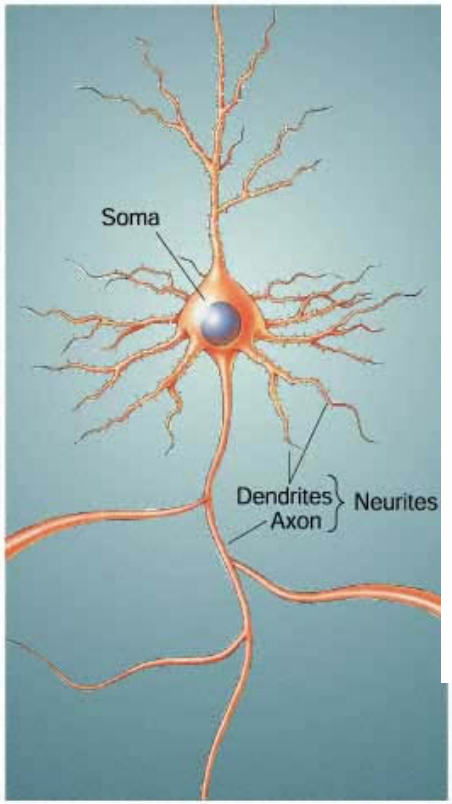
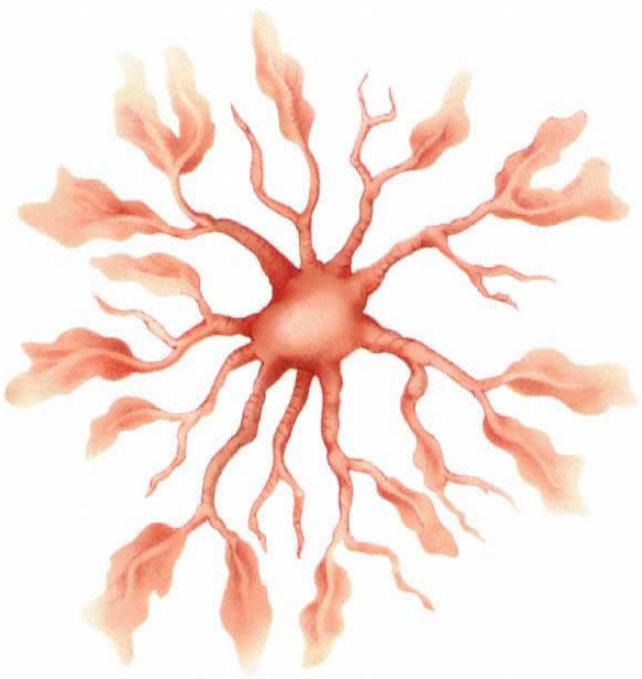
Cells of the nervous system

- There are approximately 100 billion neurons in the human brain
- There are about 100 times as many glial cells in the human brain
- Similar origin, different functions
- Other cells include ependymal cells, microglia and cells of the brain vasculature

Where do they originate from?

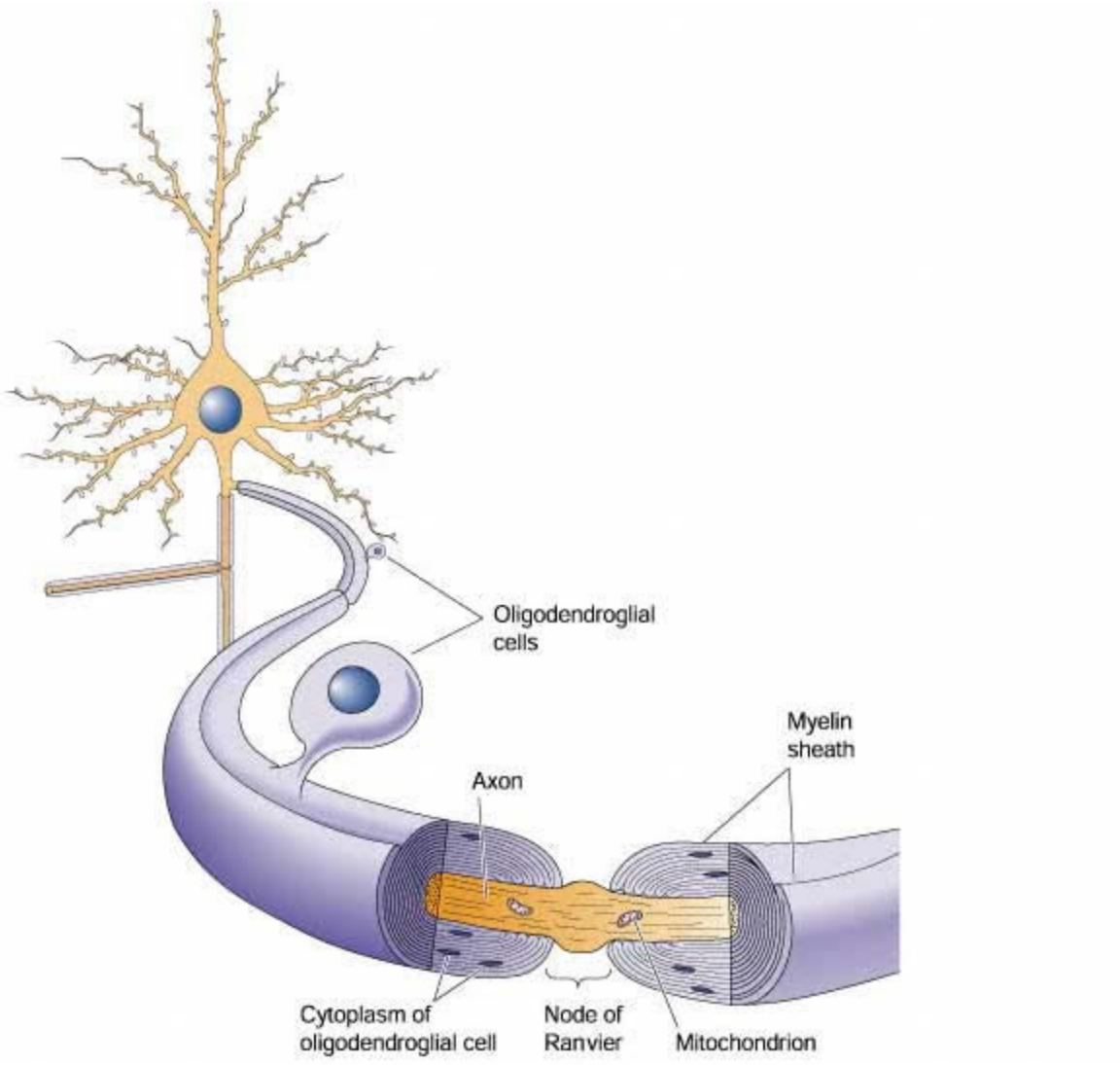
- Neurons and glia originate from neuroectoderm (progenitor stem
- Neuroblasts -> neurons
- Astroblasts -> astrocytes





Glial cells

- Astrocytes link small blood vessels inside the brain and neurons
- Regulate extracellular substances
- Astrocytes can also remove NTs from the synaptic cleft
- Oligodendrocytes send processes to axons of the neurons, aid in conduction properties of neurons
- Many neurons can be insulated by a single oligodendrocyte


Oligodendroglial cells
Myelin sheath
Axon
Cytoplasm of oligodendroglial cell
Node of Ranvier
Mitochondrion

Myelin

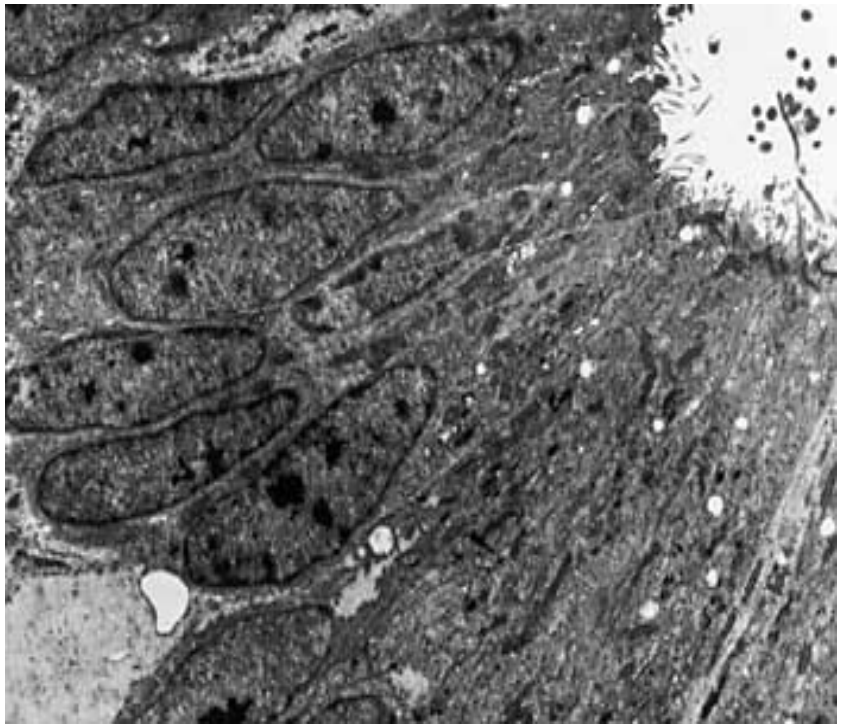
- In the CNS oligodendrocytes produce myelin
- In the PNS Schwann cell wraps around the axon
- In MS antibodies from blood pass into brain and attack myelin, especially in long pathways

Microglia

- Does not develop from neuroectoderm
- Originates from blood supply
- Function as phagocytes to remove debris left by degenerating cells
- Pericytes of the BBB are thought to be derived from the microglia

Ependymal cells

- Originate from spongioblasts
- Line the ventricular system of the brain and the central canal of the spinal cord
- Their cilia are important in propelling fluid transport



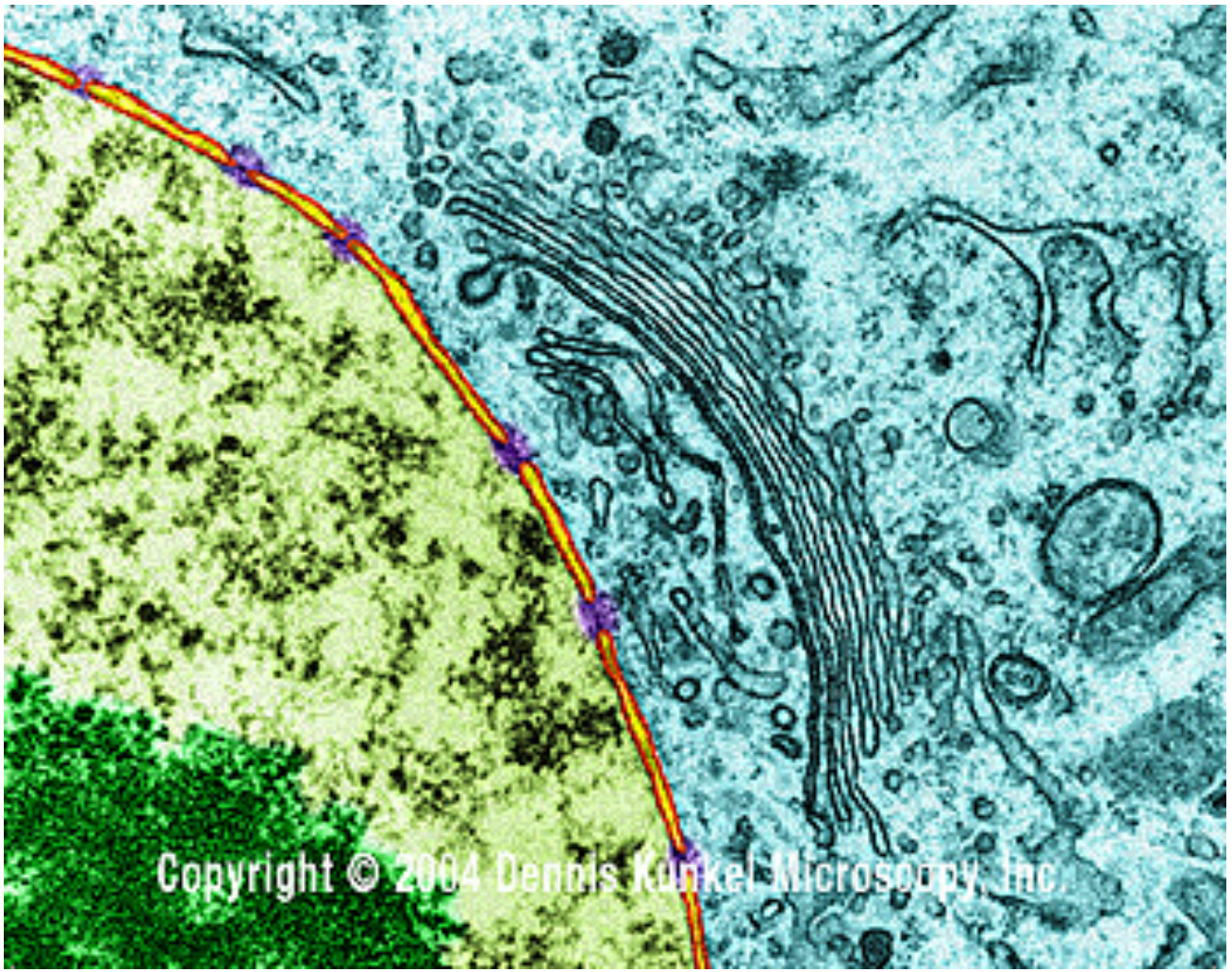
Neuron

- The cell body (soma) of the typical neuron is about 20 micrometers in diameter
- The cytoplasm contains the cytosol and all the organelles except the nucleus
- Neuronal membrane separates the neuron from the extracellular matrix, and it's many membrane-associated proteins help transfer electrical signals

The nucleus

- Spherical, centrally located, 5-10 μm across
- Contained within the nuclear envelope
- Can be visualized with Nissl stain because it contains chromosomes
- Chromosomes contain the genetic material, deoxyribonucleic acid

Nuclear envelope and pores



Protein synthesis

- mRNA transcripts emerge from nuclear pores and travel to the sites of protein synthesis
- mRNA is then translated and proteins are build by linking of specific amino acids
- Central dogma of molecular biology:

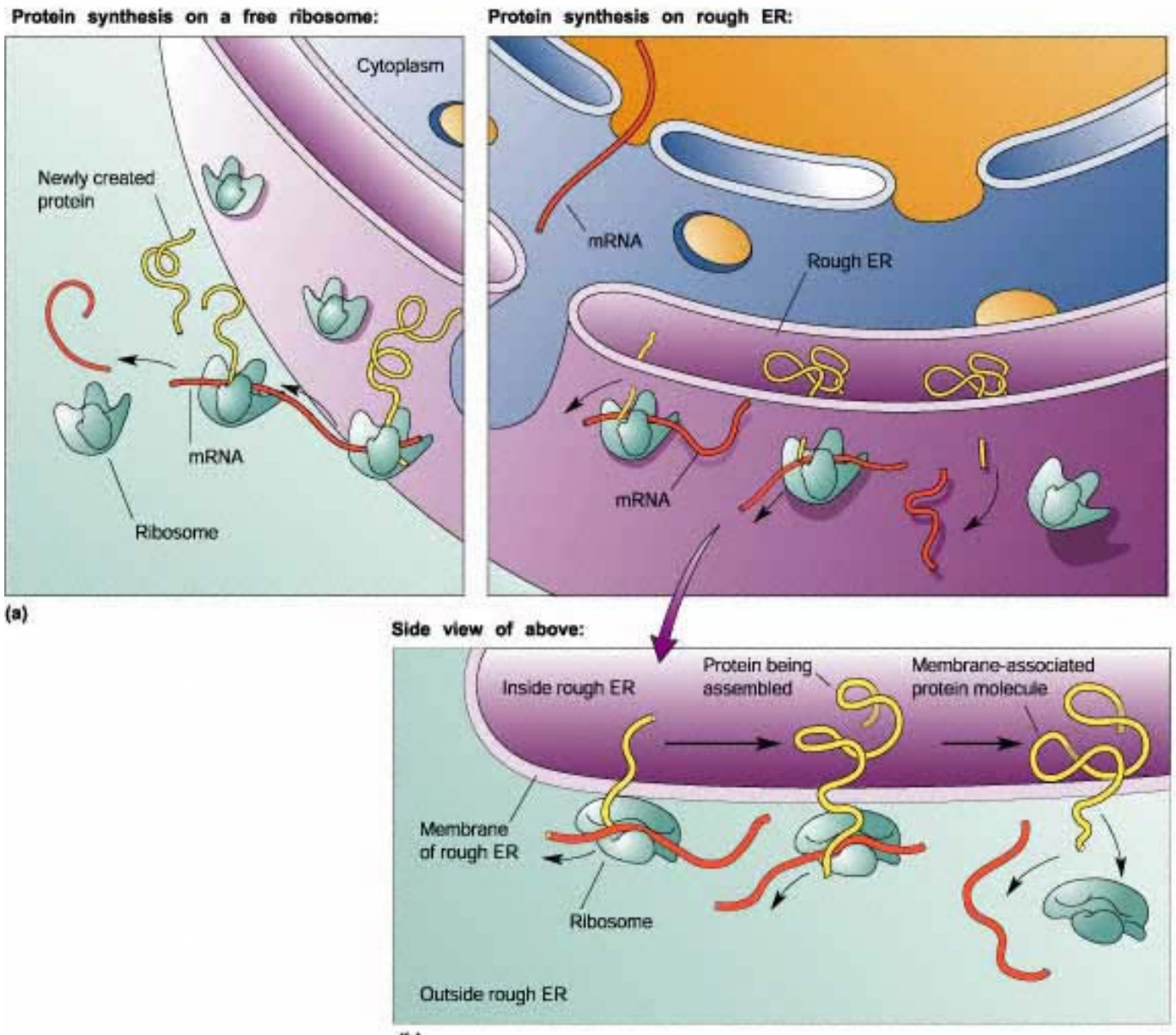
  DNA → mRNA → Protein

Rough Endoplasmic Reticulum

- Enclosed stacks of membrane dotted with ribosomes
- Stained with Nissl (Nissl bodies)
- Major site of protein synthesis in neurons
- Abounds in neurons because proteins assembled on the rough ER are inserted into the membranes

Polyribosomes

- Another site of protein synthesis
- Made up of several free ribosomes attached to each other by a single strand of mRNA
- Proteins assembled on polyribosomes reside within the cytosol of the neuron

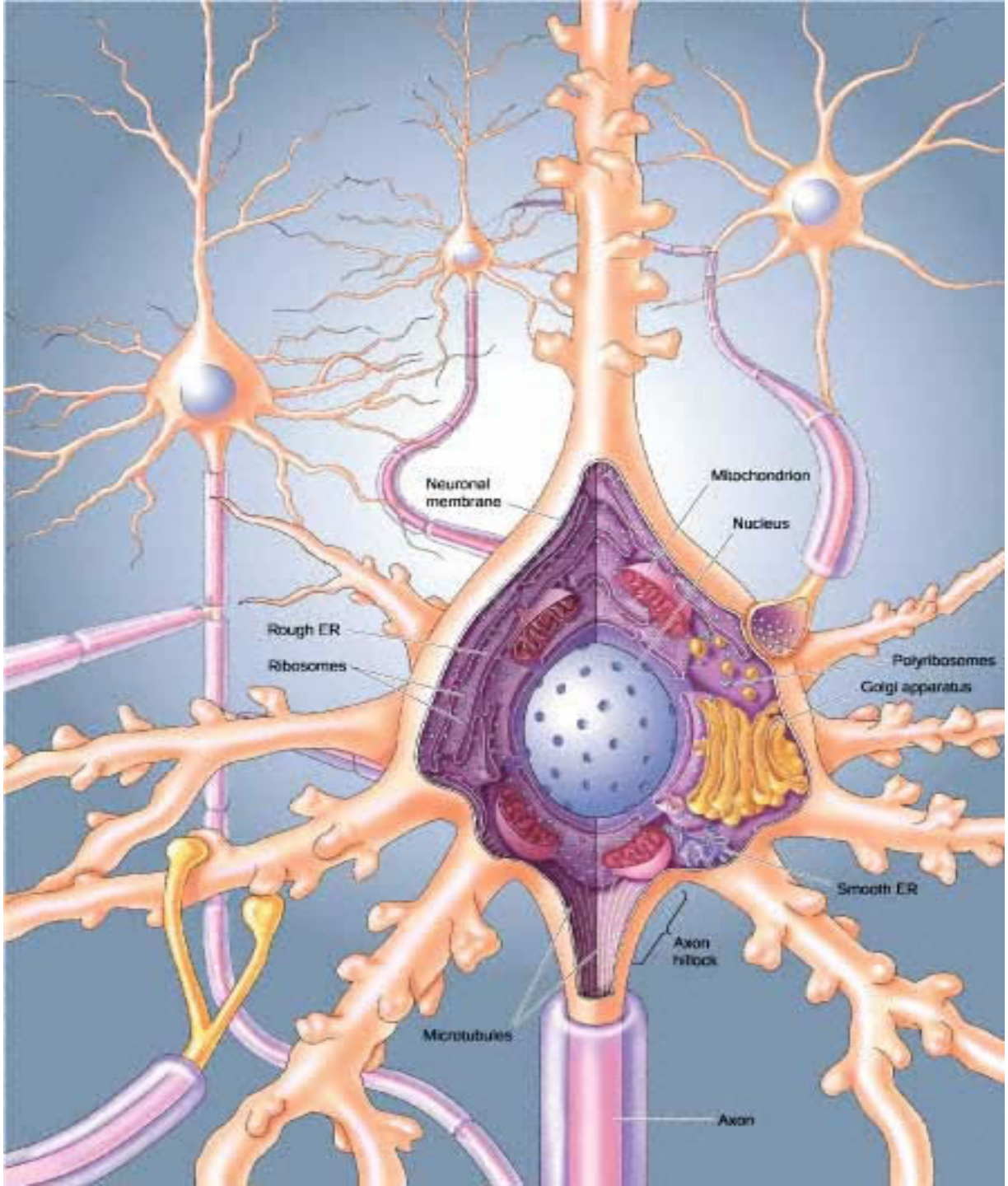

Protein synthesis on a free ribosome:
Cytoplasm
Newly created protein
mRNA
Ribosome
(a)
Protein synthesis on rough ER:
mRNA
Rough ER
mRNA
Side view of above:
Inside rough ER
Protein being assembled
Membrane-associated protein molecule
Membrane of rough ER
Ribosome
Outside rough ER
(b)

Smooth ER

- Performs different functions in different locations
- When close to rough ER it is thought to aid in folding of the proteins
- Other types of smooth ER regulate internal concentrations of substances such as calcium

Golgi apparatus

- Stack of membrane-enclosed disks in the soma that lies farthest from the nucleus
- This is where post-translational processing of proteins takes place
- Another important function of GA is sorting of certain proteins that are destined for delivery to different parts of the neuron


Neuronal membrane
Mitochondrion
Nucleus
Rough ER
Ribosomes
Polyribosomes
Golgi apparatus
Smooth ER
Axon hillock
Microtubules
Axon

The Mitochondrion

- First identified during the 19th century
- In 1948 biochemical studies with intact isolated mitochondria
- Measures about 1μm in length, but can change shape rapidly
- Within the enclosure of the outer membrane are the cristae of the inner membrane
- Two separate compartments: the internal matrix and a narrow intermembrane space

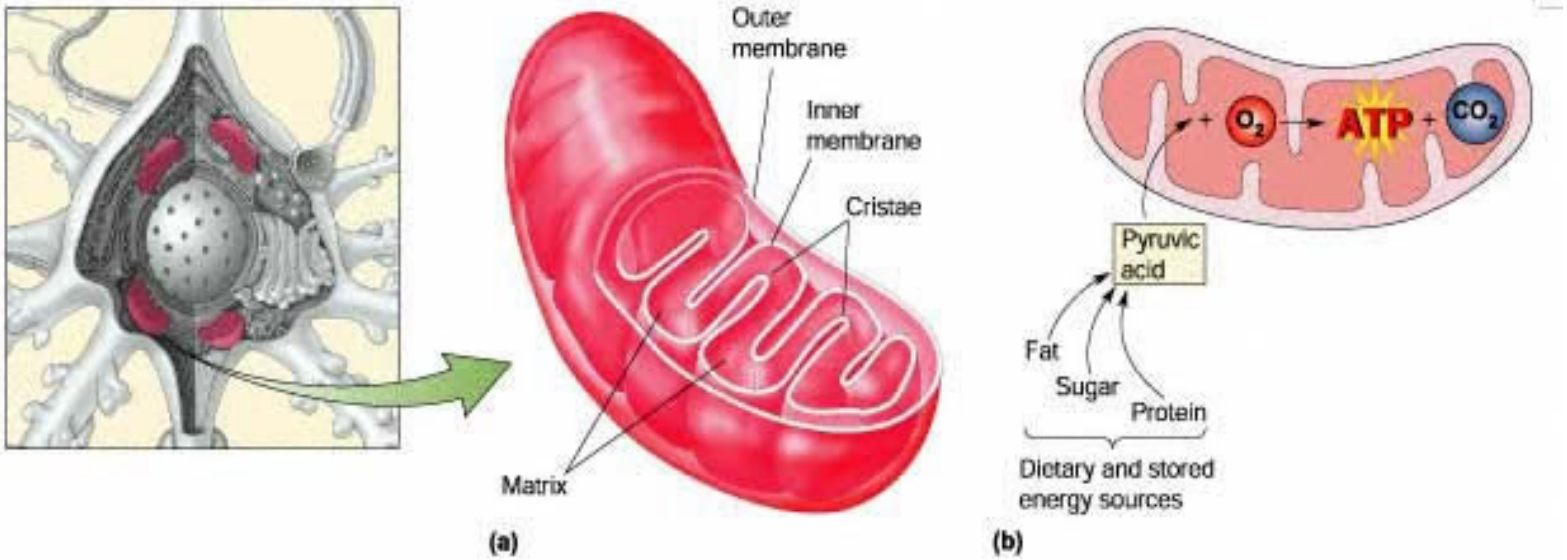
Neuronal function is dependent on mitochondria

- Mitochondria are energy-converting organelles in eucaryotic organisms
- Plastids (e.g. chloroplasts) occur in plants
- Mitochondria have their own DNA
- A number of mitochondrial diseases impair energy metabolism (Leigh's syndrome, Leber's Optic Neuropathy etc.)
- Diseases of aging (AD, PD, Huntington's)

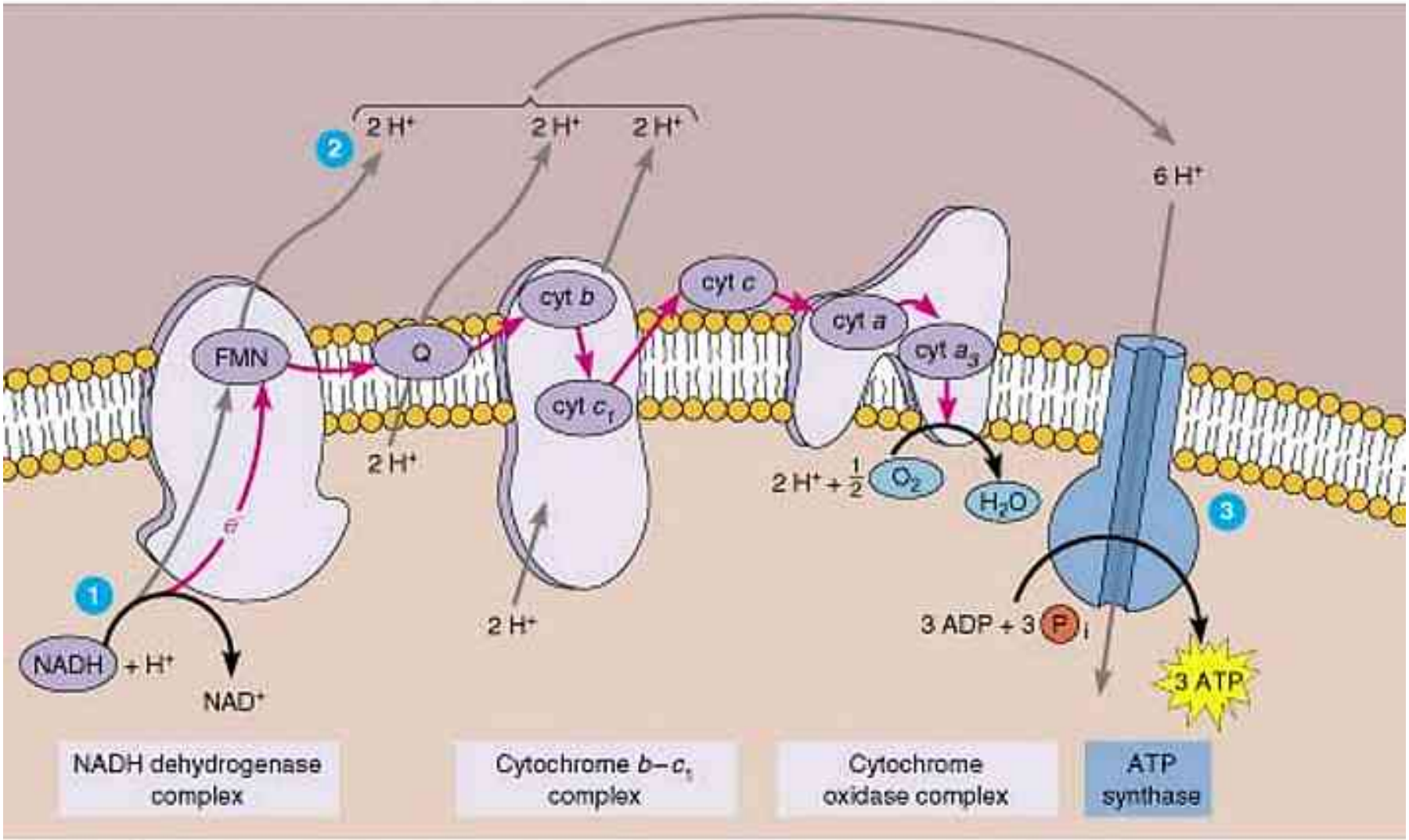
Chemiosmotic coupling

Occurs in two linked stages:

1) High-energy electrons are transferred along a series of electron carriers. Released energy is used to pump protons and this generates an electrochemical proton gradient
2) H^+ flows back down its gradient through ATP synthase, which catalyzes synthesis of ATP from ADP and phosphate (oxidative phosphorylation)


Outer membrane
Inner membrane
Cristae
Matrix
(a)
O_2
ATP
CO_2
Pyruvic acid
Fat
Sugar
Protein
Dietary and stored energy sources
(b)

ELECTRON TRANSPORT CHAIN



Cytochrome c oxidase (CO)

- Holds onto oxygen at special bimetallic center (Fe-Cu) until oxygen can pick up a total of four electrons
- Without CO cells could not use oxygen for respiration (superoxide radicals too dangerous)
- CO reaction accounts for 90% of the total oxygen uptake in most cells
- Cyanide and azide bind to CO and stop electron transfer, thereby reducing ATP production

CO as a neuronal metabolic marker

- CO is vital to neurons which depend almost solely on oxidative metabolism for their energy supply
- Active ion transport consumes most of the neuronal energy
- Increased neuronal activity is tightly coupled to increased energy metabolism

Quantitative CO histochemistry

- Allows us to determine the oxidative metabolic capacity of various regions of the nervous system
- More active neurons in a brain region have increased CO content in their mitochondria
- More active compartments within a neuron contain more mitochondria and CO activity

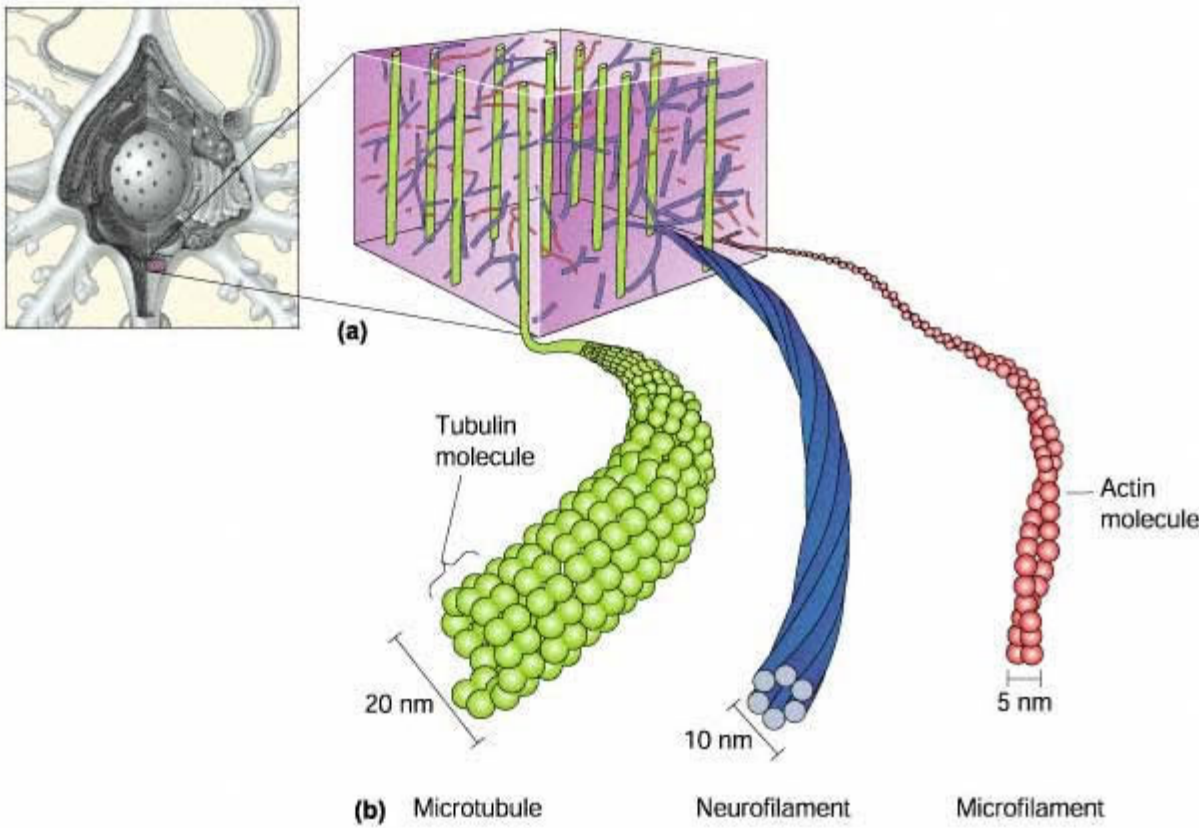
Functional mapping of metabolic activity with CO

- Baseline changes in activity which take place over a period of time can be quantified with CO histochemistry
- Quantitative CO histochemistry can be used to reveal the cumulative neural effects of learning in intact neural networks in behaving animals

CO and AD

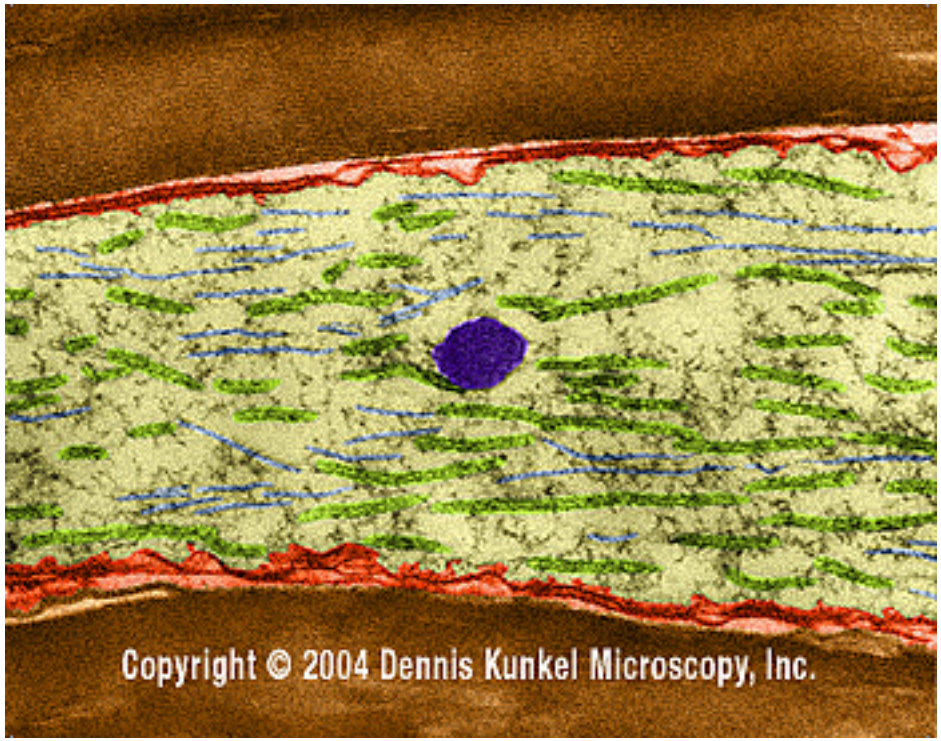
- In sporadic AD defects in CO activity have been found (Mi mutations)
- CO catalytic defect with Mi DNA oxidative damage is a reliable marker of AD
- Brain is the most vulnerable organ to show primary oxidative pathogenesis
- Muscle biopsy may be used as a diagnostic aid

The cytoskeleton



Microtubules

- Tubulin molecules strands (polymerized)
- Microtubule-associated proteins (MAPs)
- Tau protein has been implicated in AD, paired helical filaments accumulate in soma
- Possible abnormal secretion of amyloid might lead to neurofibrillary tangle formation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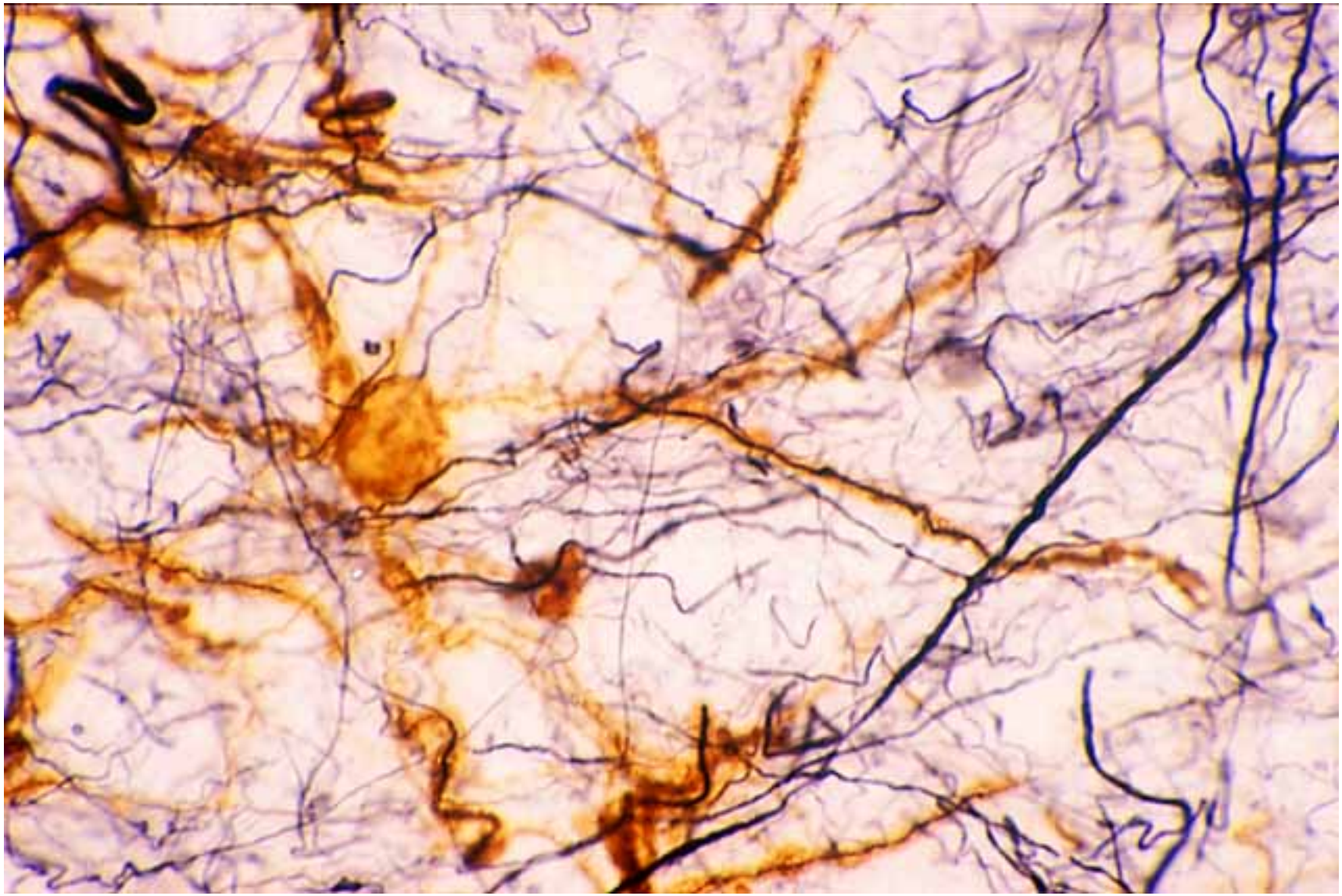
Neurofilaments

- Rather strong structurally
- Particularly concentrated in axons
- Accumulations seen in AD, ALS, giant axon neuropathies etc.
- Also have associated proteins that integrate them into a network with microtubules and microfilaments

Oligodendroglia and neurofilaments

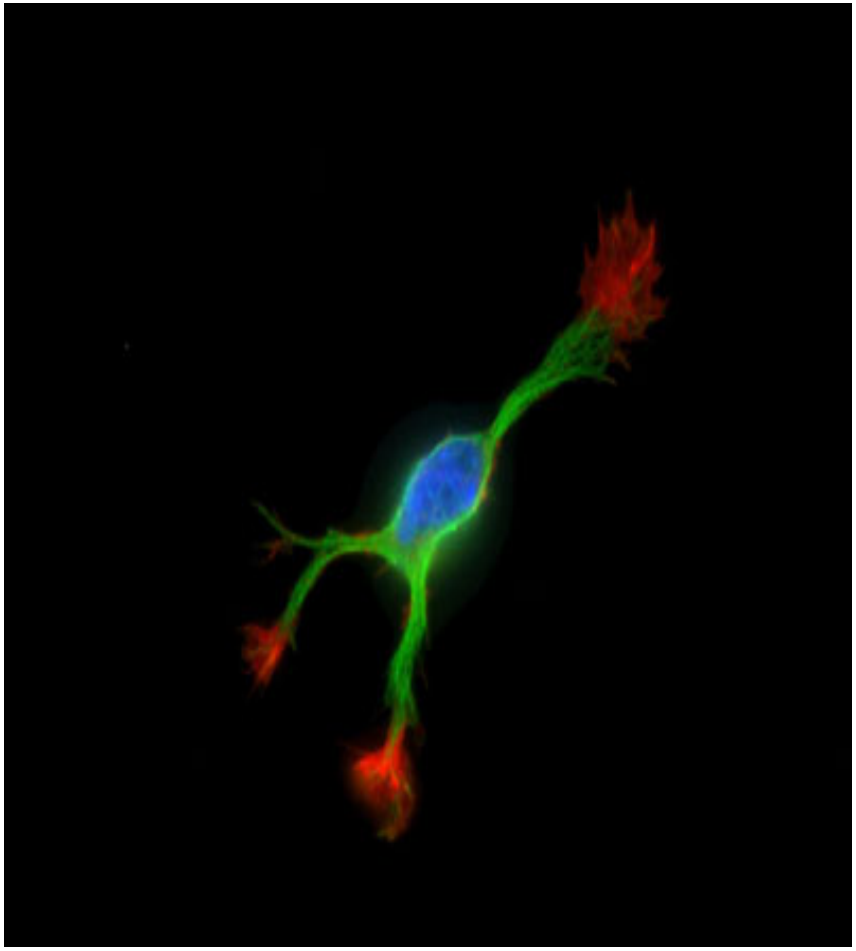


Microfilaments

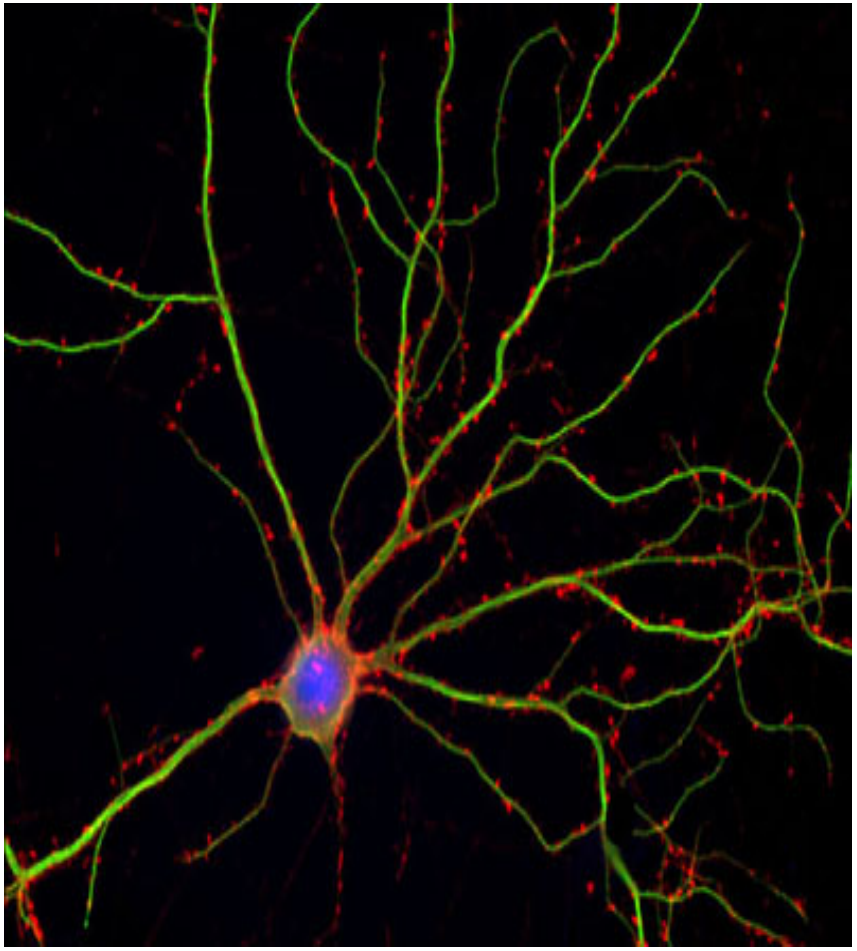
- Numerous in neurites
- Composed of actin polymers
- Associated with neuronal membrane
- Link transmembrane proteins to cytoplasmic proteins

Tissue culture

HPC neuron, 24h



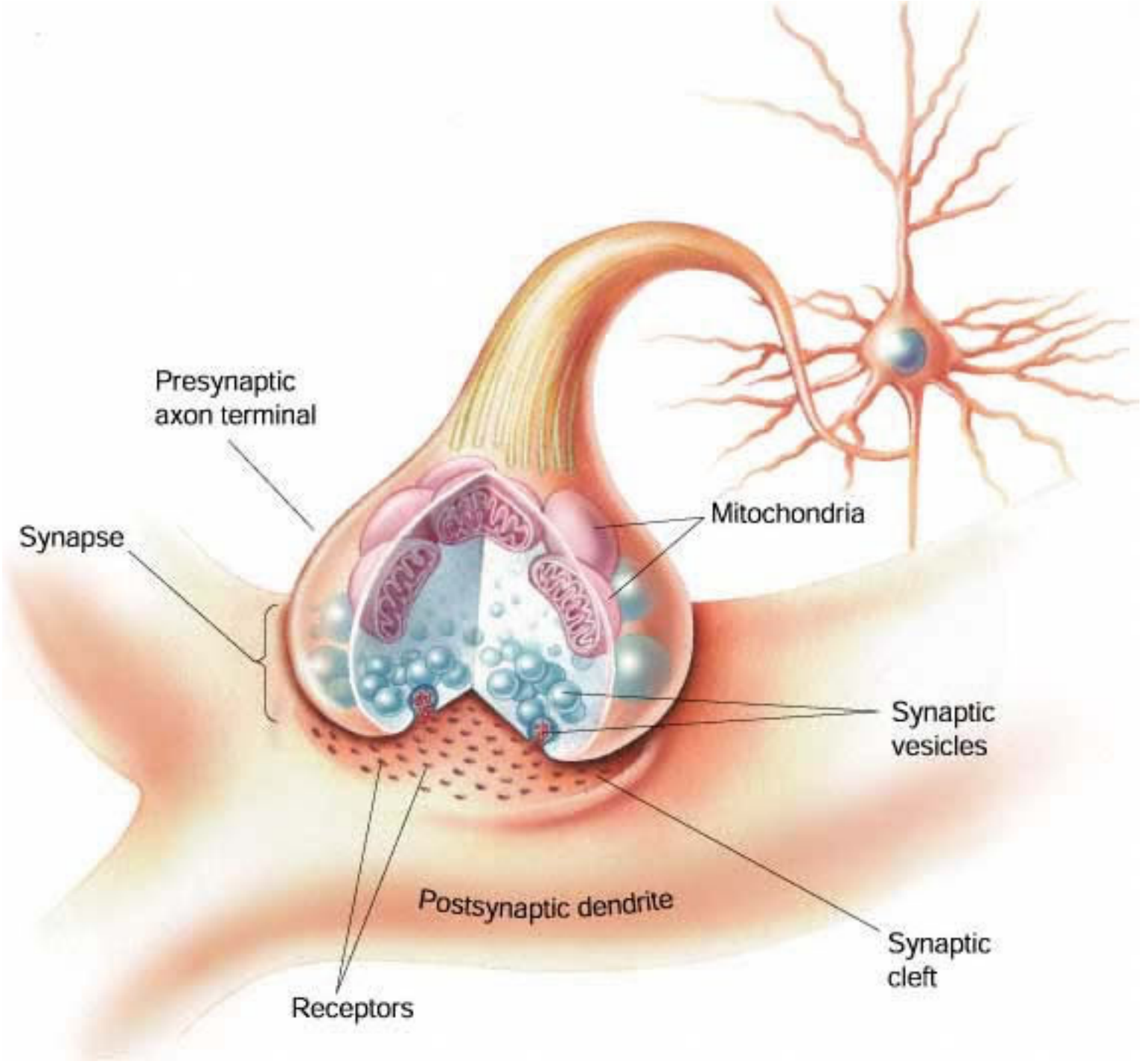
HPC neuron, 3 weeks

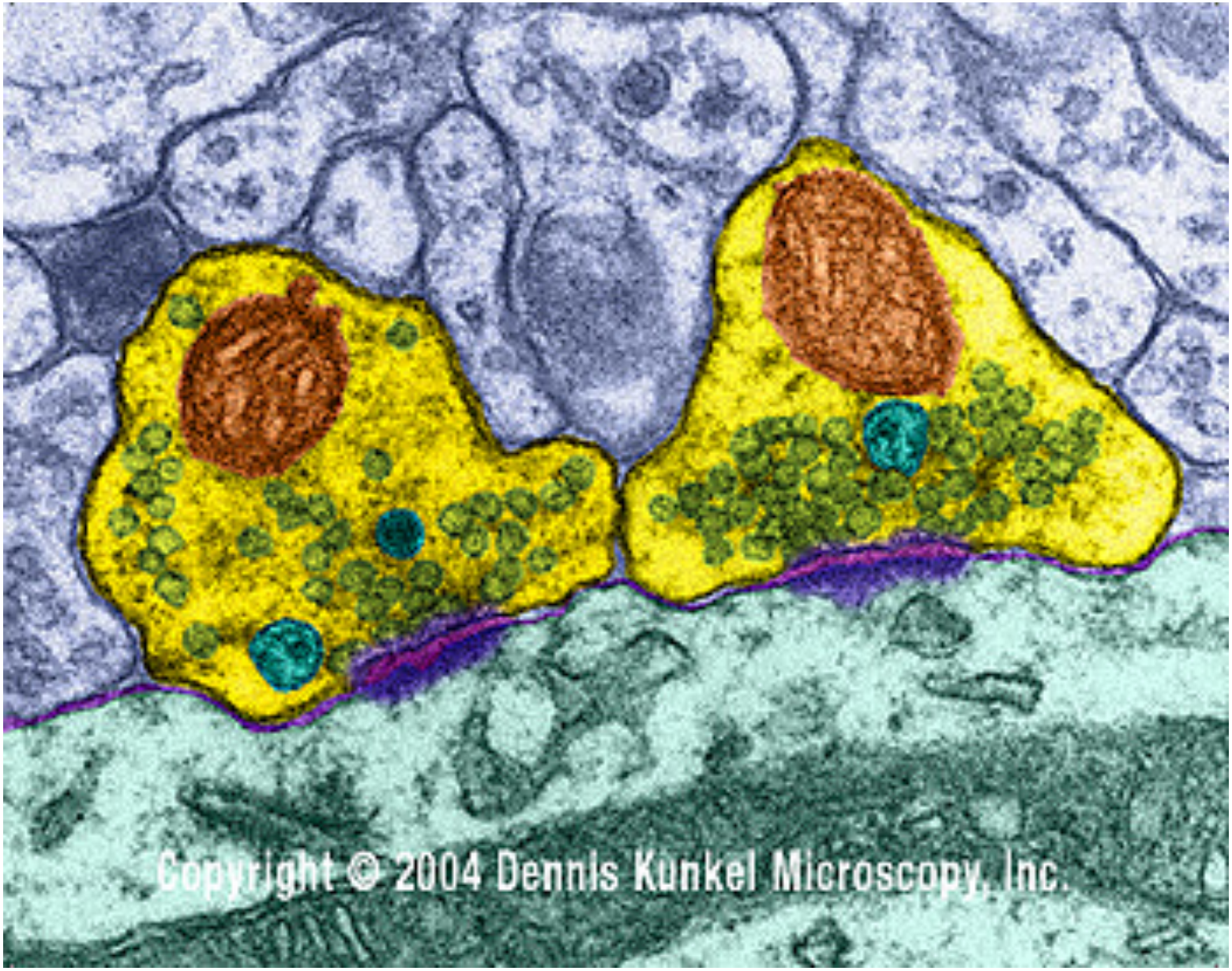


DNA- blue; μtubules- green; actin- red

The axon

- Begins at the axon hillock
- Ends at the terminal bouton
- No rough ER extends into axon
- Branches are called collaterals (can be recurrent)
- Comes in contact with other cells forming a synapse


Presynaptic
axon terminal
Synapse
Mitochondria
Synaptic
vesicles
Postsynaptic dendrite
Synaptic
cleft
Receptors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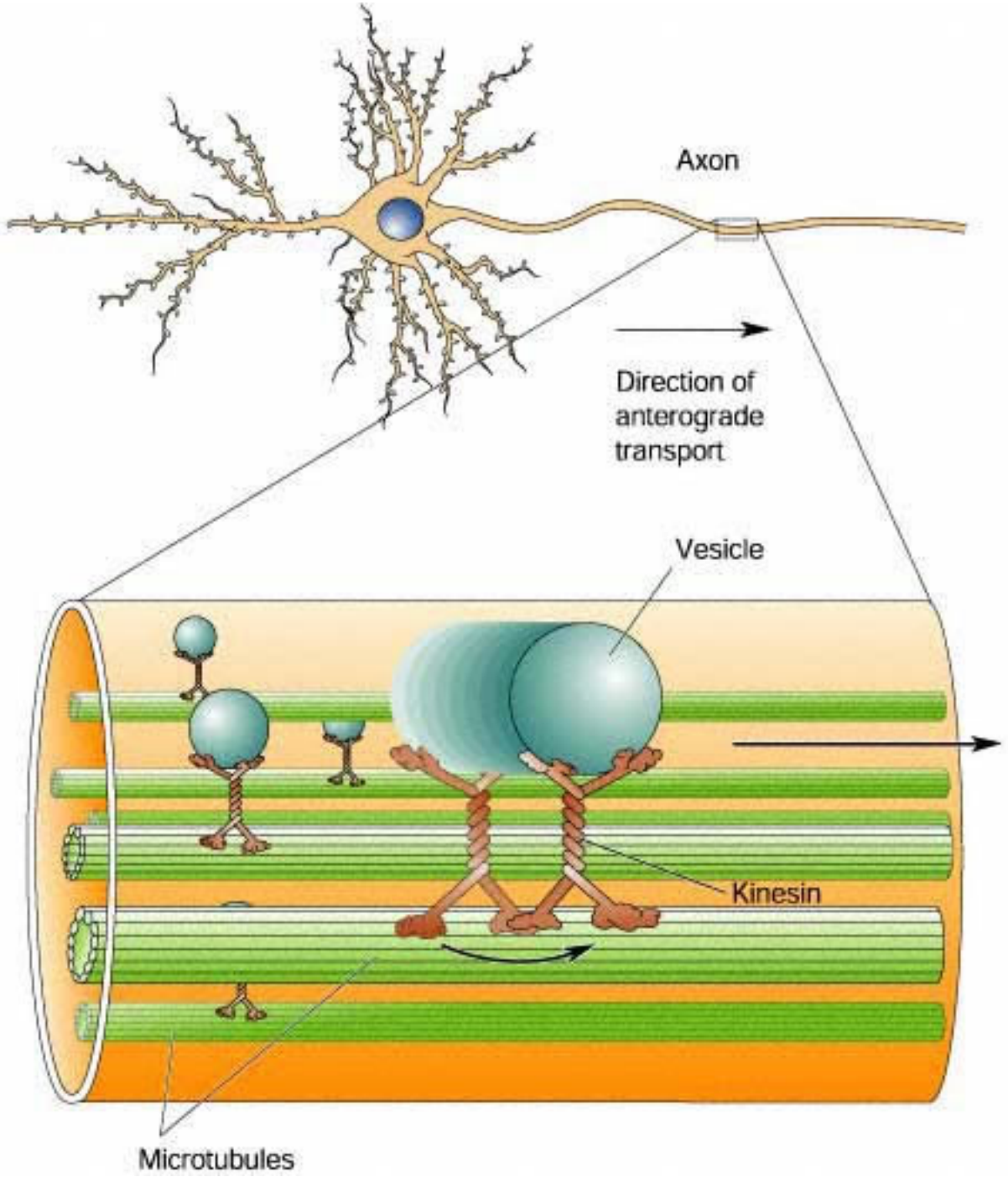
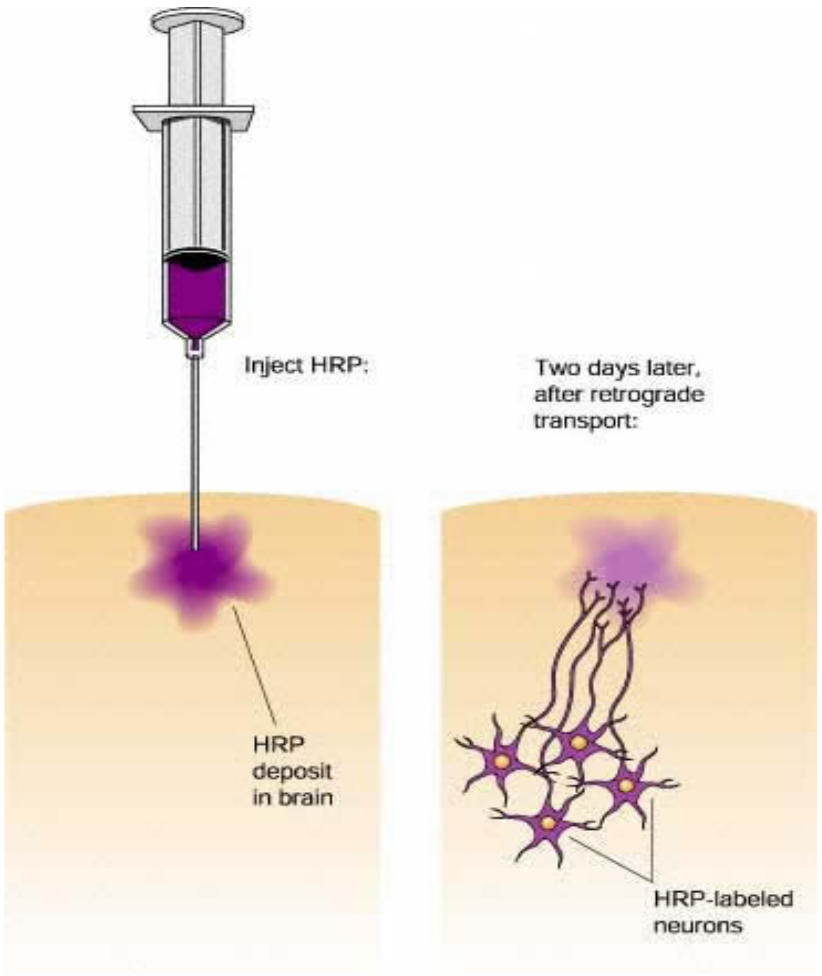
Axoplasmic transport

- Fast (1 cm/day) and slow (1-10 mm/day)
- Anterograde transport: Kinesin moves vesicles from the soma to the terminal
- Retrograde transport: from terminal to soma, dynein
- Both require ATP


Axon
Direction of anterograde transport
Vesicle
Kinesin
Microtubules

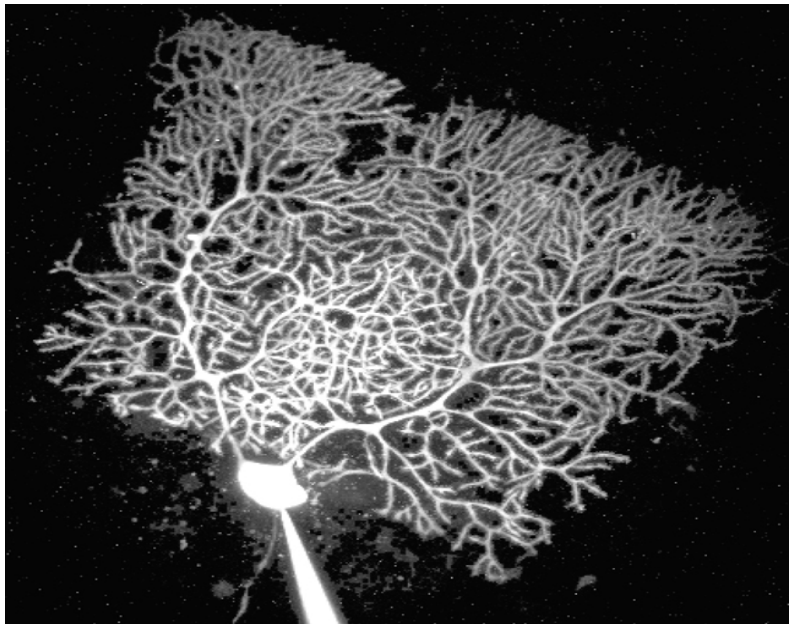
Horseradish peroxidase

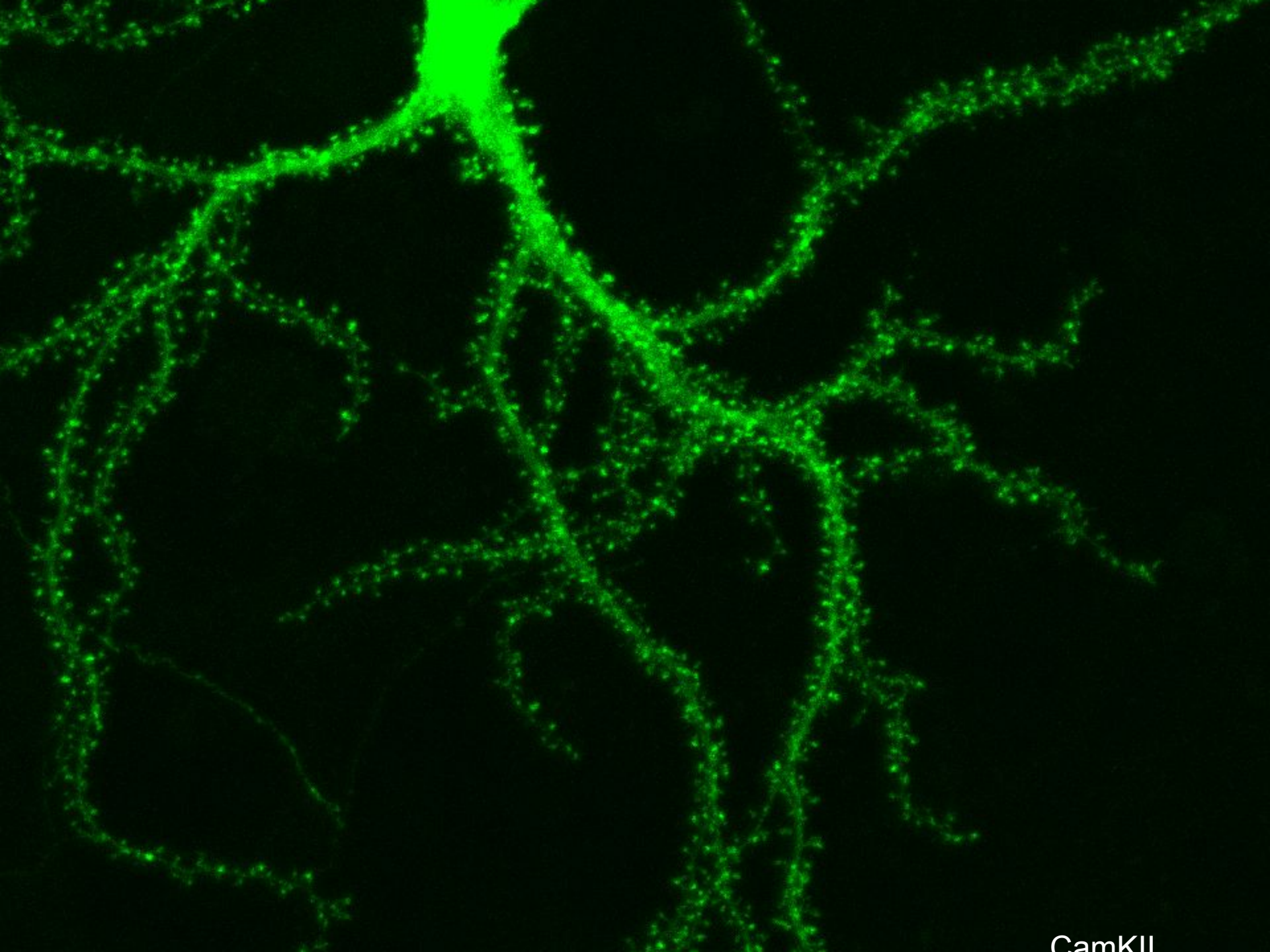
Viruses exploit retrograde transport (herpes, rabies)

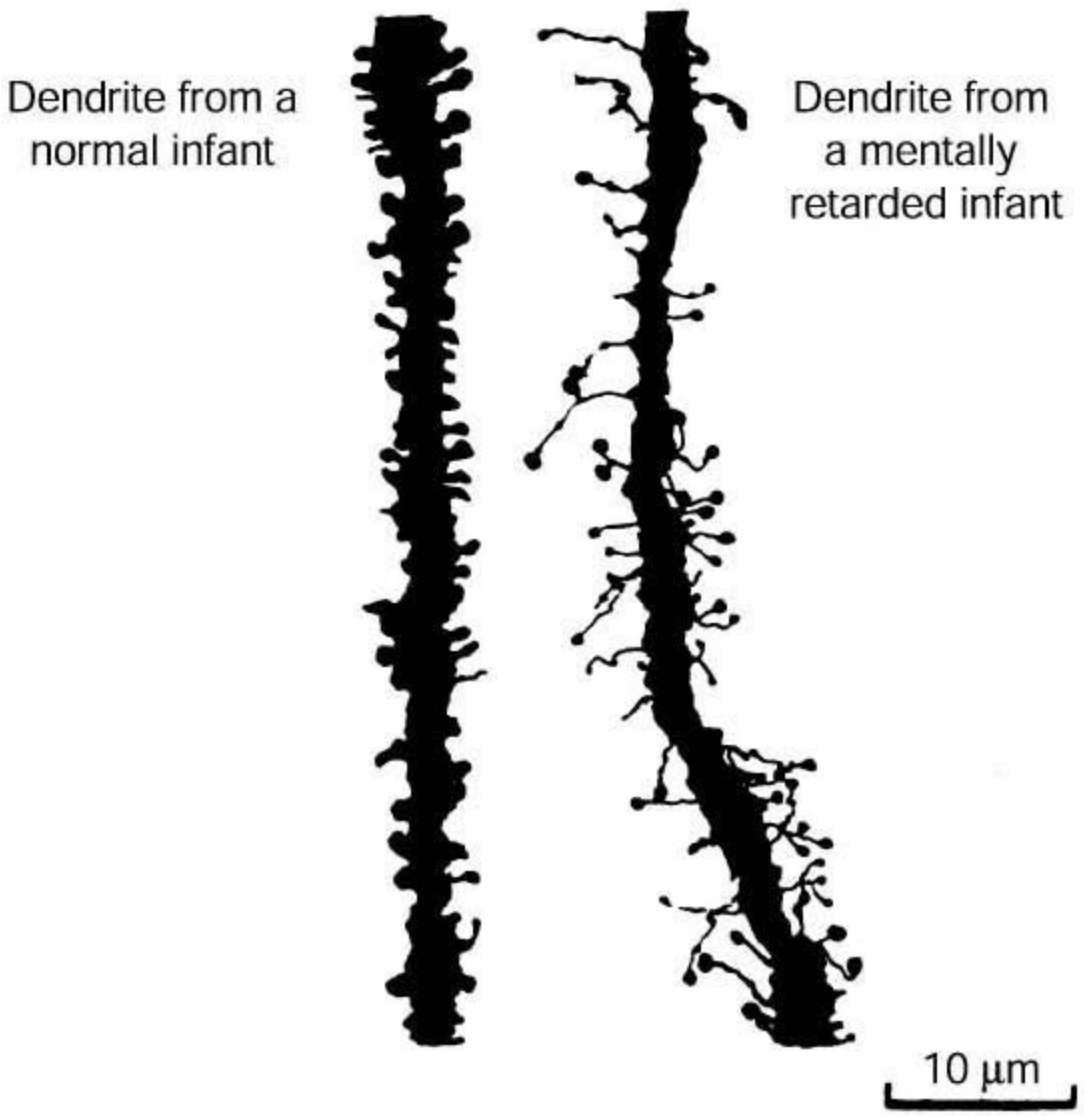


Dendrites

- Greek for “tree” → dendritic tree
- Covered in synapses
- Post-synaptic membrane has receptors
- Some dendritic branches have spines (Cajal discovered these)
- Cytoplasm does have polyribosomes

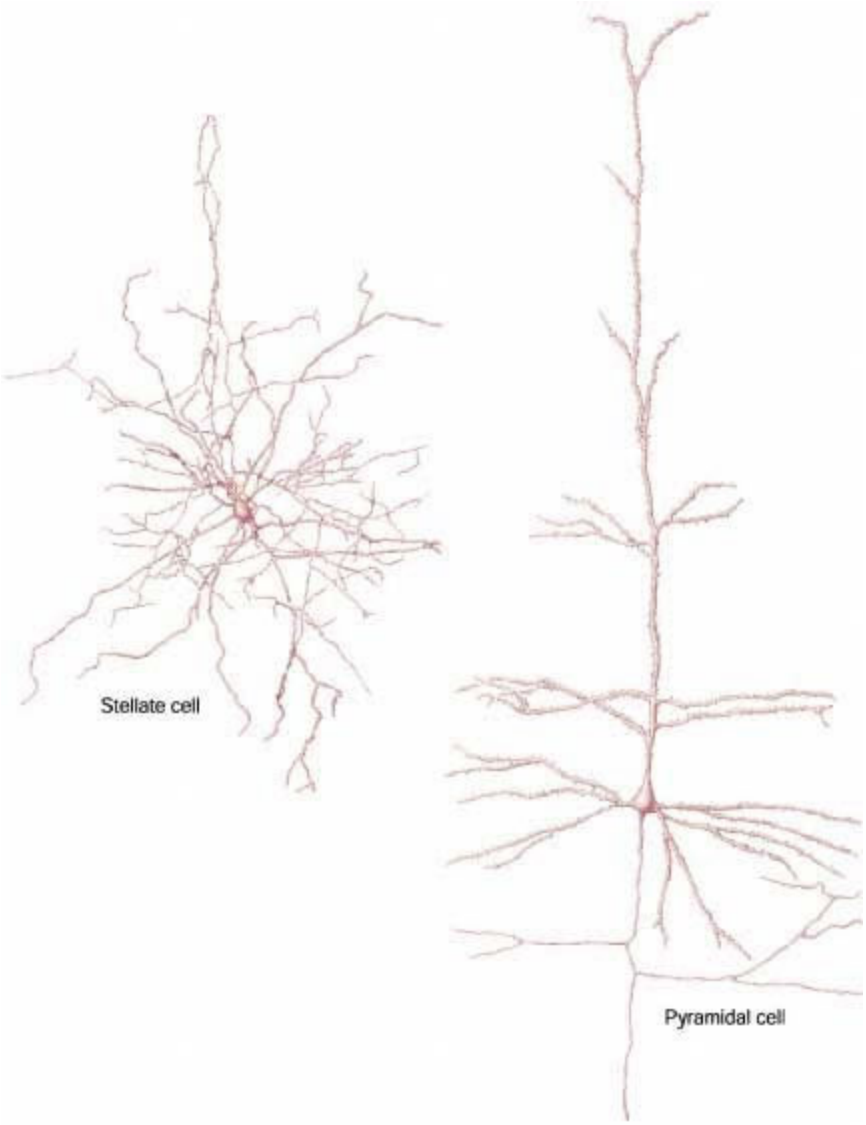


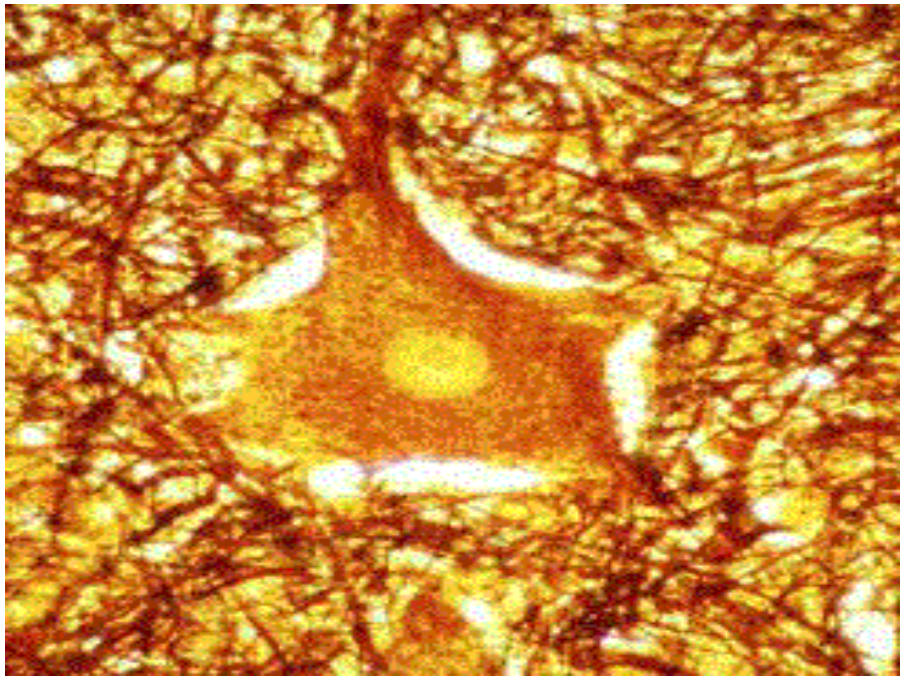

CamKII

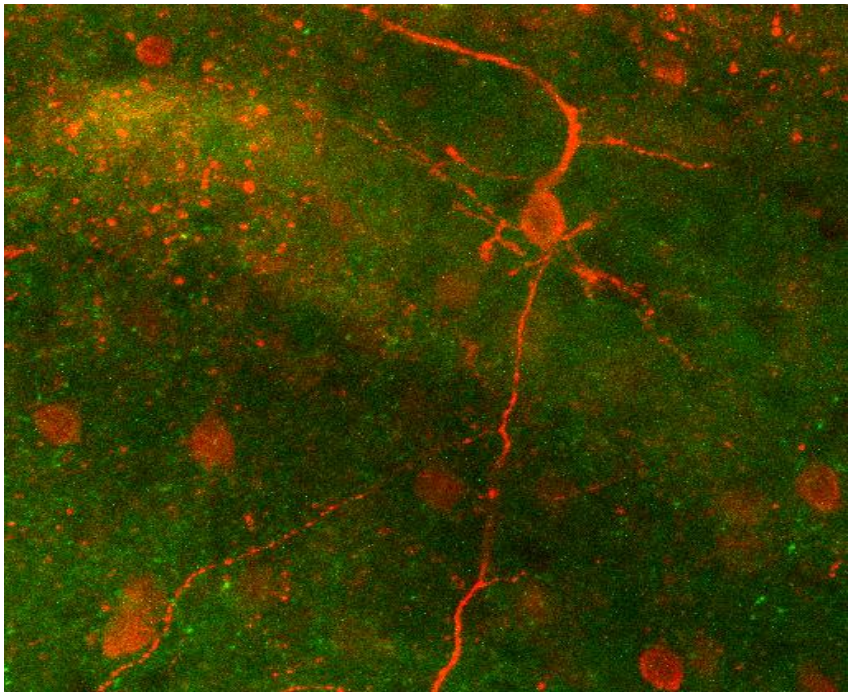

Dendrite from a normal infant
Dendrite from a mentally retarded infant
10 µm

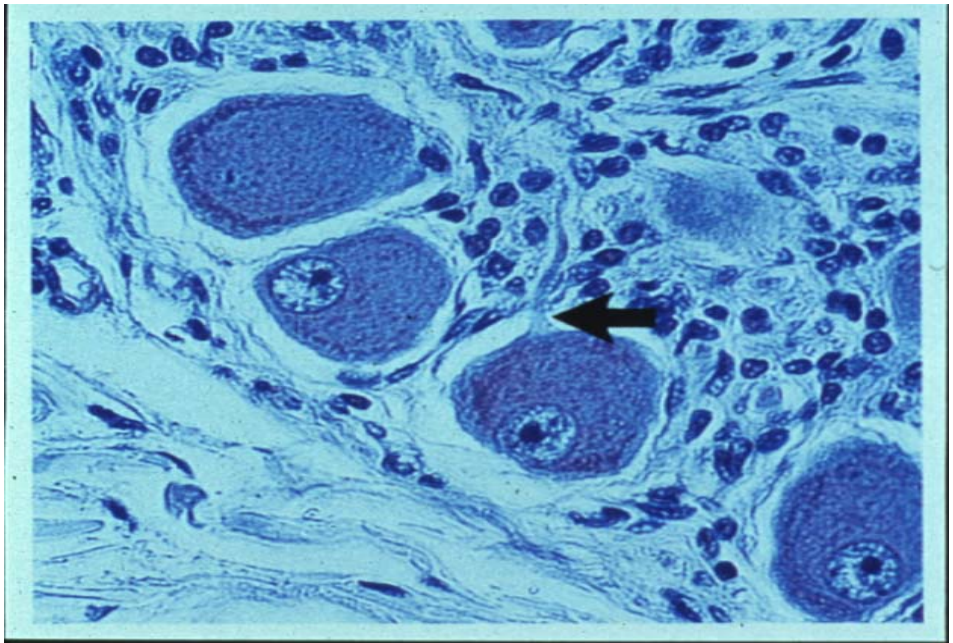
Classifying neurons

- Number of neurites (unipolar, bipolar, multipolar)
- Dendritic trees (pyramidal, stellate)
- Dendritic spines (spiny and aspinous)
- Connections (primary sensory, motor, interneurons)
- Axon length (Golgi type I, II)
- Neurotransmitter (cholinergic, serotonergic)

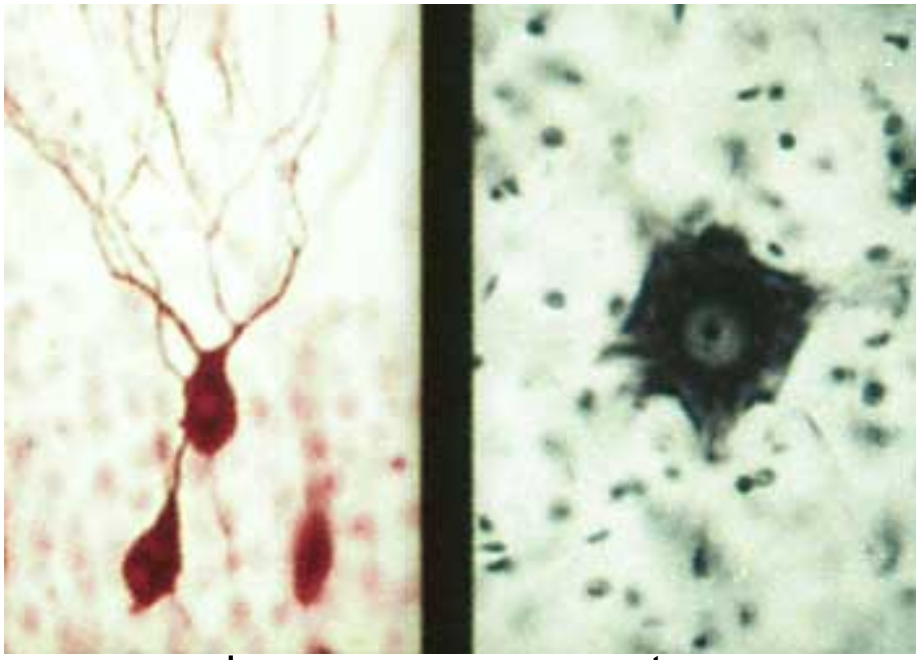

Stellate cell
Pyramidal cell







7–13 Pseudounipolar neuron (oil immersion)



granule motor