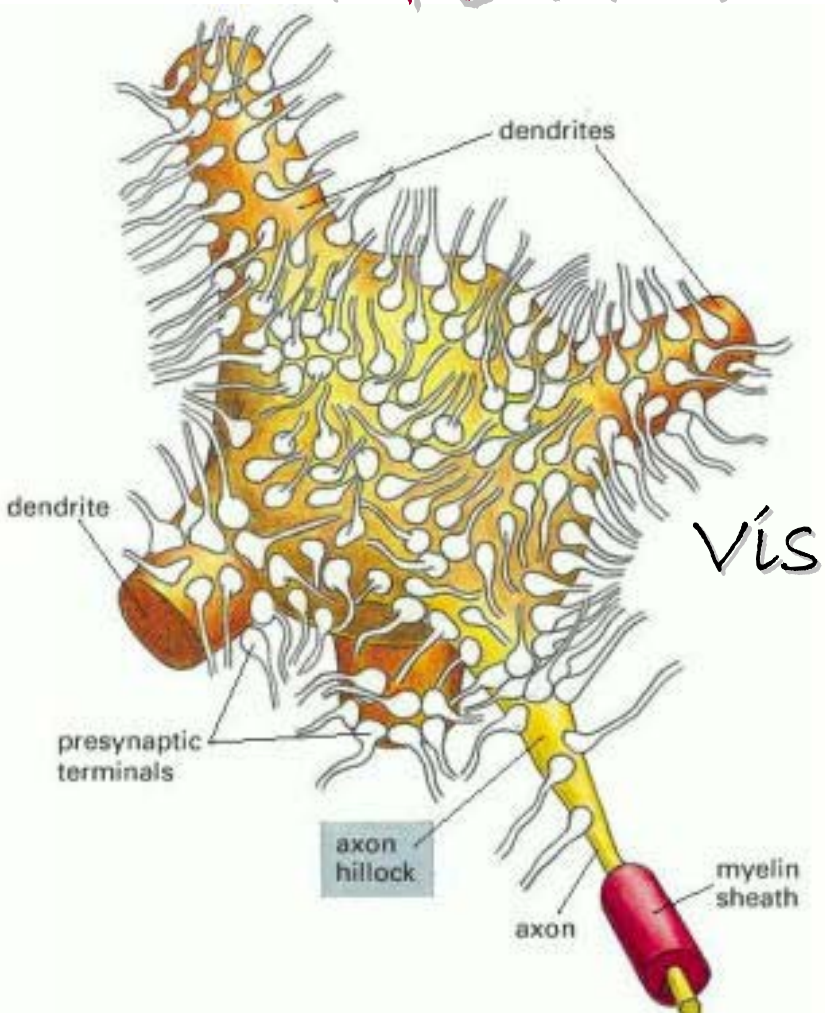
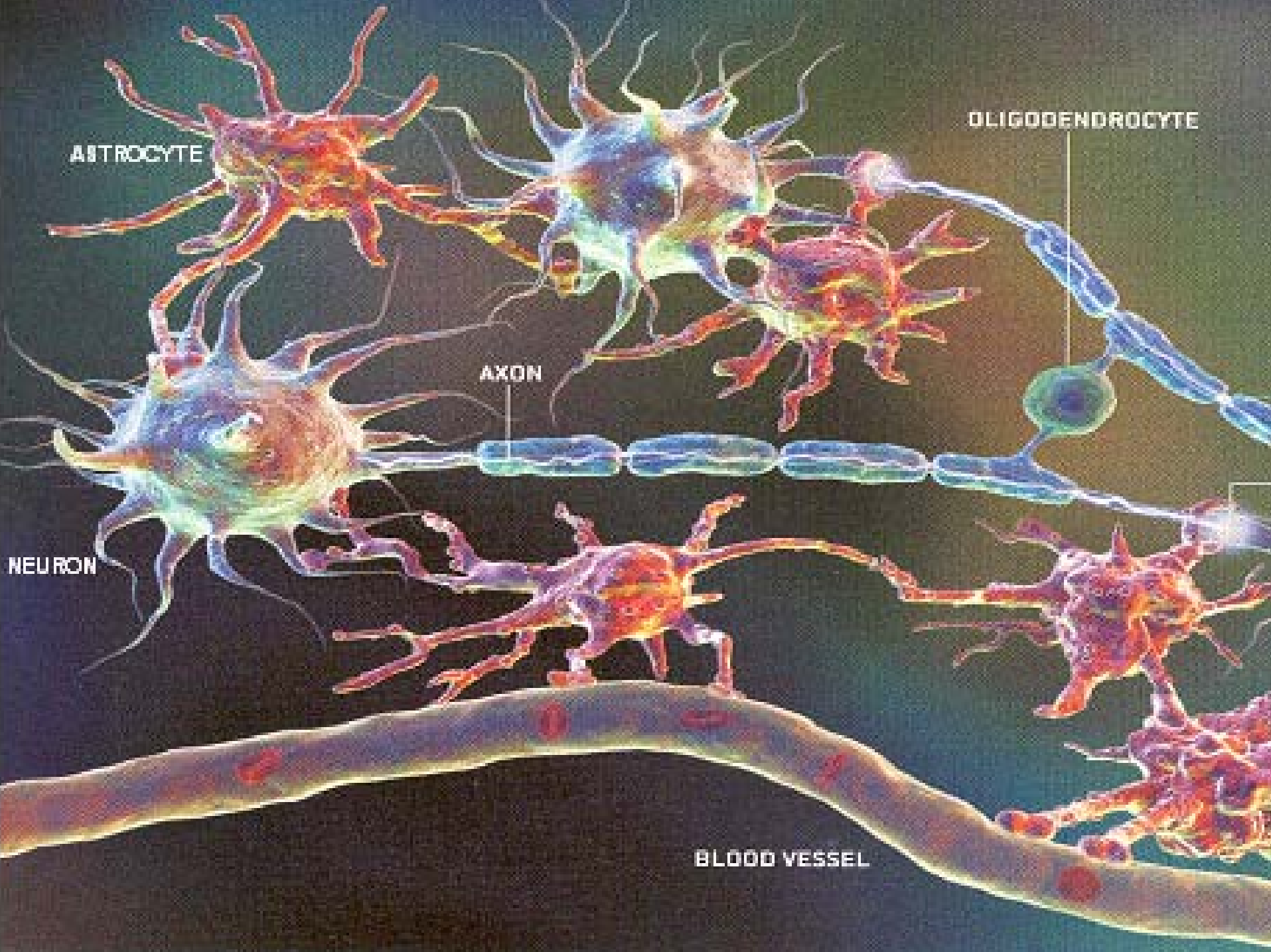
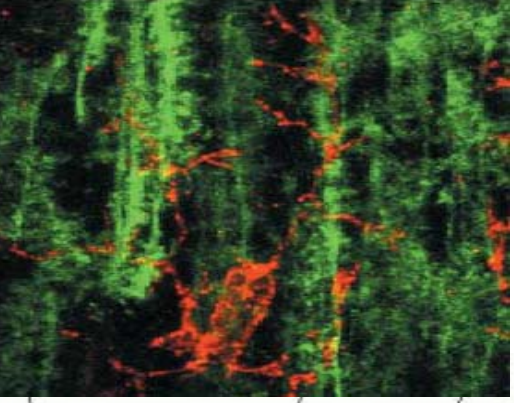
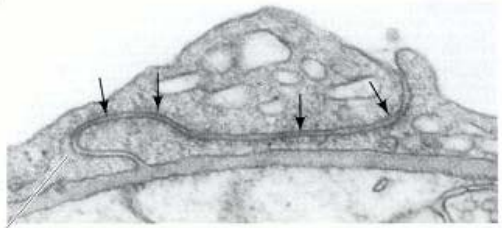
How neurons talk

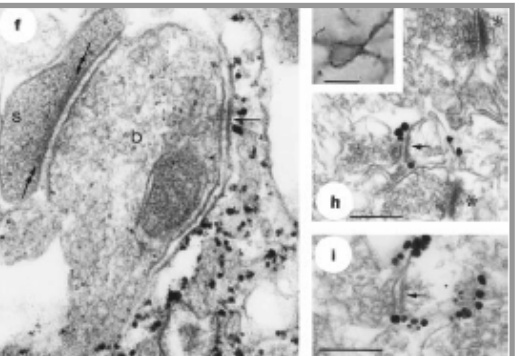


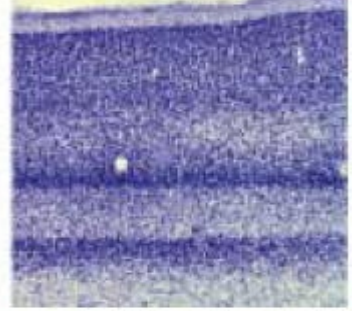
Nivedita Chatterjee
Vision Research Foundation,
Sankara Nethralaya,
Chennai

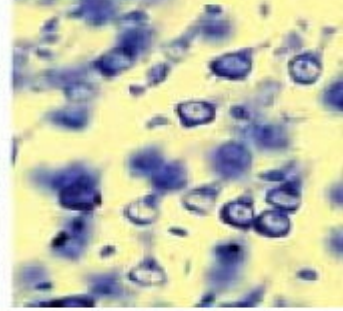

ASTROCYTE
OLIGODENDROCYTE
AXON
NEURON
BLOOD VESSEL











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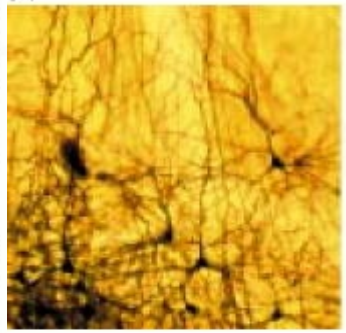

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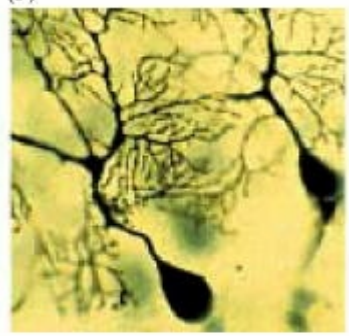
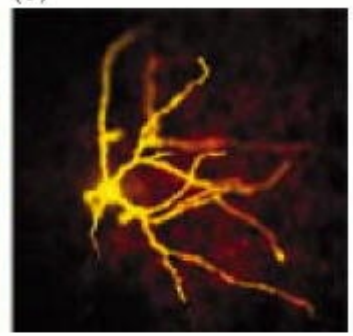


(G)



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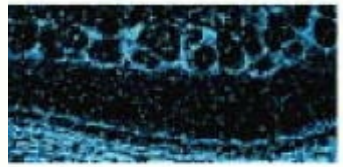
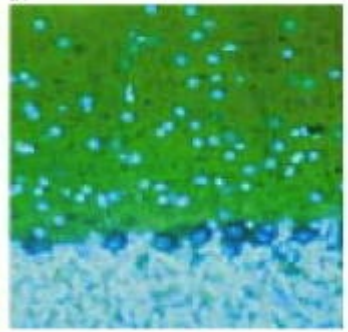
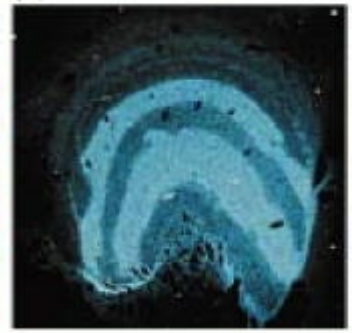
(I)



(J)



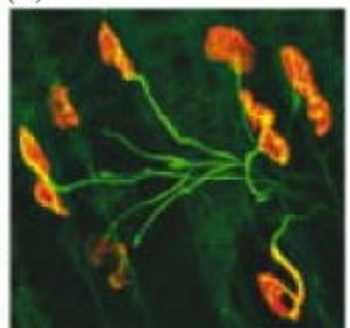
(K)



(L)

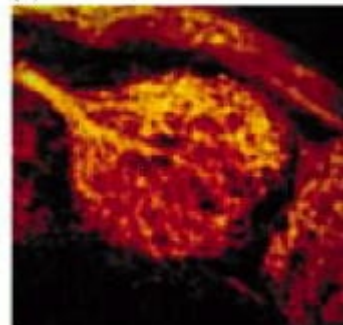
(M)

(N)

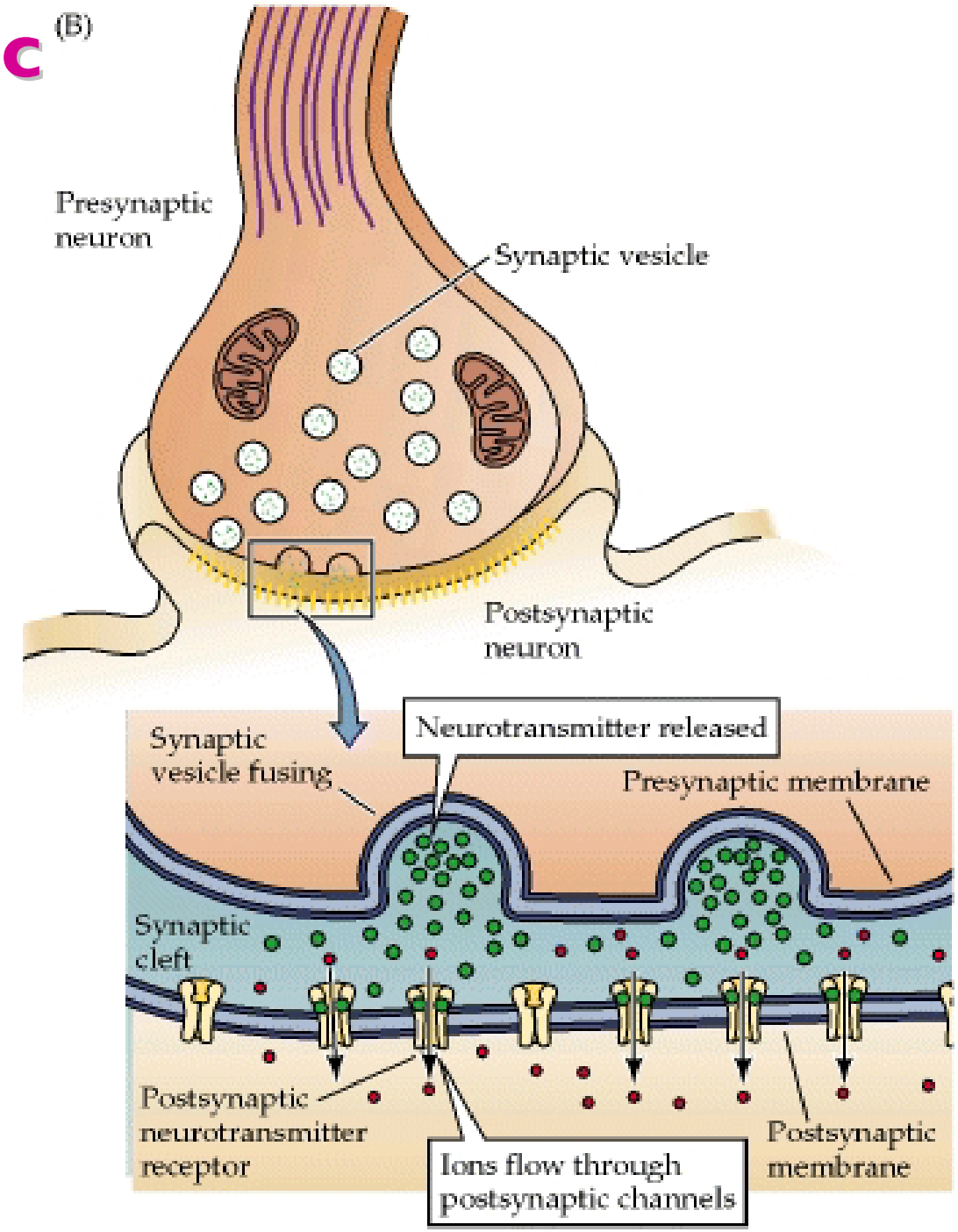


(O)

(P)

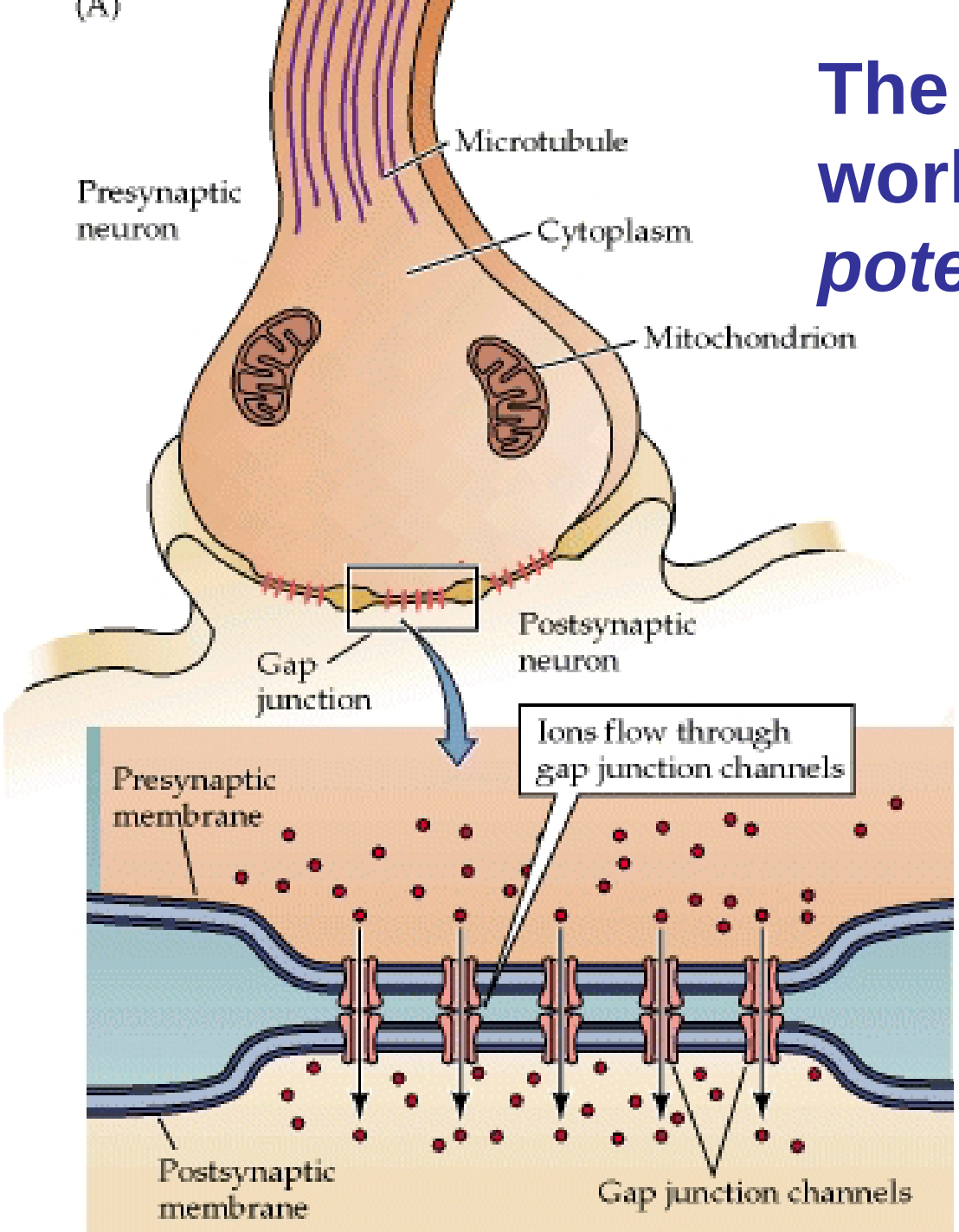


The Synaptic Bouton of a chemical synapse



Chemical synapse – with synaptic cleft

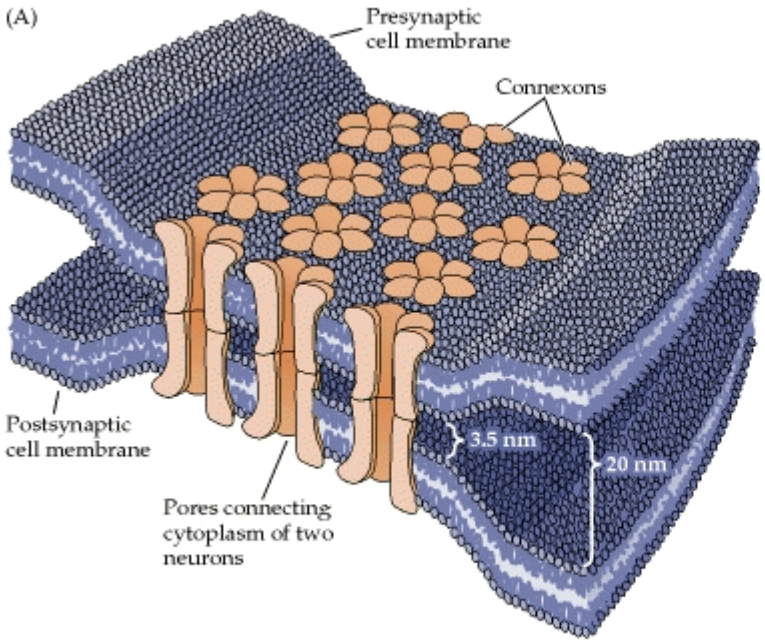
The Electrical synapse works *with graded potentials*

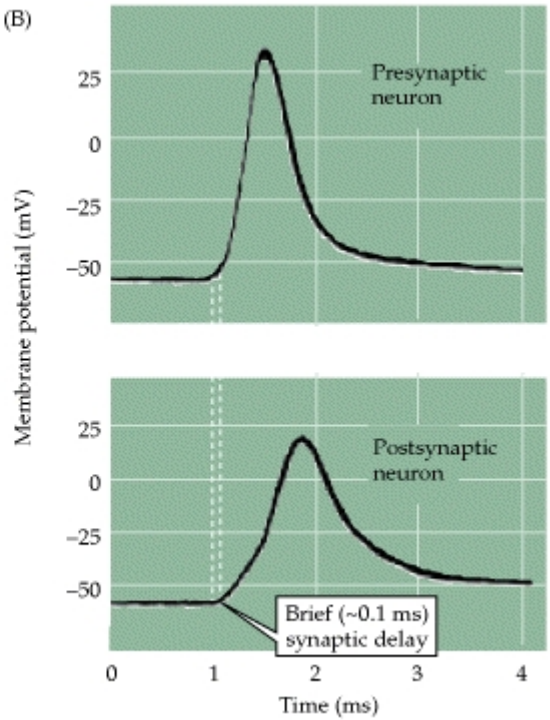


Electrical synapse – with intercellular continuity

Electrical synapses

Finally there are the gap junctions through which electrical synapses function



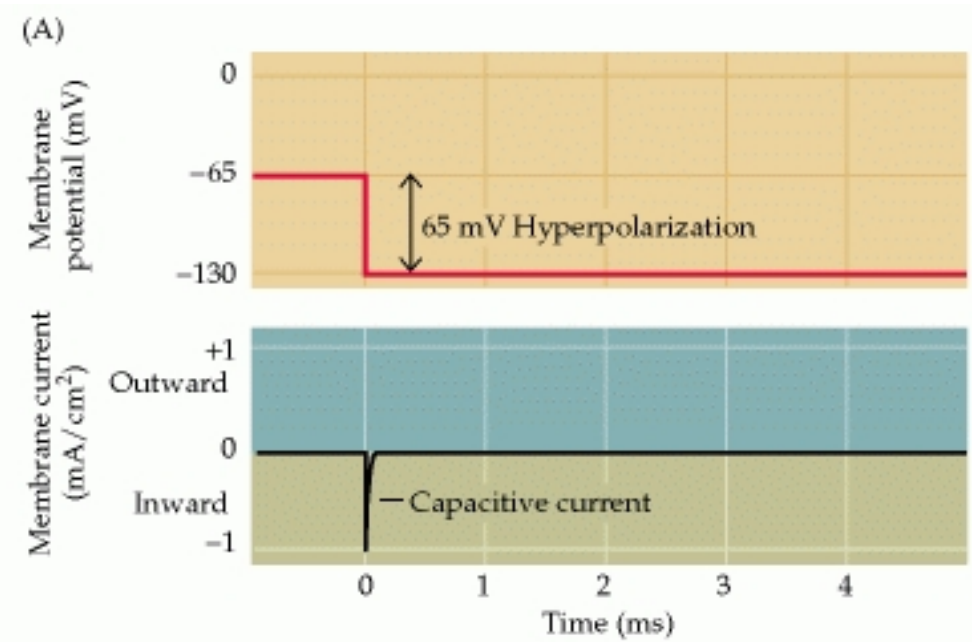


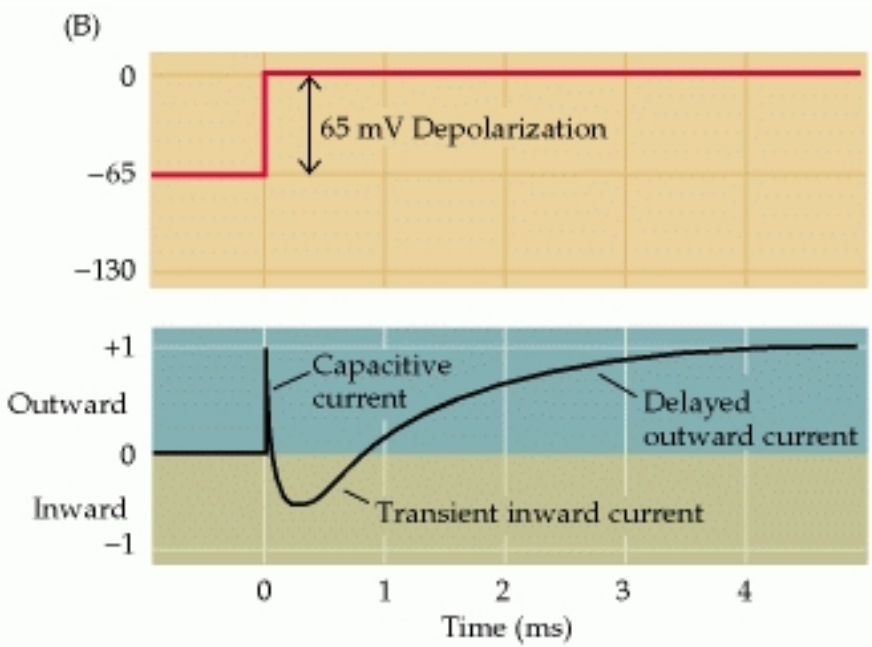
- **Fast transmission**
- **Usually Bidirectional**
- **Synchronisation of electrical activity**
- **Also allows movement of molecules <1500 dalton**

Current flow across squid axon

Depolarization

- a brief capacitive current
- a longer-lasting but transient phase of inward current
- a delayed but sustained outward current

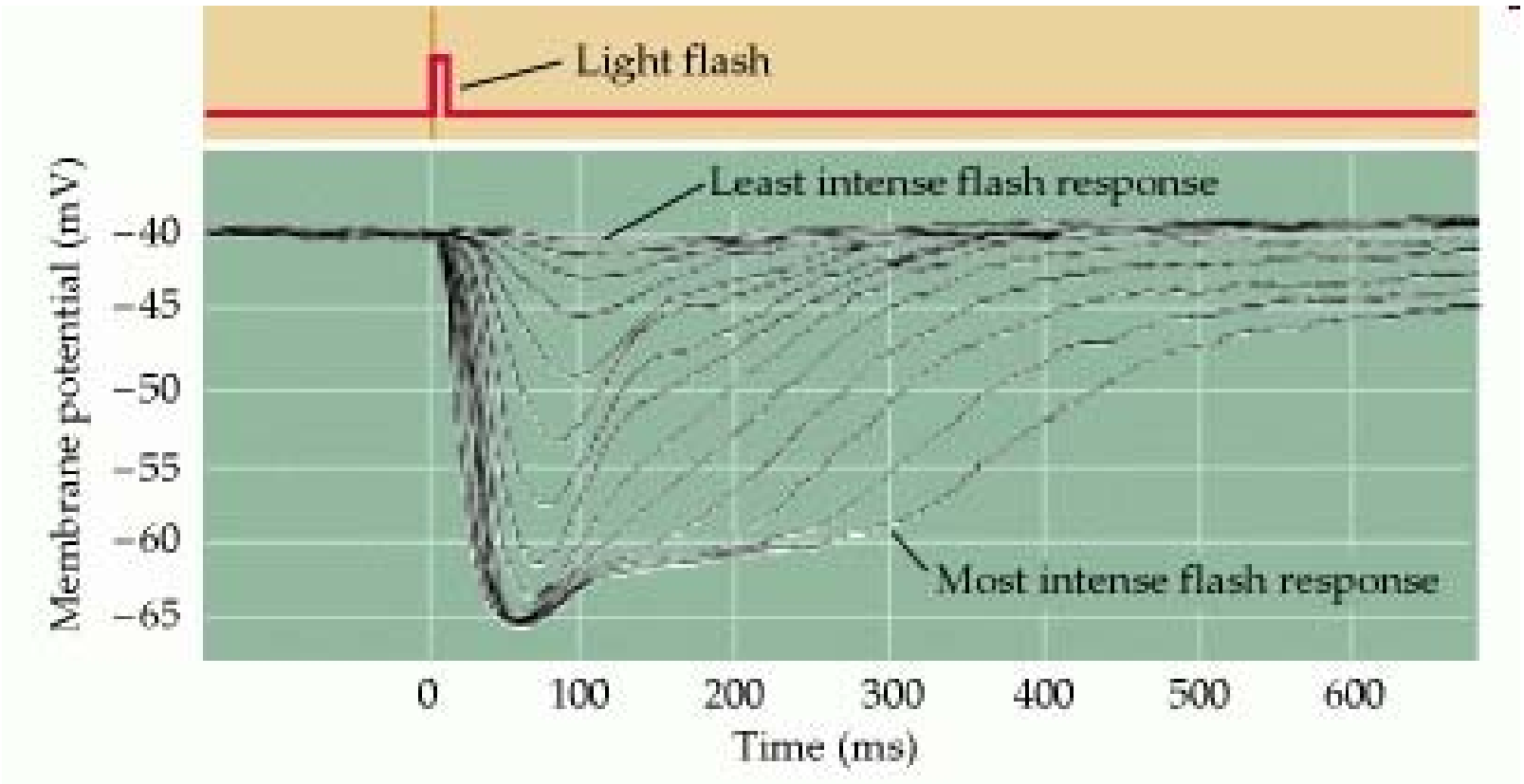




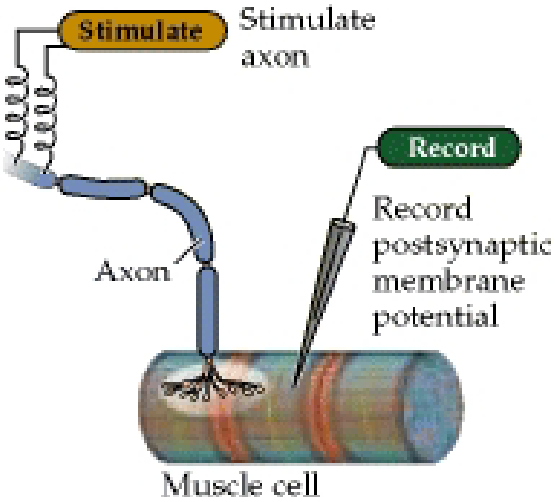
Hyperpolarisation

In the retina, hyperpolarisation is the ACTIVATED state

Light activation causes a graded change (**GRADED POTENTIAL**) in membrane potential and a corresponding change in the rate Of transmitter release onto postsynaptic neurons

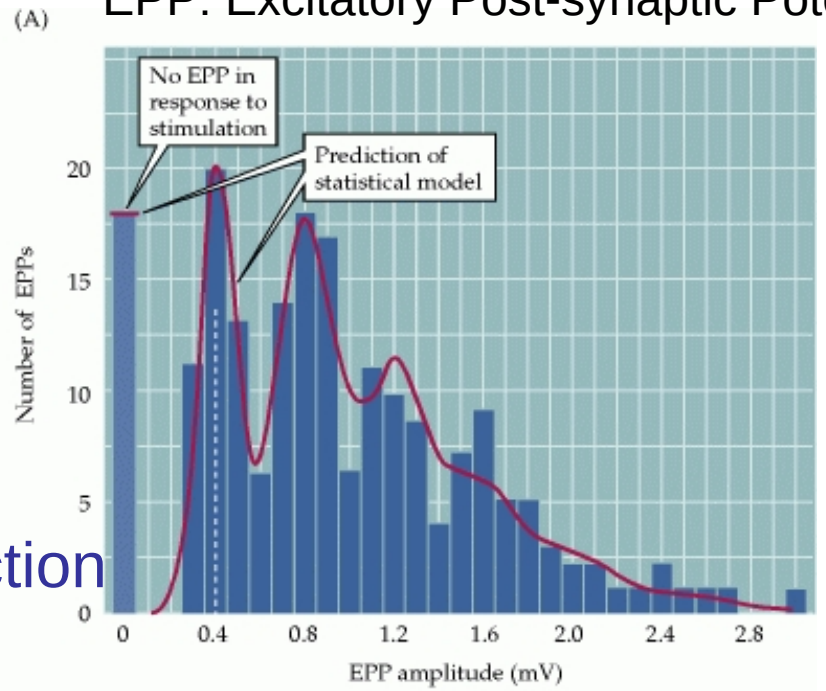


Quantal transmission at chemical synapses



Neuromuscular junction

EPP: Excitatory Post-synaptic Potential

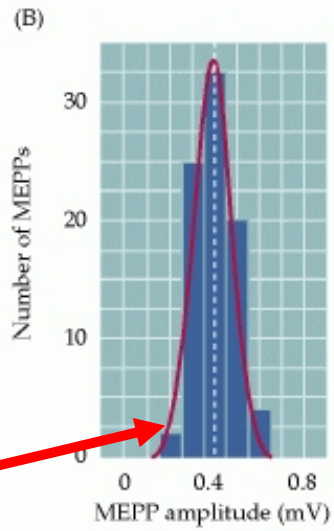


Peaks of EPP amplitudes occur in integer multiples of the mean amplitude of MEPPs

Stimulated-Fused vesicles

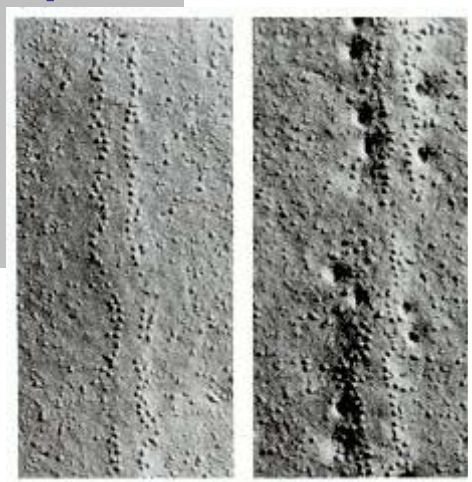
MEPP: Miniature EPP

MEPP amplitude distribution



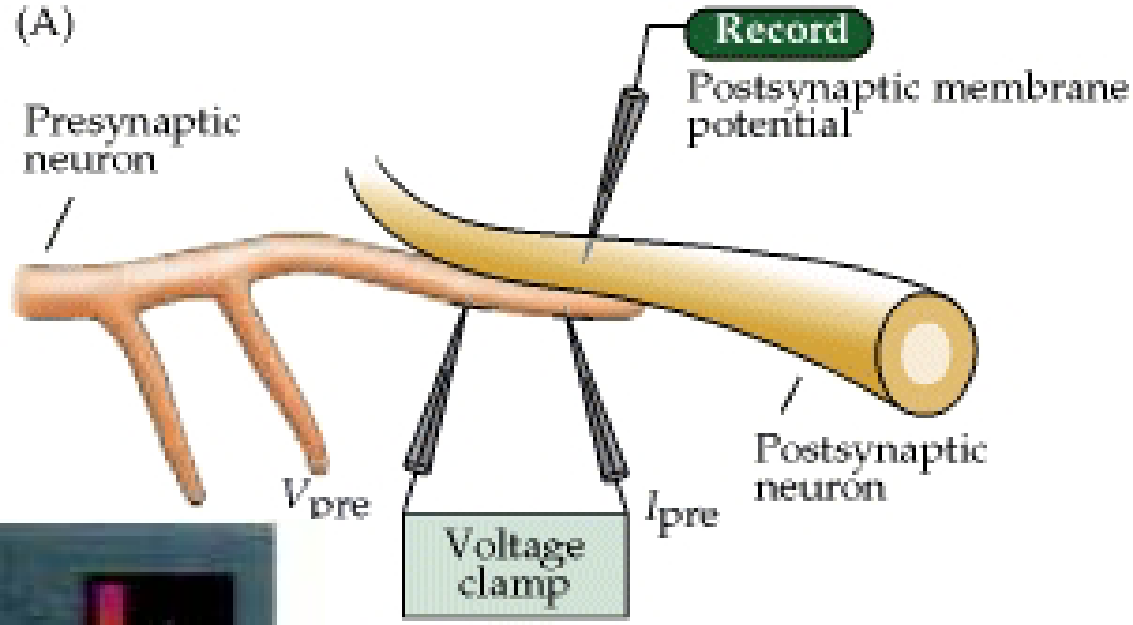
No EPP elicited

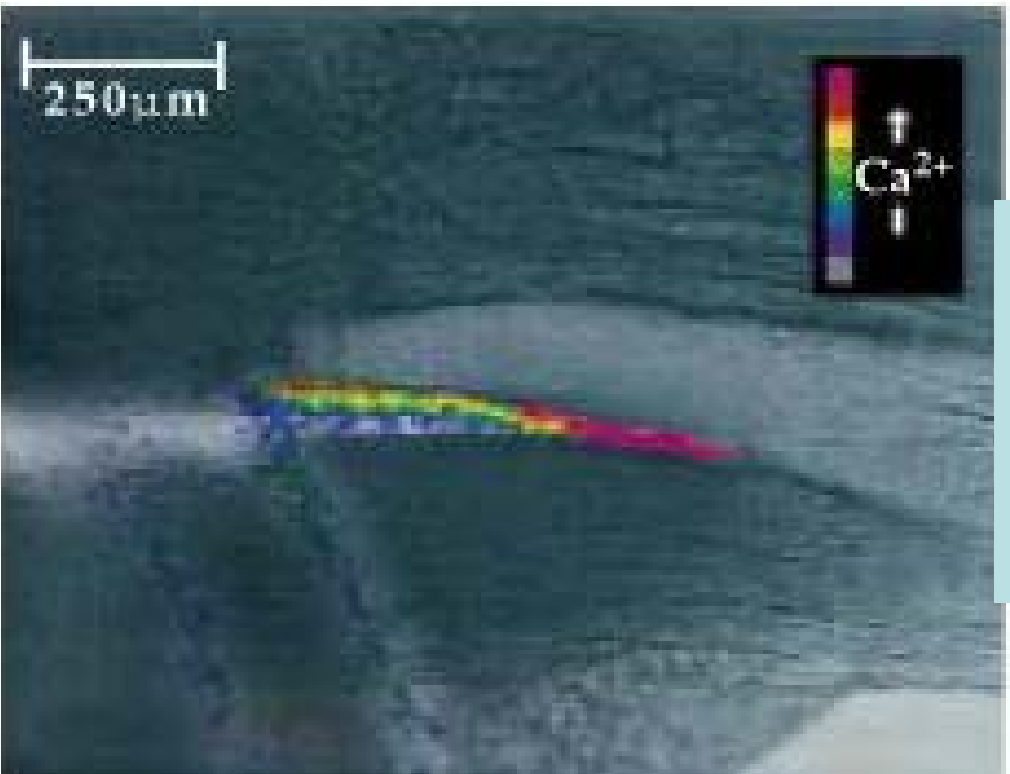
Electron-microscopical visualisation of *vesicles at the presynaptic terminal*



Unstimulated

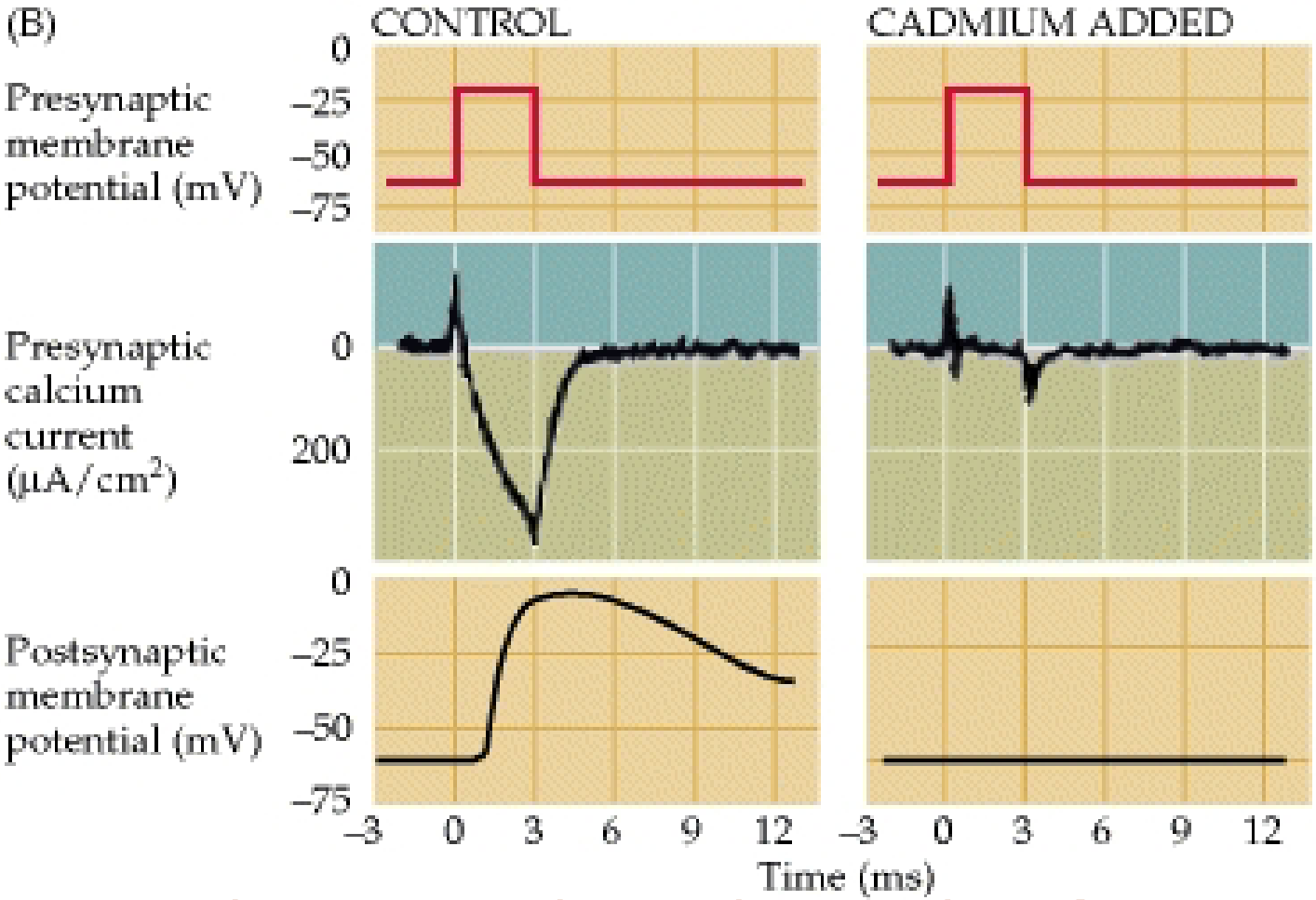
Calcium in synaptic transmission





Ca2+ entry triggers transmitter release from presynaptic terminal

Fura-2 loaded terminal show increase in Ca2+ concentration



Ca2+ current in presynaptic terminal leads to ***increase*** in postsynaptic potential

Voltage operated Calcium channel blocker Cadmium eliminates

1) Presynaptic Ca2+ current

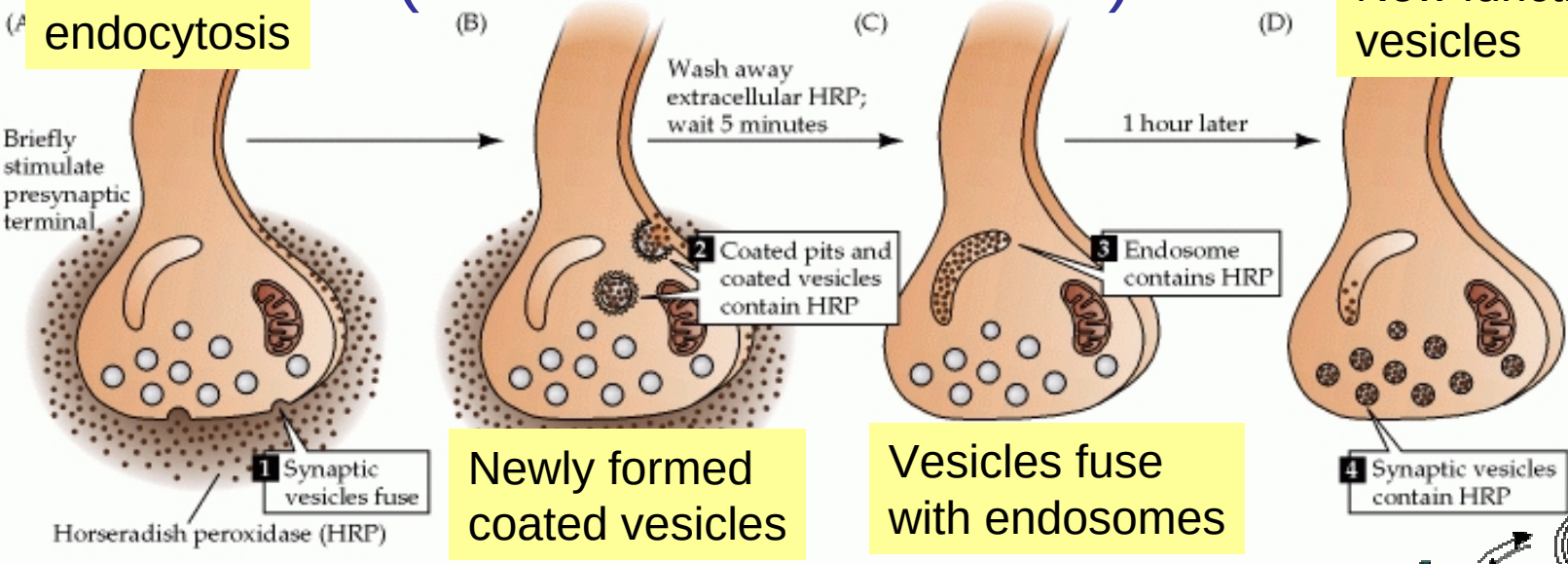
(2) rise in postsynaptic potential

Local recycling of synaptic vesicles

(Heuser-Reese Model)

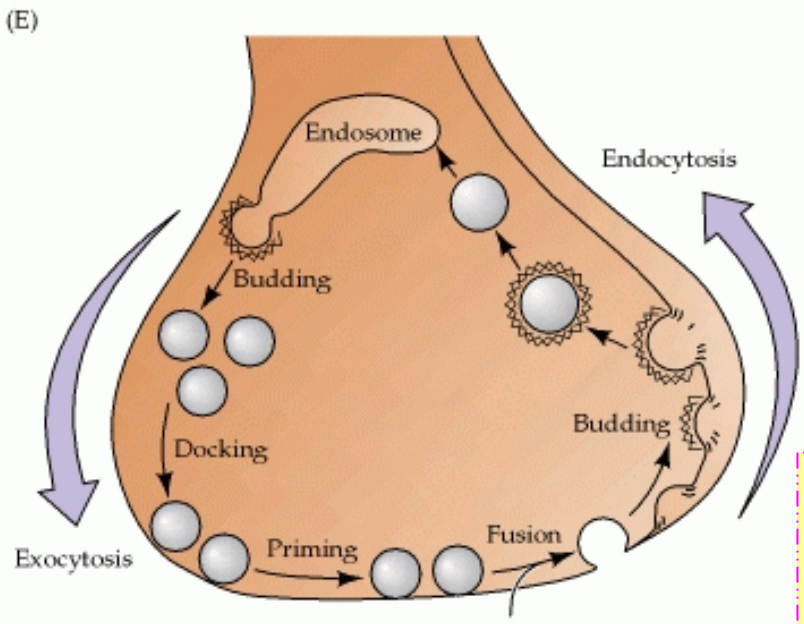
AP causes endocytosis

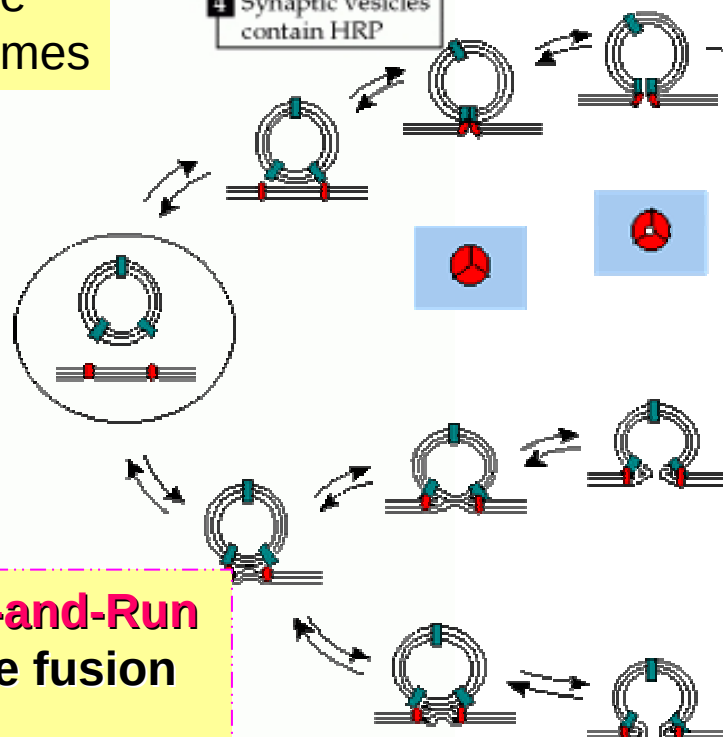
New functional vesicles



Newly formed coated vesicles

Vesicles fuse with endosomes





Alternate: Kiss-and-Run Model of vesicle fusion Cecarelli et al.

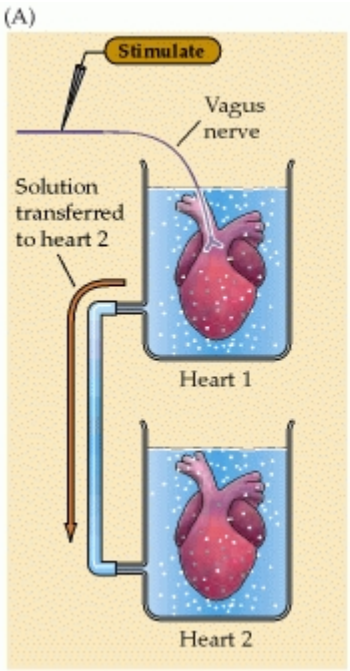
Neurotransmitters

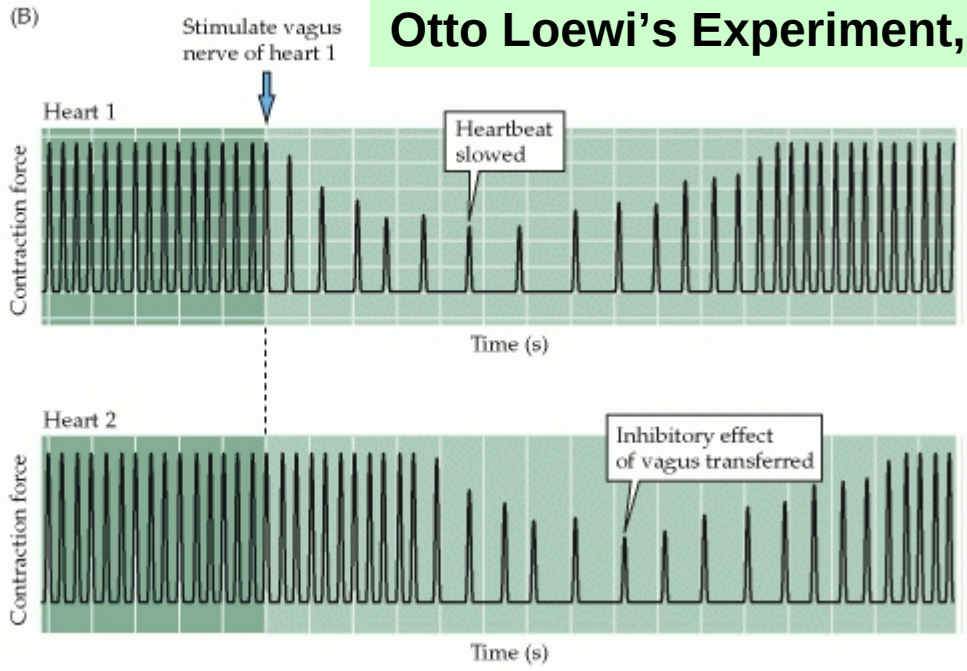
Dale's Principle – A neuron is basically either excitatory or inhibitory.
Neurons release the same set of transmitters at all of their synapses.

Neurons can release multiple types of neurotransmitters at its different synaptic ends.

Excitatory – Glutamate, Dopamine ; opens Ca2+ and Na+ channels

Inhibitory – GABA ; opens transmitter-gated Cl– or K+ channels in the postsynaptic membrane

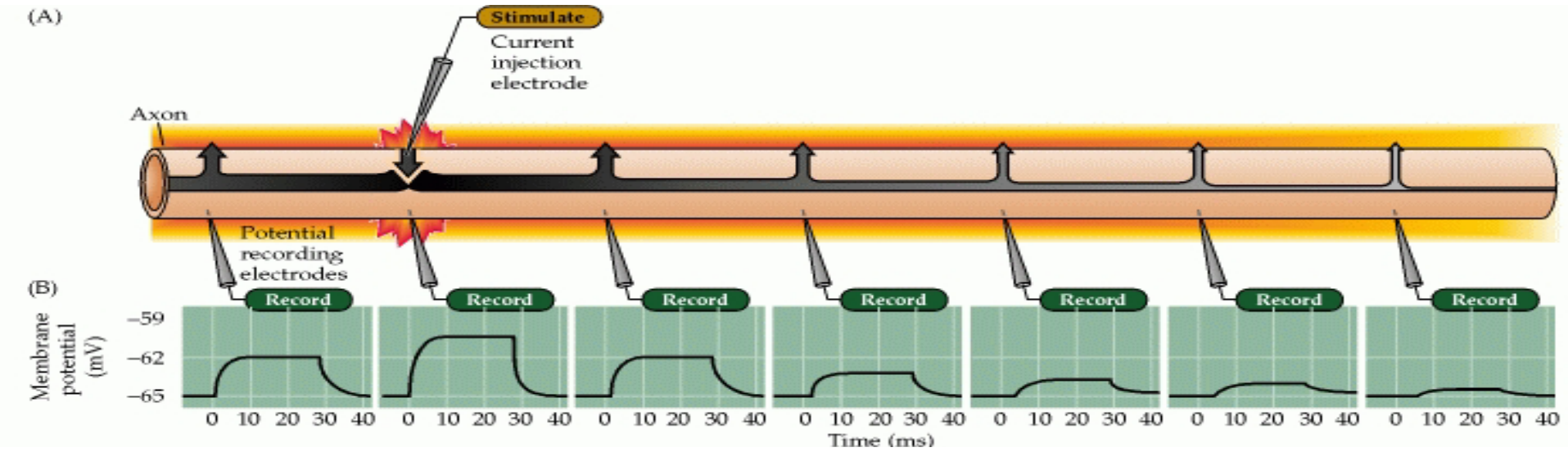


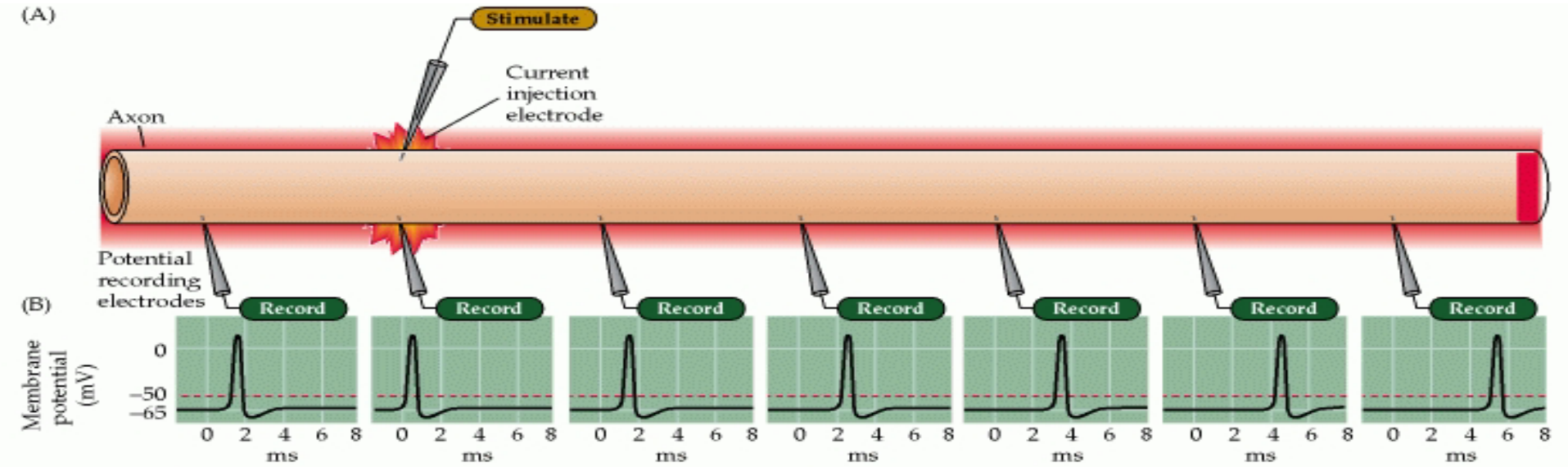


Otto Loewi's Experiment, 1926

Electrical information can be transferred from one neuron to the next by means of chemical signaling

The myelin sheath ensures that the signal strength remains strong during propagation





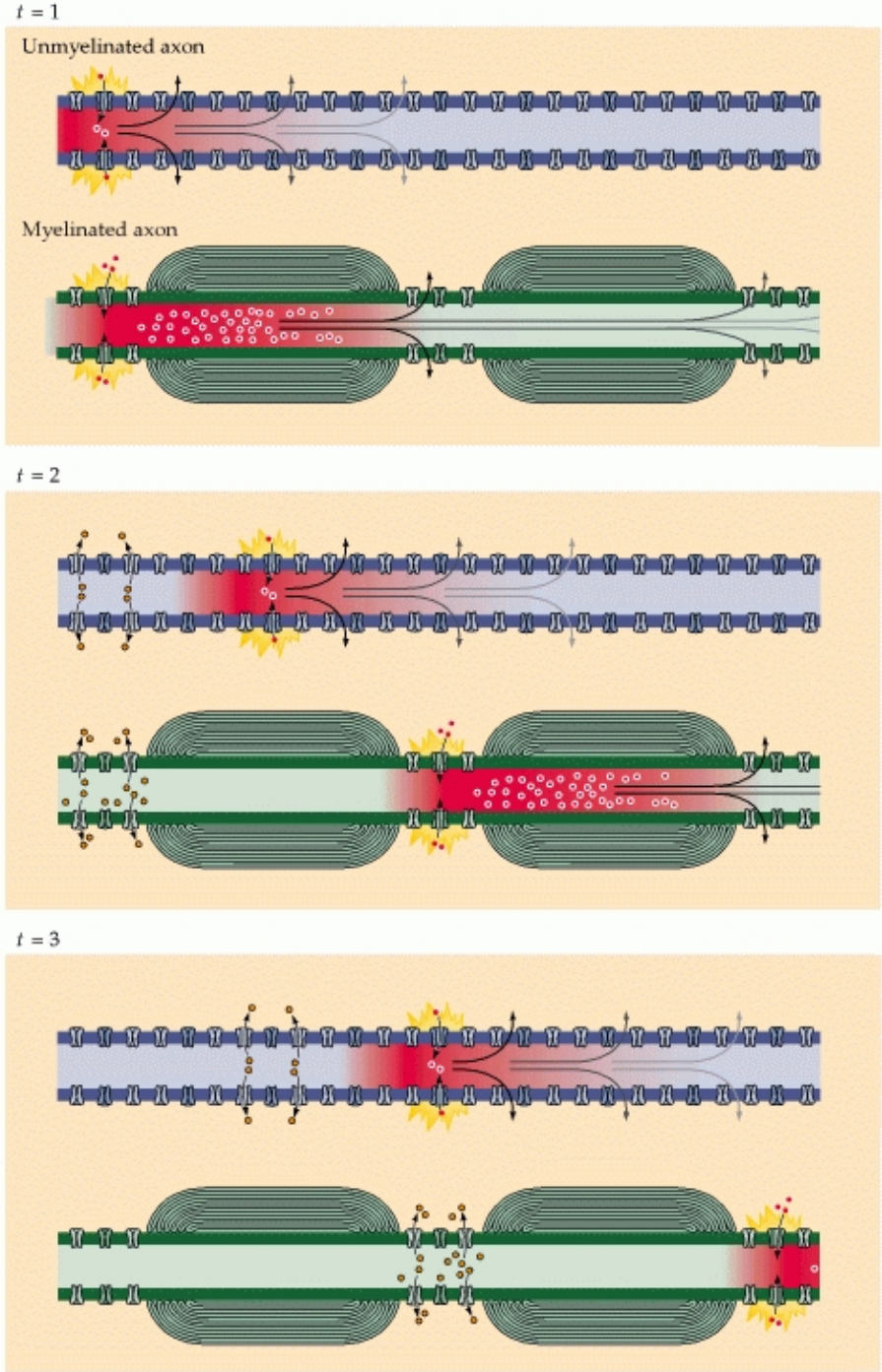
Myelinated vs. Unmyelinated axons

Unmyelinated **axon** conduction velocities 0.5 to 10 m/s,

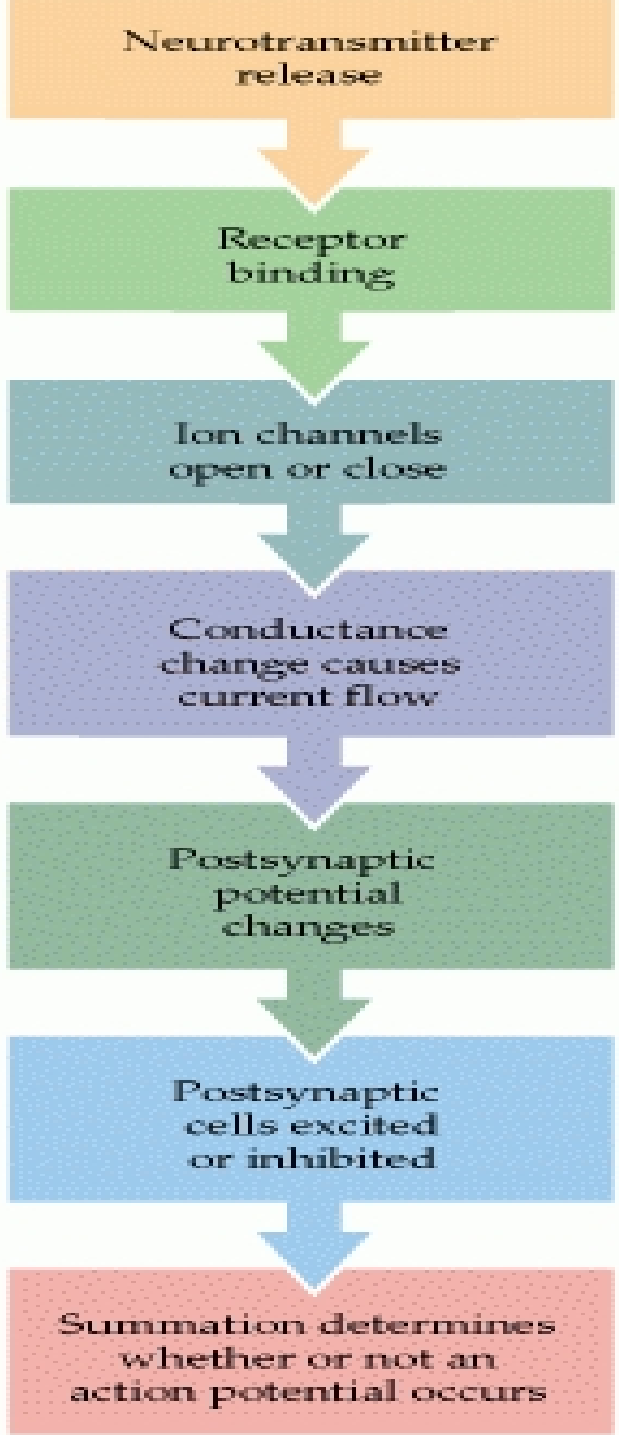
Saltatory Conduction

Localisation of ion channels at discrete paranodal regions

Myelinated **axons** conduct at velocities upto 150 m/s



Events in synaptic transmission



Action Potential

Rising phase – Depolarisation

1. Opening of Na+ selective channels
2. Entry of Na+ inside cell

Overshoot – Depolarisation

1. Open Na+ channels - prolonged
2. Entry of Na+ ions

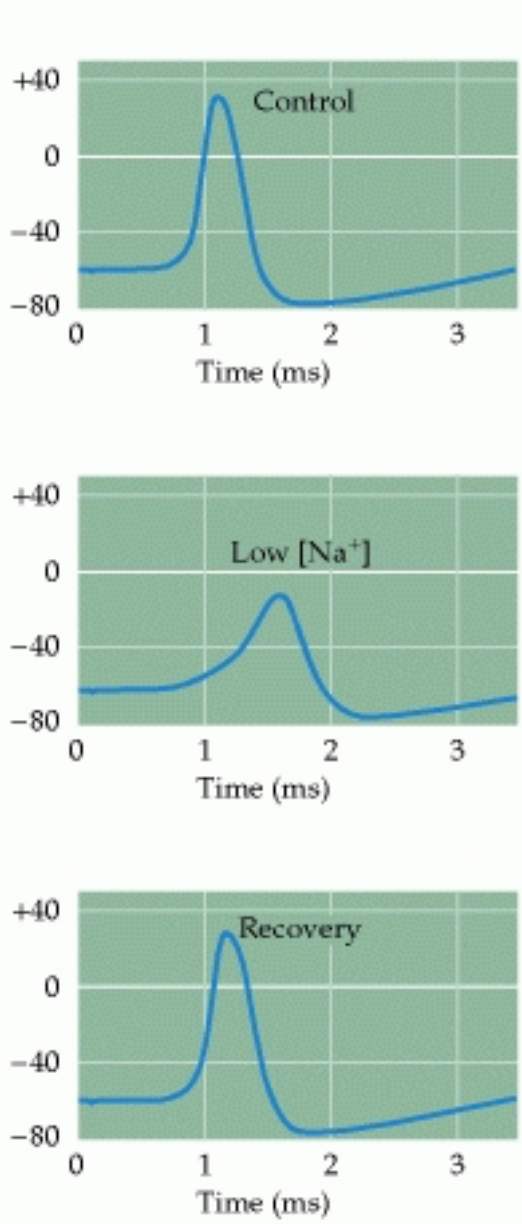
Falling phase – repolarisation

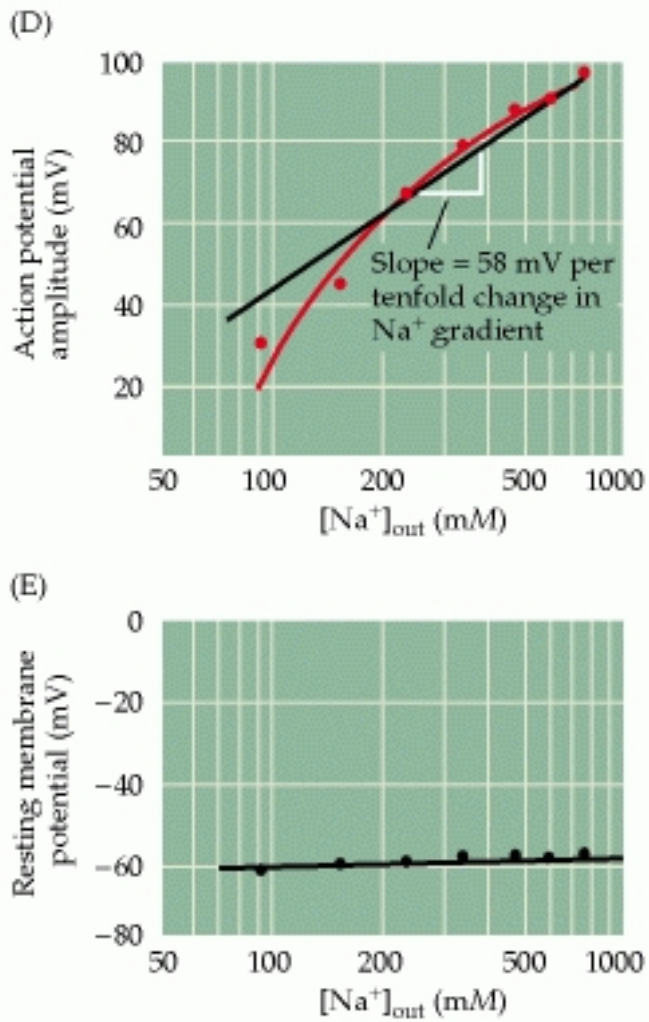
1. Desensitisation of Na+ channels,
2. Opening of K+ selective channels; K+ ions go out of cytoplasm

1. Opening of Ca2+ selective Channels; exit of Ca2+ ions

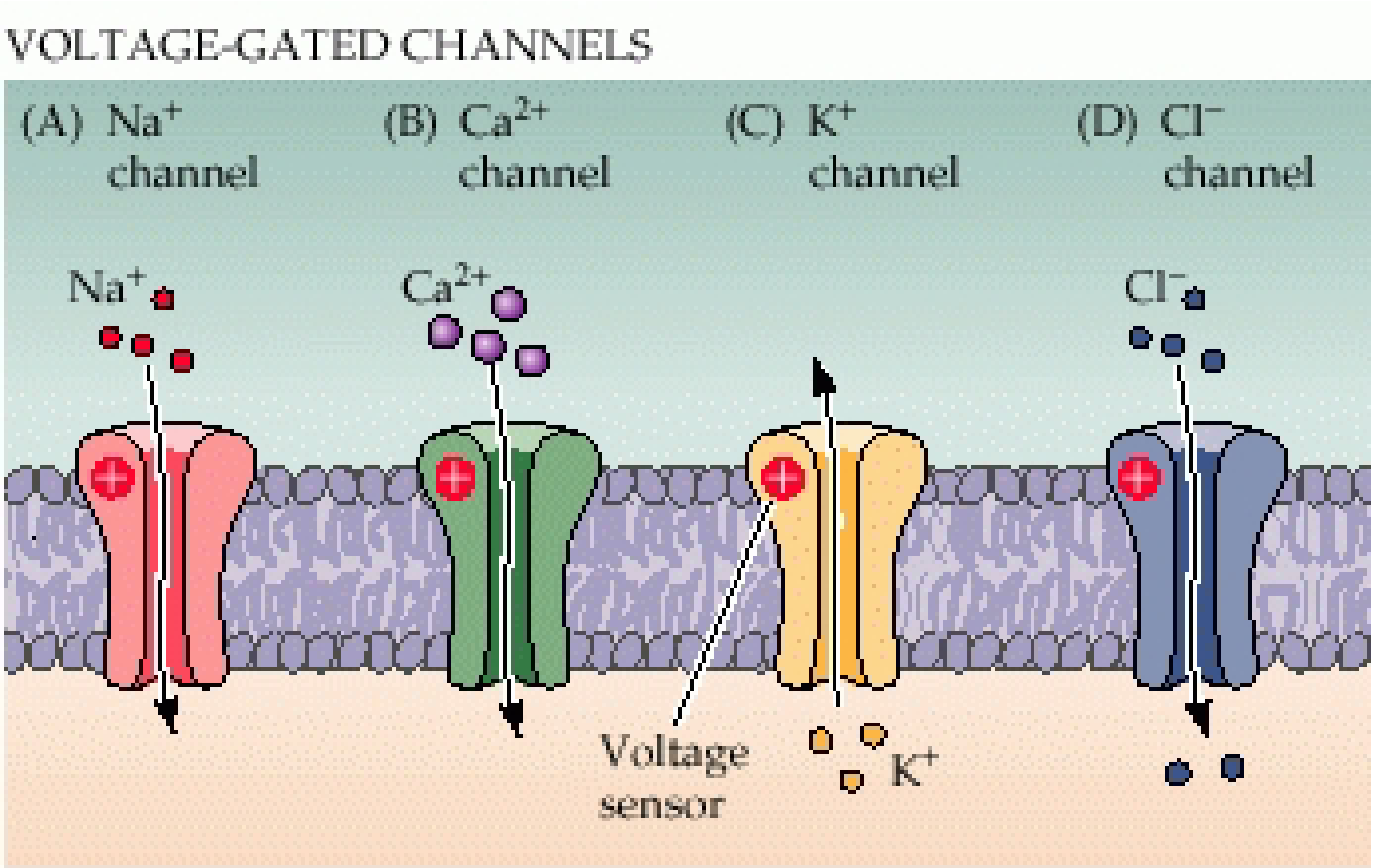
Undershoot – Hyperpolarisation

Open K+ channels; exit of K+ ions





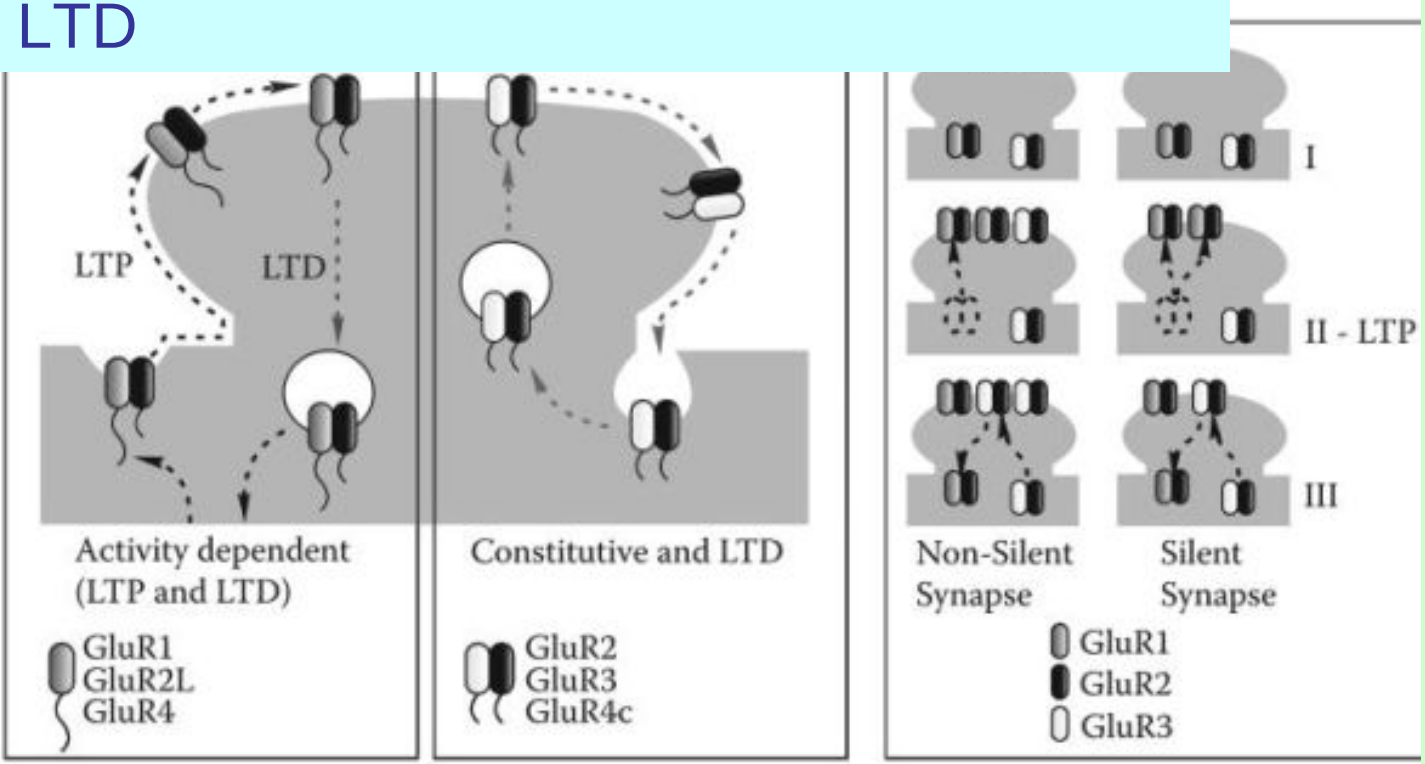
Voltage-gated channels at the Pre-synaptic terminal



Animation

- **Gated – opens to stimuli**
- **Selectivity – shows ion selectivity**
- **Saturation – Can show desensitisation**
- **Gating current – Changed permeability to membrane potential**

Synaptic AMPARs recycle in LTP and LTD



AMPA – ligand-gated channel at the postsynaptic terminal

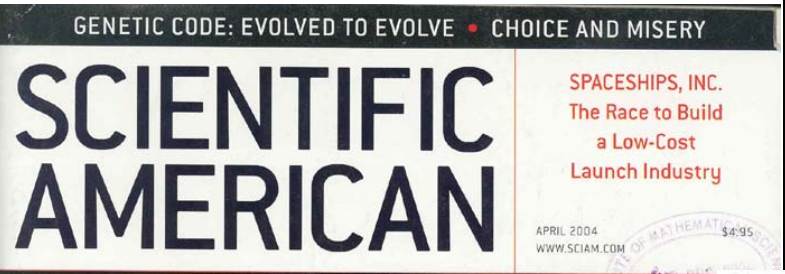
- fast excitatory neuro-transmission
- fundamental roles in synapse stabilisation & plasticity

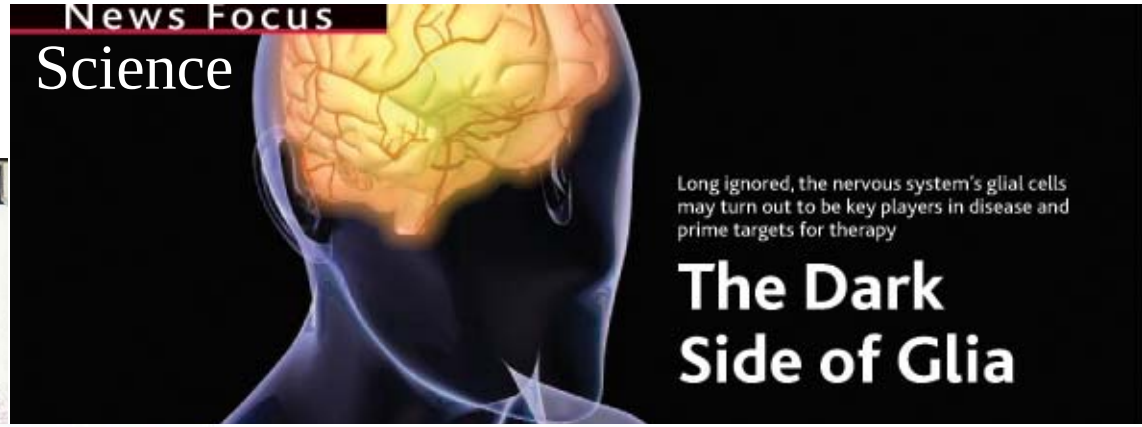
Basal - Equilibrium between surface-expressed & intracellular receptors

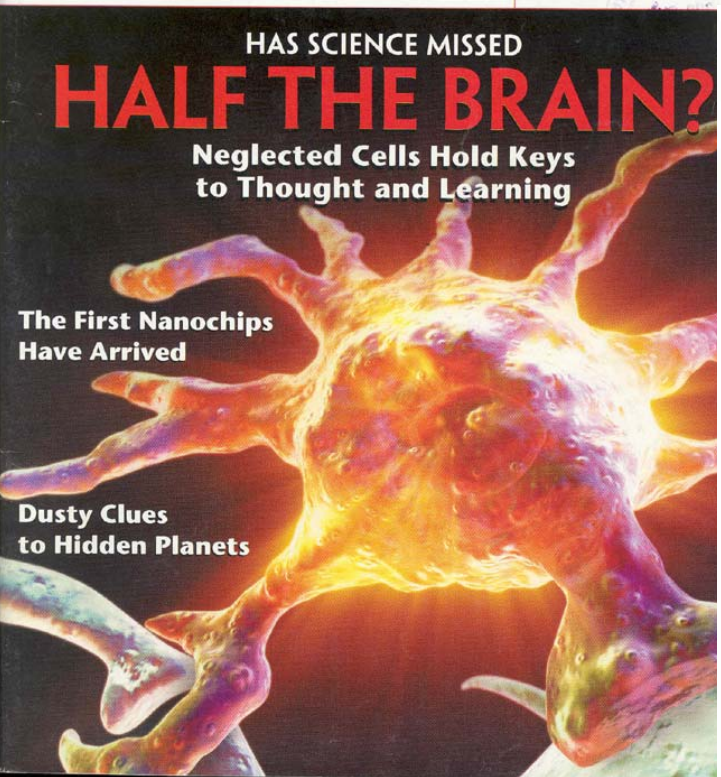
LTP - New GluR1-containing receptors are inserted into both non-silent & silent synapses

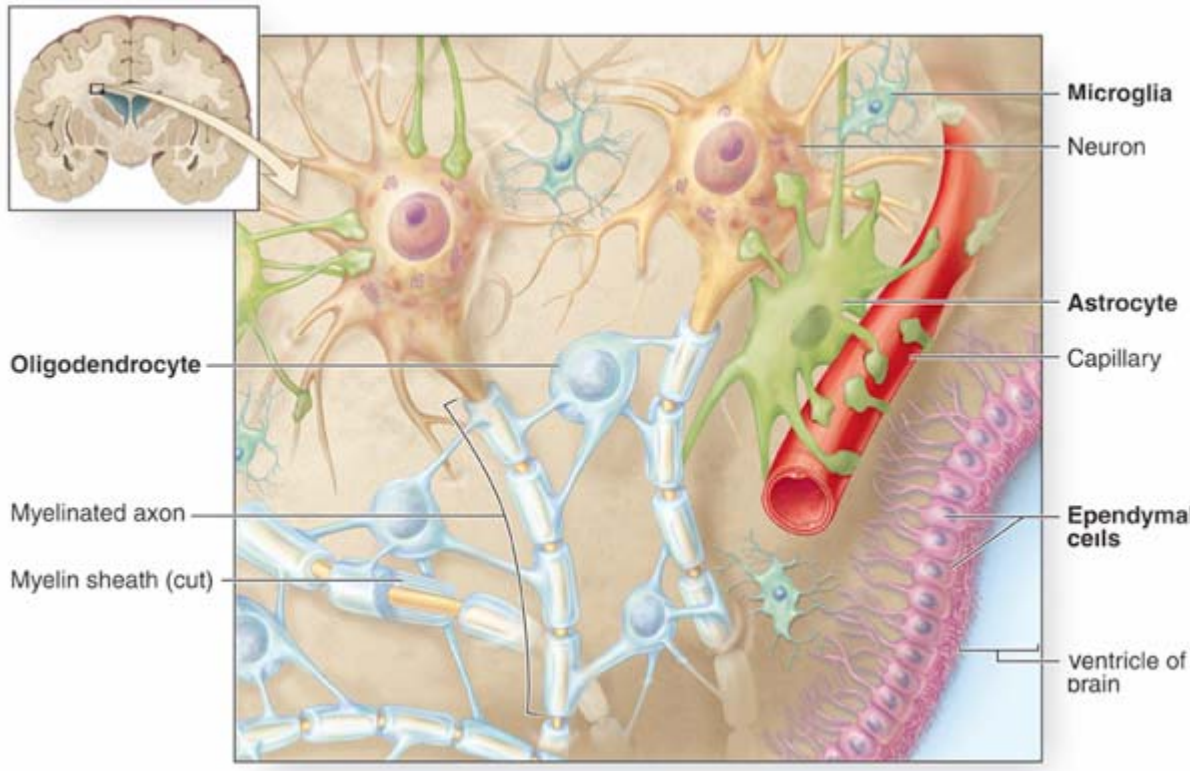
Later – New equilibrium with GluR3-containing receptors

Glia : The “Other Half” of the Brain



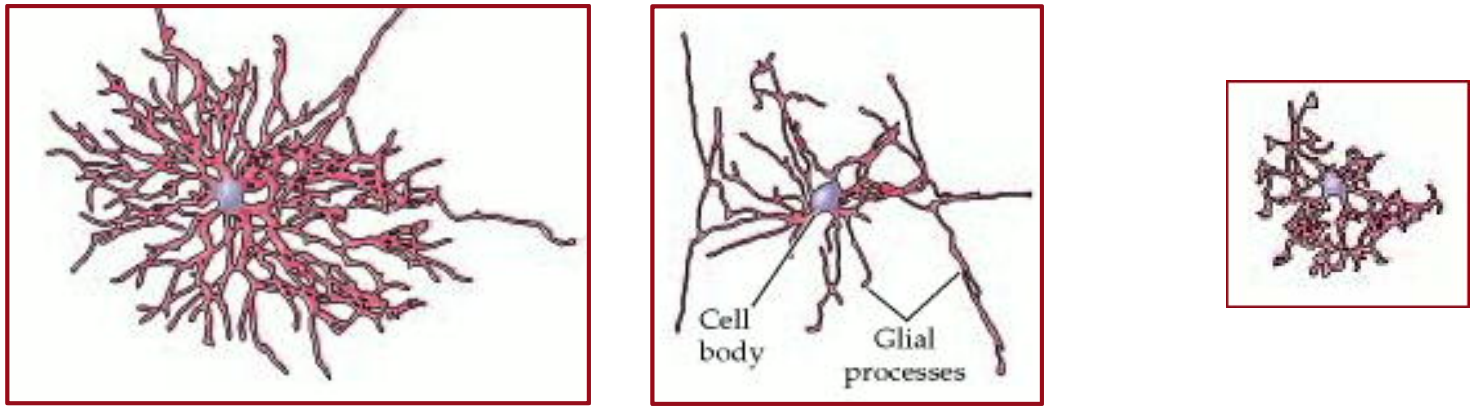






Glial cells and neurotransmission

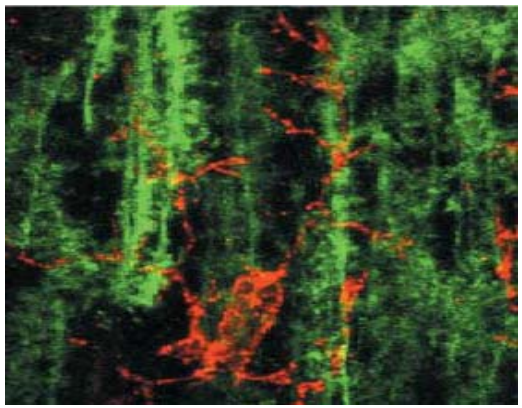
Astrocyte **Oligodendrocyte** **Microglia**



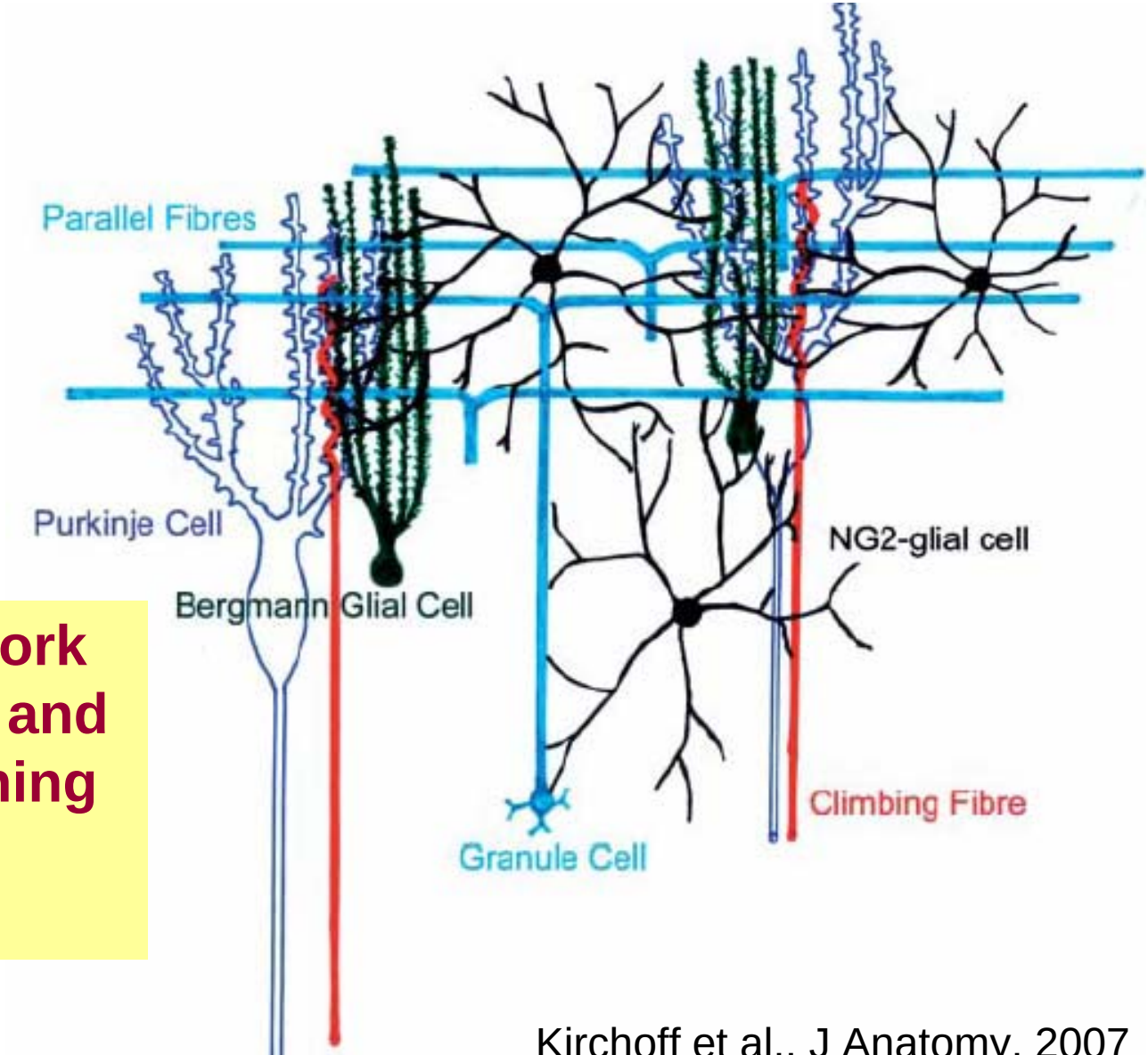
Tracings of cells as visualized by impregnation with silver salts

- **Ensheathment of synapses**
- **Glial cell activation by neurotransmittion**
- **Glial cell modulation of neuronal activity**
- **Glial cells modulate development of synaptic contacts**

Glia are intimate functional elements in the neuronal network

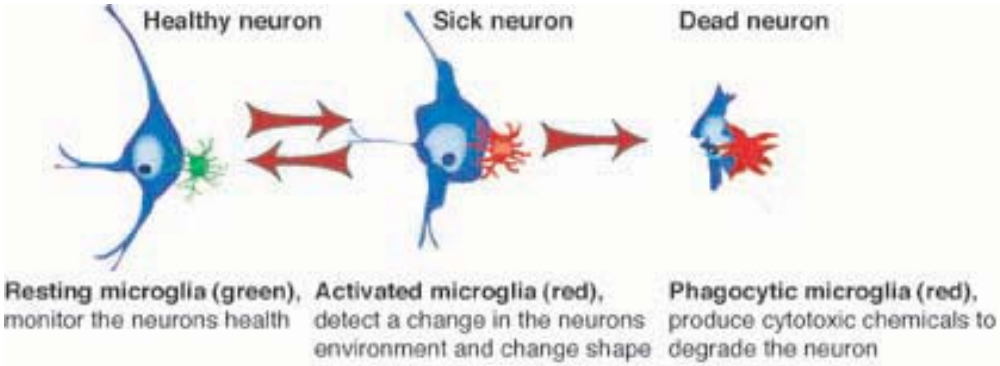


The cerebellar network with Bergmann glia and NG2+ cells intertwining the Purkinje and Granule neurons



Kirchoff et al., J Anatomy, 2007

Functions of Glia



- Maintain the ionic milieu of nerve cells
- Modulate the rate of electrical signal propagation
- Microglial cells; primary scavengers in the brain
- Provide a scaffold for neural development
- Aiding or preventing repair of injured regions
- Modulate synaptic action by uptake of neurotransmitters
- Support, modifies and defines plasticity of synaptic contacts.

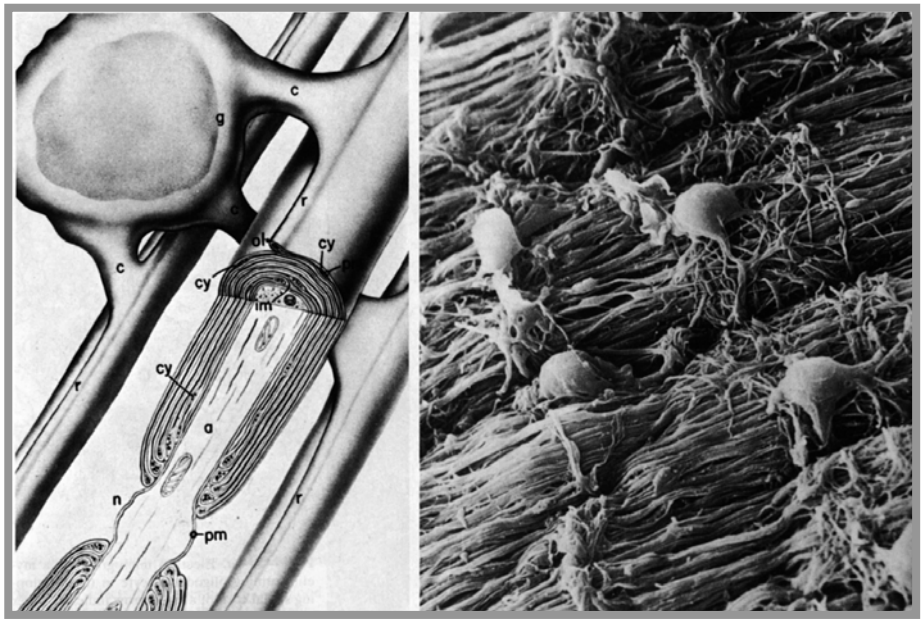
Classical roles of Glia.....

Myelination

Mopping up neurotransmitters

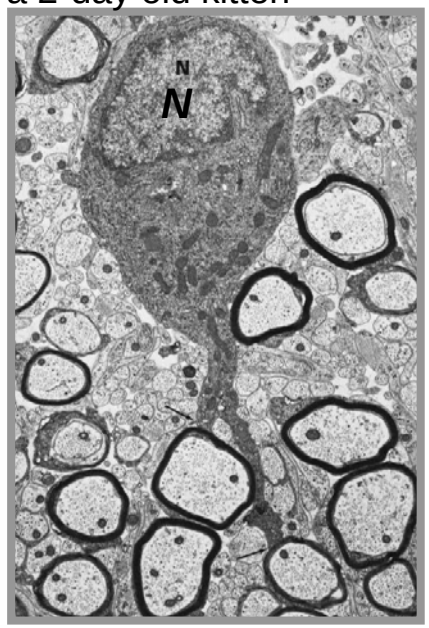
Scaffold

Oligodendrocytes are the myelinating cells of the CNS

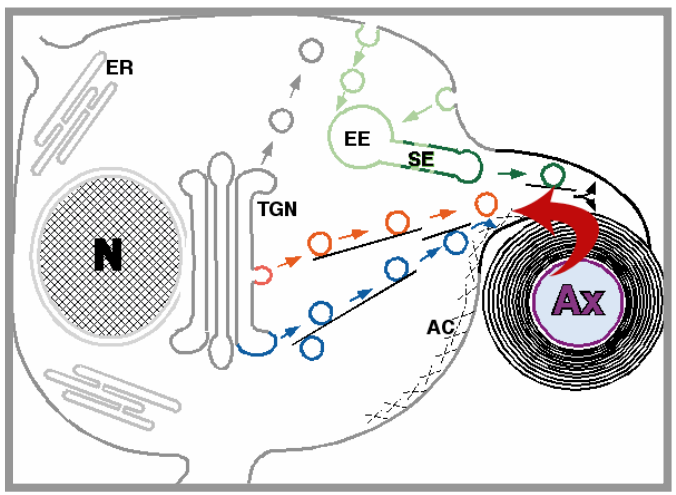


Myelinated axons

From the spinal cord of a 2-day old kitten



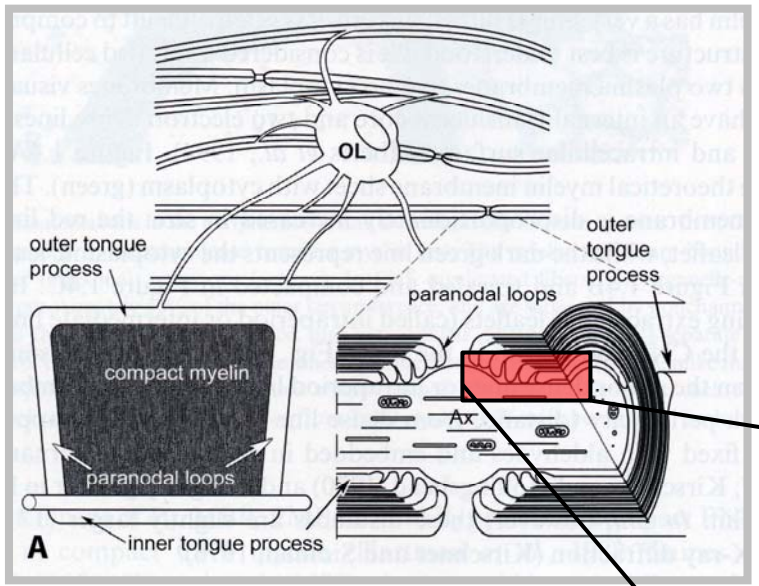
A myelinating oligodendrocyte extends cytoplasmic connections to at least two myelin sheaths

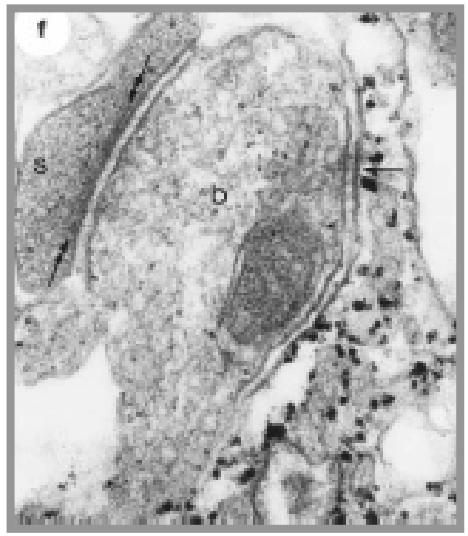


Biogenesis of myelin sheath with anterograde & retrograde signalling between neurons and oligodendrocytes.

Oligodendrocyte-Neuron Interactions at the Paranode

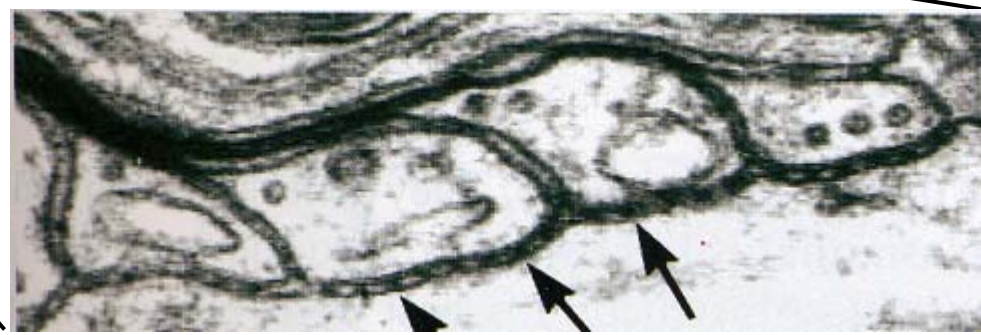
Schematic diagram of oligodendrocyte-paranode juxtaposition at the internodes





From rat CNS – immunolabelled for NG2

Immature oligodendrocytes sit cheek-by-jowl with neurons too!

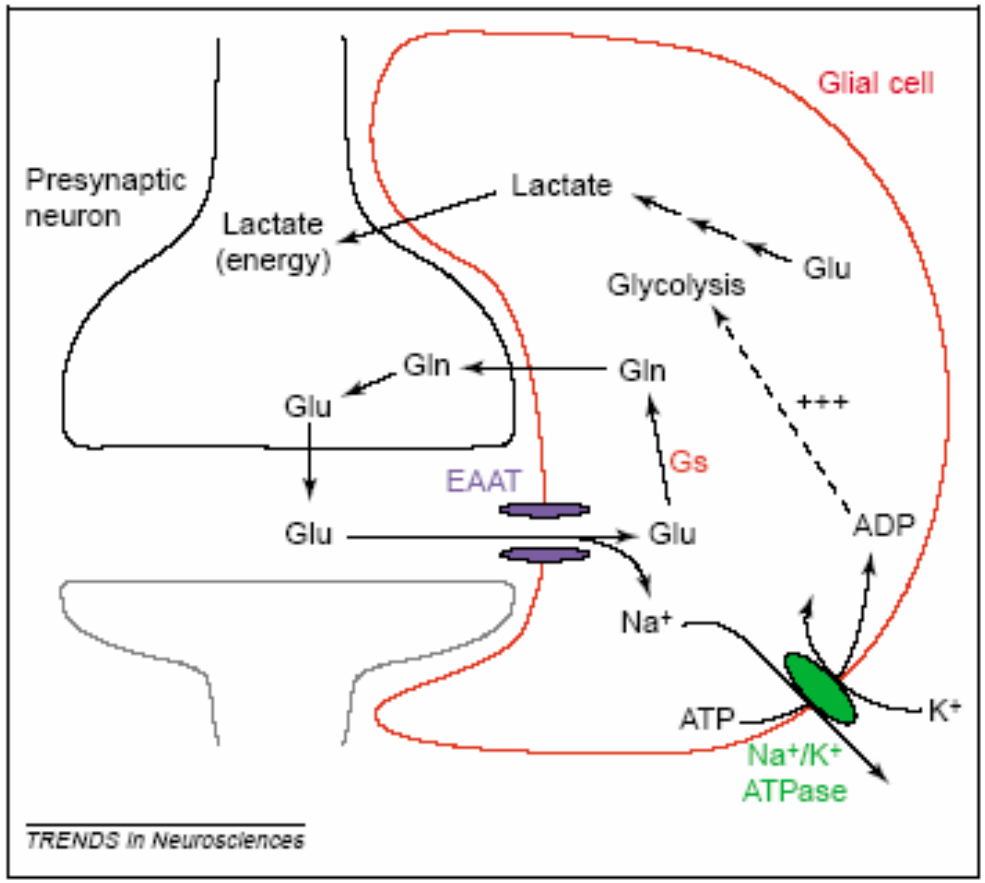


Electron micrograph image

… NT recycling & Glucose utilisation

Endfeet processes of astrocytes siphon off elevated extracellular K^+ for depositing in areas of lower K^+ levels

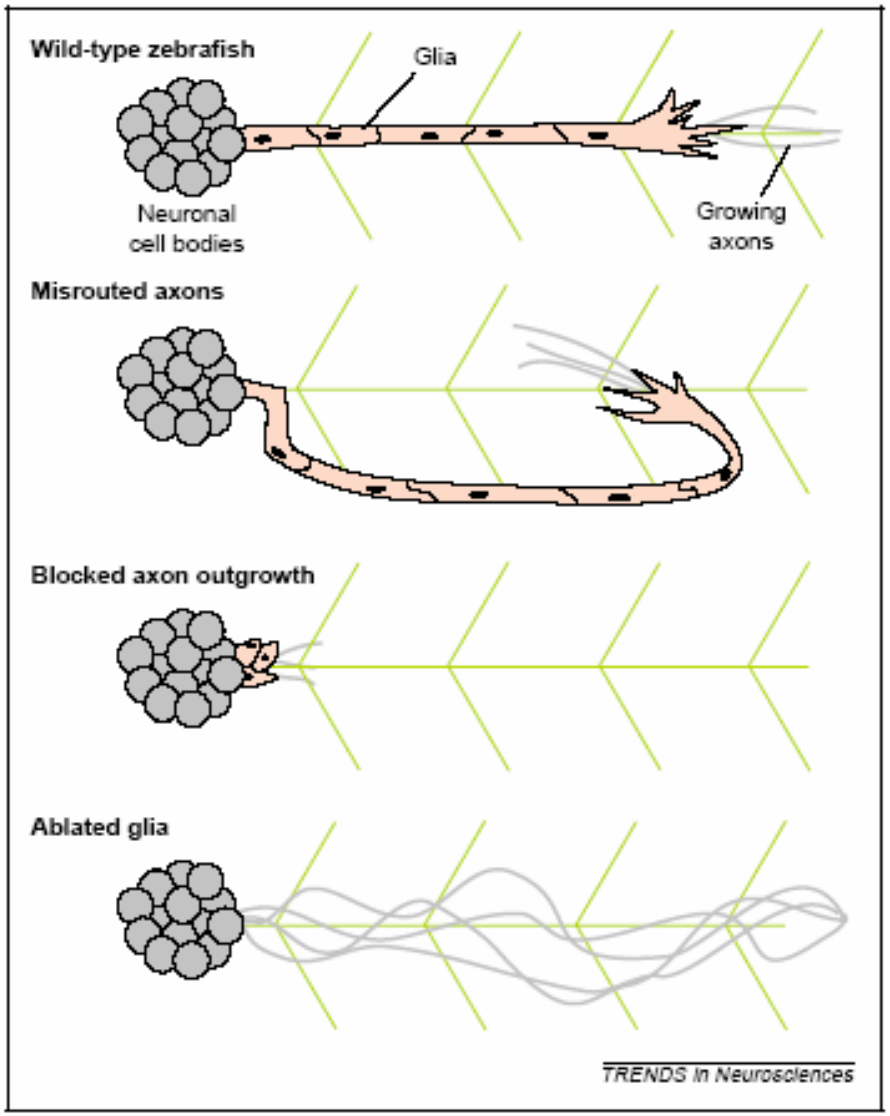
Expression of GLAST in astrocytes to mop up glutamate

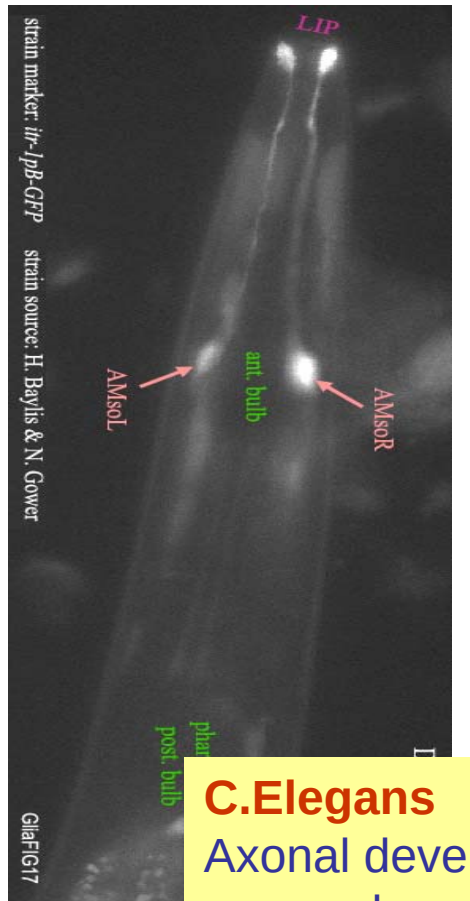


Freeman & Doherty (2006) TINS 29, 82 - 90

Glial role in ……..Nerve assembly. Bidirectional signaling between neurons & glia

Zebrafish

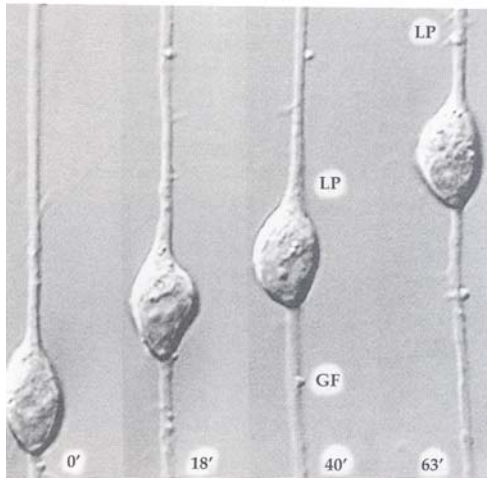




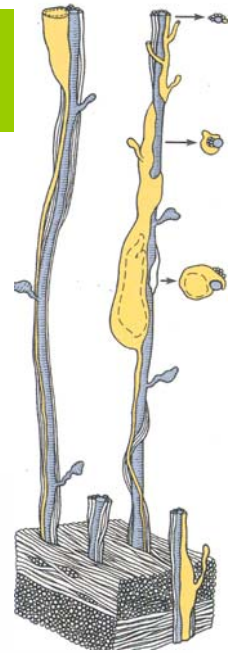
C.Elegans
Axonal development goes askew without glia

Radial glial cells ……

- Stretch through the thickness of spinal cord, retina, cerebellum, forms elongated filaments ….



Neuronal migration along radial glia in the cortex

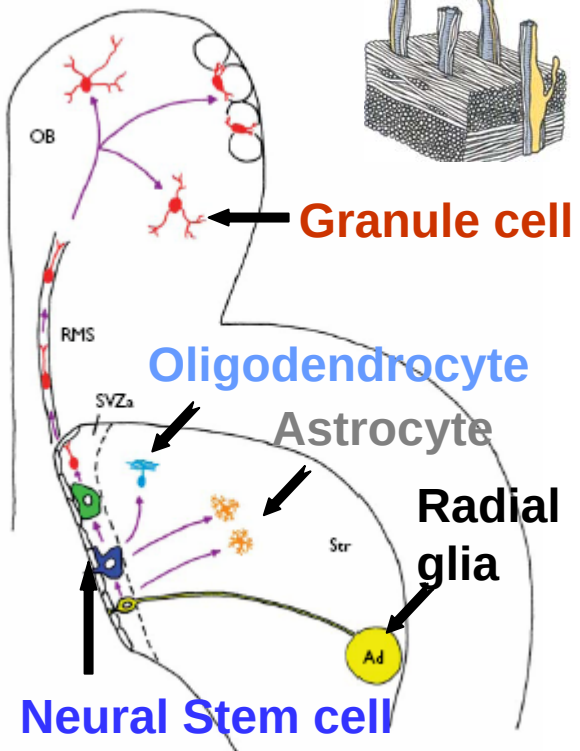


- Newly-born neurons migrate radially along the extended bipolar process of the radial glia

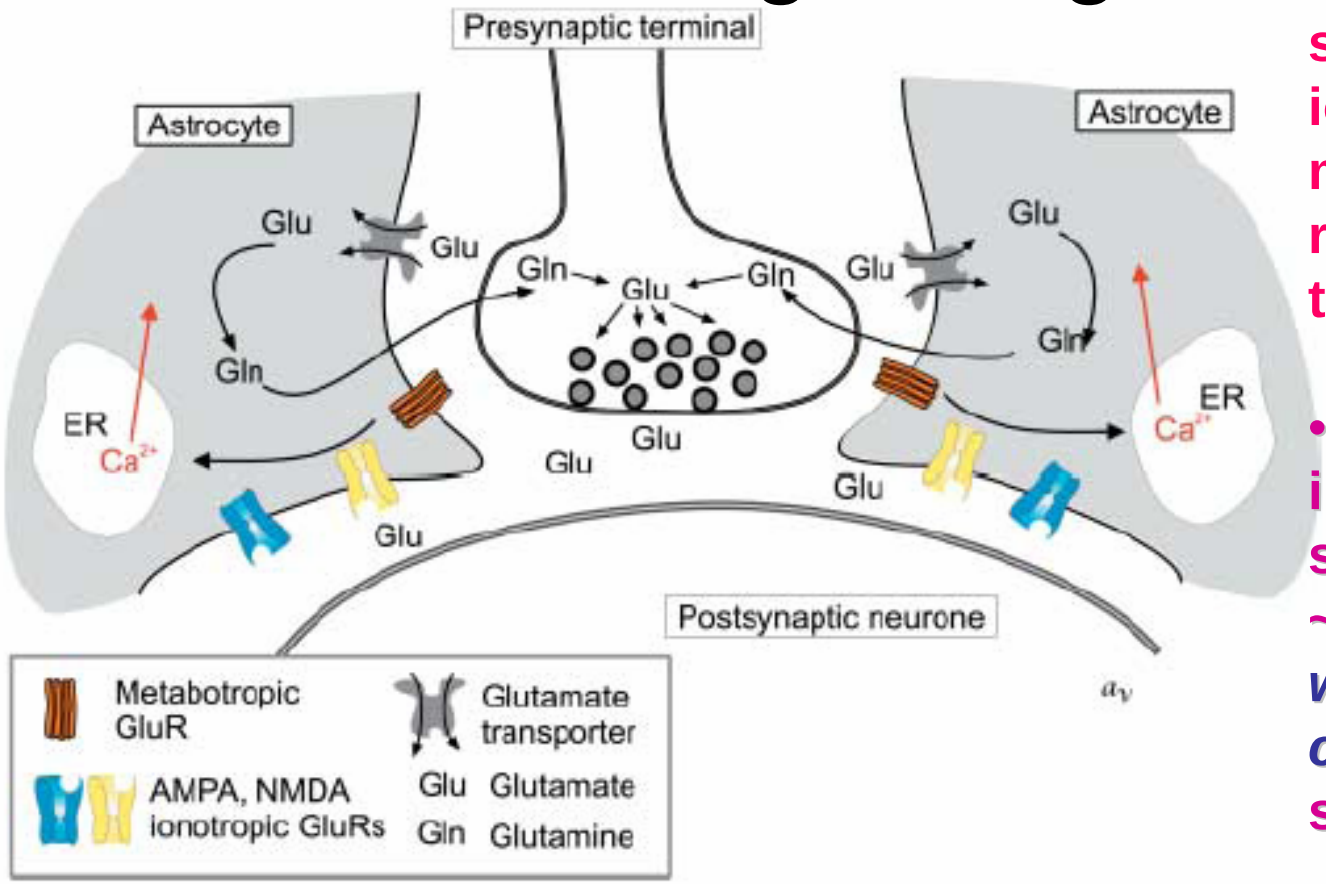
- Radial glia actively divide, producing daughter cells that include both neurons and glia.

- A subset of forebrain radial glia may serve as the founders of adult forebrain neural stem cells

- Source of progenitors for repair; upregulated in areas of neurodegeneration



NT-mediated Neuronal-Glial Signalling

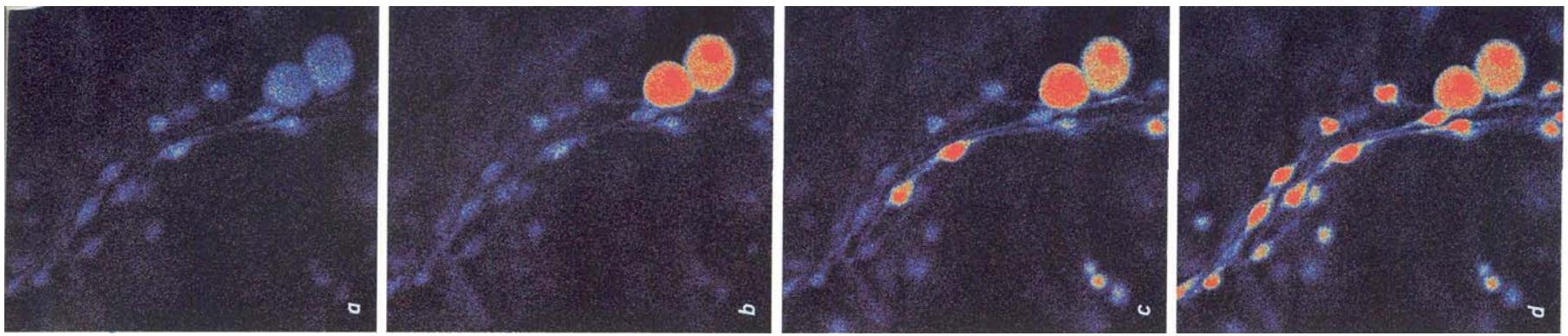


- **NT release activates several types of ionotropic, metabotropic receptors & NT transporters.**
- **Initiate a variety of intracellular signalling processes, *~ associated with propagating cytoplasmic Ca2+ signals.***

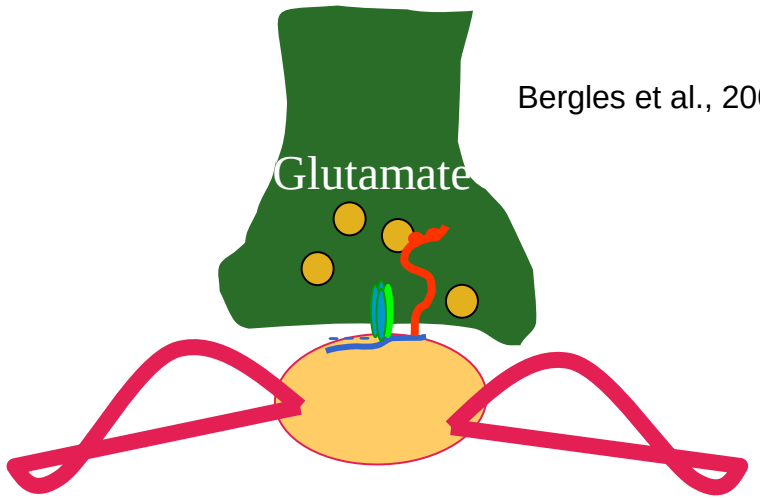
Neurotransmitter sensors expressed in glial cell membranes allows the glia to decode neuronal activity and to synchronize and integrate neuronal and glial circuitries.

Glia as an active participant in neuron-neuron signalling

Neurons & glia can communicate through Calcium waves !

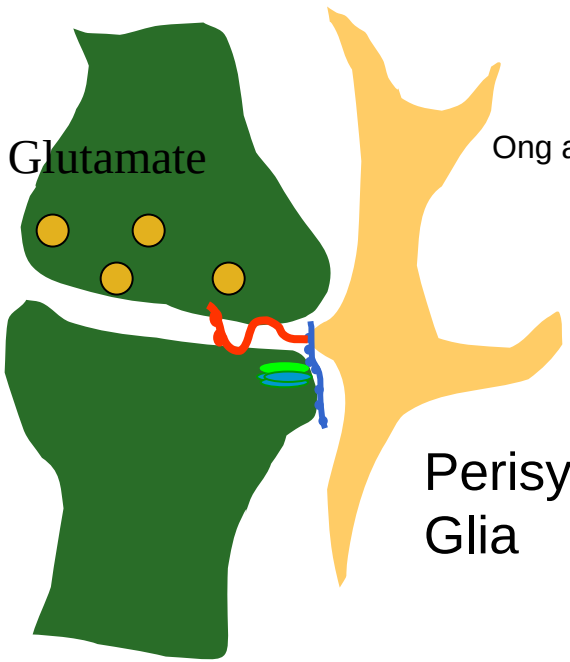


Glia as an active participant of neuron-neuron signalling



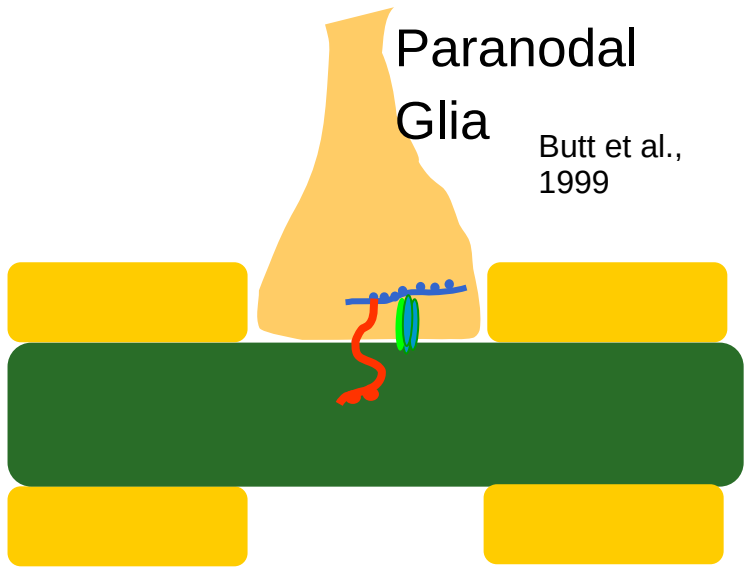
Bergles et al., 2000

Neuron-Glial Synapse



Ong and Levine 1999

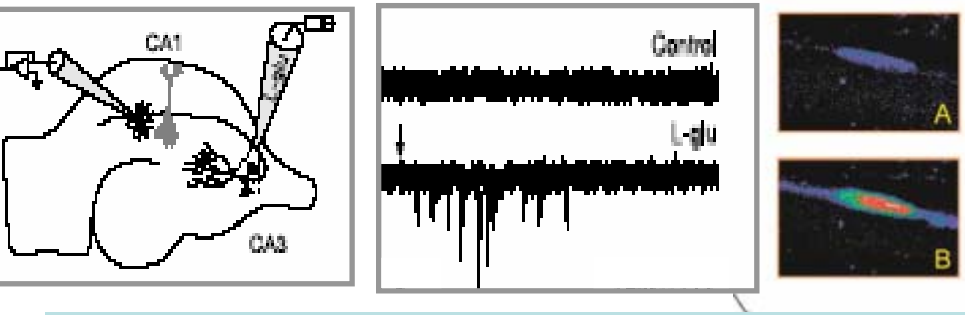
Perisynaptic Glia



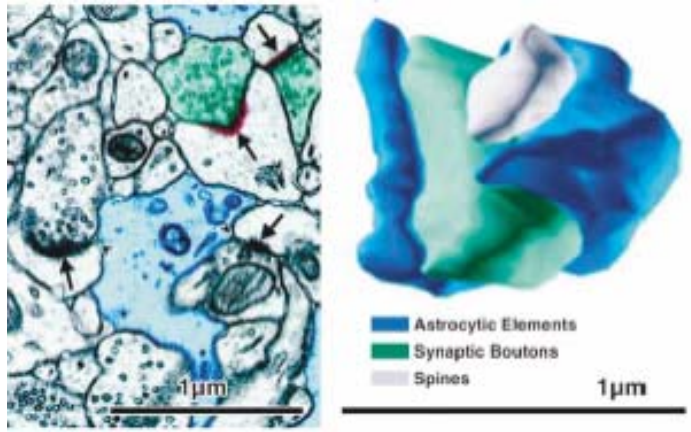
Paranodal Glia

Butt et al., 1999

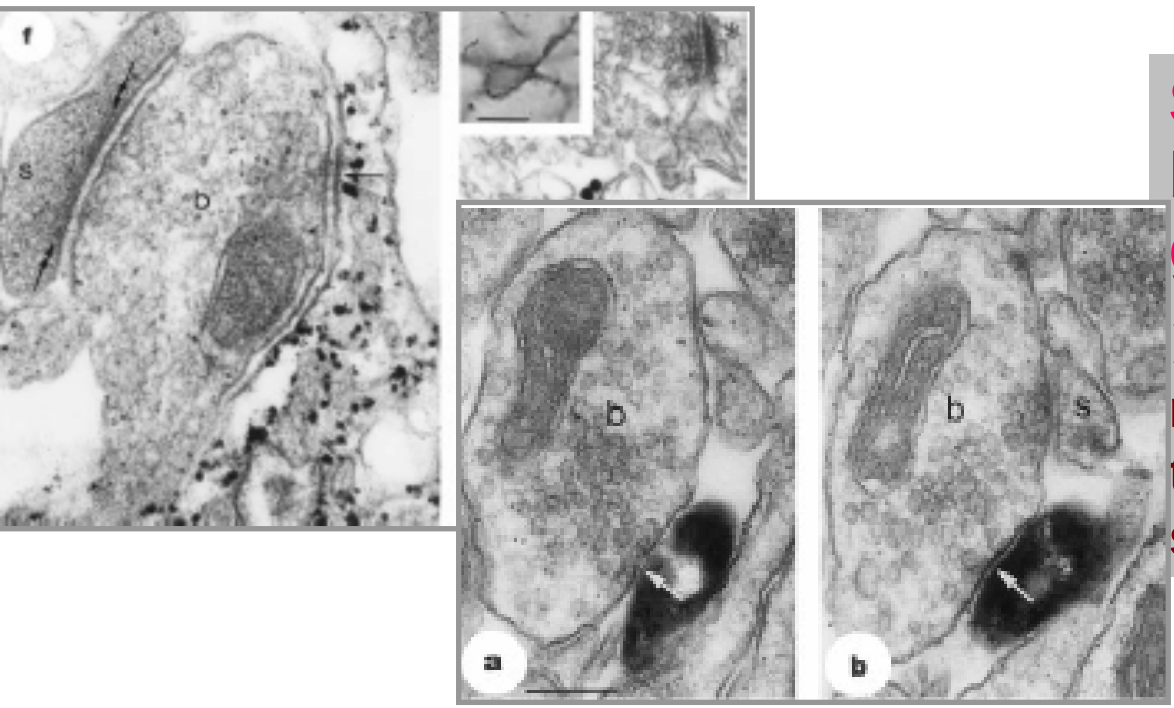
Glia sit cheek-by-jowl with neurons!



➢Glutamate application on CA1 pyramidal neurons elicited inward current bursts in OPCs.



Astrocytes in hippocampus

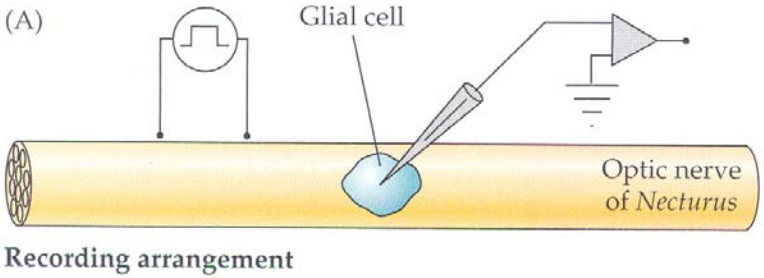


Synaptic specialisations between neurons and glia!

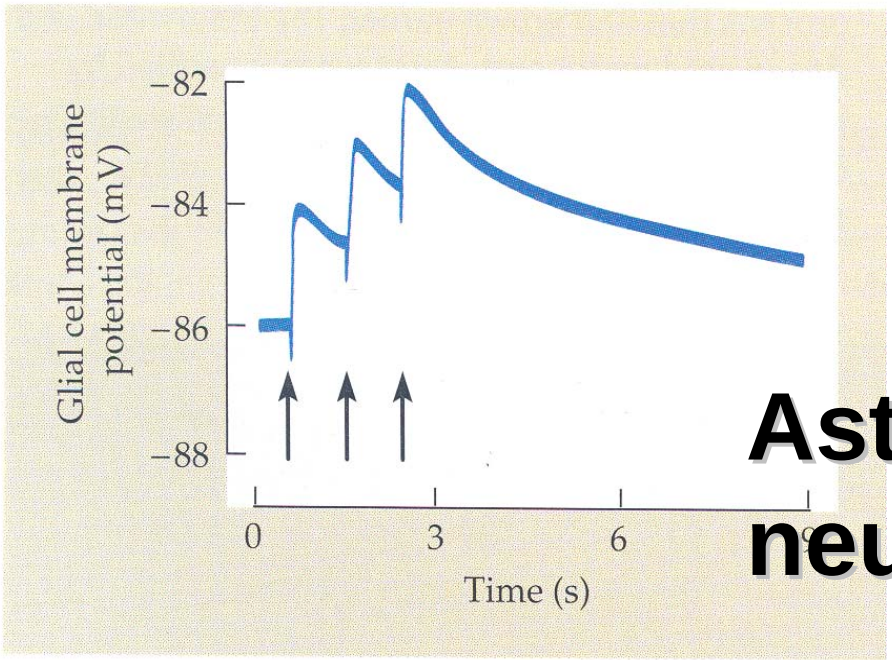
➢The post-synaptic membrane specialisation is thinner in neuron-glia synapses.

Bergles et al., 2000

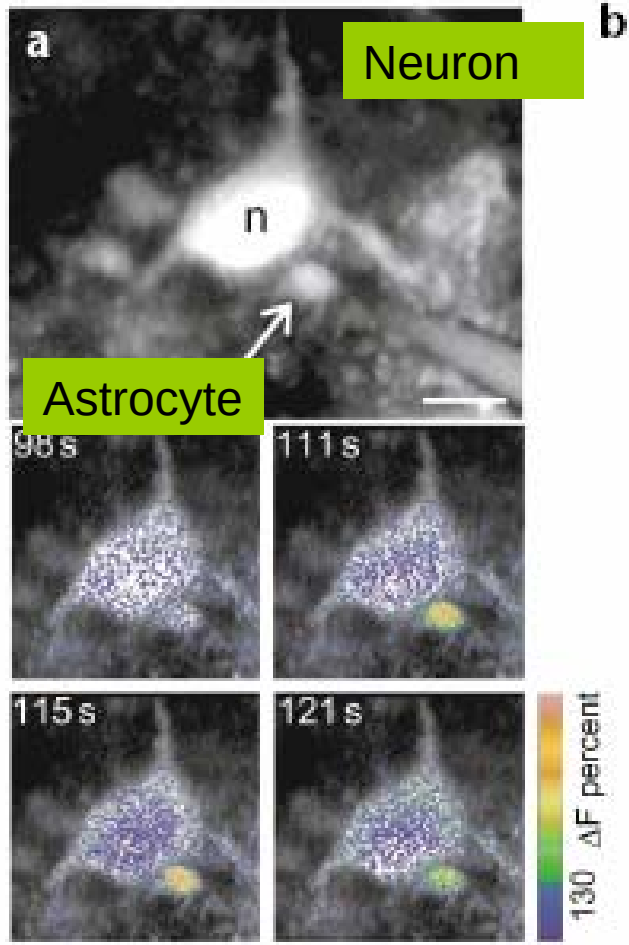
Effect of AP on glia on optic nerve of mud puppy



Recording arrangement



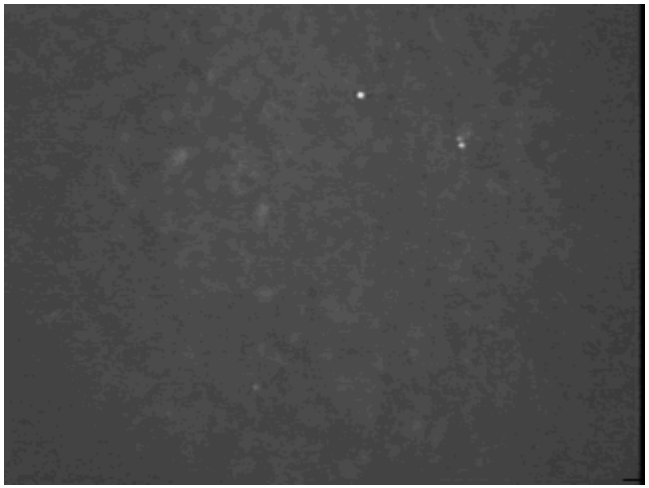
Single stimuli to axons



Astrocyte modulation of neuronal Ca^{++} levels

Calcium waves in *glial* cell syncytium

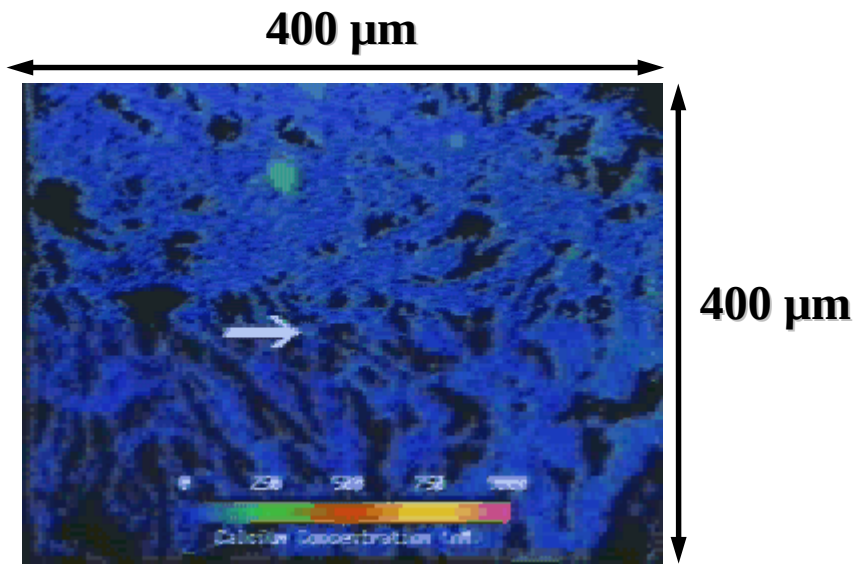
Waves of increased intercellular Ca^{++} travelling at 5-10 µm/s



Craig Charles Lab, UCLA Med School

Response of brain astrocytes to mechanical stimulation of a single cell: wave propagating from stimulated cell to many surrounding cells

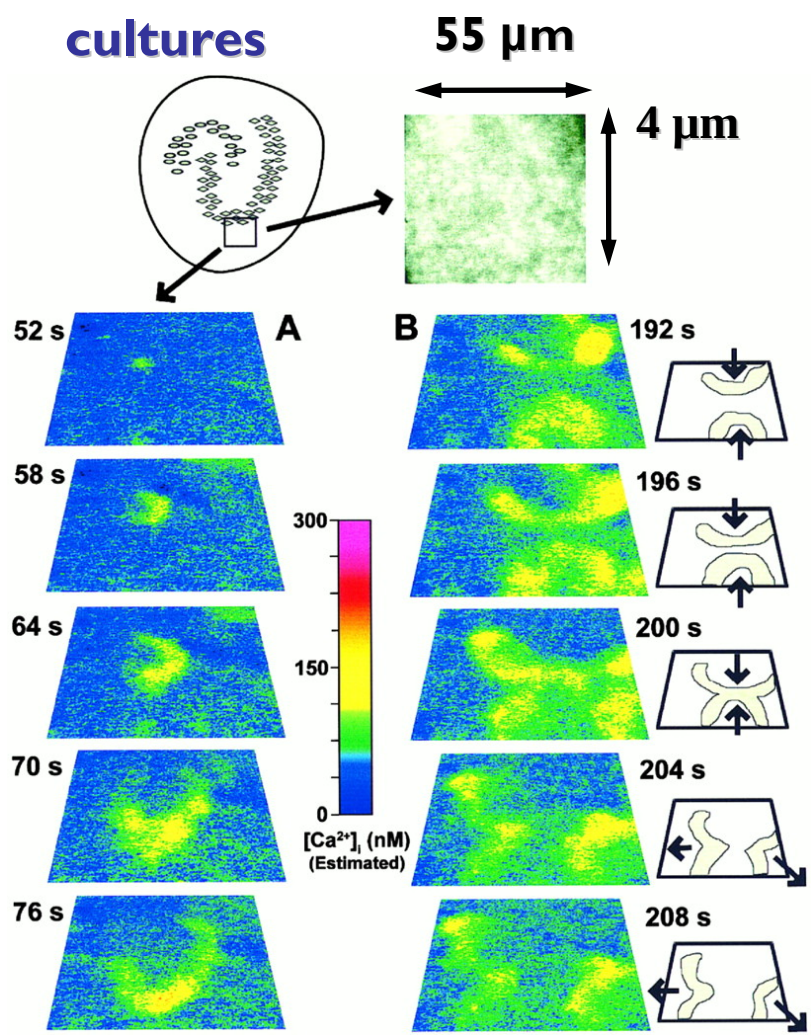
Imaging field showing fluorescence intensity of Ca^{++} indicator fluo-4

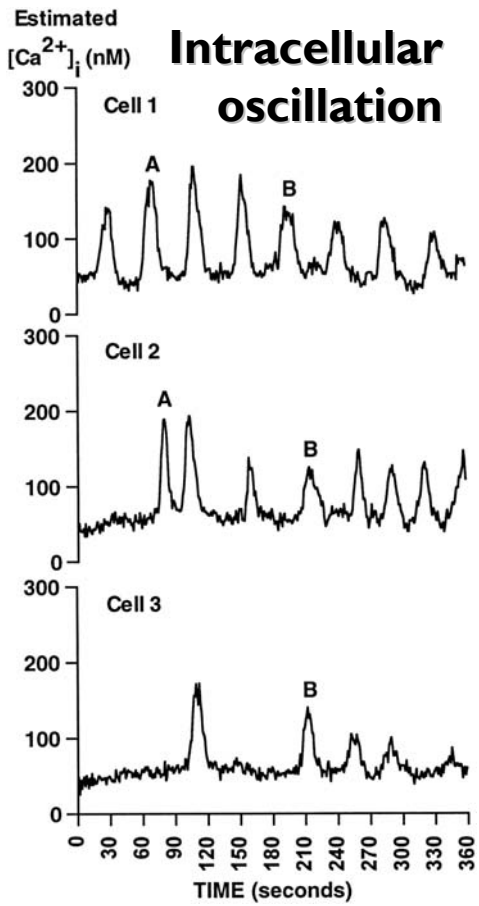


Calcium waves in glial cell culture in response to mechanical stimulation of a single cell with a micropipette

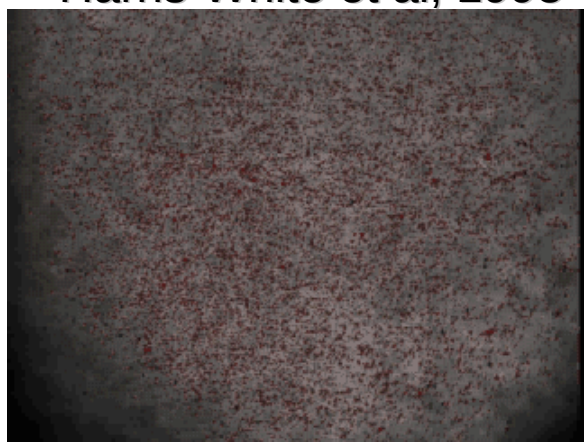
Spiral Waves in Mouse Hippocampus

Observation of intercellular Ca^{++} spiral waves in hippocampal slice cultures



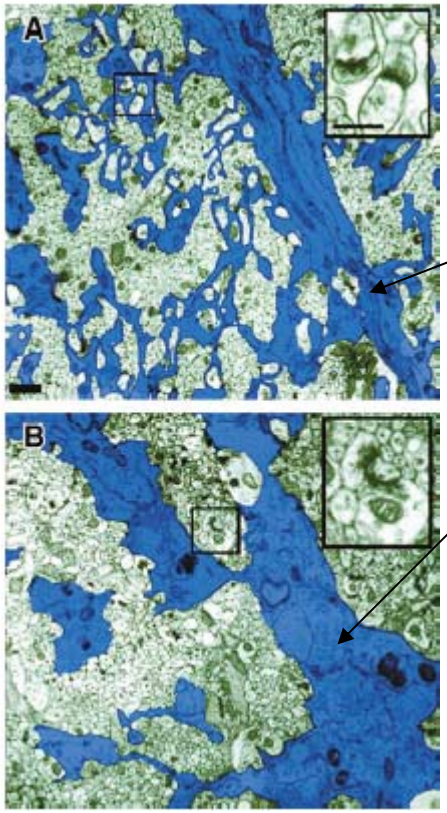


Harris-White et al, 1998



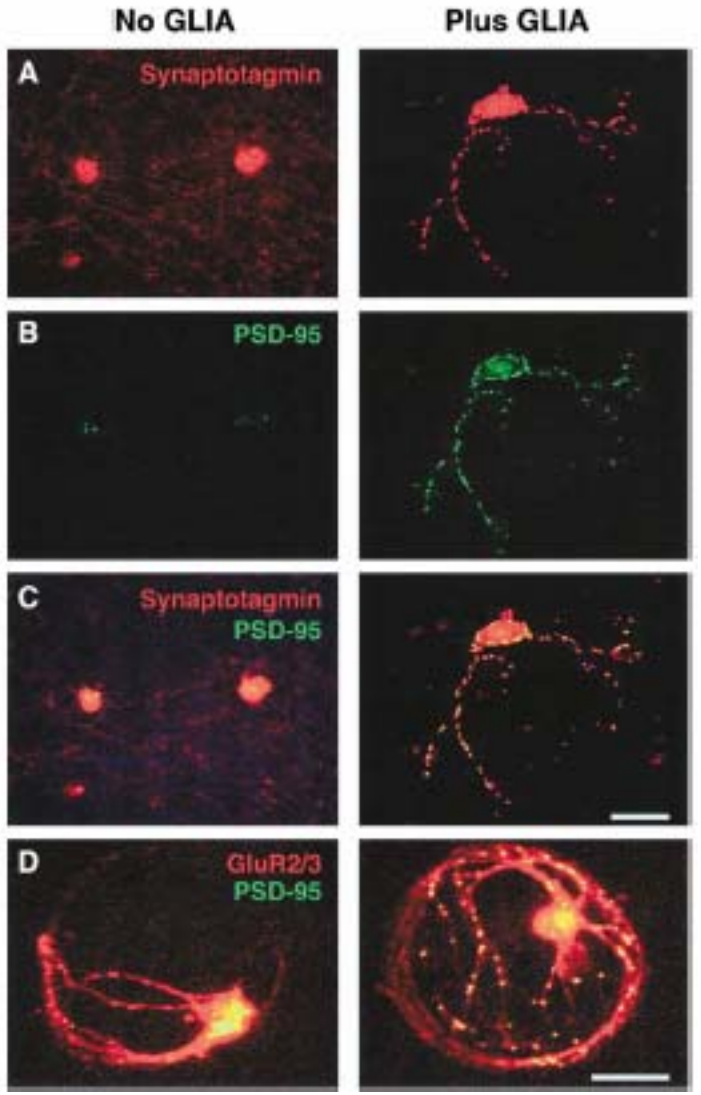
Full circle

Astrocytes increase synaptic efficiency



Bergmann glia

Synaptotagmin – presynaptic marker
PSD95 – postsynaptic marker



Glutamatergic signalling helps maintain glial ensheathment in cerebellar synapses

Thanks!

References

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