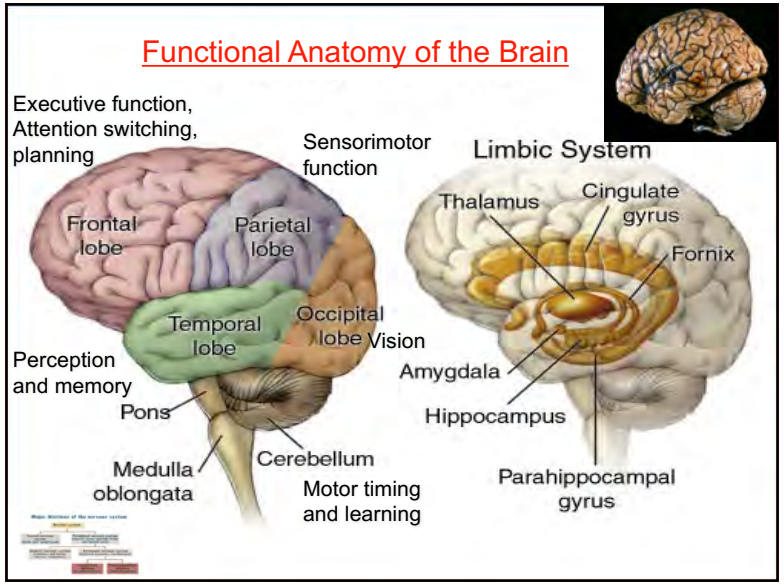
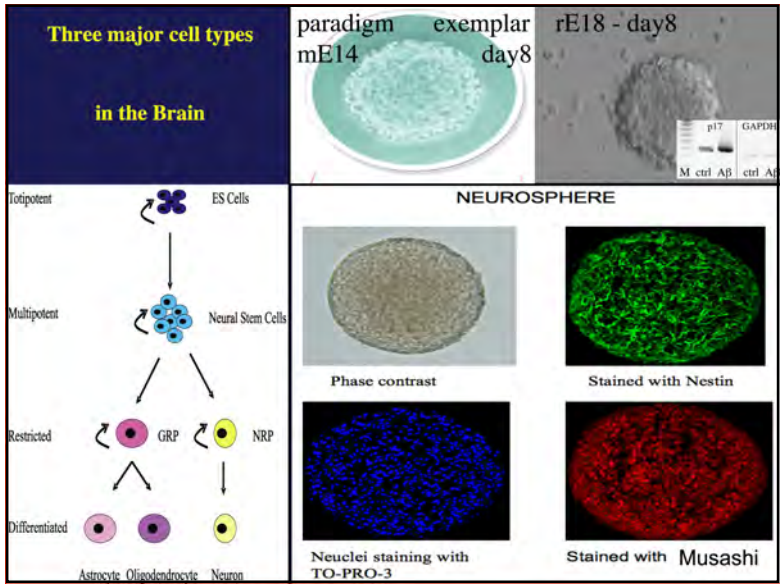
Molecular and Cellular Biology

07. Brain Cells

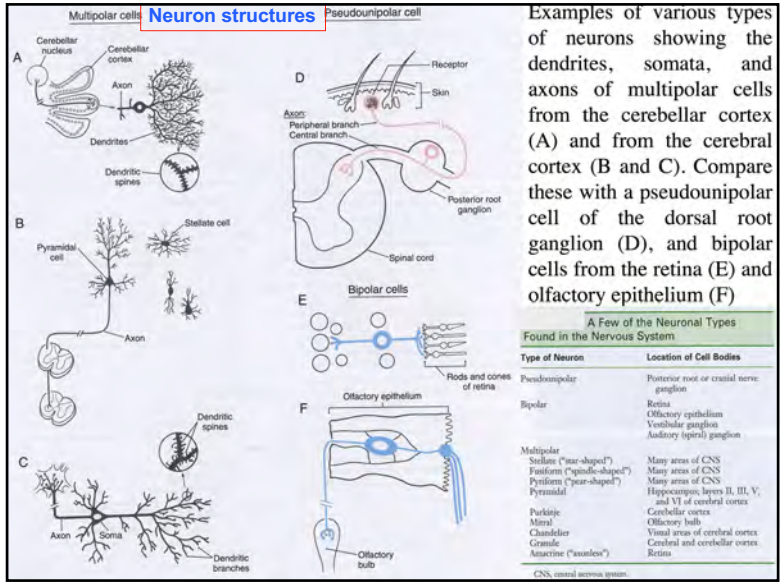
Prof. Dr. Klaus Heese





Neurons – Structure & Functions

Neuron structures



Examples of various types of neurons showing the dendrites, somata, and axons of multipolar cells from the cerebellar cortex (A) and from the cerebral cortex (B and C). Compare these with a pseudounipolar cell of the dorsal root ganglion (D), and bipolar cells from the retina (E) and olfactory epithelium (F)

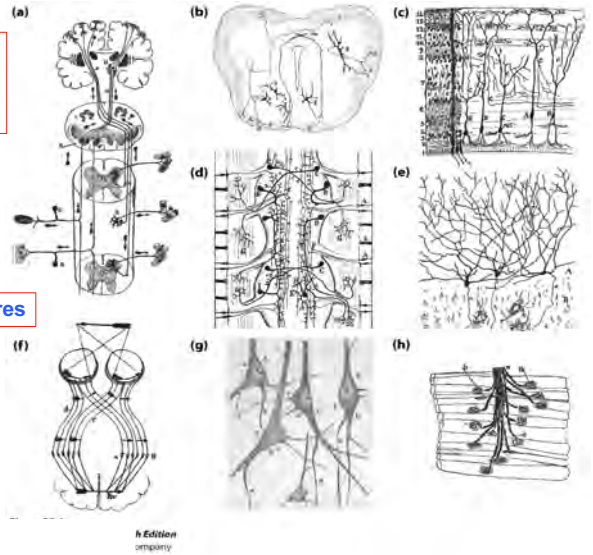
A Few of the Neuronal Types Found in the Nervous System

Type of Neuron	Location of Cell Bodies
Pseudounipolar	Posterior root or cranial nerve ganglion
Bipolar	Retina Olfactory epithelium Vestibular ganglion Auditory (spiral) ganglion
Multipolar	
Stellate ("star-shaped")	Many areas of CNS
Fusiform ("spindle-shaped")	Many areas of CNS
Pyriform ("pear-shaped")	Many areas of CNS
Pyramidal	Hippocampus; layers II, III, V, and VI of cerebral cortex
Purkinje	Cerebellar cortex
Mitral	Olfactory bulb
Chandelier	Visual areas of cerebral cortex
Granule	Cerebral and cerebellar cortex
Amacrine ("axonless")	Retina

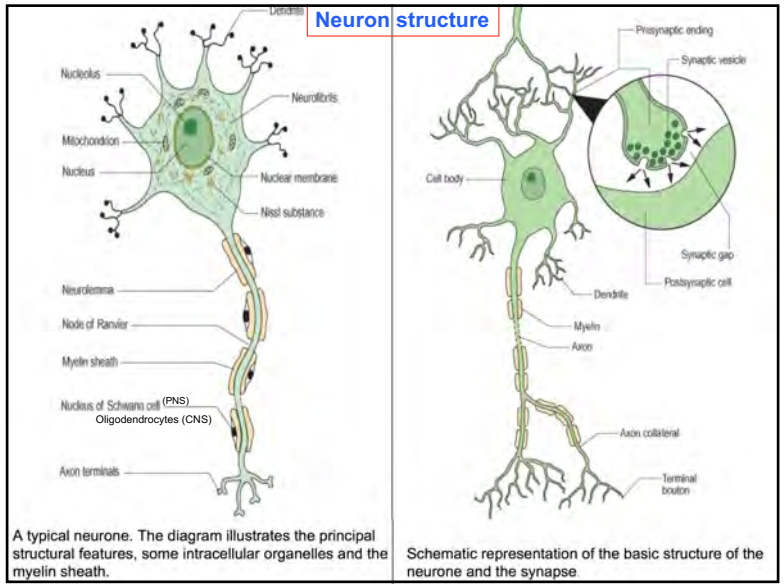
CNS, central nervous system.

Examples of various CNS neurons

Neuron structures



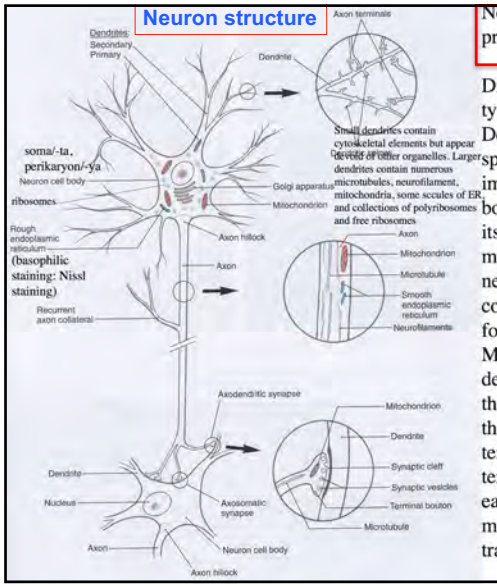
Neuron structure



A typical neurone. The diagram illustrates the principal structural features, some intracellular organelles and the myelin sheath.

Schematic representation of the basic structure of the neurone and the synapse

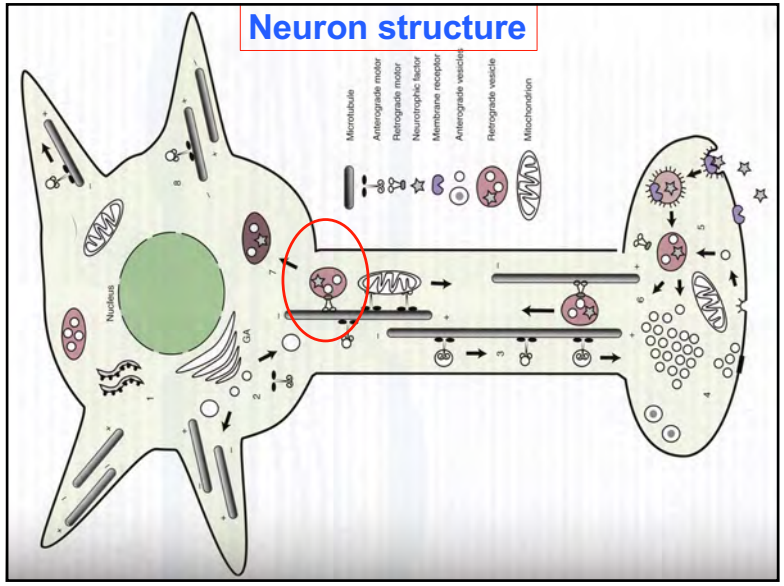
Neuron structure



Neurons: 3 tasks: receiving, processing & sending information.

Diagrammatic representation of a typical multipolar neuron. Dendrites, with their variety of spines (upper detail), branch in the immediate vicinity of the cell body, while the single axon, with its occasional recurrent collaterals, may travel great distances to the next neuron. The cell body contains the organelles essential for neuronal function. Microtubules (middle and lower details) are important structures for the transport of substances within the axon. The axon ends as a terminal arbors that forms many terminal boutons (lower detail), each containing the necessary machinery for synaptic transmission.

Neuron structure



Characteristics of Axonal Transport

Direction of Transport	Speed of Transport	Proposed Mechanism	Substances Carried
Anterograde	Fast (100–400 mm/day)	Kinesin/microtubules (ATPase)	Proteins in vesicles
		Neurotransmitters in vesicles, mitochondria	
	Slow (~1 mm/day)	Unknown	Cytoskeletal protein components (actin, myosin, tubulin) Neurotransmitter-related cytosolic enzymes
Retrograde	Fast (50–250 mm/day)	Dynein/microtubules	Macromolecules in vesicles, "old" mitochondria Pinocytotic vesicles from axon terminal
			Receptor-mediated endocytosis (growth factors)

Major microtubule proteins and microtubule motors in mammalian brain

Tubulins	
α- and β-tubulins	Neurons, glia, and nonneuronal cells except mature mammalian erythrocytes. Multigene family with some genes expressed preferentially in brain, whereas others are ubiquitous. Primary structural polypeptides of microtubules
γ-Tubulin	Present in all microtubule-containing cells, but restricted to region of microtubule-organizing center. Needed for nucleation of microtubules
Microtubule-associated proteins (MAPs)	
MAP-1a/1b	Widely expressed in neurons and glia, including both axons and dendrites. Forms are developmentally regulated phosphoproteins.
MAP-2a/2b MAP-2c	Dendrite-specific MAPs. The smaller MAP-2c is, regulated developmentally, becoming restricted to spines in adults, whereas 2a and 2b are major phosphoproteins in adult brain
LMW tau HMW tau	Tau proteins are enriched in axons and have a distinctive phosphorylation pattern in the axon, but may be found in other compartments. A single gene with multiple forms due to alternative splicing. The HMW tau is found in adult peripheral axons
Motor proteins	
Kinesin Neuron-specific kinesin	Present in all microtubule-containing cells. Associated with membrane-bound organelles and serves to move them along microtubules in fast axonal transport. The neuron-specific form is the product of a specific gene expressed in nervous tissue
Kinesin-related proteins	A diverse set of motor proteins with a kinesin-related motor domain and varied tails. Some are regulated developmentally and some are restricted to dividing cells, where they act as mitotic motors.
Axonemal dynein Cytoplasmic dynein (MAP-1c)	A set of minus-end-directed microtubule motors. Axonemal forms are associated with cilia and flagella. In nervous tissue, these may be associated with the ependyma. Cytoplasmic forms may be involved in the transport of either organelles or cytoskeletal elements

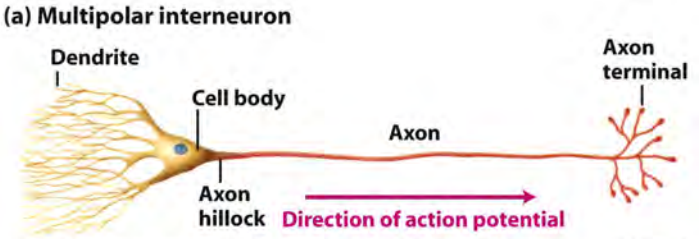
Functional and morphological hallmarks of Axons and Dendrites

Axons	Dendrites
With rare exceptions, each neuron has a single axon	Most neurons have multiple dendrites arising from their cell bodies
Axons appear first during neuronal differentiation	Dendrites begin to differentiate only after the axon has formed
Axon initial segments are distinguished by a specialized plasma membrane containing a high density of ion channels and distinctive cytoskeletal organization	Dendrites are continuous with the perikaryal cytoplasm, and the transition point cannot be distinguished readily
Axons typically are cylindrical in form with a round or elliptical cross section	Dendrites usually have a significant taper and small spinous processes that give them an irregular cross section
Large axons are myelinated in vertebrates, and the thickness of the myelin sheath is proportional to the axonal caliber	Dendrites are not myelinated, although a few wraps of myelin may occur rarely
Axon caliber is a function of neurofilament and microtubule numbers with neurofilaments predominating in large axons	The dendritic cytoskeleton may appear less organized, and microtubules dominate even in large dendrites
Microtubules in axons have a uniform polarity with plus ends distal from the cell body	Microtubules in proximal dendrites have mixed polarity, with both plus and minus ends oriented distal to the cell body
Axonal microtubules are enriched in tau protein with a characteristic phosphorylation pattern	Dendritic microtubules may contain some tau protein, but MAP2 is not present in axonal compartments and is highly enriched in dendrites
Ribosomes are excluded from mature axons, although a few may be detectable in initial segments	Both rough endoplasmic reticulum and cytoplasmic polysomes are present in dendrites, with specific mRNAs being enriched in dendrites
Axonal branches tend to be distal from the cell body	Dendrites begin to branch extensively near the perikaryon and form extensive arbors in the vicinity of the perikaryon
Axonal branches form obtuse angles and have diameters similar to the parent stem	Dendritic branches form acute angles and are smaller than the parent stem
Most axons have presynaptic specializations that may be *en passant* or at the ends of axonal branches	Dendrites are rich in postsynaptic specializations, particularly on the spinous processes that project from the dendritic shaft
Action potentials are usually generated at the axon hillock and conducted away from the cell body	Some dendrites can generate action potentials, but more commonly they modulate the electrical state of the perikaryon and initial segment
Traditionally, axons are specialized for conduction and synaptic transmission, i.e., neuronal output	Dendritic architecture is most suitable for integrating synaptic responses from a variety of inputs, i.e., neuronal input

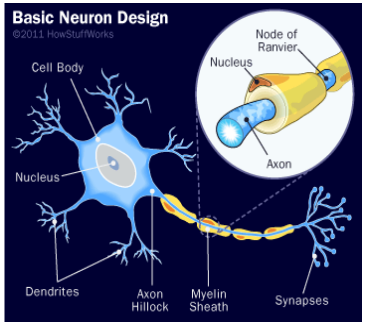
Neuron structure & Functions

Neurons and the Action Potential

Neuron structure



Neuron structure



***Cell Body**

·Has all of the necessary components of the cell
-nucleus (which contain DNA)
-endoplasmic reticulum and ribosomes
-mitochondria

·If the cell body dies, the neuron dies

***Dendrites**

·Makes connection and communicates with other cell

·Can be located on one of both end of a cell

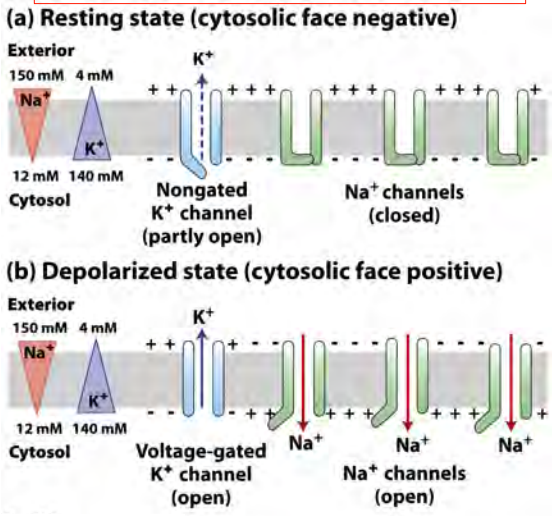
***Axon**

·Carries the electrochemical message

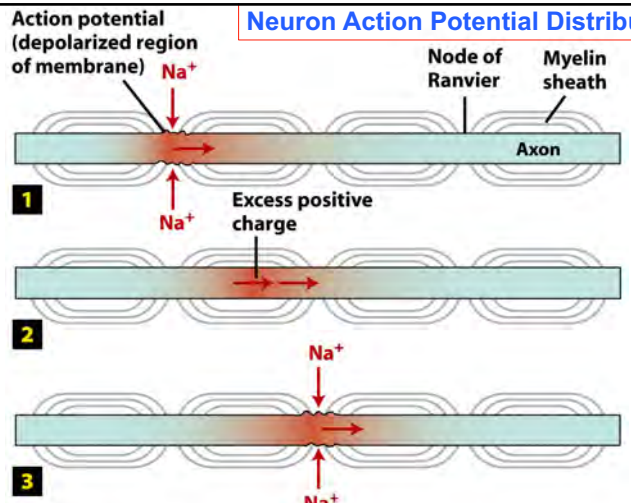
·Covered with a myelin sheath
-myelin is made of fat and protein
-it helps to speed transmission of a nerve impulse

·Myelinated neurons; peripheral nerves
Non- myelinated neurons; brain and spinal cord

Neuron Membrane Potential

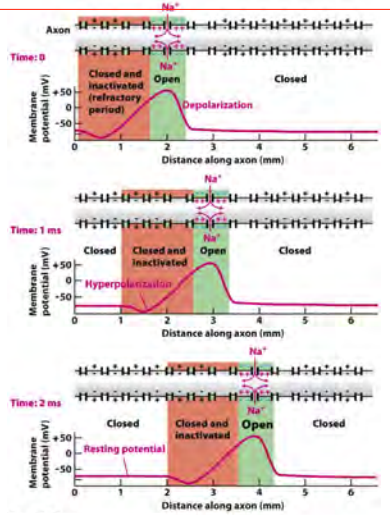


Neuron Action Potential Distribution



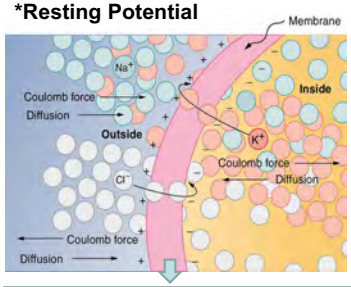
The jumping of action potentials from node to node (node of Ranvier) is referred to as saltatory conduction. Entering sodium ions are repelling positive ions to push a chain of positive ions along the axon to initiate an action potential at the next node.

Neuron Action Potential Distribution



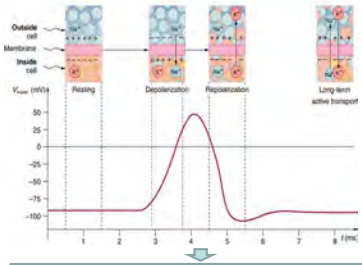
Neuron Action Potential

***Resting Potential**



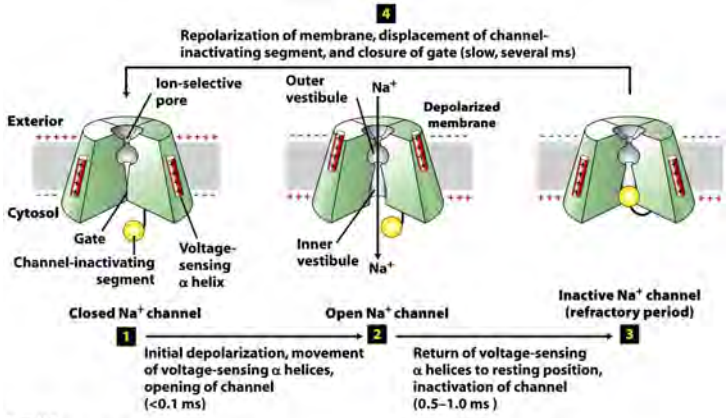
- Semipermeable
- Different concentrations of ions
- Diffusion moves K+, Cl-
- Coulomb force halts further transfer
- Positive charge on the outside, negative charge on the inside

***Action Potential**

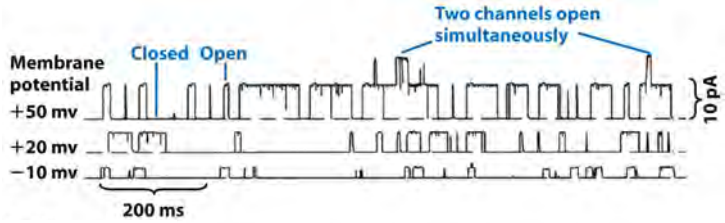


Deporlarization ➡ Repolarization ➡ Hyperpolarization ➡ Resting state

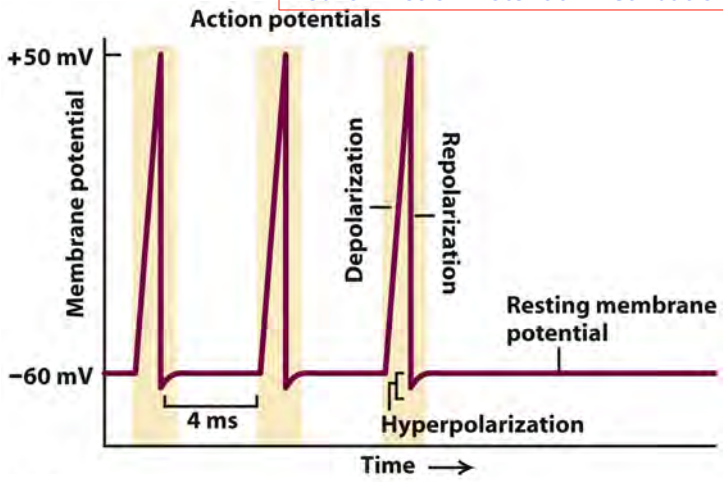
Neuron Action Potential Distribution



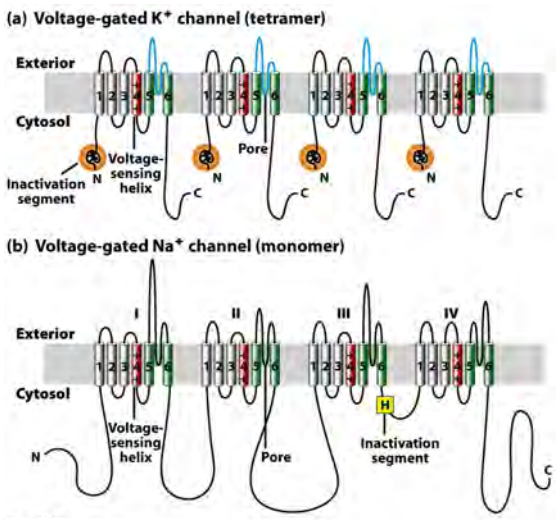
Neuron Action Potential Distribution



Neuron Action Potential Distribution



Neuron Action Potential Distribution



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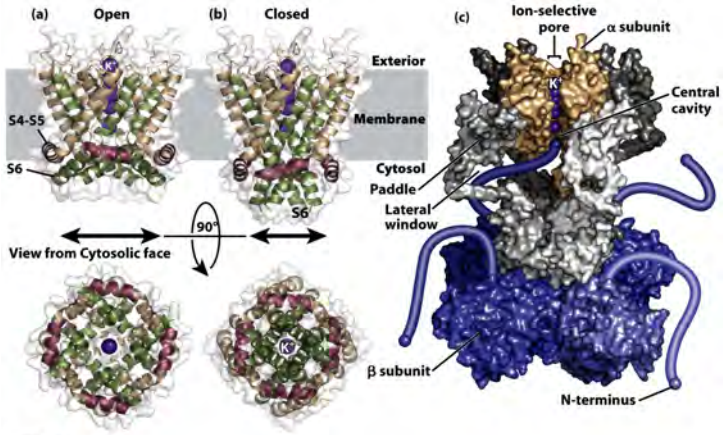
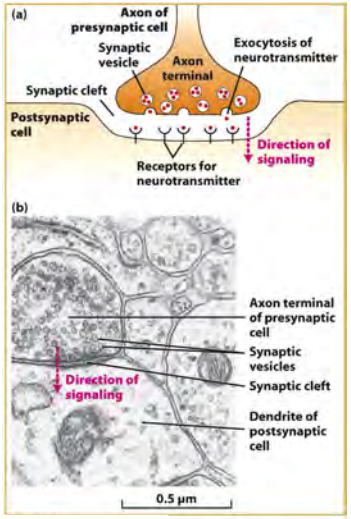
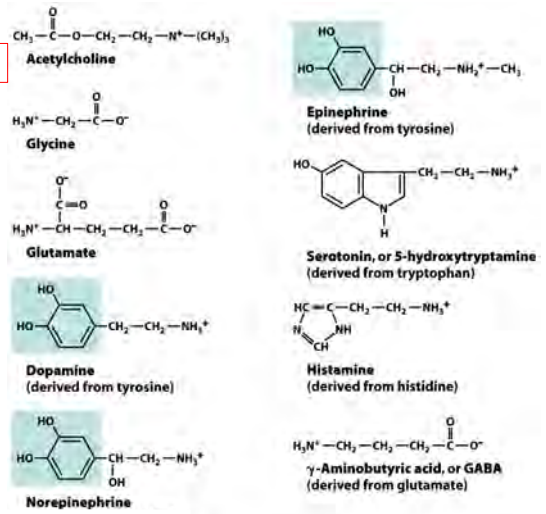


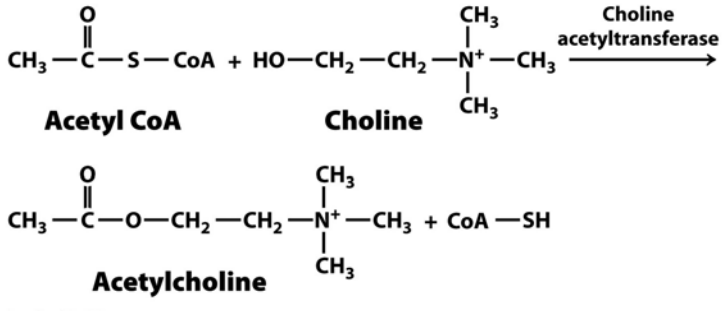
Neuron Synapses



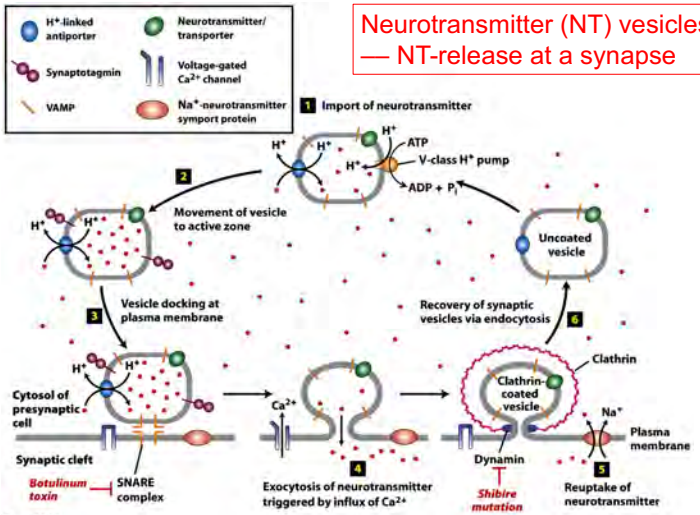
Neurotransmitters



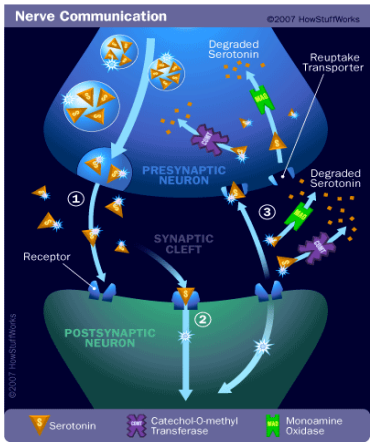
Neurotransmitters



Neurotransmitter (NT) vesicles — NT-release at a synapse



Neuron Synapses – Synaptic Transmission

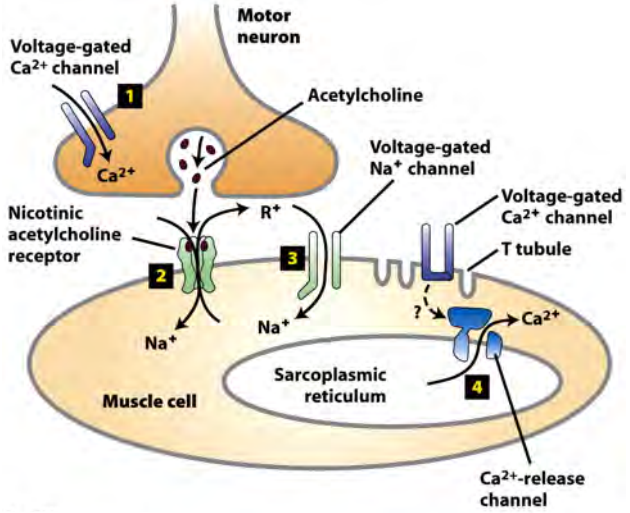


1. The presynaptic cell makes serotonin and packages it in vesicle.
2. An action potential passes down the presynaptic cell into its end terminals.
3. Serotonin passes across synaptic cleft, binds with receptors and sets up a depolarizaton.

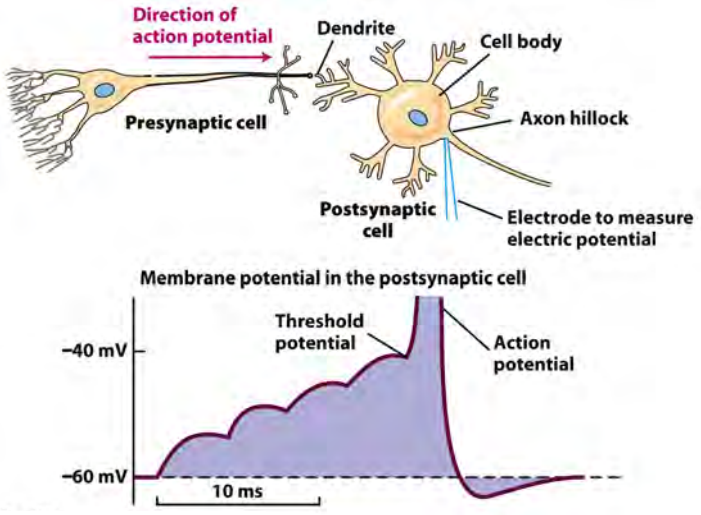
※ The remaining serotonin molecules get destroyed by enzymes. Some get taken up by specific transporters. This readies the synapse to receive another action potential.

※ Besides serotonin, acetylcholine, norepinephrine, dopamine and gamma-amino

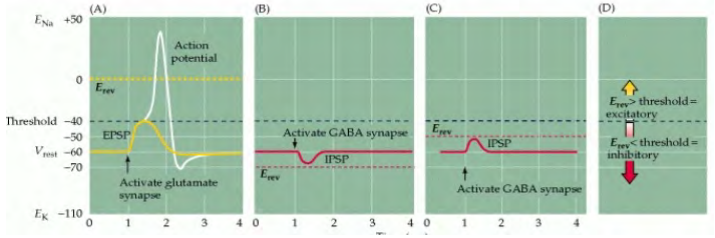
Neuron Synapses – Synaptic Transmission



Neuron Synapses – Synaptic Transmission



Neuron Synapses – Synaptic Transmission

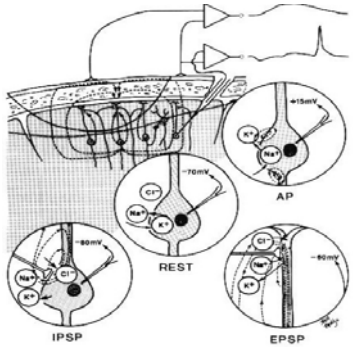


***EPSP**
- Glutamate-gated channels
- Influx of Na+
- Depolarization of the postsynaptic neuron
- Likely to carry an action potential

***IPSP**
- GABA & Glycine-gated channels
- Influx of Cl-
- Hyperpolarization of the postsynaptic neuron
- further from the threshold

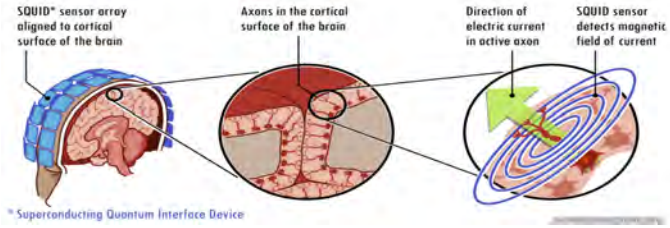
Brain Waves

Brain waves are a byproduct of EPSPs and IPSPs ,not a direct measurement of action potentials.



EEG-Eletroencephalogram

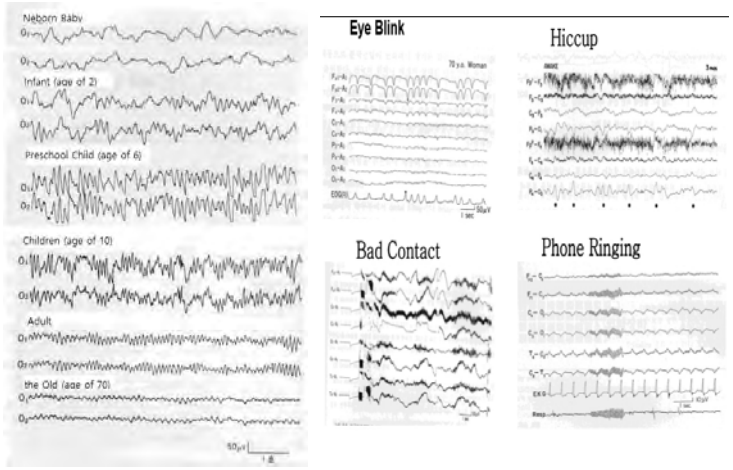
***How it works**



***Features**

- Reflect the information process of Neurons
- Diagnosis of diseases related to the brain function
- Not expensive. Non Invasive.

EEG waveforms



***Practical Use of EEG**

·Diagnostics of Brain Diseases

- Infantile mental disorder

  : learning disability, dyslexia, autism

- Functional mental disorder

  : obsessive compulsive neurosis, dysphasia

- Alzheimer's disease: early detection for brain atrophy

·Research of Brain Function

- Cognitive science: memory, learning, linguistic facility, sensitivity

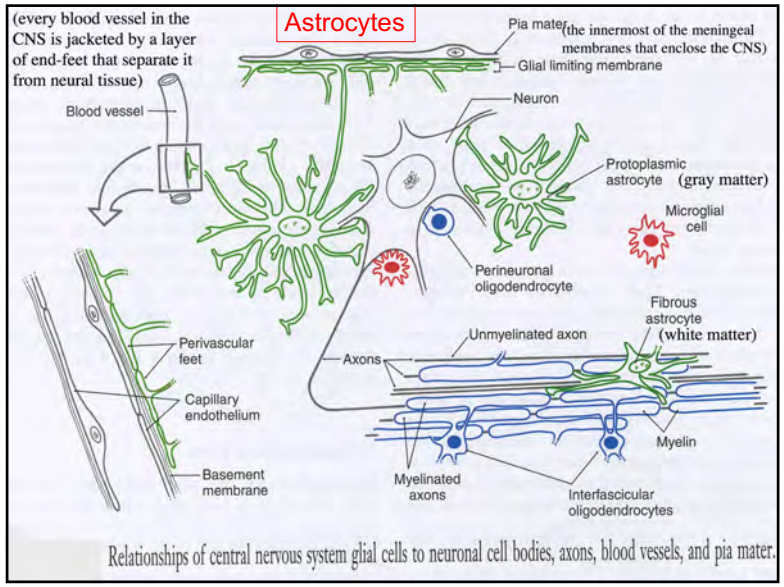
- Higher sensory sensor and motor sensor

GLIA Cells

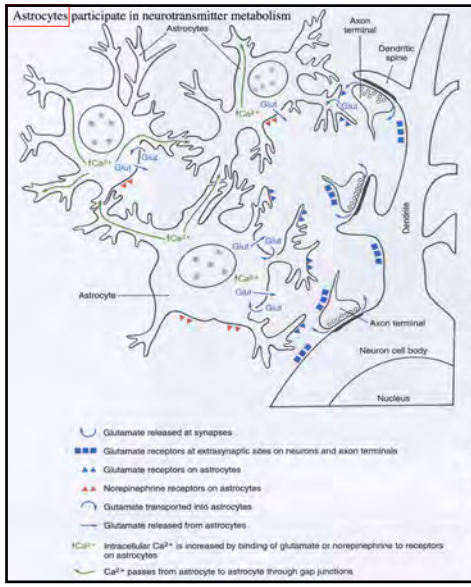
Types of Glial Cells and Their Locations and Functions

Cell Type	Location	Function(s)
CNS		
Astrocytes	Throughout the CNS; contact neuronal cells bodies, dendrites, and axons and form a complete lining around the external surfaces of the CNS and around CNS blood vessels; gray matter astrocytes are called *protoplasmic* and white matter astrocytes are called *fibrous*	Maintenance of extracellular ionic environment; secretion of growth factors; structural and metabolic support of neurons
Oligodendrocytes		
Myelinating	Form myelin sheaths around CNS axons	Myelination
Satellite cells	Surround CNS neuronal cell bodies	Unknown
Microglia	Gray and white matter of CNS	Scavenging and phagocytosis of debris following cell injury and death; secretion of cytokines
PNS		
Schwann cells	Form myelin sheaths around myelinated axons and ensheath unmyelinated axons	Myelination; biochemical and structural support of myelinated and unmyelinated axons
Satellite cells	Surround neuronal cell bodies in PNS ganglia	Unknown

CNS, central nervous system; PNS, peripheral nervous system.



Relationships of central nervous system glial cells to neuronal cell bodies, axons, blood vessels, and pia mater.



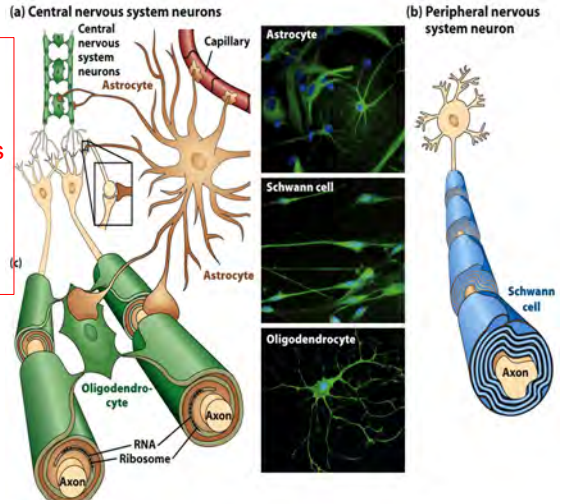
Astrocytes participate in neuronal transmission. Glutamate diffusing from active synapses (blue arrows) is taken up by astrocytes (Glu, curved arrows) to be metabolized to glutamine. Astrocyte cell surface receptors (blue and red triangles) also respond to the neurotransmitters glutamate and noreinephrine, increasing intracellular calcium (green ascending up arrowheads). The calcium increase passes via gap junction to neighboring astrocytes (green long arrows). The increase in intracellular calcium causes astrocytes to release small amounts of glutamate (Glut, straight arrows), which then affects extrasynaptic glutamate receptors (blue boxes) on neighboring neurons. Activation of extrasynaptic glutamate receptors modulates presynaptic transmitter release and postsynaptic neurons' responses (EPSPs and IPSPs) to synaptic transmission.

Myelinating glia cells:

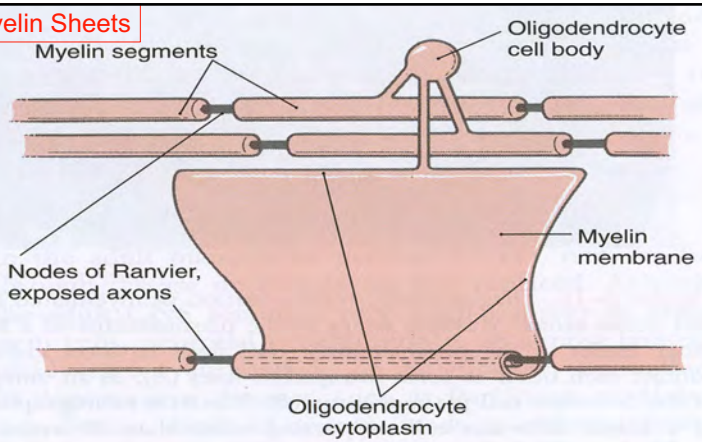
Oligodendrocytes

&

Schwann cells

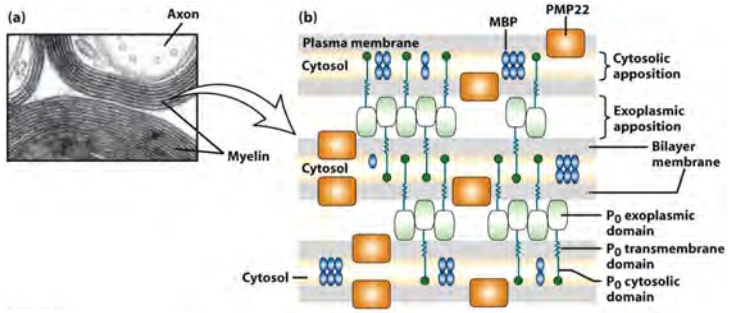


Myelin Sheets

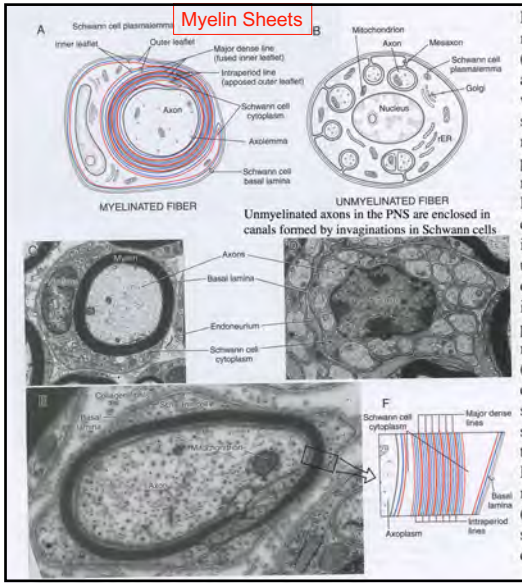


Myelin sheath formation by processes of an oligodendrocyte. The cytoplasm of the oligodendrocyte is trapped on the edges of the cell membrane as it wraps around the axon.

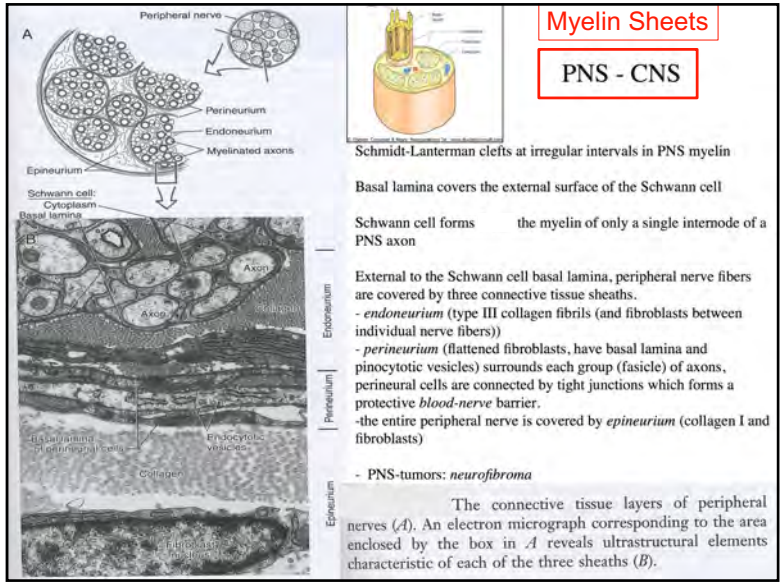
Myelin Sheets



Myelin Sheets



Diagrammatic representation of myelinated (A) and unmyelinated (B) fibers. Schwann cells ensheath all peripheral nerve axons. Multiple wraps of the plasmalemma of a schwann cell fuse to form compact myelin. The inner leaflet of the plasmalemma (red) fuses to form major dense lines, and the outer leaflets (blue) of each adjacent wrap contact each other to form intraperiod lines (A). In an unmyelinated fiber, small axons occupy troughs formed by invaginations of the Schwann cell plasmalemma (B). Electron micrographs of a myelinated fiber (C) and an unmyelinated fiber (D) composed of a single Schwann cell supporting more than 20 axons. A small myelinated fiber sectioned through part of a Schmidt-Lantermann cleft reveals the membrane composition of myelin (E). The layers of the boxed segment of myelin in 'E' are diagrammed in 'F'.



Microglia: 'Immune cells' of the CNS

Four different sources:
a) Bone marrow-derived monocytes
b) Mesodermal pial elements
c) Neural epidermal cells
d) Capillary-associated pericytes

- Phagocytose degenerating (apoptotic) cells
- Immunophenotypic properties of monocytes/macrophages
- release cytokines, growth factors, neurotrophins
- 'reactive' microglia change their morphology and protein expression pattern.
- Activated in neurodegenerative conditions (Alzheimer's disease)

Brain Energy

The nervous system, compared with other organs, is the greatest consumer of oxygen and glucose.
The fact that, in a resting adult, about 40 % of the total energy consumption is required for ion pumping in the CNS accounts for the exquisite sensitivity of the brain to damage from oxygen deprivation.
Brain: 2% of body weight but 25% of total body glucose utilization.

----> **brain:** 2% of body weight only

----> 15% of cardiac output

----> 700ml/minute or ~57ml/100g of brain tissue/minute

----> 25% of total glucose consumption

----> 20% of total oxygen consumption of the whole organism (~160μmol/100g brain tissue/min)

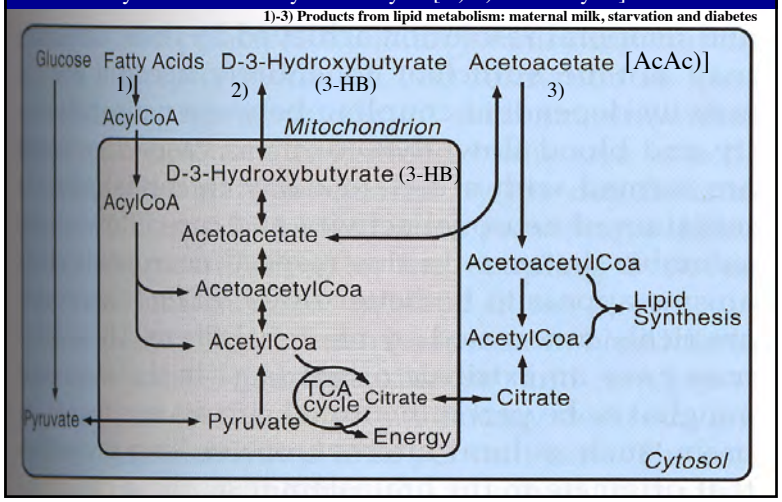
----> 40% of the total energy consumption is required for ion-pumping in the CNS

----> respiratory quotient = O_2-consumption/CO_2-production ~1

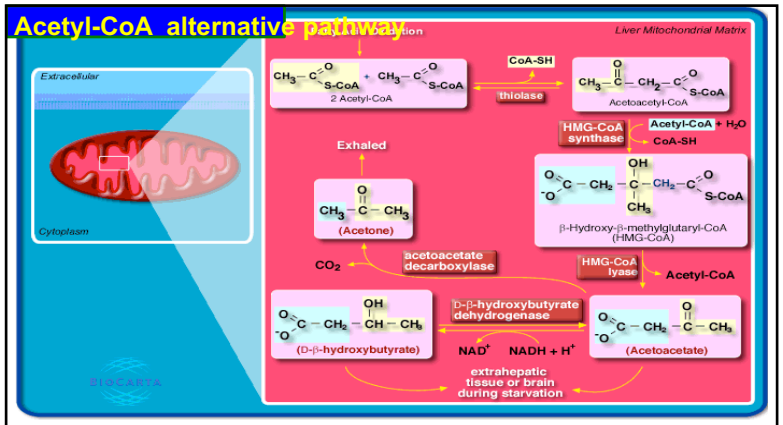
----> carbohydrates, glucose are the exclusive substrates for oxidative metabolism

'Ketone-bodies' as energy substrates for the brain

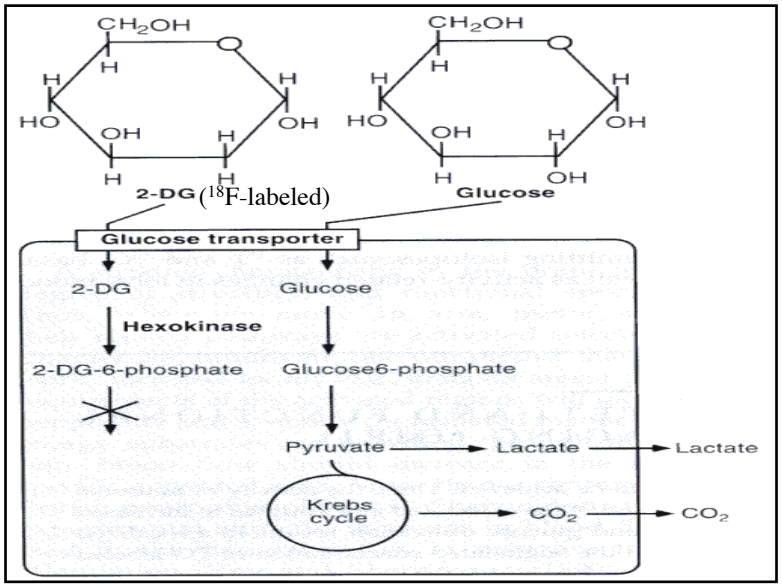
Ketone-bodies [2)&3)] oxidized in neurons, astrocytes and oligodendrocytes; but free fatty acids exclusively in astrocytes [1)-3) in astrocytes]

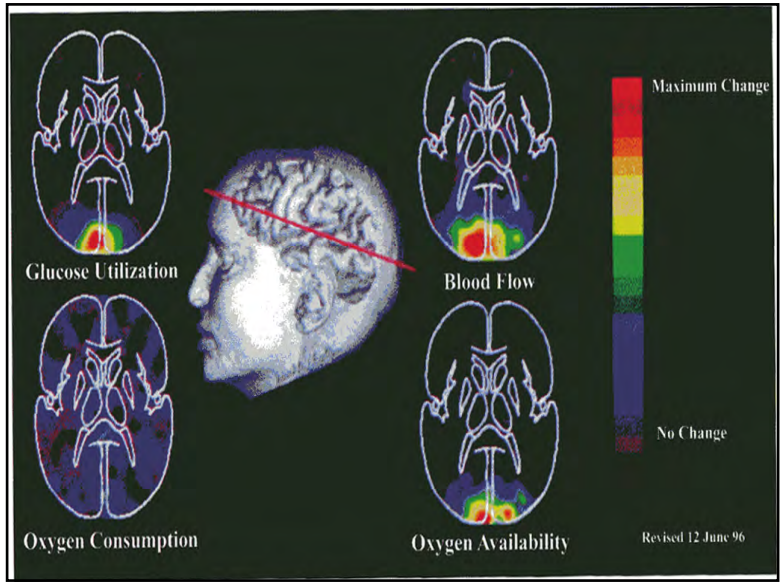


Acetyl-CoA alternative pathway



The acetyl-CoA produced by mitochondrial beta-oxidation of fatty acids enters the Kreb's cycle to produce energy, but that is not the only fate of acetyl-CoA. In liver mitochondria, some acetyl-CoA is converted to acetoacetate, beta-hydroxybutyrate, and acetone, collectively called ketone bodies. Ketone bodies are transported to other tissues such as brain, muscle or heart where they are converted back to acetyl-CoA to serve as an energy source. The brain normally uses only glucose for energy, but during starvation ketone bodies can become the main energy source for the brain. In the metabolic condition called ketosis, ketone bodies are produced faster than they are consumed by tissues and the smell of acetone can be detected on a person's breath. The smell of acetone is one indication that a person may have diabetes. The consumption of high-fat/low carbohydrate diets has been used as a weight loss program by many, intentionally inducing ketosis to consume fat stores, but these ketogenic diets can cause unwanted side effects related to increased urea production resulting from protein intake and risk of heart disease from increased cholesterol and fat intake.





Mediators of coupling Neuronal Activity to CBF

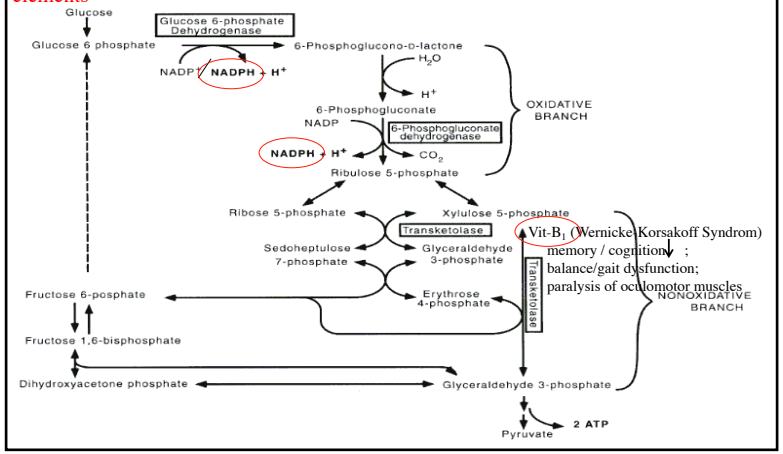
1) - K^+, adenosine, lactate, pH,
2) - Neurotransmitters: NE, 5-HT, ACh
3) - Peptides: neuropeptide-Y (NPY),
vasoactive intestinal peptide (VIP)
calcitonin gene-related peptide (CGRP),
substance-P (SP),

[2), 3) = *neurogenic mechanisms*]
and:
- NO

Regulation of cerebral blood flow is achieved mainly by control of the tone or the degree of constriction, or dilation, of the cerebral vessels. This in turn is controlled mainly by local chemical factors such as: $PaCO_2$, PaO_2, pH, …

$PaCO_2 \uparrow$, $PaO_2 \downarrow$, $pH \downarrow$, ---> dilate the blood vessels ---> blood flow $\uparrow$

In cells of the brain (as in other organs) reducing energy power is needed and provided by the reduced form of NADPH. The processing of glucose through the **Pentose Phosphate pathway** produces NADPH which is needed, e.g., for synthesis of free fatty acids from acetyl-CoA, which are components of myelin and other neuronal structural elements

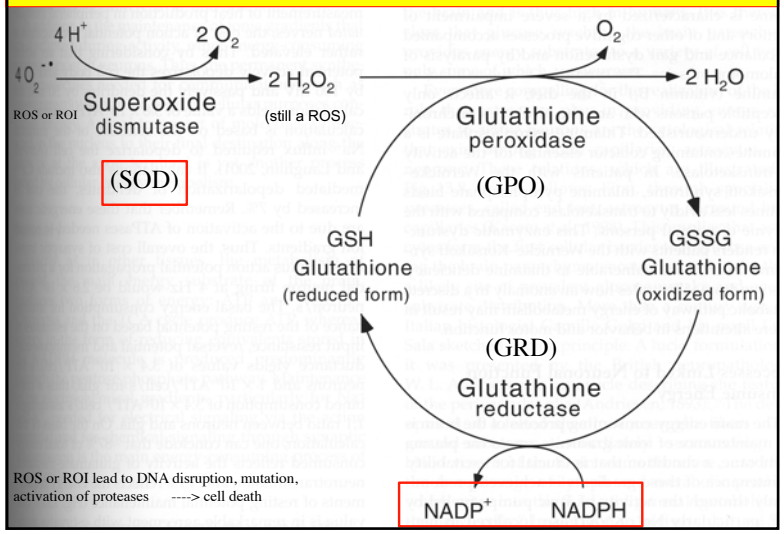


NADPH is also needed for the scavenging of reactive oxygen species (ROS)

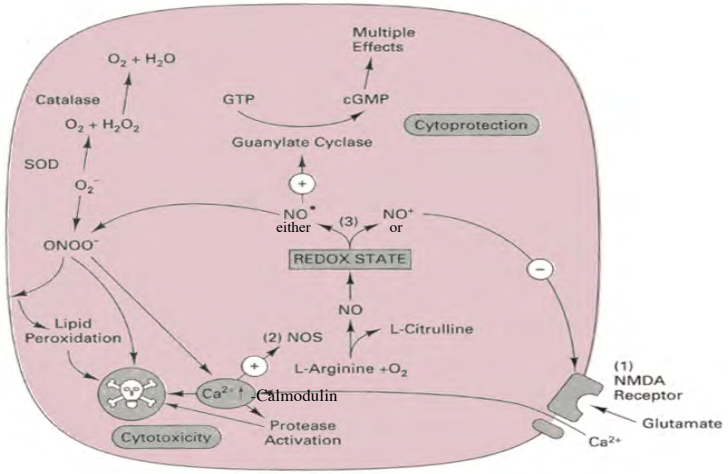
Superoxide anion, hydrogen peroxide, hydroxy radical generated as 'by-products' of certain physiological cellular processes:
Oxidative phosphorylation and activities of:
monoamine oxidase (MAO), tyrosine hydroxylase (TH),
nitric oxide synthase (NOS), cyclooxygenase (COX), lipoxigenase (lox)

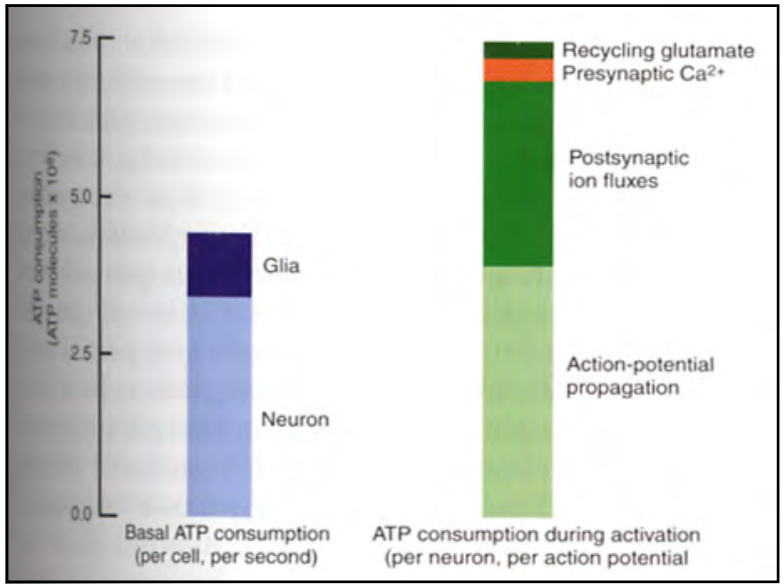
(regeneration of NAD+ from NADH must be accomplished through the conversion of pyruvate to lactate and a hydrogen ion via lactate dehydrogenase. Because this pathway is inefficient - yielding 2 molar equivalents of ATP of each mole of glucose consumed versus ~30-38 mol ATP generated under aerobic conditions - ATP production falls as levels of lactate and hydrogen ions rise and local pH levels drop.)

ROI inactivation and S-S in RedOx Reactions



Postulated mechanism whereby NO causes cytotoxicity or cytoprotection in nervous tissue





40 % energy consumption in resting body for ion-pumping in the CNS. Na^+/K^+-ATPase in neurons/glia

The main energy consuming process of the brain is the maintenance of ionic gradients across the plasma membrane, a condition that is crucial for excitability.

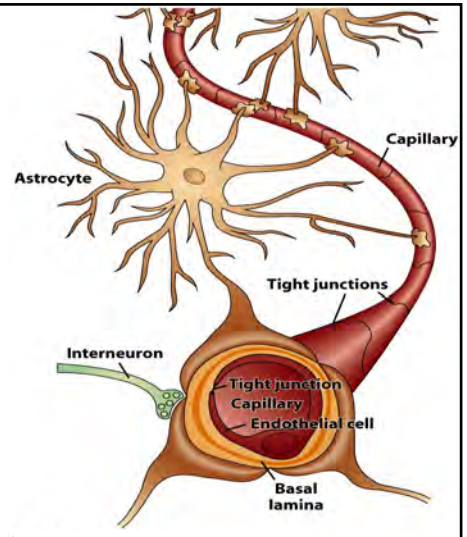
Activity of these pumps accounts for approximately 50% of basal glucose oxidation in the nervous system.

Other energy-consuming processes:
neurotransmitter synthesis, axonal transport, …

Oxidases/oxygenases/hydroxylases (e.g.: TH), utilize O_2 and incorporate it into hydroxyl groups; or MAO which deaminates oxidatively monoamine neurotransmitters to aldehydes.

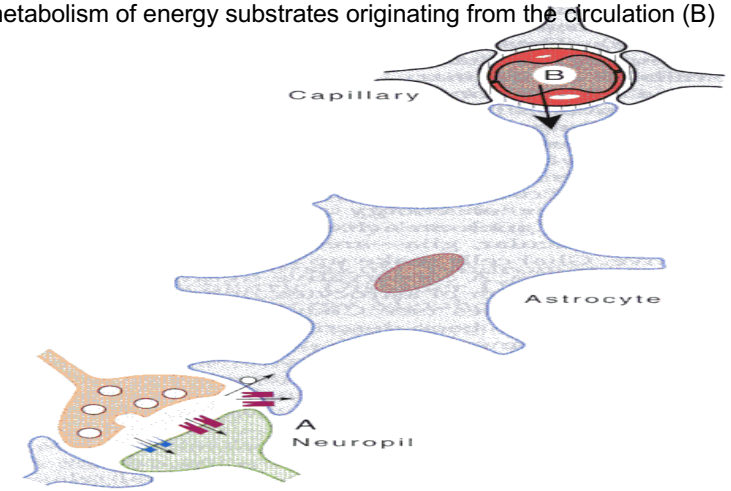
Pentose phosphate pathway provides reducing power (NADPH) for (e.g.) scavenging of ROS. … Wernicke-Korsackoff syndrome.

Astrocytes as mediators between capillaries and neuropil



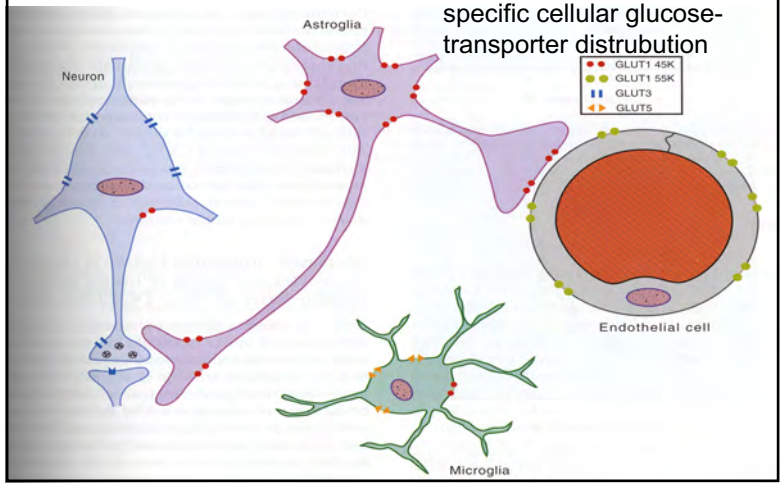
Astrocytes as mediators between capillaries and neuropil

Astrocytes sense synaptic activity (A) and couple it with uptake and metabolism of energy substrates originating from the circulation (B)

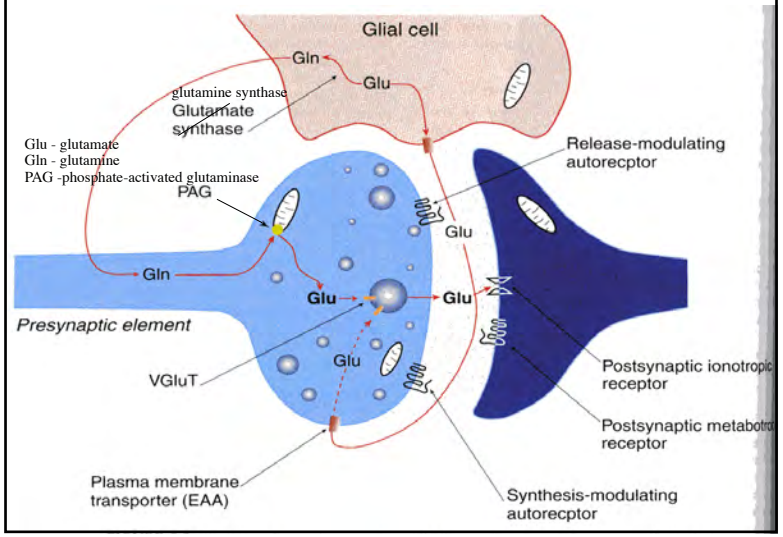


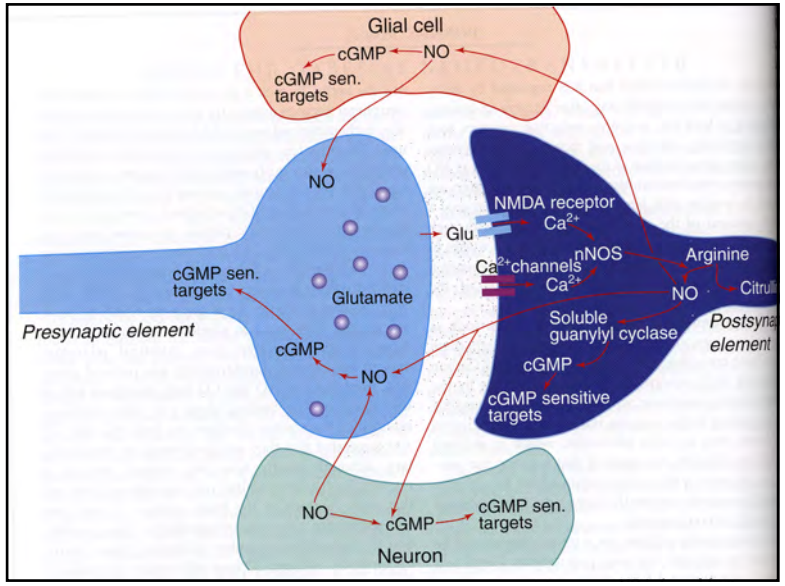
in brain: ~ 0.5-2.0 mM glucose in extracellular space; basal rate of glucose utilization is higher in astrocytes than in neurons, with values of about 20 and 6 nmol per milligram of protein per minute, respectively.

specific cellular glucose-transporter distrubution



Glutamate in neurons and astrocytes





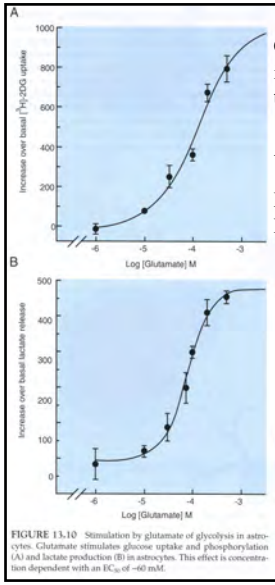


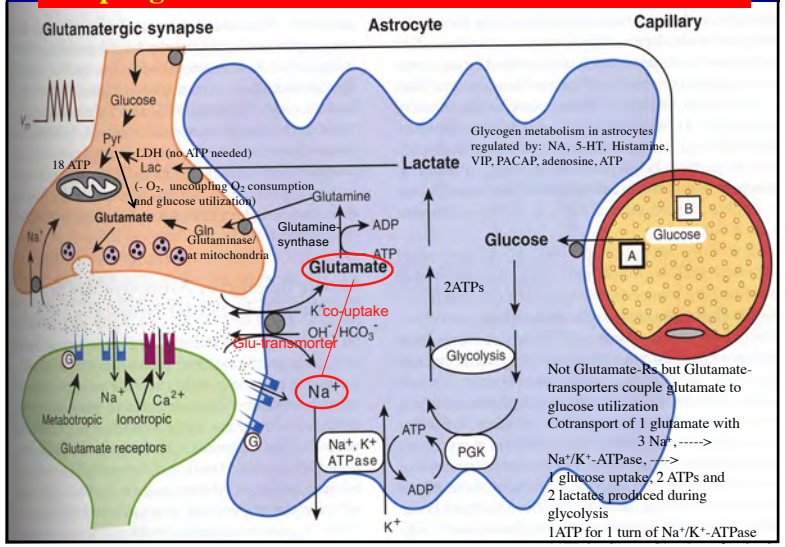
FIGURE 13.10 Stimulation by glutamate of glycolysis in astrocytes. Glutamate stimulates glucose uptake and phosphorylation (A) and lactate production (B) in astrocytes. This effect is concentration dependent with an EC_{50} of ~60 mM.

Glutamate stimulates glucose uptake and phosphorylation in a dose-dependent manner mediated by glucose-transporters.

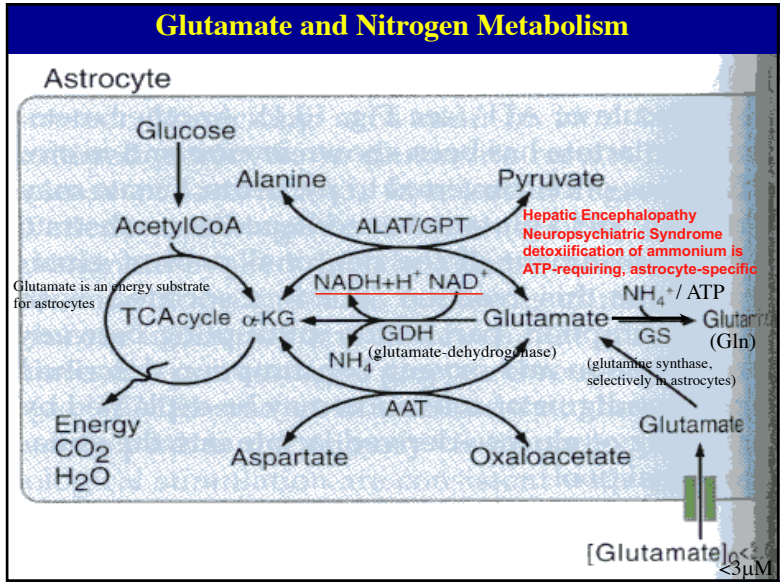
Additional functions of astrocytes:

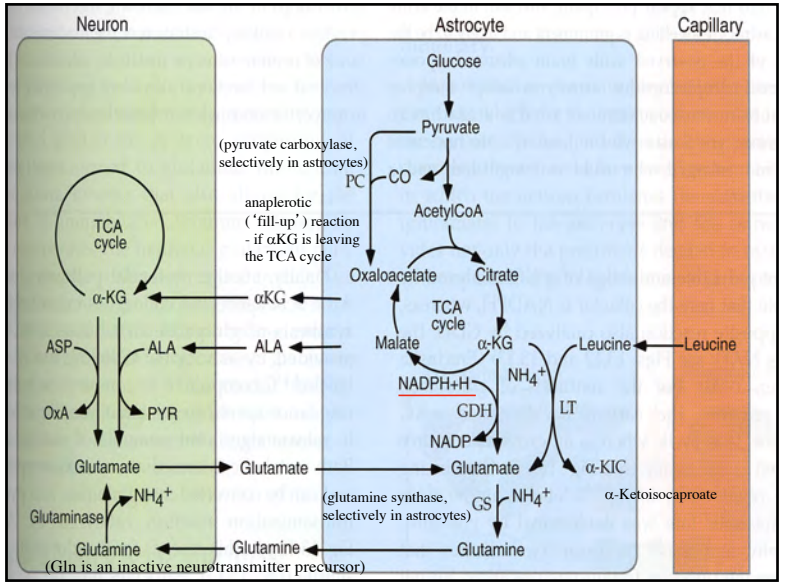
Maintenance of extracellular K^+-homeostasis
Neurotransmitter-uptake

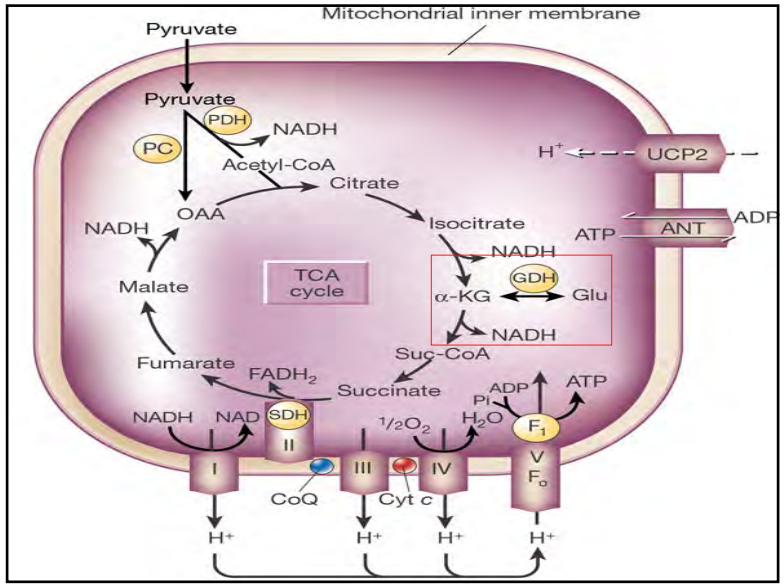
Coupling of Glutamate Action and Glucose Utilization



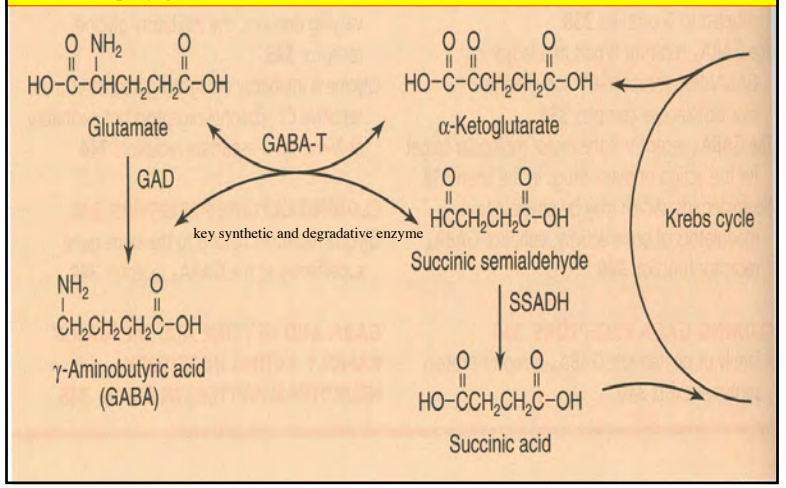
lactate formed within the brain parenchyma (e.g., through glutamat-activatcd glycolysis in astrocytes) can fulfill the energetic needs of neurons. Lactate, after conversion into pyruvate by a reaction catalyzed by lactate dehydrogenase (LDH), can provide, on a molar basis, 18 ATP through oxidative phosphorylation. Conversion of lactate into pyruvate does not require ATP, and, in this regard, lactate is energetically more favorable than the first obligatory step of glycolysis in which glucose is phosphorylated to glucose 6-phosphate at the expense of one molecule of ATP. Another metabolic fate for lactate has been shown *in vitro* and *in vivo* by MRS. Thus, once converted to pyruvate, lactate may enzymatically yield glutamate and hence be a substrate for the replenishment of the neuronal pool of glutamate. Because this reaction is not associated with oxygen consumption, part of the uncoupling between glucose utilization and oxygen consumption described in certain paradigms of activation may be explained by the processing of glucose-derived lactate into the glutamate neuronal pool.







Major difference between catecholamines and amino acid neurotransmitters
the latter are derived from glucose metabolism and
are taken up by glia and neurons



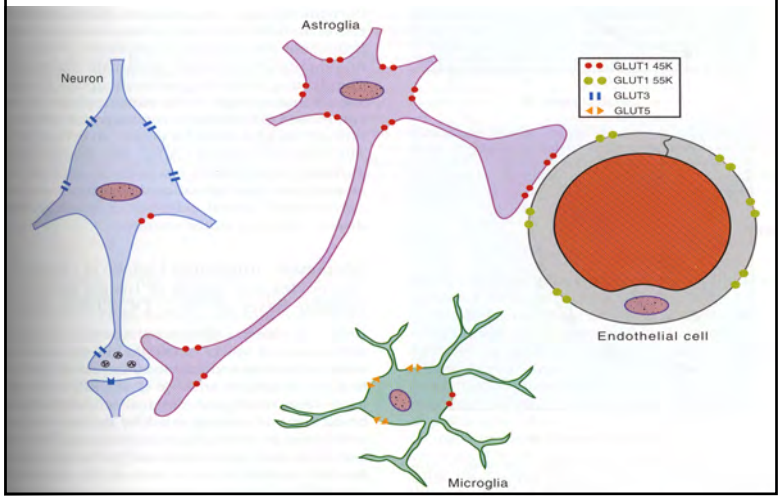
Taking home message:

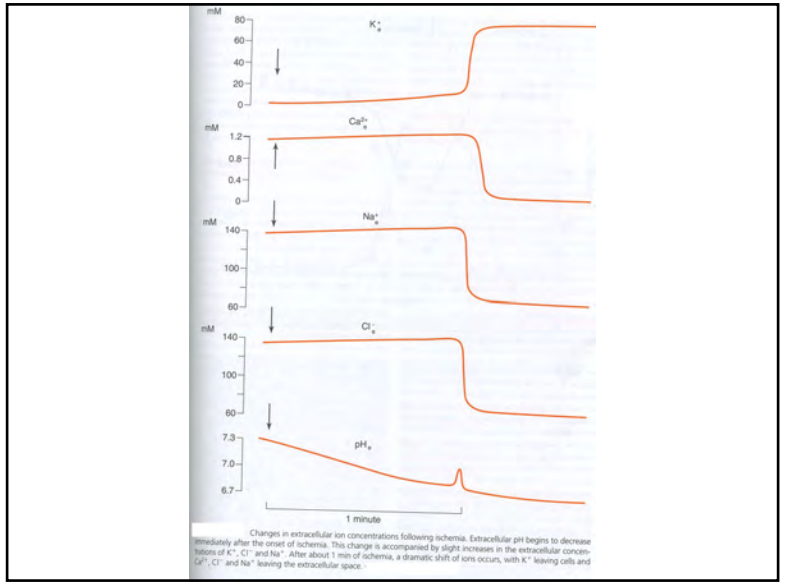
- main energy consuming process of the brain is?
- Wernicke-Korsackoff syndrome
- Coupling of Glutamate Action and Glucose Utilization

Ischemia

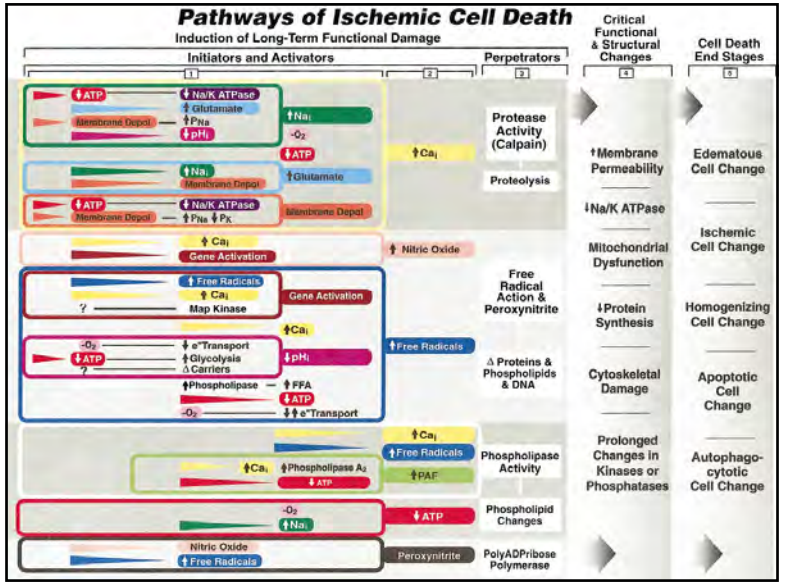
Q) Which mechanisms may contribute to ischemia-mediated neurodegeneration in the brain?

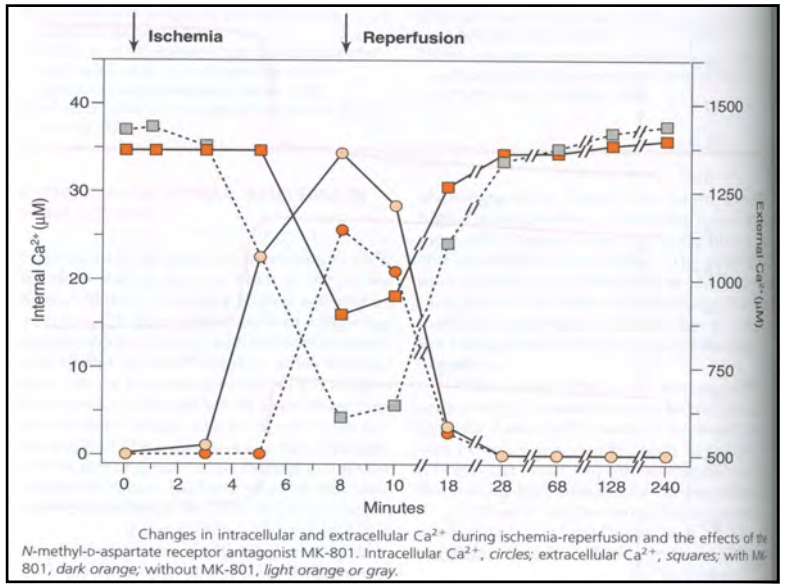
in brain: ~ 0.5-2.0 mM glucose in extracellular space; basal rate of glucose utilization is higher in astrocytes than in neurons, with values of about 20 and 6 nmol per milligram of protein per minute, respectively.



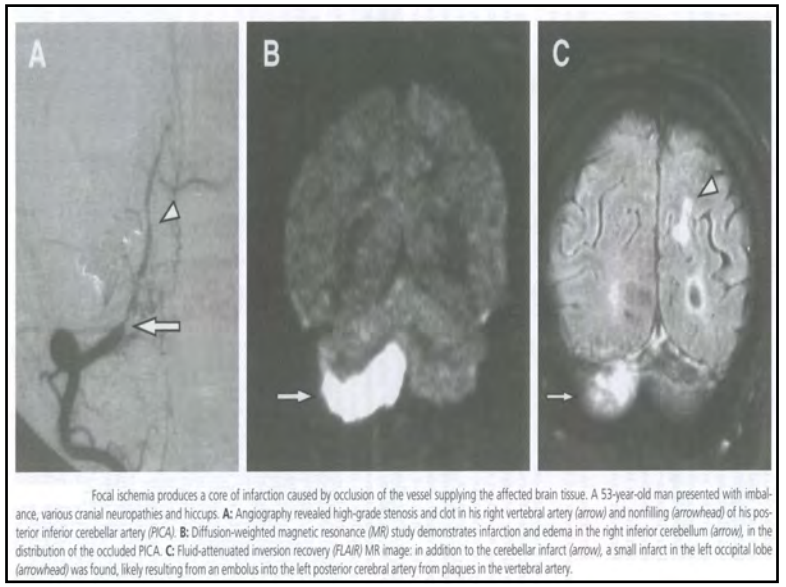


Changes in extracellular ion concentrations following ischemia. Extracellular pH begins to decrease immediately after the onset of ischemia. This change is accompanied by slight increases in the extracellular concentrations of K^+, Cl^- and Na^+. After about 1 min of ischemia, a dramatic shift of ions occurs, with K^+ leaving cells and Ca^{2+}, Cl^- and Na^+ leaving the extracellular space.

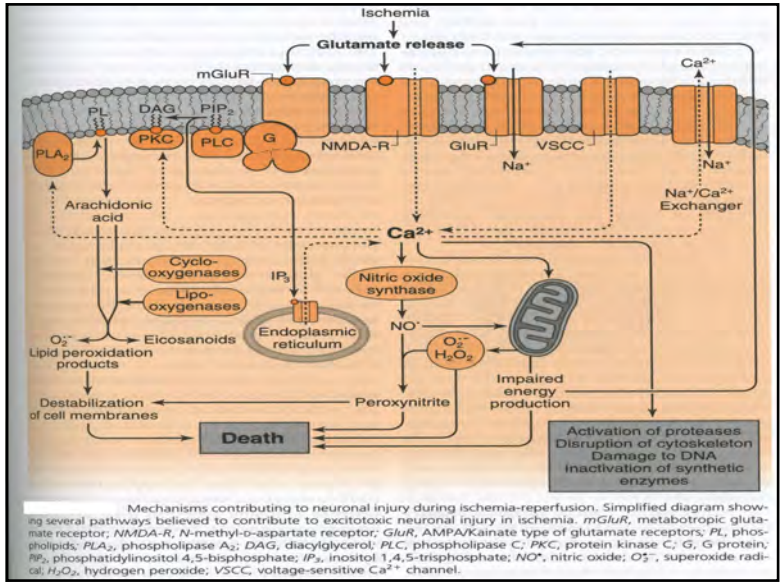




Changes in intracellular and extracellular Ca^{2+} during ischemia-reperfusion and the effects of the *N*-methyl-D-aspartate receptor antagonist MK-801. Intracellular Ca^{2+}, *circles;* extracellular Ca^{2+}, *squares;* with MK-801, *dark orange;* without MK-801, *light orange or gray.*

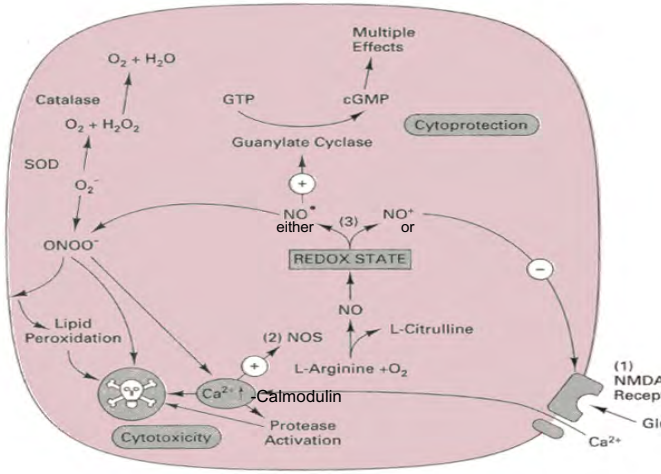


Focal ischemia produces a core of infarction caused by occlusion of the vessel supplying the affected brain tissue. A 53-year-old man presented with imbalance, various cranial neuropathies and hiccups. **A:** Angiography revealed high-grade stenosis and clot in his right vertebral artery *(arrow)* and nonfilling *(arrowhead)* of his posterior inferior cerebellar artery *(PICA)*. **B:** Diffusion-weighted magnetic resonance *(MR)* study demonstrates infarction and edema in the right inferior cerebellum *(arrow)*, in the distribution of the occluded PICA. **C:** Fluid-attenuated inversion recovery *(FLAIR)* MR image: in addition to the cerebellar infarct *(arrow)*, a small infarct in the left occipital lobe *(arrowhead)* was found, likely resulting from an embolus into the left posterior cerebral artery from plaques in the vertebral artery.

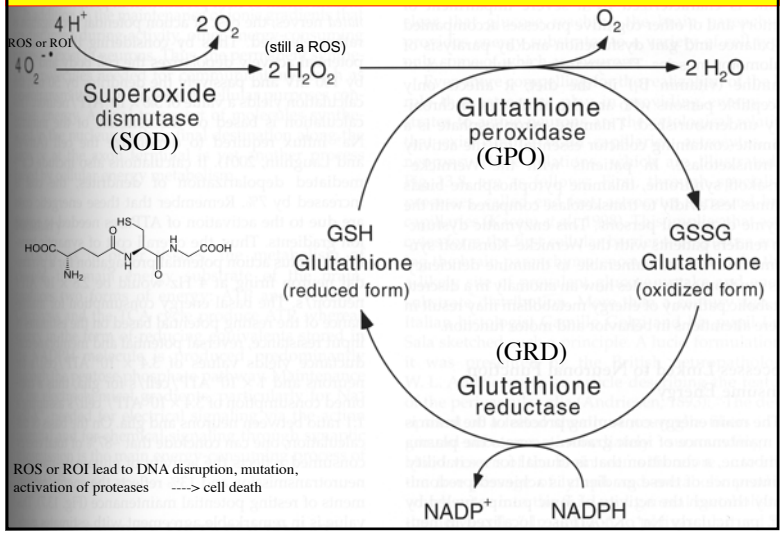


Mechanisms contributing to neuronal injury during ischemia-reperfusion. Simplified diagram showing several pathways believed to contribute to excitotoxic neuronal injury in ischemia. *mGluR*, metabotropic glutamate receptor; *NMDA-R*, *N*-methyl-D-aspartate receptor; *GluR*, AMPA/Kainate type of glutamate receptors; *PL*, phospholipids; PLA_2, phospholipase A_2; *DAG*, diacylglycerol; *PLC*, phospholipase *C*; *PKC*, protein kinase *C*; *G*, G protein; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol 1,4,5-trisphosphate; *NO*·, nitric oxide; $O_2^{\cdot-}$, superoxide radical; H_2O_2, hydrogen peroxide; *VSCC*, voltage-sensitive Ca^{2+} channel.

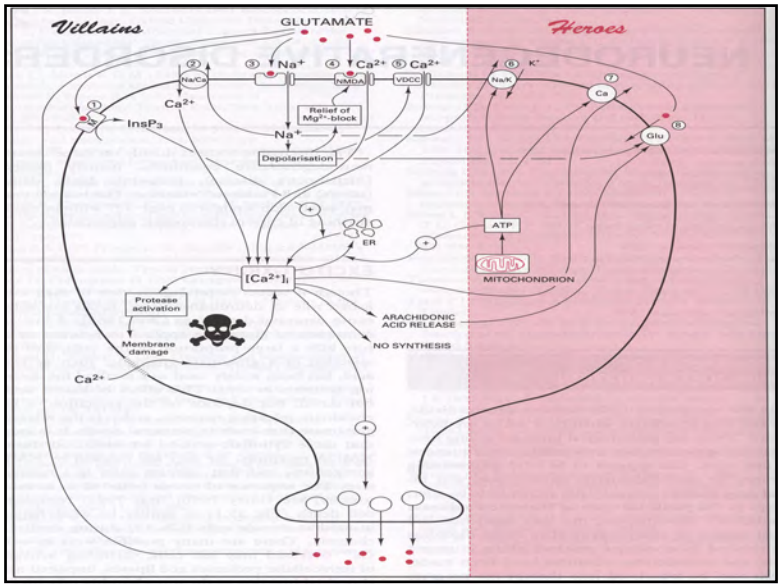
Postulated mechanism whereby NO causes cytotoxicity or cytoprotection in nervous tissue

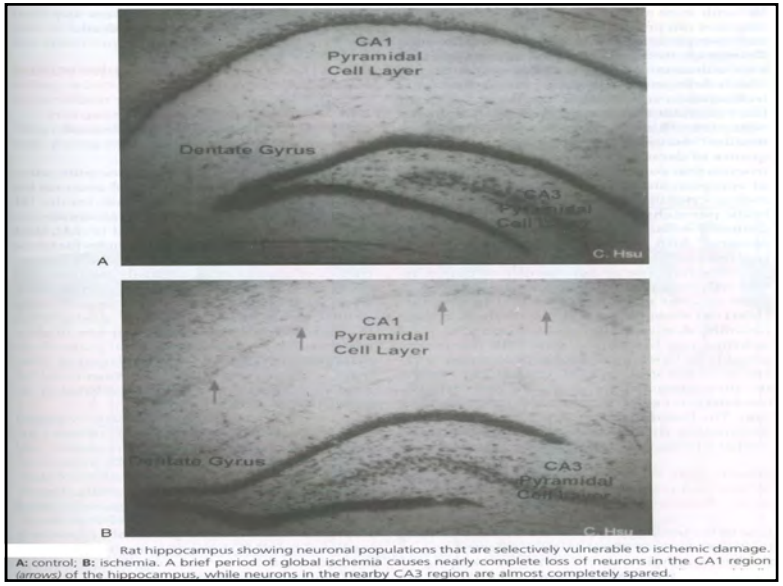


ROI inactivation and S-S in RedOx Reactions



ROS or ROI lead to DNA disruption, mutation, activation of proteases ----> cell death





Rat hippocampus showing neuronal populations that are selectively vulnerable to ischemic damage. **A:** control; **B:** ischemia. A brief period of global ischemia causes nearly complete loss of neurons in the CA1 region *(arrows)* of the hippocampus, while neurons in the nearby CA3 region are almost completely spared.