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Poltava State Medical University
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Biochemistry of the nervous tissue.

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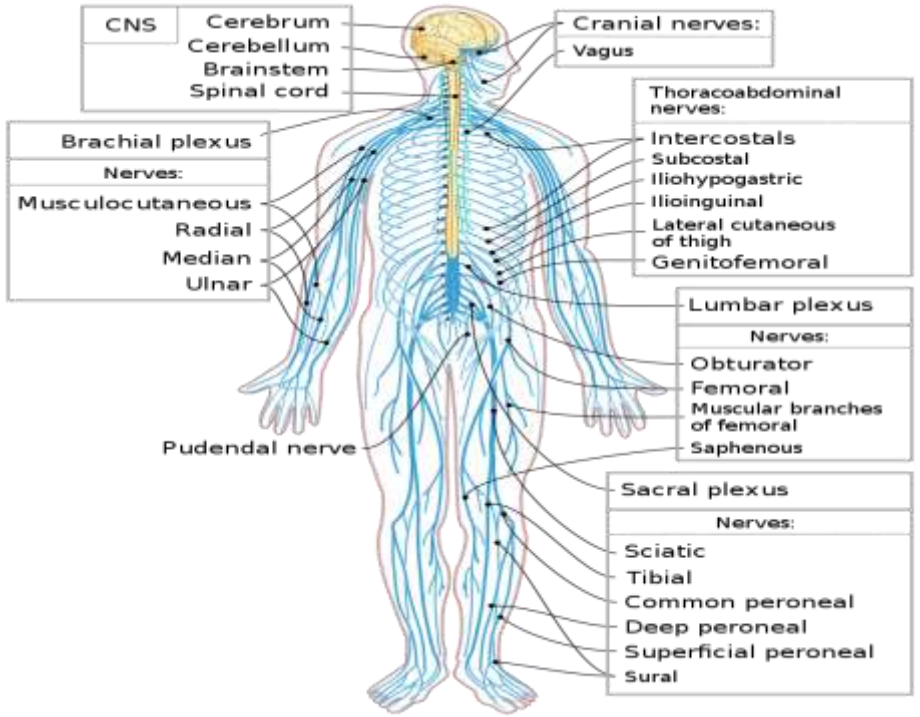
Lecture plan

- Features of biochemical composition of the nervous tissue.
- Features of metabolism of the nervous tissue.
- Neurotransmitters.

Nervous tissue

- Nervous tissue is the term for groups of organized cells in the nervous system, which is the organ system that controls the body's movements, sends and carries signals to and from the different parts of the body, and has a role in controlling bodily functions such as digestion.
- Nervous tissue consists of two main structures: **neurons and neuroglia.** Neurons, or nerves, transmit electrical impulses, neuroglia have many other functions including supporting and protecting neurons.

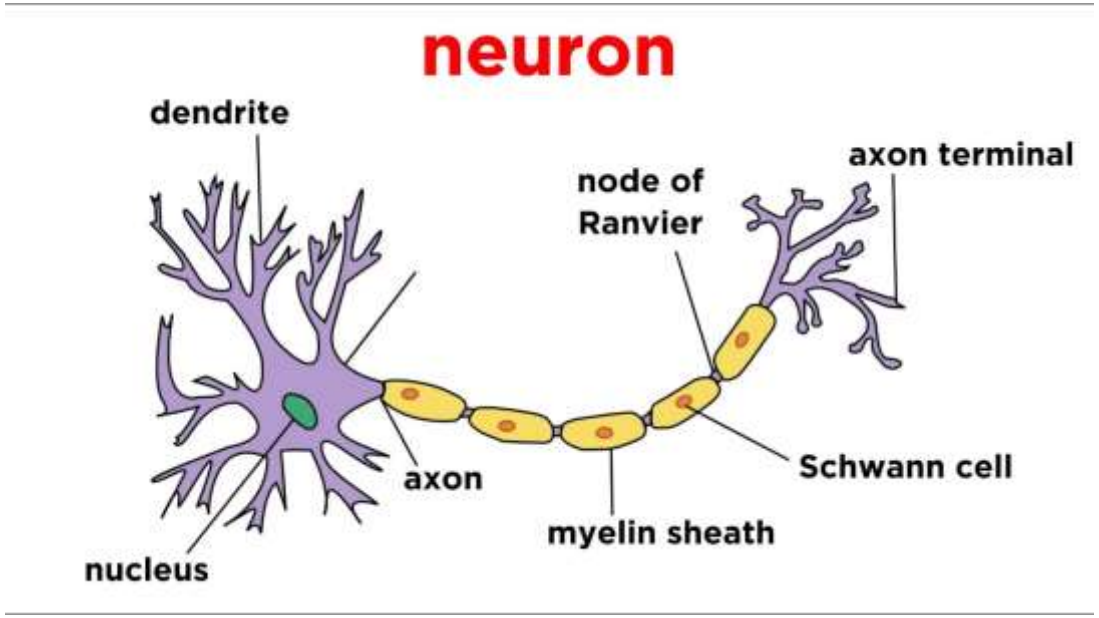


https://en.wikibooks.org/wiki/Structural_Biochemistry/Cell_Signaling_Pathways/Nervous_System#/media/File:Nervous_system_diagram-en.svg

- Nervous tissue is subdivided in: **the central (CNS) and peripheral nervous system (PNS).** ***The central nervous system*** is composed of the brain and spinal cord, which coordinates information from all areas of the body and sends nerve impulses that control all bodily movements. ***The peripheral nervous system*** consists of peripheral nerves that branch all throughout the body. It connects the CNS to the rest of the body and is directly responsible for controlling movements of specific parts of the body.
- Another subdivision of the nervous system is into the **sympathetic nervous system (SNS)** and the **parasympathetic nervous system (PSNS)**. The SNS activates in order to stimulate a fight-or-flight response in an organism when that organism encounters a threat and must decide whether to fight or flee from it. The nerves of the SNS have diverse effects on different parts of the body. Activation of the SNS causes the pupils of the eyes to dilate, inhibits digestion, increases sweat secretion, and increases the heart rate. Conversely, the PSNS is activated during moments of "rest and digest", when an organism is not facing an immediate threat. Nerves of the PSNS work to stimulate activities that can occur at rest such as digestion, waste excretion, and sexual arousal, and they also decrease the heart rate.
- The enteric nervous system (ENS) controls the gastrointestinal tract (digestive tract). This division of the nervous system, along with the SNS and PSNS, are collectively referred to as **the autonomic nervous system (ANS) vegetative nervous system.** The ANS regulates activities that are performed unconsciously; we don't have to think about digesting food for it to occur, for example. By contrast, the **somatic nervous system** (SoNS) controls voluntary body movements. It is made up of afferent and efferent nerves that send signals to and from the CNS, causing voluntary muscle contraction to occur.

Neurons

- Neurons are cells that can transmit signals called nerve impulses, or action potentials. These are the different types of neurons:
- ***Sensory, or afferent neurons***, relay information from the PNS to the CNS; different types of sensory neurons can detect temperature, pressure, and light.
- ***Motor, or efferent neurons***, send signals from the CNS to the PNS; these signals provide information to sensory neurons to "tell" them what to do (e.g., initiate muscle movement).
- ***Interneurons*** connect sensory and motor neurons to the brain and spinal cord; they act as connectors to form neural circuits and are involved with reflex actions and higher brain functions like decision-making.
- While neurons can be specialized and look very different from one another, they each have components in common. Each neuron has a ***soma, or cell body***, that contains the nucleus. ***Dendrites***, finger-like projections that receive nerve impulses, branch off from the soma. The ***axon*** is a larger projection that branches off from the soma. Nerve impulses travel along the axon in the form of an action potential. The axon splits into axon terminals, which branch off to other neurons. Neurotransmitters are released from the ends of the axon terminals, and these travel across the synaptic cleft to reach receptors on the dendrites of other neurons. In this way, neurons communicate with each other and can send signals that reach many other neurons.



https://wellnessadvocate.com/?uid=476

Gray matter and white matter

- Nerve tissue is made up of three cellular elements: **neurons** (nerve cells), **neuroglia** (cell systems), the surrounding nerve cells in the brain and spinal cord, and **glial macrophages**.
- Neurons are concentrated in the **gray matter** (60-65% of the brain matter). The **white matter** of the central nervous system and peripheral nerves consist mainly of neuroglia elements and their derivative, myelin.
- Grey matter (or gray matter) is a major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and unmyelinated axons), glial cells (astrocytes and oligodendrocytes), synapses, and capillaries. Grey matter is distinguished from white matter in that it contains numerous cell bodies and relatively few myelinated axons, while white matter contains relatively few cell bodies and is composed chiefly of long-range myelinated axons. The colour difference arises mainly from the whiteness of myelin.

- Chemical composition from gray and white matter of the human brain (percentage of wet weight)

Components	Gray matter	White matter
water	84	70
proteins	8	9
lipids	5	17
minerals	1	2

Neuroglia

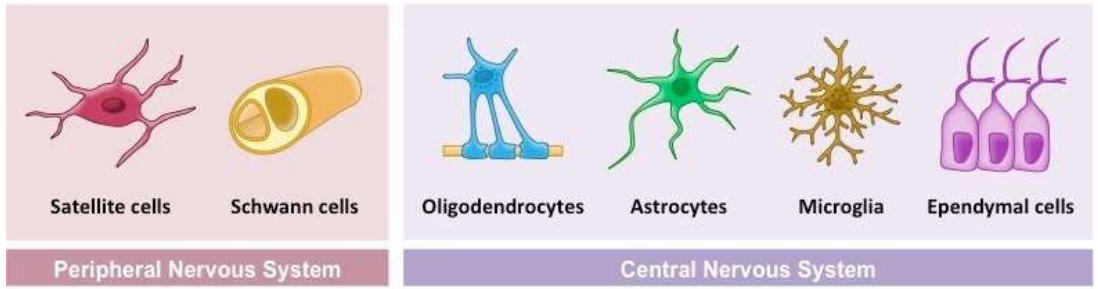
- **Neuroglia, or glial cells**, are cells that support neurons, supply them with nutrients, and get rid of dead cells and pathogens such as bacteria. They also form insulation between neurons so that electrical signals do not get crossed, and can also aid the formation of synaptic connections between neurons. There are several types of neuroglia:
- **Neuroglia in the CNS**
- There are four types of neuroglia found within the central nervous system:
- ***Astrocytes*** – maintain the blood brain barrier and preserve the chemical environment by recycling ions and neurotransmitters. They provide nutrients to neurons, maintain ion balance, and remove unneeded excess neurotransmitters from the synaptic cleft.
- ***Oligodendrocytes*** – are found in the CNS and provide physical support to neurons. They form a myelin sheath around some neurons in the CNS.
- ***Ependymal cells*** – are involved in the production of cerebrospinal fluid. There are two types of ependymal cells. Non-ciliated ependymal cells form cerebrospinal fluid, while ciliated ependymal cells help the cerebrospinal fluid circulate. Cerebrospinal fluid cushions the brain and spinal cord.
- ***Microglia*** – remove cell debris, wastes and pathogens via phagocytosis. are small macrophage cells in the CNS that protect against disease by engulfing pathogens through phagocytosis ("cell eating"). They can also destroy infected neurons and promote the regrowth of neurons.
- All of the other types of neuroglia above are larger and collectively called **macroglia.**

Neuroglia in the PNS

There are two types of neuroglia found within the peripheral nervous system:

Schwann cells – myelinate axons in the peripheral nervous system. Schwann cells also form myelin sheaths around some neurons, but they are only found in the PNS. Neurons that are myelinated can conduct electrical impulses faster than non-myelinated neurons.

Satellite cells – regulate nutrient and neurotransmitter levels around neurons in ganglia.

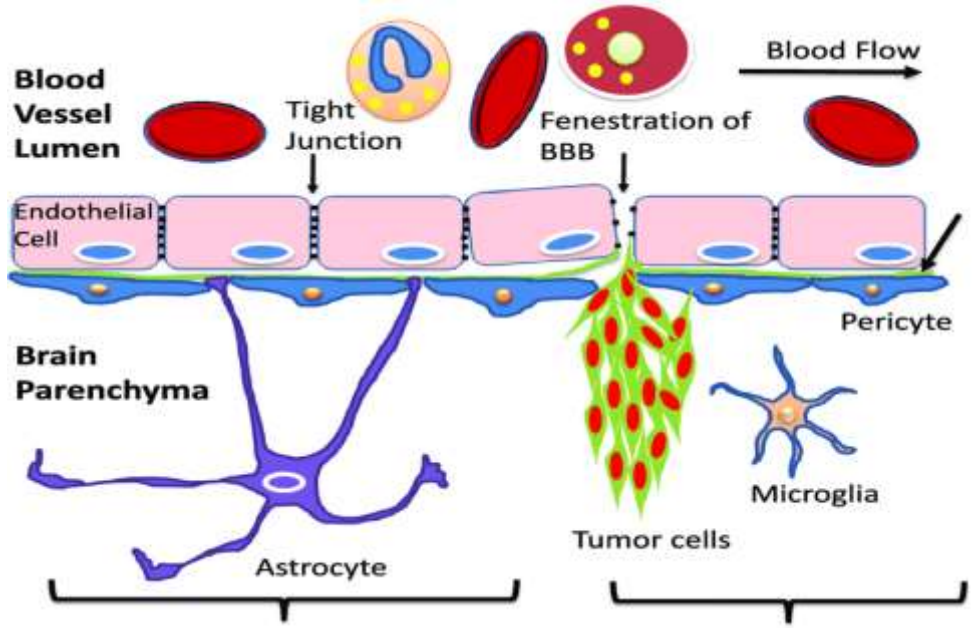


https://ib.bioninja.com.au/options/option-a-neurobiology-and/a1-neural-development/types-of-neuroglia.html

The blood–brain barrier

- **The blood–brain barrier (BBB)** is a highly selective semipermeable border of endothelial cells that prevents solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the central nervous system where neurons reside. The blood–brain barrier is formed by endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, and pericytes embedded in the capillary basement membrane. This system allows the passage of some molecules by passive diffusion, as well as the selective and active transport of various nutrients, ions, organic anions, and macromolecules such as glucose, water and amino acids that are crucial to neural function.
- The blood–brain barrier restricts the passage of pathogens, the diffusion of solutes in the blood, and large or hydrophilic molecules into the cerebrospinal fluid, while allowing the diffusion of hydrophobic molecules (O2, CO2, hormones) and small non-polar molecules. Cells of the barrier actively transport metabolic products such as glucose across the barrier using specific transport proteins. The barrier also restricts the passage of peripheral immune factors, like signaling molecules, antibodies, and immune cells, into the CNS, thus insulating the brain from damage due to peripheral immune events.
- The blood–brain barrier results from the selectivity of the tight junctions between the endothelial cells of brain capillaries, restricting the passage of solutes. At the interface between blood and the brain, endothelial cells are adjoined continuously by these tight junctions, which are composed of smaller subunits of transmembrane proteins, such as occludin, claudins, junctional adhesion molecule. Each of these transmembrane proteins is anchored into the endothelial cells by another protein complex that includes tight junction protein 1 and associated proteins.

The blood–brain barrier is composed of endothelial cells restricting passage of substances from the blood more selectively than endothelial cells of capillaries elsewhere in the body. Astrocyte cell projections called astrocytic feet (also known as "glia limitans") surround the endothelial cells of the BBB, providing biochemical support to those cells.
Several areas of the human brain are not on the brain side of the BBB. Some examples of this include the circumventricular organs, the roof of the third and fourth ventricles, capillaries in the pineal gland on the roof of the diencephalon and the pineal gland. The pineal gland secretes the hormone melatonin "directly into the systemic circulation", thus melatonin is not affected by the blood–brain barrier.



https://www.researchgate.net/figure/Blood-Brain-Barrier-BBB-architecture-in-normal-and-tumor-brain_fig3_317507172

Features of the metabolism of nervous tissue

- The composition of the nervous tissue includes highly labile substances that change with irritation.
- This tissue is intensively supplied with blood, which is accompanied by a high metabolic rate.
- The nervous tissue is characterized by a high intensity of respiration (20 times more than in the muscles). Brain mass is 2-3% of body weight, and oxygen consumption is 20-25% of all oxygen consumed.
- Nerve tissue metabolism is determined by the presence of the blood-brain barrier (BBB), which is selectively permeable to various metabolites and contributes to the accumulation of certain substances in the nervous tissue. For example, in the nervous tissue, glutamate and aspartate account for approximately 70-75% of the total amount of amino acids.

Energy and carbohydrates metabolism

- The main way of obtaining energy is aerobic oxidation of glucose. Glucose is almost the only energy substrate entering the nervous tissue, which can be used by its cells for the formation of ATP.
- The penetration of glucose into the brain tissue does not depend on the action of insulin. Glucose enters the brain from the blood by crossing the BBB through glucose transporter 1 (GLUT1)
- A constant and continuous flow of glucose and oxygen from the bloodstream is a necessary condition for the energy supply of nerve cells, since the glycogen content in the nervous tissue is negligible (0.1% of the brain mass) and cannot provide the brain with energy even for a short time.
- The largest proportion of energy in the brain is consumed for neuronal computation and information processing, e.g. the generation of action potentials and postsynaptic potentials generated after synaptic events, and the maintenance of ion gradients and neuronal resting potential. Additionally, glucose metabolism provides the energy and precursors for the biosynthesis of neurotransmitters
- ***Glucose is the main source of energy***, since only glucose enters the nerve cells through the blood brain barier (BBB). Unlike other tissues of the human body, high fatty acids do not penetrate the BBB and cannot be used as an energy source. During fasting, diabetes mellitus, the nervous tissue uses ***ketone bodies*** as an energy source.
- The high rate of glucose consumption by nerve cells is ensured by the work of the highly active brain hexokinase. Here hexokinase is not a key enzyme in all glucose pathways.
- The key enzymes of aerobic oxidation of glucose are phosphofructokinase and isocitrate dehydrogenase.
- Phosphofructokinase is inhibited by 1,6-bisphosphate, ATP and citrate, activated by fructose-6-phosphate, ADP, AMP and inorganic phosphate. The activity of isocitrate dehydrogenaseis maximal even with normal resting glucose utilization. Consequently, with increased energy consumption, there is no possibility of accelerating the tricarboxylic acid cycle.
- The energy of ATP in the nervous tissue is spent unevenly over time. A dramatic increase in energy expenditure occurs with a very rapid transition from sleep to wakefulness.

Lipids metabolism

- Most of the lipids of the nervous tissue are found in the plasma and subcellular membranes of neurons and in the myelin sheaths. The lipid content in the nervous tissue is very high.
- Functions of nerve tissue lipids:

✓ structural: are part of the cell membranes of neurons;

✓ dielectric: provide reliable electrical insulation;

✓ protective: gangliosides - active antioxidants - inhibitors of lipid peroxidation (LPO). When brain tissue is damaged, gangliosides promote its healing;

✓ regulatory: phosphatidylinositols - precursors of biologically active substances (biologically active substances), hormone receptors.

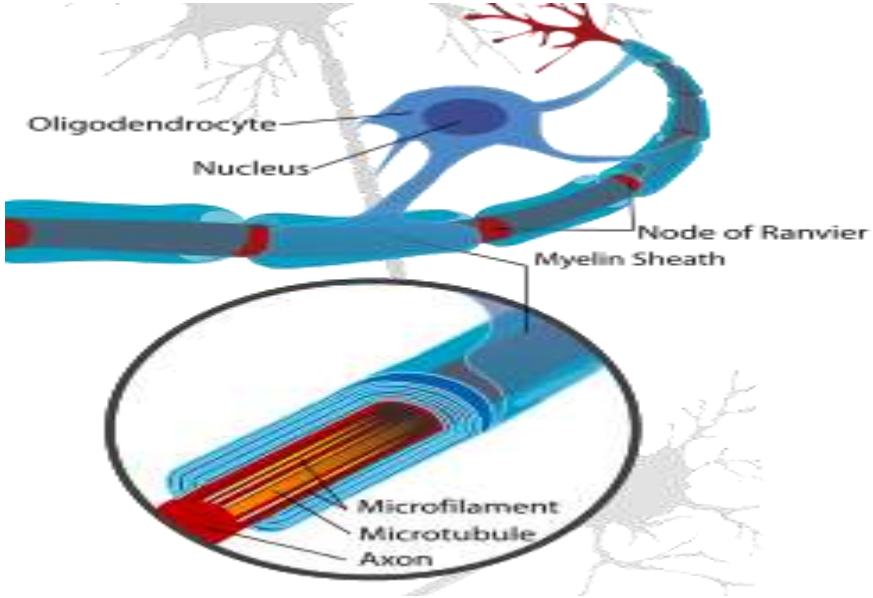
- The peculiarity of the lipid composition of the nervous tissue: there are phospholipids (PL), glycolipids (GL) and cholesterol (CS), no neutral fats. Cholesterol esters are found only in areas of active myelination. Cholesterol itself is synthesized intensively only in the developing brain. In the adult brain, the activity of OMG-CoA reductase, a key enzyme in cholesterol synthesis, is low. The content of free fatty acids in the brain is very low.
- Lipids are constantly being renewed. Their update rates vary, but overall they are slow. The synthesis of cerebrosides and gangliosides proceeds at a high rate in the developing brain during the period of myelination. In adults, almost all cerebrosides (up to 90%) are located in the myelin sheaths, and gangliosides are in neurons.
- A feature of the nervous tissue is the use of lipids as structural components. Lipids are represented by cerebrosides, gangliosides, sphingomyelins, plasmalogens, phosphatidylserines, phosphatidylcholines, phosphatidylinositols, phosphatidylethanolamines, and cholesterol. Myelin membranes have 3 layers of protein and 2 layers of lipids, which include phosphatidylserine, cerebrosides, sphingomyelins, and cholesterol. Moreover, in each lipid layer of the myelin sheath there are 5 layers, 2 of which are cholesterol, the content of which reaches up to 30%.

Myelin

- **Myelin** is a lipid-rich (fatty) substance that surrounds nerve cell axons to insulate them and increase the rate at which electrical impulsesare passed along the axon. Each myelin sheath insulates the axon over a single long section and, in general, each axon comprises multiple long myelinated sections separated from each other by short myelin sheath-gaps called ***nodes of Ranvier.***
- Myelin is formed in the ***central nervous system (CNS***; brain, spinal cord and optic nerve) by glial cells called ***oligodendrocytes*** and in the ***peripheral nervous system (PNS)*** by glial cells called ***Schwann cells***. In the CNS, axons carry electrical signals from one nerve cell body to another. In the PNS, axons carry signals to muscles and glands or from sensory organs such as the skin.
- Each myelin sheath is formed by the concentric wrapping of an oligodendrocyte (CNS) or Schwann cell (PNS) process (a limb-like extension from the cell body) around the axon. Myelin reduces the capacitance of the axonal membrane. On a molecular level, in the internodes it increases the distance between extracellular and intracellular ions, reducing the accumulation of charges. The discontinuous structure of the myelin sheath results in saltatory conduction, whereby the action potential "jumps" from one node of Ranvier, over a long myelinated stretch of the axon called the internode, before "recharging" at the next node of Ranvier, and so on, until it reaches the axon terminal.Nodes of Ranvier are the short (c. 1 micron) unmyelinated regions of the axon between adjacent long (c. 0.2 mm – >1 mm) myelinated internodes.
- Once it reaches the axon terminal, this electrical signal provokes the release of a chemical message or neurotransmitter that binds to receptors on the adjacent post-synaptic cell (e.g., nerve cell in the CNS or muscle cell in the PNS) at specialised regions called synapses.
- CNS myelin differs slightly in composition and configuration from PNS myelin, but both perform the same "insulating" function (see above). Being rich in lipid, myelin appears white, hence the name given to the "white matter" of the CNS. Both CNS white matter tracts (e.g. the optic nerve, corticospinal tract and corpus callosum) and PNS nerves (e.g. the sciatic nerve and the auditory nerve, which also appear white) each comprise thousands to millions of axons, largely aligned in parallel. Blood vessels provide the route for oxygen and energy substrates such as glucose to reach these fibre tracts, which also contain other cell types including astrocytes and microglia in the CNS and macrophages in the PNS.
- In terms of total mass, myelin comprises approximately 40% water; the dry mass comprises between 60% and 75% lipid and between 15% and 25% protein.
- Protein content includes myelin basic protein (MBP), which is abundant in the CNS where it plays a critical, non-redundant role in formation of compact myelin; myelin oligodendrocyte glycoprotein (MOG), which is specific to the CNS; and proteolipid protein (PLP), which is the most abundant protein in CNS myelin, but only a minor component of PNS myelin. In the PNS, myelin protein zero (MPZ or P0) has a similar role to that of PLP in the CNS in that it is involved in holding together the multiple concentric layers of glial cell membrane that constitute the myelin sheath.
- The primary lipid of myelin is a glycolipid called galactocerebroside. The intertwining hydrocarbon chains of sphingomyelin strengthen the myelin sheath. Cholesterol is an essential lipid component of myelin, without which myelin fails to form.

Myelin

- The "insulating" role for myelin is essential for normal motor function (i.e. movement such as walking), sensory function (e.g. hearing, seeing or feeling the sensation of pain) and cognition (e.g. acquiring and recalling knowledge), as demonstrated by the consequences of disorders that affect it, such as the genetically determined ***leukodystrophies***; the ***acquired inflammatory demyelinating disorder, multiple sclerosis; and the inflammatory demyelinating peripheral neuropathies***. Due to its high prevalence, multiple sclerosis, which specifically affects the central nervous system (brain, spinal cord and optic nerve), is the best known disorder of myelin.

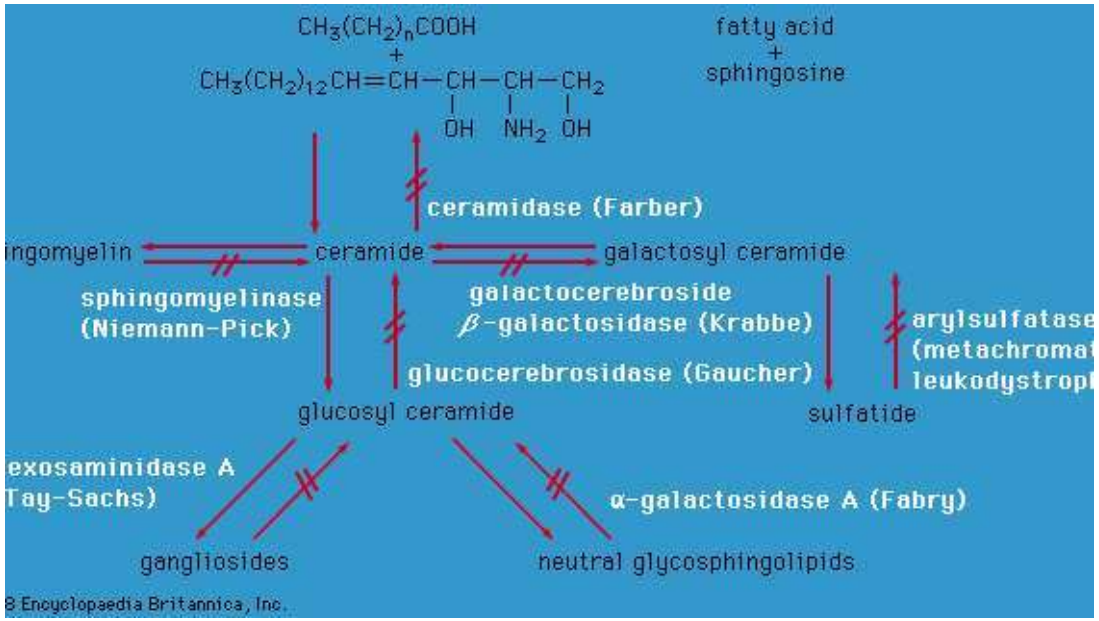


https://en.wikipedia.org/wiki/Myelin

- Multiple sclerosis (MS), also known as encephalomyelitis disseminata, is a demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to transmit signals, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems. Specific symptoms can include double vision, blindness in one eye, muscle weakness, and trouble with sensation or coordination.MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms).
- While the cause is unclear, the underlying mechanism is thought to be either destruction by the immune system or failure of the myelin-producing cells. Proposed causes for this include genetics and environmental factors being triggered by a viral infection.

Lipid storage disorder

A **lipid storage disorder (or lipidosis**) is any one of a group of inherited metabolic disorders in which harmful amounts of fats or lipids accumulate in some of the body's cells and tissues. People with these disorders either do not produce enough of one of the enzymes needed to metabolize and break down lipids or they produce enzymes that do not work properly. Over time, the buildup of fats can cause permanent cellular and tissue damage, particularly in the brain, peripheral nervous system, liver, spleen and bone marrow.



https://www.britannica.com/science/metabolic-disease/Disorders-of-lipid-metabolism

- **Gaucher disease** is caused by a deficiency of the enzyme ***glucocerebrosidase.*** Lipids can collect in the brain, spleen, liver, kidneys, lungs, and bone marrow. Symptoms may include brain damage, enlarged spleen and liver, liver malfunction, skeletal disorders and bone lesions that may cause pain and fractures, swelling of lymph nodes and (occasionally) adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelets, and yellow spots in the eyes. Individuals affected most seriously may also be more susceptible to infection.

- **Niemann-Pick** disease is a group of autosomal recessive disorders caused by a deficiency of the enzyme ***sphingomyelinase.*** Neurological complications may include ataxia (lack of muscle coordination that can affect walking steadily, writing, and eating, among other functions), eye paralysis, brain degeneration, learning problems, spasticity, feeding and swallowing difficulties, slurred speech, loss of muscle tone, hypersensitivity to touch, and some clouding of the cornea due to excess buildup of materials. A characteristic cherry-red halo that can be seen by a physician using a special tool develops around the center of the retina in 50 percent of affected individuals.

- **Fabry disease**, also known as ***alpha-galactosidase-A*** deficiency, causes a buildup of fatty material in the autonomic nervous system eyes, kidneys, and cardiovascular system. Fabry disease is the only X-linked lipid storage disease. Neurological signs include burning pain in the arms and legs, which worsens in hot weather or following exercise, and the buildup of excess material in the clear layers of the cornea (resulting in clouding but no change in vision). Fatty storage in blood vessel walls may impair circulation, putting the person at risk for stroke or heart attack.

- **Tay-Sachs disease** (also known as GM2 gangliosidosis-variant B) and its variant forms are caused by a deficiency in the enzyme ***hexosaminidase A.*** Affected children appear to develop normally for the first few months of life. Symptoms begin by 6 months of age and include progressive loss of mental ability, dementia, decreased eye contact, increased startle response to noise, progressive loss of hearing leading to deafness, difficulty in swallowing, blindness, cherry-red spots in the retina, and some paralysis. Seizures may begin in the child's second year.

Amino acid and protein metabolism

- The brain tissue intensively exchanges amino acids with the blood. For this, there are special transport systems: two for uncharged and several more for amino acids, positively and negatively charged.
- The concentration of free amino acids in the nervous tissue is 8 times higher than in the blood.
- Proteins in the brain are in a dynamic state.
- The activity of AST and ALT, converting amino acids into keto, for obtaining substrates of TCA, is great. The proteins of the gray matter and cerebellum are characterized by a high rate of renewal of especially stimulating agents (electric current, pharmaceuticals), however, under the influence of anesthesia, these processes die out.
- The brain tissue is able to synthesize nonessential amino acids.
- Ammonia is formed in the purine cycle: by hydrolytic deamination of AMP, IMP and ammonia are formed. IMP, further condensing with aspartic acid, forms adenyl succinate, which, splitting, forms again AMP (and fumarate). The fumarate in the TCA forms OAA, which maintains the level of aspartic acid by reacting with transamination with glutamic acid.

Amino acid and protein metabolism

- *Aspartate*, *glutamate*, as well as the products of their transformations or substances synthesized with their participation (glutamine, acetyl derivatives, GABA (gamma-aminobutyric acid) glutathione) constitute up to 75% of the total amount of amino acids in the nervous tissue.
- **Functions of glutamate in the nervous tissue:** glutamic acid is associated with the formation of alpha ketoglutaric acid, which takes part in the Krebs cycle.

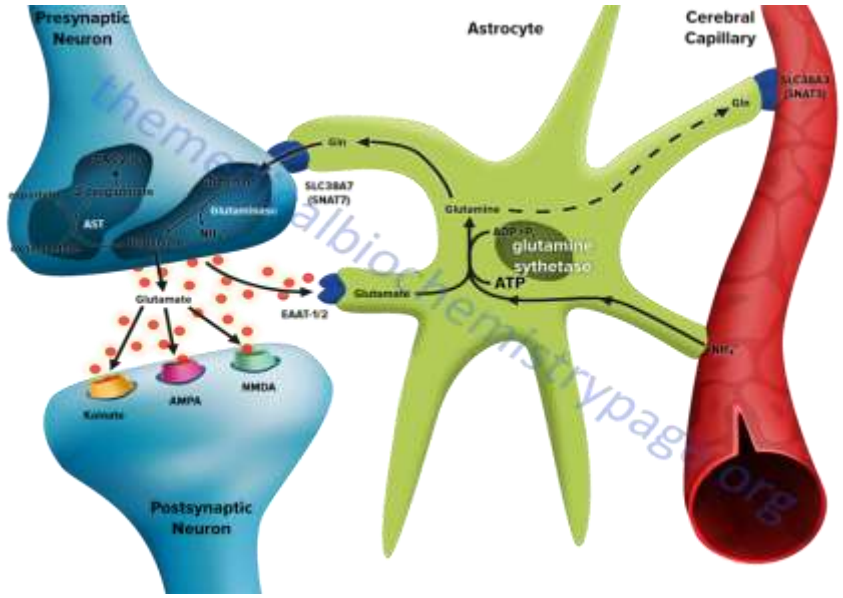
✓ synthesis of glutamine - temporary neutralization of ammonia;

✓ formation of the neurotransmitter GABA from glutamate;

✓ participation in the synthesis of glutathione - one of the components of the body's antioxidant system.

✓ Glutamate is rapidly formed from its keto analogue, □-ketoglutaric acid, during the transamination reaction and is used to form glutathione, glutamine and-aminobutyric acid.

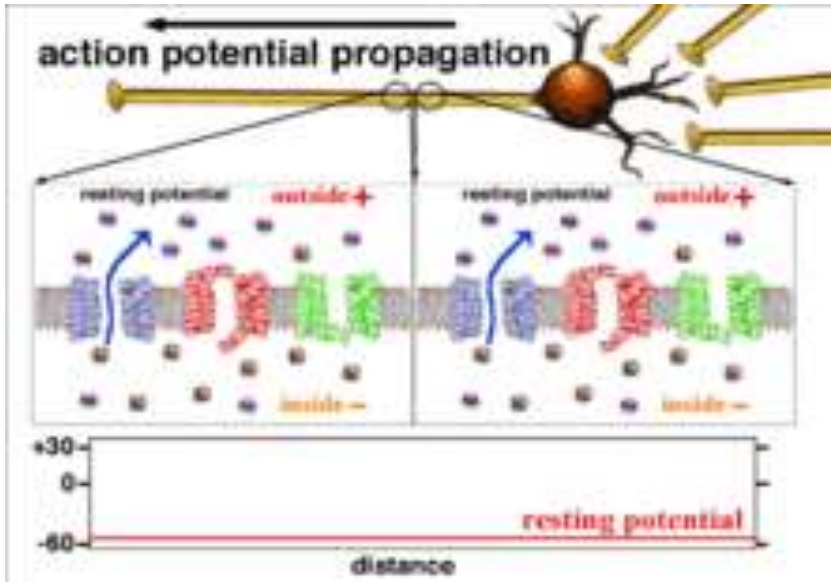
- **Brain glutamate-glutamine cycle.** Ammonium ion (NH4+) in the blood is taken up by astrocytes and incorporated into glutamate via glutamine synthetase. The glutamine then is transported to presynaptic neurons via SLC38A7 (also called sodium-coupled neutral amino acid transporter 7, SNAT7).
- Within the presynaptic neuron glutamate is formed from the glutamine via the action of glutaminase. The glutamate is packaged in secretory vesicles for release following activation of an action potential. Glutamate in the synaptic cleft can be taken up by astrocytes via the EAAT1 and EAAT2 transporters (excitatory amino acid transporters 1 and 2; also known as glial high affinity glutamate transporters). Within the astrocyte the glutamate is converted back to glutamine. Some of the astrocyte glutamine can be transported into the blood via the action of the transporter SLC38A3 (also called sodium-coupled neutral amino acid transporter 3, SNAT3).



https://themedicalbiochemistrypage.org/biochemistry-of-nerve-transmission/

Biochemical bases of the origin and conduction of a nerve impulse

- Normally, at rest, the membrane of the axon is polarized: inside the axon there are 30 times more potassium ions than sodium ions. The concentration of anions is also different. Cations inside the cell are neutralized mainly by proteins and phosphates, which cannot escape to the outside; extracellular cations (mainly Na +) are balanced by Cl–, the permeability of which is higher than that of proteins. The Na + permeability is 1/20 of the K + permeability. K +, Na + ATP-ase pumps out 3 Na + in exchange for 2 K +. Under these conditions, the inner side of the cell membrane is electronegatively charged with respect to the outer surface and the electromotive transmembrane potential is E = -70 mV.

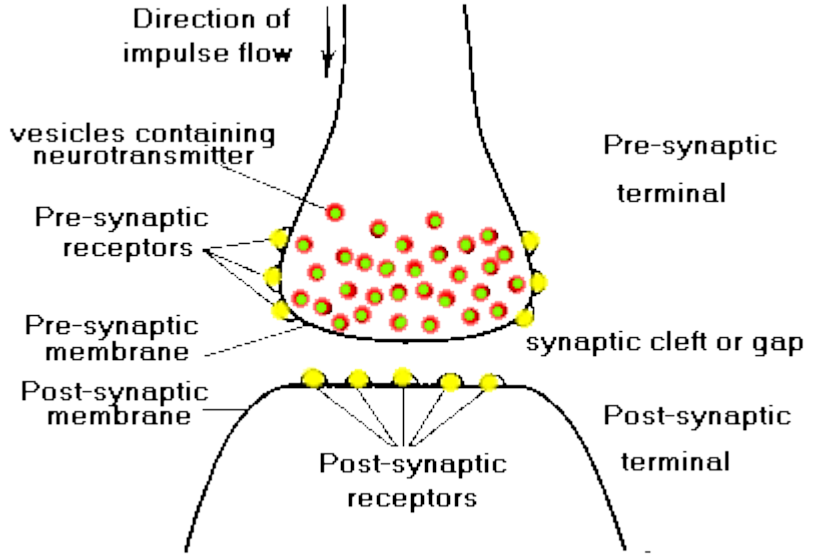


- Under the action of an exciting mediator, membrane adenylate cyclase is activated, under the influence of which c-AMP is formed from ATP, which includes a cascade mechanism of activation (by phosphorylation of proteins) of sodium-potassium ATPase (ion pump).
- Thus, with the participation of ATP, the channels for the passage of sodium ions into the axon are first opened, and then the channels for the exit of potassium ions to the outside are opened. In this state, the potential difference reaches + 40mV, a positive charge inside the axon.
- This is an action potential and, having arisen in one area, due to the diffusion of ions along the fiber, reduces the resting potential and also causes the development of an action potential here.
- This is an action potential and, having arisen in one area, due to the diffusion of ions along the fiber, reduces the resting potential and here, too, causes the development of an action potential.
- There is a wave of depolarization - a nerve impulse; then the depolarization wave propagates.
- The restoration of the membrane in a polarized form also occurs with the participation of ion pumps with the consumption of ATP.
- Consequently, for the functioning of the nervous system, the production and consumption of significant amounts of ATP is required.

https://en.wikibooks.org/wiki/Structural_Biochemistry/Cell_Signaling_Pathways/Nervous_System#:~:text=The%20nervous%20system%20is%20a,chemicals%20released%20onto%20other%20cells.

Synapse

- **Synapse** is a functional contact of specialized areas of the plasma membranes of two excitable cells. ***Consists of a presynaptic membrane, a synaptic cleft and a postsynaptic membrane.*** Cell membranes at the point of contact have thickenings in the form of plaques - nerve endings. A nerve impulse that has reached a nerve ending is not able to overcome the obstacle that has arisen in front of it - the synaptic cleft. Here, an electrical signal is converted into a chemical one.
- The presynaptic membrane contains special channel proteins that react to the membrane potential by changing their conformation and form a channel. As a result, Ca2 + ions pass through the presynaptic membrane along the concentration gradient into the nerve ending. The concentration gradient of Ca2 + is created by the work of the Ca2 + -dependent ATPase - a calcium pump. An increase in the concentration of Ca2 + inside the nerve ending causes the fusion of 200-300 vesicles filled with acetylcholine present there with the plasma membrane. Further, acetylcholine is secreted into the synaptic cleft by exocytosis and attaches to receptor proteins located on the surface of the postsynaptic membrane.
- When interacting with acetylcholine, the receptor protein changes its conformation, forming a sodium channel. The cationic selectivity of the channel is ensured by the fact that the channel gate is formed by negatively charged amino acids. Thus, the permeability of the postsynaptic membrane for sodium increases and a new impulse (or muscle fiber contraction) arises.
- Depolarization of the postsynaptic membrane causes dissociation of the "acetylcholine - protein - receptor" complex, and acetylcholine is released into the synaptic cleft. As soon as acetylcholine is in the synaptic cleft, it undergoes rapid hydrolysis by acetylcholinesterase. An intermediate enzyme-substrate complex is formed, in which acetylcholine is bound to the active center of the enzyme through serine.



https://socratic.org/questions/what-does-it-mean-for-your-body-that-dendrites-carry-impulses-toward-the-cell-bo

Neurotransmitters

- **Neurotransmitters** are substances characterized by the following characteristics:

✓ accumulate in the presynaptic structure in sufficient concentration;

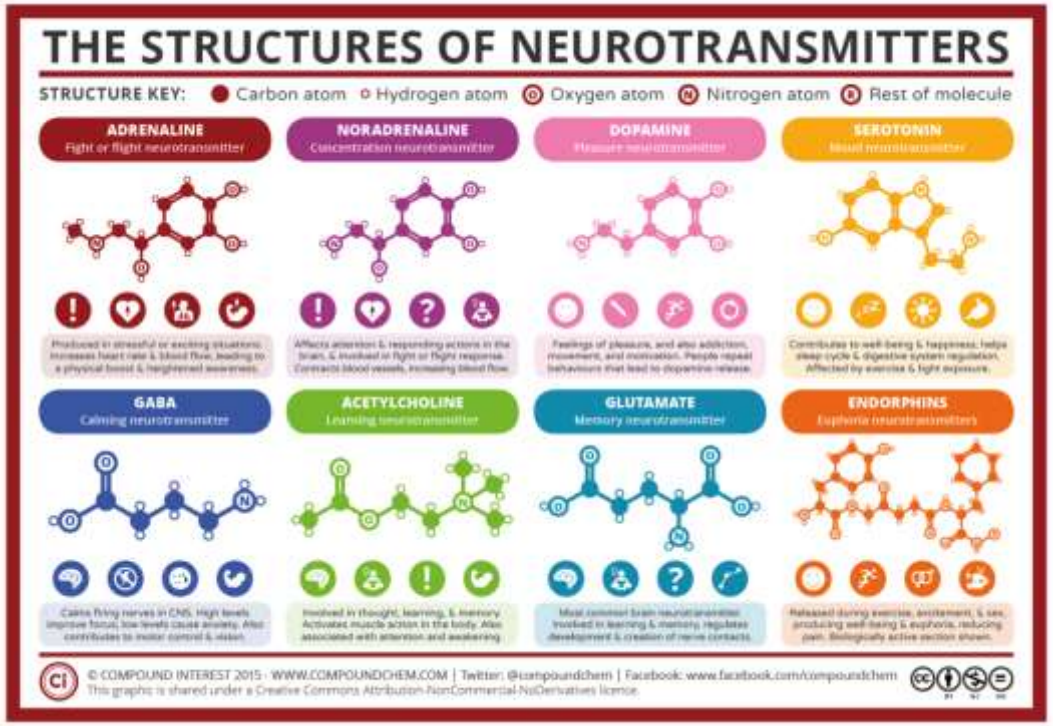
✓ are released when the impulse is transmitted;

✓ cause, after binding to the postsynaptic membrane, a change in the rate of metabolic processes and the appearance of an electrical impulse;

✓ have a system for inactivation or a transport system for removal from the synapse, which have a high affinity for them.

- Neurotransmitters provide synaptic transmission of nerve impulses. Their synthesis takes place in the body of neurons, and their accumulation takes place in special vesicles, which gradually move with the participation of systems of neurofilaments and neurotubules to the tips of axons.
- There are two main classes of neurotransmitter: ***excitatory*** and ***inhibitory.*** ***Excitatory neurotransmitters*** cause neurons to fire 'action potentials' – essentially an electrical signal – whilst ***inhibitory neurotransmitters*** prevent action potentials being fired.

Neurotransmitters



https://www.compoundchem.com/2015/07/30/neurotransmitters/

- classification of neurotransmitters by their chemical structure:

✓ **Amino acids:** glutamate, aspartate, D-serine, gamma-Aminobutyric acid (GABA), glycine

✓ **Gasotransmitters:** nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H_2S)

✓ **Monoamines:**
catecholamines: dopamine, norepinephrine (noradrenaline) epinephrine (adrenaline);

histamine; serotonin (SER, 5-HT).

✓ **Trace amines**: phenethylamine, *N*-methylphenethylamine, tyramine, 3-iodothyronamine, octopamine, tryptamine, etc.

✓ **Peptides:** oxytocin, somatostatin, substance P, cocaine and amphetamine regulated transcript, opioid peptides.

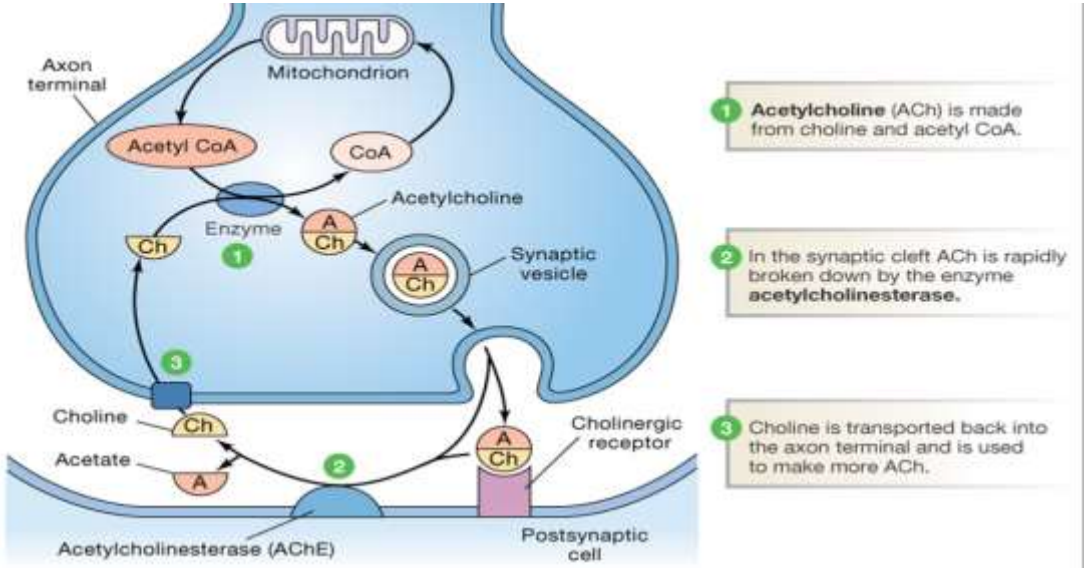
✓ **Purines:** adenosine triphosphate (ATP), adenosine

✓ **Others:** acetylcholine (ACh), anandamide, etc.

Neurotransmitters. Acetylcholine.

- Acetylcholine (ACh) is a simple molecule synthesized from choline and acetyl-CoA through the action of choline O-acetyltransferase. Neurons that synthesize and release ACh are termed cholinergic neurons.

- When an action potential reaches the terminus of a presynaptic neuron a voltage-gated calcium channel is opened. The influx of calcium ions (Ca2+) stimulates the exocytosis of presynaptic vesicles containing ACh, which is thereby released into the synaptic cleft. This vesicle mobilization and ACh exocytosis occurs within a few hundred microseconds of the action potential reaching the pre-synaptic membrane. Vesicle mobilization results from the interaction of Ca2+ with proteins of the synaptotagmin family. The interaction of Ca2+ with synaptotagmins activates these membrane targeted proteins to interact with membrane phospholipids and other proteins of the exocytotic apparatus termed SNARE proteins. SNARE proteins are required for the process of membrane fusion that is a necessary step in the interaction of exocytotic vesicle with the plasma membrane.



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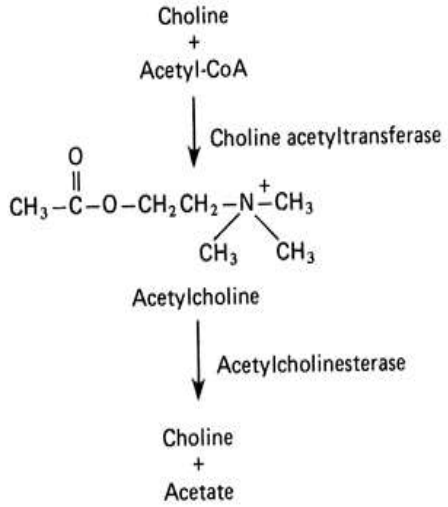
- Once released, ACh must be removed rapidly in order to allow repolarization to take place. The removal of acetylcholine is a hydrolysis reaction catalyzed by the enzyme, acetylcholinesterase (AChE). AChE is a highly active enzyme capable of hydrolyzing on the order of 25,000 molecules of ACh per second. The released choline is then taken back up by the presynaptic neuron where it can once again serve as a substrate for ACh synthesis via choline acetyltransferase.

- Two main classes of ACh receptors have been identified on the basis of their responsiveness to the toadstool alkaloid muscarine and to nicotine, respectively. These receptors are, therefore, termed the muscarinic ACh receptors (mAChRs) and the nicotinic ACh receptors (nAChRs). The muscarinic ACh receptors are G-protein coupled receptors (GPCR) and are also referred to as metabotropic receptors. The nicotinic ACh receptors are ligand-gated ion channels which are also referred to as ionotropic receptors. Both receptor classes are abundant in the human brain.



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Neurotransmitters

- **Taurine.**

✓ Formed from the amino acid cysteine. First, sulfur is oxidized in the SH-group to the residue of sulfuric acid (the process takes place in several stages), then decarboxylation. Taurine has no carboxyl group, but contains a sulfuric acid residue. Participates in the conduction of a nerve impulse in the process of visual perception.

- **Catecholamines: norepinephrine and dopamine.**

✓ They are synthesized by a general mechanism from tyrosine. The key synthesis enzyme is tyrosine hydroxylase, which is inhibited by end products.

✓ Catecholamines exhibit peripheral nervous system excitatory and inhibitory effects as well as actions in the CNS such as respiratory stimulation and an increase in psychomotor activity. The excitatory effects are exerted upon smooth muscle cells of the vessels that supply blood to the skin and mucous membranes. Cardiac function is also subject to excitatory effects, which lead to an increase in heart rate and in the force of contraction. Inhibitory effects, by contrast, are exerted upon smooth muscle cells in the wall of the gut, the bronchial tree of the lungs, and the vessels that supply blood to skeletal muscle. In addition to their effects as neurotransmitters, norepinephrine and epinephrine can influence the rate of metabolism. This influence works both by modulating endocrine function such as insulin secretion and by increasing the rate of glycogenolysis and fatty acid mobilization.

✓ The actions of norepinephrine and epinephrine are exerted upon binding to and activating the adrenergic receptors of which there are nine distinct forms. As indicated, the adrenergic receptors are all members of the GPCR family.

✓ There are two distinct types of adrenergic receptor identified as the α (alpha) and β (beta) receptors. In addition, there are two functionally distinct classes of α adrenergic receptor identified as the α1 and α2 forms.

✓ The α1 receptors consist of the α1A, α1B, and α1D receptors. The ***α1 receptors*** are coupled to Gq-type G-proteins that activate PLCβ resulting in increases in IP3 and DAG release from membrane PIP2. ***The α2 receptors*** consist the α2A, α2B, and α2C receptors. The α2 receptors are coupled to Gi-type G-proteins that inhibit the activation of adenylate cyclase and therefore, receptor activation results in reduced levels of cAMP and consequently reduced levels of active PKA.

✓ The β adrenergic receptors are composed of three types***: β1, β2, and β3*** each of which couple to Gs-type G-proteins resulting in activation of adenylate cyclase and increases in cAMP with concomitant activation of PKA. However, the β2 receptor can switch from Gs to Gi/o signaling following phosphorylation of the receptor by PKA.

✓ Dopamine binds to dopaminergic receptors identified as D-type receptors and there are five receptors identified as ***D1, D2, D3, D4, and D5***. All five dopamine receptors belong to the G-protein coupled receptor (GPCR) family. The D1 and D5 dopamine receptors are coupled to the activation of Gs-type G-proteins and, therefore, receptor activation results in activation of adenylate cyclase. The D2, D3, and D4 dopamine receptors are coupled to Gi-type G-proteins and, therefore, receptor activation results in the inhibition of adenylate cyclase. The D1 and D5 receptors constitute members of the D1-like receptor family. The D2, D3, and D4 receptors constitute members of the D2-like receptor family.

Neurotransmitters

- **Glycine**

✓ Glycine, as a free amino acid functions as a highly important neurotransmitter within the central nervous system, CNS. Glycine and GABA are the major inhibitory neurotransmitters in the CNS. The receptors to which glycine binds were originally identified by their sensitivity to the alkaloid strychnine. Strychnine-sensitive glycine receptors (GlyR) mediate the synaptic inhibition exerted in response to glycine binding. Glycinergic synapses mediate fast inhibitory neurotransmission within the spinal cord, brainstem, and caudal brain. The effects of glycine exert control over a variety of motor and sensory functions, including vision and audition. The GlyR are members of the ionotropic family of ligand-gated ion channels. The binding of glycine leads to the opening of the GlyR integral anion channel, and the resulting influx of Cl– ions hyperpolarizes the postsynaptic cell, thereby inhibiting neuronal firing.

✓ Cellular uptake of glycine, particularly within neurons in the central nervous system (CNS), is regulated by the presence of specific glycine transporters identified as GlyT.

✓ Impaired glutamatergic neurotransmission via the NMDA receptors has been associated with the symptoms of schizophrenia and the associated cognitive deficit. Pharmacologic inhibitors of GlyT1 have some utility to improve impaired NMDA receptor function in psychosis by increasing synaptic glycine concentrations. These transport inhibitors function by increasing extrasynaptic glycine concentrations via inhibition of its neuronal or glial reuptake processes. When used in combination with other antipsychotic medications, GlyT1 inhibitors have been shown to be capable of restoring disturbed gluGlycine Receptors

- **GABA (γ-Aminobutyric acid)**

✓ The amino acid derivative, γ-aminobutyrate (GABA; also called 4-aminobutyrate) is a major inhibitor of presynaptic transmission in the CNS, and also in the retina. Neurons that secrete GABA are termed GABAergic.

✓ GABA cannot cross the blood-brain-barrier and as such must be synthesized within neurons in the CNS. The synthesis of GABA in the brain occurs via a metabolic pathway referred to as the GABA shunt. Glucose is the principal precursor for GABA production via its conversion to 2-oxoglutarate (α-ketoglutarate) in the TCA cycle. Within the context of the GABA shunt the 2-oxoglutarate is transaminated to glutamate by GABA α-oxoglutarate transaminase (GABA-T).

✓ Glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamic acid to form GABA.

✓ The activity of GAD requires pyridoxal phosphate (PLP) as a cofactor. PLP is generated from the B6 vitamins (pyridoxine, pyridoxal, and pyridoxamine) through the action of pyridoxal kinase. Pyridoxal kinase itself requires zinc for activation. A deficiency in zinc or defects in pyridoxal kinase can lead to seizure disorders, particularly in seizure-prone pre-eclamptic patients (hypertensive condition in late pregnancy).

✓ GABA exerts its effects by binding to two distinct receptor subtypes. The GABA-A (GABAA) receptors are members of the ionotropic receptors. The GABA-B (GABAB) receptors belong to the class C family of metabotropic G-protein coupled receptors (GPCR). The GABA-A receptors are members of the ionotropic receptor family and are chloride channels that, in response to GABA binding, increase chloride influx into the GABAergic neuron. The GABA-B receptors are coupled to a G-protein that activates an associated potassium channel that when activated by GABA leads to potassium efflux from the cell. The anxiolytic drugs of the benzodiazepine family exert their soothing effects by potentiating the responses of GABA-A receptors to GABA binding.

Neurotransmitters

- **Serotonin**

✓ Serotonin (5-hydroxytryptamine, 5HT) is formed by the hydroxylation and decarboxylation of tryptophan.

✓ The greatest concentration of 5HT (90%) is found in the enterochromaffin cells of the gastrointestinal tract. Most of the remainder of the body's 5HT is found in platelets and the CNS. Platelets themselves are incapable of synthesizing serotonin but acquire it from plasma via the action of the serotonin transporter (SLC6A4). The effects of 5HT are felt most prominently in the cardiovascular system, with additional effects in the respiratory system and the intestines. Vasoconstriction is a classic response to the administration of 5HT.

✓ Neurons that secrete 5HT are termed serotonergic. Following the release of 5HT, a portion is taken back up by the presynaptic serotonergic neuron in a manner similar to that of the reuptake of norepinephrine.

✓ **Serotonin Receptors.** The function of serotonin is exerted upon its interaction with specific receptors. At least 15 serotonin receptors have been cloned and are classified in seven families: 5HT1, 5HT2, 5HT3, 5HT4, 5HT5, 5HT6, and 5HT7.

✓ Most of these receptors are of the metabotropic family and thus, coupled to G-proteins that affect the activities of either adenylate cyclase or phospholipase Cβ (PLCβ). The 5HT3 class of receptors are ion channels (ionotropic receptors). Like other ionotropic receptors, the 5HT3 receptors are composed of five subunits and are either homopentameric or heteropentameric where in the heteropentameric form there is always at least one 5HT3A subunit..

✓ Some serotonin receptors are presynaptic and others postsynaptic. The 5HT2A receptors mediate platelet aggregation and smooth muscle contraction. The 5HT3 receptors are present in the gastrointestinal tract and are related to emesis (vomiting). Also present in the gastrointestinal tract are 5HT4 receptors where they function in secretion and peristalsis. The 5HT6 and 5HT7 receptors are distributed throughout the limbic system of the brain and the 5HT6 receptors have high affinity for antidepressant drugs.

Neurotransmitters. Peptides.

- **Peptides function as both neurotransmitters and hormones.** They contain from 3 to several tens of amino acid residues. They function only in the higher parts of the nervous system.
- ***Classification of peptides:***

✓ neurohypophyseal hormones (vasopressin, liberins, statins) - both hormones and mediators;

✓ gastrointestinal peptides (gastrin, cholecystokinin). Gastrin makes you feel hungry, cholecystokinin makes you feel full, stimulates contraction of the gallbladder and pancreatic function;

✓ opiate-like peptides (analgesic peptides, endorphins). Interact with the same receptors as opiates (morphine), mimicking their action;

✓ sleep peptides. The molecular nature has not been established. Administration to animals induces sleep;

✓ memory peptides (scotophobin). Accumulates in rat brains during dark avoidance training;

✓ peptides - components of the renin-angiotensin system. The introduction of angiotensin-P into the thirst center of the brain causes the appearance of this sensation and stimulates the secretion of antidiuretic hormone.

- Peptides are formed in reactions of limited proteolysis, are destroyed by the action of proteinases.

Biochemical basis for the occurrence of certain diseases of the nervous system

- **Myasthenia gravis** is a disease based on an increase in cholinesterase activity, as a result of which the mediator acetylcholine is rapidly cleaved and conductivity is blocked at the level of the myoneural synapse. Clinically - pathological muscle fatigue, paresis, weakness. Correction (treatment) - the introduction of proserin, which is a competitive inhibitor of cholinesterase.
- **Schizophrenia** is a disease of the central nervous system, in which the accumulation of a mediator of serotonin occurs in the synapses, which leads to irritation of the corresponding parts of the brain, accompanied by hallucinations and thought disorders.
- **Depressive states** are diseases of the central nervous system associated with depletion of neurotransmitters in the central nervous system.

Compounds affecting synaptic transmission of nerve impulses

- **Nicotine.** Tobacco alkaloid. Simulates the action of acetylcholine on "nicotinic" receptors.
- **Muscarine.** Amanita mushroom alkaloid AtapNa tyssapa. It mimics the action of acetylcholine on muscarinic receptors.
- **Tubocurarine.** The main component of curare venom, obtained from some South American plants. Blocks receptors in the neuromuscular synapses of skeletal muscles. It is used as a muscle relaxant.
- **Dihydroergotamine.** A recovery product of ergotamine, an ergot alkaloid. Blocks a-adrenergic receptors. It is used in the treatment of migraines.
- **Strychnine.** Chilibuha seed alkaloid. Binds to glycine receptors, inhibiting the attachment of glycine to them. It is used as a tonic; in case of an overdose, convulsions occur.
- **Morphine.** Opium alkaloid, drug. It connects with enkephalin receptors, mimicking their action. It is used as a pain reliever.

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