MINISTRY OF PUBLIC HEALTH OF UKRAINE

O. O. BOGOMOLETS NATIONAL MEDICAL UNIVERSITY

Department of Bioorganic and Biological Chemistry

Methodical recommendations for consideration of the topic

"Biochemistry of nerve tissue"

on "Biological and bioorganic chemistry"

FOR STUDENTS OF THE 2ST YEAR OF STUDY OF MEDICAL and STOMATOLOGICAL FACULTIES

Kyiv-2020

Compilers:

Obernikhina N.V., Ph.D.in chemistry, associated professor of bioorganic and biological chemistry department in O. O.Bogomolets National Medical University;

Mykhailova A.G., teaching fellow associated of bioorganic and biological chemistry department in O. O. Bogomolets National Medical University;

Pradii T.P., teaching fellow associated of bioorganic and biological chemistry department in O. O.Bogomolets National Medical University.

Sanzhur T.S., teaching fellow associated of bioorganic and biological chemistry department in O. O. Bogomolets National Medical University.

Edited by *Gayova L.V.,* Dr. Sci. Med., professor, head of bioorganic and biological chemistry department in O.O. Bogomolets National Medical University.

Approved:

At the cycle commission meeting for medical and biological disciplines in O. O. Bogomolets National Medical University in the form Methodical recommendations for the topic "Biochemistry of nerve tissue" from the discipline "Biological and bioorganic chemistry" for students of the 2st year of study of medical and stomatological faculties, protocol № 4 from 11th of February 2019.

At the meeting of the bioorganic and biological chemistry department in O. O. Bogomolets National Medical University in the form Methodical recommendations for the topic "Biochemistry of nerve tissue" from the discipline "Biological and bioorganic chemistry" for students of the 2st year of study of medical and stomatological faculties, protocol № 10 from 19th of December 2018.

O.O. BOHOMOLETS

KYIV NATIONAL MEDICAL UNIVERSITY

DEPARTMENT OF BIOLOGICAL CHEMISTRY

BIOCHEMISTRY OF NERVE TISSUE AND NEUROTRANSMITTERS

Guide for practical work on Biological Chemistry

Methodical instructions are made for students of the 2nd year of medical and dental faculties

Kyiv - 2020

Topic: Nerve tissue: Structure, Chemical composition and Metabolism

Relevance of the topic. Nervous tissue has common features with other tissues as well as specific features due to the nature of the functions that the nervous system performs in the whole organism. Understanding the molecular mechanism nervous system functions, studying the chemical composition and metabolism in normal and pathological conditions allow us to develop modern methods for the diagnosis and treatment of nervous diseases.

Teoretical questions.

1. Nerve tissue: general characteristics of structure and functions.
2. Communication between Neurons. Synapse.
3. Neurotransmitters and receptors.
   3.1. Types of neurotransmitter receptors.
4. Neurotransmitters.
   4.1. Acetylcholine
   4.2. Biogenic amines. Catecholamines
   4.3. Amino Acids (glycine, glutamic acid, GABA).
5. The glutamate-glutamine (GABA) cycling.
6. Neuropeptides.
7. Chemical composition of the nervous tissue.
   7.1. Brain proteins
8. Energy metabolism of the CNS.
9. Metabolisms of ammonia in the CNS.

Chapter 1. THEORETICAL REVIEW.

1. Nerve tissue: general characteristics of structure and functions.

The human nervous system consists of two main parts, the central nervous system ***(CNS)*** and the peripheral nervous system ***(PNS)***. The CNS contains the brain and spinal cord. The PNS comprises the nerve fibers that connect the CNS to every other part of the body. The PNS includes the motor neurons that are responsible for mediating voluntary movement. The PNS also includes the autonomic nervous system which encompasses the ***sympathetic*** nervous system, the ***parasympathetic*** nervous system. The sympathetic and parasympathetic nervous systems are tasked with the regulation of all involuntary activities. Nervous tissue can also be described as gray matter and white matter on the basis of its appearance in unstained tissue. These descriptions are more often used in the CNS. Gray matter is where nuclei are found and white matter is where tracts are found. In the PNS, ganglia are basically gray matter and nerves are white matter. Nervous tissue contains two major cell types, neurons and glial cells. Neurons are the cells responsible for communication through electrical signals. Glial cells are supporting cells, maintaining the environment around the neurons.

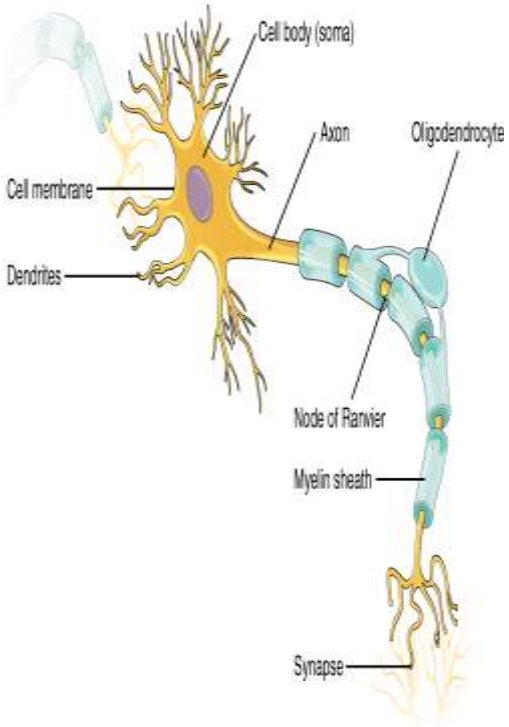


Figure 1. Parts of a Neuron. The major parts of the neuron are labeled on a multipolar neuron from the CNS.

The brain is made up of approximately 100 billion neurons, and trillions of glial cells. An important part of the function of neurons is in their structure, or shape. The three-dimensional shape of these cells makes the immense numbers of connections within

the nervous system possible. The brain is made up of approximately 100 billion neurons, and trillions of glial cells. An important part of the function of neurons is in their structure, or shape. The three-dimensional shape of these cells makes the immense numbers of connections within the nervous system possible. Neurons are polarized cells, based on the flow of electrical signals along their membrane. Neurons are having one, and only one, axon – a fiber that emerges from the cell body and projects to target cells and dendrites, which receive information from other neurons at specialized areas of contact called ***synapses***. Signals are received at the dendrites, are passed along the cell body, and propagate along the axon towards the target, which may be another neuron, muscle tissue, or a gland. ***Figure 1*** shows the relationship of these parts to one another. This gives the neuron a polarity meaning that information flows in this one direction. Neurons produce special chemicals called neurotransmitters that are released at the synapse and serve to transmit a signal to another nerve or to a muscle and gland. Many axons are wrapped by an insulating substance called myelin, which is actually made from glial cells. Myelin acts as insulation.

Glial Cells. Glial Cells, or neuroglia or simply glia, are the other type of cell found in nervous tissue. They are considered to be supporting cells, and many functions are directed at helping neurons complete their function for communication. There are six types of glial cells. Four of them are in the central nervous system (CNS), and two are in the PNS. In the CNS, ***astrocytes, oligodendrocytes, microglia, and ependymal cells*** are found. Astrocytes are important for maintaining the chemical environment around the neuron and are crucial for regulating the blood-brain barrier. Oligodendrocytes are the myelinating glia in the CNS. Microglia act as phagocytes and play a role in immune surveillance. Ependymal cells are responsible for filtering the blood to produce cerebrospinal fluid, which is a circulatory fluid that performs some of the functions of blood in the brain and spinal cord because of the blood-brain barrier (BBB) (***Figure 2.)***. In the PNS, satellite cells are supporting cells for the neurons, and Schwann cells insulate peripheral axon.

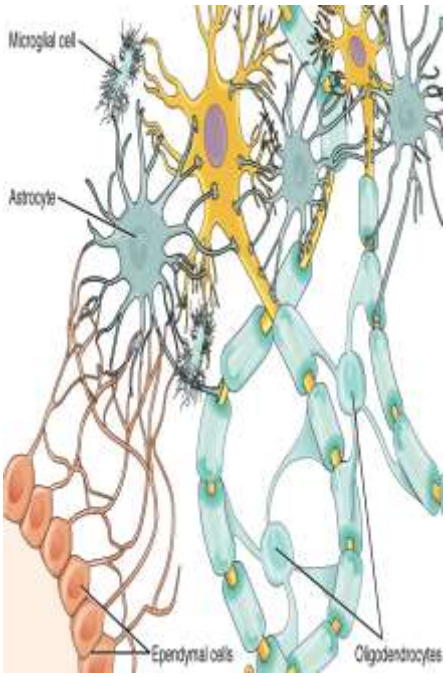


Figure 2. Glial Cells of the CNS. The CNS has astrocytes, oligodendrocytes, microglia, and ependymal cells that support the neurons of the CNS in several ways.

Myelin. Many axons are wrapped by an insulating substance called myelin, which is actually made from glial cells. The membranes of the cells forming the myelin are in close contact, which provides high resistance and low capacitance, thus providing the axon with effective isolation and preventing longitudinal propagation of the pulse. Myelin is a lipid-rich (fatty) substance formed in the central nervous system (CNS) by glial cells called oligodendrocytes and in the peripheral nervous system (PNS) by Schwann cells (***Figure 3.)***.

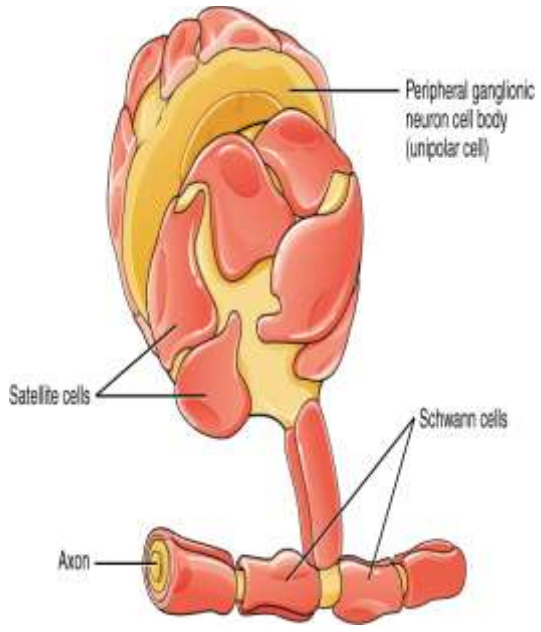


Figure 3. Glial Cells of the PNS. The PNS has satellite cells and Schwann cells.

Myelin, however, is more than just the membrane of the glial cell. Myelin insulates nerve cell axons to increase the speed at which information (encoded as an electrical signal) travels from one nerve cell body to another (as in the CNS) or, for example, from a nerve cell body to a muscle (as in the PNS). The main function of myelin is to quickly conduct a nerve impulse along axons. There are gaps in the myelin covering of an axon. Each gap is called a node of Ranvier and is important to the way that electrical signals travel down the axon.

Due to the fact that ion currents cannot pass through myelin, the input and output of ions is carried out only in the interception region. This leads to an increase in the speed of the nerve impulse. Thus, an impulse is carried out approximately 5-10 times faster in myelinated fibers than in non-myelinated fibers.

*2. Communication between Neurons. **Synapse.***

The Synapse is the point of connection between two neurons or between a neuron and a muscle or gland. The synapse consists of three elements: the presynaptic membrane which is formed by the terminal button of an axon; the postsynaptic membrane which is composed of a segment of dendrite or cell body; the space between these two structures which is called the synaptic cleft **(*Figure 4*)**.

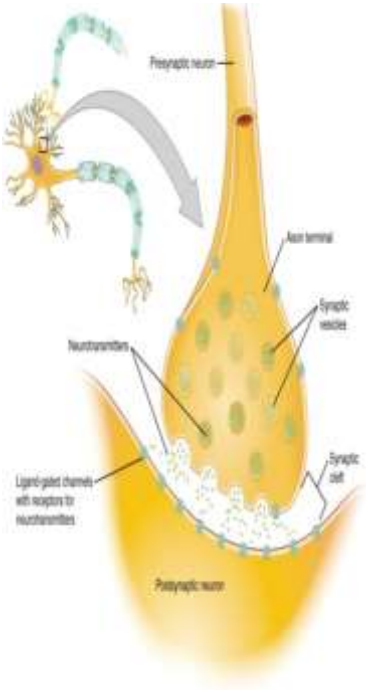


Figure 4. The Synapse.

There are two types of connections between electrically active cells, chemical synapses and electrical synapses. In a ***chemical synapse***, a chemical signal namely, a neurotransmitter is released from one cell and it affects the other cell. In an ***electrical synapse***, there is a direct connection between the two cells so that ions can pass directly from one cell to the next. The basis of the electrical signal is the controlled distribution of ions across the membrane. Transmembrane ion channels regulate when ions can move in or out of the cell, so that a precise signal is generated. This signal is the action potential, which has a very characteristic shape based on voltage changes across the membrane in a given time period. The membrane is normally at rest with established Na^+ and K^+ concentrations on either side. A stimulus will start the

depolarization of the membrane, and voltage-gated channels will result in further depolarization followed by repolarization of the membrane. A slight overshoot of hyperpolarization marks the end of the action potential. While an action potential is in progress, another cannot be generated under the same conditions. While the voltage-gated Na^+ channel is inactivated, absolutely no action potentials can be generated. Once that channel has returned to its resting state, a new action potential is possible, but it must be started by a relatively stronger stimulus to overcome the K^+ leaving the cell.

3. Neurotransmitters and receptors.

Neurotransmitters are stored in the nerve cell's bulbous ends (axons). When an action potential reaches the axon terminals, Ca^{2+} channels open. The concentration of Ca^{2+} increases and the Ca^{2+} ion associates with proteins in the outer surface of neurotransmitter vesicles. The neurotransmitter is released into the small gap between the cells, known as the ***synaptic cleft***. The interaction of neurotransmitter with the receptor on postsynaptic membrane either prompts or inhibits continued electrical impulses along the nerve. Receptors are specific for the neurotransmitter, and the two fit together like a key and lock. One neurotransmitter binds to its receptor and will not bind to receptors for other neurotransmitters, making the binding a specific chemical event (***Figure 4***). There are than 300 known neurotransmitters. There are several groups of neurotransmitters that are found at various synapses in the nervous system.

Neurotransmitters are generally classified into two main categories related to their overall activity, excitatory or inhibitory. Excitatory neurotransmitters exert excitatory effects on the neuron, thereby, increasing the likelihood that the neuron will fire an action potential. Major excitatory neurotransmitters include glutamate, epinephrine and norepinephrine. Inhibitory neurotransmitters exert inhibitory effects on the neuron, thereby, decreasing the likelihood that the neuron will fire an action potential. Major inhibitory neurotransmitters include

GABA, glycine, and serotonin. Some neurotransmitters, can exert both excitatory and inhibitory effects depending upon the type of receptors that are present.

Types of neurotransmitter receptors. As the example above suggests, we can divide the receptor proteins that are activated by neurotransmitters into two broad classes:

- **Ligand-activated ion channels**: These receptors are membrane-spanning ion channel proteins that open directly in response to ligand binding.
- **Metabotropic receptors**: These receptors are not themselves ion channels. Neurotransmitter binding triggers a signaling pathway, which may indirectly open or close channels (or have some other effect entirely).

The first class of neurotransmitter receptors are ***ligand-activated ion channels***, also known as ***ionotropic receptors***. They undergo a change in shape when neurotransmitter binds, causing the channel to open. This may have either an excitatory or an inhibitory effect, depending on the ions that can pass through the channel and their concentrations inside and outside the cell. Ligand-activated ion channels are large protein complexes. They have certain regions that are binding sites for the neurotransmitter, as well as membrane-spanning segments that make up the channel.

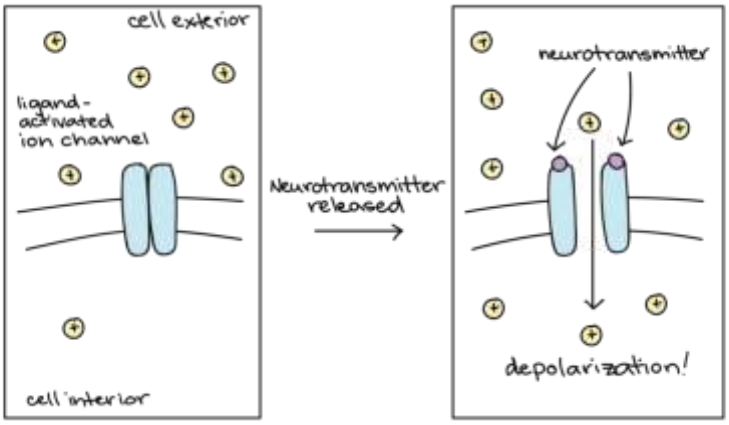


Diagram of ligand-activated channel. When neurotransmitter binds to the channel, it opens and cations flow down their concentration gradient and into the cell causing a depolarization.

Ligand-activated ion channels typically produce very quick physiological responses. Current starts to flow (ions start to cross the membrane) within tens of microseconds of neurotransmitter binding, and the current stops as soon as the neurotransmitter is no longer bound to its receptors. In most cases, the neurotransmitter is removed from the synapse very rapidly, thanks to enzymes that break it down or neighboring cells that take it up.

The second class of neurotransmitter receptors are ***metabotropic receptors.*** Activation of the second class of neurotransmitter receptors only affects ion channel opening and closing indirectly. In this case, the protein to which the neurotransmitter binds – the neurotransmitter receptor is not an ion channel. Signaling through these metabotropic receptors depends on the activation of several molecules inside the cell as ***G protein coupled receptors (GPCR)*** and often involves a second messenger pathway. Because it involves more steps, signaling through metabotropic receptors is much slower than signaling through ligand-activated ion channels.

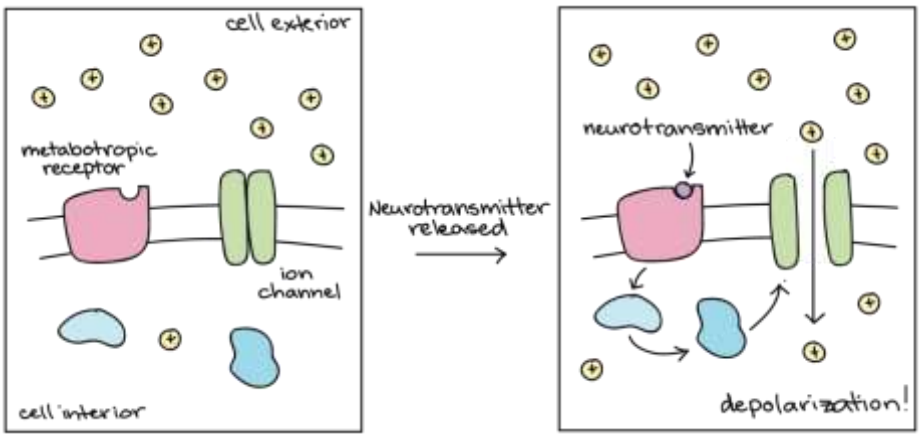
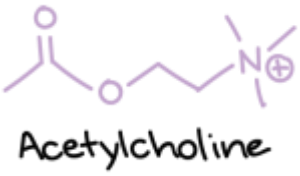


Diagram of one way that a metabotropic receptor can act. The ligand binds to the receptor, which triggers a signaling cascade inside the cell. The signaling cascade causes the ion channel to open allowing cations to flow down their concentration gradient and into the cell, resulting in a depolarization.

Some metabotropic receptors have excitatory effects when they're activated (make the cell more likely to fire an action potential), while others have inhibitory

effects. Often, these effects occur because the metabotropic receptor triggers a signaling pathway that opens or closes an ion channel.

4. Neurotransmitters.



Acetylcholine, the first neurotransmitter discovered, was originally described as "vagus stuff" by Otto Loewi because of its ability to mimic the electrical stimulation of the vagus nerve. It is now known to be a neurotransmitter at all autonomic ganglia, at many autonomically innervated organs. Acetylcholine is a key neurotransmitter at neuromuscular junctions (where nerves connect to muscles) and at many synapses in the CNS.

Synthesis of Acetylcholine. Acetylcholine (ACh) is a simple molecule synthesized from choline and acetyl-CoA through the action of choline O-acetyltransferase.(CAT)

CAT is produced in the cholinergic cell body and transported down the axon to the nerve endings. Both CAT and ACh may be found throughout the neuron, but their highest concentration is in axon terminals. The presence of CAT is the "marker" that a neuron is cholinergic, only cholinergic neurons contain CAT. The majority of the ACh in nerve endings is contained in clear (as viewed in the electron microscope) 100 um vesicles. A small amount is also free in the cytosol. Vesicle-bound ACh is not accessible to degradation by ***acetylcholinesterase***. The uptake of ACh into storage vesicle occurs through an energy-dependent pump.

When an action potential reaches the terminus of a presynaptic neuron a voltage-gated calcium channel is opened. The influx of calcium ions (Ca^{2+})

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. 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.

The cholinergic system has two types of receptors: the ***nicotinic receptor*** and the ***muscarinic receptor***. Both of these receptors are named for drugs that interact with the receptor in addition to acetylcholine. Nicotine will bind to the nicotinic receptor and activate it similar to acetylcholine. Muscarine, a product of certain mushrooms, will bind to the muscarinic receptor. Nicotinic receptors are located at the NMJ, autonomic ganglia and sparsely in the CNS. The ***NMJ nicotinic ACh receptor*** consists of five polypeptide subunits: two α subunits and one each of β, δ, and γ (***Figure 5***). A funnel-shaped internal ion channel is surrounded by the five subunits. The binding surface of the receptor appears to be primarily on the α subunits, near the outer surface of the molecule. The subunits contain recognition sites for agonists, reversible antagonists, and ***α-toxins*** (cobra α-toxin) and α-bungarotoxin). Whereas the NMJ nicotinic receptor is composed of four different species of subunit (2 α, β, γ, δ), the neuronal nicotinic receptor also is composed of only two subunit types (2 α and 3 β).

The nicotinic AChRs are ligand-gated ion channels that form pores in cells' plasma membranes, mediating fast signal transmission at synapses. They are involved in a wide range of physiological processes, and can be either neuronal or muscle-type. The binding of acetylcholine to nicotinic AChRs brings about their activation. When two molecules of acetylcholine bind a nicotinic AchR, a conformational change occurs in the receptor, resulting in the formation of an ion

pore. At the neuromuscular junction, the opening of a pore produces a rapid increase in the cellular permeability of sodium and calcium ions, resulting in the depolarisation and excitation of the muscle cell, thereby producing a muscular contraction. They are is responsible for muscle tone.

The many types of neuronal nicotinic AChRs are located at synapses between neurons, such as in the CNS where they are involved in cognitive function, learning and memory, arousal, reward, motor control and analgesia.

The Nicotinic Receptor is an Ion Channel

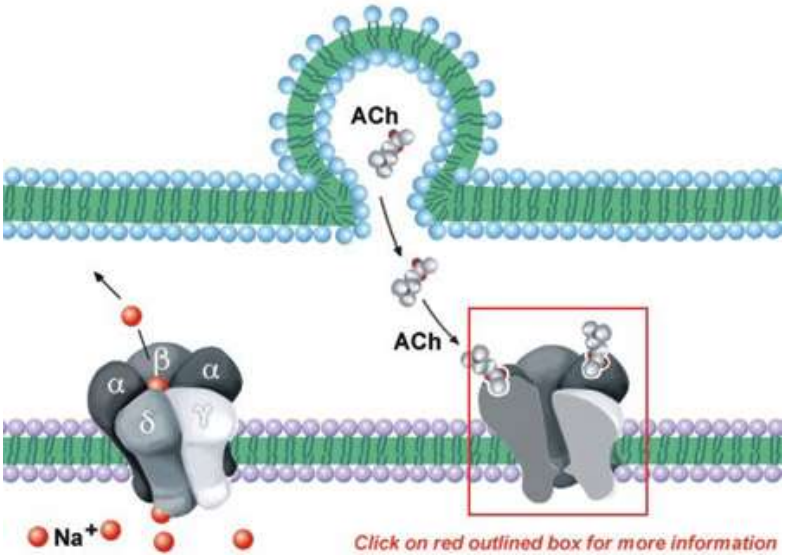


Figure 5. Schematic of the five subunit nicotinic ACh receptor in the postsynaptic membrane at the NMJ. ACh binds to the two a subunits. The bottom half shows the molecular structure of each a subunit of the nicotinic receptor based on cDNA derived amino acid sequence. The β, γ and δ subunits have an analogous structure to the α subunit.

The Muscarinic Receptor is Coupled to G-Proteins

Muscarinic receptors, classified as ***G protein coupled receptors (GPCR)***, are located at parasympathetic autonomically innervated visceral organs, on the sweat glands and piloerector muscles and both post-synaptically and pre-synaptically in the CNS. The muscarinic receptor is composed of a single polypeptide. Seven

regions of the polypeptide are made up of 20-25 amino acids arranged in an α-helix. Because each of these regions of the protein is markedly hydrophobic, they span the cell membrane seven times as depicted. The fifth internal loop and the carboxyl-terminal tail of the polypeptide receptor are believed to be the site of the interaction of the muscarinic receptor with G proteins. The site of agonist binding is a circular pocket formed by the upper portions of the seven membrane-spanning regions. ACh has excitatory actions at the neuromuscular junction, at autonomic ganglion, at certain glandular tissues and in the CNS. It has inhibitory actions at certain smooth muscles and at cardiac muscle.

The responses mediated by muscarinic receptors through G proteins include:

- ***Inhibition of Adenylate Cyclase.*** Reduced cAMP production leads to reduced activation of ***cAMP-dependent protein kinase***, reduced heart rate, and contraction strength.
- ***Stimulation of Phospholipase C.*** The muscarinic receptor activates phosphoinositide-specific phospholipase C, it activate hydrolysis of ***phosphatidylinositol bisphosphate***. The result is yields two second messengers; ***inositol trisphosphate*** (IP_3) and ***diacylglycerol*** (DAG). The DAG activates ***protein kinase C*** and increase Ca^{2+} release from the intracellular storage site.
- ***Activation of K^+ Channels:*** In response to muscarinic cholinergic receptor stimulation, a GTP binding protein also can interact directly with K^+ channels to increase K^+ conductance. This conductance increase increases the resting membrane potential in myocardial and other cell membranes leading to inhibition.

Muscarinic receptors are involved in a large number of physiological functions including heart rate and force, contraction of smooth muscles and the release of neurotransmitters. There are five subtypes of muscarinic AChRs based on pharmacological activity: M1-M5. All five are found in the CNS, while M1-M4 are also found in various tissues

Cholinergic Agonists and Antagonists. Numerous compounds have been identified that act as either agonists or antagonists of cholinergic neurons (see Table 1).

Table 1 of Several Natural Cholinergic Agonists and Antagonists

	Source of Compound	**Mode of Action**
Agonists		
Nicotine	alkaloid prevalent in the tobacco plant	activates nicotinic class of ACh receptors, locks the channel open
Muscarine	alkaloid produced by *Amanita muscaria* mushrooms	activates muscarinic class of ACh receptors
α-Latrotoxin	protein produced by the black widow spider	induces massive ACh release, possibly by acting as a Ca^{2+} ionophore
Antagonists		
atropine (and related compound scopolamine)	alkaloid produced by the deadly nightshade, *Atropa belladonna*	blocks ACh actions only at muscarinic receptors
Botulinus toxin	eight proteins produced by *Clostridium botulinum*	inhibits the release of ACh
α-Bungarotoxin	protein produced by *Bungarus* genus of snakes	prevents ACh receptor channel opening
d-Tubocurarine	active ingredient of curare	prevents ACh receptor channel opening at motor end-plate

Biogenic amines.

They include three classes of neurotransmitters:

- ***Catecholamines***
  - ***Dopamine*** (DA), ***norepinephrine*** (NE, also called ***noradrenaline***) and ***epinephrine*** (E, also called ***adrenaline***).
- ***Indolamines***
  - ***Serotonin*** (5-hydroxytryptamine; 5-HT); is the principal member of this group of compounds. The name serotonin is derived from the fact that this

substance was first isolated from the serum based on its ability to cause an increase in blood pressure.

- ***Histamine*** – has been recognized as a neurotransmitter in the CNS only within the past fifteen years.

Catecholamines. The principal catecholamines are ***norepinephrine, epinephrine*** *and* ***dopamine***. These compounds are formed from the amino acid tyrosine. Tyrosine is produced, primarily, in the liver from phenylalanine through the action of phenylalanine hydroxylase. The tyrosine is then transported to catecholamine-secreting neurons where a series of reactions convert it to dopamine, to norepinephrine and finally to epinephrine (***Figure 6***).

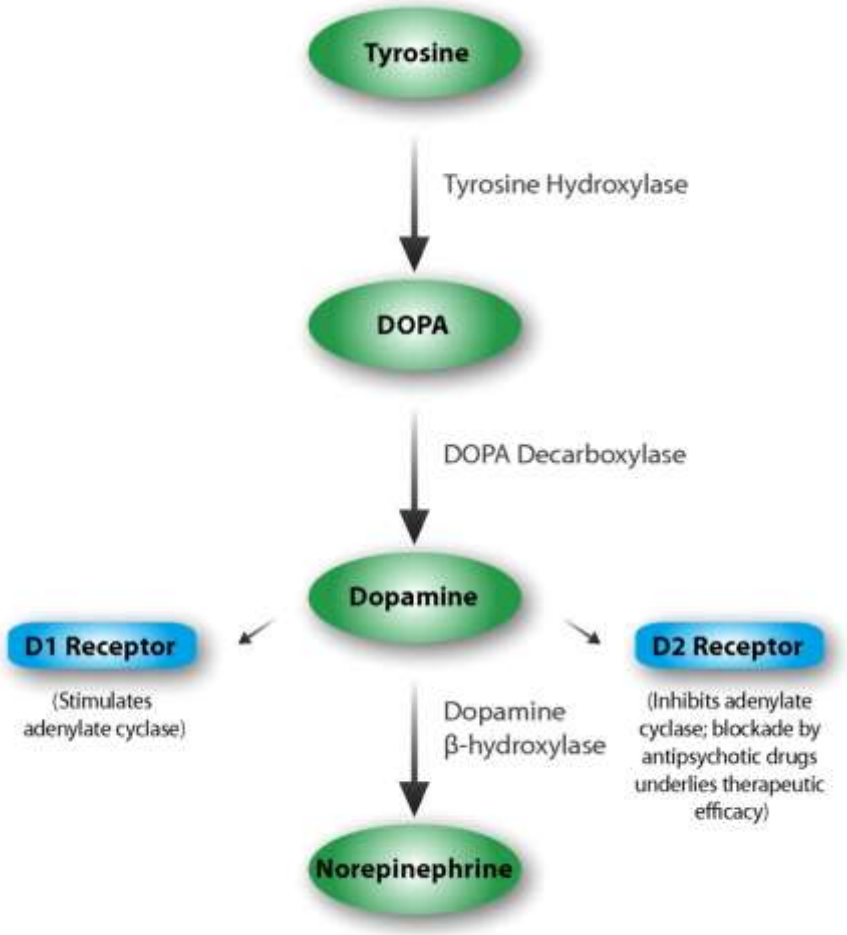
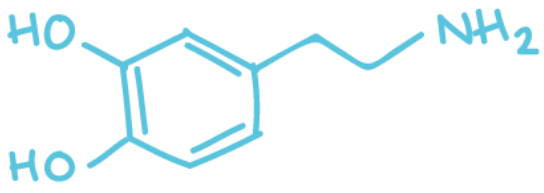


Figure 5. Synthesis of the catecholamines from tyrosine.

Within the ***substantia nigra*** locus of the brain, and some other regions of the brain, synthesis proceeds only to dopamine. Within the ***locus coeruleus*** region of the brain the end product of the pathway is norepinephrine. The presence of high concentrations of tyrosine in the ***locus coeruleus*** and the ***substantia nigra*** leads to increased melanin synthesis which confers on these brain regions a dark bluish coloration observable in brain sections. Indeed, these brain regions are so-called due to the dark bluish-black pigmentation. The Latin term, ***substantia nigra***, means "black substance". The Latin word ***coeruleus*** means "dark blue, blue, or blue-green". Within adrenal medullary chromaffin cells, tyrosine is converted to norepinephrine and epinephrine.

Tyrosine is converted to each of the three catecholamines through a series of four reactions. The tissue from which the neurotransmitter/hormone is derived expresses a specific set, or all, of these enzymes such that only dopamine (***substantia nigra***) is the result, or only norepinephrine (***locus coeruleus***), or both norepinephrine and epinephrine (adrenal medulla). DOPA decarboxylase (also known as aromatic L-amino acid decarboxylase) is encoded by the DDC gene. Dopamine β-hydroxylase is a critical vitamin C (ascorbate) and copper (Cu^{2+})-dependent enzyme.

Dopamine.



Dopamine

Dopamine and his receptors play an essential role in daily life functions. This neurotransmitter and its receptors affect movement, emotion, motivation and the reward system in the brain. Dopamine receptors are expressed in the central

nervous system, specifically in the hippocampal dentate gyrus and subventricular zone. Dopamine receptors are also expressed in the periphery, more prominently in kidney and vasculature.

There are five types of Dopamine receptors, which include D1, D2, D3, D4, D5. Each receptor has a different function.

The function of each dopamine receptor:

- D1: memory, attention, impulse control, regulation of renal function, locomotion
- D2: locomotion, attention, sleep, memory, learning
- D3: cognition, impulse control, attention, sleep
- D4: cognition, impulse control, attention, sleep
- D5: decision making, cognition, attention, renin secretion

The five different dopamine receptors can subdivide into two categories. D1 and D5 receptors group together, and D2, D3, D4 are together in a separate subgrouping. D1 and D5 receptors couple to G stimulatory sites and activate adenylyl cyclase. D2 through D4 receptors couple to G inhibitory sites, which inhibit adenylate cyclase and activate K^+ channels. The D1 receptor is the most abundant out of the five in the central nervous system, followed by D2, then D3, D5 and least abundant is D4. D1 receptors help regulate the development of neurons when the dopamine hormone binds to it.

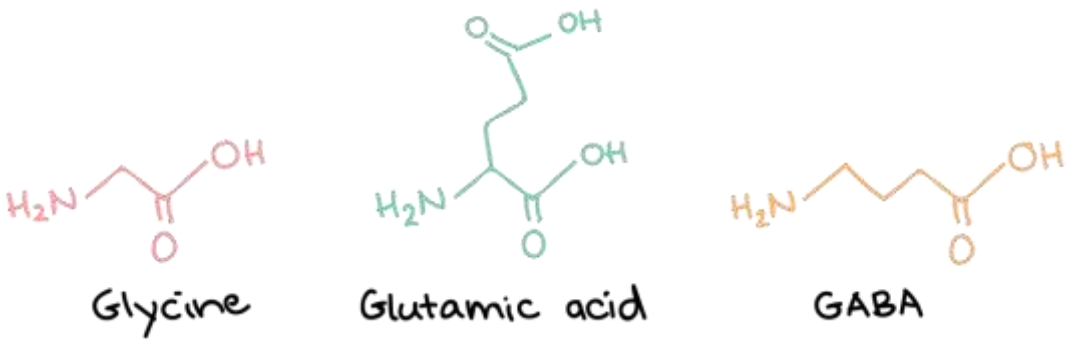
Clinical Significance. Many different diseases involve increased or decreased dopamine leading to different effects. The two primary are Parkinson disease and schizophrenia.

Parkinson disease: If the dopaminergic neurons in the nigro-striatal pathway degenerate, this causes a dysregulation of motor control, a hallmark of Parkinson's Disease. A disease caused by decrease amount of dopamine in the ***substantia nigra*** (in the nigrostriatal pathway). Symptoms include resting tremor, bradykinesia, shuffling gait, postural instability. Treatment for Parkinson disease includes medications that target to increase dopamine availability.

Schizophrenia is associated with an increase in dopaminergic activity. Symptoms include delusions, disorganized speech, hallucinations, disorganized behavior. Treatment for schizophrenia includes medications that target to decrease dopamine availability.

***Catecholamine Catabolism*.** Epinephrine and norepinephrine are catabolized to inactive compounds through the sequential actions of catecholamine-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). Compounds that inhibit the action of MAO have been shown to have beneficial effects in the treatment of clinical depression, even when tricyclic antidepressants are ineffective. The utility of MAO inhibitors was discovered serendipitously when patients treated for tuberculosis with isoniazid showed signs of an improvement in mood; isoniazid was subsequently found to work by inhibiting MAO.

Amino Acids (glycine, glutamic acid, GABA).



These amino acids (GABA - gamma-aminobutyric acid, a derivative of glutamate) have an amino group and a carboxyl group in their chemical structures. Glutamate is one of the 20 amino acids that are used to make proteins. Each amino acid neurotransmitter would be part of its own system, namely the glutamatergic, GABAergic, and glycinergic systems. They each have their own receptors and do not interact with each other. Amino acid neurotransmitters are eliminated from the synapse by reuptake. A pump in the cell membrane of the presynaptic element, or

sometimes a neighboring glial cell, will clear the amino acid from the synaptic cleft so that it can be recycled, repackaged in vesicles, and released again.

Glutamate is a key component in normal brain function. It is believed that over half the synapses that occur in the brain release glutamate as a neurotransmitter. It is an excitatory relative of GABA. An excessive amount of glutamate (usually come from brain damage or a stroke) is very toxic to neurons and may result in brain cell death. Glutamate and gamma-aminobutyric acid (GABA) are the major neurotransmitter in the brain. Inhibitory GABA and excitatory glutamate work together to control many processes, including the brain's overall level of excitation. A balanced interaction is required to maintain the physiological homeostasis, while prolonged imbalance can lead to disease.

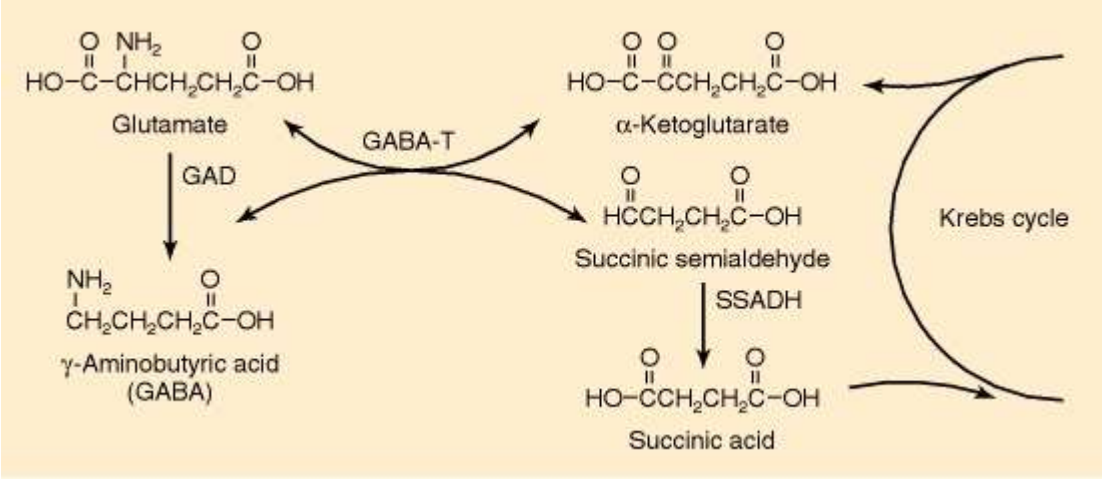
5. The glutamate-glutamine (GABA) cycling.

Three enzymatic reactions are involved in the GABA metabolic pathway, called the GABA shunt. GABA mainly synthetized through a decarboxylation of glutamate catalyzed by glutamate decarboxylase, coenxyme is pyrodoxal phosphate. GABA is subsequently transported into the mitochondrion where it is catabolized by GABA transaminase to succinic semialdehyde (SSA). SSA can be oxidized by the mitochondrial succinic semialdehyde dehydrogenase to produce succinate or reduced to γ-hydroxybutyrate (GHB) by the cytosolic γ-hydroxybutyrate dehydrogenase.

The GABA accumulated in the cytosol is then transferred to the mitochondria and converted first to Succinic semialdehyde and then to Succinic acid, which enters the Krebs cycle.

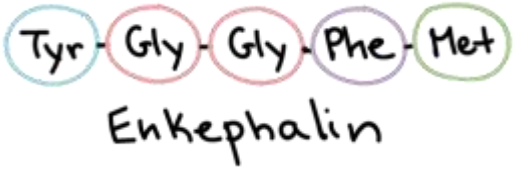
The GABA shunt is a closed-loop process with dual purpose of producing and conserving the supply of GABA. GABA is present in high concentrations (millimolar) in many brain regions. These concentrations are about 1000 times higher than concentrations of classical monoamine neurotransmitter in the same regions. This is in accord with the powerful and specific action of GABAergic

neurons in this regions. Glucose is the principal precursor for GABA production in vivo, although pyruvate and other amino acids also can act as precursors.



The GABA shunt

6. Neuropeptides.



The ***neuropeptide*** is a neurotransmitter molecule made up of chains of amino acids connected by peptide bonds. There are a great many different neuropeptides. As many as 50 different peptides have been shown to exert their effect on neural cell function. Some neuropeptides are quite short, such as ***Met-enkephalin***, which is five amino acids long. Others are long, such as ***Beta-endorphin***, which is 31 amino acids long. Neuropeptides are often released at synapses in combination with another neurotransmitter, and they often act as hormones in other systems of the body, such as ***Vasoactive intestinal peptide (VIP)*** or **Substance P**, which carries pain signals and **Neuropeptide Y**, which stimulates eating and may act to prevent seizures. Several of these peptide transmitters are derived from the larger protein ***proopiomelanocortin*** (POMC). Neuropeptides are responsible for mediating sensory and emotional responses including pain and pleasure, hunger, sex, drive etc.

7. Chemical composition of the nervous tissue.

Nerve tissue is composed of: Water – 80 percent; Solids – 20 per cent.

The solids are mainly composed of proteins, lipids, small amounts of organic extracts and inorganic salts. Proteins are about 38 to 40 per cent of the total solids. They include different globulins, nucleoproteins, and a characteristic albuminoid called neurokeratin. The lipid contents are 50 to 54 per cent of the total solids.

The important lipids are phospholipids, cholesterol, cerebrosides, amino-lipids, and sulphur containing lipids. The principal inorganic salts are potassium phosphate and chloride, with smaller amounts of sodium and other alkaline elements. Potassium is highly significant in the nerve impulse.

The water content of brain is little more than that of spinal cord. In brain too the grey matter which represents a concentration of nerve cell bodies contains more water than the whole matter where the nerve fibres are mainly found. A fraction of the brain proteins remains combined with copper forming ceruloplasmin.

An increased deposition of copper is found in the brain tissue in Wilson's disease. White matter and the peripheral nerves contain a little more cerebrosides, free cholesterol, and sphingomyelin than the brain grey matter. The considerable increase in the concentration of sphingomyelin is found in Niemann-Pick disease.

Nervous tissue is characterized by high lipid and protein content. It does not contain large amounts of saccharides. Complex lipids (e.g. phospholipids and sphingophospholipids) and unesterified cholesterol are the most abundant lipids. Most of the lipids of the nervous system are found in myelin sheaths. Lipids account for about 70–80% of the myelin dry mass, in contrast to other membranes where lipids make up approximately 40%. The major lipid constituents of myelin are cholesterol, glycerophospholipids, and glycosphingolipids. In addition to the above-mentioned lipids, other less abundant lipid species are present in myelin and in brain cells. These include derivatives of cholesterol, especially 24S-hydroxycholesterol, and neuroactive steroids, and derivatives of long chain fatty

acids such as prostaglandins, to name a few. Under physiological conditions, plasma cholesterol cannot be taken up either by glial cells or neurons, therefore all the cholesterol necessary for myelin biogenesis and reshaping, synthesis of neuroactive steroids, etc., is directly synthesized in the brain and circulated between glial cells and neurons by means of transporters.

Neurons are known to be able to synthesize the longest fatty acids in the human body and the presence of **very long chain FA** is quite usual (often in the form of hydroxy acids). Fatty acids are essential moieties for the synthesis of glycerophospholipids and sphingolipids, especially in myelinating cells, i.e. oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system. Fatty acids can be either synthesized in situ or taken up from systemic circulation. Non esterified fatty acids, present in plasma as albumin complexes, cross the blood brain barrier and reach brain cells, mainly by means of a rather simple mechanism, that is by passive diffusion. Fatty acids are then used as building blocks of complex lipids or for the synthesis of neuromodulatory lipids, e.g. prostaglandins. It is worth noting that, despite the high-energy content of aliphatic chains, only a minor percentage of fatty acids is used as fuel for ATP production in brain cells. Low rate oxidation of fatty acids, in both neurons and glial cells, coupled with active glycolysis in astrocytes, displays some key biochemical advantages, i.e. more rapid generation of ATP, lower oxygen consumption, and less risk of generating reactive oxygen species, which altogether result extremely useful to the brain. Polyunsaturated fatty acids (PUFAs) hold a very special position, being essential for brain growth and development and supporting cognitive development and memory. TAG are missing.

Brain proteins. Proteins of nervous tissue have an indispensable role as ***channels, transporters***, ***receptors*** and neurotransmitters. The most important transporter of neuronal membrane is the ***Na^+/K^+-ATPase***, responsible for a continuous maintenance of the ***resting membrane potential***, even at the cost of a

high energy consumption. It makes up 70 % of the total energy expenditure of neurons and 30 % in the case of other cells.

Nerve tissue contains neurospecific proteins, which have a special structure and function. Neurospecific proteins can appear in cerebrospinal fluid or blood serum with damage to nerve tissue and the development of certain pathological conditions of the body.

Substance P (SP protein) refers non-specific proteins. Substance P is an 11-amino acid peptide that belongs to the tachykinin neuropeptide family that includes neurokinin A and B. It is distributed in both the central and peripheral nervous systems and plays an important role in the regulation of the neuronal life cycle, the transmission and perception of pain, autonomic reflexes, and vasodilation. Substance P has also been implicated in the development of cancer; it is overexpressed in many different cancers and can induce the proliferation of tumor cells, angiogenesis, and migration. SP serves to generally enhance cellular immunity. It appears to have several effects on mast cells that contribute to neurogenic inflammation. For example, it stimulates mast cell degranulation and release of histamine. Many additional roles for SP have been described. It was found that SP improves wound healing when administered exogenously to a laser-induced skin wound.

Calbindin, a highly conserved protein with Ca^{2+}-sensing and Ca^{2+}-buffering capabilities, is abundant in brain and sensory neurons. This protein contains six EF-hand subdomains, four of which bind Ca^{2+} with high affinity. Calbindin can be reconstituted from six synthetic peptides corresponding to the six EF-hands, indicating a single-domain structure with multiple interactions between the EF-hand subdomains. In this study, we have undertaken a detailed characterization of the Ca^{2+}-binding and oligomerization properties of each individual EF-hand peptide using CD spectroscopy and analytical ultracentrifugation. Under the conditions tested, EF2 is monomeric and does not bind Ca^{2+}, whereas EF6, which binds Ca^{2+} weakly, aggregates severely. We have therefore focused this study on the high-affinity binding sites, EF-hands 1, 3, 4, and 5. Our sedimentation

equilibrium data show that, in the presence of Ca^{2+}, EF-hands 1, 3, 4, and 5 all form dimers in solution in which the distribution between the monomer, dimer, and higher order oligomers differs. The processes of Ca^{2+} binding and oligomerization are linked to different degrees, and three main mechanisms emerge. For EF-hands 1 and 5, the dimer binds Ca^{2+} more strongly than the monomer and Ca^{2+} binding drives dimerization. For EF-hand 4, dimer formation requires only one of the monomers to be Ca^{2+}-bound. In this case, the Ca^{2+} affinity is independent of dimerization. For EF-hand 3, dimerization occurs both in the absence and presence of Ca^{2+}, while oligomerization increases in the presence of Ca^{2+}.

Amyloid precursor protein (APP) is an integral membrane protein expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated as a regulator of synapse formation, antimicrobial activity, and iron export. APP is best known as the precursor molecule whose proteolysis generates ***beta amyloid (Aβ)-tau protein,*** a polypeptide containing 37 to 49 amino acid residues, whose amyloid fibrillar form is the primary component of amyloid plaques found in the brains of Alzheimer's disease patients.

Alzheimer’s disease (AD), the leading cause of dementia worldwide, is characterized by the accumulation of the β-amyloid peptide (Aβ) within the brain along with hyperphosphorylated and cleaved forms of the microtubule-associated protein. Genetic, biochemical, and behavioral research suggest that physiologic generation of the neurotoxic Aβ peptide is the crucial step in the development of AD. APP is a single-pass transmembrane protein expressed at high levels in the brain and metabolized by a series of proteases. Why Aβ accumulates in the brains of elderly individuals is unclear but could relate to changes in APP metabolism or Aβ elimination.

8. ***Energy metabolism of the CNS.***

Although brain constitutes only 2 % of the total body weight its metabolic demands are extremely high. It utilizes around 20 % of the total oxygen and 20 % of the total glucose consumption. The biggest share of its consumption is used to maintain the membrane potential through Na^+/K^+-ATPase and other processes involved in transport of ions across the membrane.

Brain is at the same time the most sensitive organ to oxygen or glucose deficit. Shortage of oxygen causes unconsciousness within few tenths of seconds and the damage to neuronsbecomes irreversible after about 5 minutes. The rate of neuronal death depends on many factors, for example temperature. People with hypothermia have significantly reduced cellular metabolism and thus the demands for oxygen and nutrients supply decrease leading to a longer survival in their absence.

The brain daily consumption glucose is about ***120 g***. The penetration of glucose into the brain tissue is not dependent on insulin action, it doesn't cross the blood-brain barrier. The effect of insulin appears only in the peripheral nerves.

Regarding other energy sources, our brain (unlike most of the other peripheral tissues) ***does not utilize fatty acids***. Transported in bloodstream bound to the albumin, fatty acids are unable to cross the hematoencephalic barrier. However, during a long-term starvation brain metabolism ***adapts to the consumption of ketone bodies*** (synthesized from the excess of acetyl-CoA). A full adaptation develops approximately within three weeks of starvation. After this period, the brain is able to ***cover up to 50% of its energy expenditure from the oxidation of ketone bodies***.

9. Metabolisms of ammonia in the CNS.

Ammonia is able to freely cross the hematoencephalic barrier. If its concentration in blood increases (the upper physiological limit is around 50

μmol/l) it significantly interferes with the brain metabolism. Ammonia incorporates into α-ketoglutarate and glutamate thus stopping the Krebs cycle and causing a depletion of ATP together with accumulation of glutamine and glutamate in astrocytes. Metabolisms of both astrocytes and neurons collapse. Excess of glutamate leads to a disruption in its transport from synaptic cleft and causes a change in osmotic relationship between the inner and outer environment. The resulting influx of water leads to a brain edema (intracellular at first and later extracellular as well).

There are many conditions that may cause hyperammonemia, for example an insufficient synthesis of urea due to the damage to liver function.

Chapter 2. PRACTICAL PART .

Practical work.

Task number 1. Determination of cholinesterase activity in blood serum using Michel's titration method.

Principle of the method. The base method for the enzymatic hydrolysis of acetylcholine with the formation of acetic acid, which is determined by titration with sodium hydroxide.

Progress. In two tubes 1 ml of acetylcholine is added 1.5%, 1 ml of the test serum is added to one of them (tested), and 1 ml of pre-inactivated (at 56° C for 30 min.) Serum is added to another test tube (control). In each of the tubes, 2 to 3 drops of phenolphthalein are added, followed by titration with 0.01 M sodium hydroxide. ***Calculation***: Subtract the difference V = Vd – Vk, where Vd is the amount of ml of 0.01 M NaOH, which went to titration of the test sample; Vк is the number of ml of 0.01 M NaOH, which went to titration of the control sample. Normal values: 2 - 4 ml of 0.01M sodium hydroxide, which went to titration with 1 ml of whey. Normal activity values: 45 - 95 μmol / (s-l).

Make a conclusion.

Clinical and diagnostic significance. The activity of cholinesterase (CE) in healthy people can vary considerably, however, it is quite stable in one and the

same person. CHE (butyrylcholinesterase) refers to the secretory enzymes of liver cells. Unlike most other enzymes, its activity in the blood in diseases of this organ decreases, as the mechanisms of enzyme synthesis in hepatocytes are violated. Significant decrease in CHE activity is observed in acute and chronic hepatitis, liver cirrhosis, malignant liver tumors. Determination of CHE activity in blood serum is used most often as a prognostic criterion for acute and especially chronic lesions of the liver parenchyma with organophosphorous poisons. The degree of decrease in enzyme activity indicates the severity and spread of liver cell damage. CHE activity in serum slightly increases with certain mental illnesses, especially with manic-depressive psychosis, anxiety states and depressive neuroses, with schizophrenia, multiple sclerosis, especially in patients with progressive form of the pathological process, which is accompanied by a clear demyelination. A significant increase in AChE activity in the amniotic fluid may indicate severe damage to the fetal nervous system**.**

Situational challenges

Task number 1.

Patients with alcohol receive the bulk of calories with alcohol. They may have a characteristic deficiency of thiamine (Vernicke-Korsakov's syndrome), in which there is a violation of the functions of the nervous system, psychosis, memory loss.

Reducing the activity of a multi-enzyme complex due to these changes?

Which coenzyme form of thiamine is included in this complex?

Answer standard: Pyruvate decarboxylase complex.

Wernicke-Korsakov syndrome is a neurodegenerative process caused by thiamine deficiency. Coenzyme form of thiamine are thiamine dyphosphate; Thiamine is contained in the membranes of axons and participates in biochemical reactions in neurons. With thiamin deficiency, acetylcholine mediator synthesis is disturbed, which is characterized by central and peripheral neuropathy and leads to

disruption to the functions of the nervous, cardiovascular and endocrine and digestive systems. The vitamin B1 deficiency leads to beriberi disease.

Task number 2

It is known that the brain for energy supply uses glucose, why does glycogen, which makes up the energy reserve of the organism, do not form a reserve in such an important tissue as the brain?

Answer standard: Constant and continuous inflow of glucose and oxygen from the bloodstream is a necessary condition for energy supply of nerve cells. A rigid dependence on the intake of glucose is due to the fact that the glycogen content in the nerve tissue is negligible (0.1% of the brain mass) and can not provide the brain with energy even for a short time. High rate of glucose consumption by nerve cells is provided, first of all, by the work of highly active brain hexokinase.

Task number 3

When you drink alcohol, you get addicted to it.

What biochemical mechanisms are at the heart of alcoholism?

Answer standard: Ethanol modifies opioid receptors and the content of endogenous opioid neuropeptides in the brain: β-endorphin, enkephalins, endomorphins.

Ethanol under the action of the enzyme alcohol dehydrogenase quickly turns into acetic aldehyde, which is many times more toxic than the alcohol itself. Acetic aldehyde is associated with the exchange of biogenic amines, mainly serotonin and dioxyphenylamine, a disruption in the metabolism of the latter leads to the formation of morphine-like substances (normorphine, codeine, norcodeine) in the brain. This leads to a predilection for alcohol.

Key Terms.

Alzheimer's disease: A debilitating form of *dementia*, this progressive and irreversible *neurodegenerative disease* results in the development of protein plaques and tangles that damages *neurons* and interfere with neural signaling, ultimately affecting *memory* and other important *cognitive* skills.

amyloid-beta (Aβ) protein: A naturally occurring protein in brain cells. Large, abnormal clumps of this protein form the *amyloid plaques* that are a physiological hallmark of *Alzheimer's disease*. Smaller groupings (oligomers) of Aβ seem more toxic to brain cells and are thought by many researchers to play an important role in the *Alzheimer's disease* process.

amyloid plaque: The sticky, abnormal accumulations of *amyloid-beta protein* aggregate around *neurons* and *synapses* in the *memory* and intellectual centers of the brain, in people with *Alzheimer's*. These are sometimes referred to as neuritic plaques or senile plaques. While amyloid plaques have long been considered markers of *Alzheimer's*, they are also found to some extent in many cognitively normal elderly people. The plaques' role in *Alzheimer's* neurodegeneration remains unclear.

biogenic amine: Class of neurotransmitters that are enzymatically derived from amino acids but no longer contain a carboxyl group

blood-brain barrier: A protective barrier that separates the brain from the blood circulating across the body. The blood-brain barrier is semipermeable, meaning it allows the passage of water as well as molecules like *glucose* and other *amino acids* that help promote neural function.

Endorphins (contracted from endogenous morphine): Endogenous opioid neuropeptides and peptide *hormones* produced by the brain, in response to pain or *stress*. They are produced and stored in the pituitary gland. They work similarly to a class of drugs called opioids.

ion channel: A pore in the membrane of a *neuron* that allows *ions* to pass through, helping to shape *action potentials*.

ionotropic receptor: Neurotransmitter receptor that acts as an ion channel gate, and opens by the binding of the neurotransmitter

ligand-gated channels: Another name for an ionotropic receptor for which a neurotransmitter is the ligand

metabotropic receptor: Neurotransmitter receptor that involves a complex of proteins that cause metabolic changes in a cell

muscarinic receptor: Type of acetylcholine receptor protein that is characterized by also binding to muscarine and is a metabotropic receptor

myelin: The fatty substance that encases most *nerve cell axons*, helping to insulate and protect the nerve fiber and effectively speeding up the transmission of *nerve impulses*.

myelin sheath: Lipid-rich layer of insulation that surrounds an axon, formed by oligodendrocytes in the CNS and Schwann cells in the PNS; facilitates the transmission of electrical signals

nicotinic receptor: Type of acetylcholine receptor protein that is characterized by also binding to nicotine and is an ionotropic receptor

node of Ranvier: Gap between two myelinated regions of an axon, allowing for strengthening of the electrical signal as it propagates down the axon

Parkinson's disease: A *neurodegenerative disorder* characterized by tremor, slowed movement, and speech changes due to the death of *dopamine neurons* located in the *substantia nigra*.

reuptake: A process by which released *neurotransmitters* are absorbed for subsequent re-use.

schizophrenia: A *neurodevelopmental disorder* characterized by disordered thinking, delusions, and hallucinations. It affects less than 1% of Americans.

stroke: A neurological event that occurs when the blood supply to the brain is blocked, depriving the tissue of oxygen, or when there is a bleed into the brain due to the rupturing of an artery.

substantia nigra: This small region in the *midbrain* is part of the brain's reward system. In *Parkinson's disease*, the *dopamine neurons* in this region die off, leading to the disorder's movement-related and *cognitive* symptoms.

tau protein: A type of protein abundantly found in *neurons*. When this protein is not adequately cleared from the brain, it can form tangles that are a key pathology of several *neurodegenerative disorders* including *frontotemporal degeneration*, *CTE*, and *Alzheimer's disease*.

Nerve tissue: Structure, Chemical composition and Metabolism

Tests from Krok – 1 restractor «A»)

1. Cell membrane restpotential changed from-85 to-90mV. It can becaused by activation of the following cell membrane channels:

A. *Potassium

B. Sodium

C. Potassium and sodium

D. Calcium E. Potassium and calcium

2. An 84-year-old patient suffers from parkinsonism. One of the pathogenetic development elements of this disease is deficiency of a certain mediator in some of the brain structures. Name this mediator:

A. *Dopamine

B. Adrenaline

C. Noradrenaline

D. Histamine

E. Acetylcholine

3. A 50-year-old man came to a hospital with complaints of memory disorders, painful sensations along the nerve trunks, decreased mental ability, circulatory disorders and dyspepsia. Anamnesis states excessive alcohol consumption. What vitamin deficiency can result in such symptoms?

A. *Thiamine

B. Niacin

C. Retinol

D. Calciferol

E. Riboflavin

4. A patient with parkinsonism was prescribed levodopa, which led to rapid improvement of the patient's condition. What is the mechanism of action of this drug?

A. *Stimulation of dopamine synthesis

B. Muscarinic acetylcholine receptor blockade

C. Stimulation of dopamine receptors

D. Anticholin esterase action

E. Muscarinic acetylcholine receptor stimulation

5. Decarboxylation of glutamate induces production of gamma aminobutyric acid (GABA) neurotransmitter. After breakdown, GABA is converted into a metabolite of the citric acid cycle, that is:

A. *Succinate

B. Citric acid

C. Malate

D. Fumarate

E. Oxaloacetate

6. Degenerative changes in posterior and lateral columns of spinal cord (funicular myelosis) caused by methylmalonic acid accumulation occur in patients with *B*12-deficiency anemia. This results in synthesis disruption of the following substance:

A. *Myelin

B. Acetylcholine

C. Norepinephrine

D. Dopamine

E. Serotonin

7. Disruption of nerve fiber myelinogenesis causes neurological disorders and mental retardation. These symptoms are typical for hereditary and acquired alterations in the metabolism of:

A. *Sphingolipids

B. Neutral fats

C. Higher fatty acids

D. Acetylcholine

E. Dopamine

8. A patient with signs of emotional lability that result in troubled sleep has been prescribed nitrazepam. Specify the sleep inducing mechanism of this drug:

A. *GABA-ergic system activation

B. Blockade of opiate receptors

C. Inhibition of stimulating amino acids

D. H1-histamine receptors stimulation

E. Supression of serotonergic neurotransmission

9. A patient complained about dizziness, memory impairment, periodical convulsions. It was revealed that these changes were caused by a product of decarboxylation of glutamic acid. Name this product:

A. *GABA

B. Pyridoxal phosphate

C. TDP

D. ATP

E. UDP

10. A patient presents with dysfunction of the cerebral cortex accompanied by epileptic seizures. He has been administered a biogenic amine synthetized from glutamate and responsible for central inhibition. What substance is it?

A. *γ-aminobutyric acid

B. Serotonin C.

Dopamine

D. Acetylcholine

E. Histamine

11. An unconscious patient was taken by ambulance to the hospital. On objective examination the patient was found to have no reflexes, periodical convulsions, irregular breathing. After laboratory examination the patient was diagnosed with hepatic coma. Disorders of the central nervous system develop due to the accumulation of the following metabolite:

A. *Ammonia

B. Urea

C. Glutamine

D. Bilirubin

E. Histamine

12. An alcoholic suffers from alcoholic psychosis with evident psychomotor agitation. What neuroleptic drug should be administered for emergency aid?

A. *Aminazine

B. Diazepam

C. Sodiumbromide

D. Reserpine

E. Halothane

13. A patient who has been taking a drug for a long time cannot abruptly stop its use, because this may lead to psychic and somatic dysfunctions. Name the syndrome of different disorders caused by a drug withdrawal:

A. *Abstinence

B. Sensibilization

C. Idiosyncrasy

D. Tachyphylaxis

E. Cumulation

14. Depressions and emotional insanities result from the deficit of noradrenalin, serotonin and other biogenic amines in the brain. Their concentration in the synapses can be increased by means of the antidepressants that inhibit the following enzyme:

A. *Monoamine oxidase

B. Diamine oxidase

C. L-amino-acid oxidase

D. D-amino-acid oxidase

E. Phenylalanine-4-monooxygenase

15. Pharmacological effects of antidepressants are based upon blocking (inhibiting) the enzyme that acts as a catalyst for the breakdown of biogenic amines noradrenalin and serotonin in the mitochondria of cephalic neurons. What enzyme takes part in this process?

A. *Monoamine oxidase

B. Transaminase

C. Decarboxylase

D. Peptidase

E. Lyase

16. A 9-month-old infant is fed with artificial formulas with unbalanced vitamin *B*6 concentration. The infant presents with pellagral dermatitis, convulsions, anaemia. Convulsion development might be caused by the disturbed formation of:

A. *GABA

B. Histamine

C. Serotonin

D. DOPA

E. Dopamine

17. Cerebral trauma caused increase of ammonia formation. What aminoacid takes part in removal of ammonia from cerebral tissue?

A. *Glutamic

B. Tyrosine

C. Valine

D. Tryptophan

E. Lisine

18. Ammonia is a very toxic substance, especially for nervous system. What substance takes the most active part in ammonia detoxication in brain tissues?

A. *Glutamic acid

B. Lysine

C. Proline

D. Histidine

E. Alanine

19. A patient presented to a hospital with complaints about quick fatigability and significant muscle weakness. Examination revealed an autoimmune disease that causes functional disorder of receptors in the neuromuscular synapses. This will result in the disturbed activity of the following mediator:

A. *Acetylcholine

B. Noradrenaline

C. Dopamine

D. Serotonin

E. Glycine

20. Glutamate decarboxylation results in formation of inhibitory transmitter in CNS. Name it:

A. *GABA

B. Glutathione

C. Histamine

D. Serotonin

E. Asparagine

21. In an excitable cell the ion channels were blocked. It hasn't changed essentially the value of rest potential, but the cell lost its ability to generate AP (action potential). What channels were blocked?

A. *Natrium

B. Potassium

C. Natrium and potassium

D. Chloric

E. Calcium

Recommended literature:

1. Біологічна хімія/Ю.І.Губський, І.В.Ніженковська, М.М.Корда та ін.; за ред. Ю.І.Губського, І.В.Ніженковської. – К.: ВСВ «Медицина», 2016. – С. 507 – 525.

2. Губський Ю.І. Біологічна хімія. – Київ-Тернопіль: Укрмедкнига, 2000. – 508 с.

3. Губський Ю. І. Біологічна хімія. – Київ-Вінниця: Нова книга, 2009. С. 625 – 644.

4. Гонський Я.І., Максимчук Т.П. Біохімія людини. - Тернопіль:Укрмедкнига, 2002. – 744с.

5. Скляров О.Я., Фартушок Н.В., Бондарчук Т.І. Біологічна хімія. - Тернопіль: ТДМУ, 2015. – С. 601 – 620.

6. Біологічна хімія. Тести та ситуаційні задачі. / За ред. О.Я. Склярова. – Львів.: Вид-во ЛНМУ, 2015. – С. 437-450.

7. Клінічна біохімія - За ред. Склярова О.Я. –Київ: Медицина, 2006. -432 с.

8. Клінічна біохімія. Курс лекцій для студентів вищих навчальних медичних закладів / За редакцією проф. Склярова О.Я., Львів, 2004.

9. Практикум з біологічної хімії /За ред. проф. О.Я. Склярова. – К.: Здоров'я, 2002. – 298

Additional literature:

1. Биохимия с упражнениями и задачами: учебник для вузов / под ред. чл.-корр. РАН Е.С. Северина. М.: ГЭОТАР-Медиа, 2010. – 384 с.

2. Биохимия с упражнениями и задачами: учебник для вузов / под ред. чл.-корр. РАН Е.С. Северина. – М.: ГЭОТАР-Медиа, 2011. – 624 с.

3. Біохімічний склад рідин організму та їх клініко-діагностичне значення /За ред. проф. Склярова О.Я., Київ: Здоров'я, 2004. – 191с.

4. Біохімія ензимів. Ензимодіагностика. Ензимопатологія. Ензимотерапія / Скляров О., Сольскі Я., Великий М., Фартушок Н., Бондарчук Т., Дума Д.– Львів: Кварт.- 2008 –218 с.

5. Вільм Ф. Ганонг. Фізіологія людини. - Львів: БаК, 2002. – 767с.

6. Марри Р., Греннер Д., Мейес П., Родуэлл В. Биохимия человека. Т.2. – М.: Мир; Бином. Лаборатория знаний, 2009. – С. 5-14, 35-81.