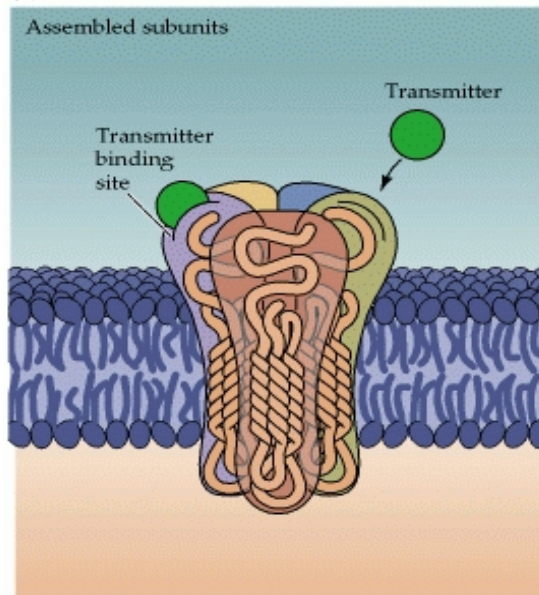
<http://www.sinauer.com/neuroscience4e/animations6.2.html>



(B)

Receptor class	Glutamate	GABA _B	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	GABA _B R1	D1 _A	α1	H1	5-HT 1	A type	M1
	mGlu R1	GABA _B R2	D1 _B	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

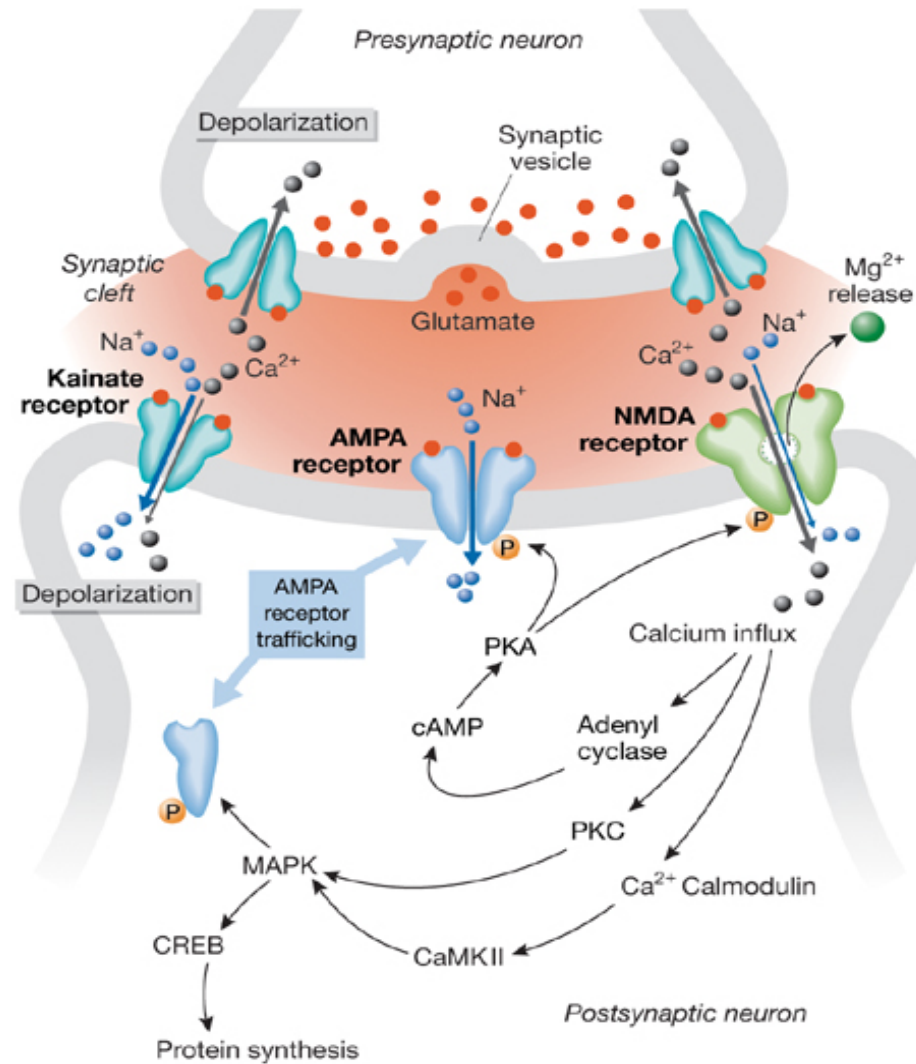
(B)



(C)

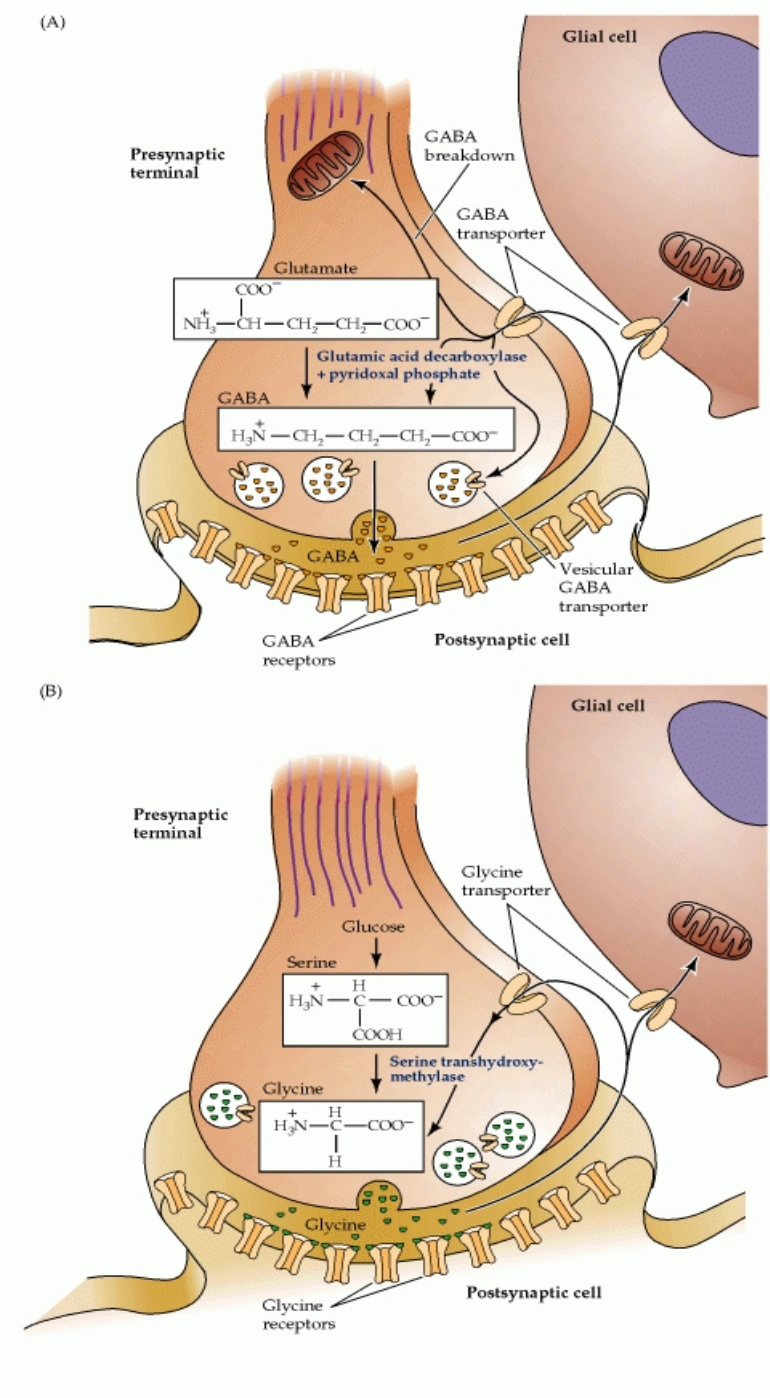
Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α ₁₋₇	α1	α ₂₋₉	5-HT ₃	P _{2X1}
	Glu R2	NR2A	Glu R6	β ₁₋₄	α2	β ₁₋₄		P _{2X2}
	Glu R3	NR2B	Glu R7	γ ₁₋₄	α3	γ		P _{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P _{2X4}
		NR2D	KA2	ε	β			P _{2X5}
				ρ ₁₋₃				P _{2X6}
								P _{2X7}

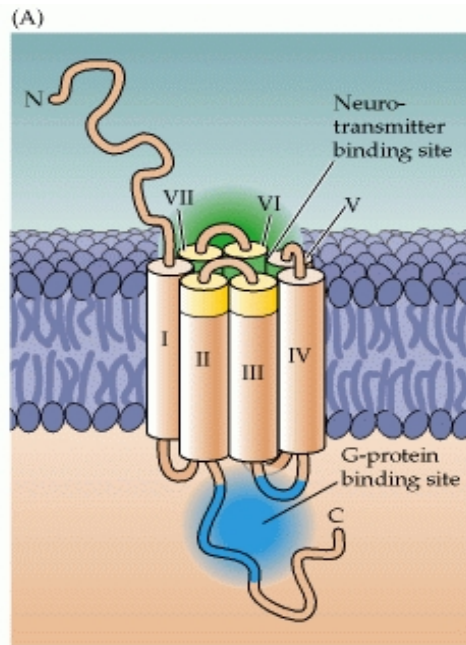
Glutamat Farmacologia



Excitotoxicitat

GABA, Glicina Síntesi

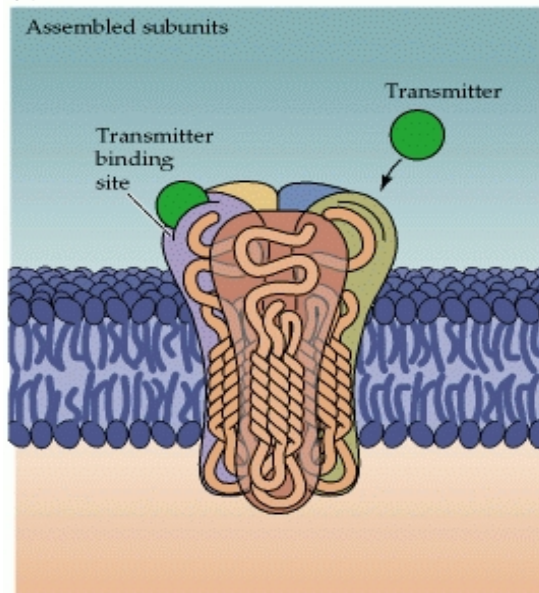




(B)

Receptor class	Glutamate	GABA _B	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	GABA _B R1	D1 _A	α1	H1	5-HT 1	A type	M1
	mGlu R1	GABA _B R2	D1 _B	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

(B)



(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α ₁₋₇	α1	α ₂₋₉	5-HT ₃	P _{2X1}
	Glu R2	NR2A	Glu R6	β ₁₋₄	α2	β ₁₋₄		P _{2X2}
	Glu R3	NR2B	Glu R7	γ ₁₋₄	α3	γ		P _{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P _{2X4}
		NR2D	KA2	ε	β			P _{2X5}
				ρ ₁₋₃				P _{2X6}
								P _{2X7}

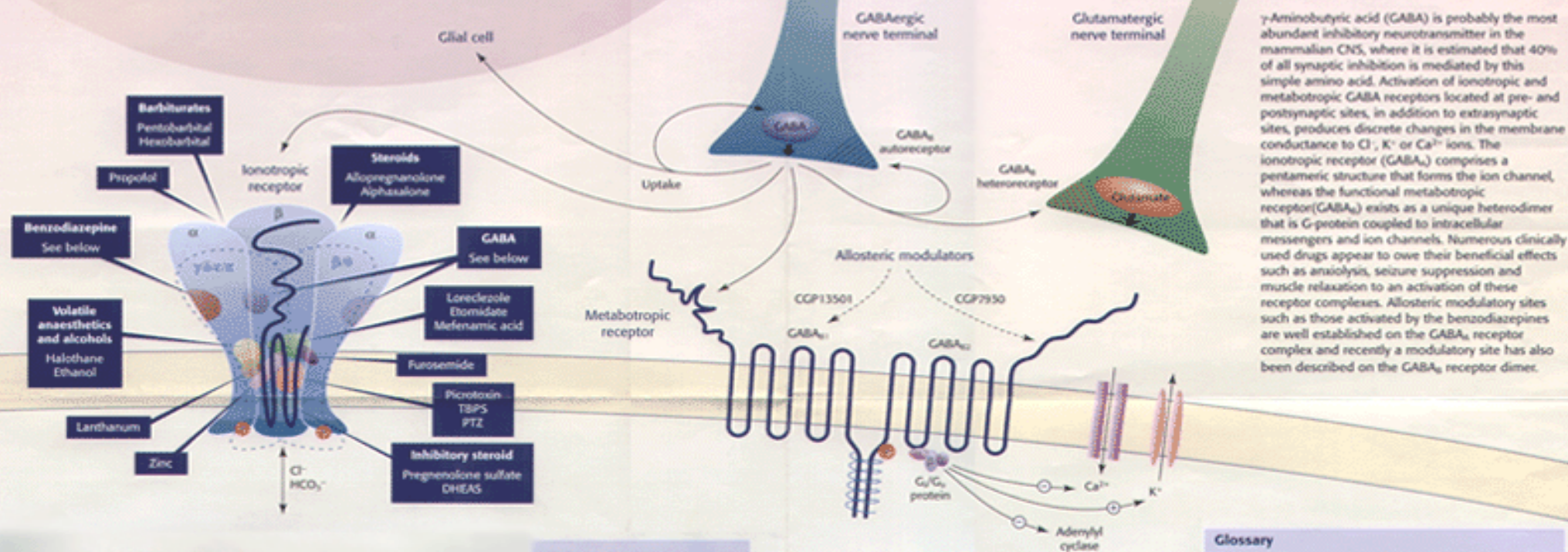
The GABA Receptors

Norman Bowery, Paul Whiting and Keith Wafford

TOCRIS

TOCRIS Cookson Inc.
Tel: +44 (0)117 962 6551
Fax: +44 (0)117 962 6552
customerservice@tocris.co.uk

Neurochemicals • Pharmacological Probes • Peptide
Signal Transduction Agents • Biochemicals • Radioligands
Advancing Research for the Life Scientist



γ -Aminobutyric acid (GABA) is probably the most abundant inhibitory neurotransmitter in the mammalian CNS, where it is estimated that 40% of all synaptic inhibition is mediated by this simple amino acid. Activation of ionotropic and metabotropic GABA receptors located at pre- and postsynaptic sites, in addition to extrasynaptic sites, produces discrete changes in the membrane conductance to Cl^- , K^+ or Ca^{2+} ions. The ionotropic receptor (GABA_A) comprises a pentameric structure that forms the ion channel, whereas the functional metabotropic receptor (GABA_B) exists as a unique heterodimer that is G-protein coupled to intracellular messengers and ion channels. Numerous clinically used drugs appear to owe their beneficial effects such as anxiolysis, seizure suppression and muscle relaxation to an activation of these receptor complexes. Allosteric modulatory sites such as those activated by the benzodiazepines are well established on the GABA_A receptor complex and recently a modulatory site has also been described on the GABA_B receptor dimer.

GABA_A postsynaptic receptor

Structure

Pentameric arrangement of subunits (4TM) to form anionic channel. A family of subunits exist each with unique anatomical distributions: α 1-6, β 1-3, γ 1-3, δ , ϵ , κ , θ . Several subunits are alternatively spliced (e.g. γ 2, β 2). Subunit composition determines pharmacology (e.g. γ 2 confers benzodiazepine sensitivity).

GABA site

Agonists

* GABA, * muscimol, * isoguvacine, * THIP, PHS.

Antagonists/inverse agonists

* bicuculline, gabazine.

Benzodiazepine site

Agonists

diazepam, flunitrazepam, * zolpidem.

Antagonists

* flumazenil.

Inverse agonists

DMCM, β -CCM.

GABA_C postsynaptic receptor

Structure

Subfamily of GABA_A receptors. Similar structure to GABA_A anionic channel. Homo- or heteromeric arrangement composed of ρ 1-3.

Agonists

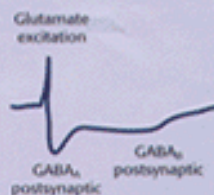
* CACA, * GABA, * isoguvacine.

Antagonists

APMPA, * TPMPA.

Typical synaptic event

GABA_B presynaptic activation can reduce all three membrane events



GABA_B postsynaptic receptor presynaptic autoreceptor and heteroreceptor

Structure

7TM heterodimer comprising GABA_{B1} (6 isoforms 1a-1f) plus GABA_{B2} (35% homology with GABA_{B1}).

Agonists

* (-) baclofen, CGP44532, APMA, APMPA.

Antagonists

* saclofen, * phaclofen, * CGP55348, CGP56742, * CGP46381, * CGP55845A, CGP62349, * CGP54626, * SCH50911.

Allosteric modulators

* CGP7930, * CGP13501, GS39783.

TRENDS

hosted online by
Blackwell Science

For subscription information, contact our subscription department by email, fax, telephone or e-mail.
Current Issue, Subscription Department,
PO Box 231, Osney Mead, Oxford, UK, OX2 0EL,
Tel: +44 (0)1865 475 600, Fax: +44 (0)1865 441 425,
e-mail: it.subscriptions@oxon.blackwell-science.com

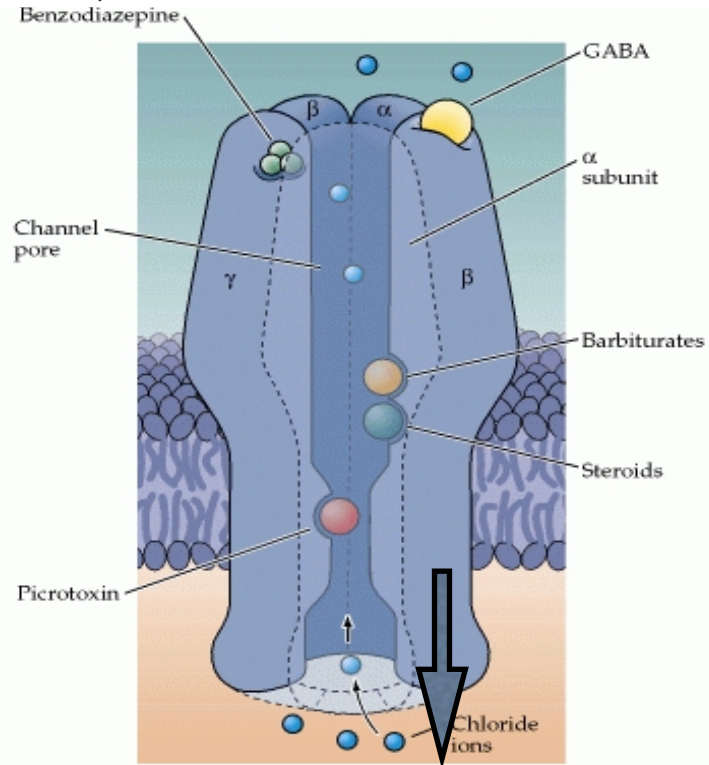
Dr P.J. Whiting and Dr K.A. Wafford
Neuroscience Research Centre
Merrill Sharp and Doherty Research Laboratories
Salford Park, Eastwick Road,
Harlow, Essex, UK, CM20 2QR
e-mail: paul.whiting@merrill.com
e-mail: keith.wafford@merrill.com

Prof. N.G. Bowery
Department of Pharmacology
The Medical School
Edgbaston
Birmingham, UK, B15 2TT
e-mail: n.g.bowery@pharm.ac.uk

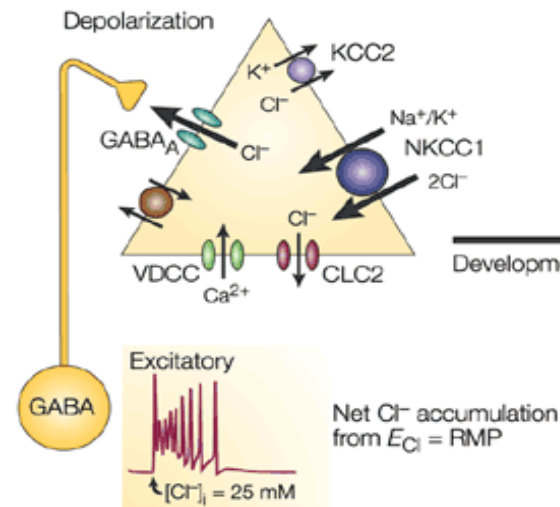
Glossary

APMPA	3-Aminopropyl(methyl)phosphonic acid
APMA	3-Amino-propyl phosphonic acid
β -CCM	β -Carboline methyl ester
CACA	cis-4-Aminocrotonic acid
CGP13501	3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2,2-dimethyl-propionamide
CGP35348	3-Amino-propyl-diethylmethyl phosphonic acid
CGP36742	3-Amino-propyl-n-butyl phosphonic acid
CGP44532	(S)-2-Hydroxy-3-aminopropyl(methyl) phosphonic acid
CGP46381	3-Amino-propyl(cyclohexylmethyl) phosphonic acid
CGP54626	(3-N)-((S)-3,4-Dichlorophenyl)methylamino-2-(S)-hydroxypropyl-cyclohexylmethyl phosphonic acid
CGP55845	(3-N)-((S)-3,4-Dichlorophenyl)methylamino-2-(S)-hydroxypropyl-benzyl phosphonic acid
CGP62349	3-(1-(R)-2-(S)-Hydroxy-3-hydroxy-(4-methoxy-benzyl)-phosphonyl-propylamino)ethyl benzoic acid
CGP7930	2,6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol dehydroepiandrosterone sulfate
DHEAS	Methyl 6,7-dimethoxy-4-ethyl- β -carboline-3-carboxylate
DMCM	2-(3-Carboxypropyl)-3-amino-6-(4-methoxyphenyl)-pyridinium bromide
Gabazine (SR 95531)	N,N'-Dicyclohexyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine
GS39783	Piperidine-4-sulfonic acid
PHS	Phenylsarcosine
PTZ	(+)-(S)-5,5-Dimethylmorpholine-2-acetic acid
SCH-50911	1-Butylbicyclohexylphosphonate
TBPS	4,5,6,7-Tetrahydrooxazolo[5,4-g]pyridin-3-yl
THIP	(1,2,5,6-Tetrahydropyridine-4-yl)methylphosphonic acid
TPMPA	Phosphorylation site
*	Available from TOCRIS
TM	Transmembrane

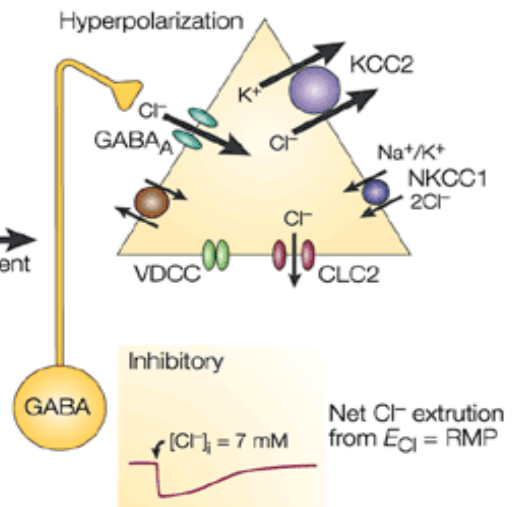
GABA, Glicina



a High $[Cl^-]_i$ (immature)

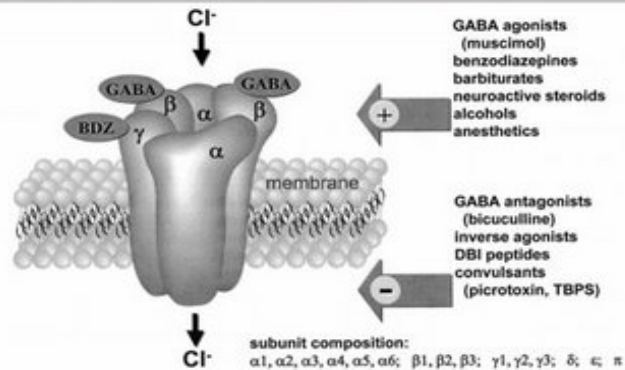


b Low $[Cl^-]_i$ (mature)

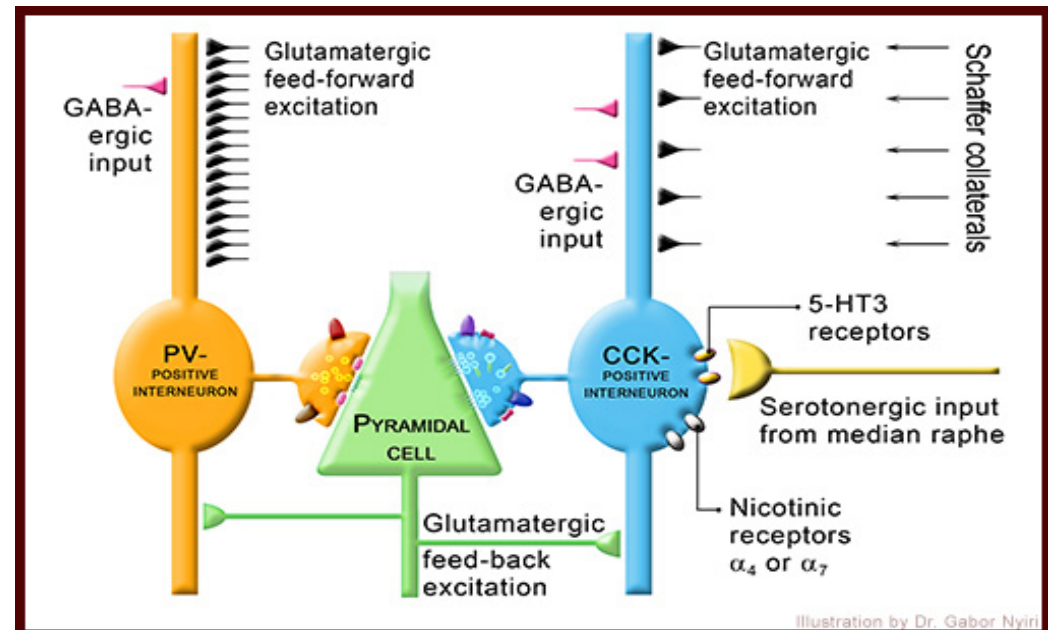
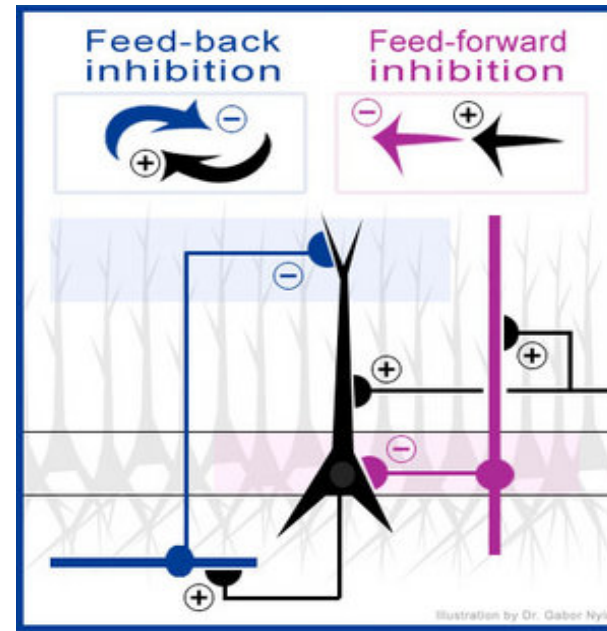
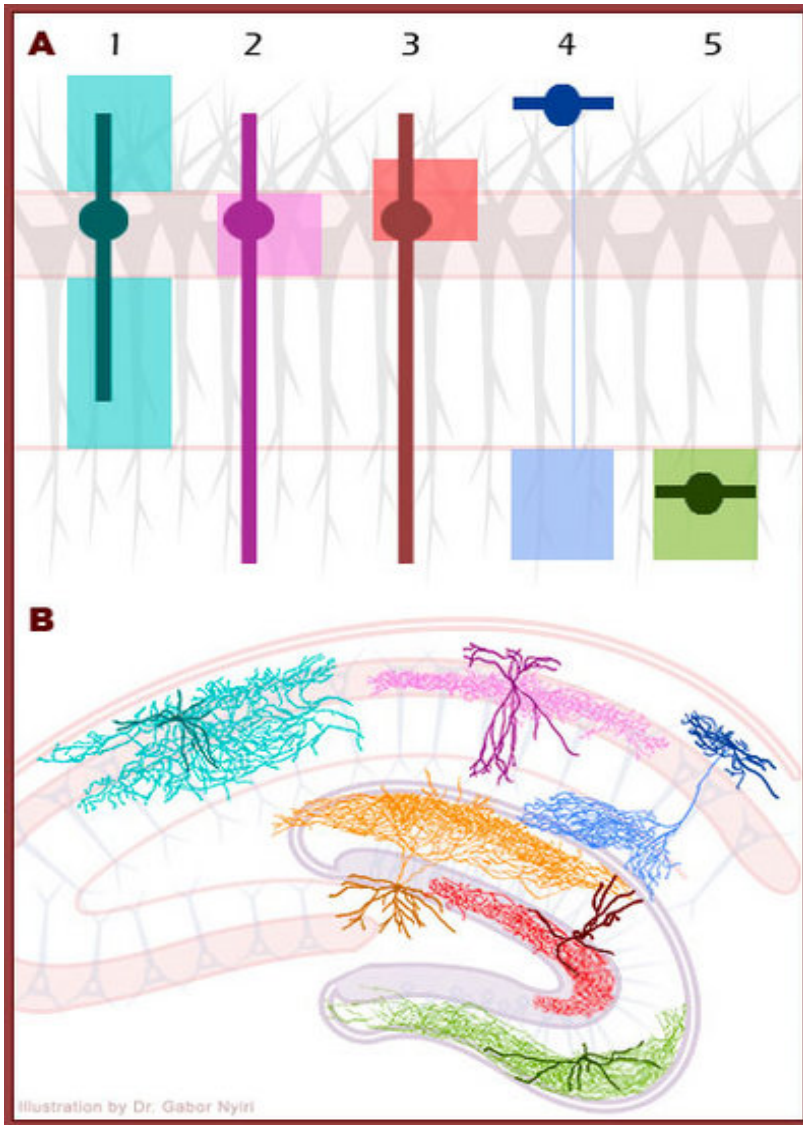


Nature Reviews | Neuroscience

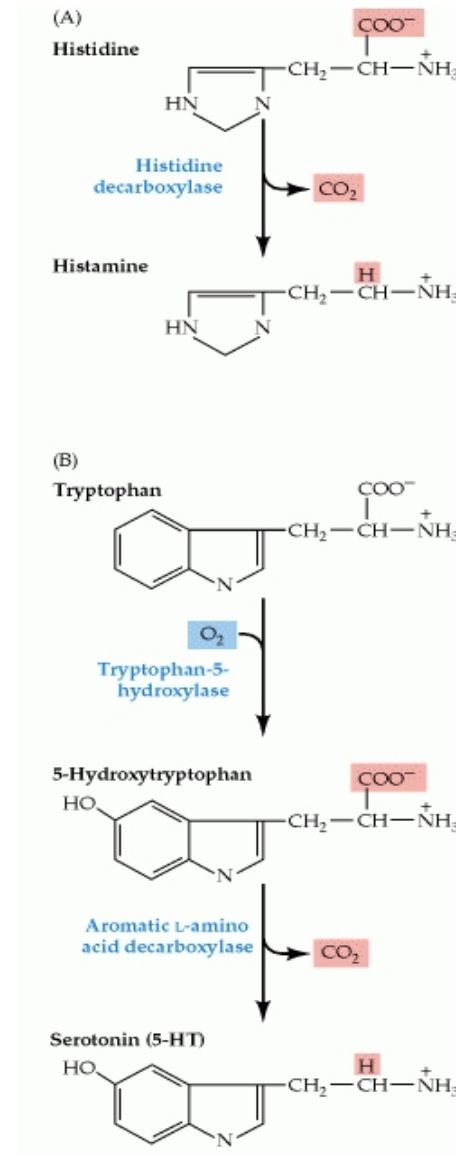
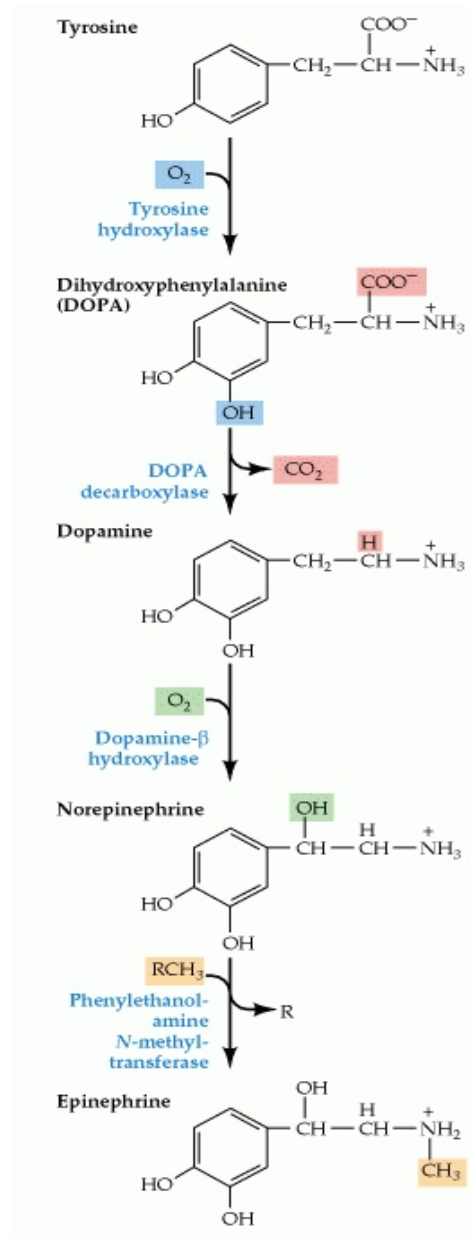
CANALES IÓNICOS: COMPLEJO DEL ÁCIDO GAMMA AMINO BUTÍRICO (GABA)



GABA, Glicina Interneurones

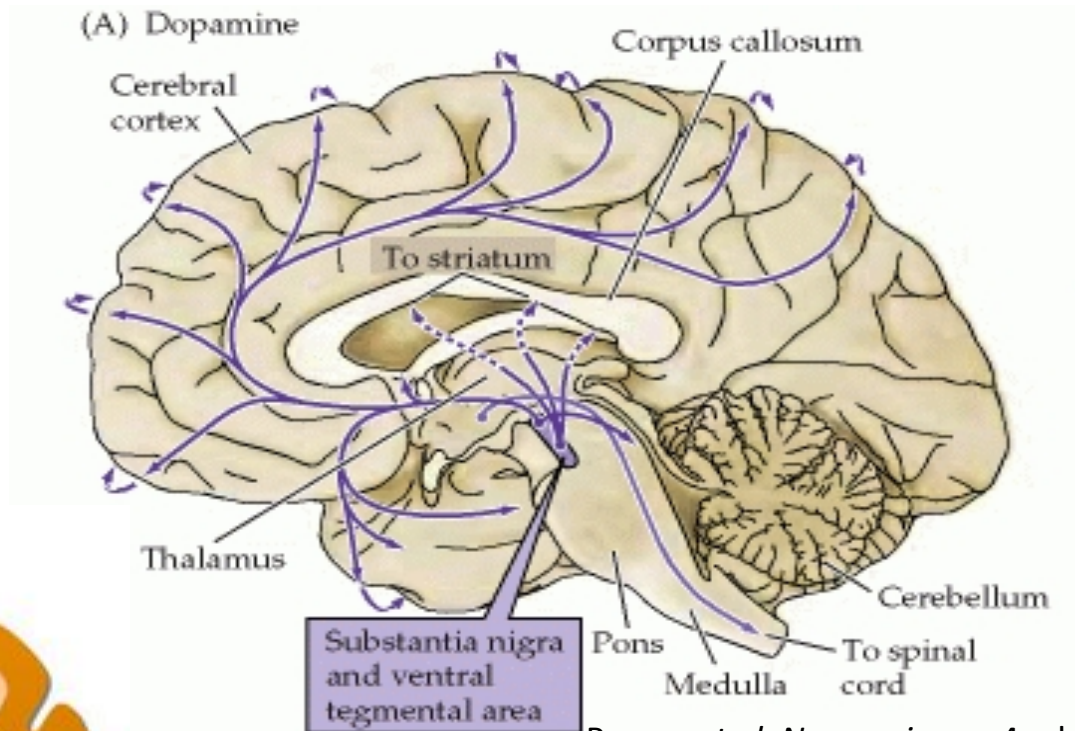


Amines biogéniques

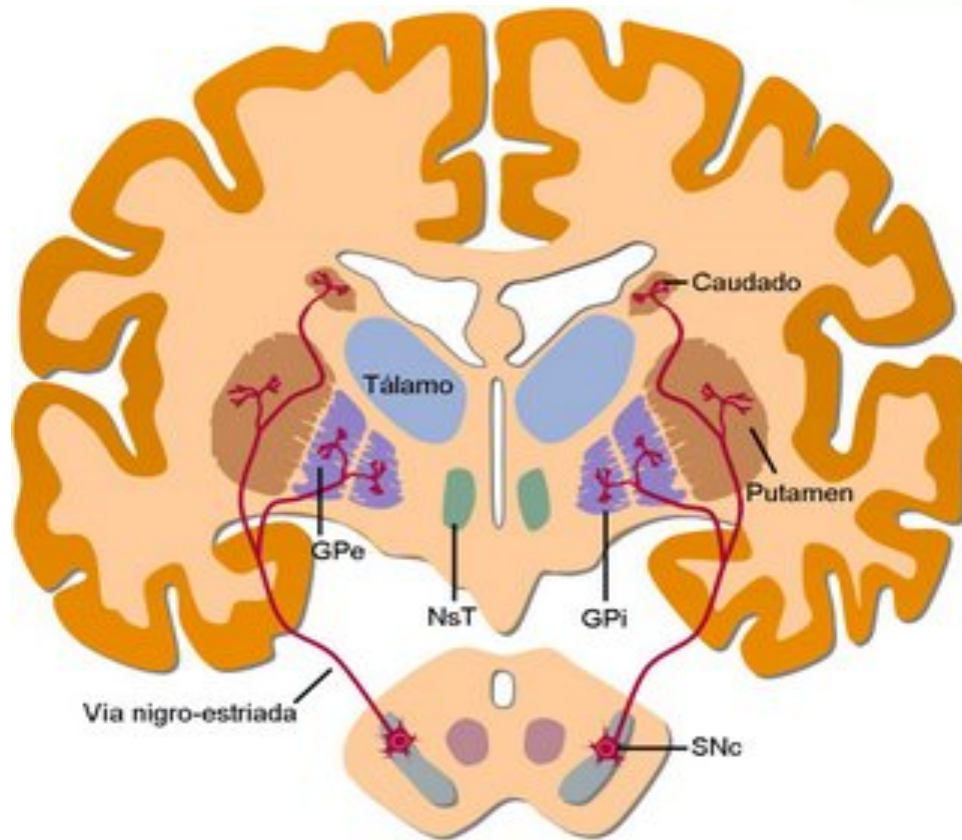


Amines biogèniques

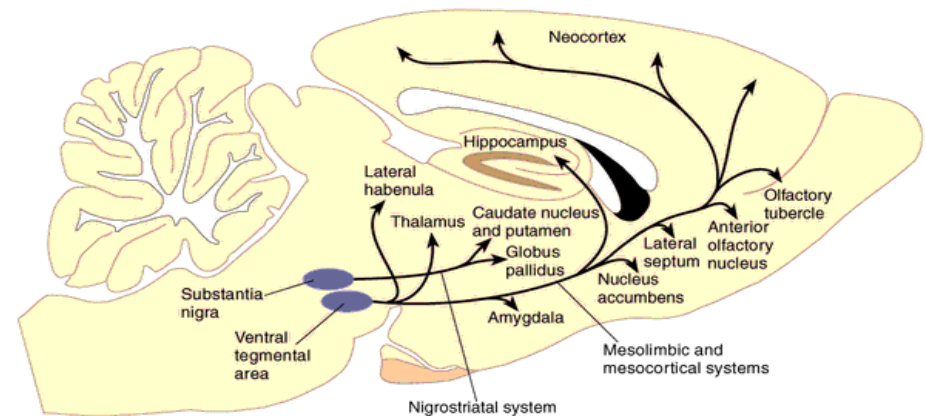
Dopamina



Purves *et al.* Neuroscience, 4 ed.



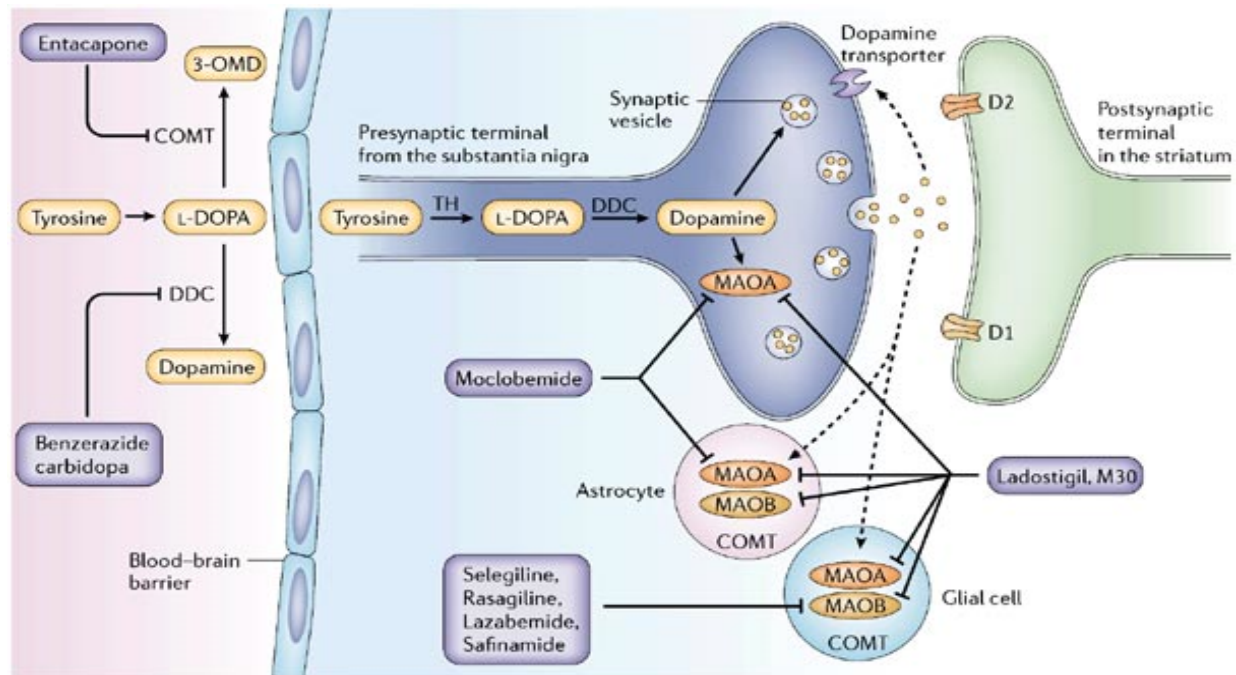
► Schematic Midsagittal Section of a Rat Brain, Showing the Locations of the Most Important Groups of Dopaminergic Neurons and the Distribution of Their Axons and Terminal Buttons

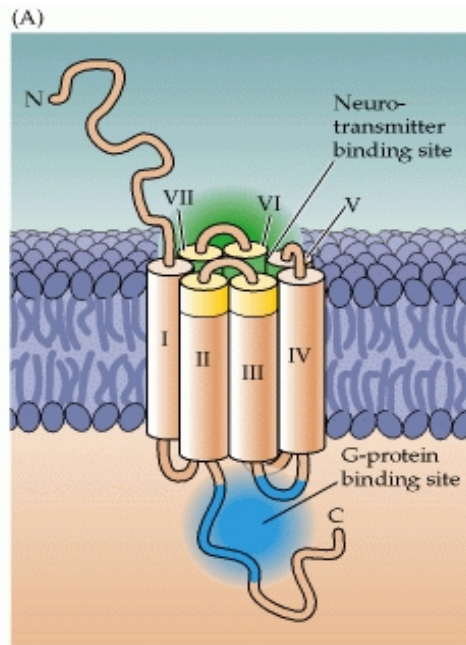


Amines biogèniques

Dopamina

<http://www.sinauer.com/neuroscience4e/animations6.3.html>

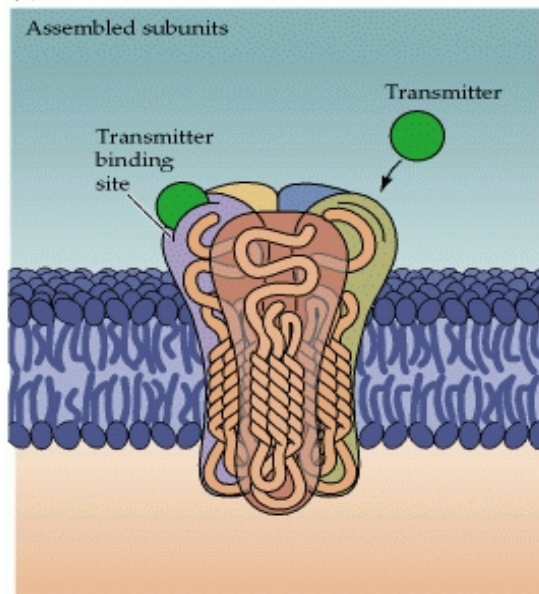




(B)

Receptor class	Glutamate	GABA _B	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	GABA _B R1	D1 _A	α1	H1	5-HT 1	A type	M1
	mGlu R1	GABA _B R2	D1 _B	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

(B)



(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α ₁₋₇	α1	α ₂₋₉	5-HT ₃	P _{2X1}
	Glu R2	NR2A	Glu R6	β ₁₋₄	α2	β ₁₋₄		P _{2X2}
	Glu R3	NR2B	Glu R7	γ ₁₋₄	α3	γ		P _{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P _{2X4}
		NR2D	KA2	ε	β			P _{2X5}
				ρ ₁₋₃				P _{2X6}
								P _{2X7}



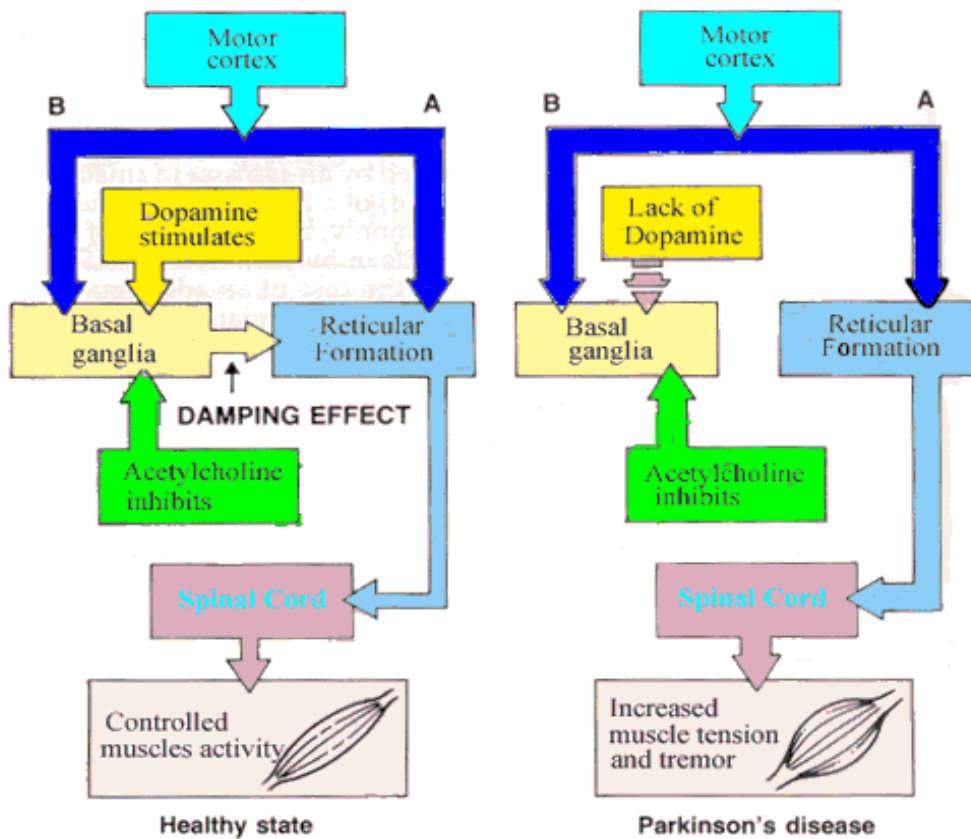
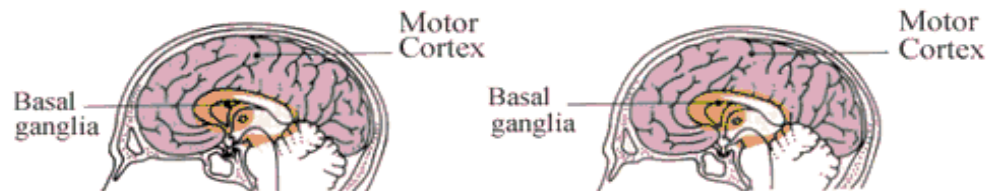
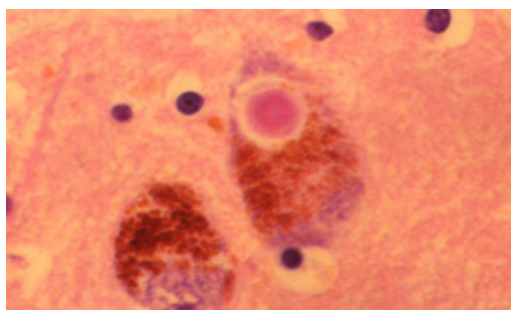
Sección de corte de la parte media del cerebro donde es visible una porción de la sustancia negra



Disminución de la sustancia negra como se observa en el mal de Parkinson

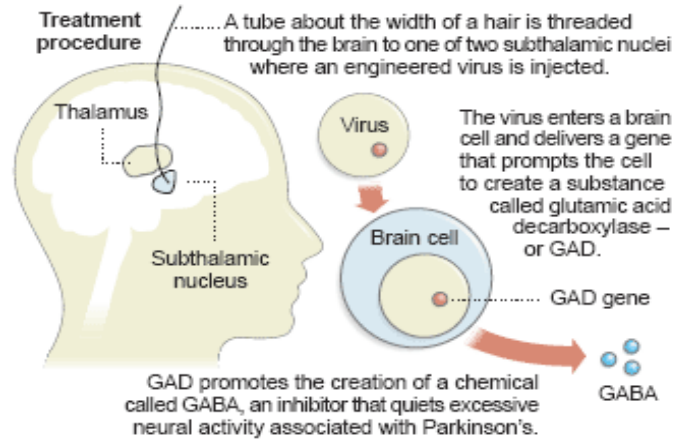


ADAM



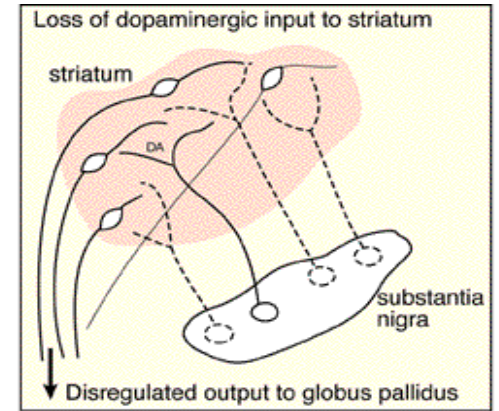
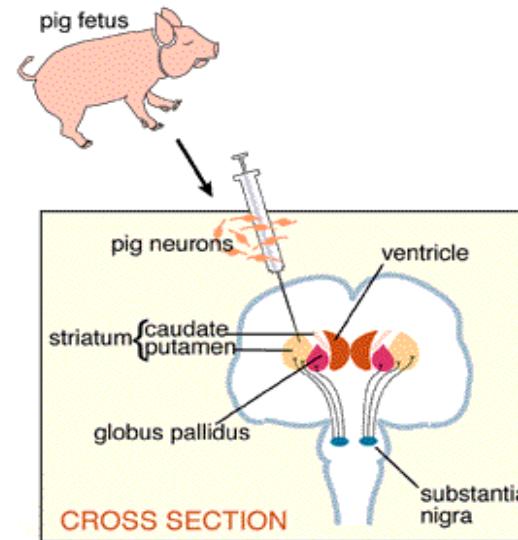
New step in Parkinson's treatment

Preliminary evidence suggests that an experimental gene therapy procedure could ease Parkinson's symptoms with no side effects.

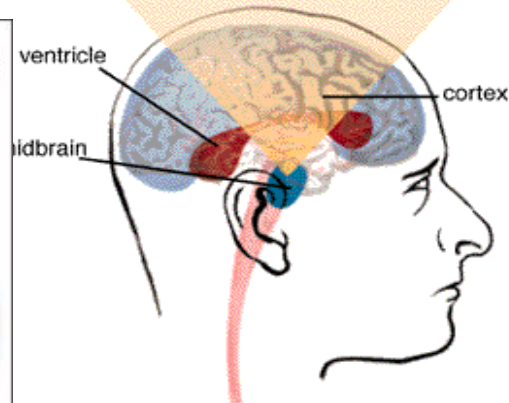
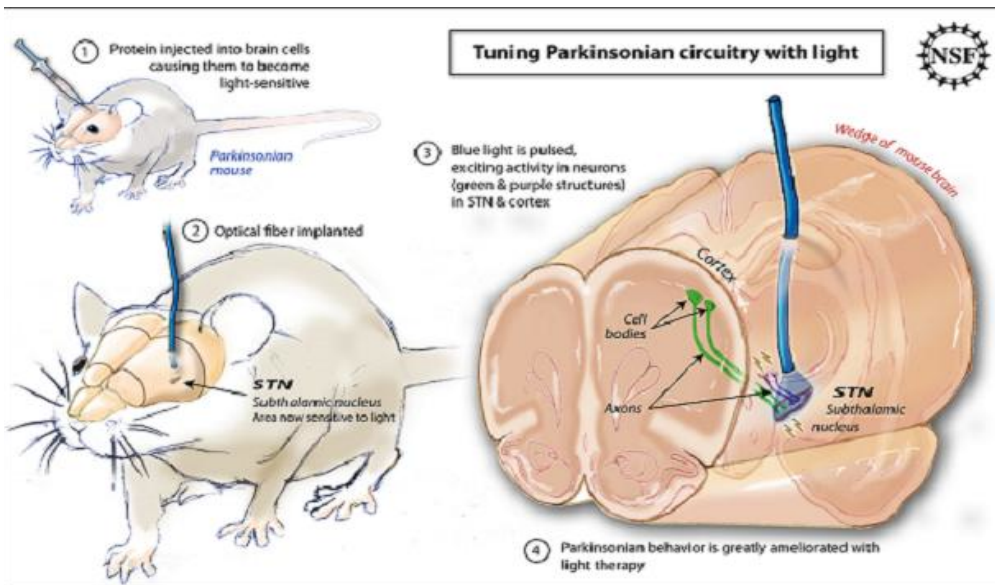
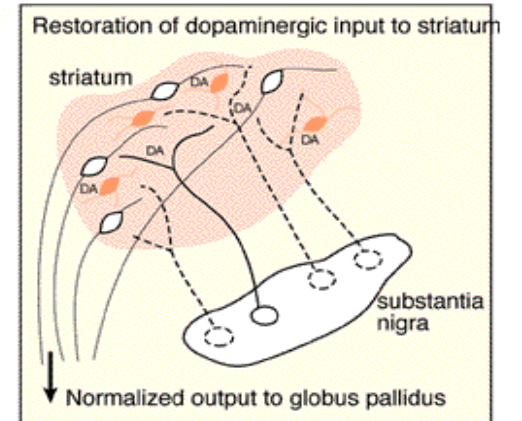


SOURCE: NewYork-Presbyterian Hospital-Weill Cornell Medical Center

AP

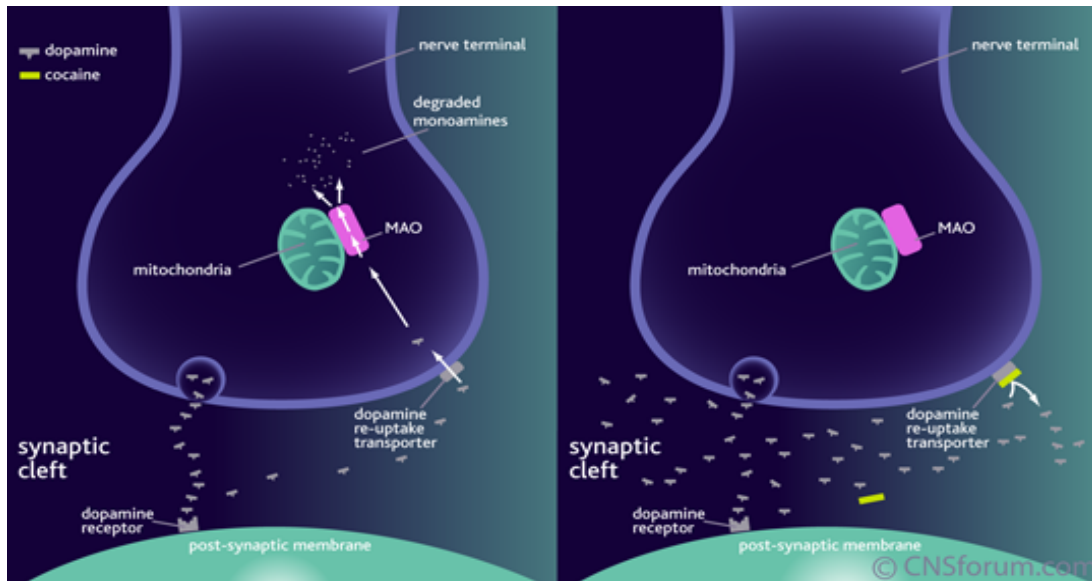
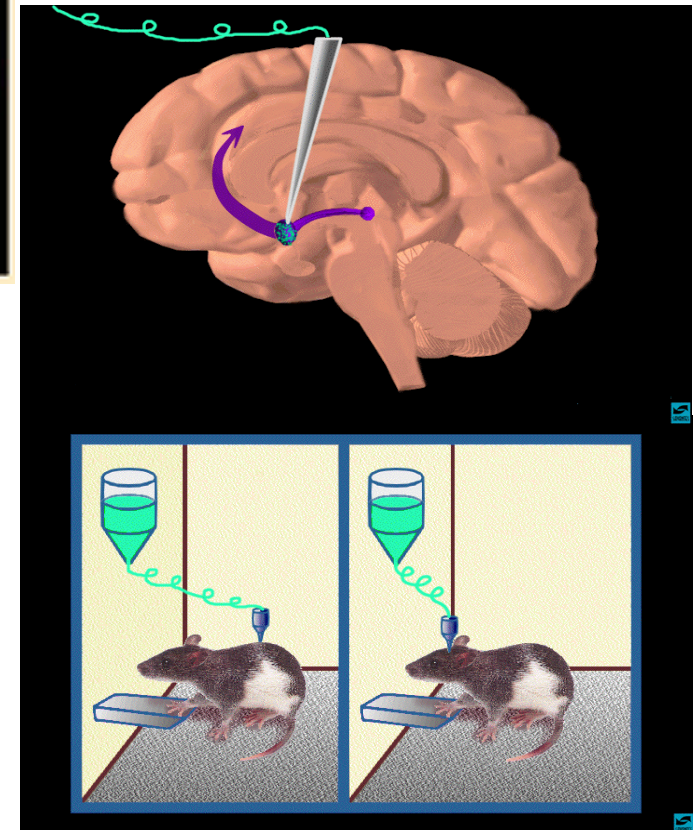
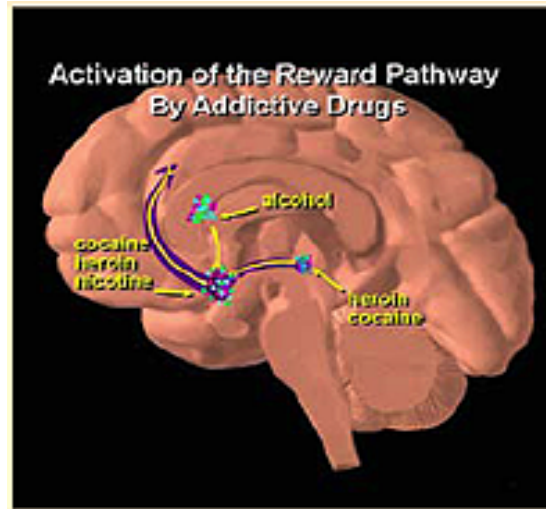
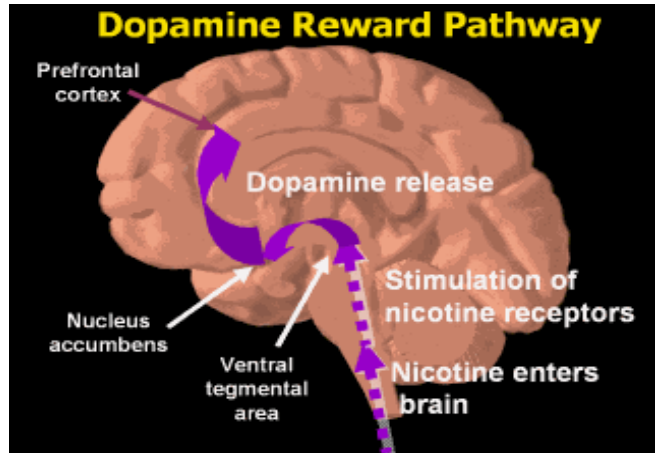


transplantation of pig neurons



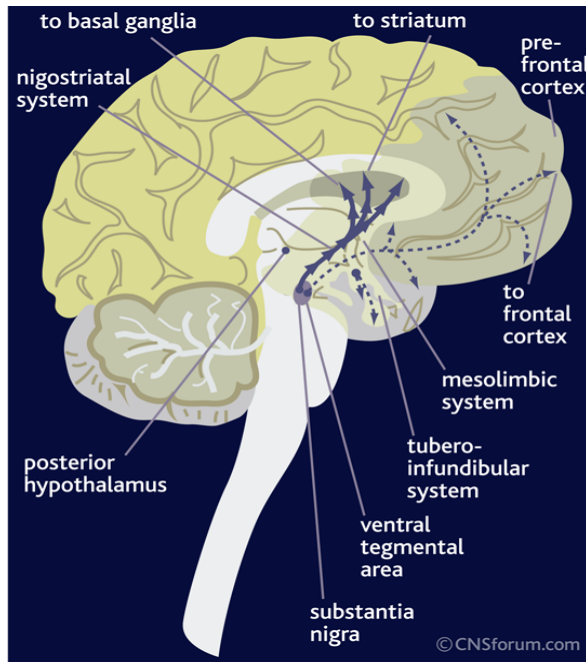
Amines biogèniques

Dopamina / sistema de recompensa/addicció



Amines biogèniques

Dopamina/esquizofrènia



Dopamine theory

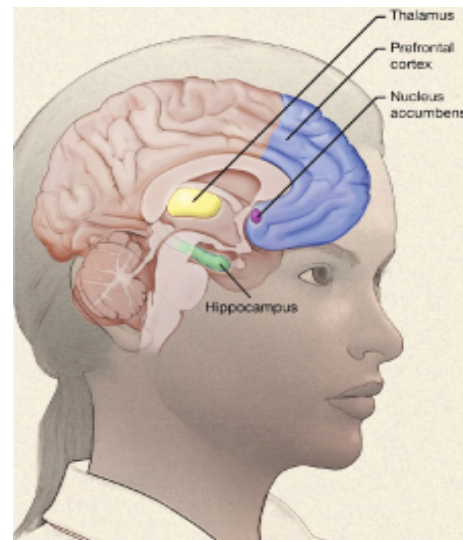
The dopamine (DA) theory was proposed in 1965 (Merzer & Stahl 1976), and is supported by a good deal of indirect evidence. The best evidence comes from pharmacological observations in man and experimental animals.

Amphetamine releases DA in the brain, and can produce in man a behavioral syndrome indistinguishable from an acute schizophrenic episode – very familiar to doctors who treat drug-users.

In animals DA release causes a specific pattern of stereotyped behavior, which resembles the repetitive behaviors often seen in schizophrenic patient.

Potent D2- receptor agonists (e.g. apomorphine and bromocriptine) produce similar effects in animals, and these drugs, like amphetamine, exacerbate the symptoms of schizophrenic patients.

24



The image above shows regions of the brain involved in learning and memory. People with schizophrenia have fewer and more poorly functioning nicotinic receptors in some of these regions, especially the hippocampus, cortex, and cells that wrap the thalamus. Research indicates that nicotine may improve cognitive and sensory deficits of schizophrenia by increasing deficient levels of the chemical dopamine in areas of the brain like the nucleus accumbens and prefrontal cortex.

Amines biogèniques

Norepinefrina

Son/vigília

Atenció

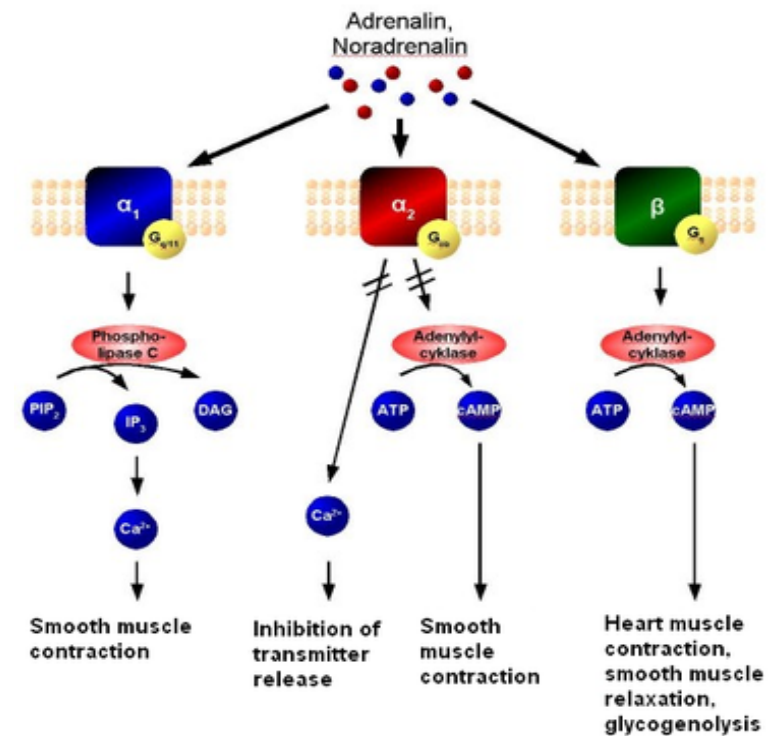
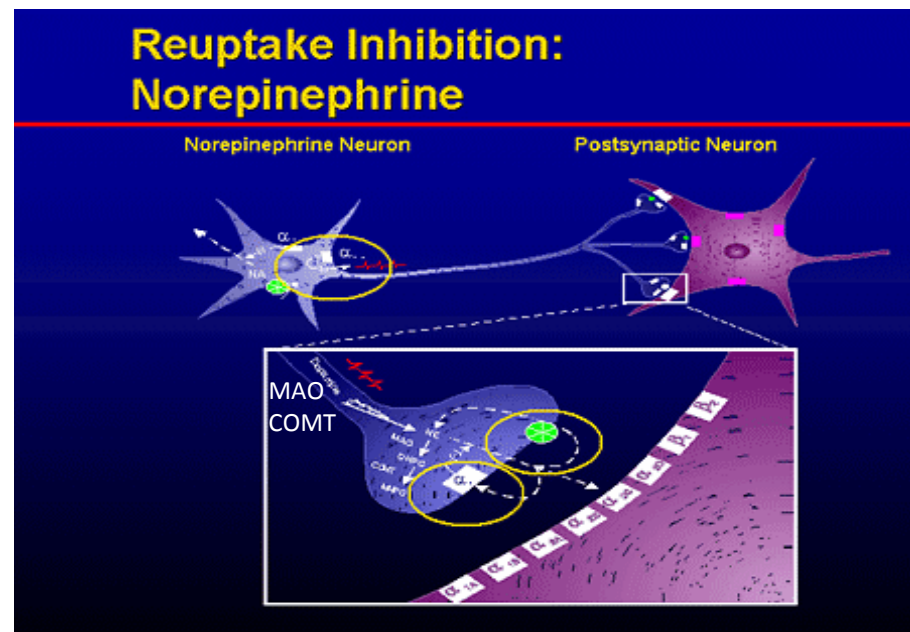
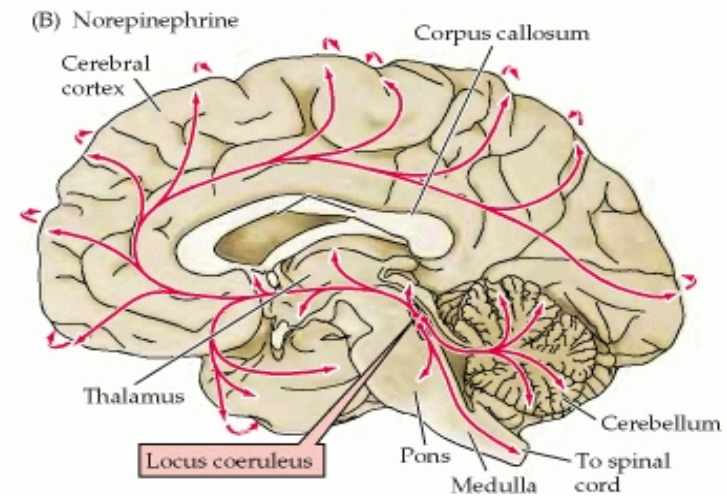
Comportament alimentari

Neurones ganglionars del sistema simpàtic



Sistema motor visceral

<http://www.sinauer.com/neuroscience4e/animations6.4.html>



Epinefrina

Escasses neurones en SNC

Amines biogèniques Histamina

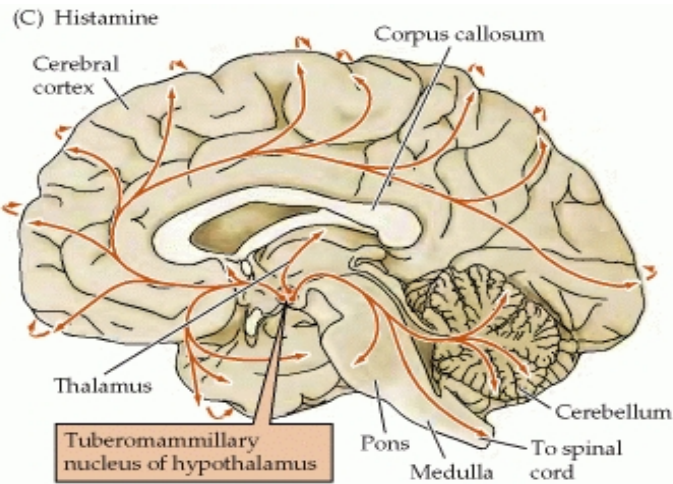


FIGURE 4.
Production and degradation of histamine

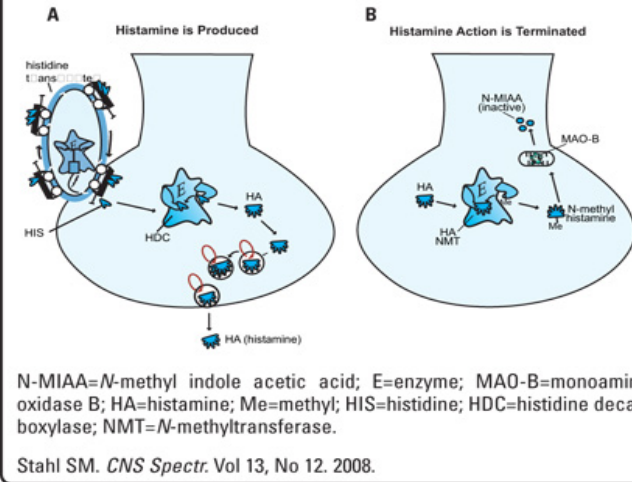
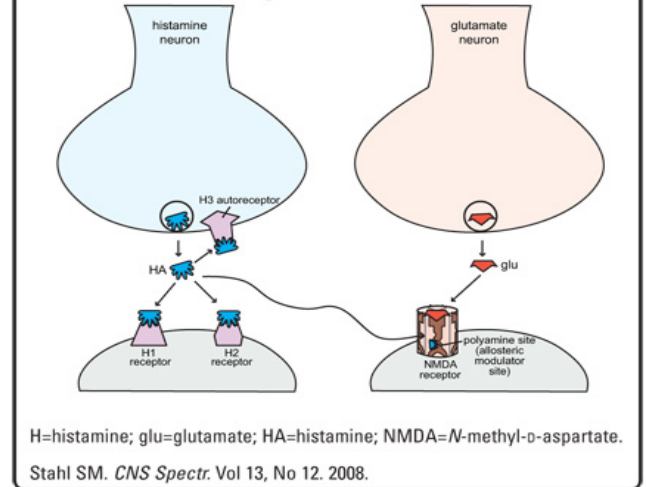
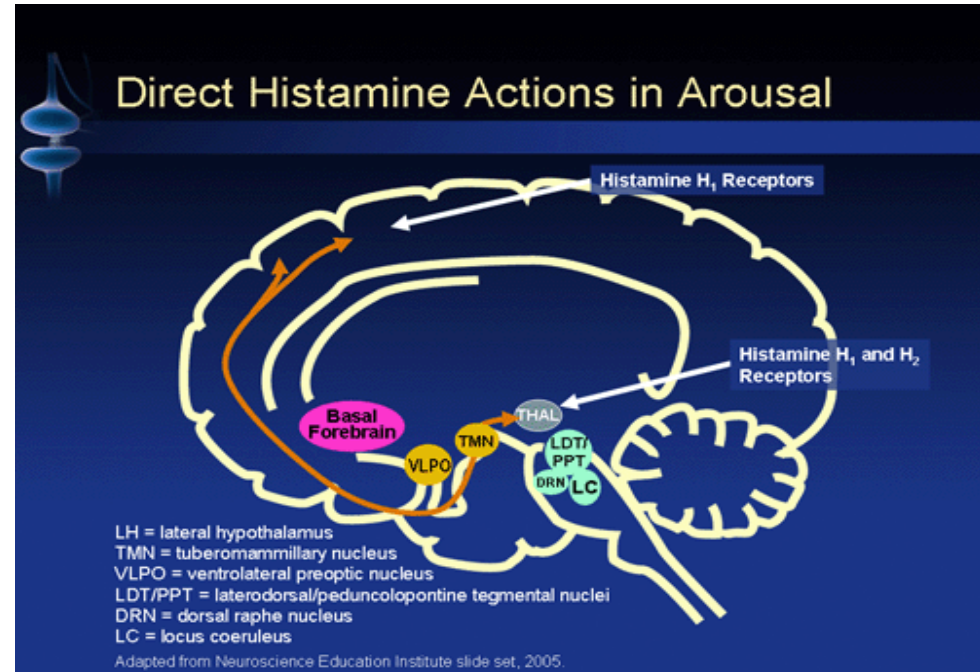
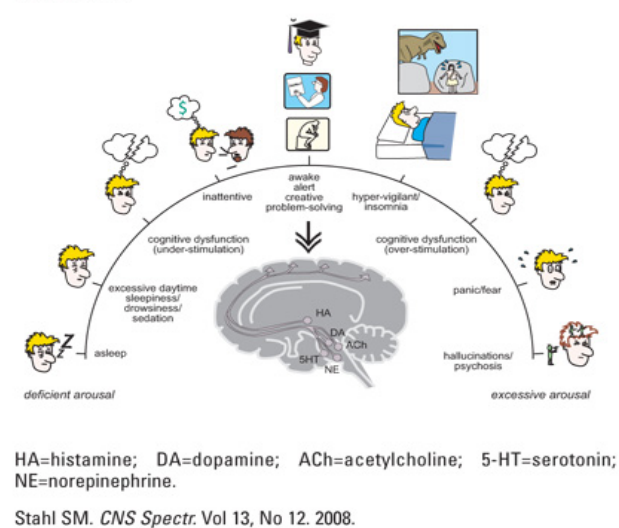


FIGURE 5.
Histamine receptors



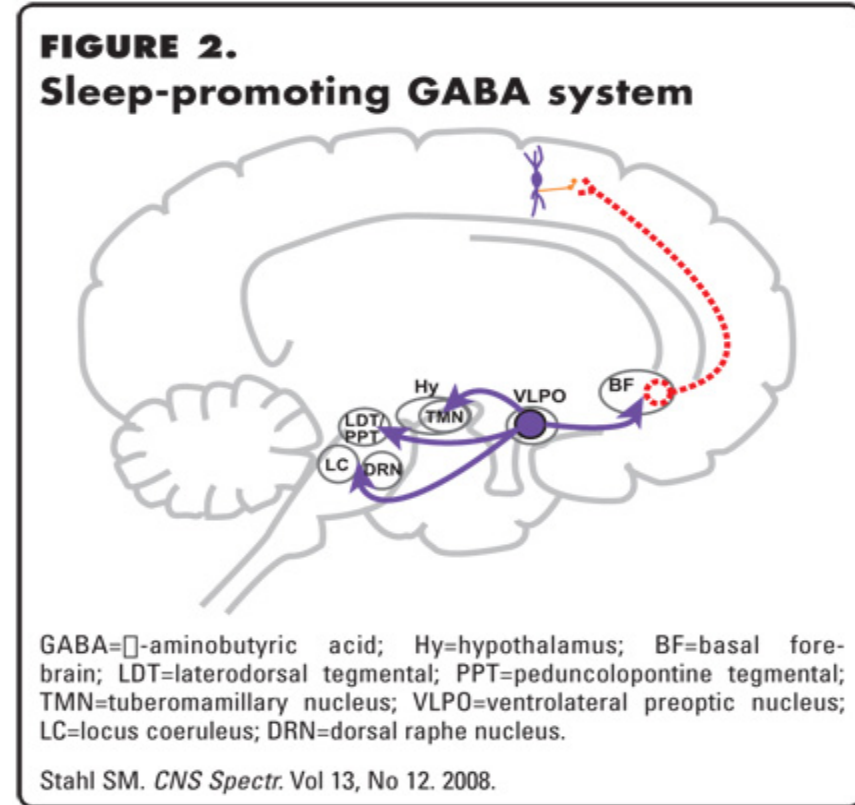
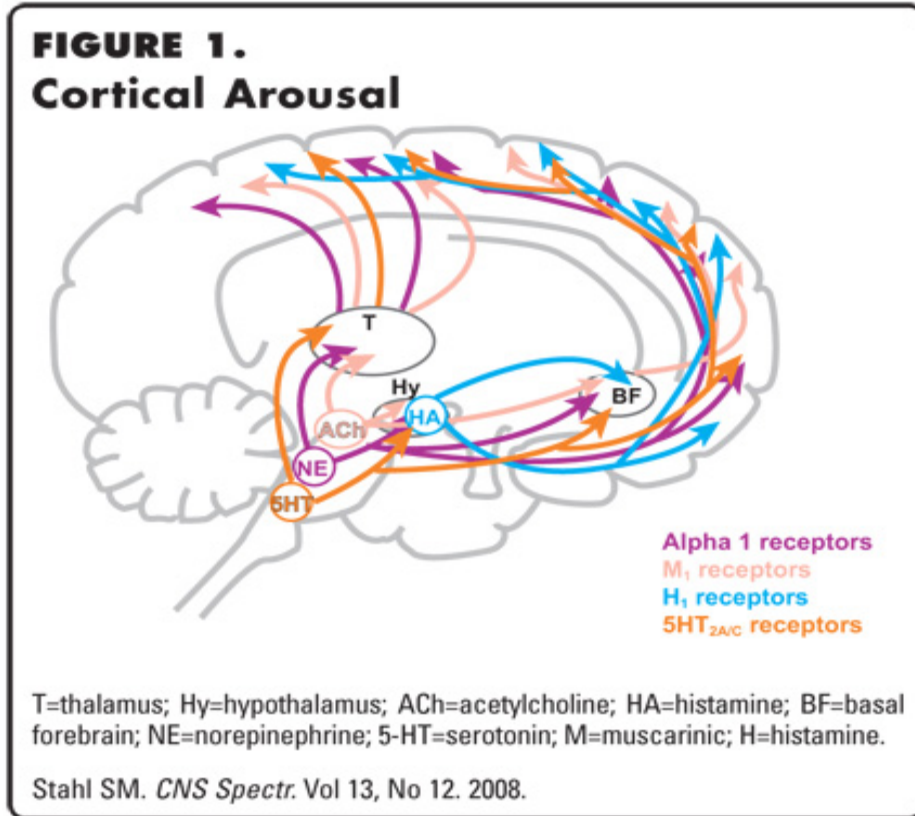
Purves et al. *Neuroscience*, 4 ed.

FIGURE 3.
Arousal spectrum of sleep and wakefulness



Amines biogèniques

Histamina

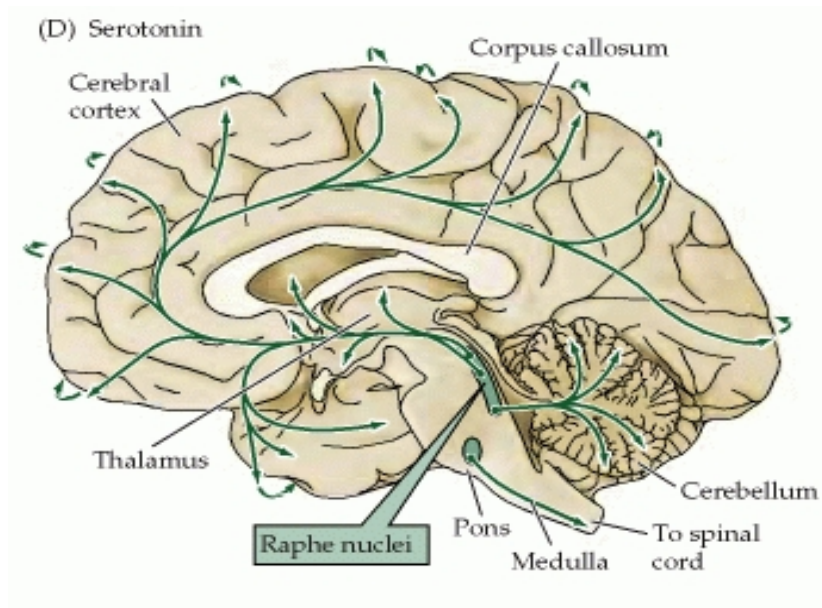


Control de mareig por regulació de funció vestibular

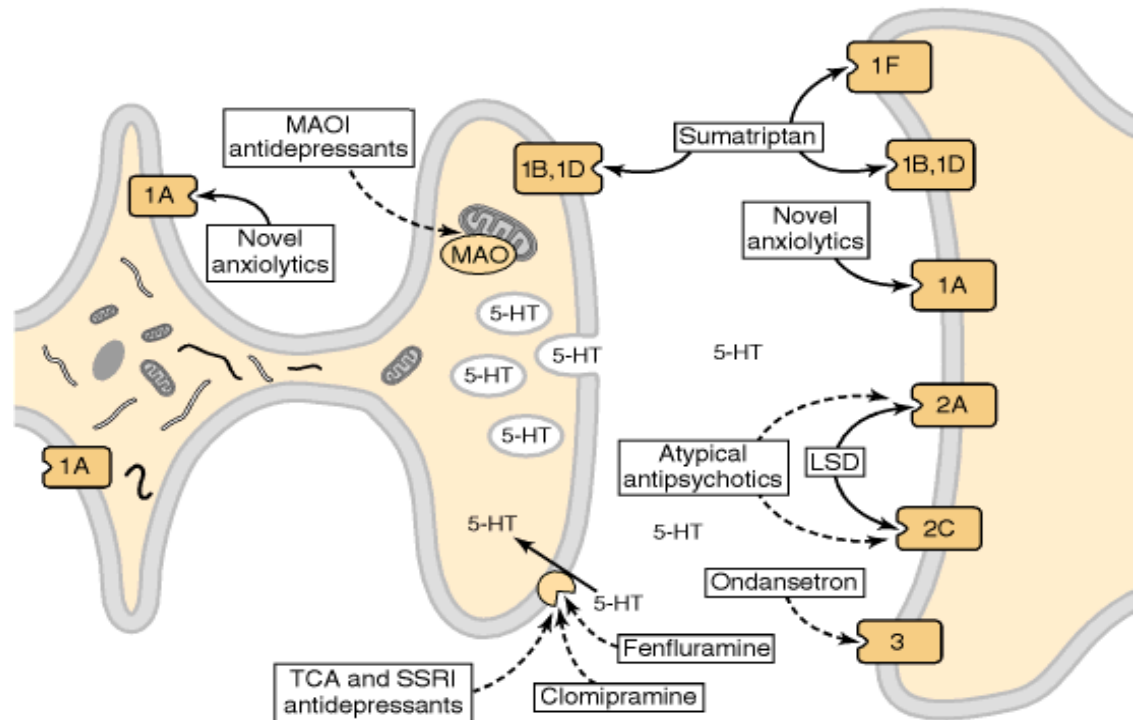
Antagonistes de receptors H2 en estómac

Amines biogèniques

Serotonina

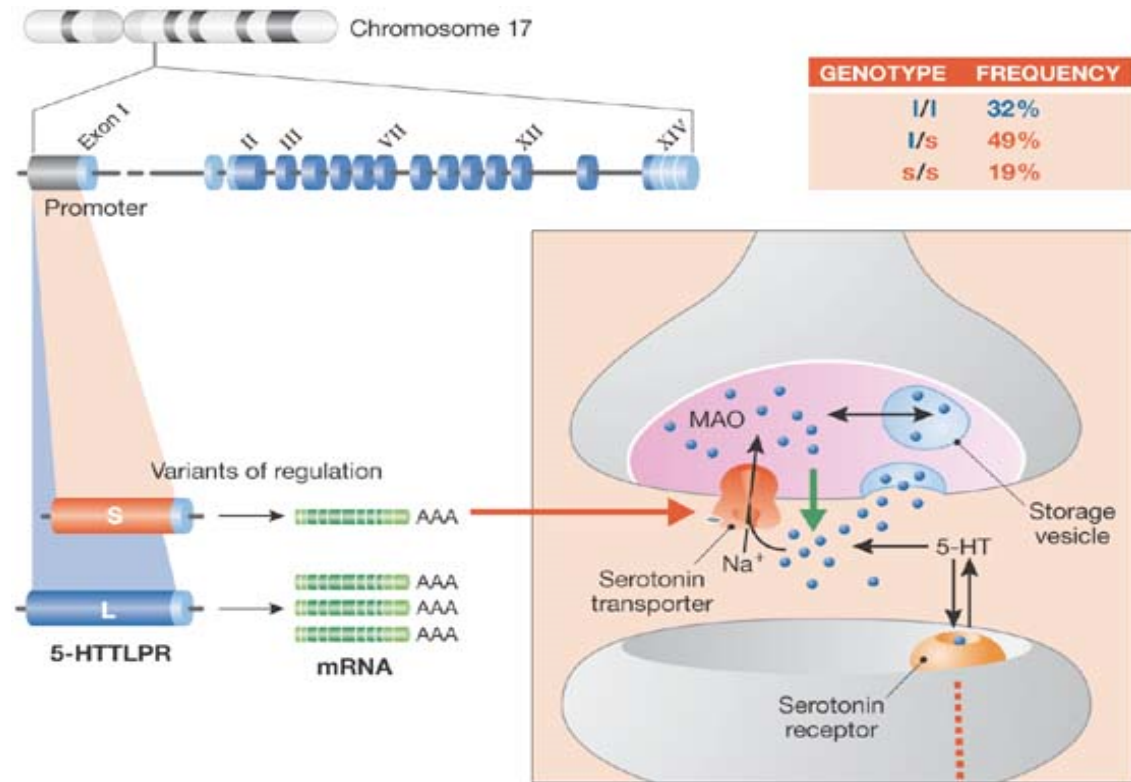
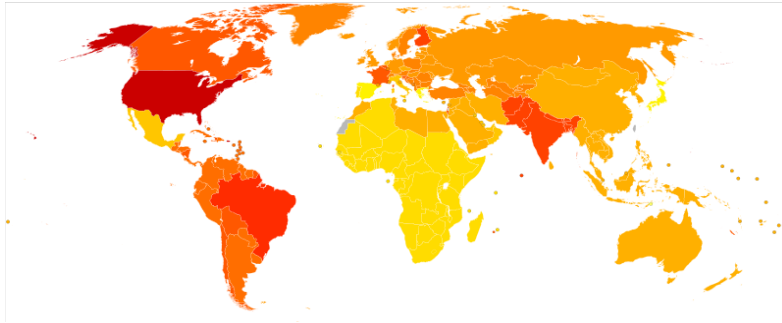


Purves et al. Neuroscience, 4 ed.



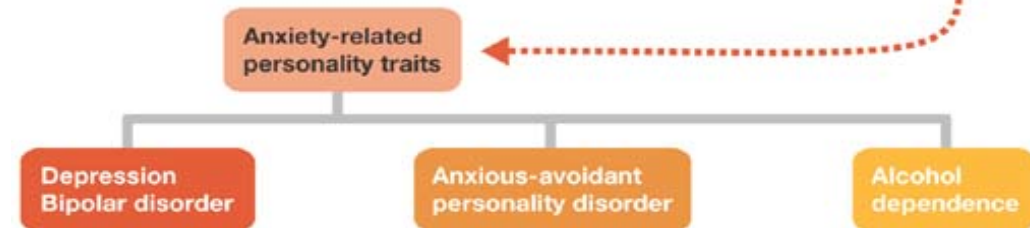
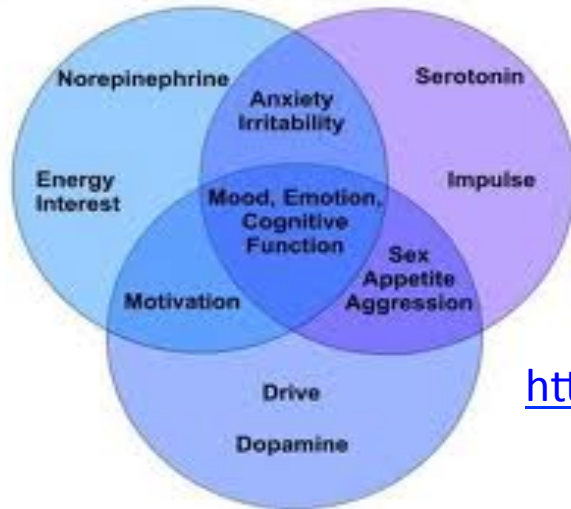
Amines biogèniques

Serotonina/depressió



Medscape® www.medscape.com

Figure 3. Role of NE and 5HT in the generation of depressive symptoms

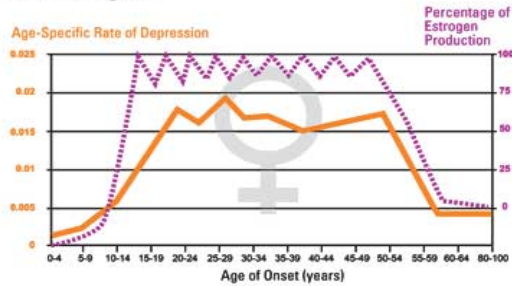


<http://www.muyinteresante.com.mx/ciencia/285675/gen-felicidad>

Amines biogèniques

Serotonina/depressió

FIGURE 1.
Incidence of depression in women across the lifecycle*

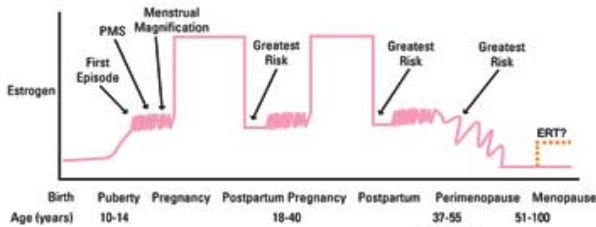


* As estrogen levels rise, so does the risk of depression. When estrogen levels fall in conjunction with menopause, the risk of depression is also reduced. During childbearing years, the risk of depression is 2-3 times higher than in men of the same age.³

Stahl SM. Sex-specific and sexual function-related psychopharmacology. In: *Essential Psychopharmacology*. 2nd ed. New York, NY: Cambridge University Press; 2000:539-568.

Wise DD, Felker A, Stahl SM. *CNS Spectr*. Vol 13, No 8. 2008.

FIGURE 3.
The risk of depressive symptoms in women is affected by several occurrences: puberty, menstrual cycles, postpartum period, and perimenopause*



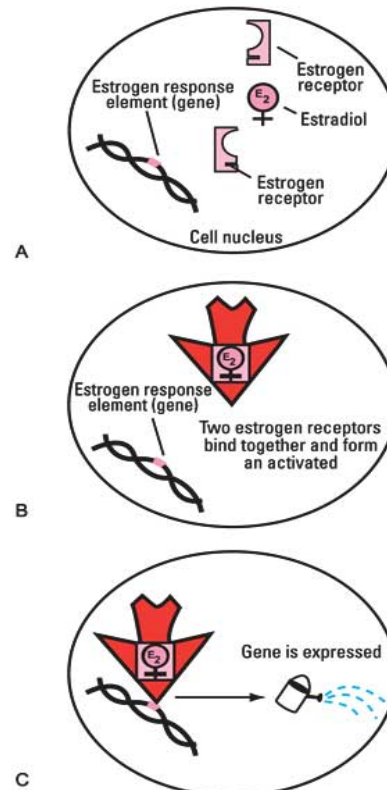
* Puberty may be associated with first episodes of depression in women, whereas the greatest risk of depression may occur during postpartum period and perimenopause.³

PMS=premenstrual syndrome; ERT=estrogen-replacement therapy.

Stahl SM. Sex-specific and sexual function-related psychopharmacology. In: *Essential Psychopharmacology*. 2nd ed. New York, NY: Cambridge University Press; 2000:539-568.

Wise DD, Felker A, Stahl SM. *CNS Spectr*. Vol 13, No 8. 2008.

FIGURE 4.
(A) Estrogen binds to estrogen receptors, modulating gene expression. Unlike neurotransmitter receptors, estrogen receptors are located in the neuronal cell nucleus. Thus, the receptor is near the gene. (B) Estradiol activation of genes requires dimerization to initiate transcription. (C) Gene products expressed by this process include monoamine-regulating proteins and brain-derived neurotrophic factor³

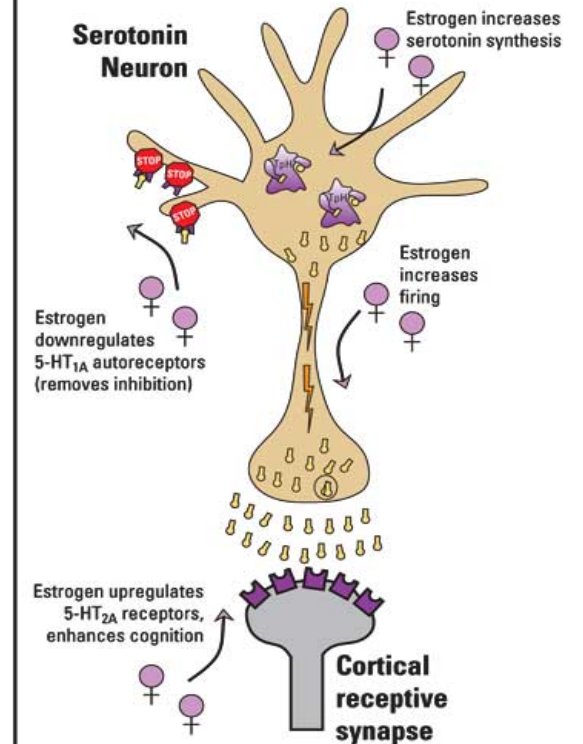


E₂=estradiol.

Stahl SM. Sex-specific and sexual function-related psychopharmacology. In: *Essential Psychopharmacology*. 2nd ed. New York, NY: Cambridge University Press; 2000:539-568.

Wise DD, Felker A, Stahl SM. *CNS Spectr*. Vol 13, No 8. 2008.

FIGURE 7.
Estrogen exerts generally positive effects on serotonergic raphe neurons and on their cortical postsynaptic targets*



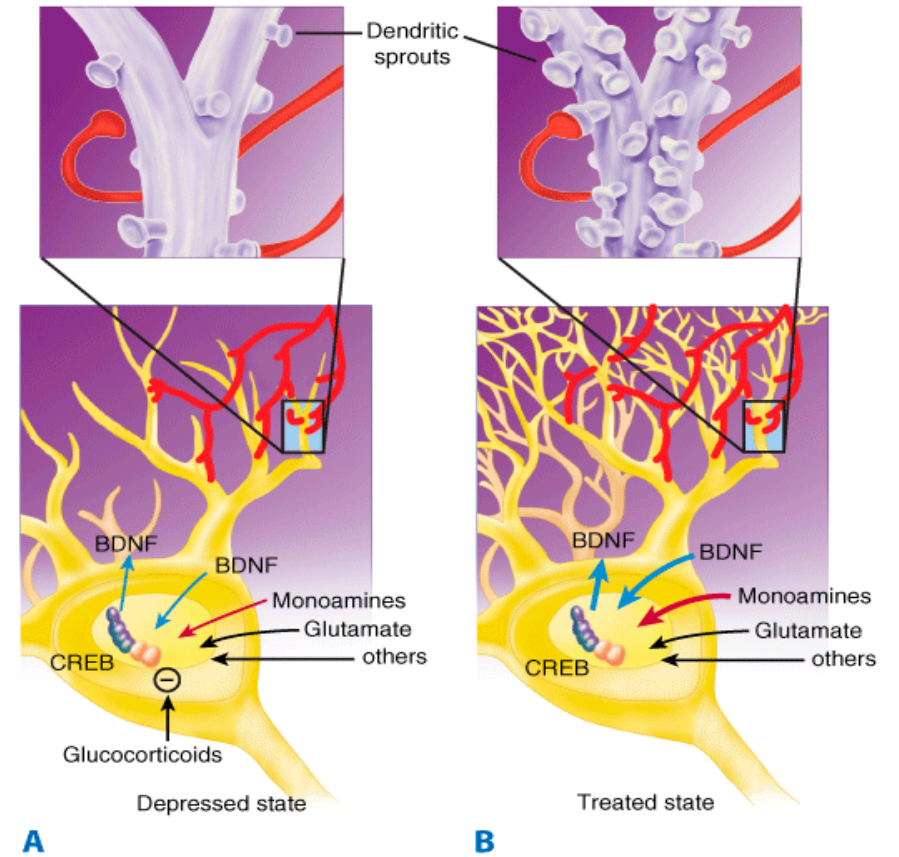
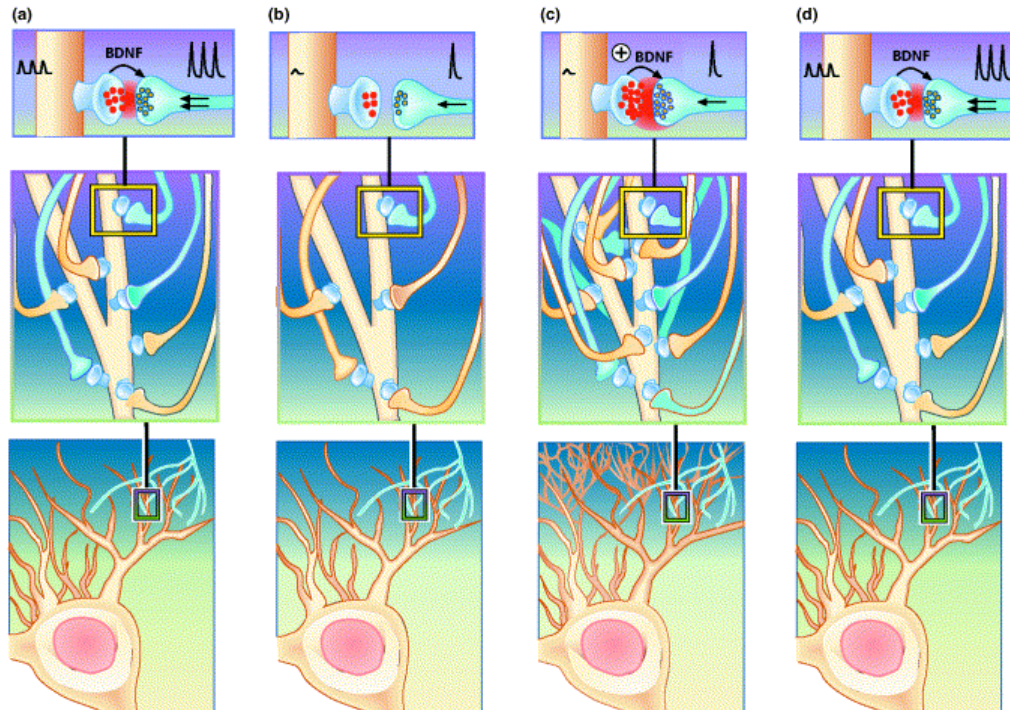
* TpH is the key synthetic enzyme for 5-HT.

TpH=tryptophan hydroxylase; 5-HT=serotonin.

Wise DD, Felker A, Stahl SM. *CNS Spectr*. Vol 13, No 8. 2008.

Amines biogèniques

Serotonina/depressió

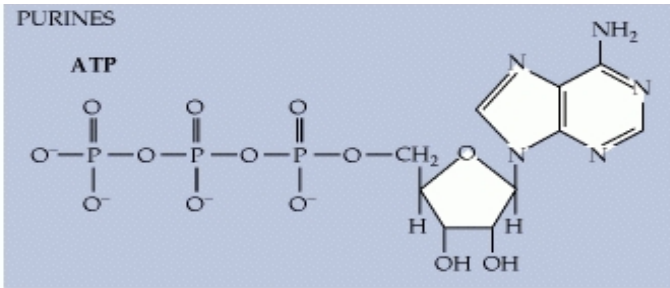


Source: Katzung B.G, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

ATP i altres purines

Aplicació extracel·lular d'ATP (o AMP i adenosina) a neurones --> resposta elèctrica



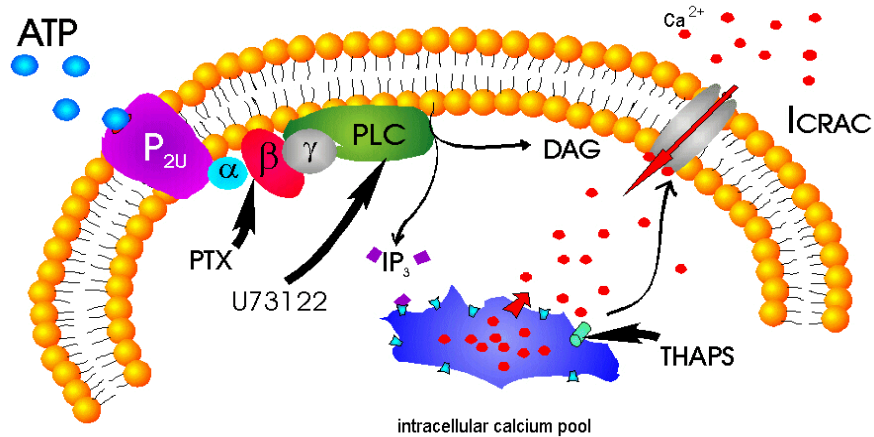
Purves et al. Neuroscience, 4 ed.

ATP neurotransmissor a motoneurons de m. espinal i ganglis sensorials i autònoms

CNS: algunes neurones HC

NO neurotransmissor clàssic: no en vesic. sinàpt., excitosi no induïda per Ca²⁺

Generat per ATP a partir d'enzims extracel·lulars



(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α_{1-7}	α_1	α_{2-9}	5-HT ₃	P _{2X1}
	Glu R2	NR2A	Glu R6	β_{1-4}	α_2	β_{1-4}		P _{2X2}
	Glu R3	NR2B	Glu R7	γ_{1-4}	α_3	γ		P _{2X3}
	Glu R4	NR2C	KA1	δ	α_4	δ		P _{2X4}
		NR2D	KA2	ϵ	β			P _{2X5}
				ρ_{1-3}				P _{2X6}
								P _{2X7}

(B)

Receptor class	Glutamate	GABA _B	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	GABA _B R1	D1 _A	α_1	H1	5-HT 1	A type	M1
	mGlu R1	GABA _B R2	D1 _B	α_2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β_1	H3	5-HT 3	A2a	M3
Class II			D3	β_2		5-HT 4	A2b	M4
mGlu R2			D4	β_3		5-HT 5	A3	M5
mGlu R3						5-HT 6	P type	
Class III						5-HT 7	P2x	
mGlu R4							P2y	
mGlu R6							P2z	
mGlu R7							P2t	
mGlu R8							P2u	

Purves et al. Neuroscience, 4 ed.

Neurotransmissors peptídics

Síntesi, empaquetament i alliberament diferents a molècules menudes

Prepropèptids

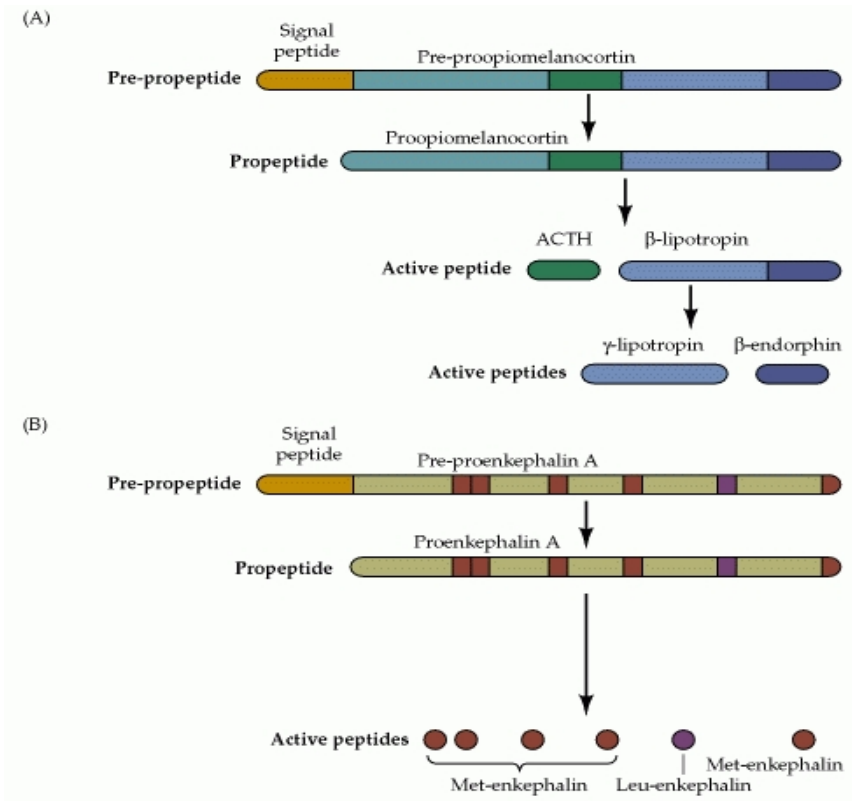
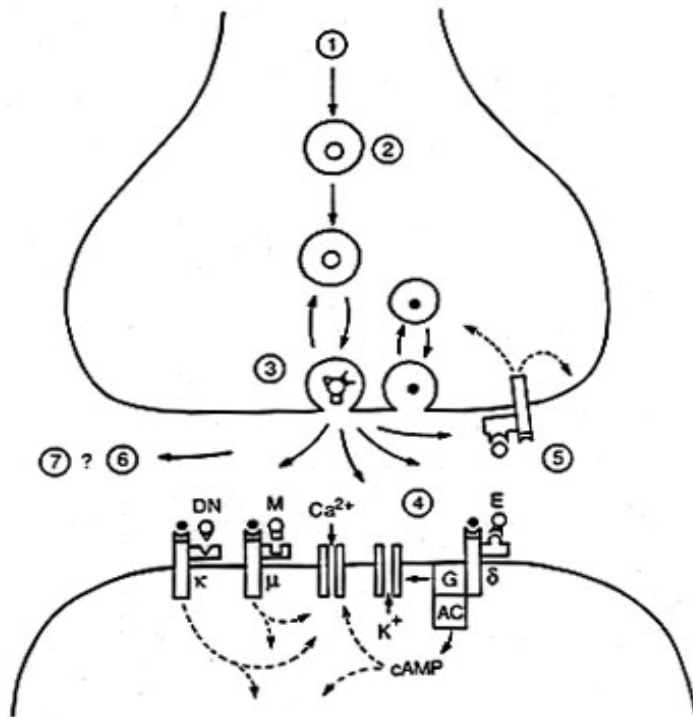
Poden produir més d'un pèptid actiu

Neuropèptids: generalment s'alliberen juntament amb neurotransmissors menuts. Sinapsis

peptidèrgiques: senyals complexos

Destruïts per peptidases a part extracel·lular MP

1) pèptids cervell/digestius, 2) opioides, 3) pituïtaries, 4) hormones secretades per hipotàlem, 5) altres



Neurotransmissors peptídics

Síntesi, empaquetament i alliberament diferents a molècules menudes

Prepropèptids

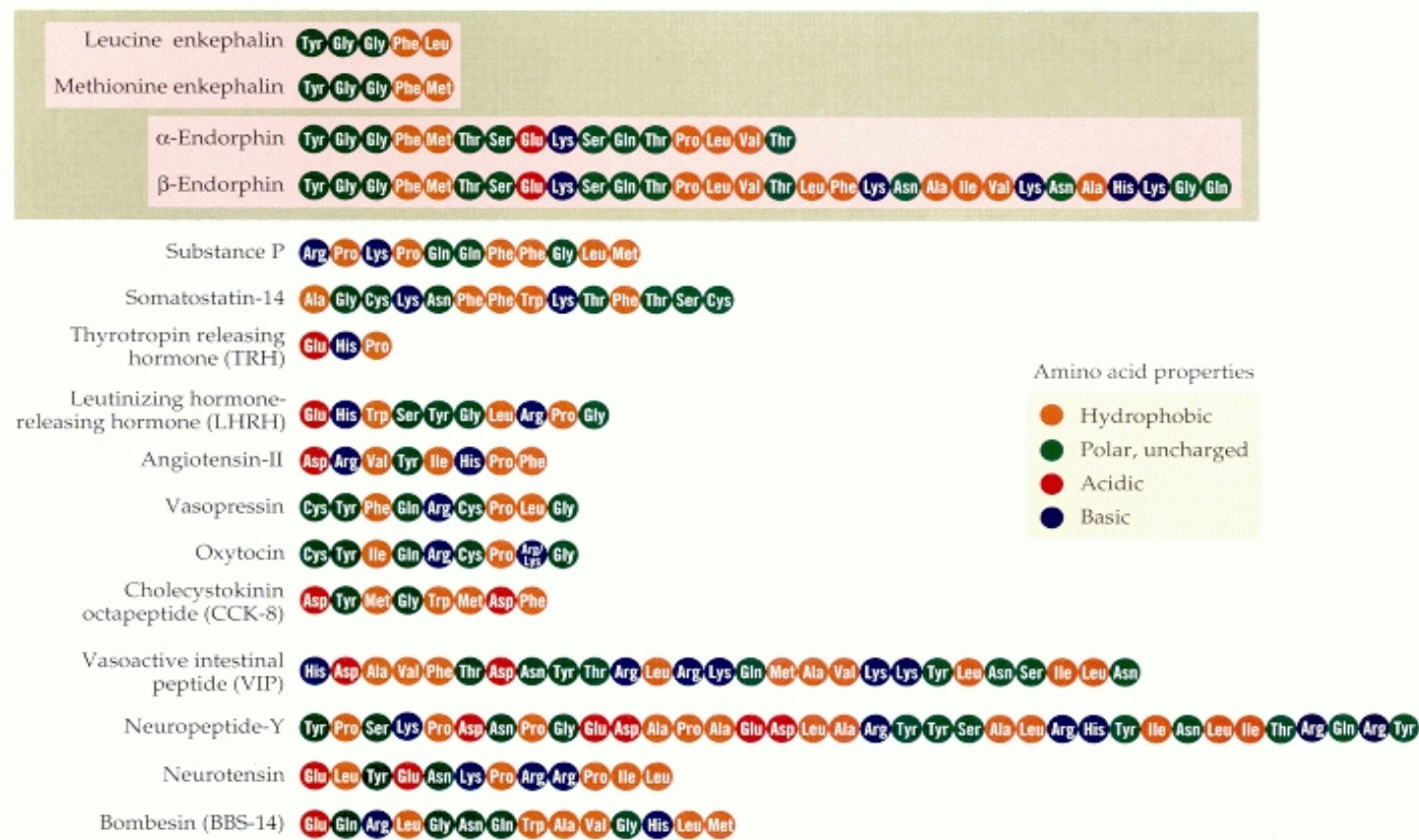
Poden produir més d'un pèptid actiu

Neuropèptids: generalment s'alliberen juntament amb neurotransmissors menuts. Sinapsis

peptidèrgiques: senyals complexos

Destruïts per peptidases a part extracel·lular MP

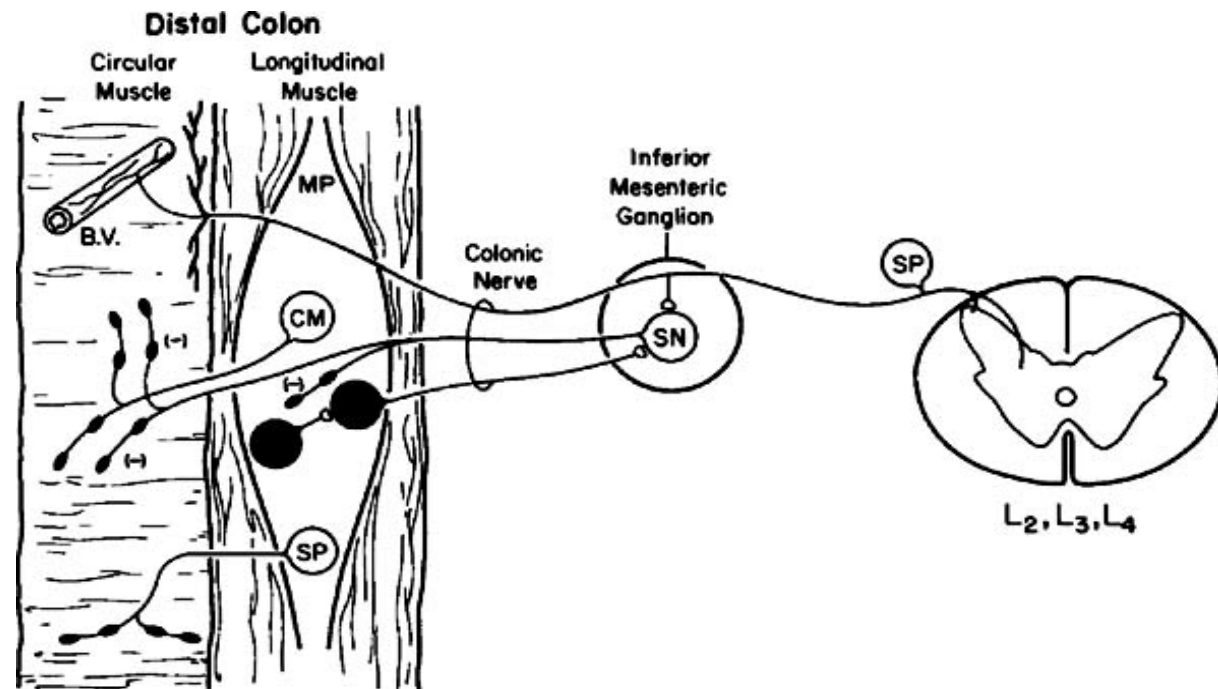
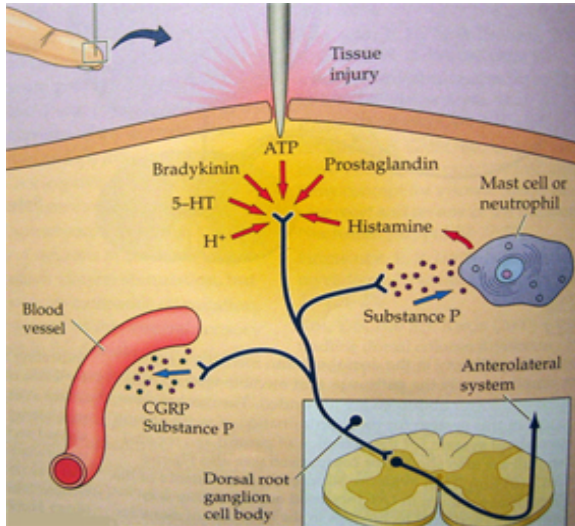
1) pèptids cervell/digestius, 2) opioides, 3) pituïtaries, 4) hormones secretades per hipotàlem, 5) altres:



Neurotransmitters peptídics

Substància P

cervell/digestiu



Neurotransmissors peptídics

Opioides

Perspectiva històrica

Opiacis

Opioides sintètics

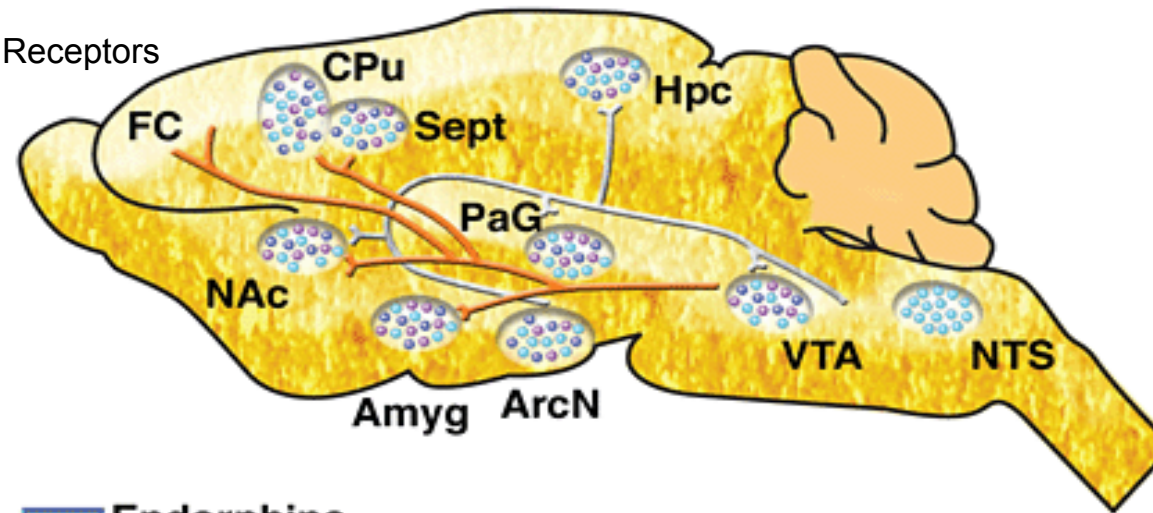
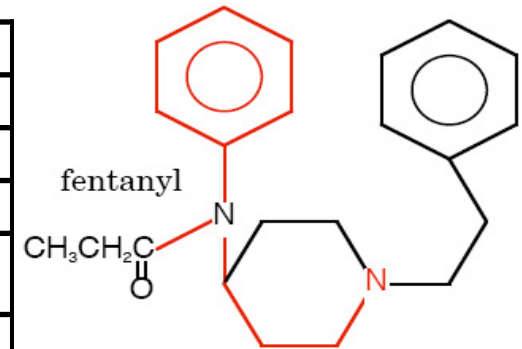
Opioides endògens

Distribució

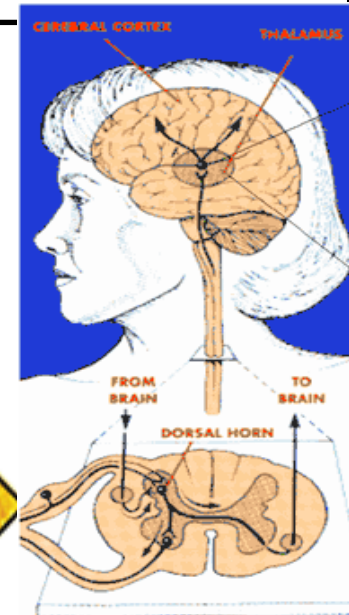
Acció depressora

Receptors

Name	Amino acid sequence ^b
Leucine-enkephalin	Tyr-Gly-Gly-Phe-Leu-OH
Methionine-enkephalin	Tyr-Gly-Gly-Phe-Met-OH
β-Endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln- Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-
	Val-Lys-Asn-Ala-His-Lys-Gly-Gln-OH
α-Neoendorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys
Dynorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys- Leu-Lys-Trp-Asp-Asn-Gln-OH

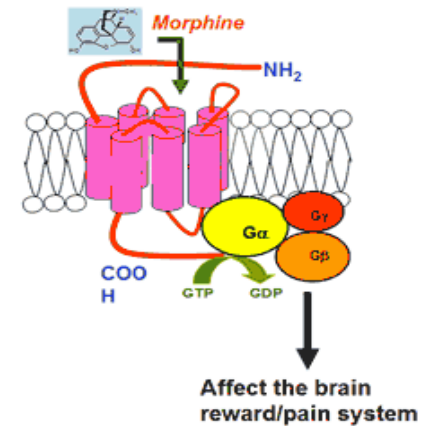


- █ Endorphins
- █ Enkephalins
- █ Dynorphins
- █ Mesolimbic dopaminergic system



Mu Opioid Receptor:

located on the membrane of neuronal cells

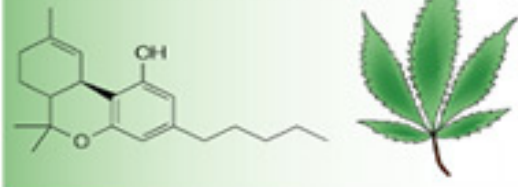


Neurotransmitters no convencionales

Endocannabinoides

Plant-derived cannabinoid

Δ^9 -Tetrahydrocannabinol (THC)

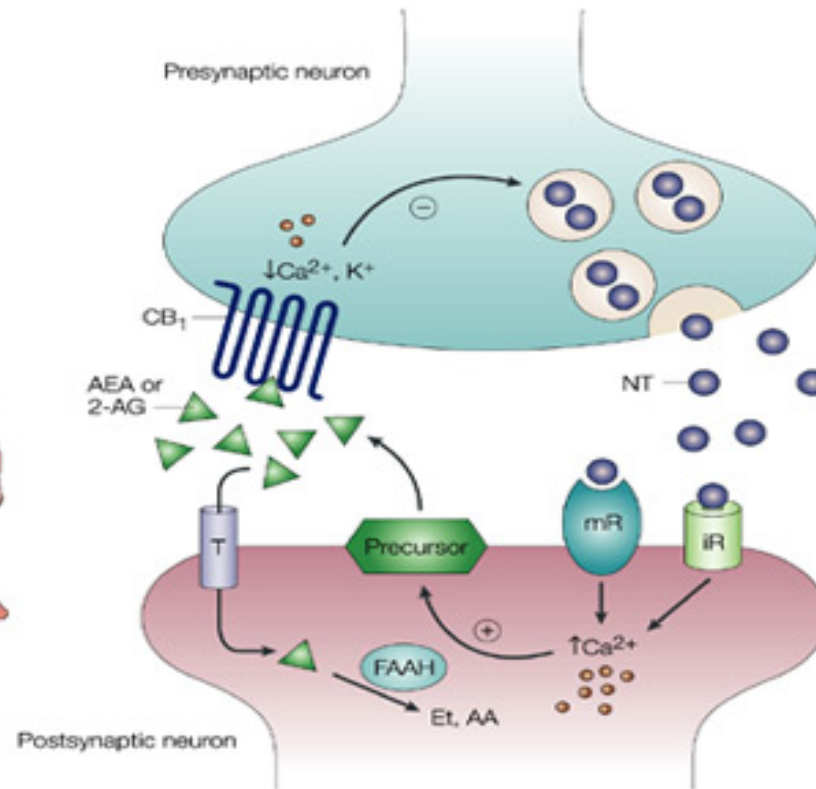


Endogenous cannabinoids

Anandamide (AEA)

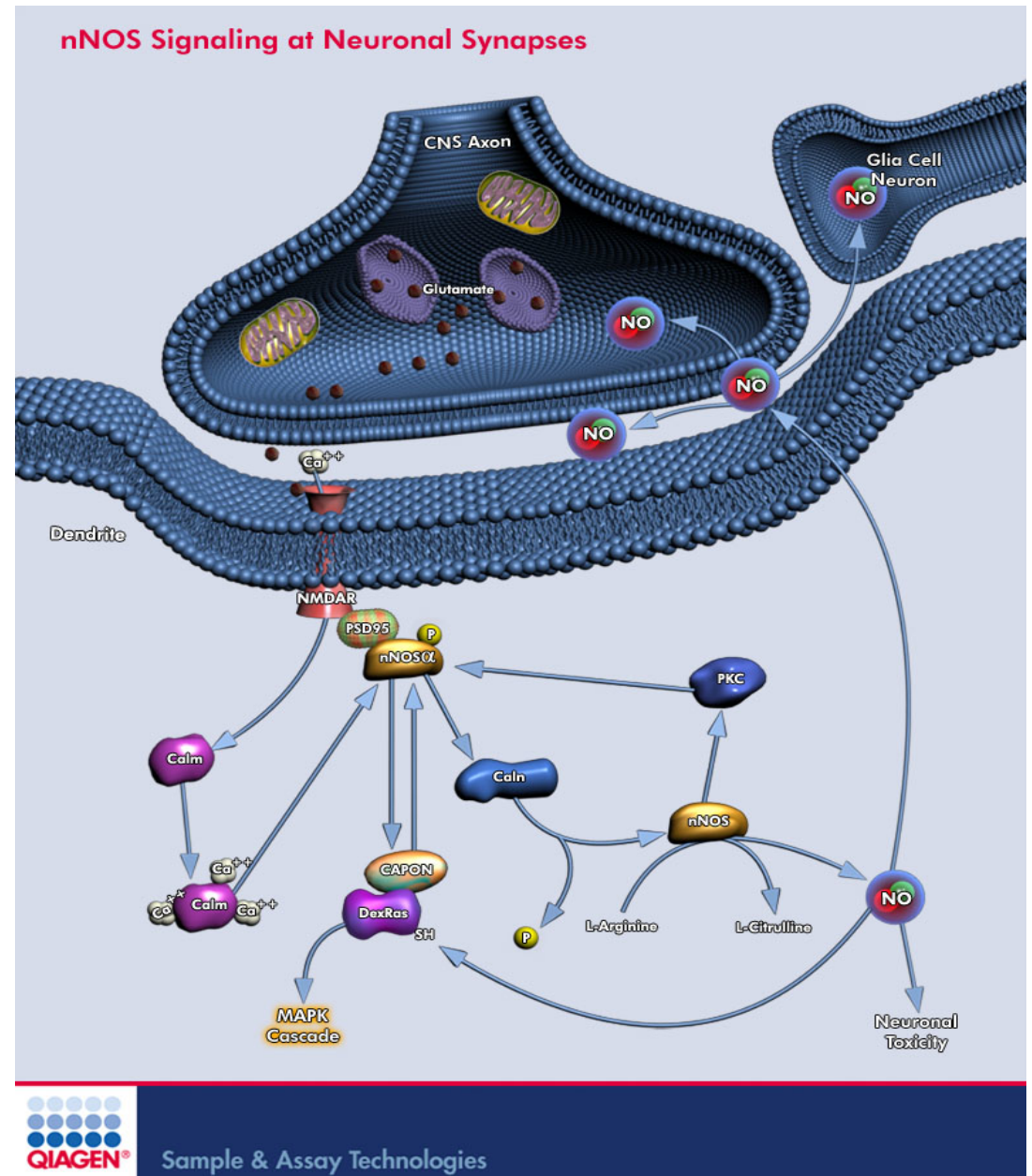
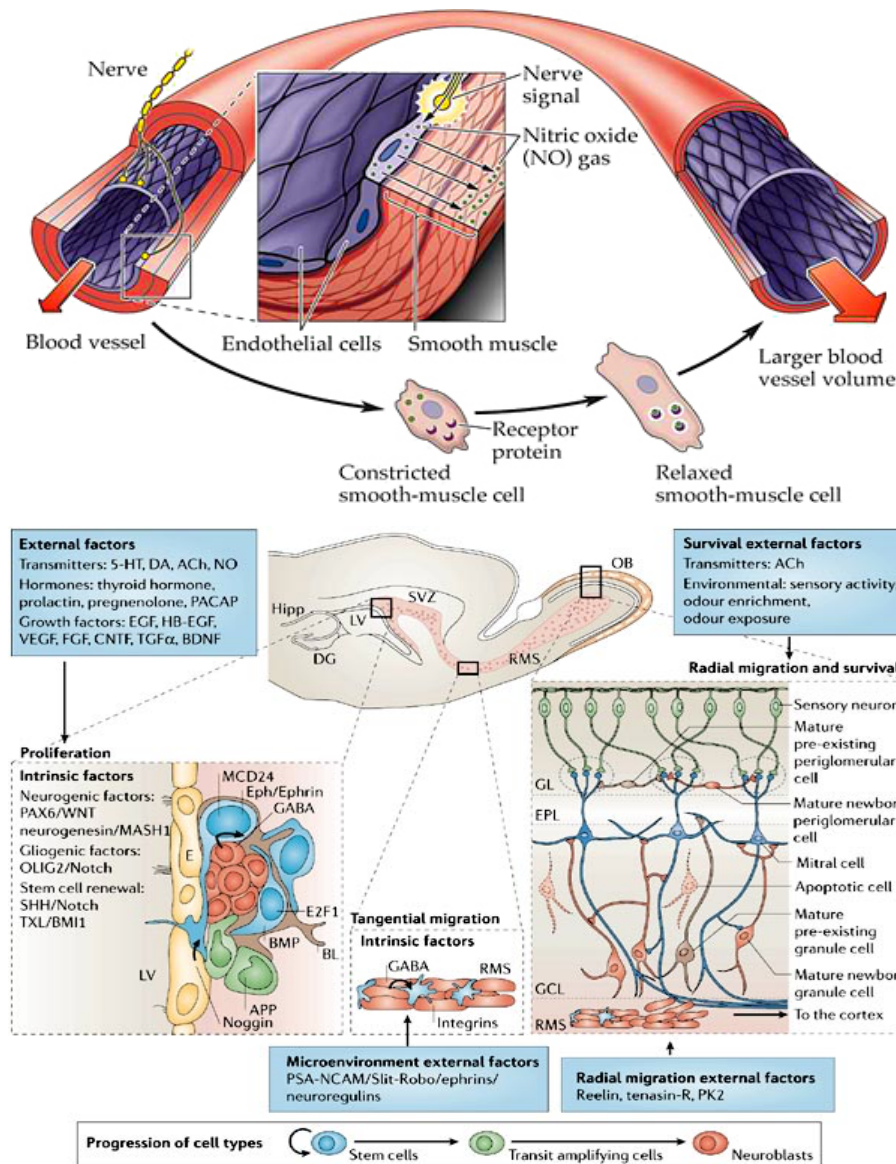


2-Arachidonoylglycerol (2-AG)



Neurotransmitters no convencionales

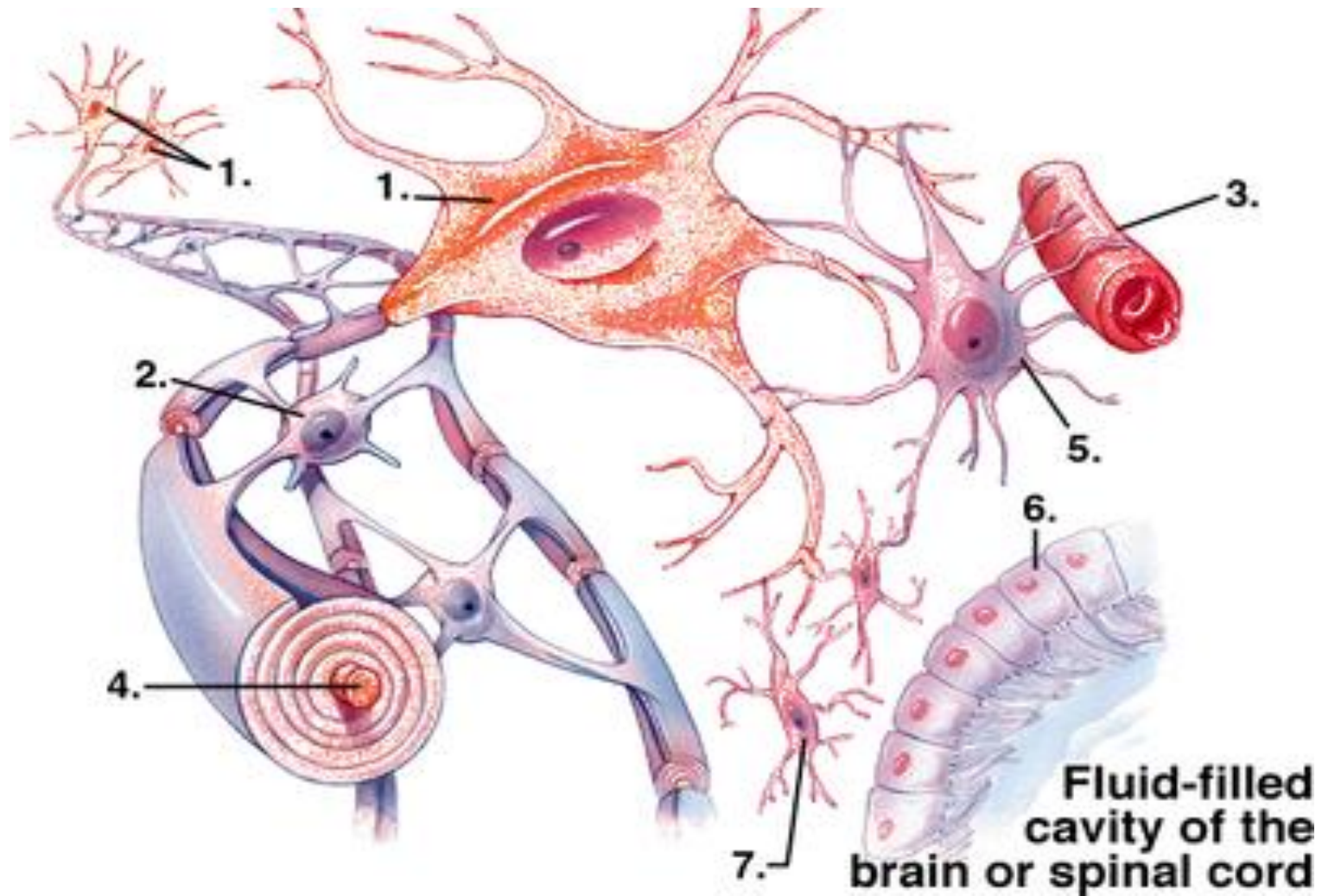
Òxid nítric



Sample & Assay Technologies

Tema 4

La glia: Paper en el desenvolupament del sistema nerviós, la funció neural i la neurodegeneració

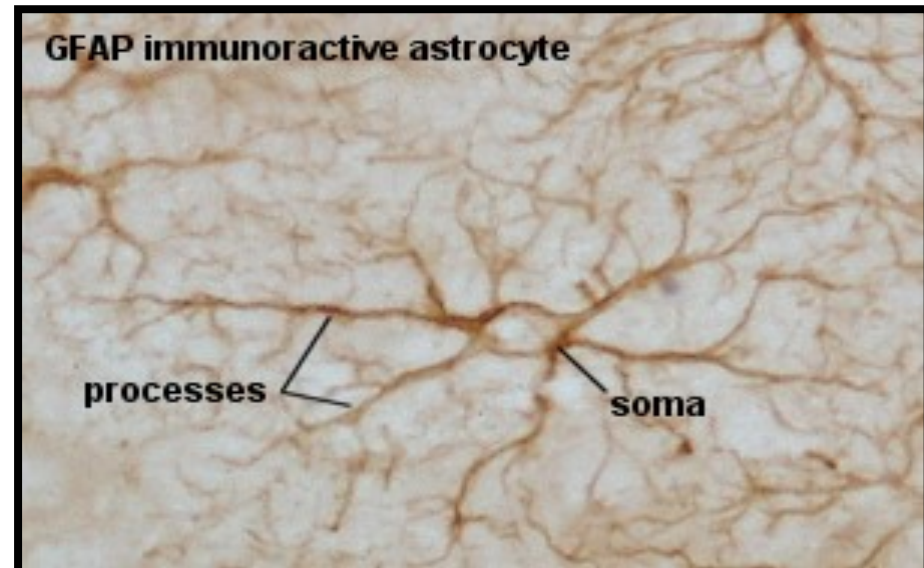
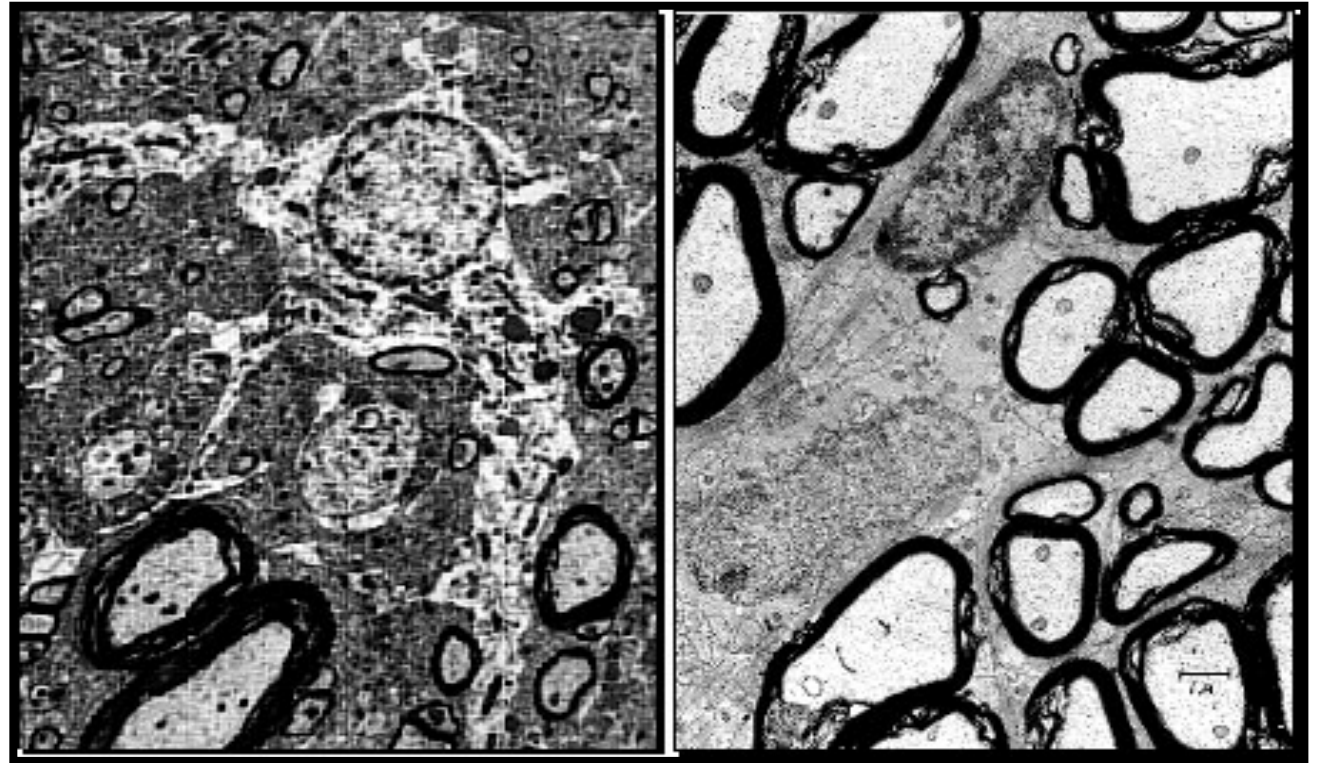


Astròglia

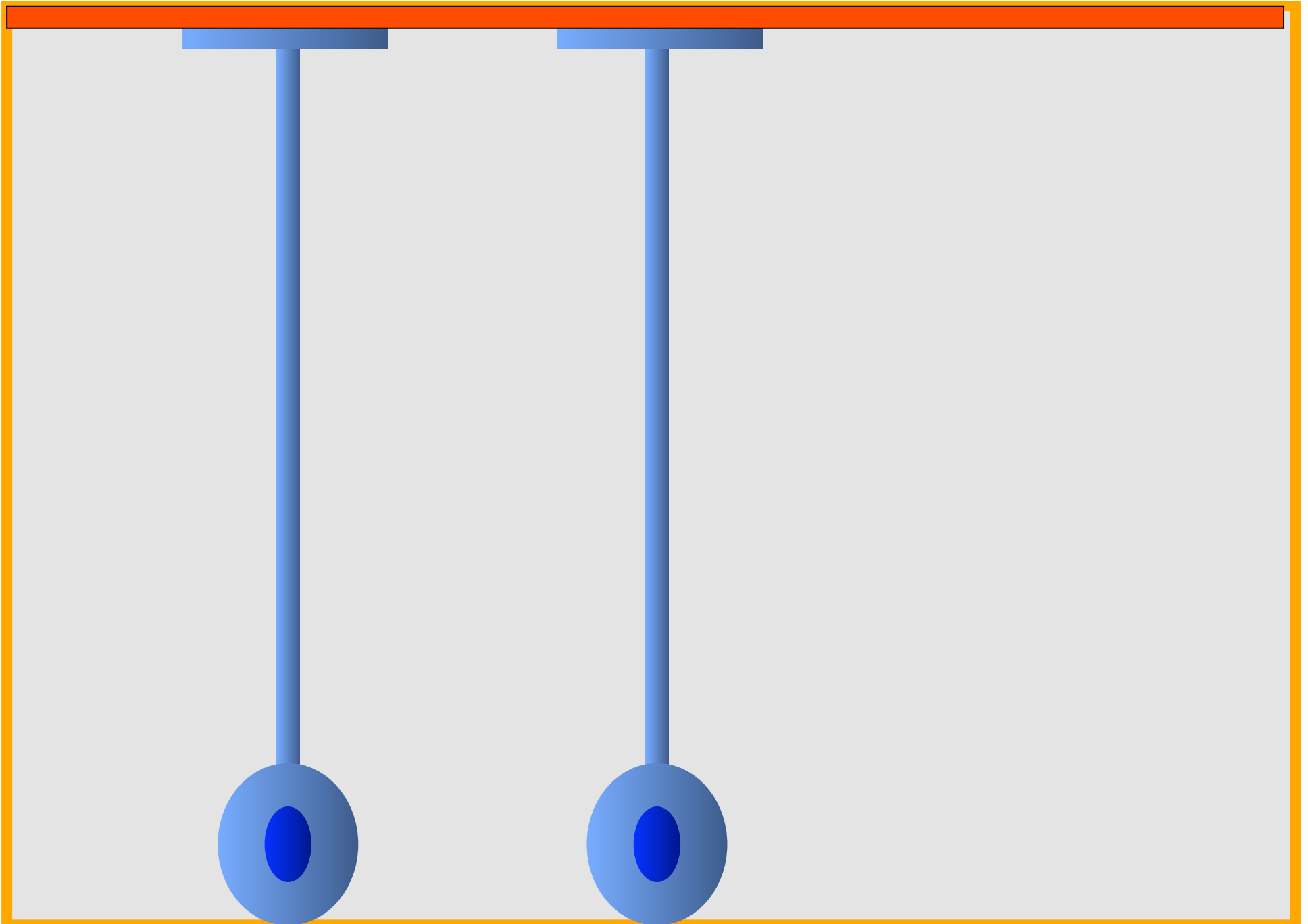
- Cèl. = astròcits
- Cèl. estrellades
- Moltes ramificacions
- Peus perivasculars
- MGLS
- * Astròcits fibrosos
- > Substància blanca
- Branques llargues rectes i llises

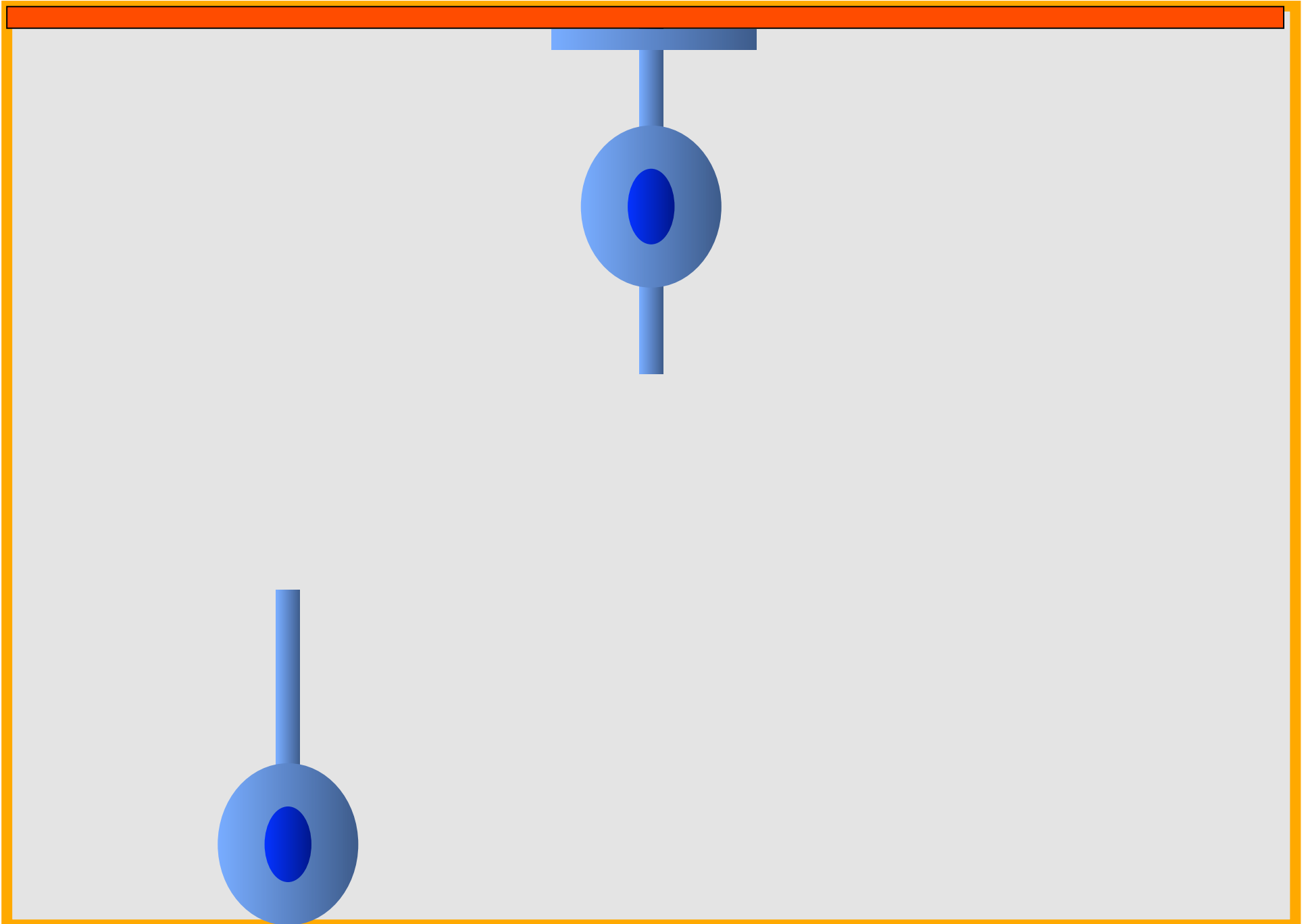
- * Astròcits protoplàsmics
- > Substància gris
- Prolongacions radials
- + abundants
- + curtes
- + grosses

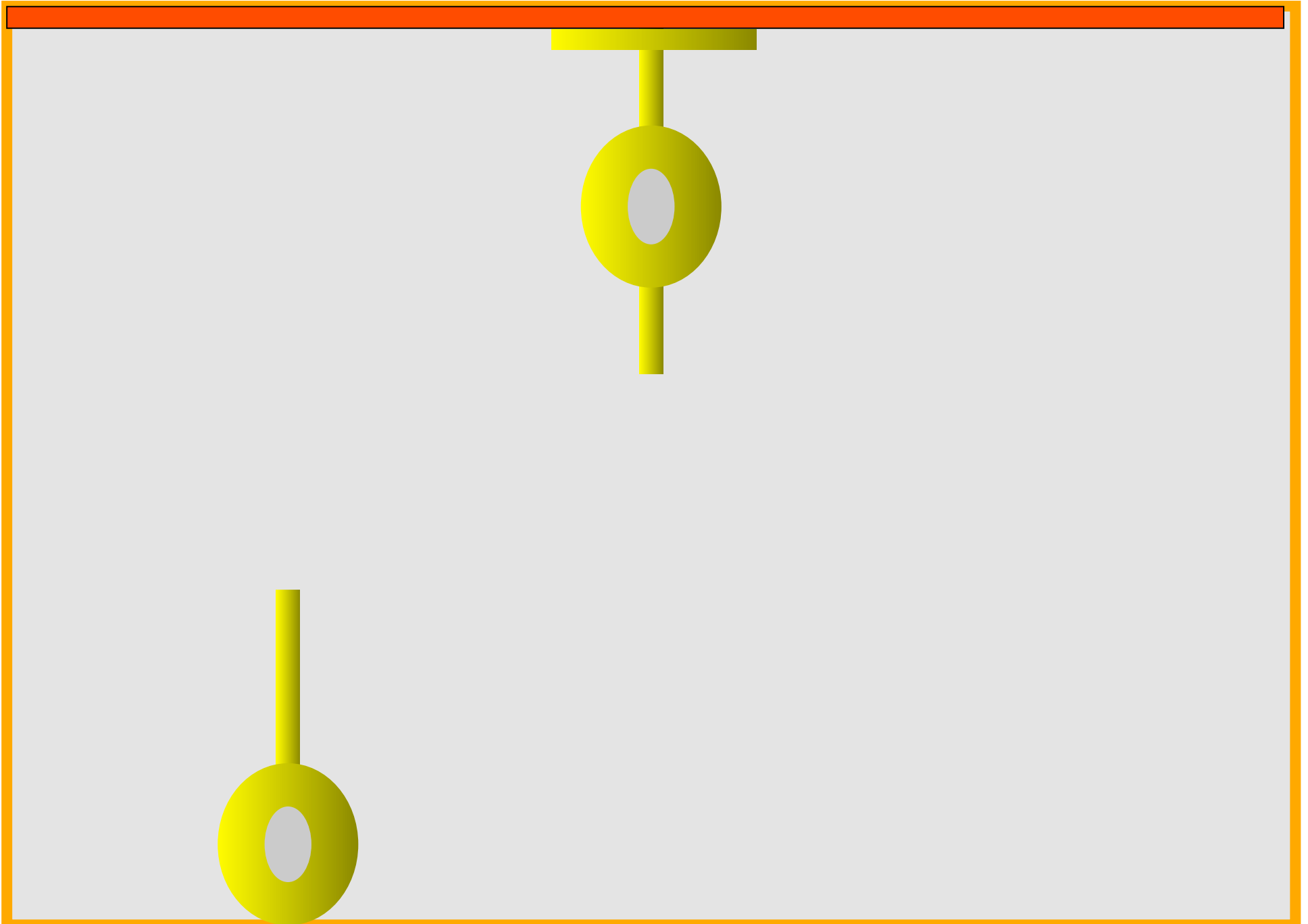
- * Marcadors
- GFAP
- S100
- Glutamina-sintasa

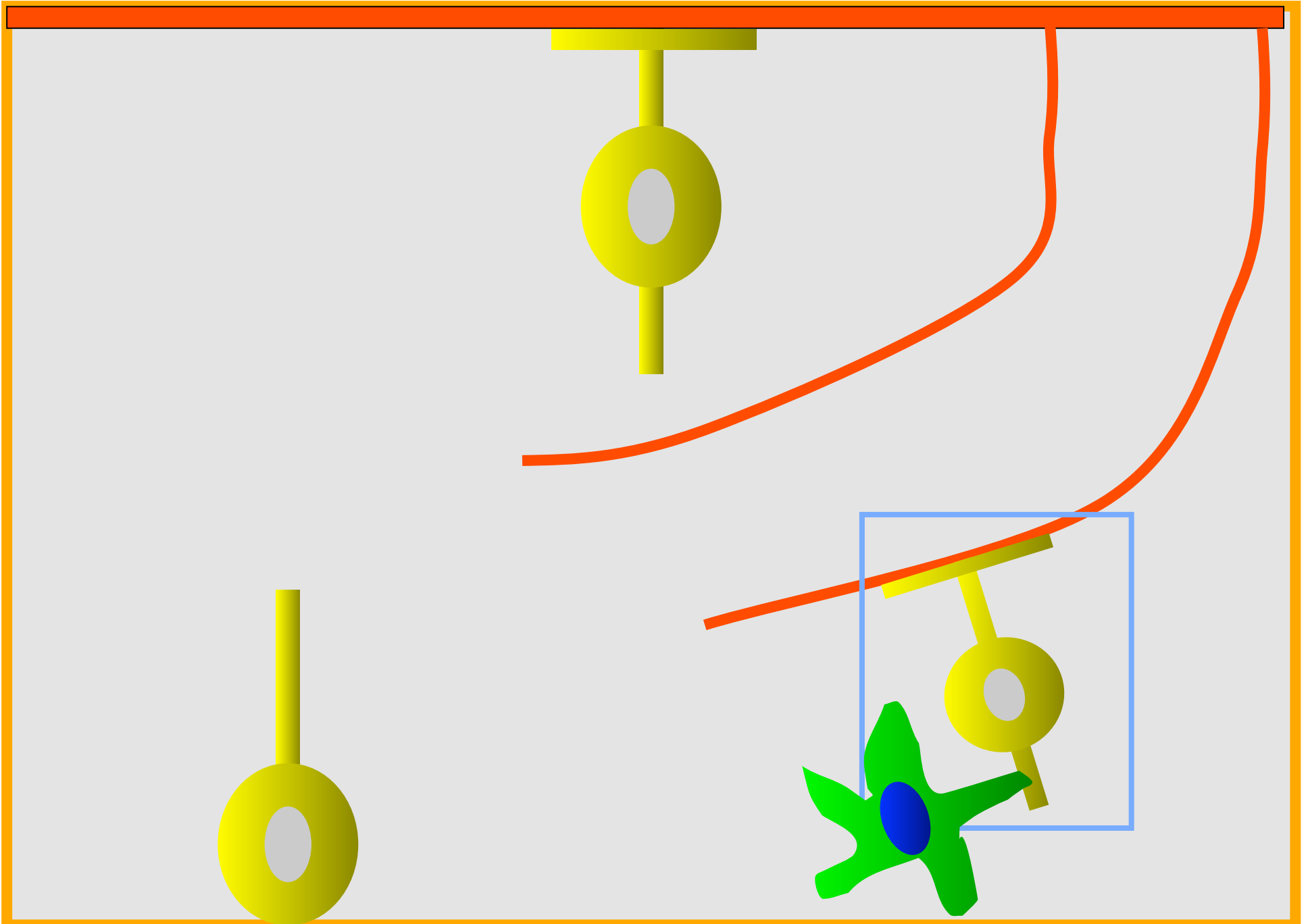


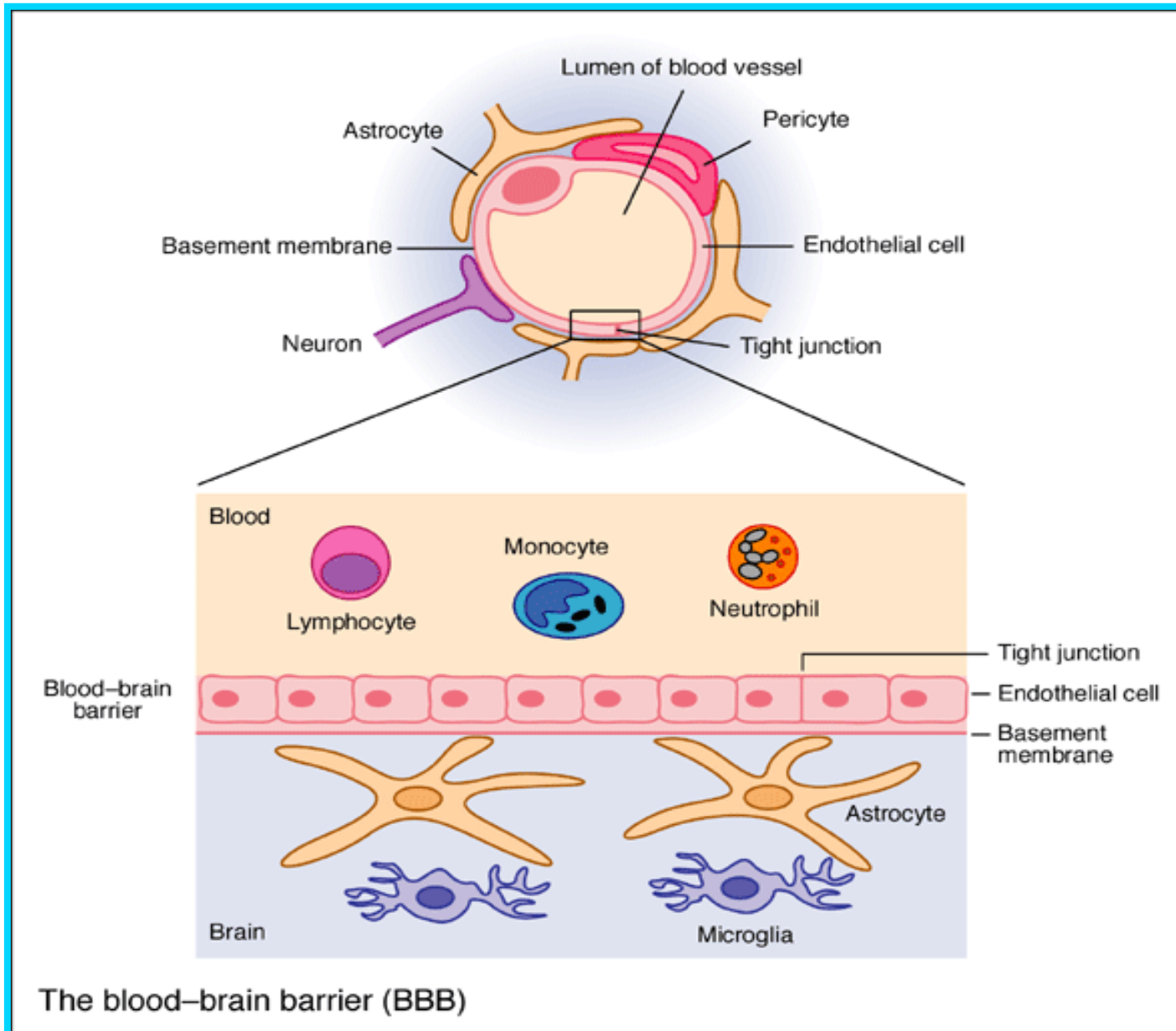
Transformació de glia radial en diferents tipus de formes astrocitàries



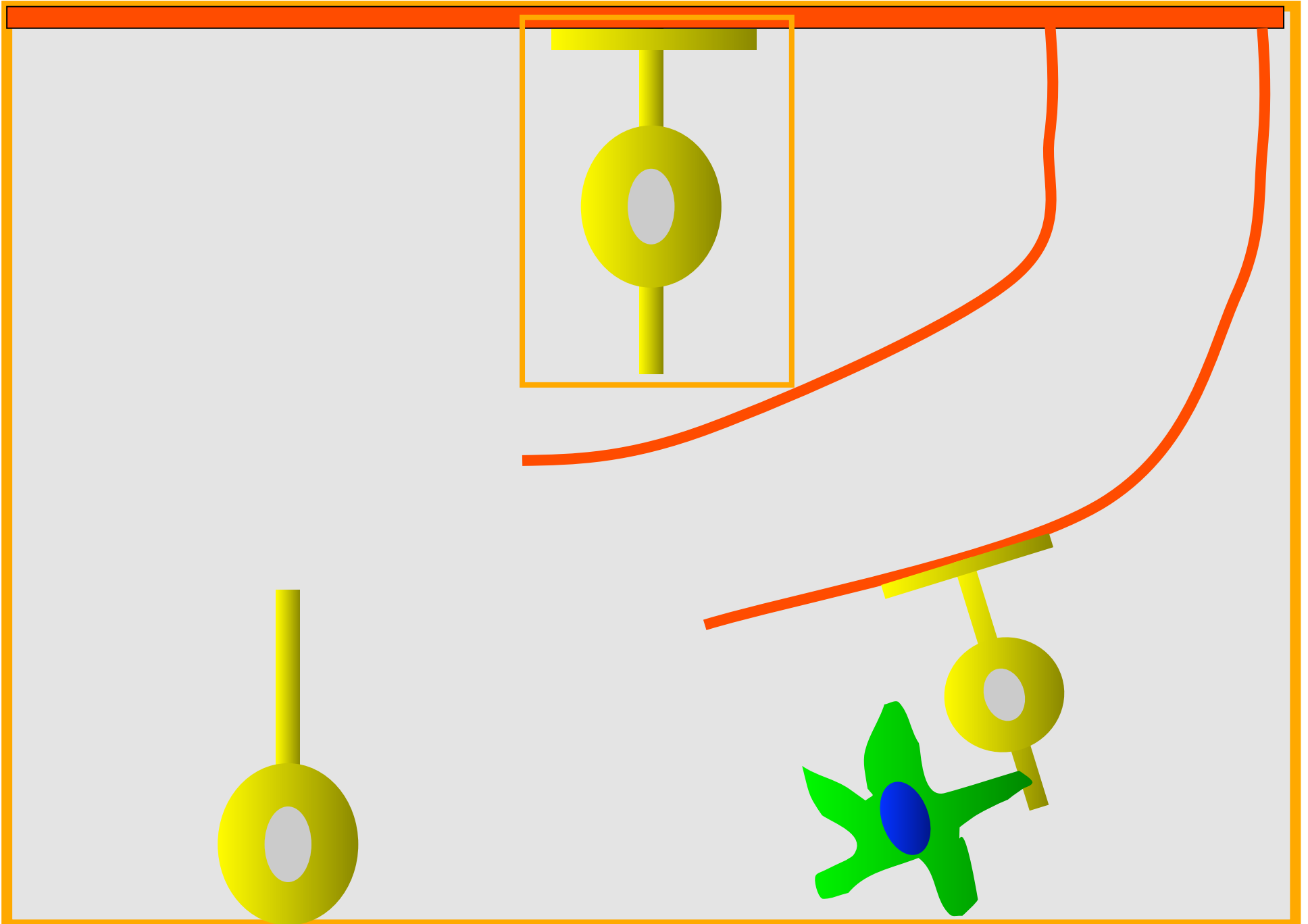


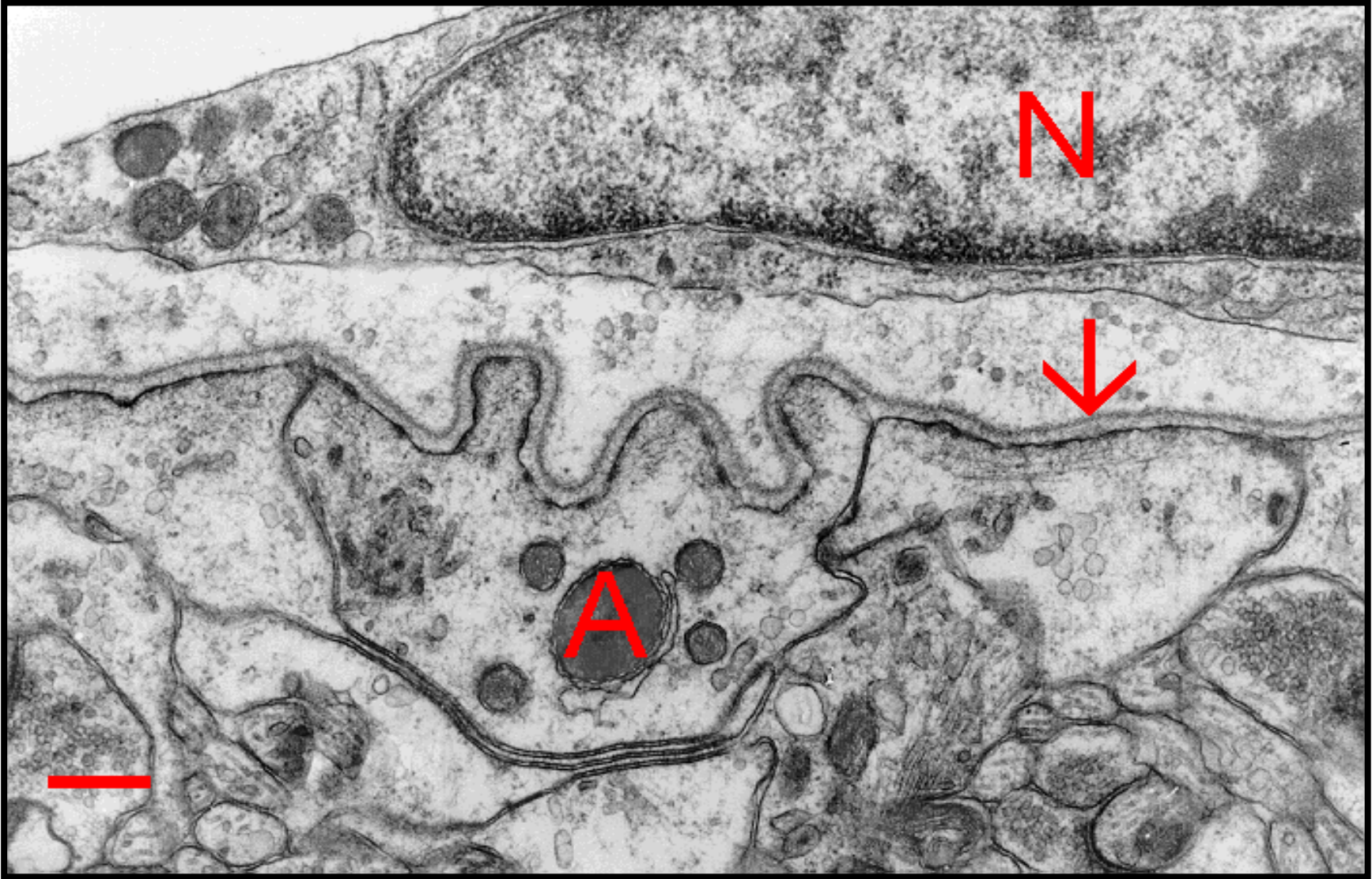


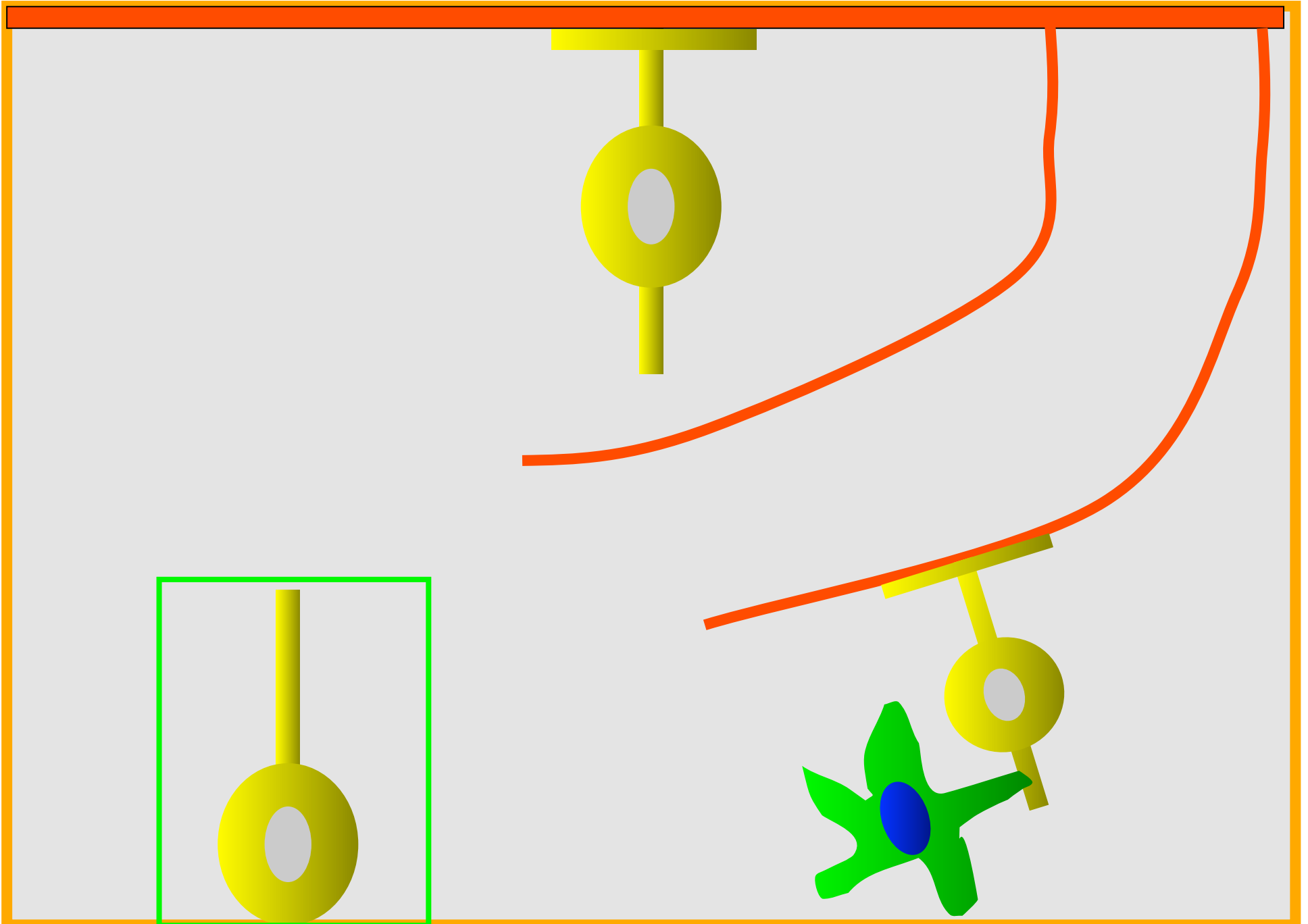


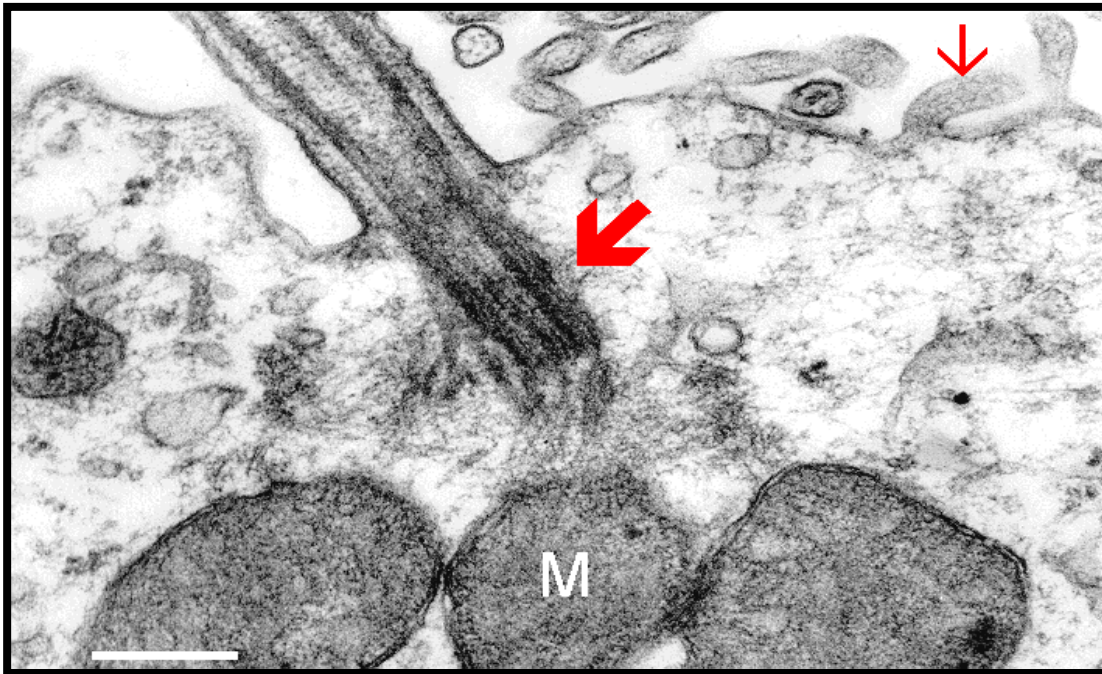
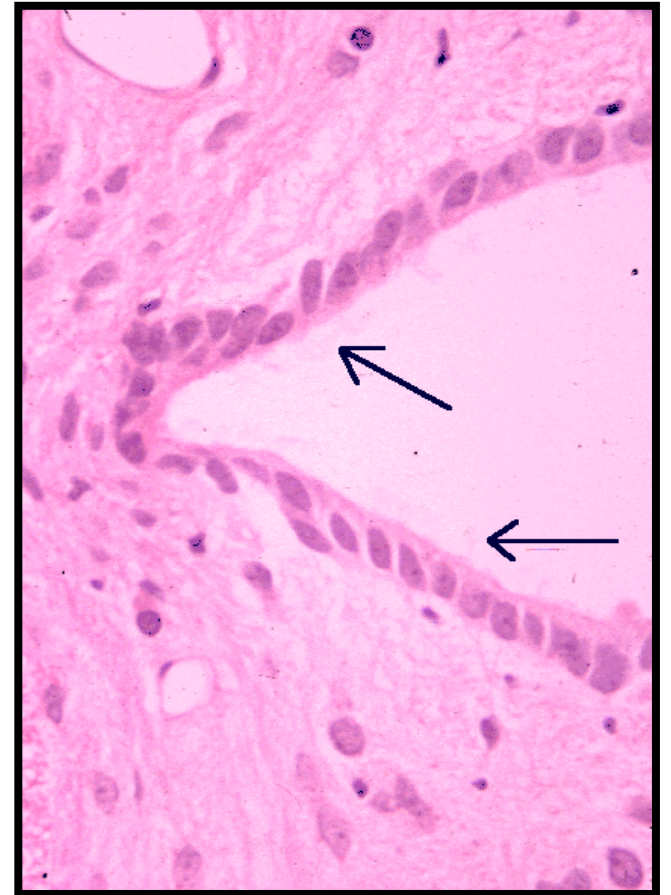
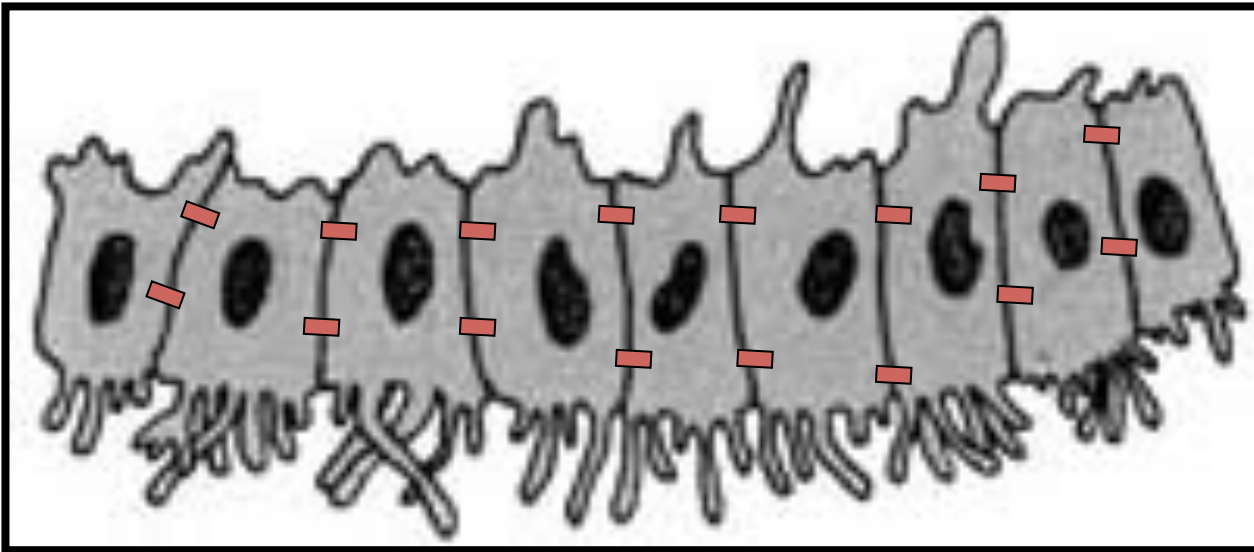


The blood-brain barrier (BBB)









Ultraestructura d'astròcits

Nucli

- Irregular
- Cromat. ± laxa, ↓ grumolls perifèrics
- Nuclèol no patent
- Cisterna perinucl. dilatada

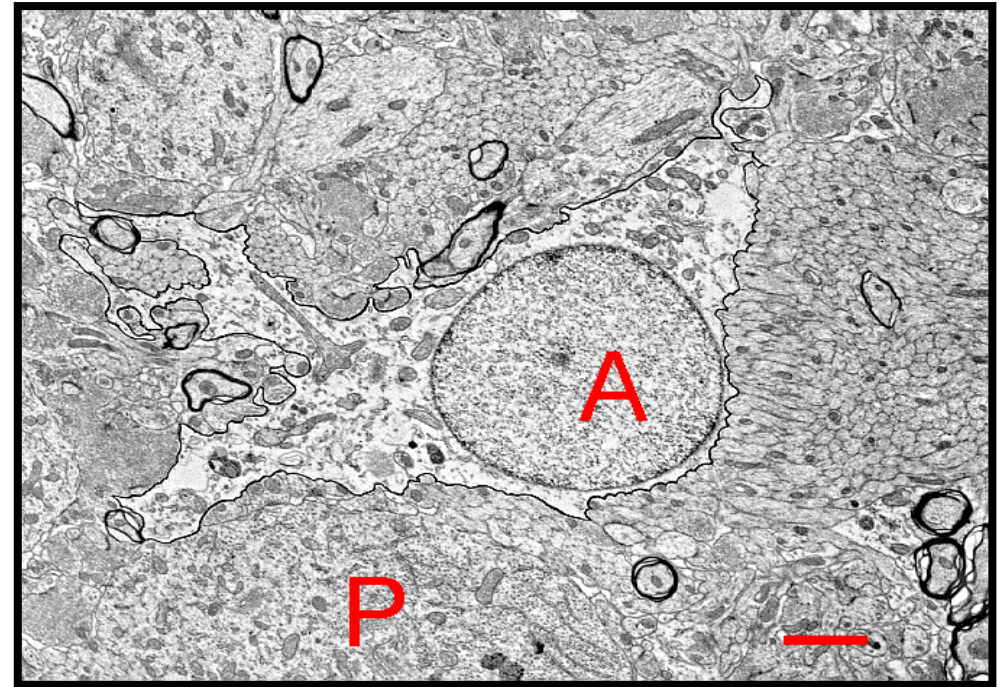
Citoplasma

* Soma

- Matriu clara
- ↓ RE
- ↓ Golgi
- Grans mitoc.
- Glucogen ↑ ↑
- Feixos de filam. interm.
= gliofilam. (GFAP)

* Ramificacions

- Gliofilaments
- Mitoc.
- Glucogen
- Peus perivasc.
- MGLS
- Revest. somes i dendr.



Ultraestructura d'astròcits

Nucli

- Irregular
- Cromat. ± laxa, ↓ grumolls perifèrics
- Nucleol no patent
- Cisterna perinucl. dilatada

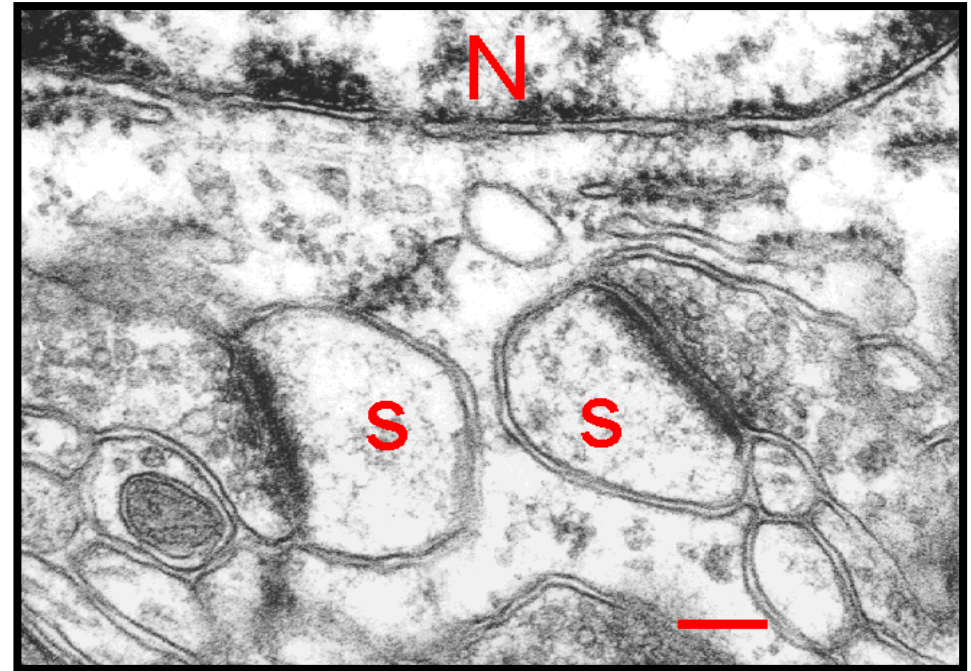
Citoplasma

* Soma

- Matriu clara
- ↓ RE
- ↓ Golgi
- Grans mitoc.
- Glucogen ↑ ↑
- Feixos de filam. interm.
= gliofilam. (GFAP)

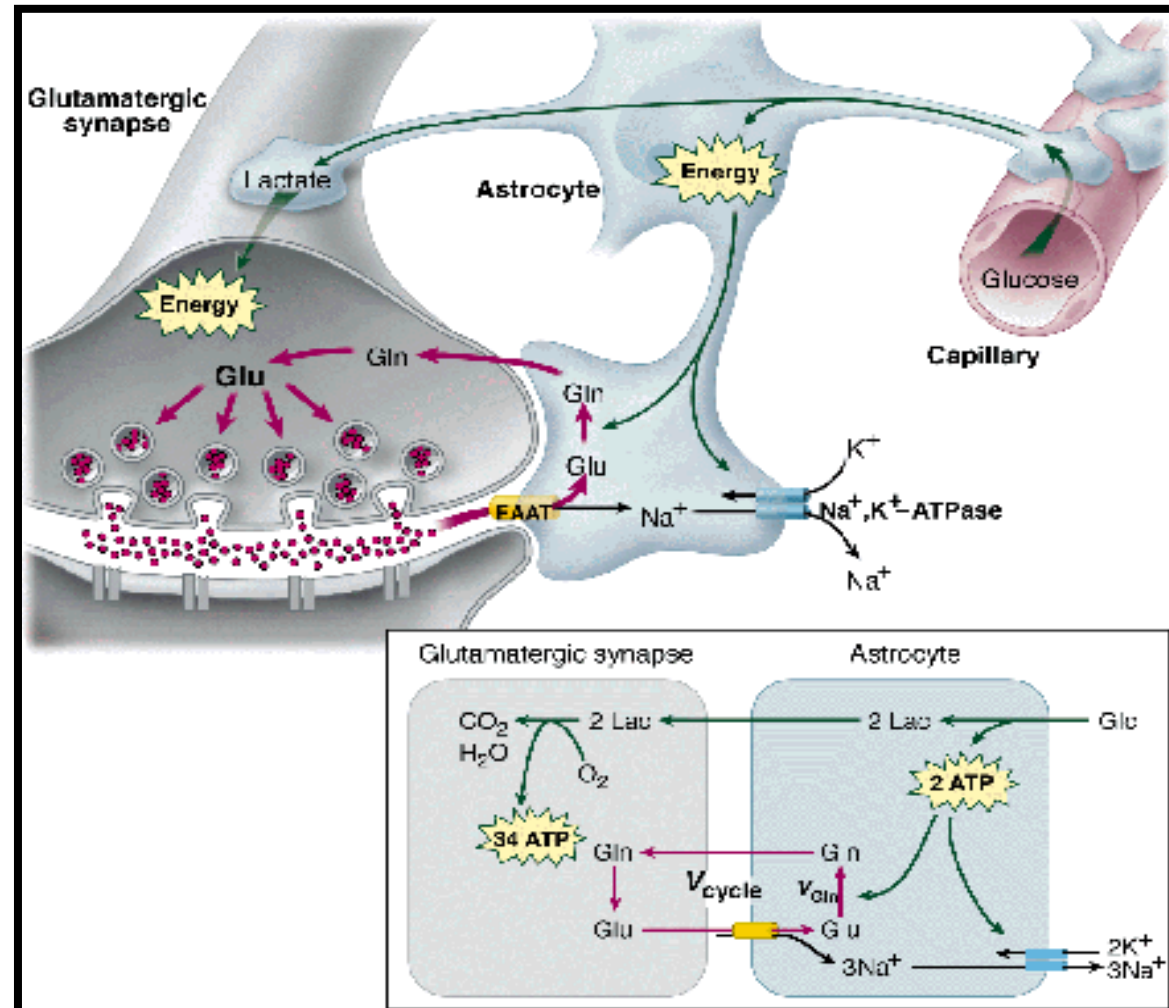
* Ramificacions

- Gliofilaments
- Mitoc.
- Glucogen
- Peus perivasc.
- MGLS
- Revest. somes i dendr.



Funcions d'astròcits

- Suport estructural: citosq. \uparrow (glia rad.)
- Reparació i neteja
- Aïllament d'elements mesodèrmics
- Recobriment de superf. no recept.
- Metabolisme de neurotransm.
- Homeòstasi del K^+



Funcions d'astròcits

- Suport estructural: citosq. ↑ (glia rad.)
- Reparació i neteja
- Aïllament d'elements mesodèrmics
- Recobriment de superf. no recept.
- Metabolisme de neurotransm.
- Homeòstasi del K⁺



New roles for astrocytes: The nightlife of an 'astrocyte'. La vida loca!

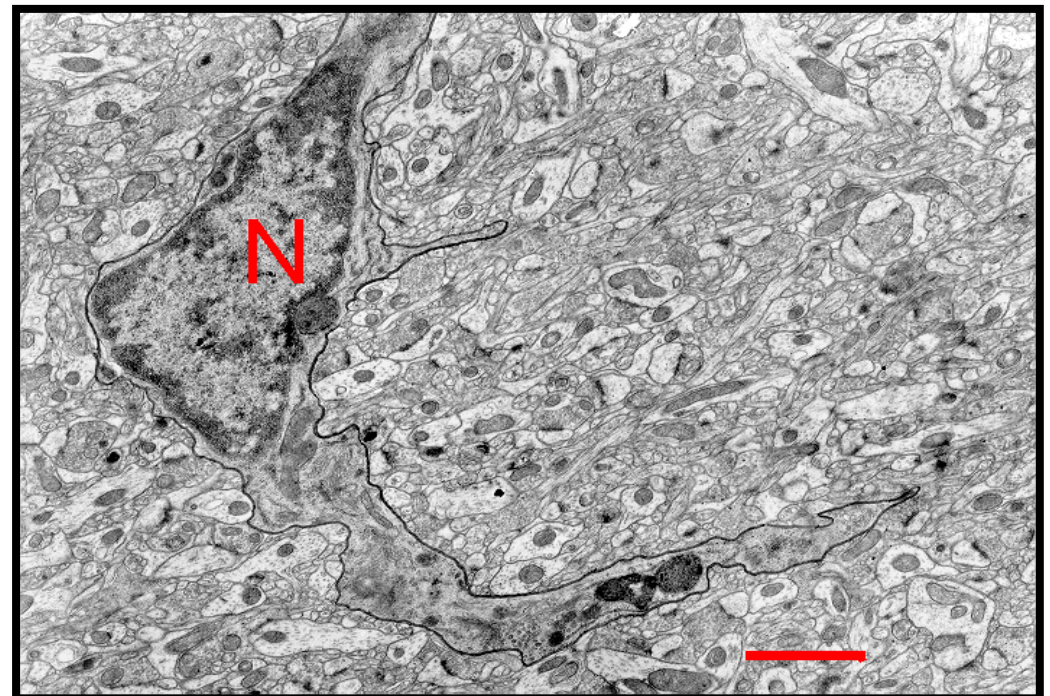
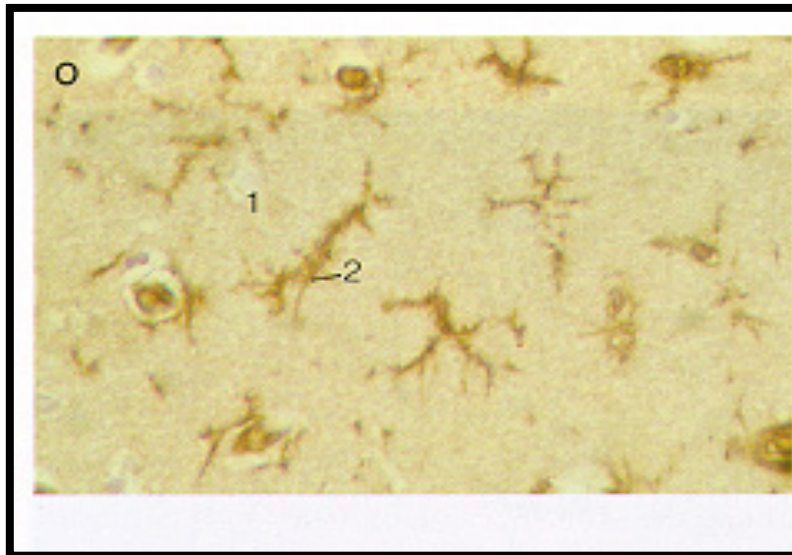
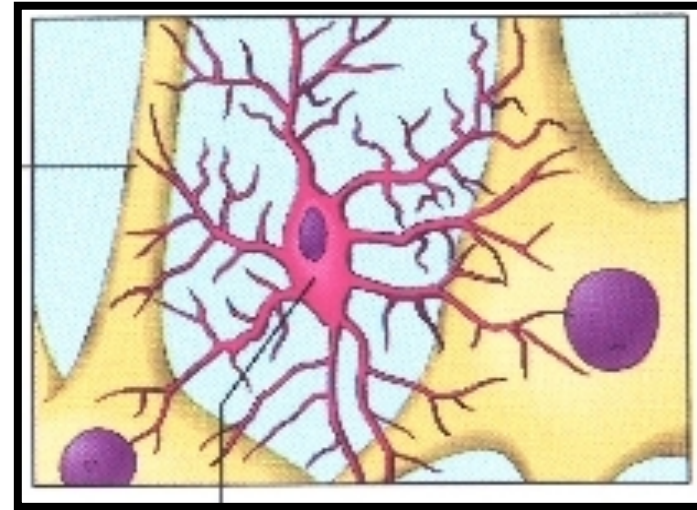
Philip J. Horner¹ and Theo D. Palmer²

¹University of Washington, Department of Neurosurgery, Harborview R&T Building, 325 Ninth Ave – Box 359655, Seattle, WA 98104, USA

²Stanford University, Department of Neurosurgery, MSLS P309, Mail Code 5487, 1201 Welch Road, Stanford, CA 94305-5487, USA

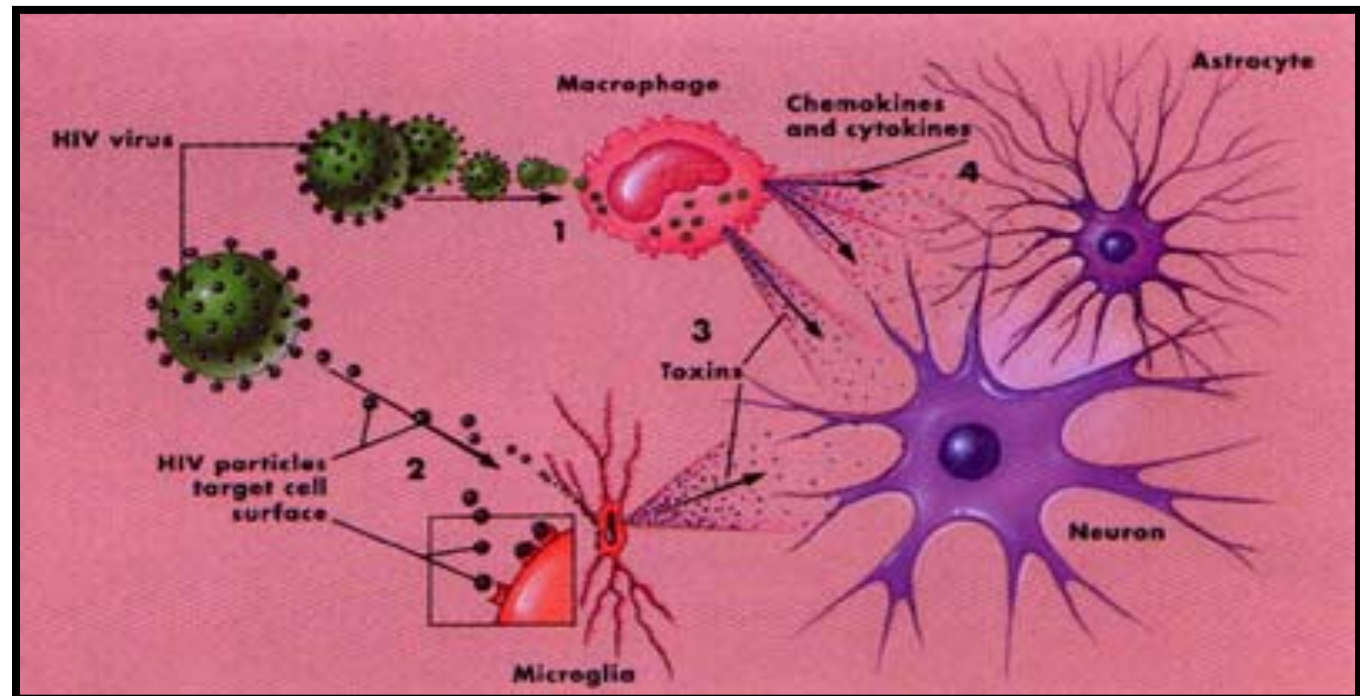
Micròglia

- Cèl. d'origen mesodèrmic
- SMF
- Soma fusiforme o estrellat
- 1 o + ramif. amb branques 2^{àies}
- Nucli irregular
- Cromatina en grumolls
- Poc citopl.
- * Marcadors
 - NDPasa
 - Marcadors de macròfags
 - Lectines
- * Funció



Micròglia

- Cèl. d'origen mesodèrmic
- SMF
- Soma fusiforme o estrellat
- 1 ó + ramif. amb branques 2^{àries}
- Nucli irregular
- Cromatina en grumolls
- Poc citopl.
- * Marcadors
 - NDPasa
 - Marcadors de macròfags
 - Lectines
- * Funció



Oligodendròglia

- * Formació de beines de mielina
- * Clars--> Intermedis --> Obscurs
- Cos cel·lular esfèric o poligonal
- Ramificacions curtes
- Nucli ↓
- ↓ citoplasm.

* C. DE SCHWAN --> SNP

* Marcadors

CNP

(Cyclic nucleotide diphosphatase)

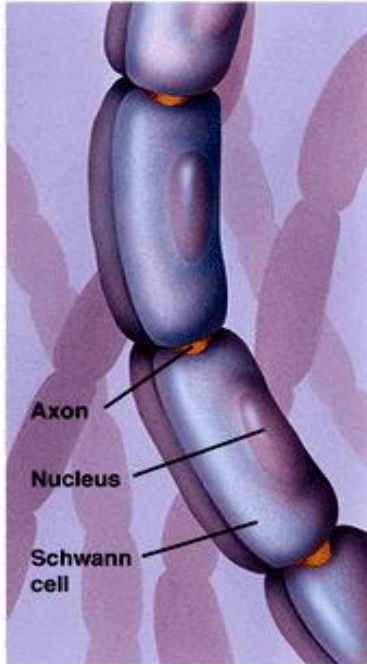
MBP



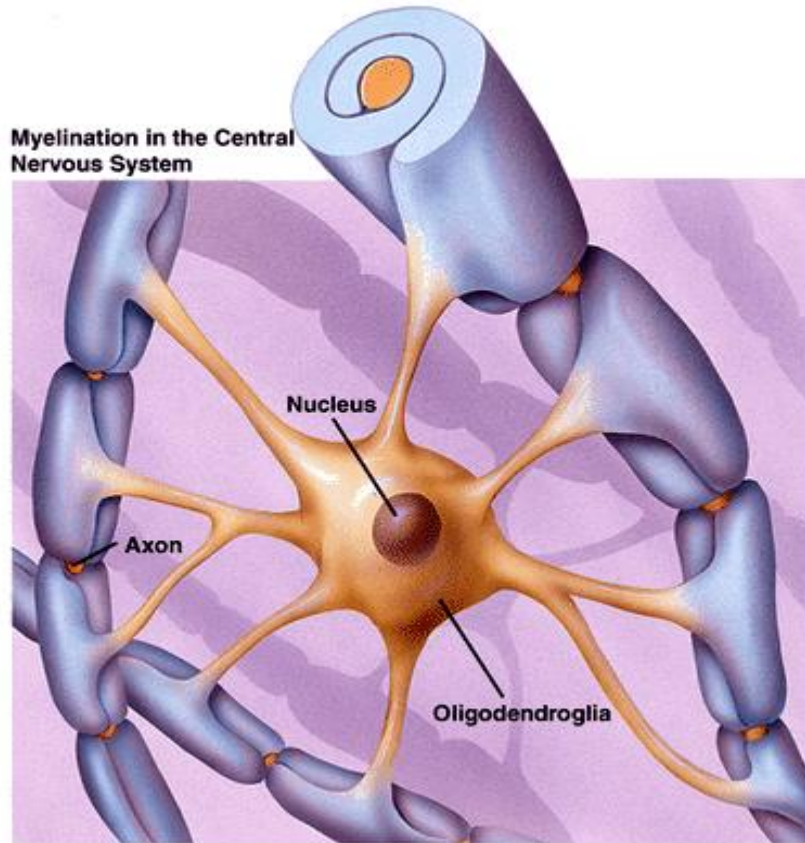
Oligodendroglia

► Myelination of PNS and CNS Axons

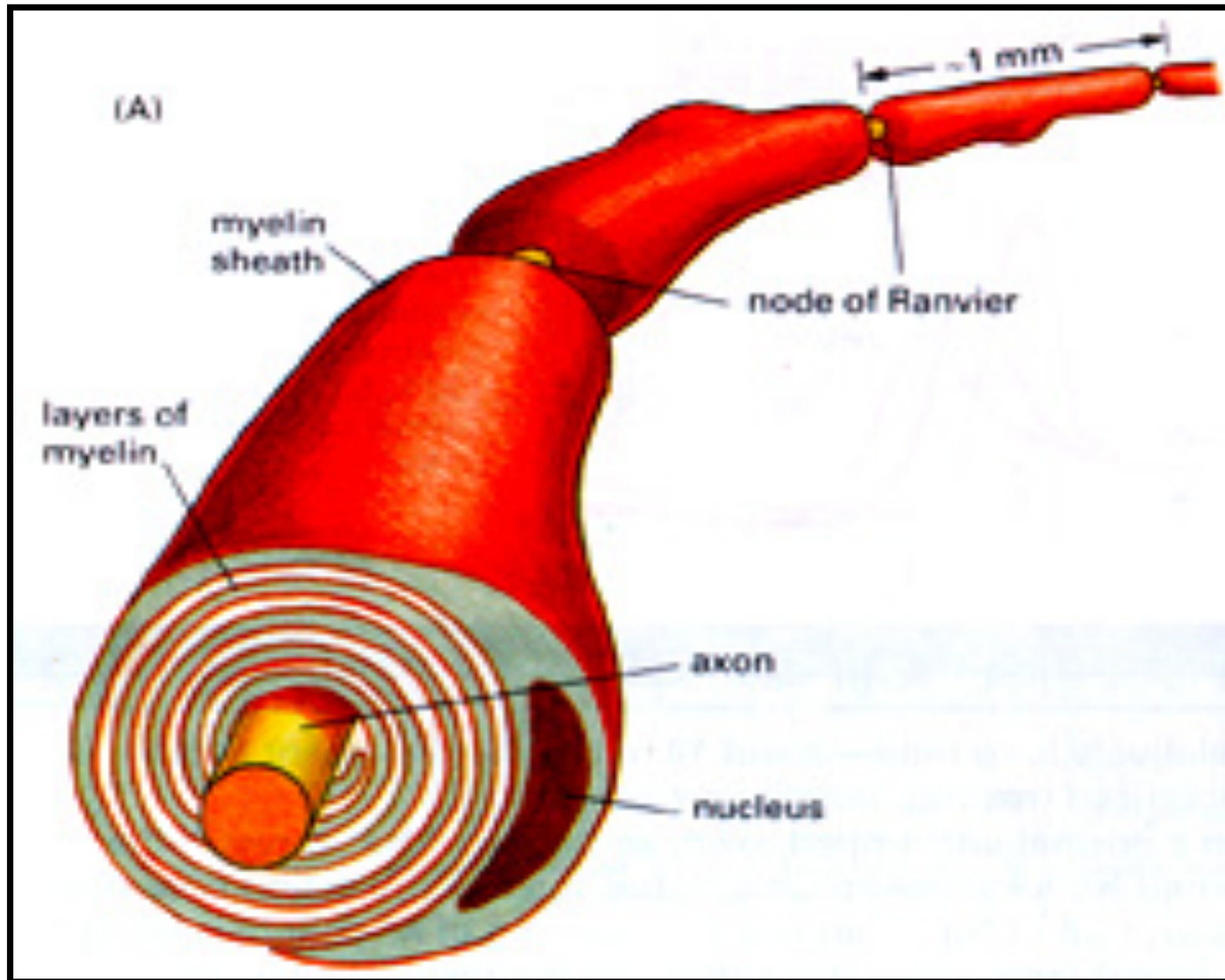
Myelination in the Peripheral Nervous System



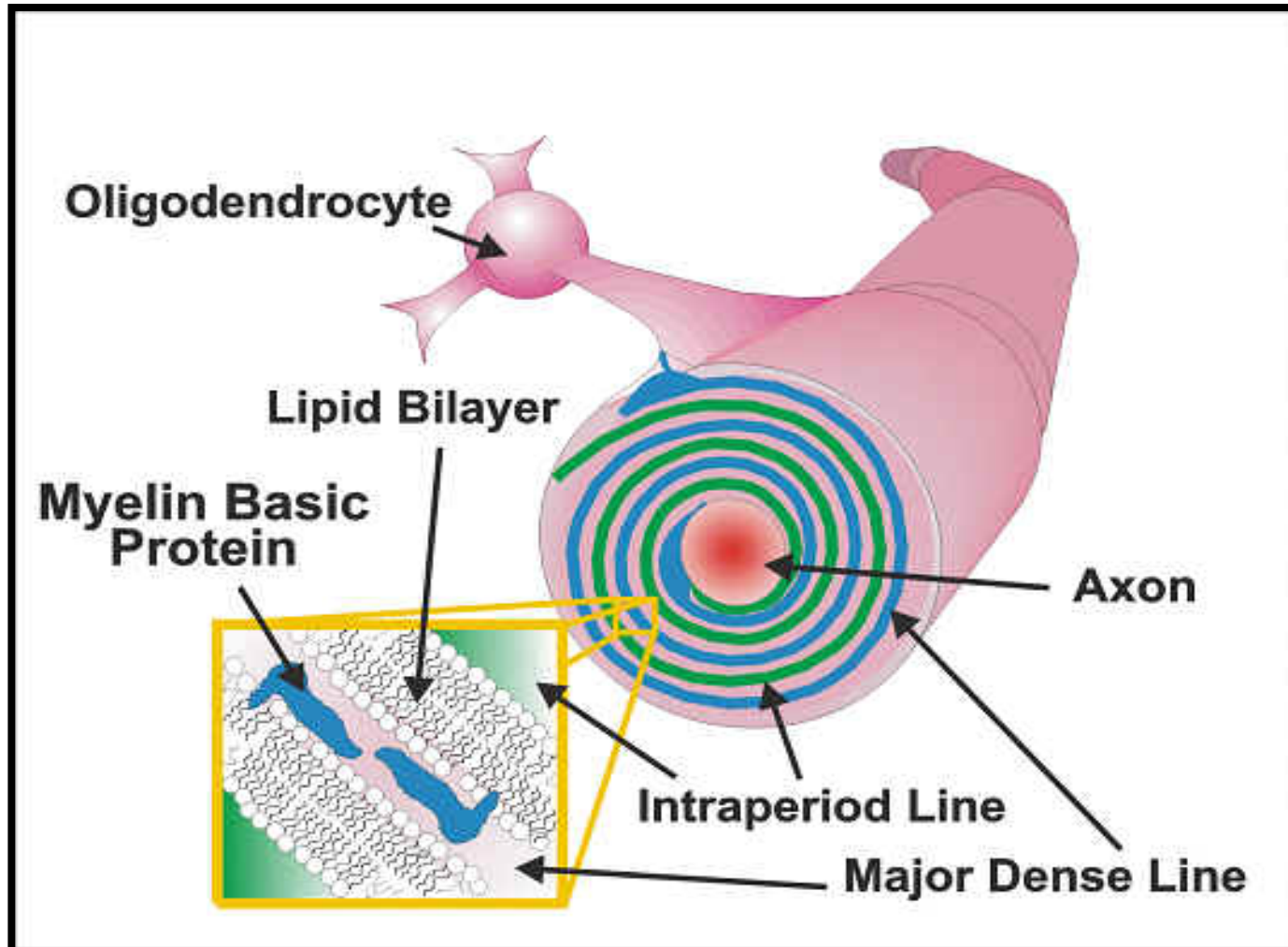
Myelination in the Central Nervous System



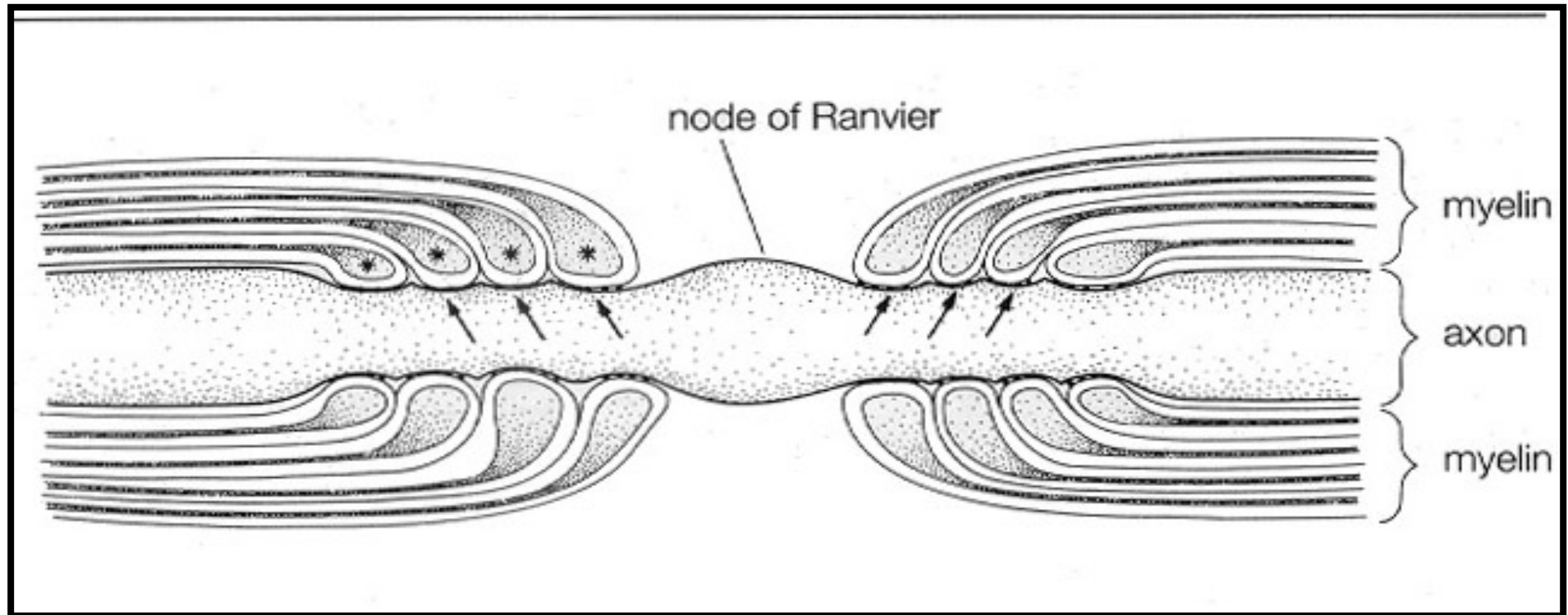
Oligodendroglia



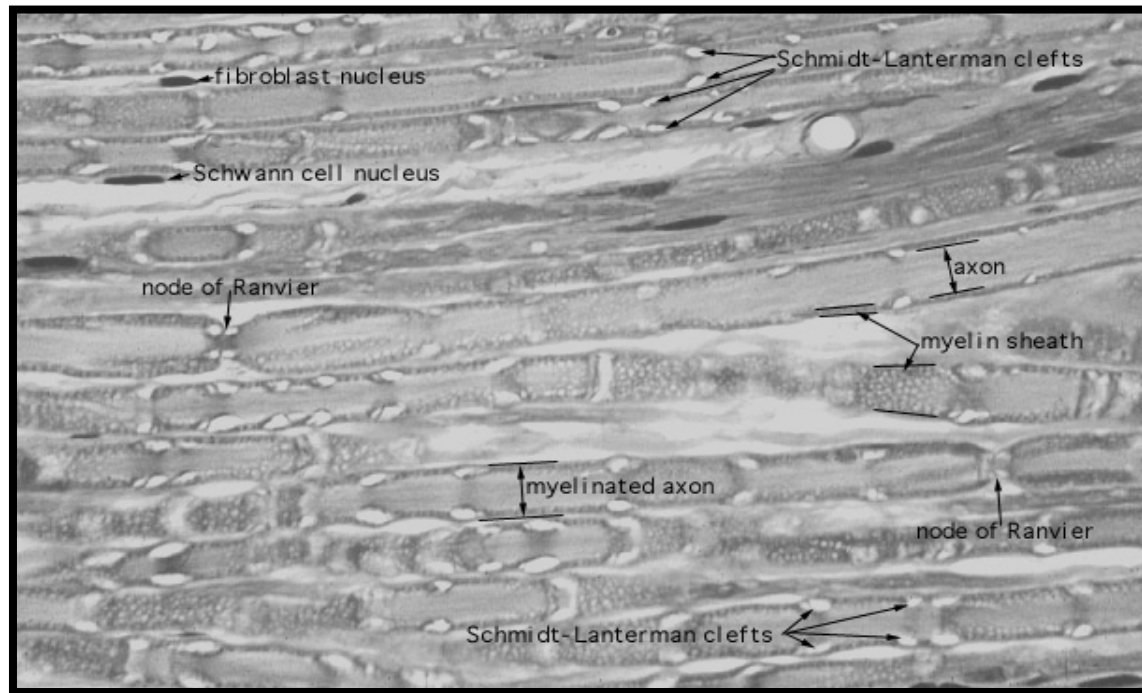
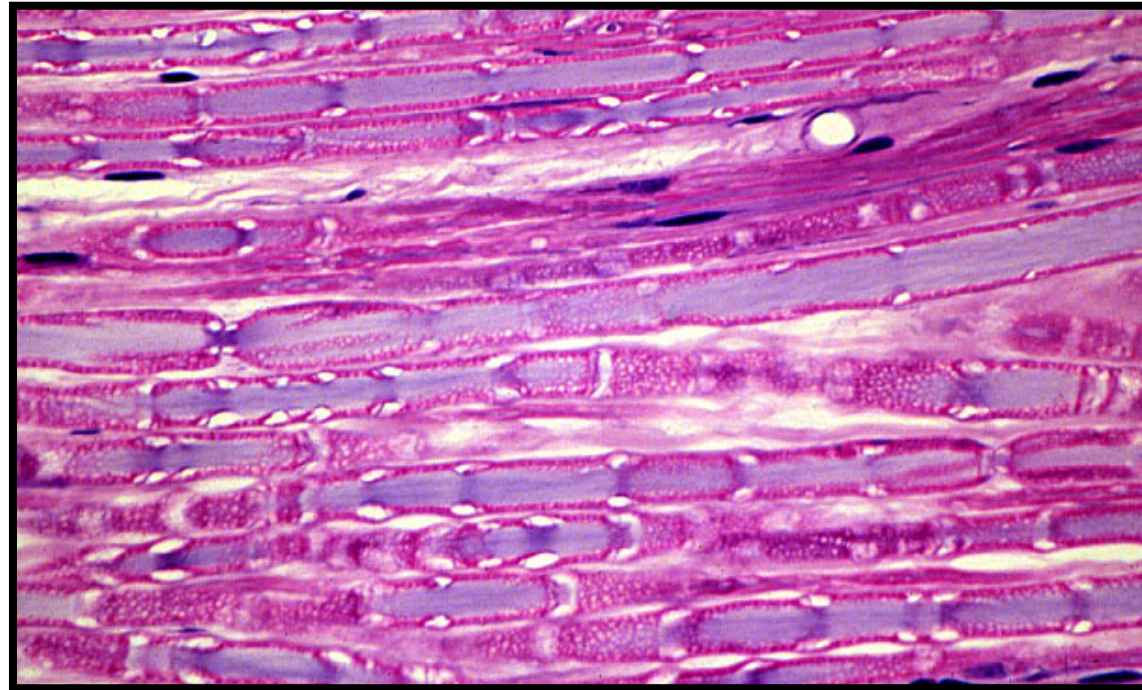
Oligodendroglia



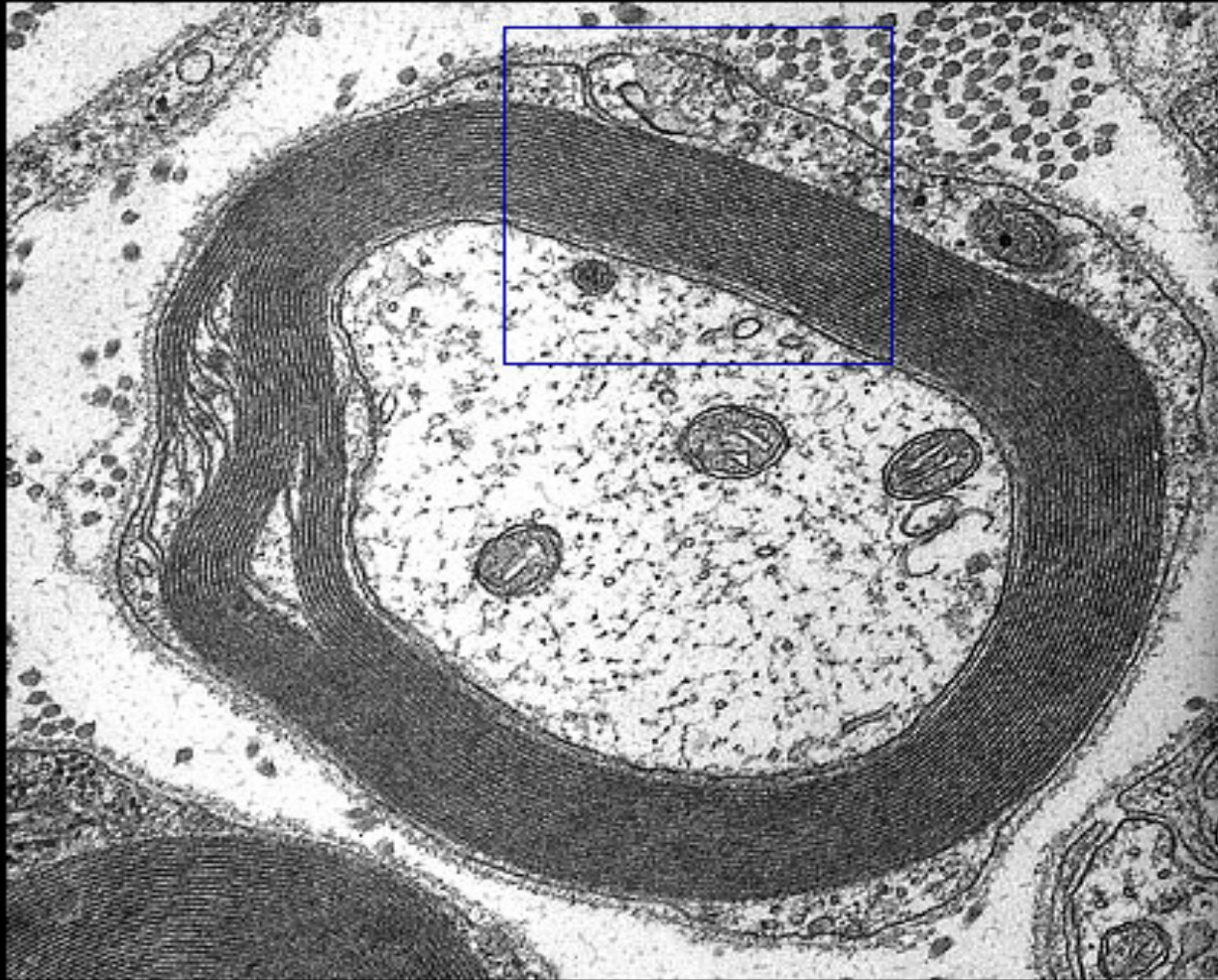
Oligodendroglia



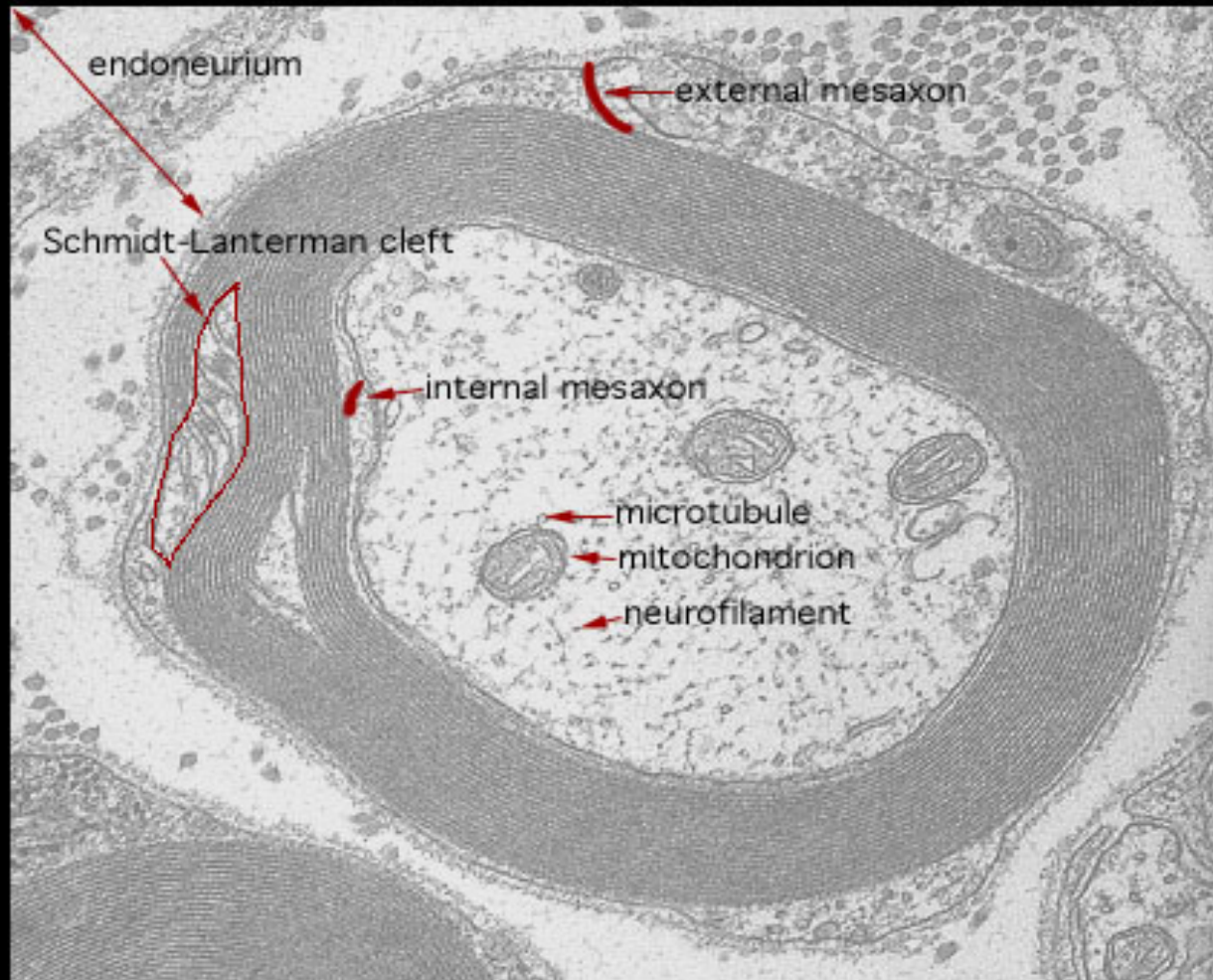
Oligodendròglia



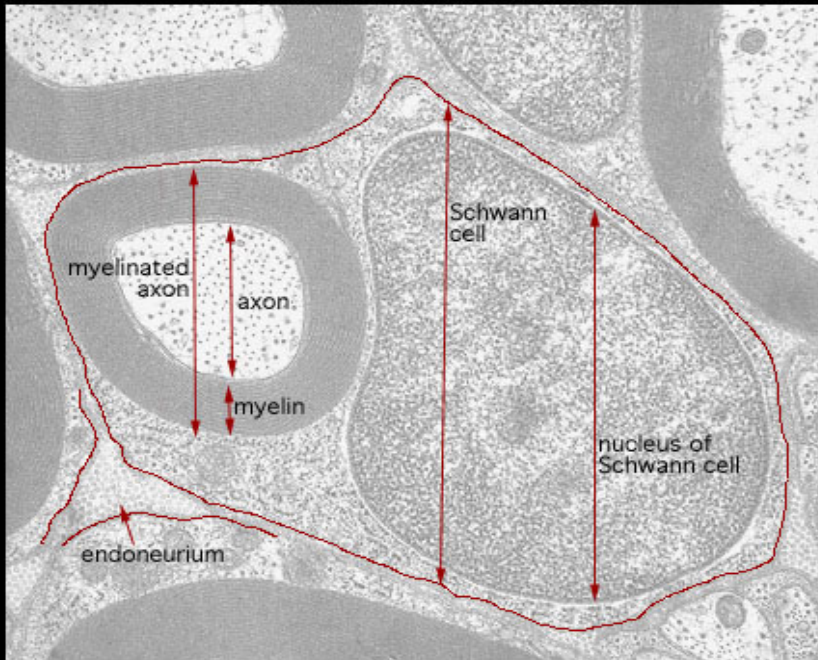
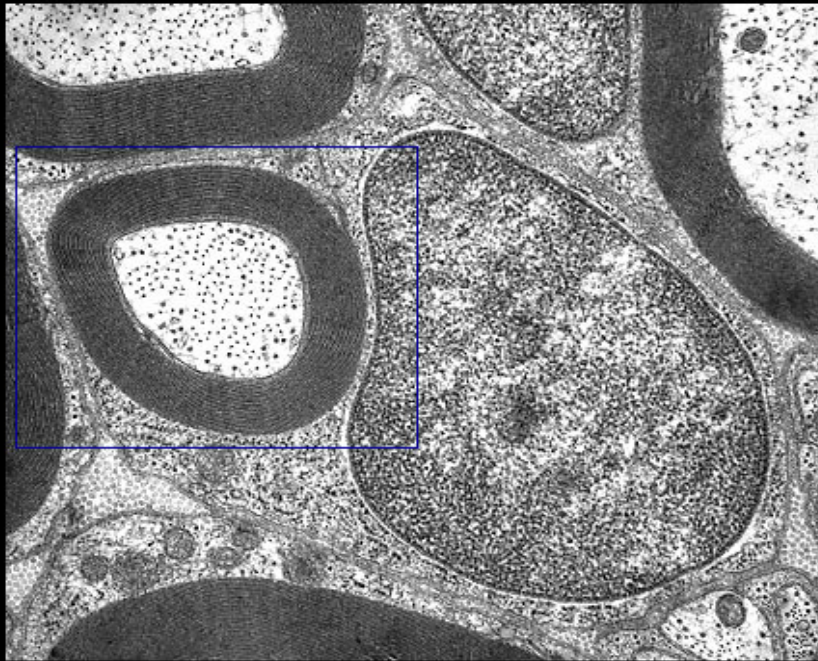
Oligodendròglia



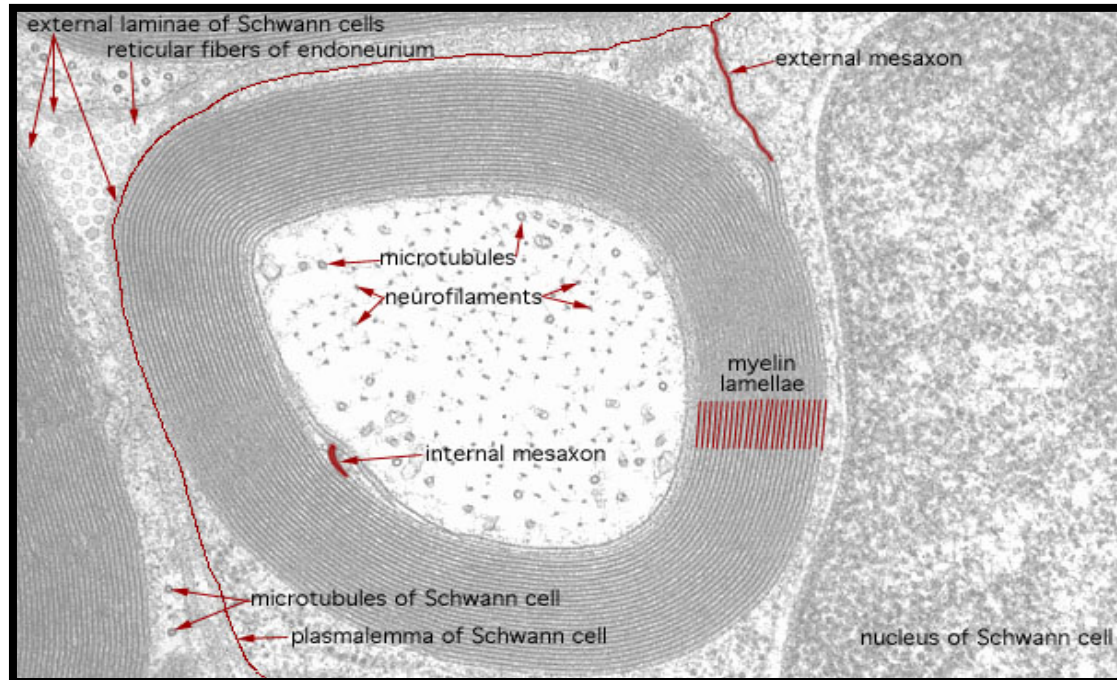
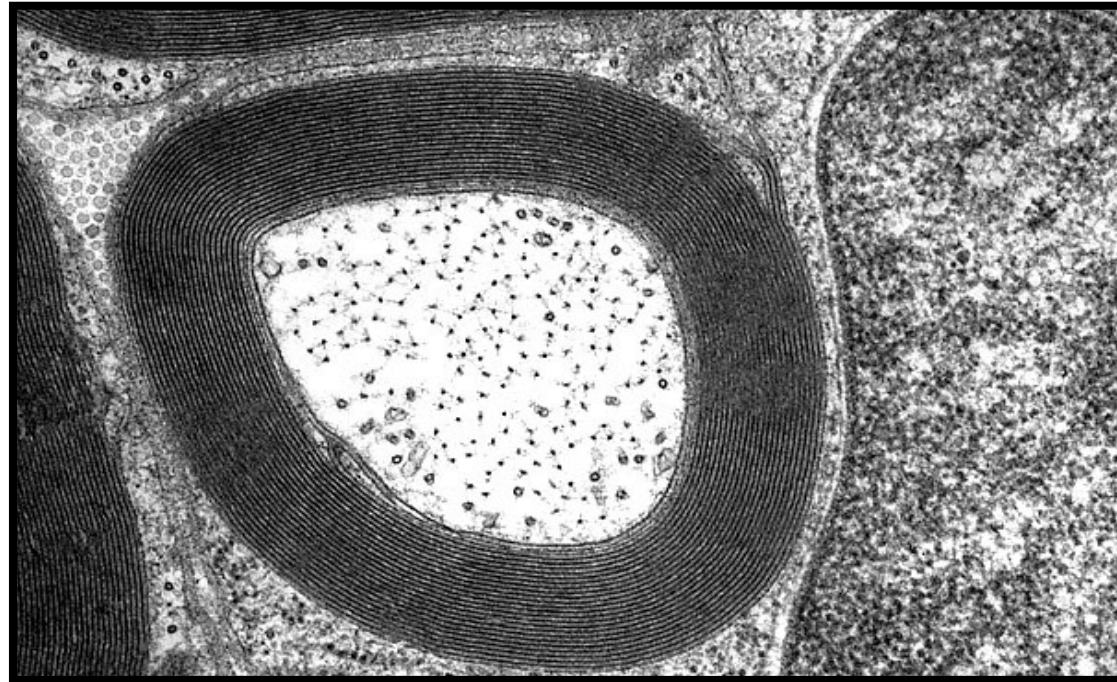
Oligodendròglia



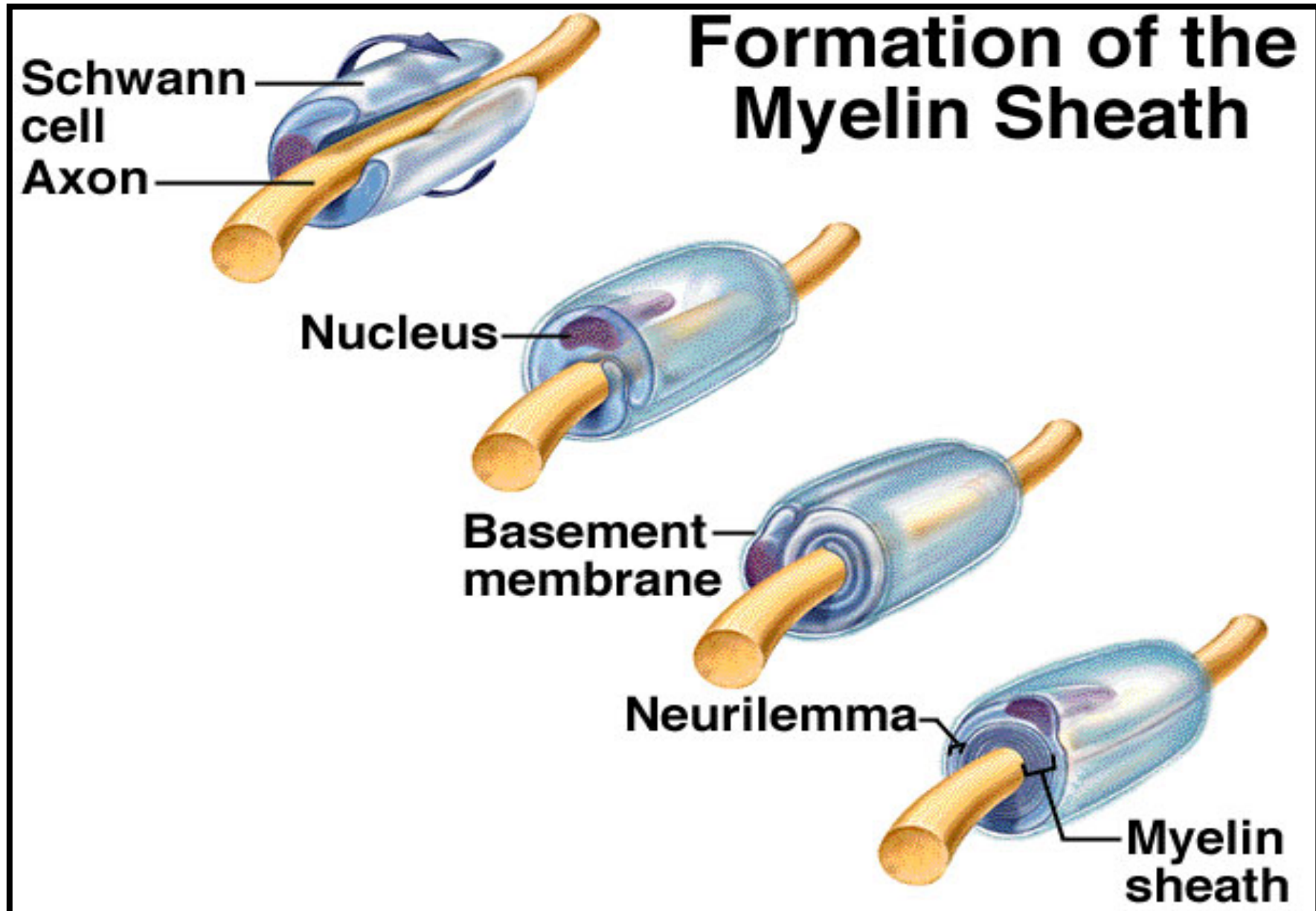
Oligodendroglia



Oligodendròglia

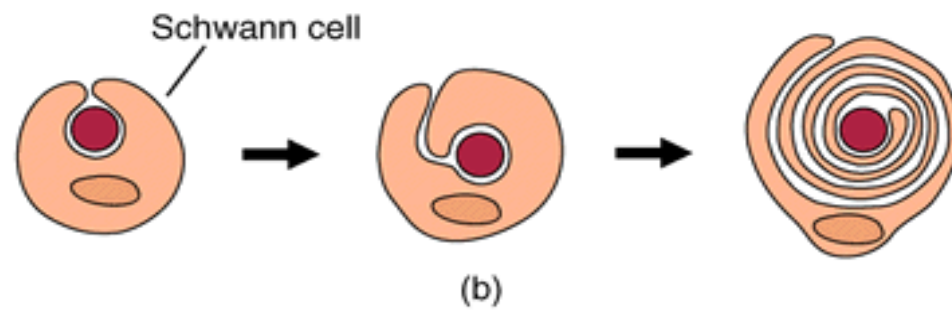
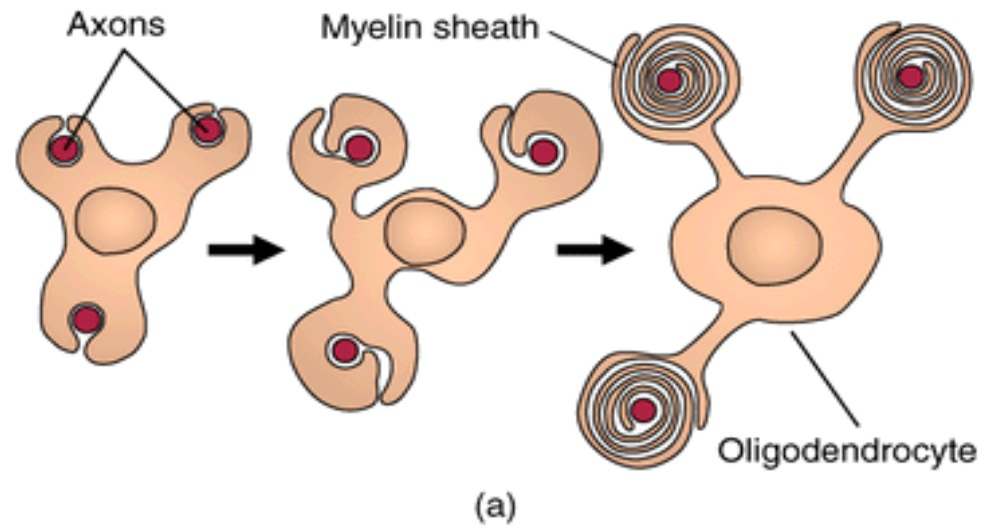


Oligodendroglia



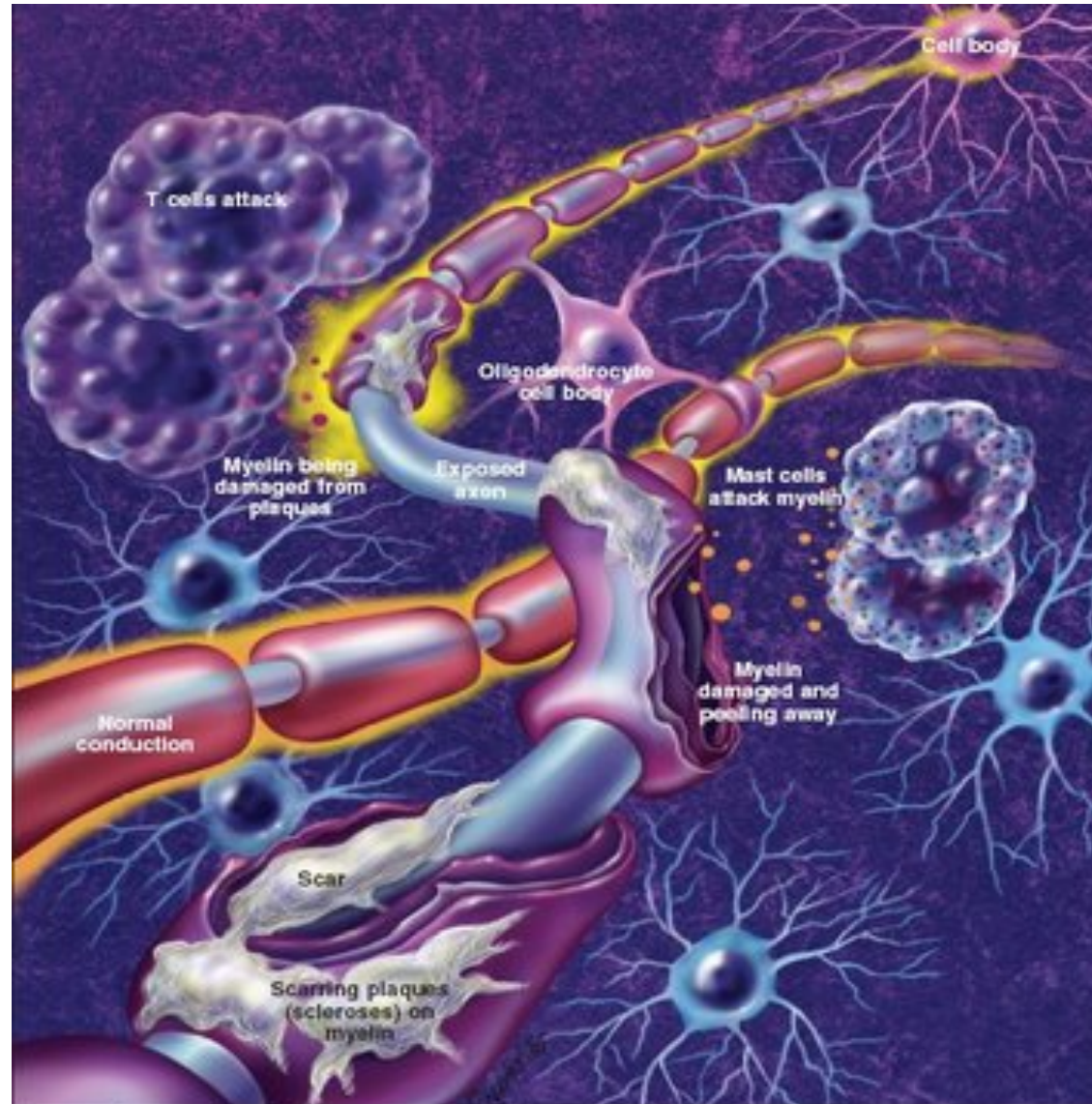
Oligodendroglia

► Formation of Myelin



Oligodendròglia

Conducció saltatòria / Esclerosi múltiple



Inflammation, loss of myelin, scarring, and axonal damage represent the neurological insults that characterize MS.