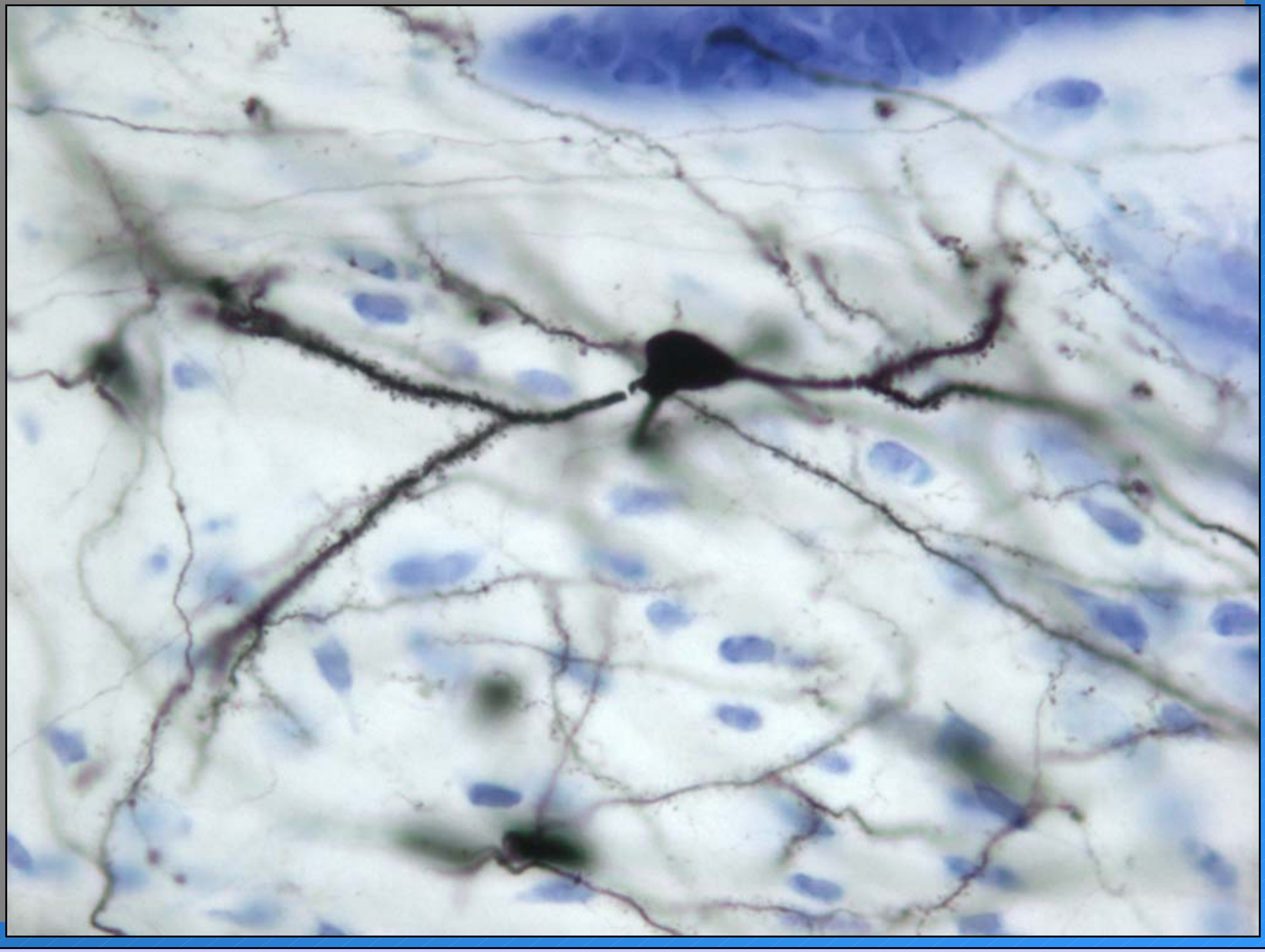
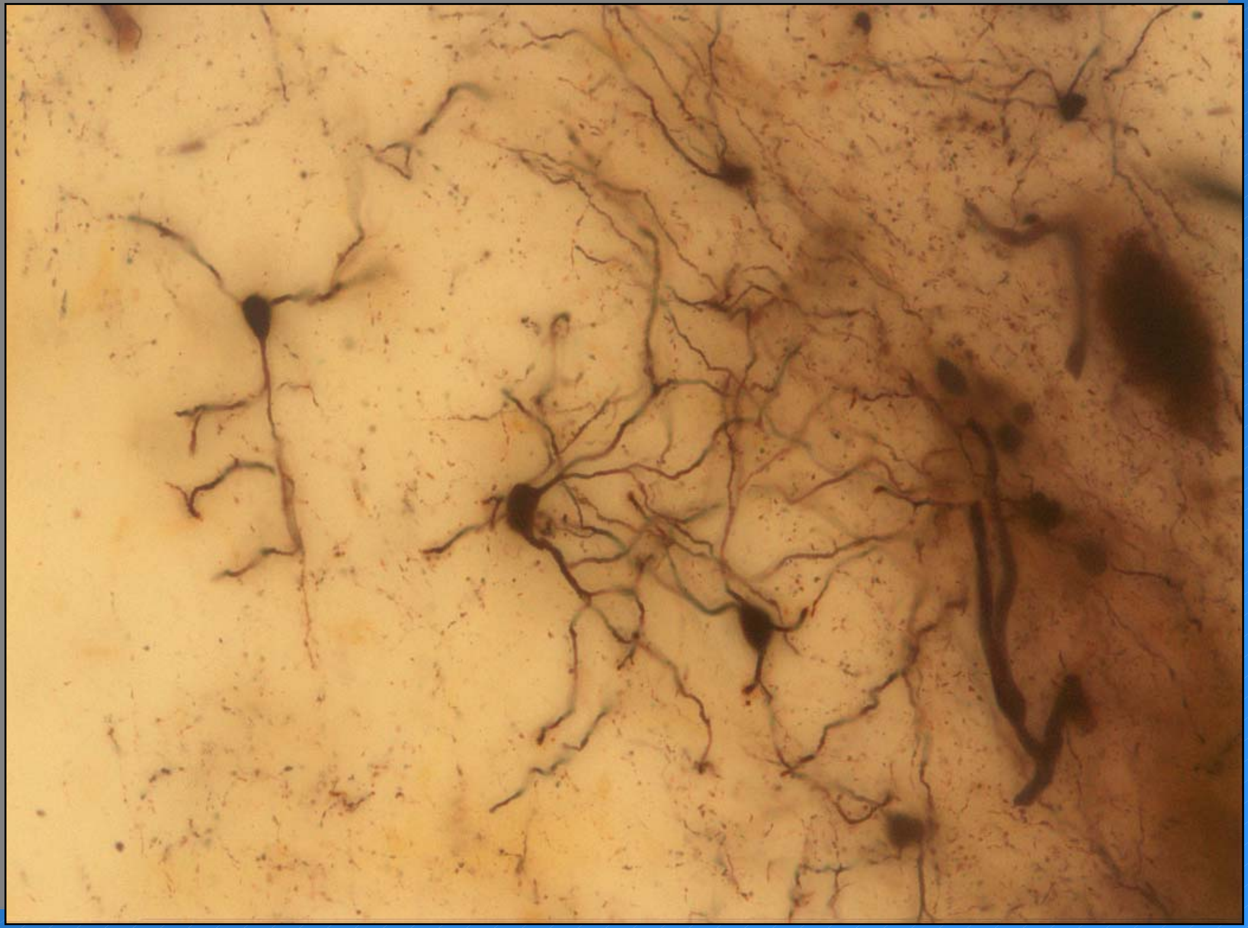
LAS NEURONAS SON CÉLULAS CON MORFOLOGÍAS EXTREMADAMENTE COMPLEJAS...



High magnification photomicrograph of a septo-hypothalamic projection neuron of the lateral septum of a lizard brain retrogradely labelled in a tracing experiment. Note the multipolar morphology and the numerous dendritic spines of this cell type. Nissl counterstaining.

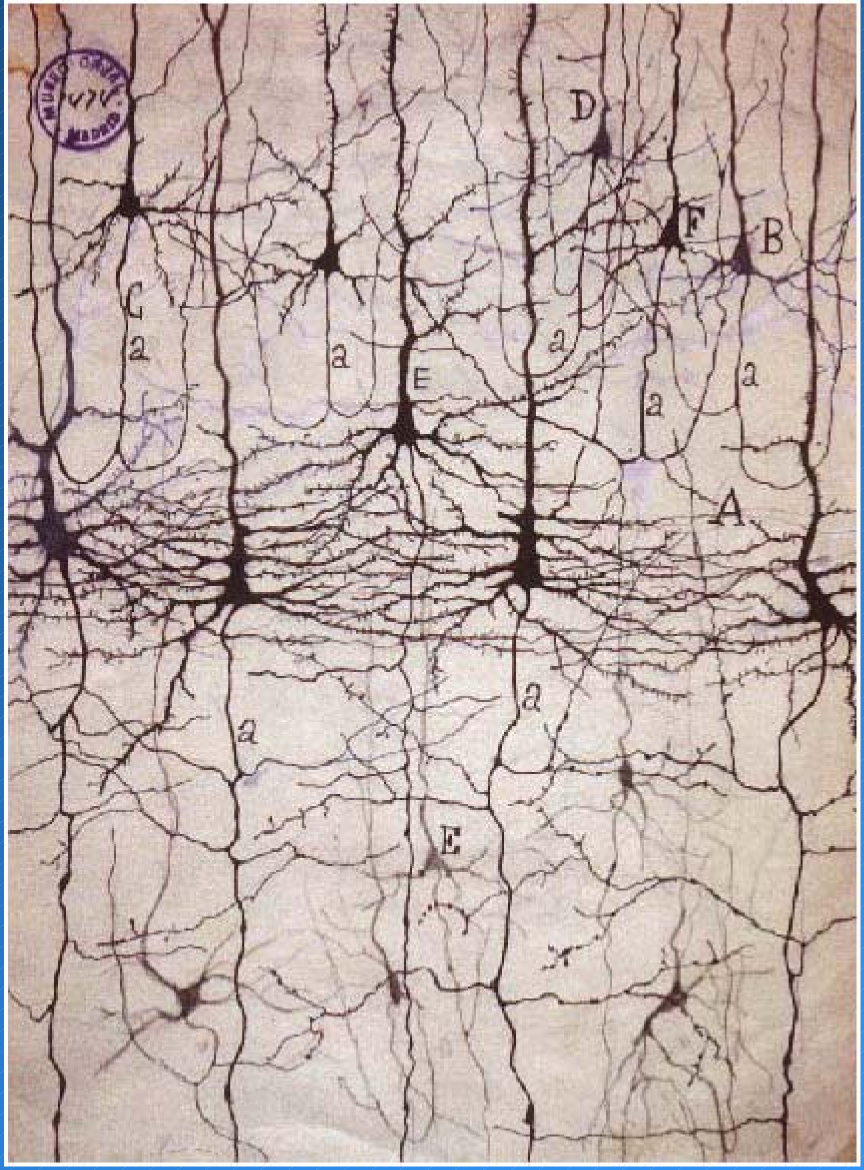
Fuente: Lanuza and Martínez-García (2008) *Evolution of Septal Nuclei*. In: Binder et al. (eds.), Encyclopedia of Neurocience (Springer)

… ADEMÁS DE VARIADAS …



High magnification photomicrograph of Golgi-stained cells in the lateral septum of the rat brain illustrating the morphological diversity. Fuente: Lanuza and Martínez-García (2008) *Evolution of Septal Nuclei*. In: Binder et al. (eds.), Encyclopedia of Neurocience (Springer)

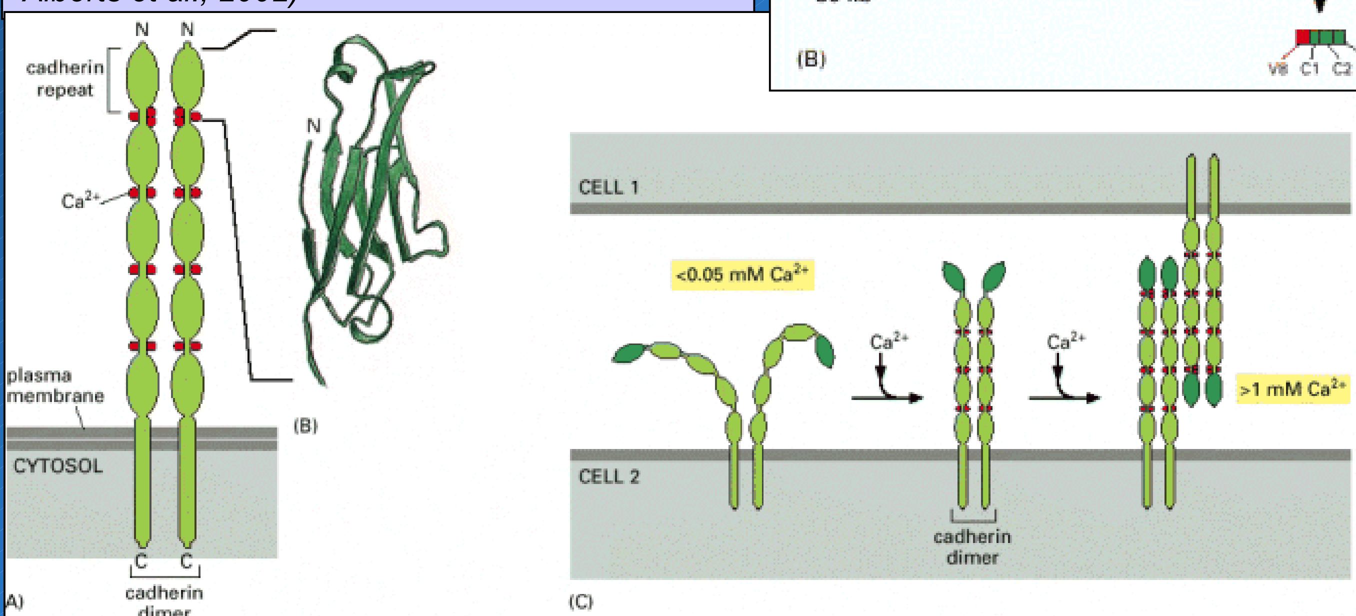
...QUE ADEMÁS HAN DE CONECTARSE ENTRE SÍ FORMANDO CIRCUITOS AÚN MÁS COMPLEJOS

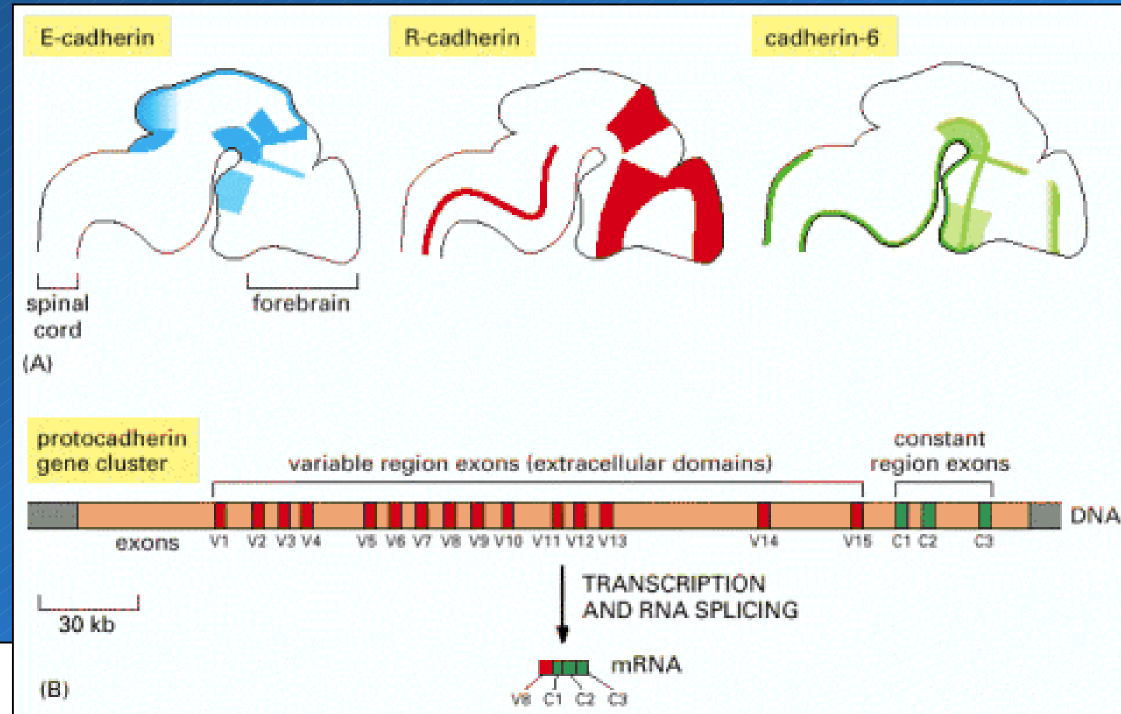


Dibujo de Cajal que muestra neuronas de la corteza vsual del gato impregnadas mediante la técnica de Golgi, publicado en 1921 (Textura de la corteza visual del gato. Archivos de Neurobiología 2: 338-368). Fuente: MIT Encyclopedia of the Cognitive Sciences, MIT Press, Cambridge, MA (1998).

Numerosos tipos diferentes de cadherinas neurales participan en las adhesiones generadas por los axones en crecimiento

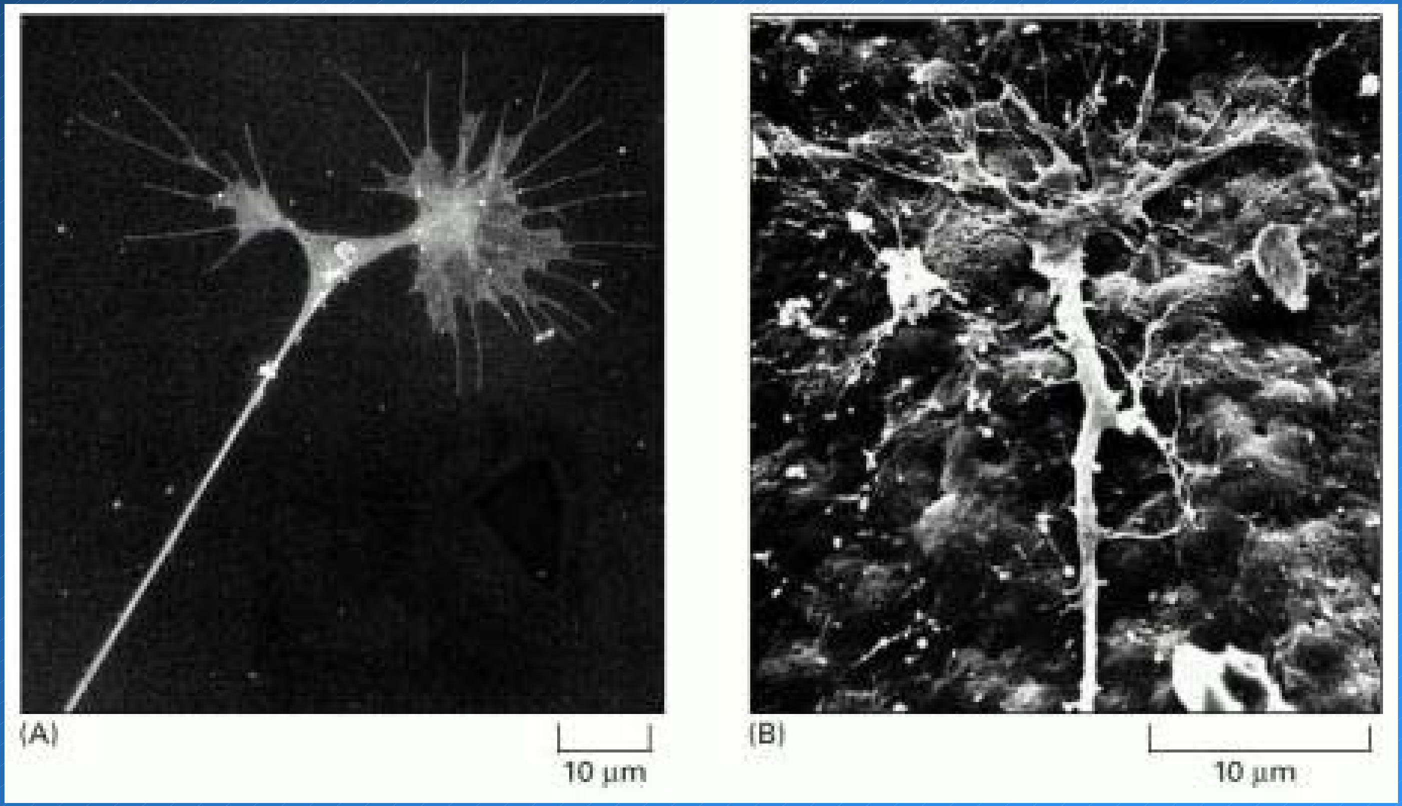
The structure and function of cadherins. (A) A classical cadherin molecule. The protein is a homodimer, with the extracellular part of each polypeptide folded into five cadherin repeats. There are Ca2+-binding sites between each pair of repeats. (B) The crystal structure of a single cadherin repeat, which resembles an immunoglobulin (Ig) domain. (C) The influence of extracellular Ca2+. As the amount of Ca2+ increases, the extracellular parts of the cadherin chains become more rigid. When enough Ca2+ is bound, the cadherin dimer extends from the surface, where it can bind to a cadherin dimer on a neighboring cell. If Ca2+ is removed, the extracellular part of the protein becomes floppy and is degraded by proteolytic enzymes.*(Fuente: Alberts et al., 2002)*





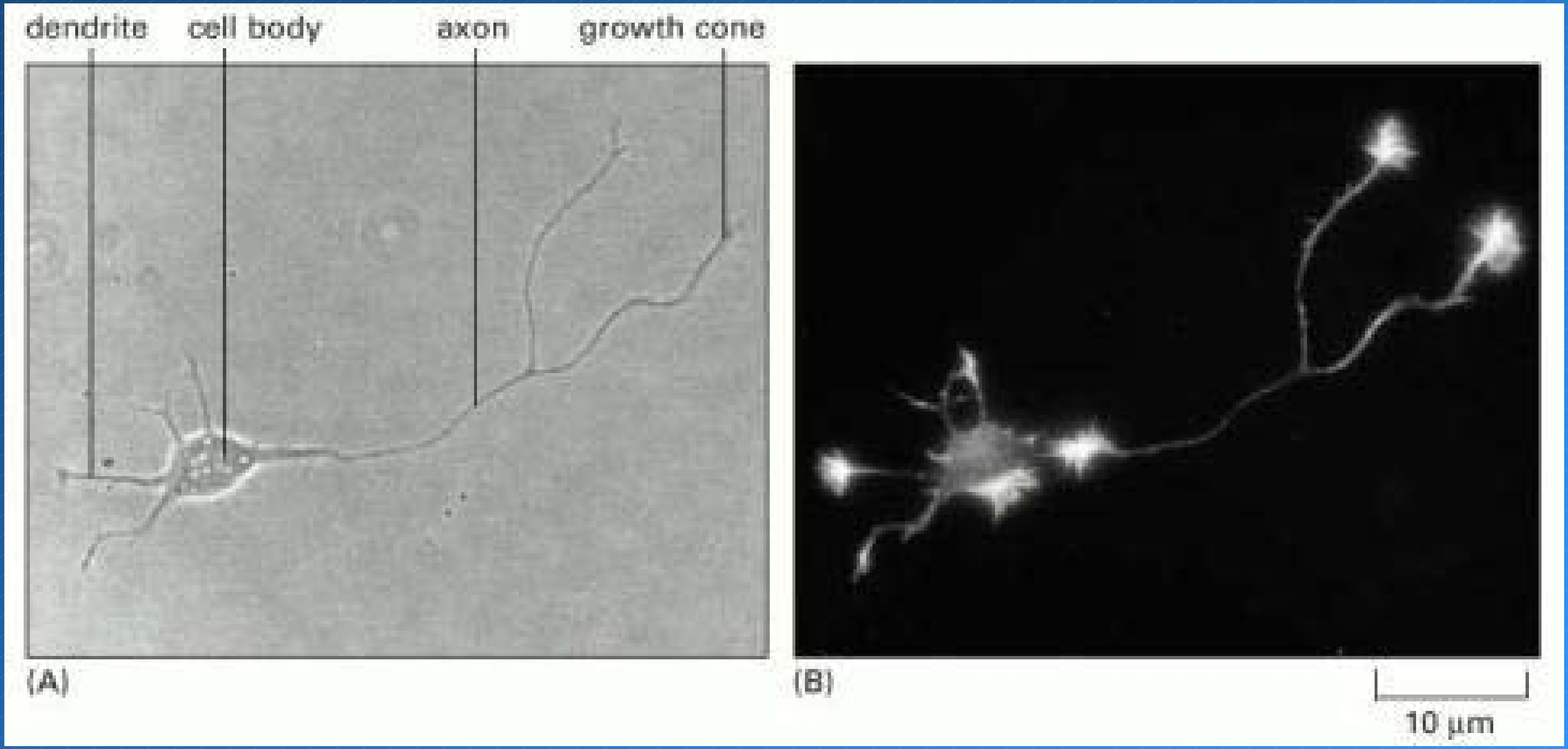
Cadherin diversity in the central nervous system. (A) Expression patterns for three classical cadherins in the embryonic mouse brain. (B) The arrangement of exons that encode the members of one of the three known protocadherin families of nonclassical cadherins in humans. *(Fuente: Alberts et al., 2002)*

CONSTRUCCIÓN DE LA ARQUITECTURA NEURONAL: CRECIMIENTO DEL CONO AXÓNICO



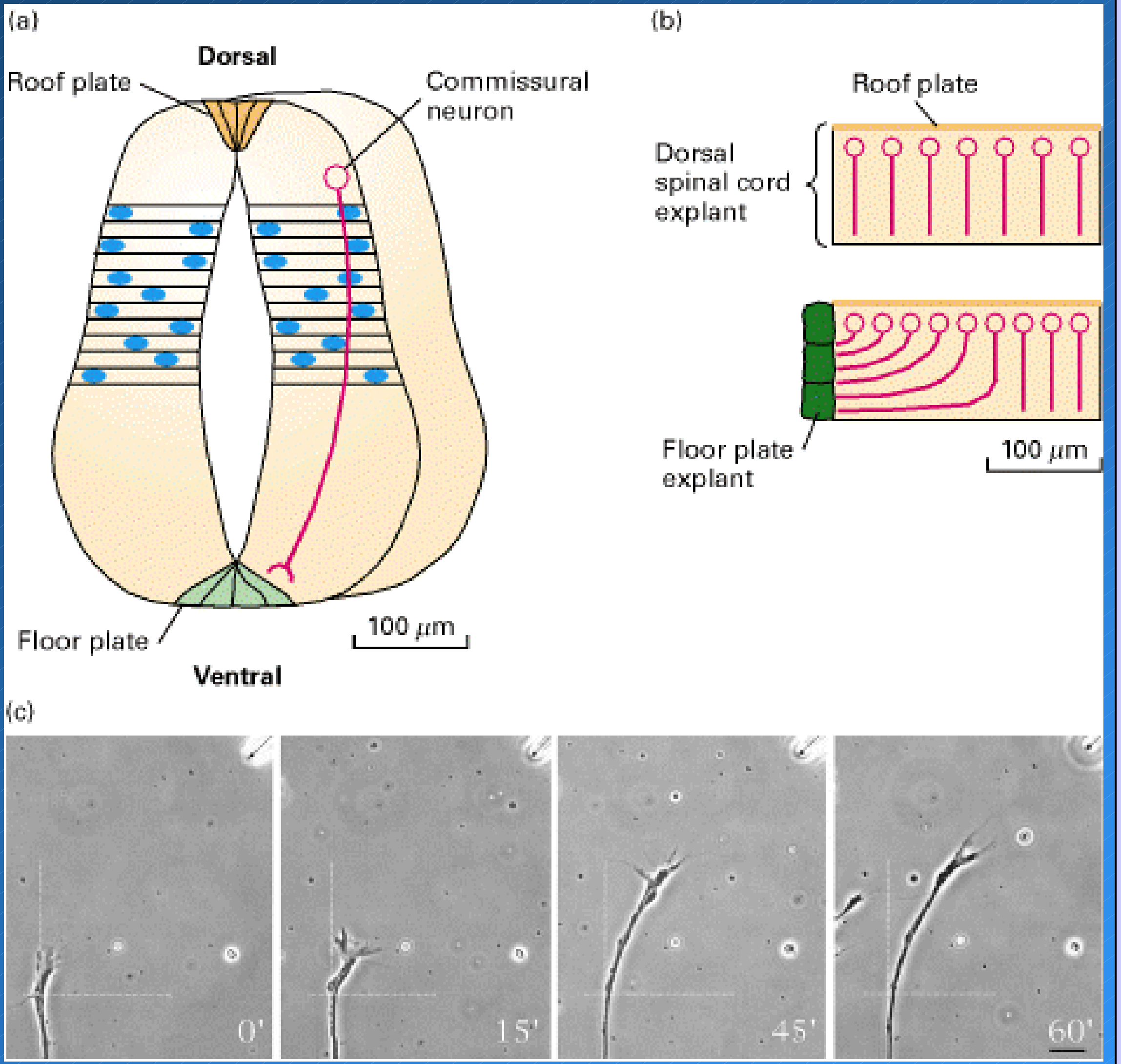
Neuronal growth cones. (A) Scanning electron micrograph of two growth cones at the end of a neurite, put out by a chick sympathetic neuron in culture. Here, a previously single growth cone has recently split into two. Note the many filopodia and the large lamellipodia. The taut appearance of the neurite is due to tension generated by the forward movement of the growth cones, which are often the only firm points of attachment of the axon to the substratum. (B) Scanning electron micrograph of the growth cone of a sensory neuron crawling over the inner surface of the epidermis of a *Xenopus* tadpole.
(Fuente: Alberts et al., 2002)

Conos de crecimiento en axones y dendritas



Formation of axon and dendrites in culture. *A young neuron has been isolated from the brain of a mammal and put to develop in culture, where it sends out processes. One of these processes, the future axon, has begun to grow out faster than the rest (the future dendrites) and has bifurcated. (A) A phase-contrast picture; (B) the pattern of staining with fluorescent phalloidin, which binds to filamentous actin. Actin is concentrated in the growth cones at the tips of the processes that are actively extending and at some other sites of lamellipodial activity.* *(Fuente: Alberts et al., 2002)*

Descubrimiento de las moléculas de guía axonal



Experimental demonstration that chemoattractants direct neuronal outgrowth in vertebrates.

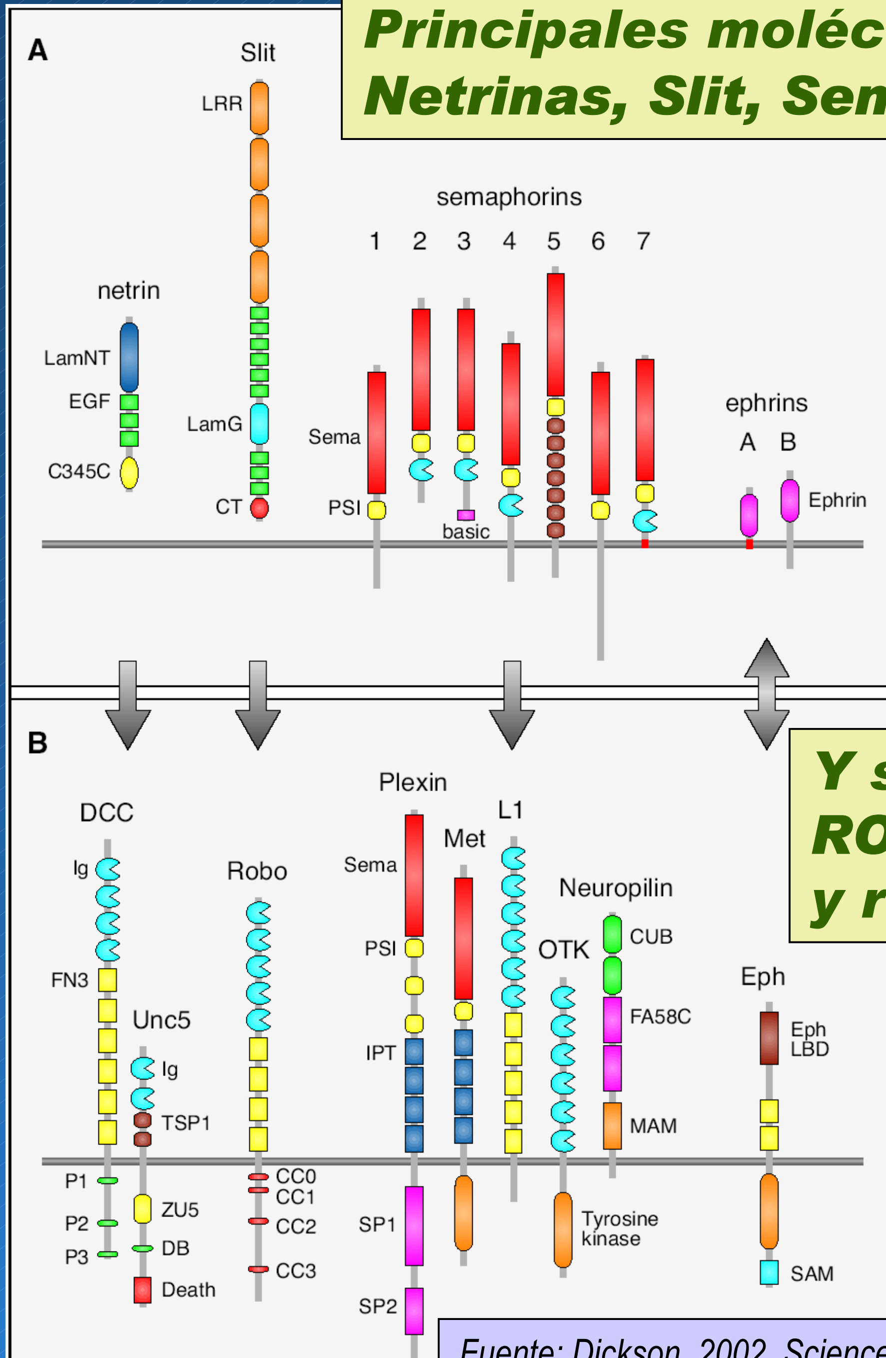
(a) In the embryonic spinal cord, cell bodies of commissural neurons (red) are located near the dorsal roof plate. During normal development, they grow ventrally toward the floor plate.

(b) Explants of the dorsal spinal cord and floor plate were arranged in a collagen gel as diagrammed and co-cultured for 40 hours. Staining for a specific cell-surface marker on commissural neurons showed that outgrowth was directed toward the floor-plate tissue.

(c) Growth cones of Xenopus retinal neurons growing in culture turned towards purified netrin released in pulses from a micropipette in the upper right-hand corner. Moving the position of the source of the netrin induced the growth cones to reorient toward the micropipette (de la Torre et al., 1997, Neuron 19:1211).

Fuente: Lodish et al., 2000

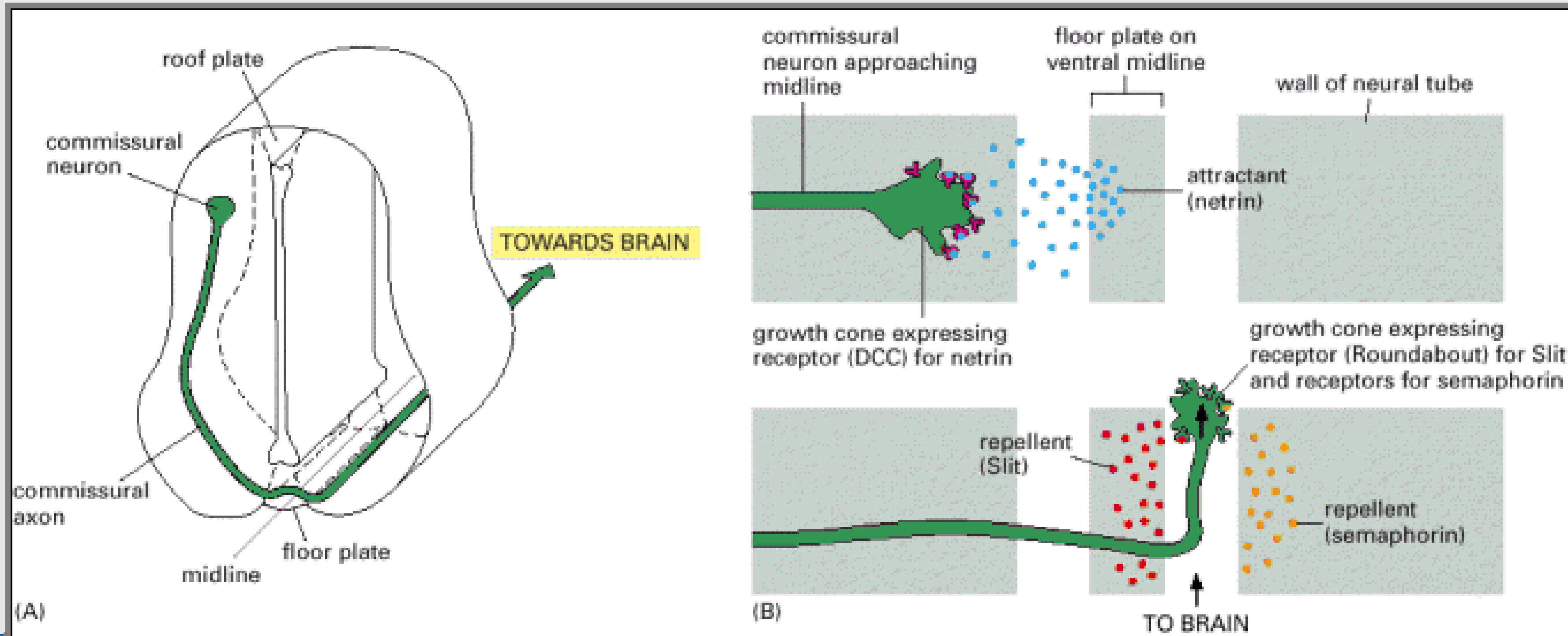
Principales moléculas de guía axonal: Netrinas, Slit, Semaforinas, y Efrinas.



Y sus receptores: DCC, ROBO, Plexinas/Neuropilina, y receptores de Efrinas

Fuente: Dickson, 2002. Science 298: 1959

Mapa de moléculas guía para los axones comisurales de la médula espinal

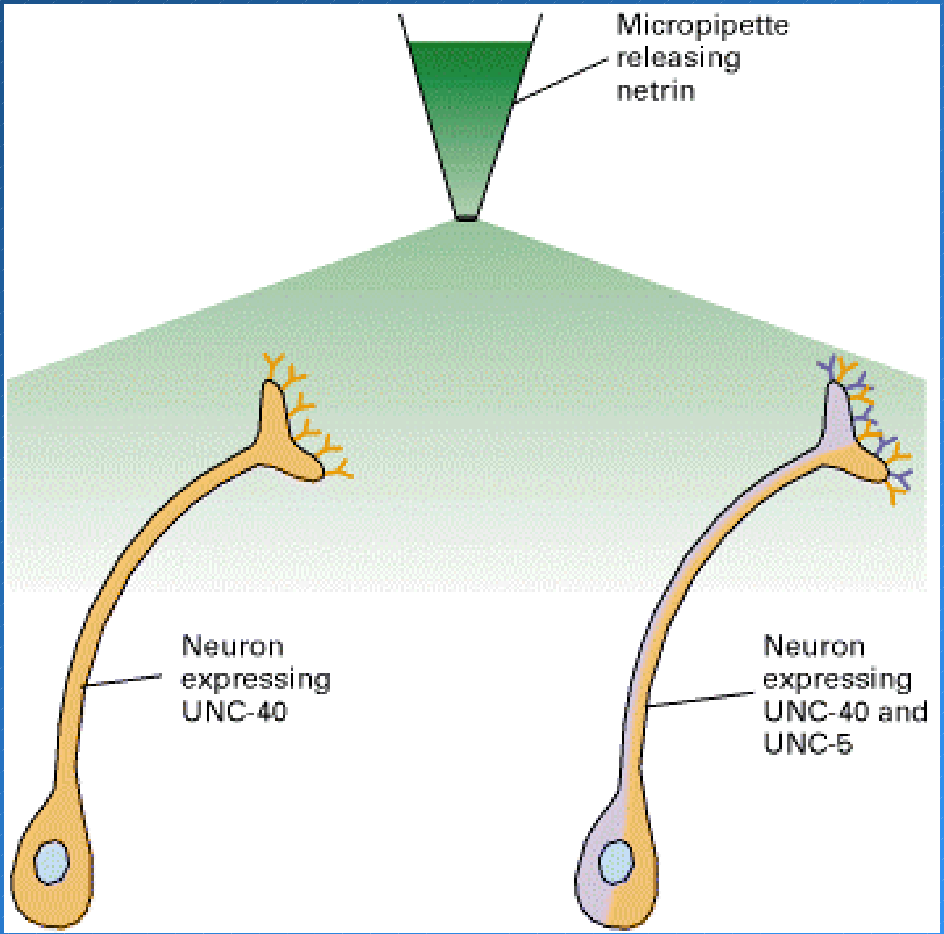


The guidance of commissural axons.

(A) The pathway taken by commissural axons in the embryonic spinal cord of a vertebrate.

(B) The signals that guide them. The growth cones are first attracted to the floorplate by netrin, which is secreted by the floor-plate cells and acts on the receptor DCC in the axonal membrane. As they cross the floor plate, the growth cones upregulate their expression of Roundabout, the receptor for a repellent protein, Slit, that is also secreted by the floor plate. Slit, binding to Roundabout, not only acts as a repellent to keep the cells from re-entering the floor plate, but also blocks responsiveness to the attractant netrin. At the same time, the growth cones switch on expression of receptors for another repellent protein, semaphorin, that is secreted by the cells in the side walls of the neural tube. Trapped between two repellent territories, the growth cones, having crossed the midline, travel in a tight fascicle up toward the brain. *(Fuente: Alberts et al., 2002)*

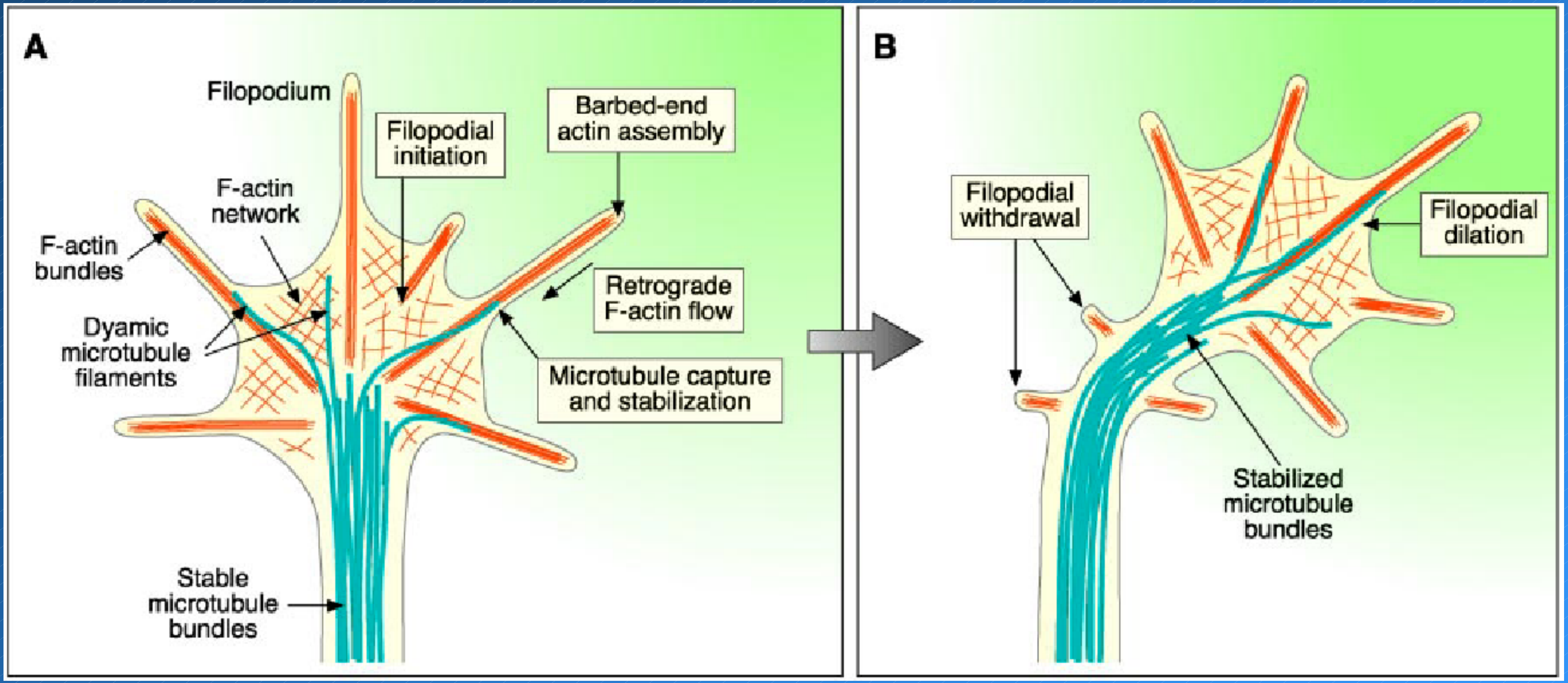
Una misma molécula puede ser atractiva o repelente para los axones en crecimiento, en función de los receptores que éstos expresen



Netrin can act both as a chemoattractant and as a chemorepellent.
Xenopus neurons expressing UNC-40 (also called DCC) are attracted to netrin, whereas when the same neurons coexpress UNC-5 and UNC-40, they are repelled by netrin.

(Fuente: Lodish et al., 2000)

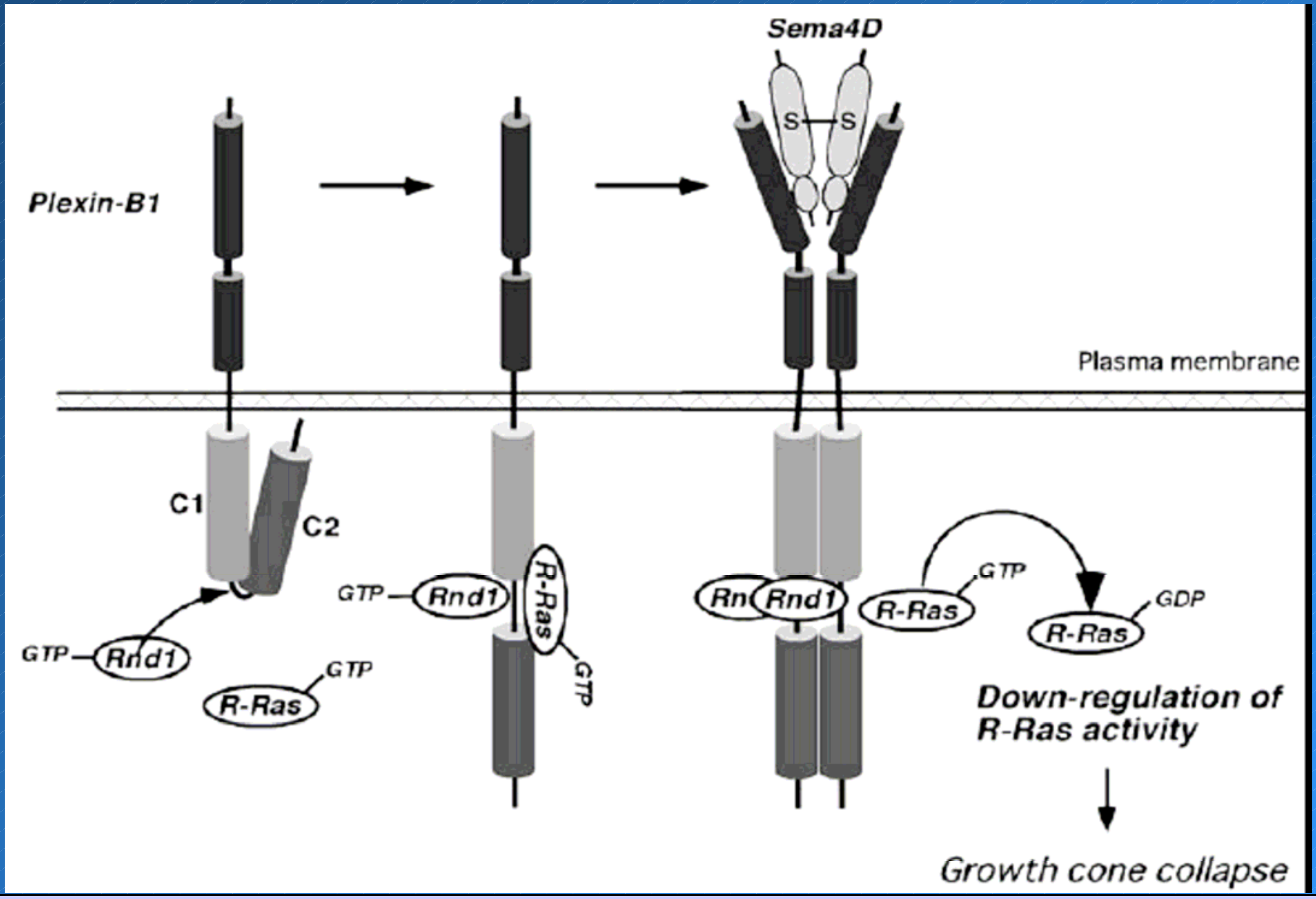
“Conduciendo” el cono de crecimiento



A model showing one way in which a growth cone might turn toward an attractant (green).

Fuente: Dickson, 2002. Science 298: 1959

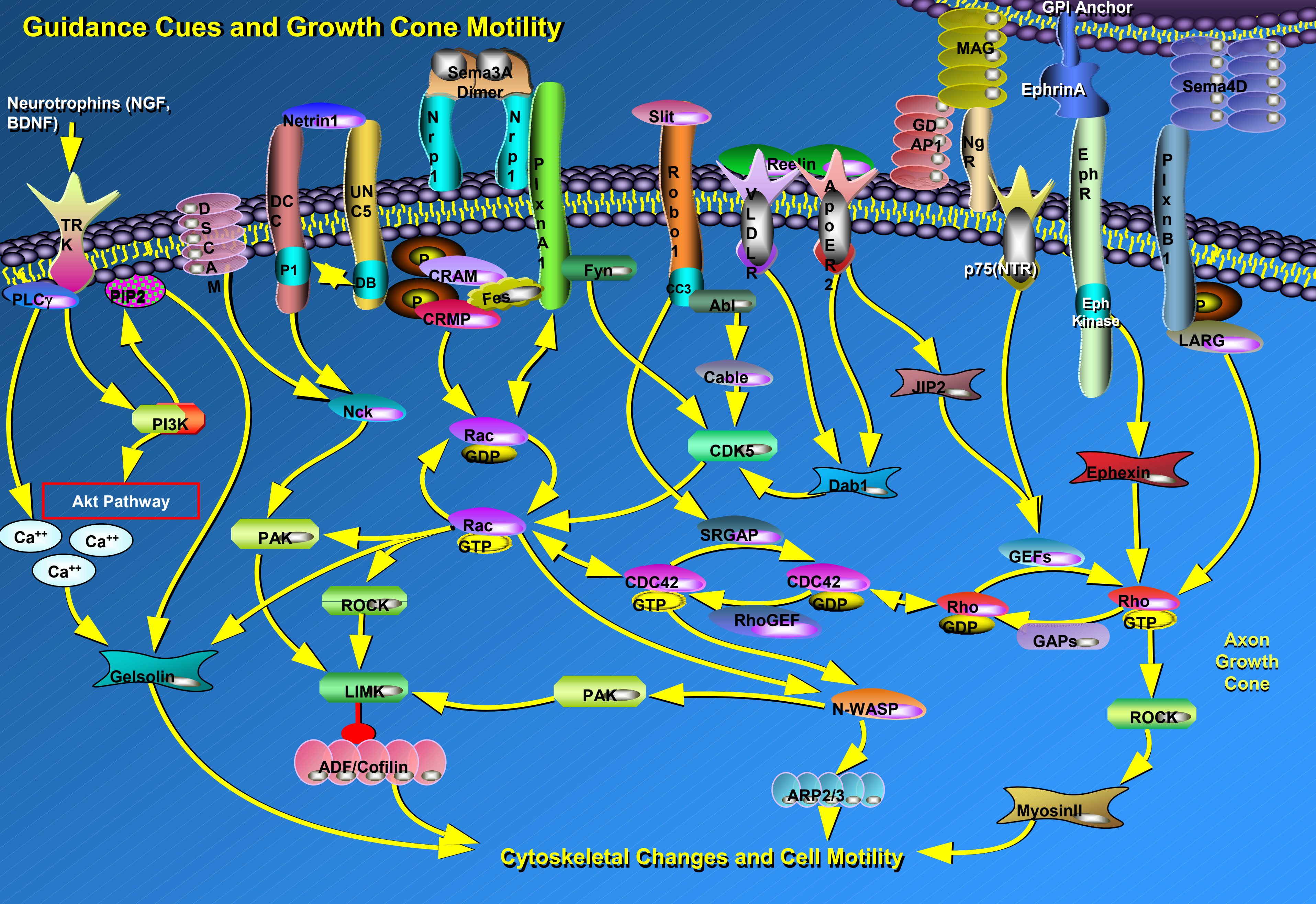
Señalización activada por Semaforinas – Plexina B1 y reorganización del citoesqueleto



Model for signal transduction of the Sema4D-Plexin-B1/Rnd1 complex through R-Ras GAP activity. The C1 and C2 domains of the cytoplasmic tail of Plexin-B1 encode R-Ras GAP. The C1 and C2 domains interact with each other, and Rnd1 binding to the region between C1 and C2 domains disrupts this interaction, allowing the receptor to associate with GTP-bound R-Ras. Sema4D-induced clustering of the Plexin-B1/Rnd1 complex promotes the hydrolysis of GTP by R-Ras. Downregulation of R-Ras activity reduces cell adhesion, leading to growth cone collapse.

(Fuente: Negishi et al., 2005 Cell Mol Life Sci 62:1363)

En resumen...


Guidance Cues and Growth Cone Motility
Glial Cell
GPI Anchor
MAG
EphrinA
Sema4D
Sema3A Dimer
Neurotrophins (NGF, BDNF)
Netrin1
Slit
Reelin
GD AP1
Ng R
Nrp1
Nrp1
PlxnA1
TRK
DSCAM
DCC
UNC5
Robo1
VLDLR
ApoER2
p75(NTR)
EphR
PlxnB1
P1
DB
P
CRAM
P
Fes
CRMP
Fyn
CC3
Abl
Eph Kinase
P
LARG
PLCγ
PIP2
PI3K
Akt Pathway
Ca++
Ca++
Ca++
Nck
Rac GDP
Rac GTP
Cable
CDK5
Dab1
JIP2
Ephexin
GEFs
PAK
ROCK
LIMK
ADF/Cofilin
Gelsolin
SRGAP
CDC42 GTP
CDC42 GDP
RhoGEF
Rho GDP
Rho GTP
GAPs
PAK
N-WASP
ARP2/3
ROCK
MyosinII
Axon Growth Cone
Cytoskeletal Changes and Cell Motility