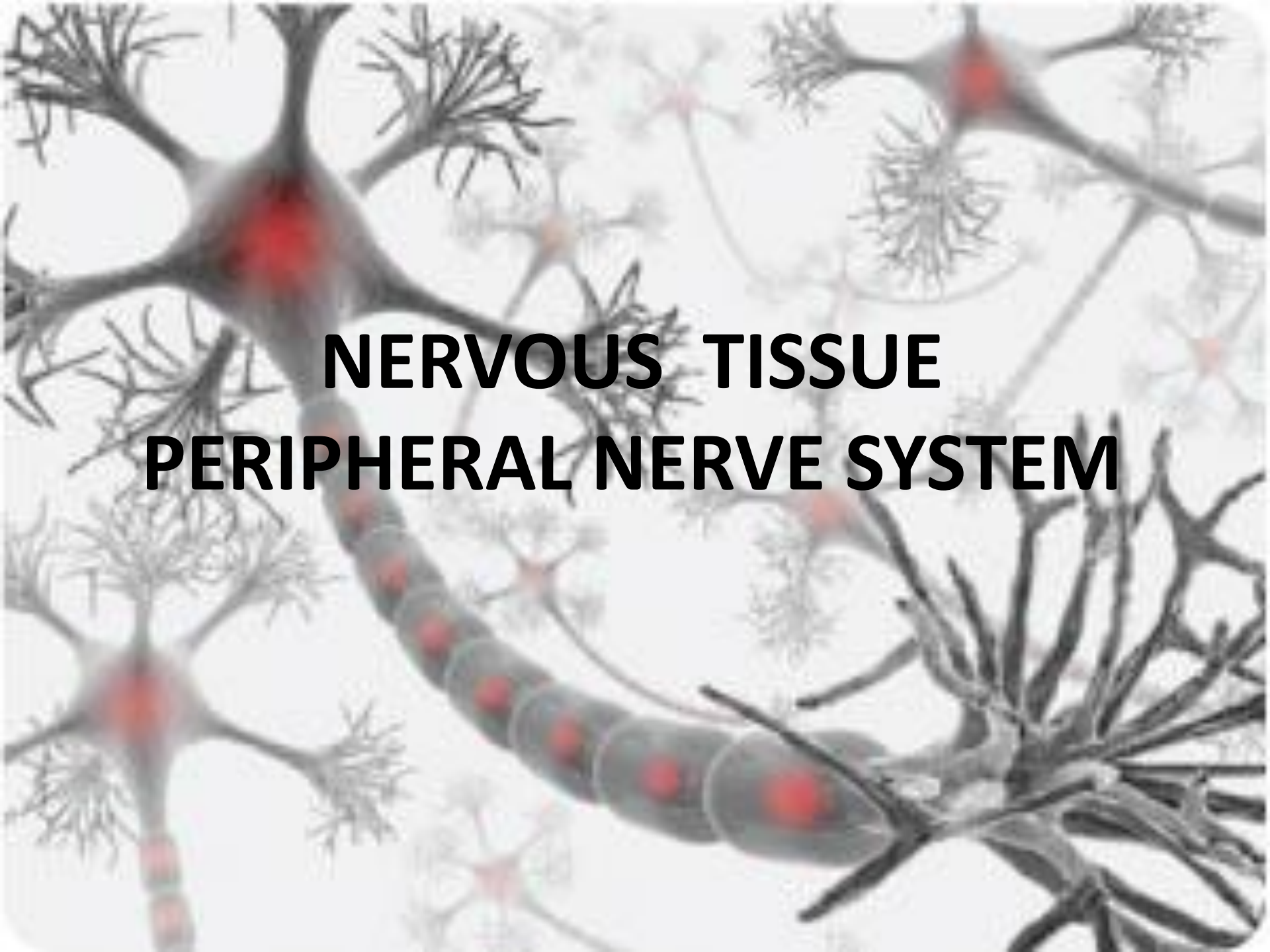
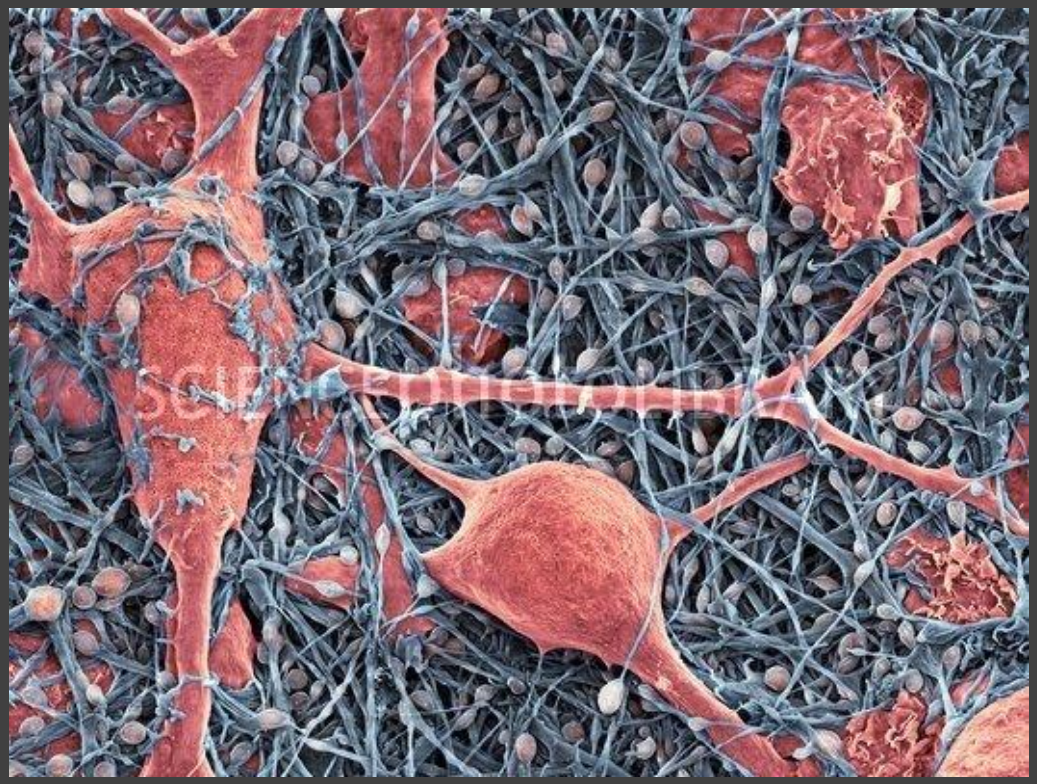


NERVOUS TISSUE
PERIPHERAL NERVE SYSTEM

NERVOUS TISSUE

develops from ectoderm

neurons (red)



glial cells (blue)

nerve cells

support and protect neurons

FUNCTIONS:

- organization and coordination of organism activity (intellect, consciousness, sub consciousness, motion, visceral and gland activity)
- receiving, conducting, processing and transmission impulses about organism condition and environment.

ORIGIN OF NERVOUS TISSUE (Ectoderm)

Neural tube

anterior end
brain

neuroglia, ependyma
neurons

caudal end
spinal cord

Neural crest cells

PNS
sensory components

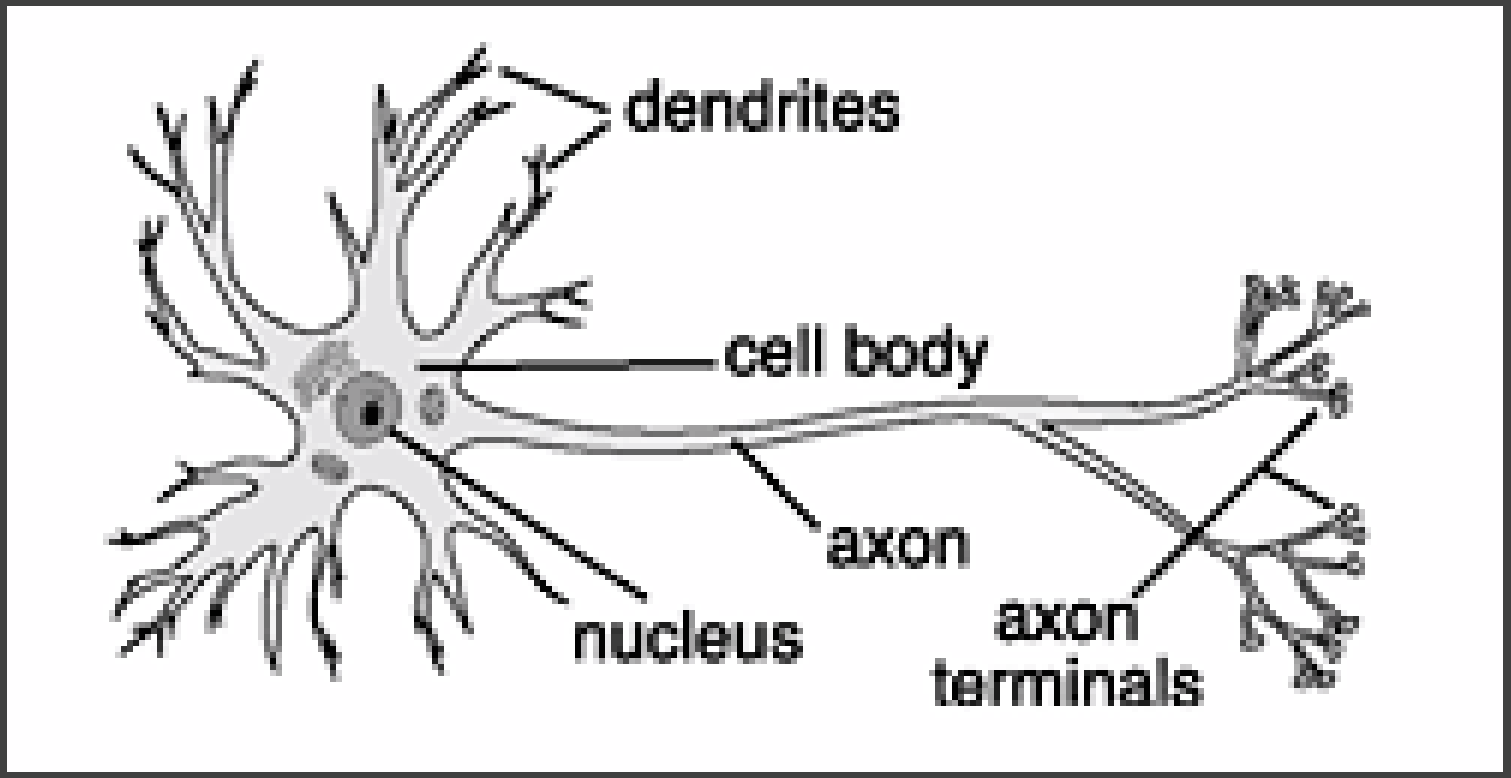
ganglia

satellite cells
Schwann cells

NEURON

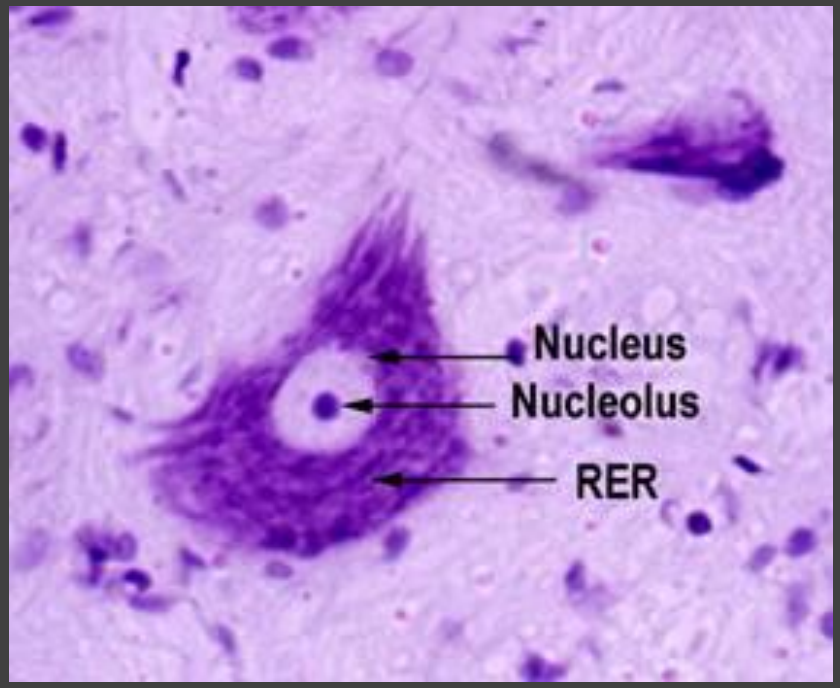
cell body
(perikaryon)

processes
(axon and dendrites)



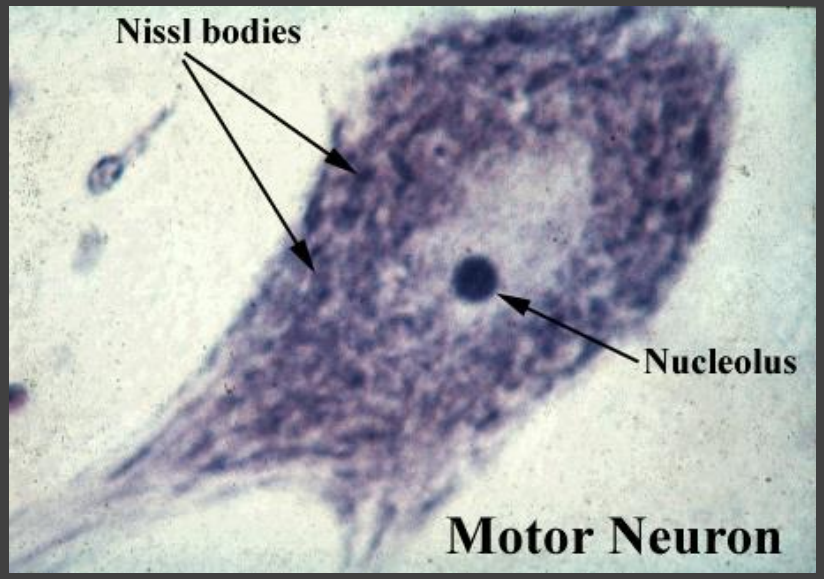
PERIKARYON (cell body)

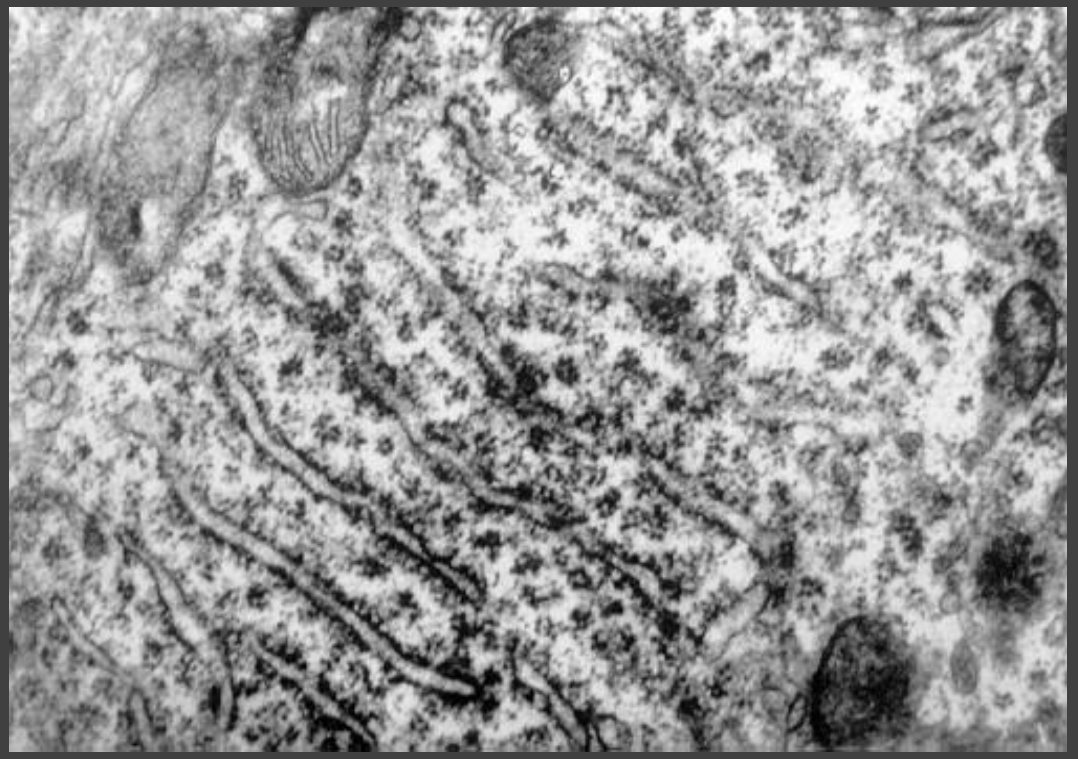
Contains:
- nucleus (1 or 2) with dispersed chromatin
- abundant RER and polyribosomes (Nissl bodies or tigroid)
- neurofilaments (type IV),
- microtubules + MAP-2



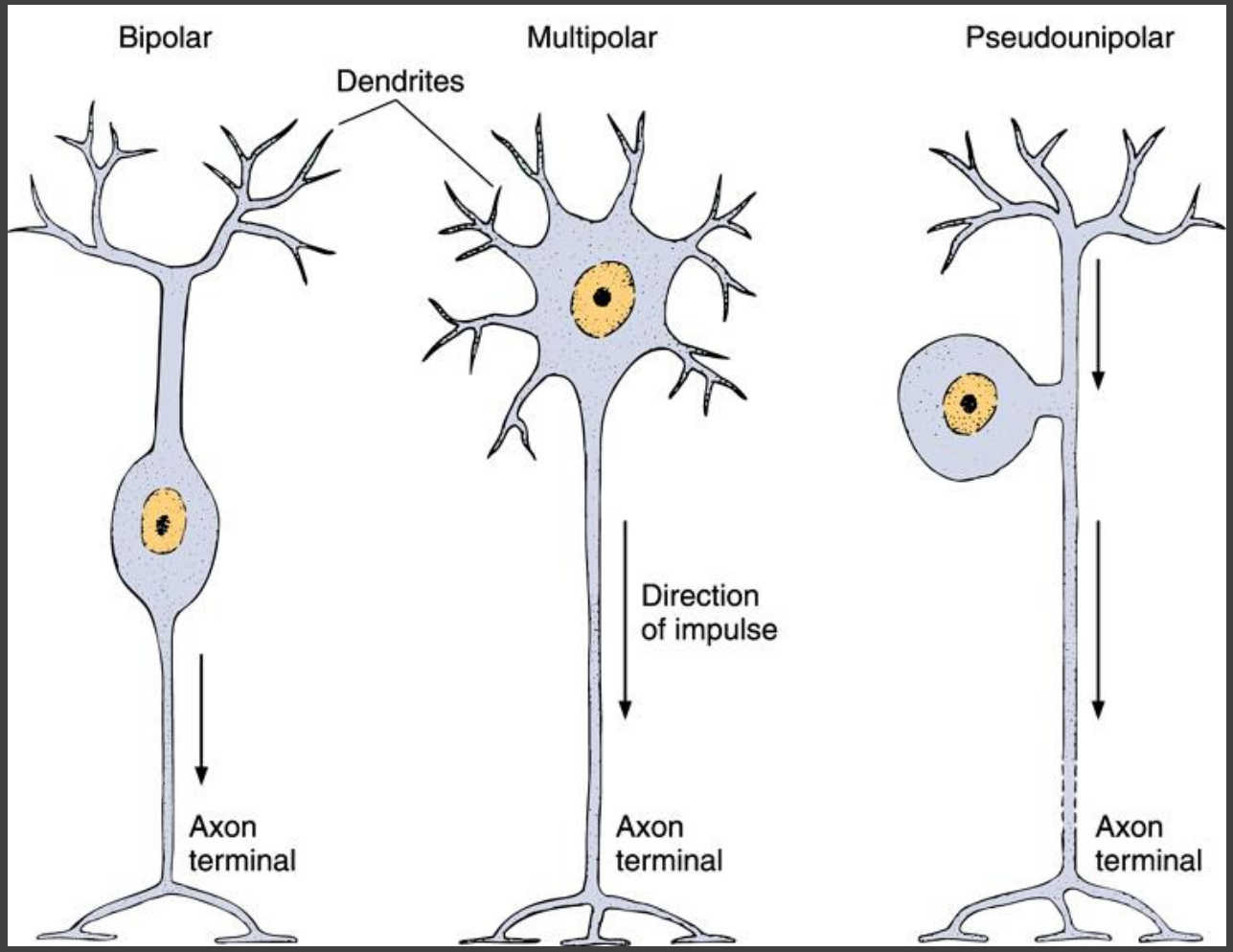
FUNCTIONS:
- synthesis of macromolecules
- control of the distribution of proteins throughout the cell

NISSL BODIES





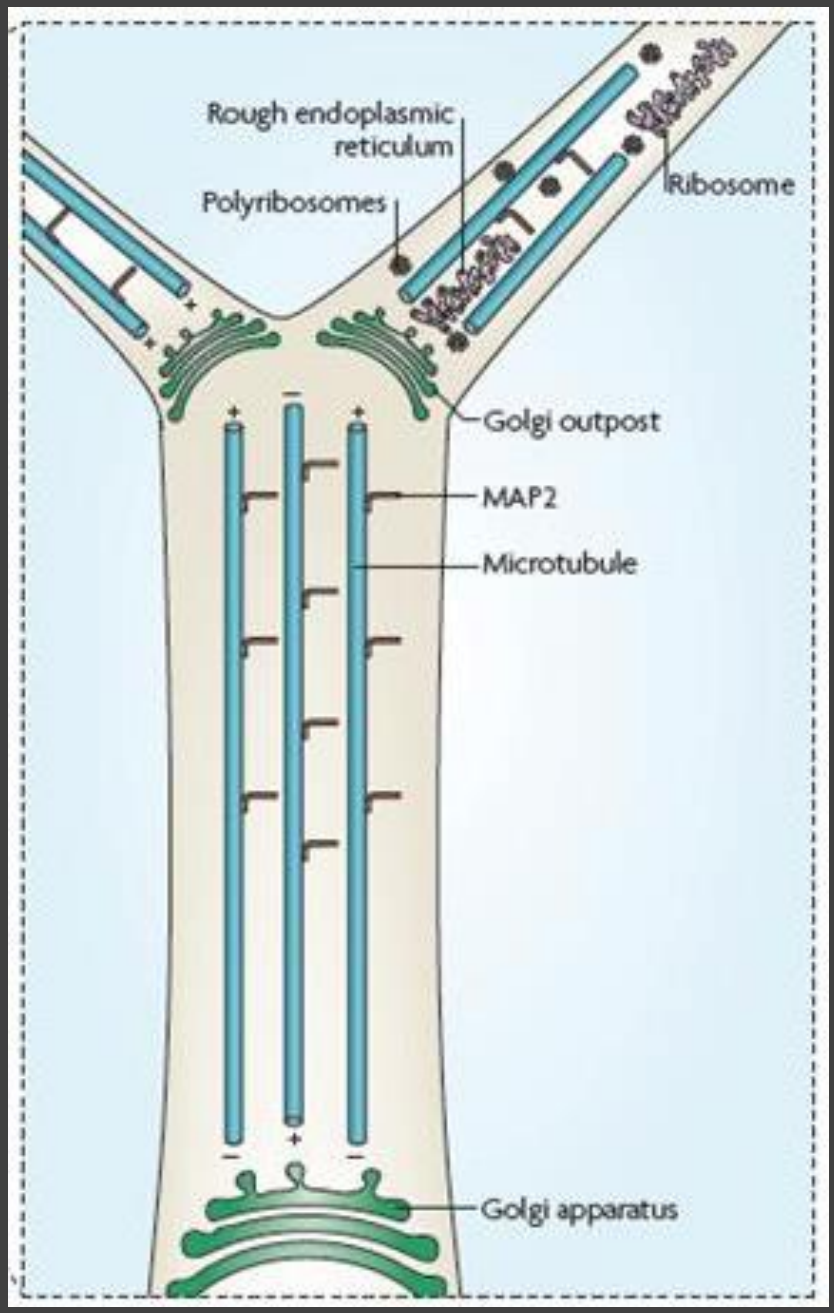
MAIN TYPES OF NEURONS



Dendrites

Contain:
- Microtubules + MAP-2
- small bundles of neurofilaments,
- RER and ribosomes (Nissl bodies) only in region nearest to cell body

Dendrites - **functions:**
- receiving stimuli
- transmission of nerve impulses
- integration multiple impulses - numerous synapses
- anterograde and retrograde transport of macromolecules

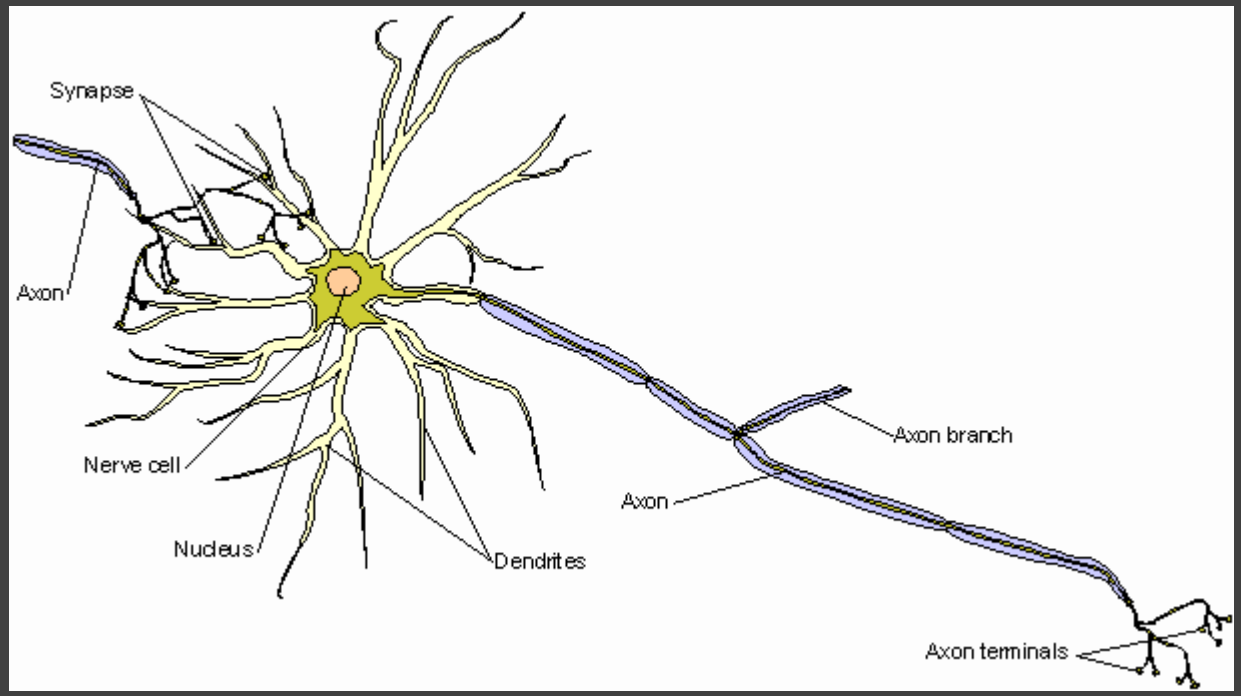


AXON

- length up to 1m, constant diameter, axon hillock without Nissl bodies

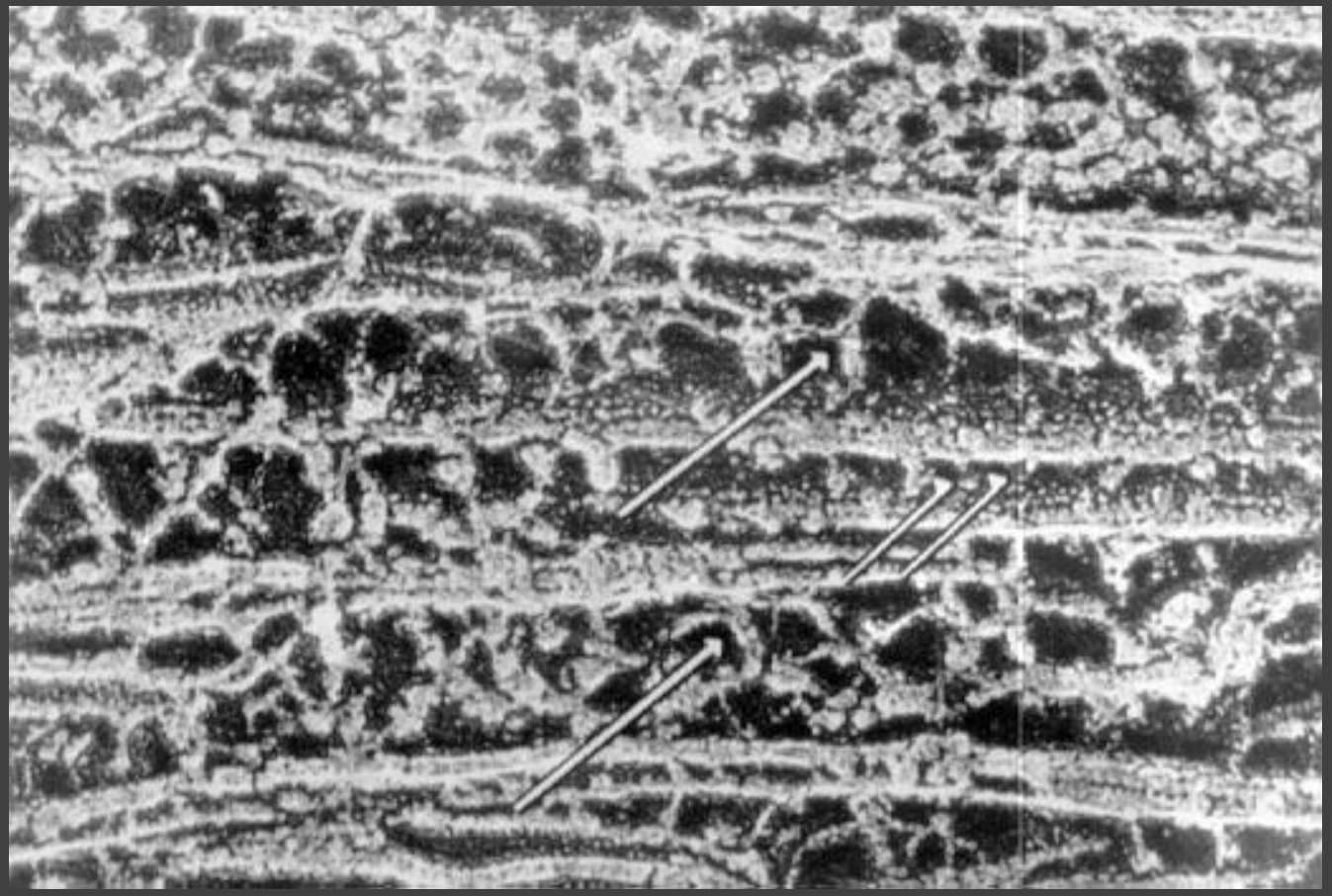
- collateral axons (lateral branches), terminal arbor

- abundant microtubules + *tau* and neurofilaments (regulation of the axon's diameter)



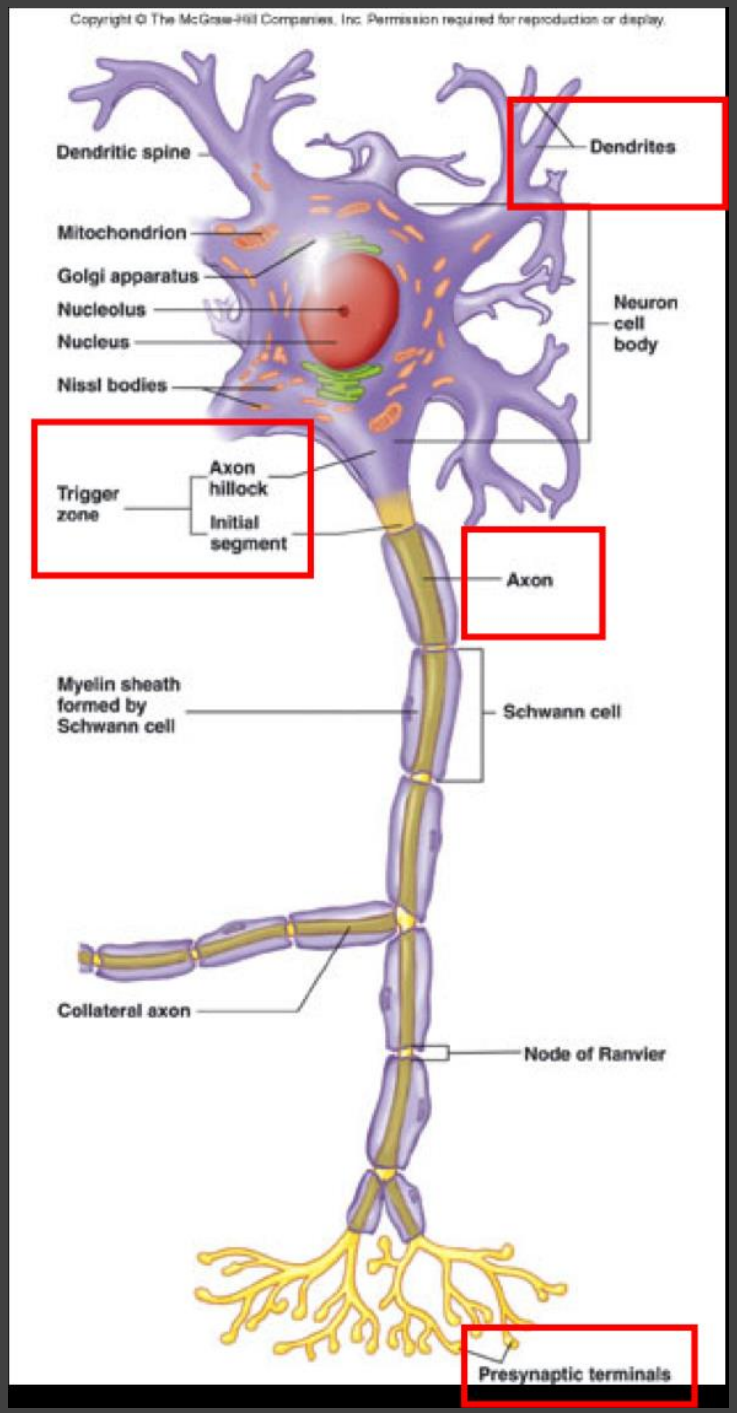
Axoplasm of nerve fiber from rat ischiadic nerve

Tau proteins bind microtubules (arrows)



-initial segment –the portion of axon emanating immediately from axon hillock to the beginning of first myelin sheath

-spike trigger zone is the place, where excitatory and inhibitory impulses are summed to determine whether propagation of action potential is to occur.

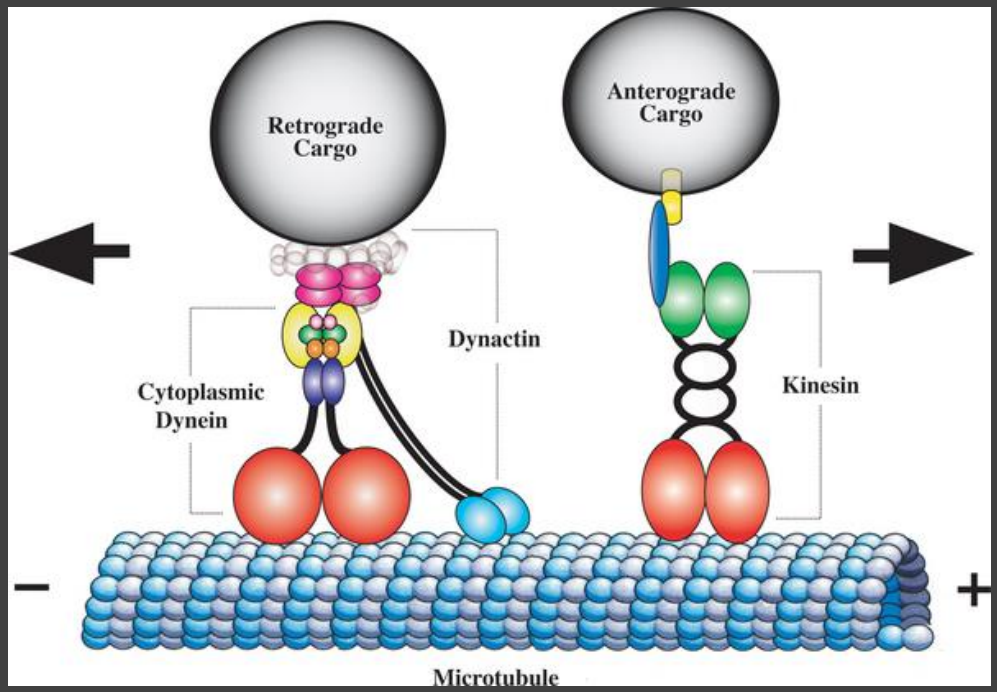


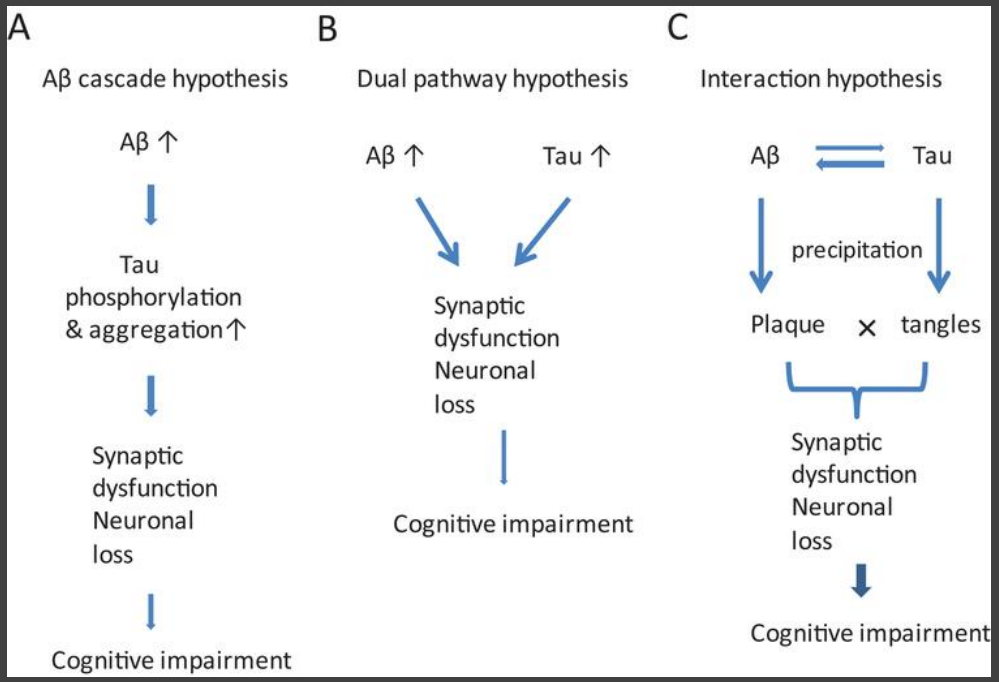
AXON - FUNCTIONS:

- conduction of impulses **from cell body toward the synapses** and transmission them to other neurons, muscle cells or glands.

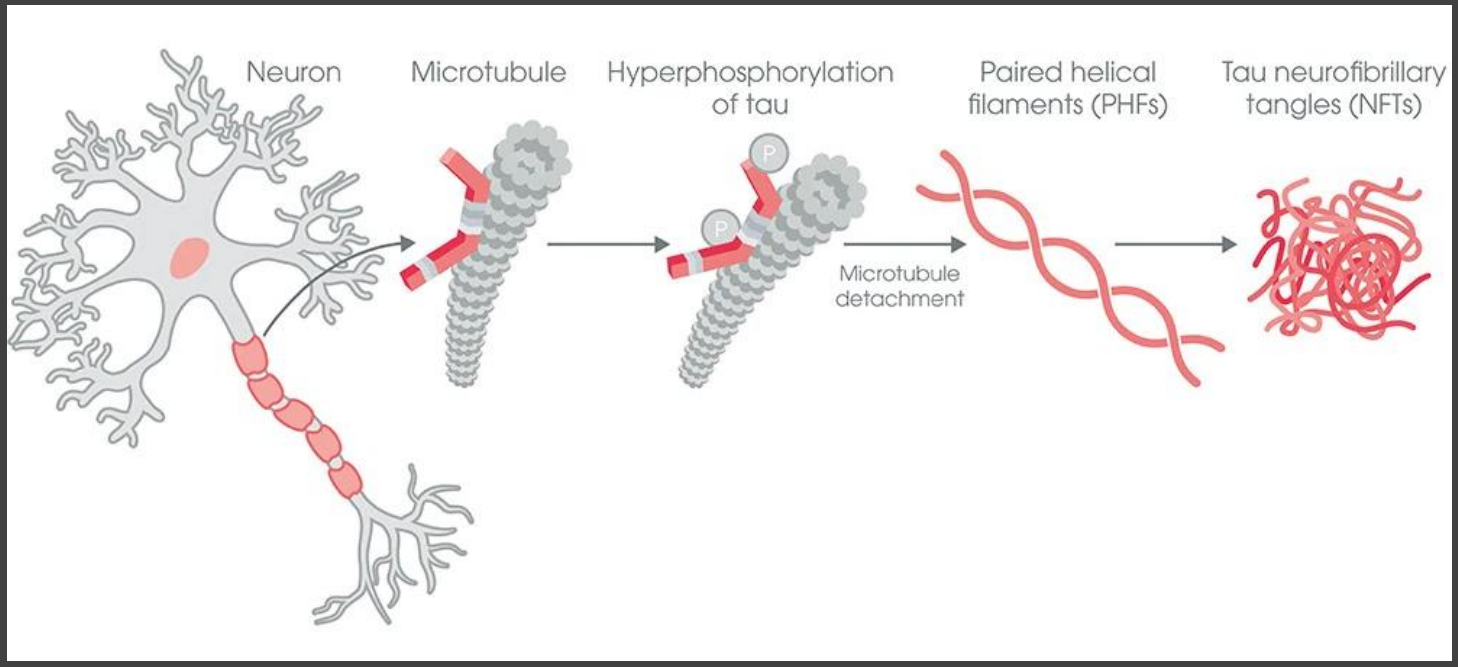
- **anterograde** transport (organelles, vesicles, macromolecules)

- **retrograde** transport (neurofilament proteins, subunits of microtubules, macromolecules and endocytic material)





Neurodegenerative disorders – Alzheimer's Disease



GENERATION AND CONDUCTION OF NERVE IMPULSES

Resting potential (-90mV)– arises because of two mechanisms.

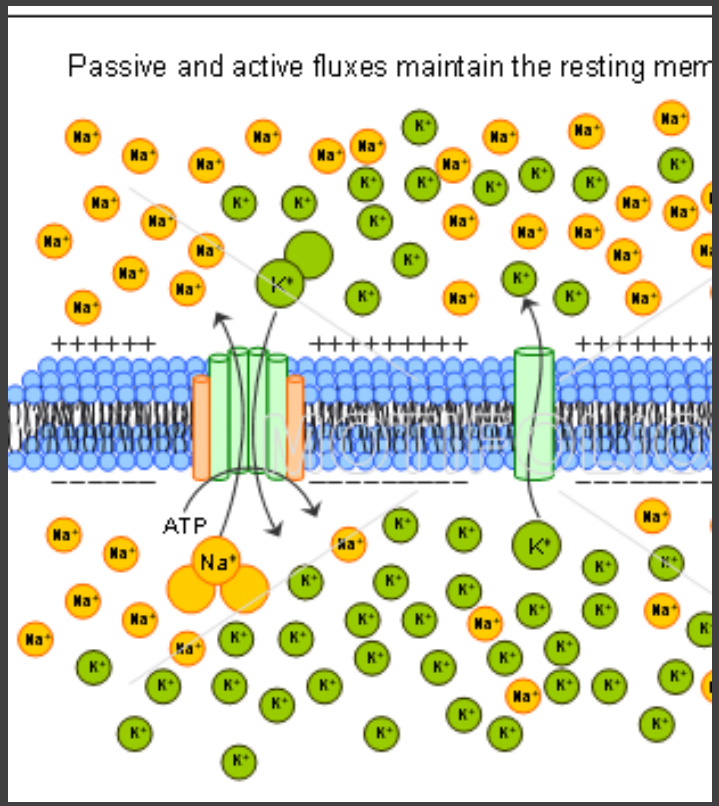
1. Na^+ /K^+ pumps

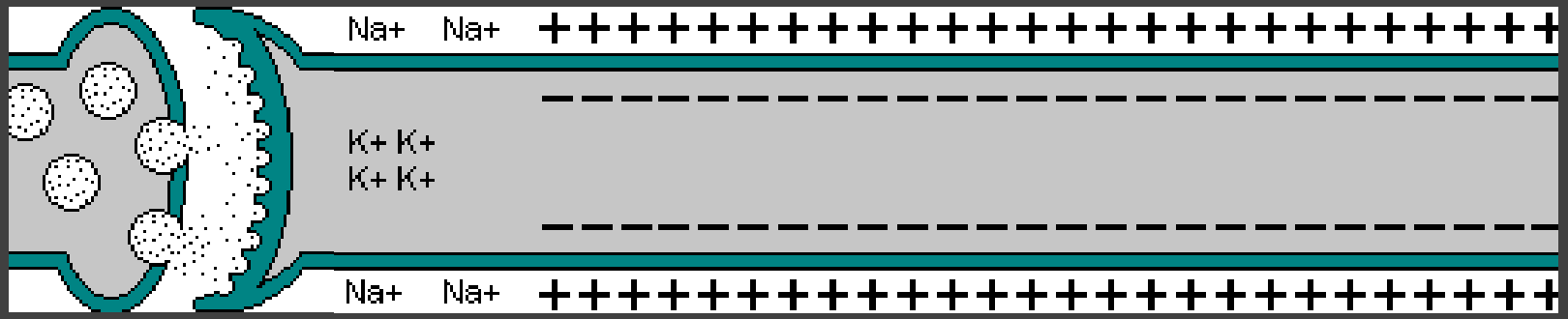
-pump Na^+ out of the cell, and K^+ into the cell in ratio 3 : 2 (for every 3 sodium ions pumped out, 2 potassium ions enter the cell)

2. K^+ leak channels

-permit free flow of K^+ out of the cell (Na^+ can enter to the cell but in ratio K^+: Na^+ 100:1).

The concentration of K^+ ions is higher inside the cell, whereas Na^+ ions outside the cell.





Membrane depolarization

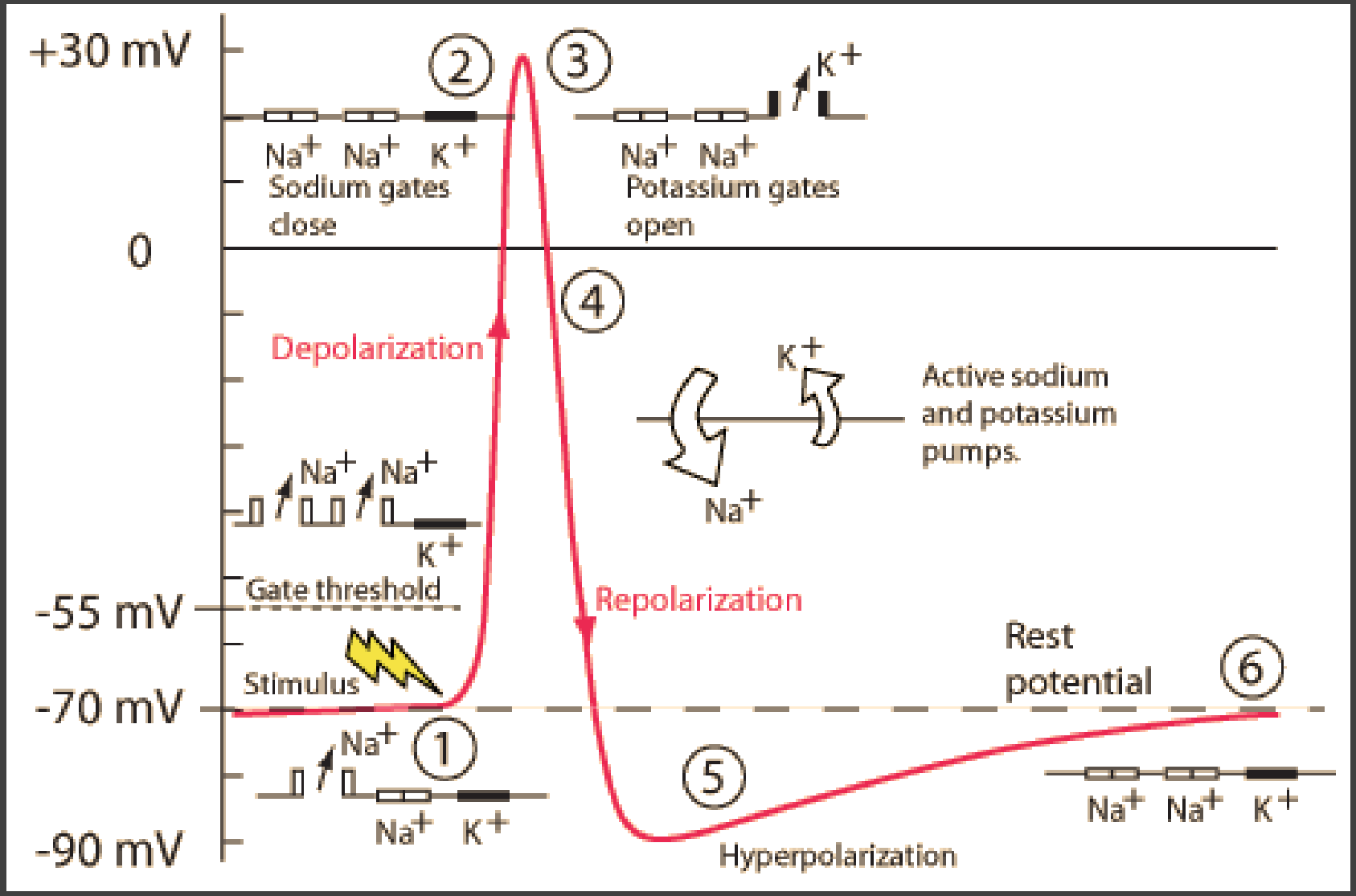
- opening Na^+ channels and Na^+ flow into the cell - **reversal of the resting potential**

- **refractory period** - Na^+ channels become inactivated for 1-2 msec

-**and Hyperpolarization - voltage-gated K^+ channels** open - the efflux of K^+ out, **Na^+/K^+ pumps** activate and **pump Na^+** outside

- **Resting potential -** voltage-gated K^+ channels and Na^+ channels close

The cycle of membrane depolarization, hyperpolarization and return to the resting potential – **action potential**

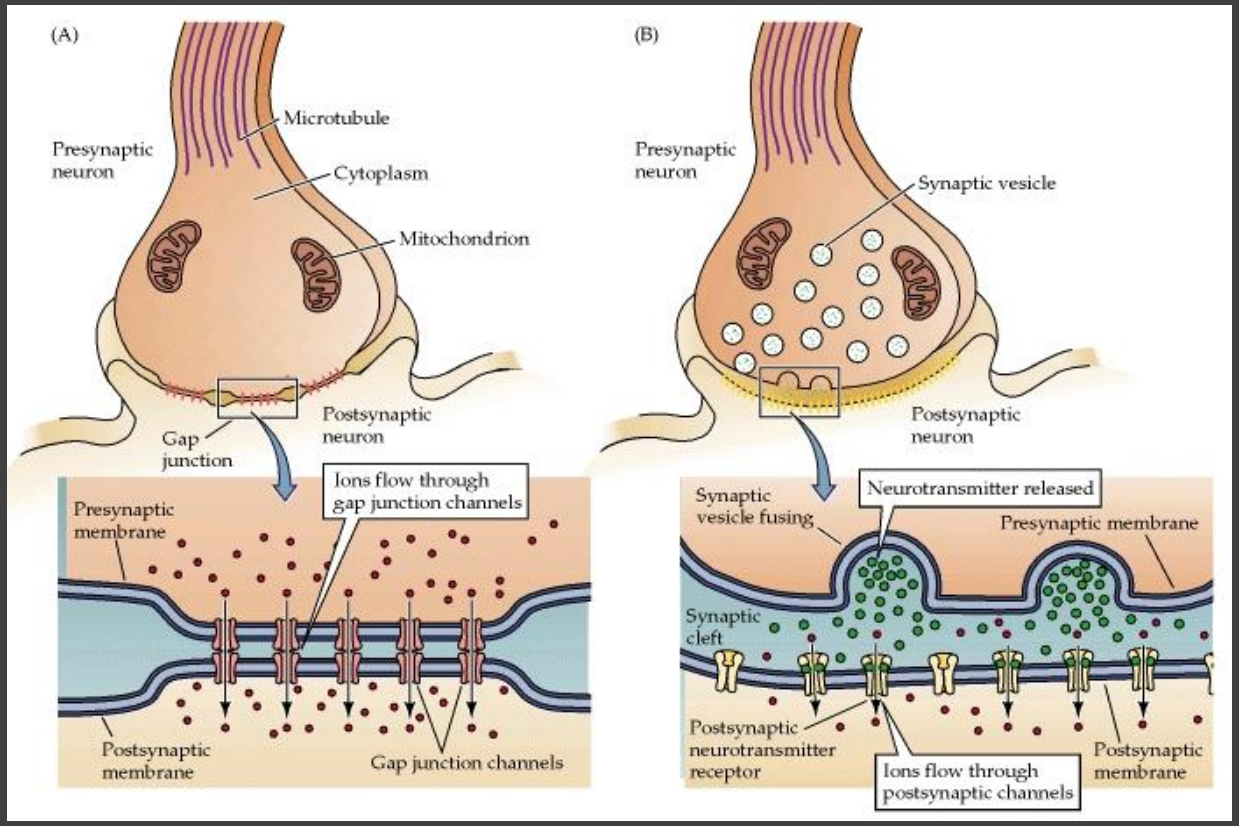

+30 mV
0
-55 mV
-70 mV
-90 mV
2
3
Na+ Na+ K+
Sodium gates close
K+
Na+ Na+
Potassium gates open
4
Depolarization
K+
Active sodium and potassium pumps.
Na+
Na+ Na+
K+
Gate threshold
Repolarization
Stimulus
Rest potential
6
1
Na+
Na+ K+
5
Hyperpolarization
Na+ Na+ K+

SYNAPSE

the site of impulse transmission
from the neuron to another neuron, muscle cell or cell of gland.

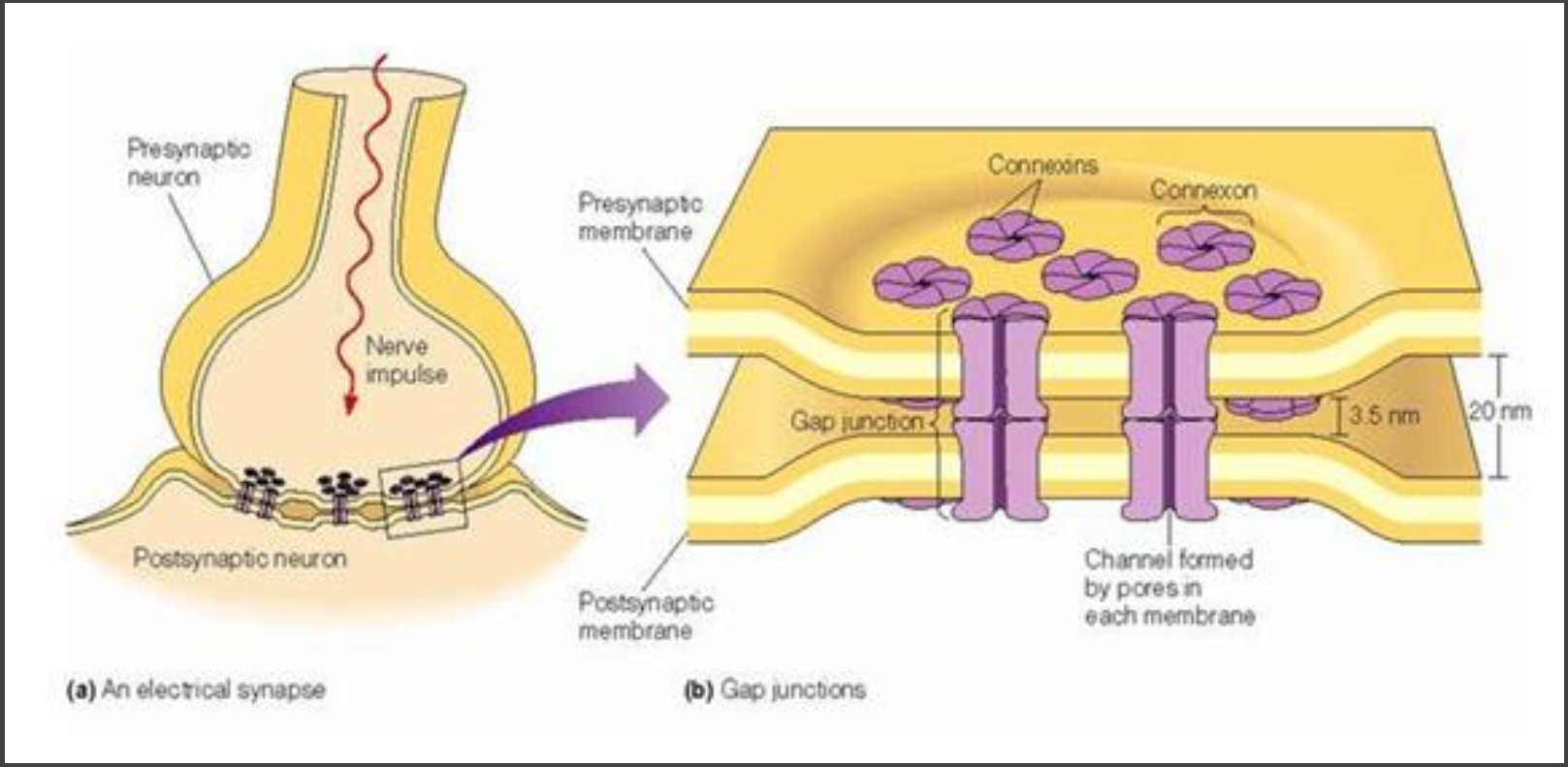
ELECTRICAL SYNAPSES
- present in brain stem, retina and cerebral cortex.
- contain gap junctions

CHEMICAL SYNAPSES are the most common manner of communication between nerve cells.



ELECTRICAL SYNAPSE

- **nexus (gap junction)**
-Cell-cell adhesion
-Formed from connexins

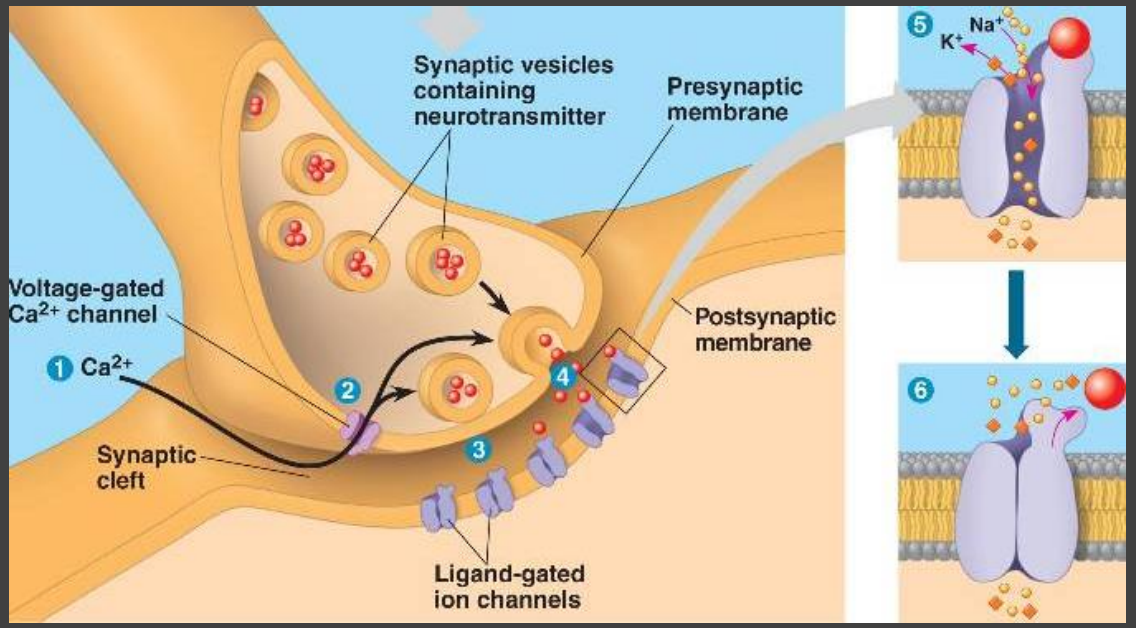


CHEMICAL SYNAPSE

-**Presynaptic membrane** (transmitting cell) with synaptic vesicles with neurotransmitters

-**Synaptic cleft**

-**Postsynaptic membrane** (receiving cell) with gated ion-channel receptors for neurotransmitters. Binding of neurotransmitters causes opening of ion channels, which permits the passage of ions, altering the membrane permeability and reverse its membrane potential.



NEUROTRANSMITTERS

<table>
<tr><th colspan="2">SMALL-MOLECULE TRANSMITTERS</th><th>PEPTIDES</th><th>GASES</th></tr>
<tr><td colspan="2">1. Acetylcholine
2. Amino acids: glutamate, glycine, GABA
3. Biogenic amines – monoamines i catecholamines: serotonine, dopamine, noradrenaline, adrenaline</td><td rowspan="3">Motyline, substance P, neuropeptyde Y, neurotensin, VIP, oksytocin</td><td rowspan="3">NO, CO</td></tr>
<tr><th>EXCITATORY</th><th>INHIBITORY</th></tr>
<tr><td>Glutamate, acetylocholine, dopamine, noradrenaline</td><td>GABA, glycine</td></tr>
</table>

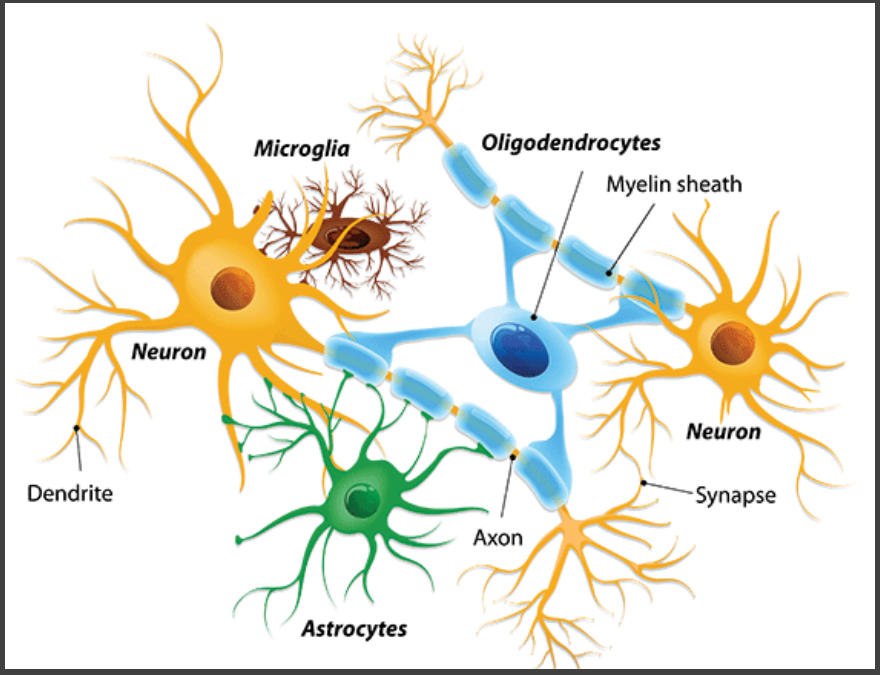
OTHERS – adenosine, anandamide

NEUROGLIAL CELLS

- physical support for neurons
- supply nutrients and oxygen to neurons
- destroy pathogens and remove dead neurons
- **Neuroglial cells undergo mitosis**

Types of glial cells

- Ependymal cells
- Astrocytes
- Oligodendrocytes
- Microglial cells
- Schwann cells (located in PNS)

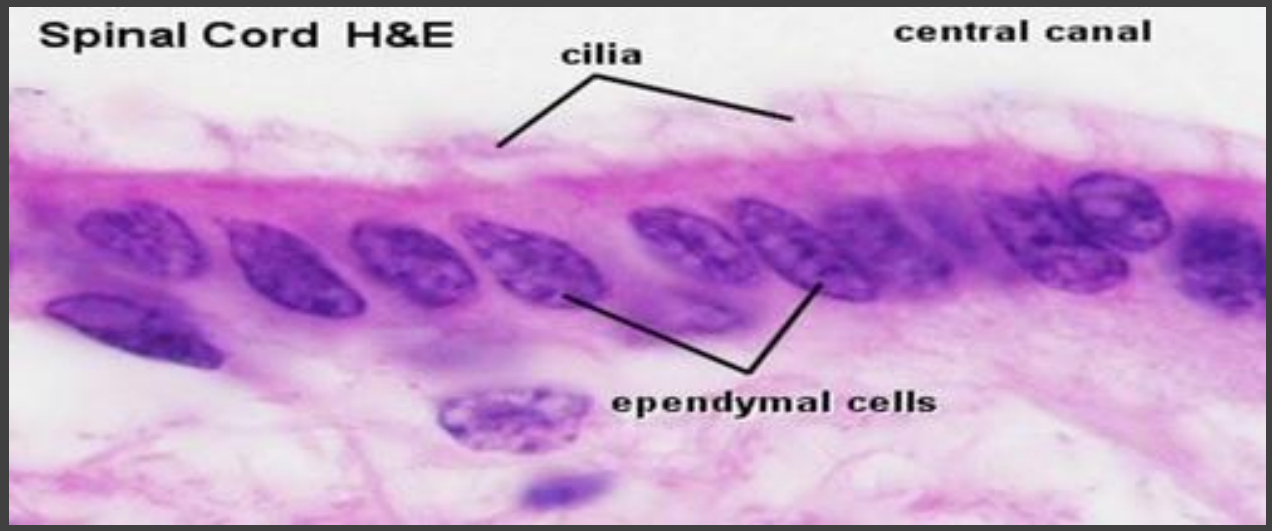


EPENDYMOCYTES

– cuboidal epithelial cells lining ventricles of the brain and central canal of the spinal cord forming ependyma.

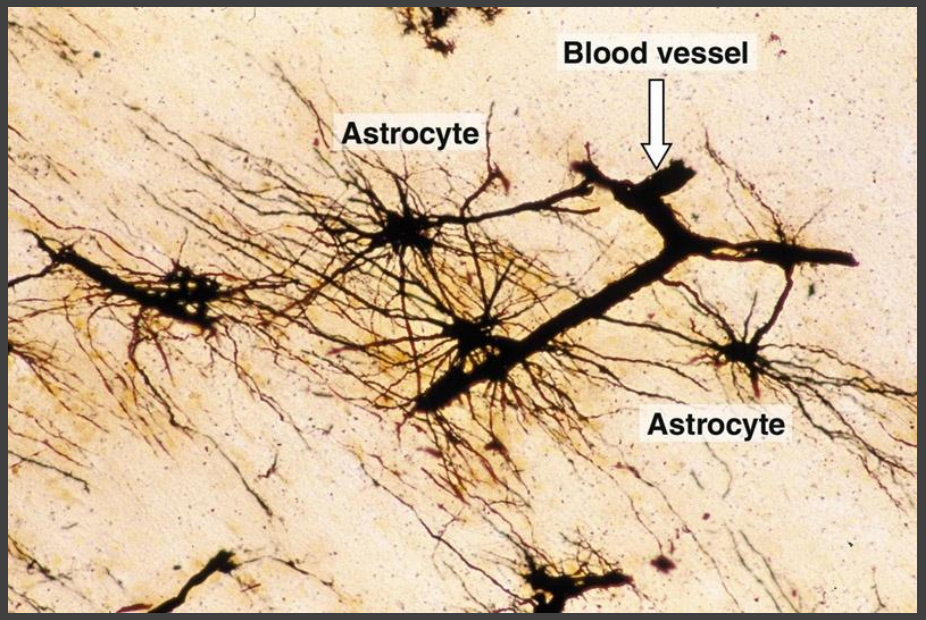
- contain cilia or microvilli.
- create and secrete cerebrospinal fluid (CSF)
- contain stem cells ???

TANYCYTES – III brain chamber



ASTROCYTES

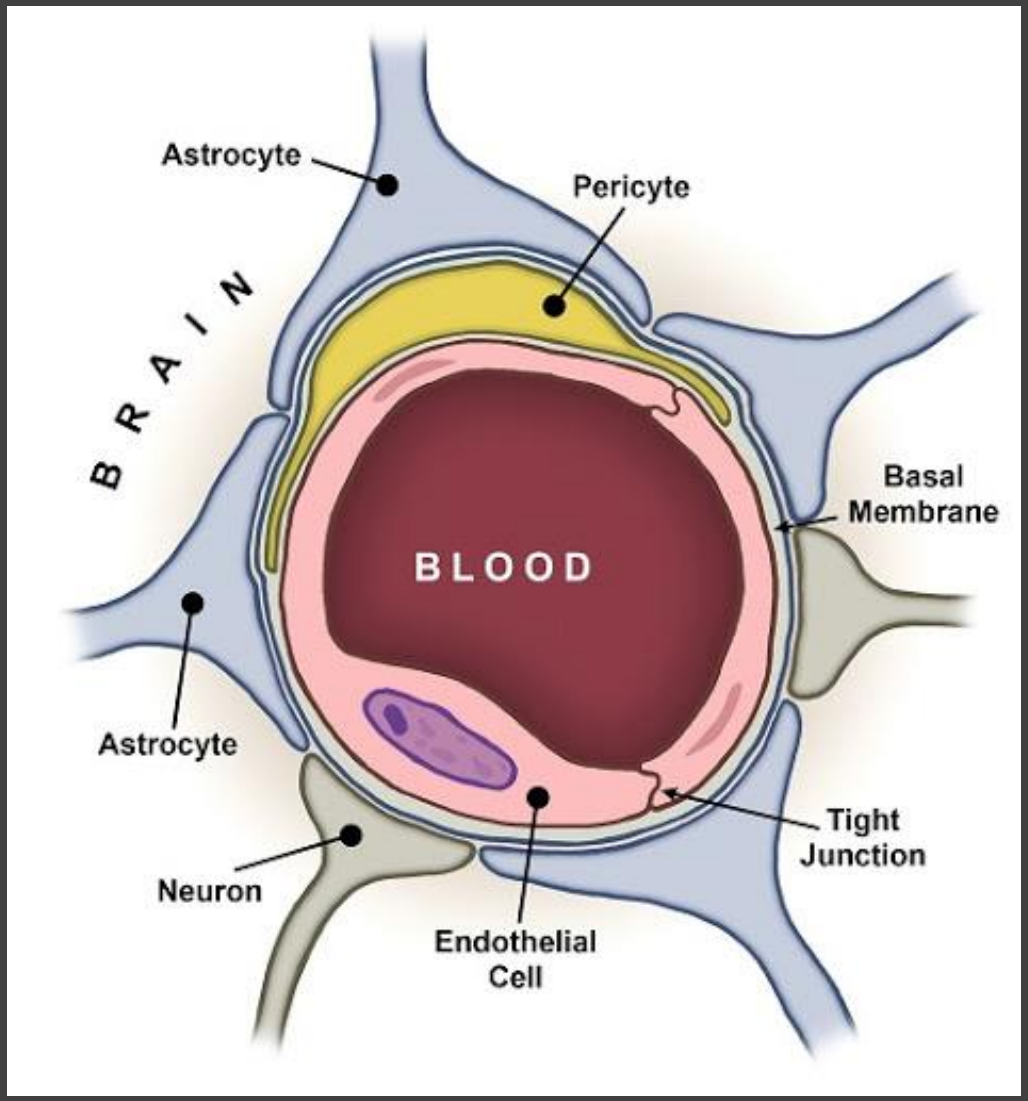
- The largest of the neuroglial cells
- Protoplasmic astrocytes (grey matter of CNS)
- Fibrous astrocytes (white matter of CNS)

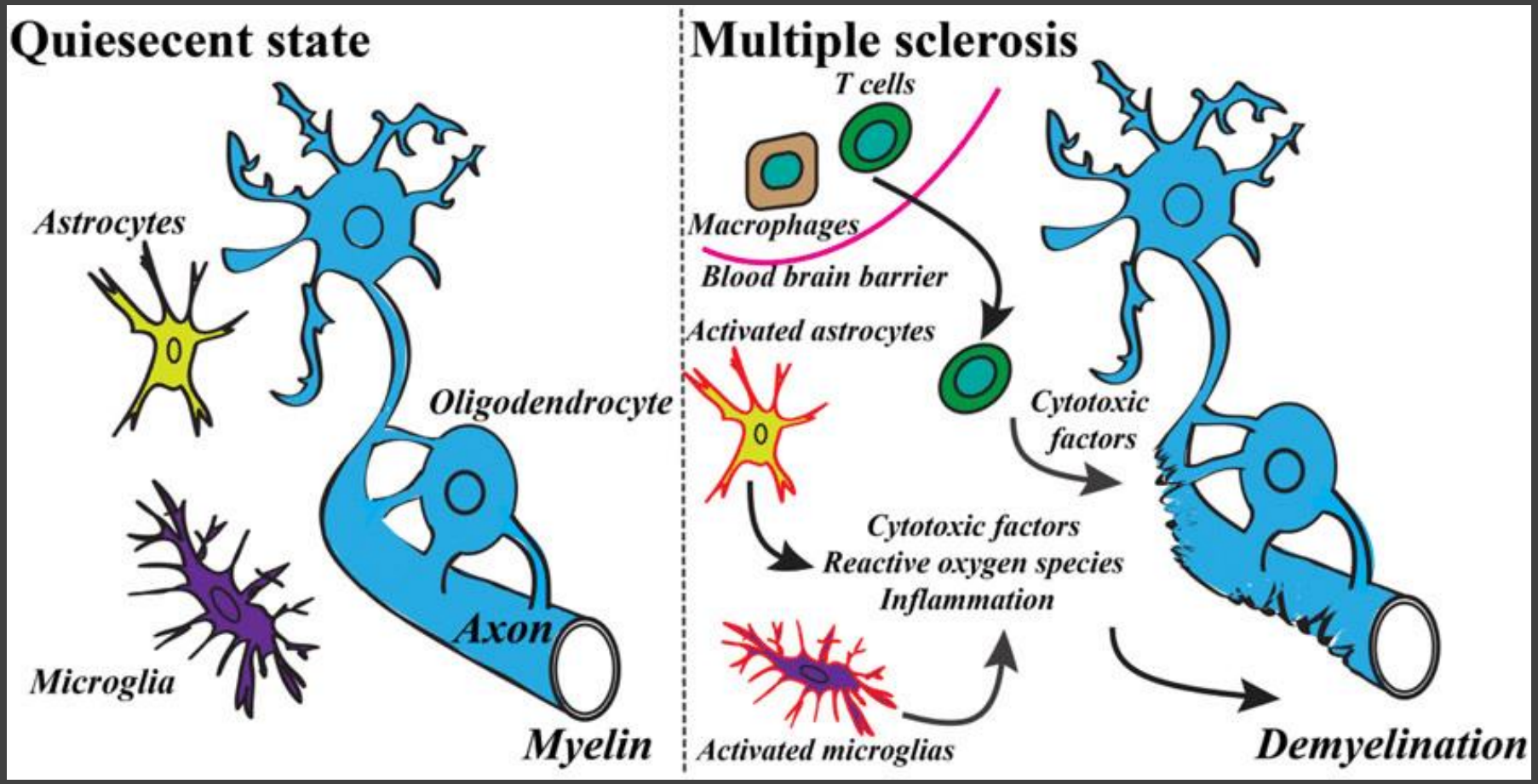


Function of astrocytes

- separation of blood vessels from direct contact with nerve tissue **(blood-brain barrier)**
- transport nutrients to neurons by transcytosis (***Transcytosis*** is the process by which various macromolecules are transported across the interior of a cell)
- maintenance of extracellular **ion balance (**express potassium channels)
- production, storage and secretion **neurotransmitters** and enzymes inactivating them
- regulate the transmission of electrical impulses within the brain.

Blood-brain barrier



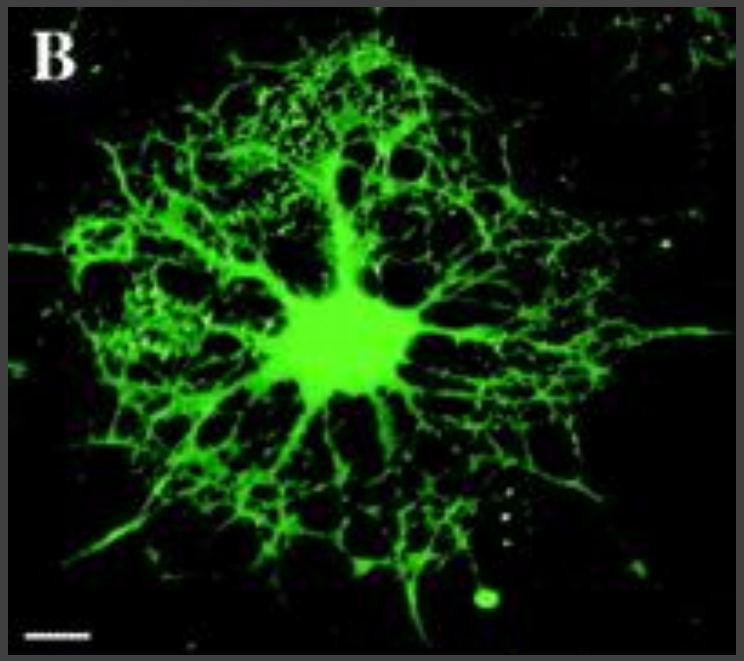

Quiesecent state
Astrocytes
Oligodendrocyte
Axon
Microglia
Myelin
Multiple sclerosis
T cells
Macrophages
Blood brain barrier
Activated astrocytes
Cytotoxic factors
Cytotoxic factors
Reactive oxygen species
Inflammation
Activated microglias
Demyelination

OLIGODENDROCYTES

- located in white and gray matter of CNS

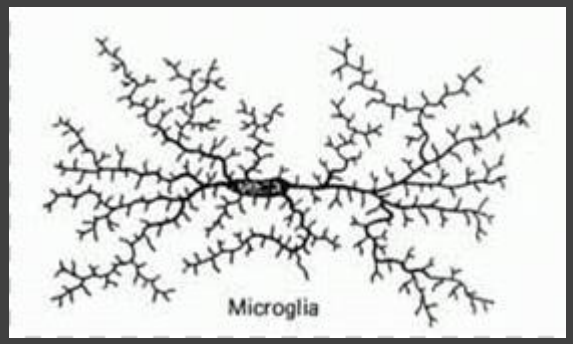
- posses a few processes with sparse branching.

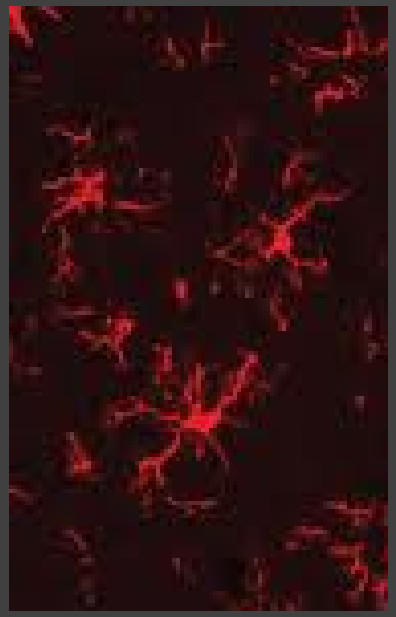
- **Interfascicular oligodendrocytes** produce the myelin sheath around the axons in CNS.
- **Satellite oligodendrocytes** are located close to cell bodies of large neurons; their function is not clear.

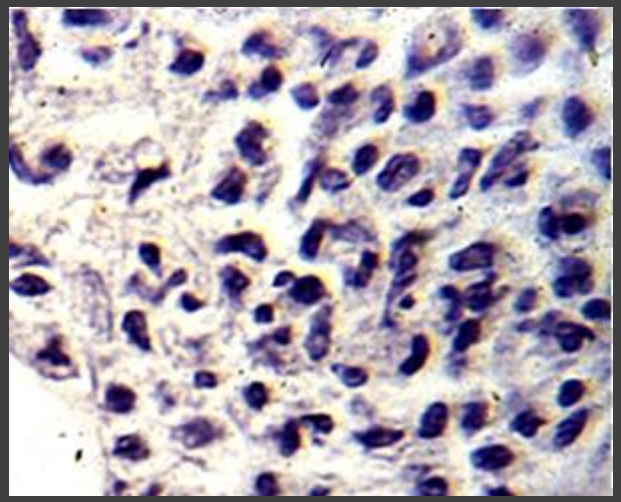


MICROGLIAL CELLS

- belong to mononuclear phagocyte system and derived from mesoderm
- exhibit irregular short processes, and spines on the cell body and processes
- function as phagocytes in clearing debris in CNS and in protecting nerve cells from pathogens and tumor formation



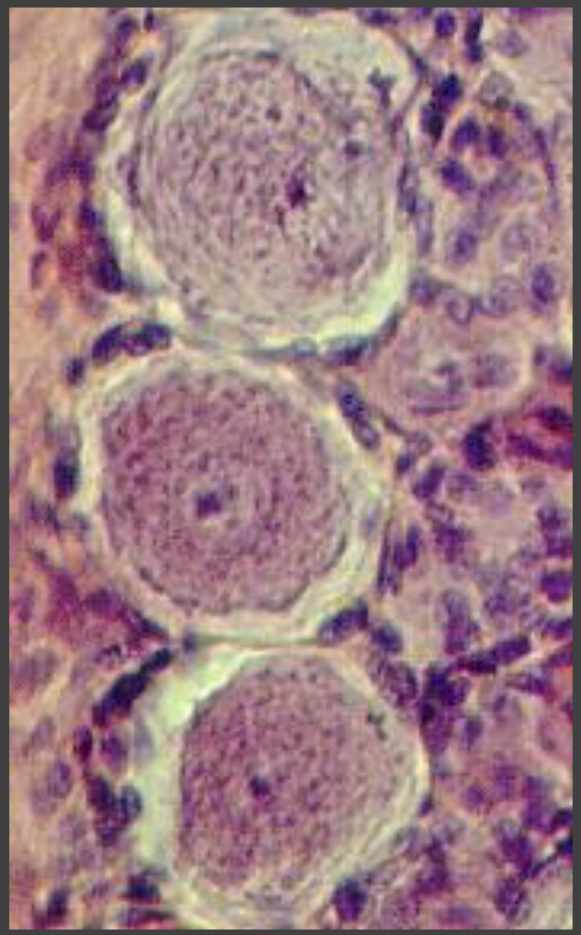




GLIAL CELLS OF PERIPHERAL NERVOUS SYSTEM (PNS)

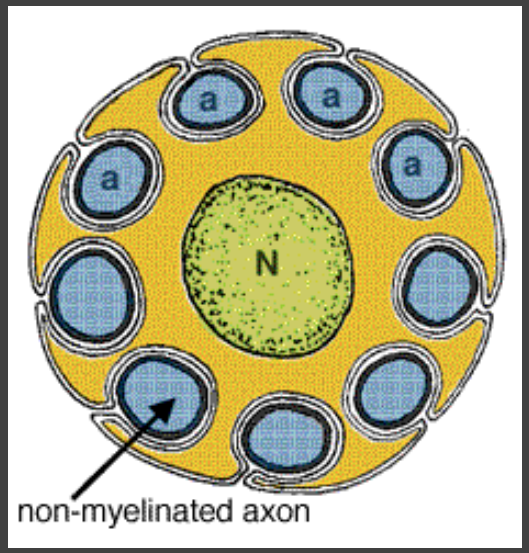
SATELLITE CELLS – envelop the cell bodies of unipolar neurons of sensory ganglia

LEMMOCYTES –Schwann cells – form both myelinated and unmyelinated coverings over axons in PNS

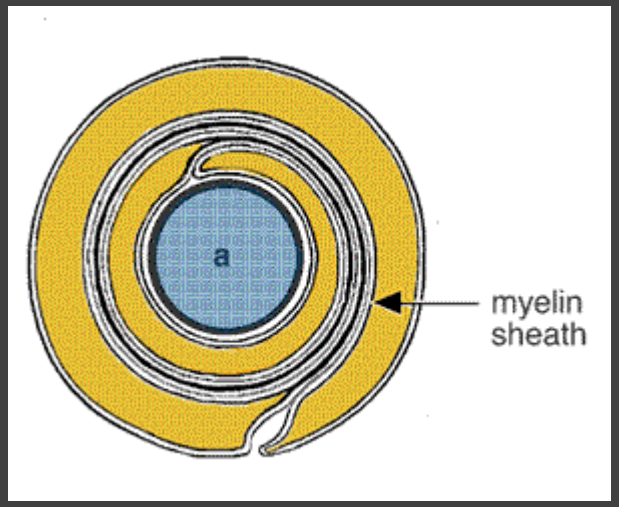


Axon sheath

1. Unmyelated axons



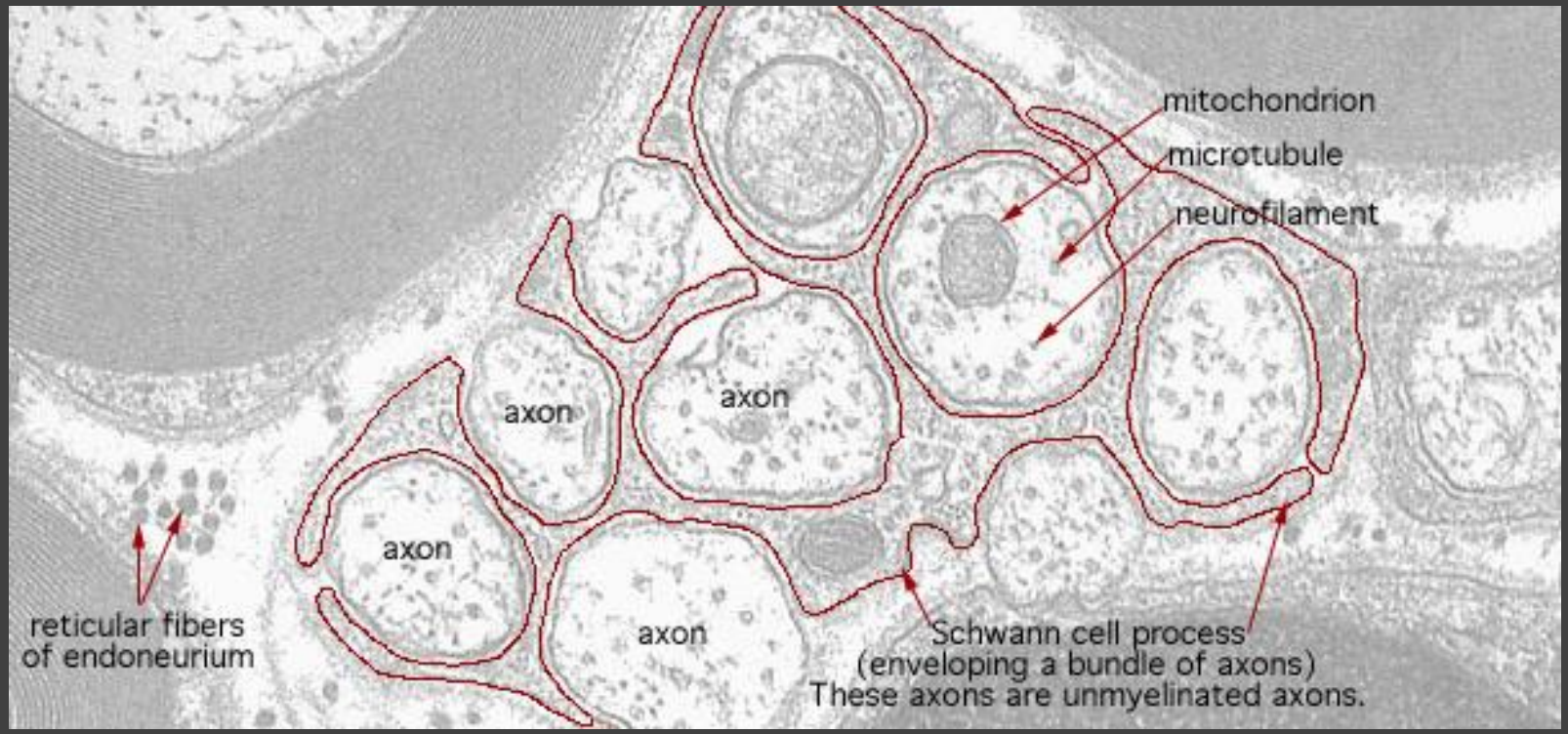
3. Myelated axons



NEUROLEMMA

Unmyelinated axons – surrounded by a single layer of Schwann cell plasma membrane and cytoplasm of the Schwann cell

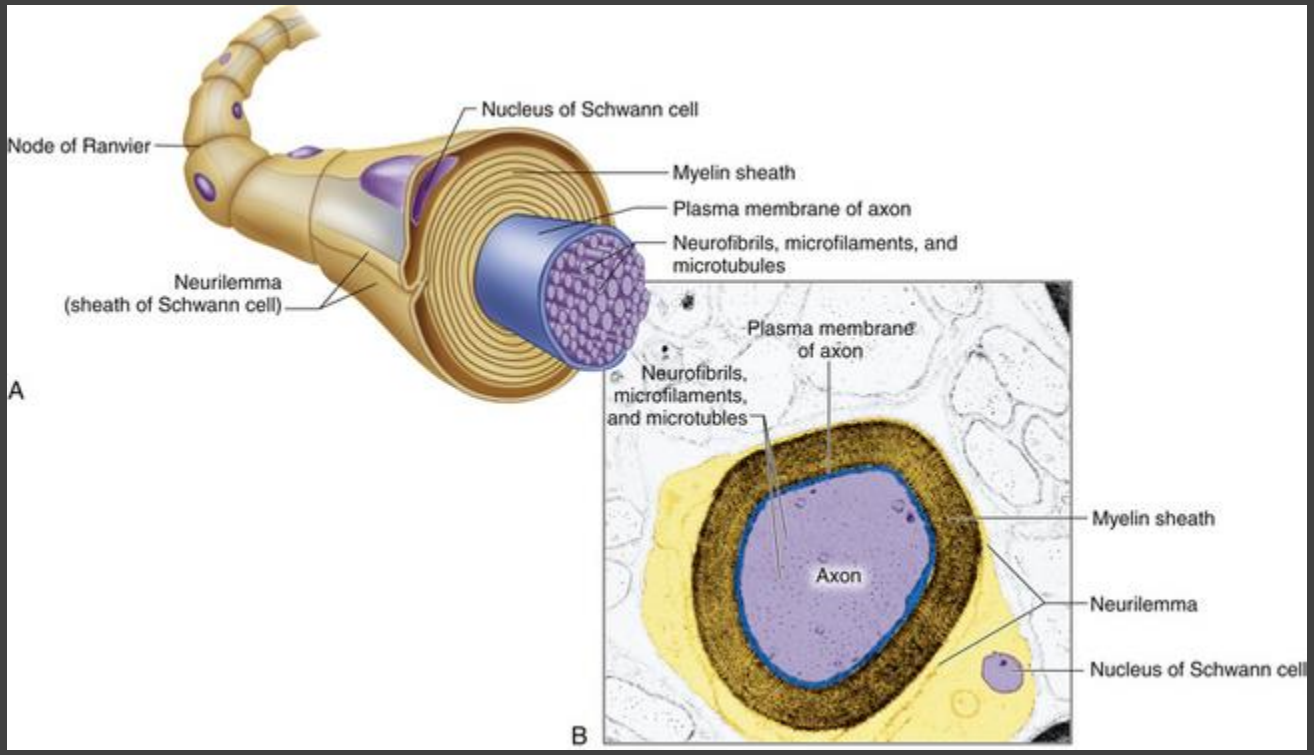
- several unmyelinated axons may be enveloped by a single Schwann cell
- the outermost cytoplasmic layer of Schwann cells that surrounds the axon of the neuron forms **neurolemma**



FORMATION OF MYELIN SHEATH IN PNS

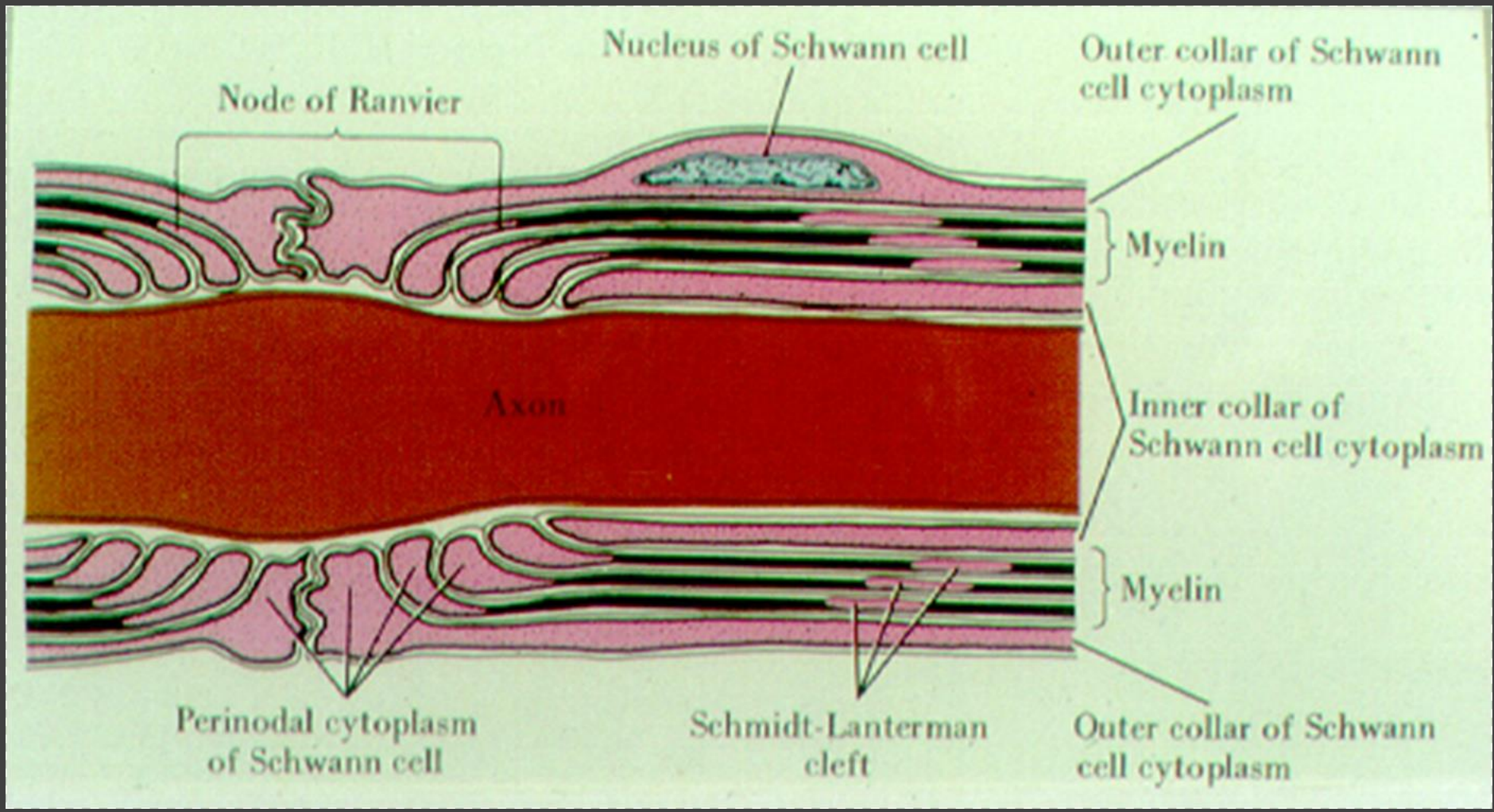
- whole Schwann cell wraps its membrane around the axon and forms one internodal segment

- the cytoplasm is squeezed into the body of Schwann cell

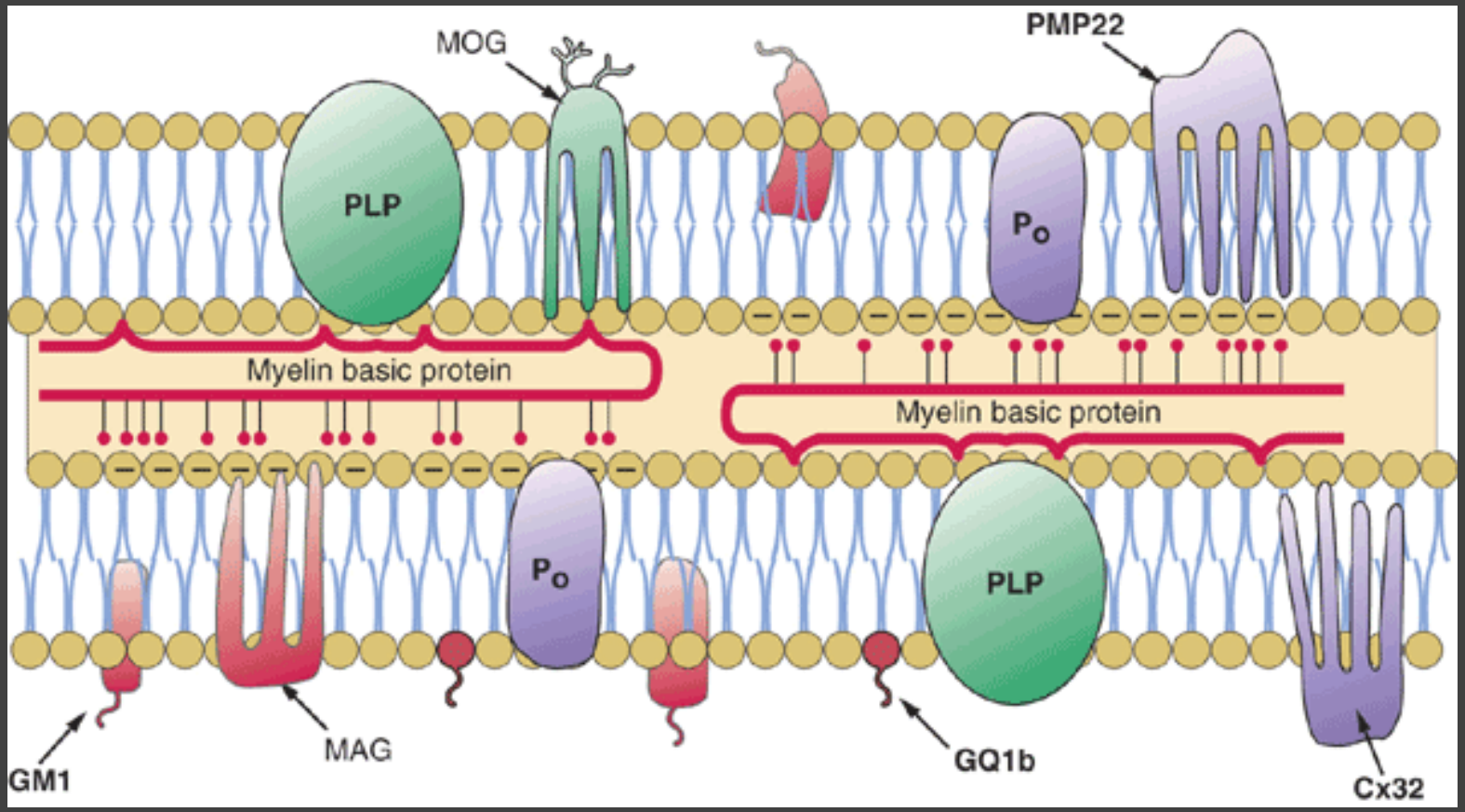


Schematic structure of nerve fiber

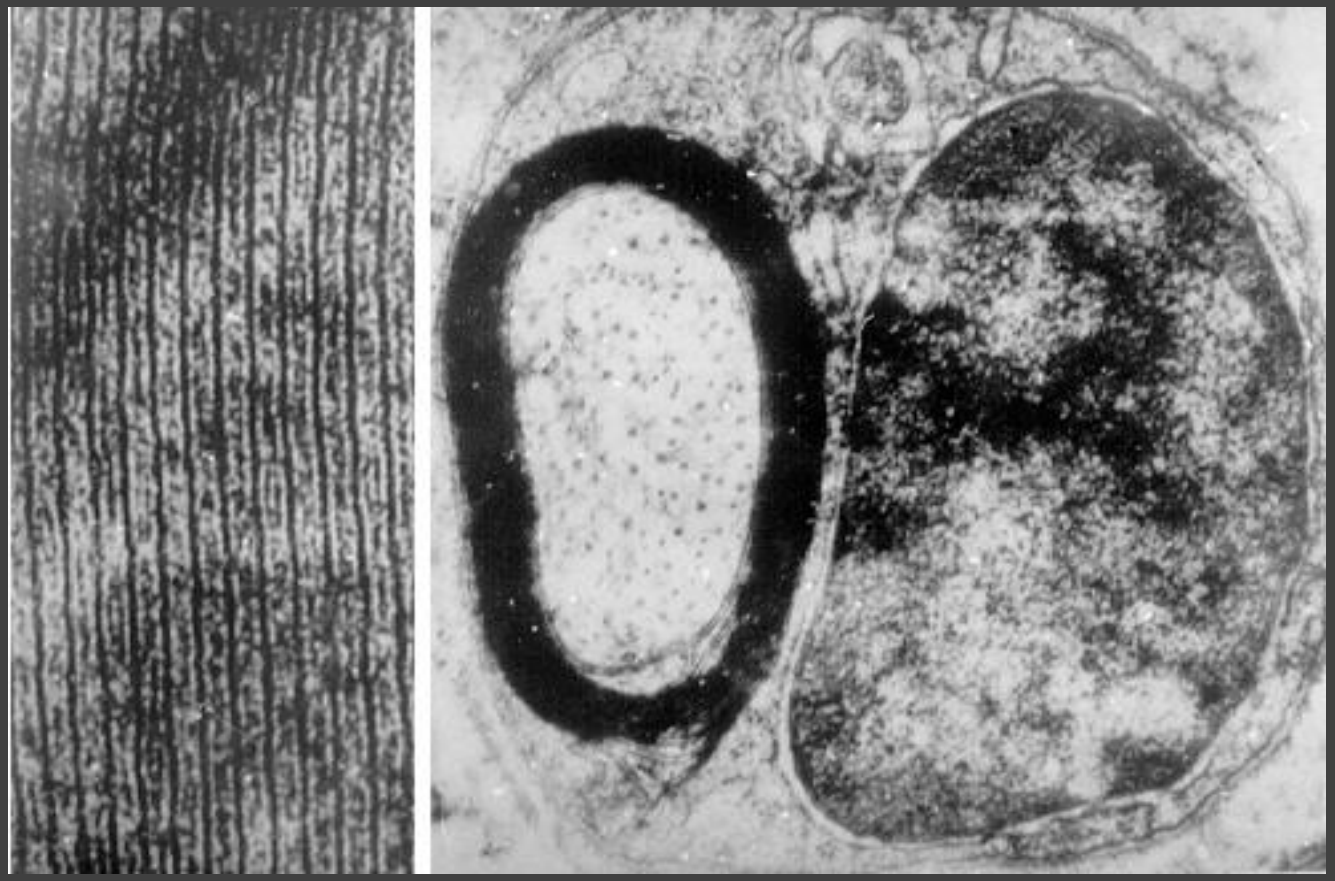
Schwann cell produces basal lamina, which covers the outer portion of this cell, adjacent node of Ranvier and overlapped area of adjacent Schwann cell. Thus whole axon is covered by a basal lamina.



Myelin Basic Protein - MBP



PERIPHERAL NERVE FIBER – ELECTRON MICROSCOPE



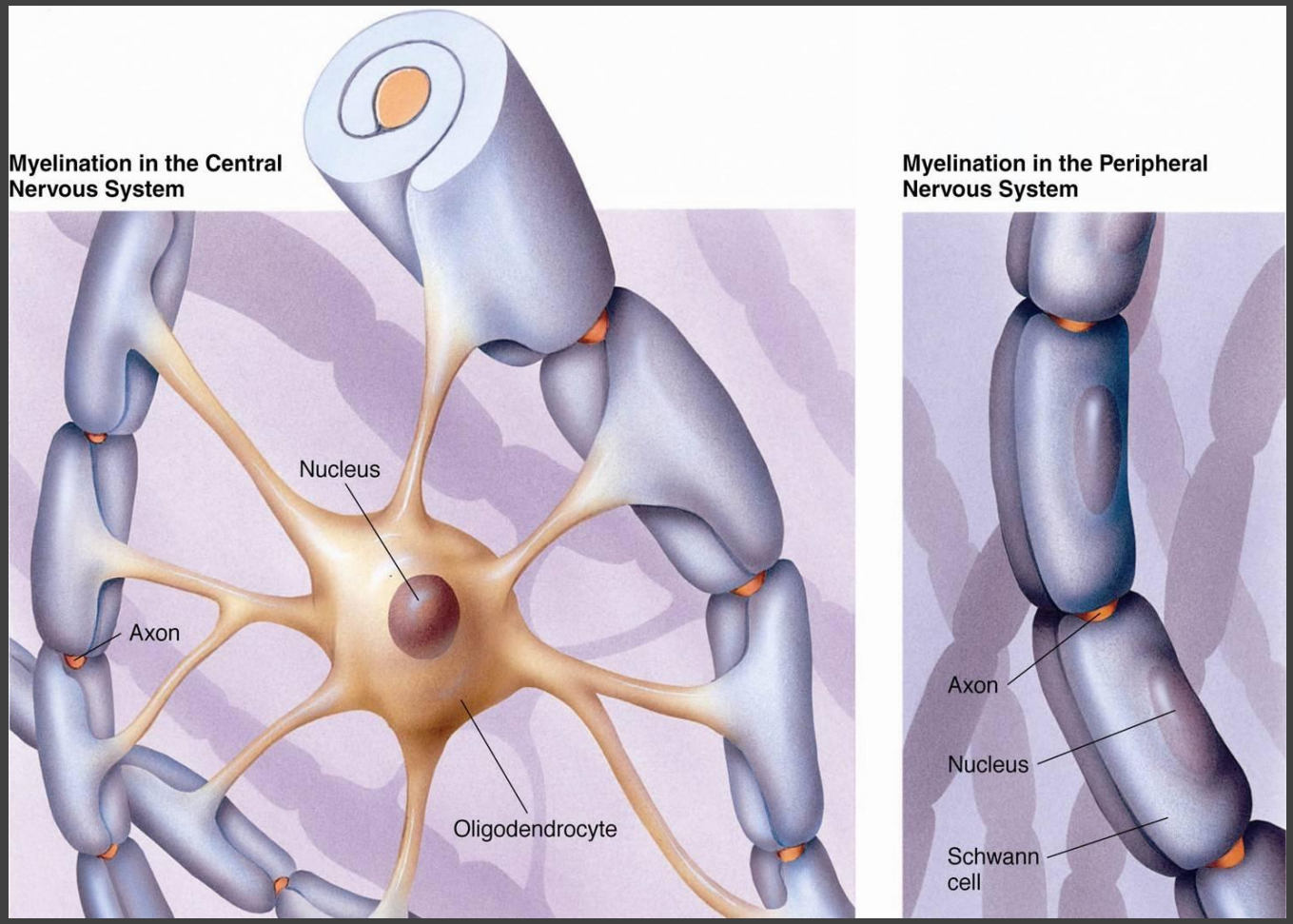
MYELINATION IN

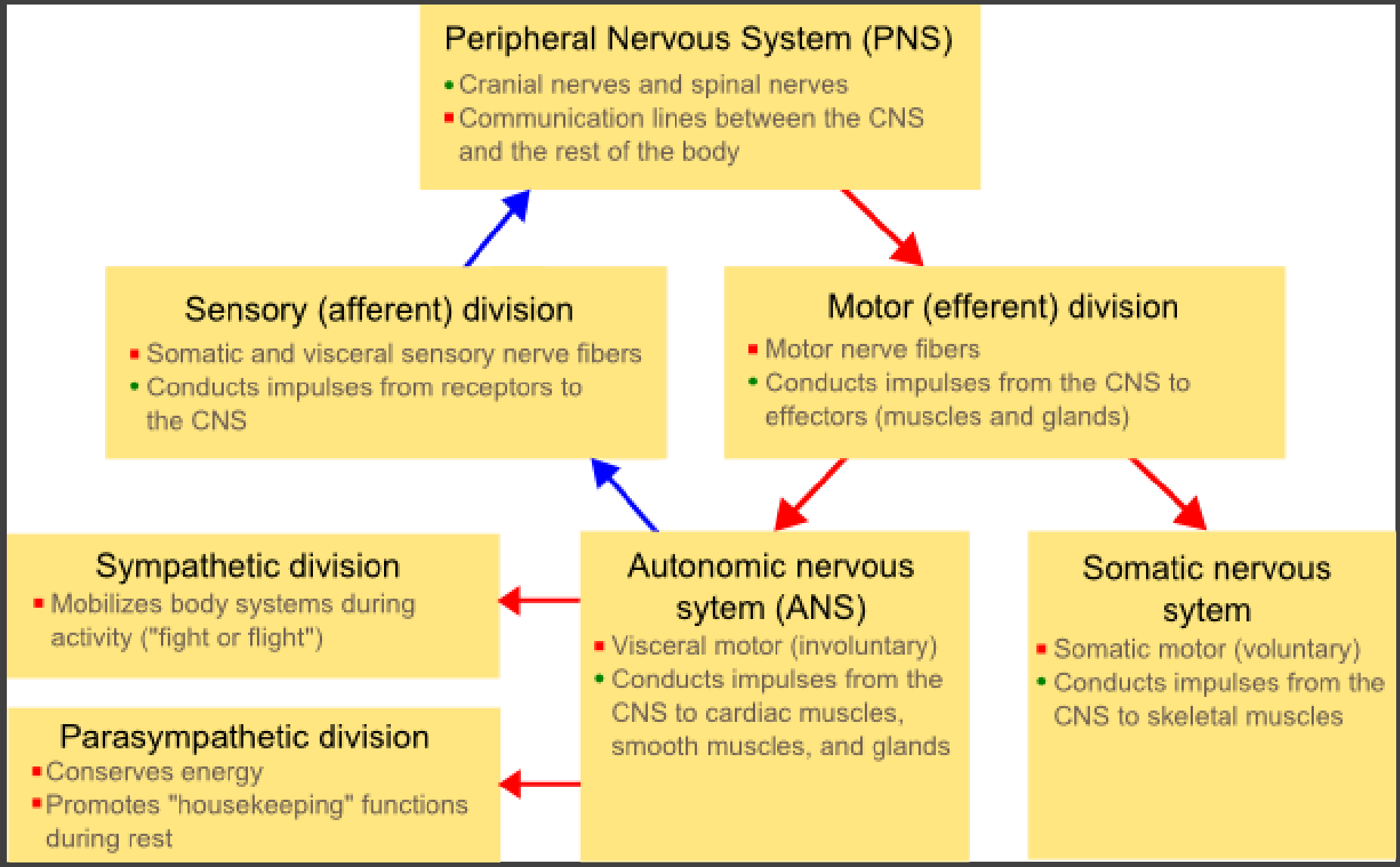
CNS

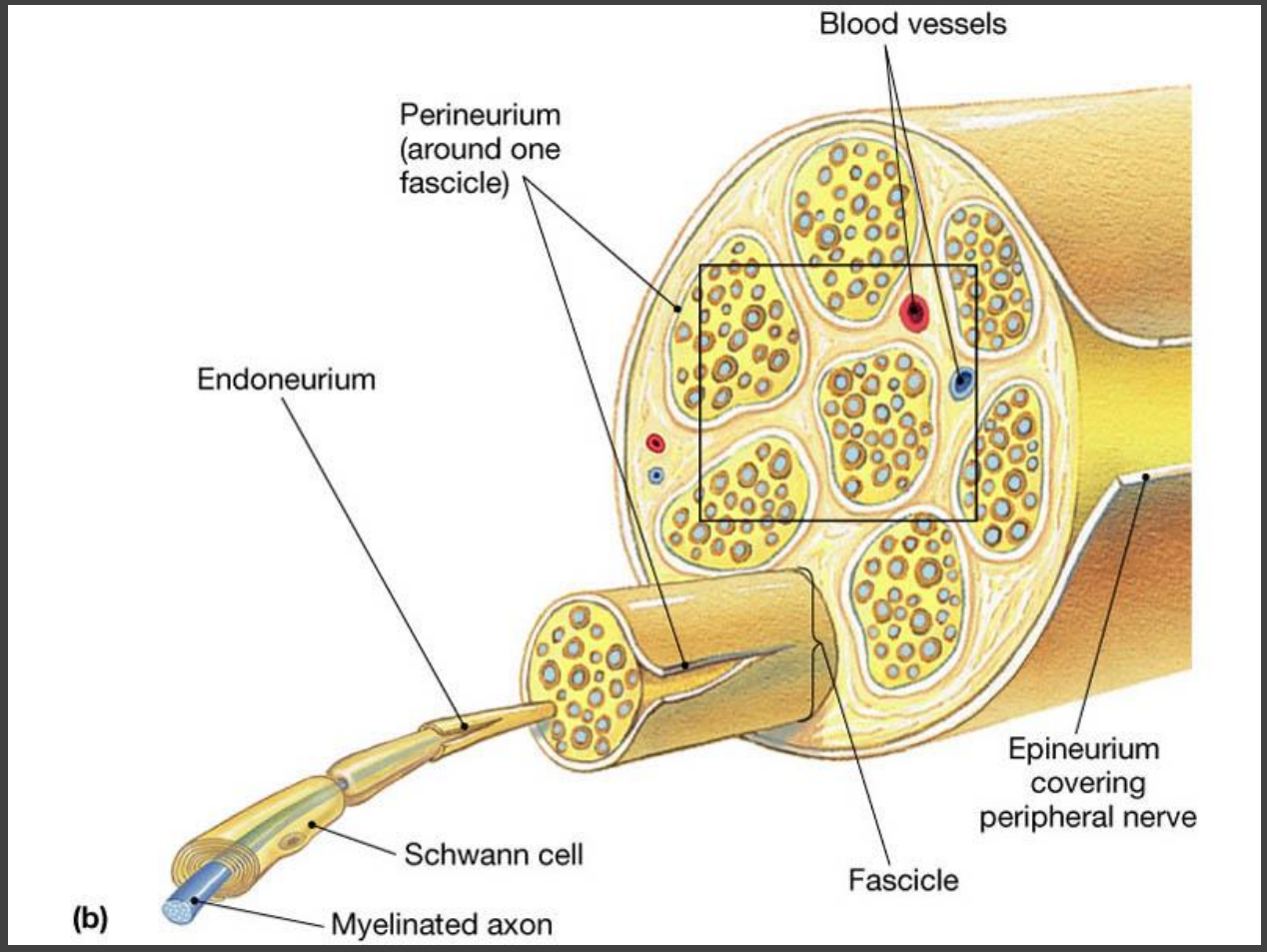
one oligodendrocyte- some internodal segments – some axons

PNS

one Schwann cell – one internodal segment - one axon




Peripheral Nervous System (PNS)
Cranial nerves and spinal nerves
Communication lines between the CNS and the rest of the body
Sensory (afferent) division
Somatic and visceral sensory nerve fibers
Conducts impulses from receptors to the CNS
Motor (efferent) division
Motor nerve fibers
Conducts impulses from the CNS to effectors (muscles and glands)
Sympathetic division
Mobilizes body systems during activity ("fight or flight")
Parasympathetic division
Conserves energy
Promotes "housekeeping" functions during rest
Autonomic nervous sytem (ANS)
Visceral motor (involuntary)
Conducts impulses from the CNS to cardiac muscles, smooth muscles, and glands
Somatic nervous sytem
Somatic motor (voluntary)
Conducts impulses from the CNS to skeletal muscles



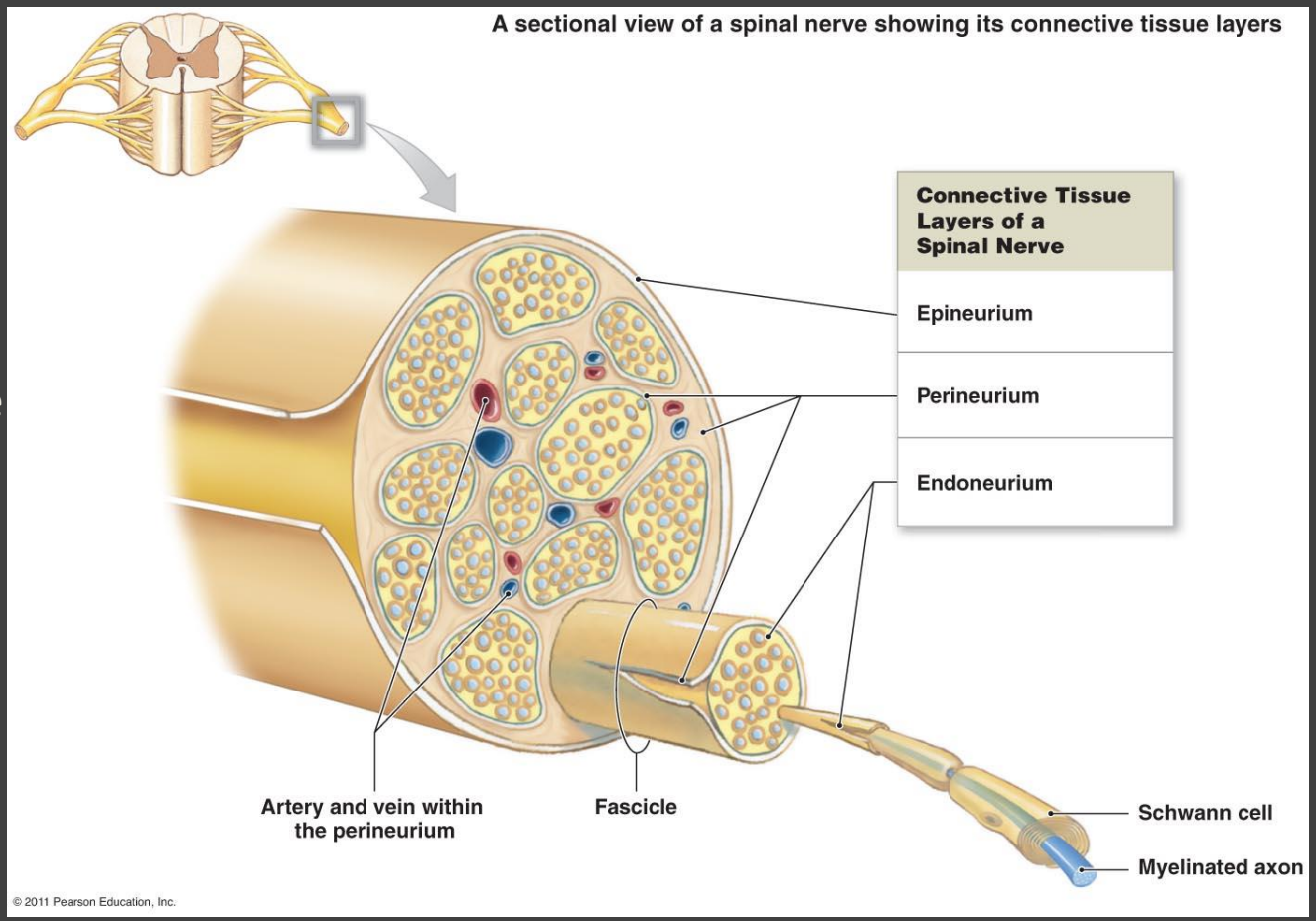
Peripheral nerve – collection of bundles of nerve fibers (axon with its sheats) with connective tissue investments.

PERIPHERAL NERVE – CONNECTIVE TISSUE INVESTMENTS

EPINEURIUM
Outermost layer, covers the nerve, dense, irregular connective tissue

PERINEURIUM
Middle layer, covers each bundle of nerve fibers, dense connective tissue (thinner than epineurium)

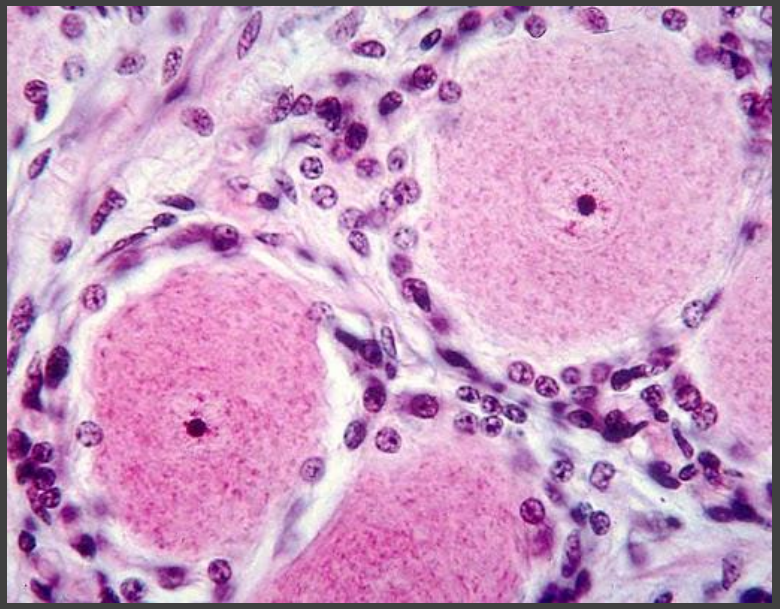
ENDONEURIUM
Innermost layer, surrounds the individual nerve fibers (axons), loose connective tissue

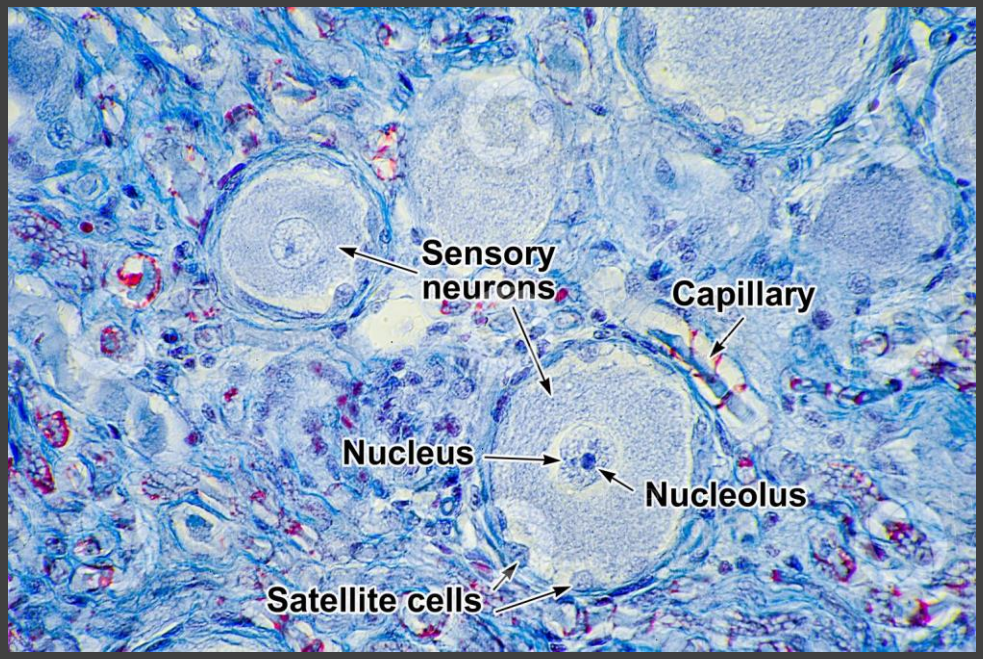


Ganglion

CAPSULE – dense connective tissue

STROMA – loose connective tissue proper with fibroblasts, fibers, macrophages, blood vessels

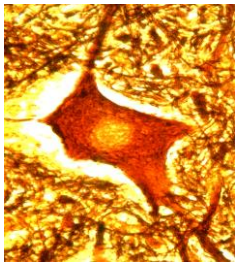




Seminar: Structure, organization and function of peripheral and central nervous system.
Practical class: Nervous tissue. Nervous system.

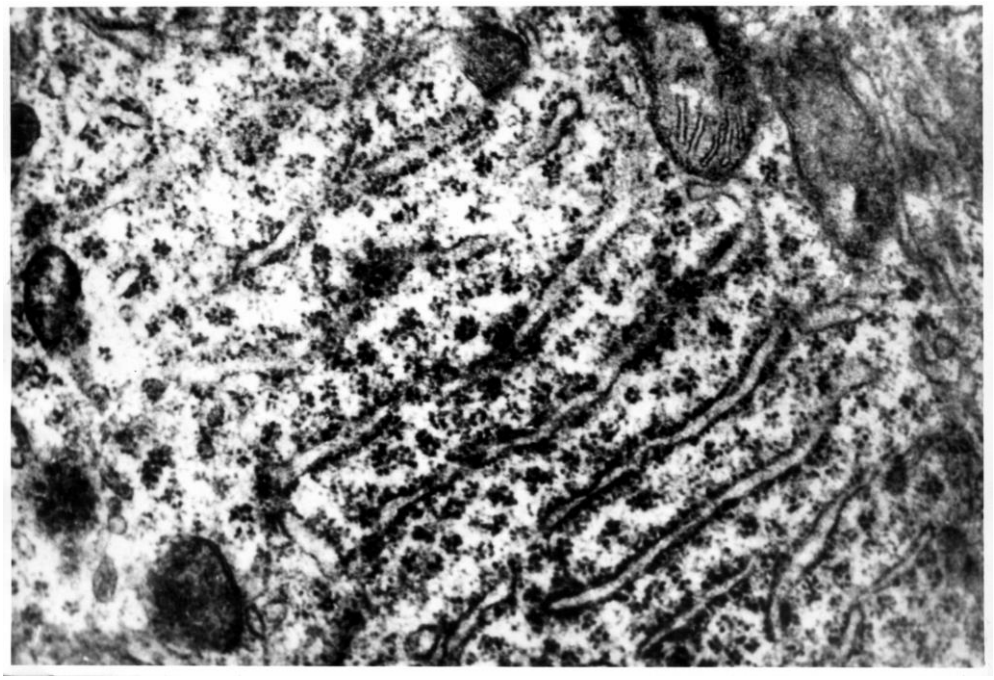
- **isolated nerve fiber (slide # 25),**
- **peripheral nerve (slide # 27),**
- **peripheral nerve – impregnated with OsO_4 (slide # 26),**
- **dorsal root ganglion (slide # 76),**
- **nerve cells in the spinal cord – tigroid (slide # 75),**
- **brain (slide # 77),**
- **cerebellum (slide # 79),**

- **axon (EM # 79),**
- **Nissl bodies (EM # 18),**
- **tau protein (EM # 37),**



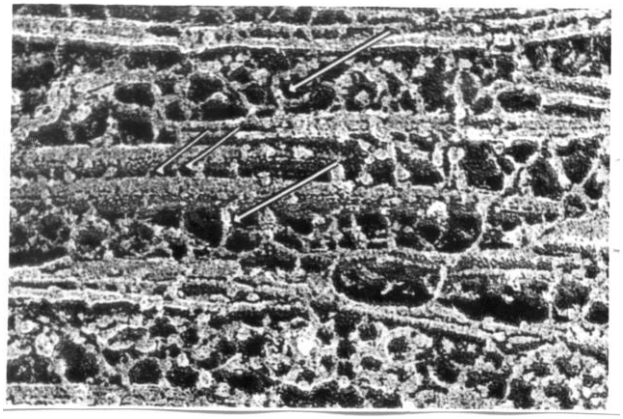
motoneuron

- **molecular structure of tau & MAP proteins (fig. # 77)**
- **diagram of an axon and its cover - that is, the myelin and Schwann cell - as seen with the light microscope (fig. # 64),**
- **diagram of an axon and its covering sheaths in longitudinal section to show the relationship between the axon, myelin, and the cytoplasm of the Schwann cell and the node of Ranvier (fig. # 65),**
- **diagram to aid in conceptualising of the relationship of myelin and cytoplasm of a Schwann cell (fig. # 66).**



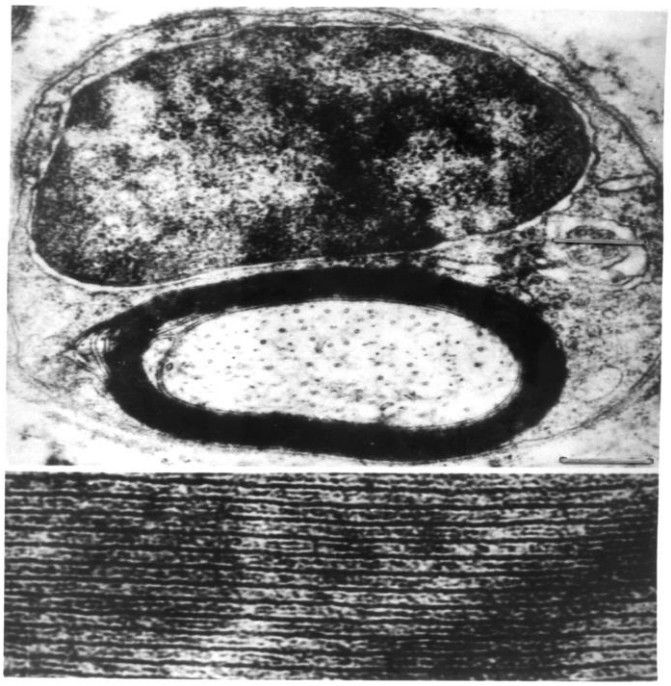
EM - 18

Tigroid (Nissl body) in Purkinje cell from rat cerebellum. Tigroid represents rough endoplasmic reticulum of nerve cells.



EM - 37

Electron micrograph showing axoplasm from rat ischiadic nerve with microtubules connected by short bridges (arrows) consisting of Tau protein.



EM-79

Cross-section of a single myeliniated nerve fiber from the rat ischiadic nerve.
The micrograph showing nucleus and cytoplasm of Schwann cell and myelin sheath surrounding nerve fiber (axon). At the bottom of micrograph a fragment of myelin sheath is shown. The regular dark lines are called major dense lines and represent the line of fusion of cytoplasmic surfaces of Schwann cell membranes. The less regular lines are called intraperiodic lines and are sites of close contact of the extracellular surfaces of adjacent layers of Schwann cell membranes.

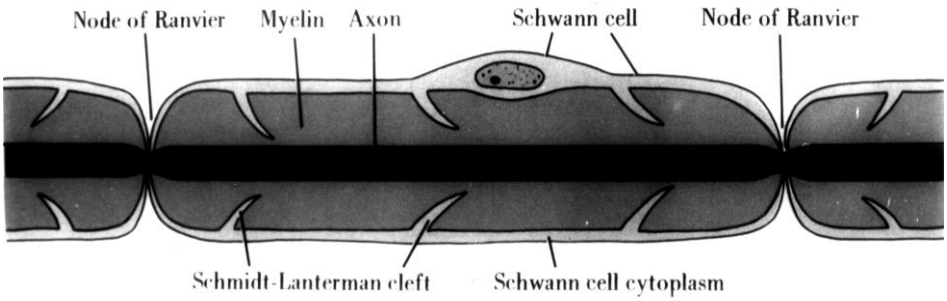


Fig. no. 64

Diagram of an axon and its cover - that is, the myelin and Schwann cell - as seen with the light microscope. A single Schwann cell (also referred to as the sheath of Schwann or the neurilemma) surrounds the axon from one node of Ranvier to the next. The Schmidt-Lanterman cleft represents cytoplasm of the Schwann cell.

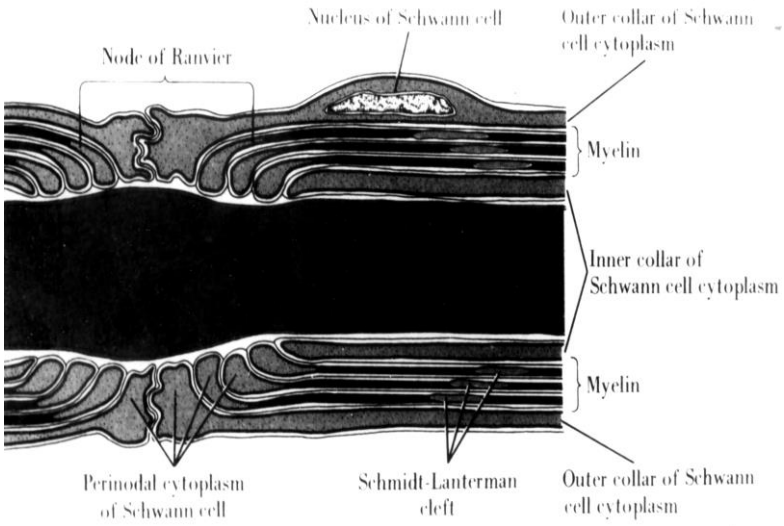


Fig. no. 65

Diagram of axon and its covering sheaths in longitudinal section to show the relationship between the axon, the myelin, and the cytoplasm of the Schwann celand the node of Ranvier. Schwann cell cytoplasm is present at four locations. These are the inner and outer cytoplasmic collars of the Schwann cell, the perinodal location, and the Schmidt-Lanterman clefts. It should be noted that the cytoplasm throughout the Schwann cell is continuous, and it is not a series of cytoplasmic islands it appears in the diagram. The node of Ranvier is the location where successive Schwann cells meet. The adjacent plasma membranes of the Schwann cells are not tightly apposed at the node, and extracellular fluid has free access to the neuronal plasma membrane. Also, the node is where depolarization of the neuronal plasma membrane occurs during the transmission of the nerve impulse.

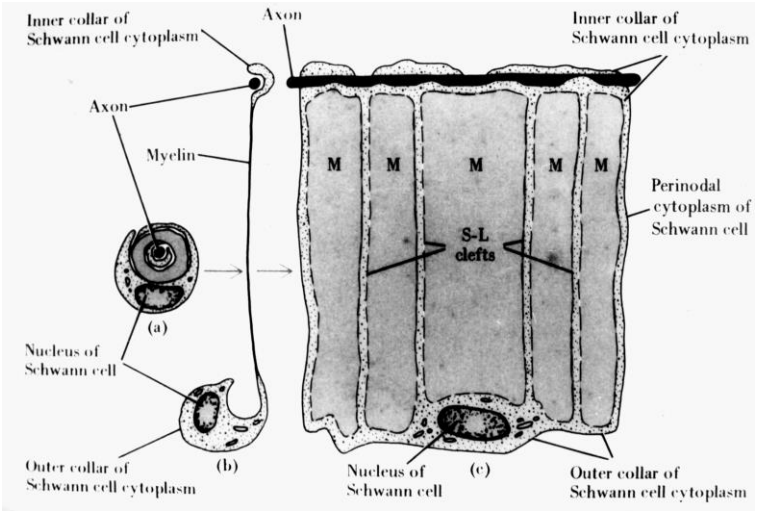


Fig. no. 66

Diagrams to aid in conceptualizing the relationship of myelin and cytoplasm of a Schwann cell.
(a) A cross-section of a myelinated axon.
(b) A hypothetically uncoiled Schwann cell viewed on edge.
(c) The same uncoiled Schwann cell in face view.
Note how the cytoplasm of the Schwann cell is continuous.
S-L clefts = Schmidt-Lanterman clefts;
M = myelin.

Microtubule MAPping

Minireview

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Fifteen years have passed since microtubule-associated proteins (MAPs) were first identified as proteins that copurify with tubulin during repeated cycles of assembly. Initial interest focused on the ability of neuronal MAPs to stimulate microtubule nucleation and elongation from purified tubulin in vitro. These properties were always unsatisfying, not only because an alarming list of other agents could supplant the assembly-inducing properties, but also because the restricted focus on assembly ignored other potential MAP functions. Recently, a flurry of reports, primarily using molecular genetics, has uncovered unexpected in vivo properties of MAPs.

The original MAPs were isolated from mammalian neurons and named according to the three major size classes of polypeptides: MAP1 (>250 kd), MAP2 (~200 kd), and tau (35–65 kd). MAP1 is a bit of a misnomer in that the size class to which it refers contains at least three polypeptides (MAP1A, MAP1B, and MAP1C) that are probably unrelated. Ironically, although the MAP1 components are the least studied, MAP1C is the only neuronal MAP with an accepted function—it is the long-anticipated cytoplasmic dynein (Paschal and Vallee, 1987) that powers transport along microtubules of components in a direction from the nerve tip back toward the cell body. MAP1C is not restricted to neurons, however, and probably serves similar (but as yet undocumented) transport functions in other cell events, possibly during mitosis.

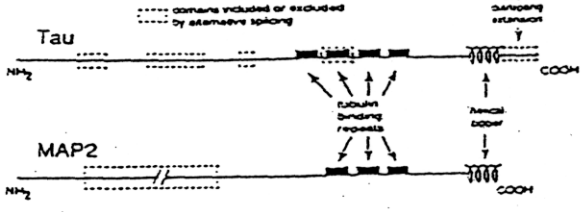
Interest in tau was renewed when it was recognized by several groups to be a major component of the abnormal, intracellular tangles of filaments that accumulate in the brains of patients with Alzheimer's disease. Distressingly heterogeneous in size, the various taus were initially feared to be proteolytic products of the larger MAPs. This is not the case; rather, a single tau gene produces multiple polypeptides through alternative RNA splicing. Five of the 14 exons of the >63 kb bovine tau gene may be included or deleted during splicing, and three different carboxyl termini utilized (Himmler, 1989), resulting in a minimum of 64 potential tau polypeptide products.

The determination of the primary structures of both tau (Lee et al., 1988) and MAP2 (Lewis et al., 1988) revealed a common feature: both proteins carry a similar set of three (sometimes four) imperfect, 18 amino acid repeats that comprise a portion, but probably not the entirety, of the tubulin binding domain. (The schematic illustrates the salient features of these two MAPs). An adrenal MAP (~190 kd) also carries a similar microtubule binding domain (Aizawa et al., 1989). Although these findings raised the possibility that this repeat is a general feature of microtubule binding proteins, no such domain is present on kinesin (Yang et al., 1989), a more recently discovered MAP that moves particles along microtubules in the direction opposite to that of MAP1C. The sequence of the 2464 amino acid MAP1B polypeptide (also known as MAP1.2, MAP1(X), and MAP5) has revealed a basic domain containing multiple copies of the short motif KKEE or KKEV (Nobel et al., 1989). Assembly experiments revealed that this repeat element represents the tubulin binding domain of MAP1B, but it too is unrelated to that of tau and MAP2.

Immunolocalization of MAP2 and tau gave the first clue as to what properties they might contribute. Although they are coexpressed within most neurons, they localize to separate subcellular compartments. Tau is restricted to axons, the thin tubes that constitute the conducting unit of the neuron. MAP2 is found largely in dendrites, the arborized extensions of the cell body that serve as the neuron's chief signal receptor apparatus. How this segregation is achieved is unsettled, particularly because these MAPs share a common tubulin binding domain. Microinjection of biotinylated MAP2 into primary cultures of neurons has revealed that MAP2 can be transported into axons as well as dendrites. The odd thing is that in axons MAP2 barely binds to microtubules and is rapidly degraded (Hirokawa and Okabe, 1989).

What do tau and MAP2 do? This has been addressed in two ways: first, microinjection of tau into fibroblasts (which do not express their own tau gene) clearly demonstrated that tau both induced additional tubulin assembly and stabilized microtubules against depolymerization without an obvious change in filament organization (Drubin and Kirschner, 1986). Furthermore, in transfected fibroblast lines that express a single tau cDNA either transiently (Kanai et al., 1989; Lewis et al., 1989) or stably (Kanai et al., 1989), tau accumulation led to a dramatic reorganization of microtubules into bundles and an increase in total tubulin content. Equally striking bundling was observed when MAP2 was expressed by transfection (Lewis et al., 1989).

Insight into the mechanism of bundling came from the analysis of a series of truncated MAP2 and tau products (Lewis et al., 1989). While MAP2 has long been known to project from the surface of the microtubule, it is not this long amino-terminal domain that is responsible for cross-bridging. Rather, the important feature is a short, hydrophobic α-helical domain that resides at the carboxyl terminus of the short arm that lies beyond the tubulin binding repeats (see figure). MAP2 dimerizes through this domain



and thus cross-links adjacent microtubules. This interaction is homologous to, and can be functionally replaced by, an authentic leucine zipper from the yeast transcription factor GCN4. Even MAP2C, an embryonic form of MAP2 that lacks 1324 amino acids through an alternative splice (Papandrikopoulou et al., 1989), retains cross-bridging activity (Lewis et al., 1989).

Of the dozen or so tau isoforms now cloned, all but one terminate with a hydrophobic zipper domain similar to that of MAP2. Expression of these isoforms induces bundling, whereas the one exception, which contains an additional 25 amino acids as a consequence of an alternative 5′ splice site in exon 13, does not cross-link microtubules. Presumably this extension disrupts the ability of the zipper domains to dimerize. While there is no truly satisfying explanation of why bundling is not observed using microinjection, it could be due to too little (or too much) tau injected or the specific isoforms present in the purified tau. In any event, it seems certain that some tau and MAP2 isoforms can cross-link microtubules.

The in vivo implications for tau and MAP2 cross-linking are far-reaching. First, it would be astonishing (although as yet untested) if the well-documented microtubule instability (reviewed in Kirschner and Mitchison, 1986) were not suppressed in cells expressing tau or MAP2 at reasonable levels. Second, both MAP2 and tau yield intermicrotubule cross-bridges about 20 nm in length, similar to the closest-spaced microtubules in neurons. The average microtubule spacing in both dendrites and axons is greater than this, but this could be a consequence of high levels of expression during transfection and a consequent tightening of microtubules within the bundle. Further, because microtubules in axons are all oriented with their plus ends distal to the cell body whereas filament polarity is random in dendrites, major features of neuronal morphogenesis may be determined by the ability of (axonal) tau to bundle only microtubules oriented with the same polarity, while (dendritic) MAP2 causes antiparallel filament bundling.

Bundling of a qualitatively different sort has been found for a newly identified MAP named dynamin. This 100 kd polypeptide was identified by Shpetner and Vallee (1989) as one of three polypeptides that bind to microtubules in a nucleotide-dependent manner, the other two being the translocators MAP1C and kinesin. Released from microtubules in the presence of GTP and AMPPNP, purified dynamin was shown to induce the formation of hexagonally packed bundles of microtubules spaced 13 nm apart. The binding is extraordinarily cooperative, yielding portions of a microtubule covered with dynamin, while adjacent domains are completely unbound. In addition, in the presence of ATP, the bundles fragment and elongate, indicating dynamin-induced sliding between microtubules. Dynamin thus joins MAP1C and kinesin as known mechanochemical enzymes capable of exerting force on a microtubule. The in vivo role of dynamin is still obscure, particularly because the close-packed bundling seen in vitro is not observed in neurons. However, as in the case of MAP1C and kinesin, dynamin is probably not restricted to neurons, and it is plausible that it (or a relative) contributes to mitotic spindle organization and movement, particularly during microtubule sliding at anaphase B (when the pole-to-pole distance increases).

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