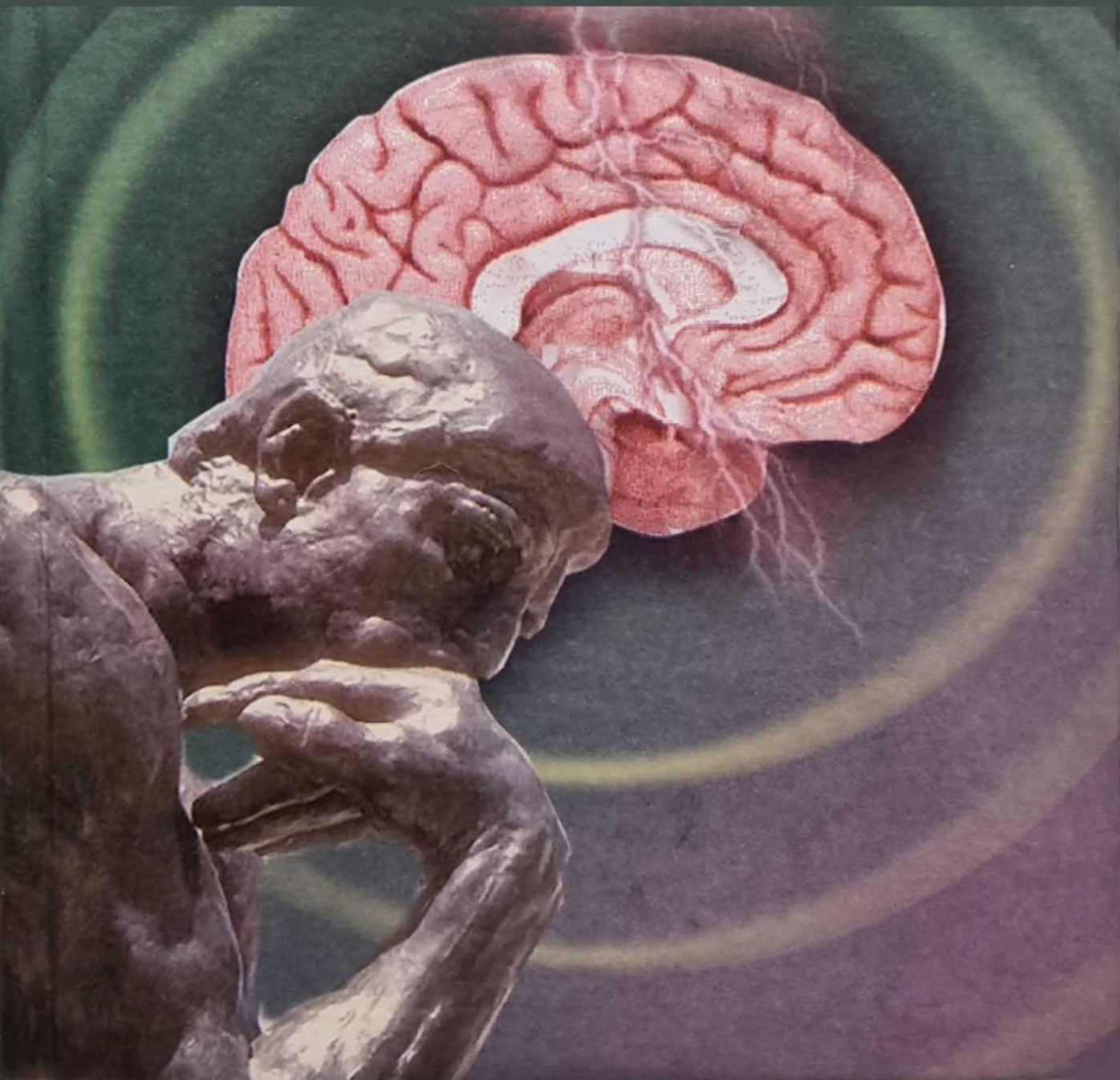
Dr E.B. ARUSHANIAN

MEDICAL IMPROVEMENT OF THE COGNITIVE BRAIN FUNCTION (NOOTROPICS)



Federal State-Funded Educational Institution of Higher Vocational Education the “Stavropol State Medical University” of the Ministry of Health of the Russian Federation

Faculty of Pharmacology

E.B. Arushanian, E.V. Beier

MEDICAL IMPROVEMENT OF THE COGNITIVE BRAIN FUNCTION

(question-answer form)

Student Text Manual

Stavropol, 2016

E.B. Arushanian. Medical Improvement of the Cognitive Brain Function (Question-Answer Form): Student Text Manual / E.B. Arushanian, E.V. Beier – Stavrolop: Publishing House of the Stavropol State Medical University, 2016

ISBN 978-5-89822-438-7

In the question-answer form the text manual sets forth modern views on the organization of the brain's cognitive activity, and neurophysical and neurochemical mechanisms which are interested in this. The authors review pathochemical and pathophysiological aspects of cognitive impairments that accompany organic brain aging, stroke, TBI, neurodegenerative pathology of Alzheimer's type or Parkinsonism, and neuro-intoxication. Based on that, cellular and systemic processes which define the specific action of nootropics are discussed. Other properties of nootropics are also considered, and the original classification of modern nootropics is suggested.

This edition is designed for students of all faculties of medical universities and colleges.

Book cover: "The Thinker", sculpture by Auguste Rodin

ISBN 978-5-89822-438-7

THE HEADING

INTRODUCTION

The so-called nootropic drugs (nootropics) take a special place among various groups of psychotropics. They came into clinical practice much later than other substances of this type, and completed the formation of psychopharmacology as an independent branch of pharmacological science, which had begun in the middle of the last century.

By the nature of their influence on brain processes nootropics can be classified as psychoanaleptics, i.e. agents that revive the psyche. Psychoanaleptics are also represented by psychomotor stimulants (caffeine, phenamine) that eliminate functional mental insufficiency, and by mood-enhancing antidepressants. By their pharmacological properties, nootropics are closer to the former. But unlike them, while reviving the psyche, nootropics do not interfere significantly with the motor sphere, and are of little effect with a one-time use. In addition, their action is mainly revealed against the background of organic pathology of the brain.

The term "nootropics" was first proposed by C. Giurgea in 1972 (from Greek "noos" - thinking, mind and "tropos" - direction, affinity). It implied the influence of substances on impaired processes of higher nervous activity. Later that definition was updated to substances that work not just on weakened higher integrative functions of the brain, but also on pathologically changed cognitive processes in the form of deterioration of memory, attention, and learning without any signs of typical psychopathology. For this reason, it would probably be more accurate to consider another term "cognitive enhancers", which is more frequently used in Western literature.

We must admit that the number and range of today's nootropics still does not meet the current needs. This is also due to the fact that in modern society, the fight against organic mental insufficiency must be recognized as one of the top priorities. Perhaps the main reason is a marked increase in life expectancy in industrialized countries, and, as a consequence, an inevitable increase in the incidence of dementia.

According to expert estimates, the average rate of moderate to severe dementia in the 65-year-old population is 5-6%. But it then exponentially increases and doubles approximately every 5 years, with Alzheimer's disease being the most common type of dementia. Recent epidemiological studies have shown that in the United States, for example, about 4 million people are affected by this pathology. In this country the share of people over 65 y.o. will reach 60 million by 2020, of whom 9 million are predicted to have Alzheimer's disease. Hence, the urgency to develop new medications and drug therapies for cognitive pathology is quite obvious.

CHAPTER I. SOME PHYSIOLOGICAL ASPECTS OF COGNITIVE PROCESSES

1. Question: What are the main mechanisms of memory?

Answer: With regard to cognitive activity in general, two firmly interconnected phenomena that constitute its core are memory and learning. Acquisition, storage, and reproduction of information that comes to the brain are the main tasks of mnemastic processes that underlie the cognition of the surrounding world. These tasks are fulfilled by means of various mechanisms, which have already been described repeatedly and in detail (Borodkin Y.S., Shabanov P.D., 1986), which allows us to dwell only on several moments that are important for understanding the pharmacology of nootropics.

Despite the lack of a unified theory of the origin of memory and the variety of approaches to its typification, in a simplified form we can distinguish three main types of memory, which differ significantly in their genesis: short-term (electrophysiological), intermediate (neurochemical) and long-term (structural-biochemical). The first one is based on electrical processes that urgently occur in association of neurons. They are interconnected by excitatory and inhibitory relations and form closed chains, through which impulses encoding new information circulate. However, it is retained only for a short time (within a minute).

Intermediate memory is a transitional state from short-term to long-term which lasts up to several hours. At this point, electrical signals trigger more permanent neurochemical shifts, related to life and effects of the mediator at pre- and postsynaptic levels. Membrane ion permeability is altered through mobilization of postsynaptic receptors, and secondary mediators like cAMP or nitric oxide are activated inside neurons. Long-term memory (lasts for days, months and even a lifetime) is characterized by deep reorganization of plastic protein metabolism and functional shifts in the core apparatus of cells, and structural changes in the neuron itself.

In a utilitarian approach to memory issues from a physiological and pharmacological standpoint, it is necessary to approximately answer several questions: Which brain formations is memory connected to in the first place? How are neurotransmitter systems involved in it? What mechanisms on the biochemical and morphological levels are involved in the consolidation of the memory trace?

The task of distinguishing strictly limited zones in the brain or within a single structure that would provide for mnestic processes appears impossible. Trace phenomena which are typical of memory are detected in any association of neurons and are attributed to general properties of the nervous system. However, in spite of the fact that this statement is evident, among the multitude of cerebral formations we can still single out those whose work is more connected with the organization of memory. Results of animal experiments with electric stimulation and destruction of certain centers and observations of people with local traumatic or tumor brain damages provide convincing evidence supporting this statement.

Among the structures that are more specifically related to storage and reproduction of information that comes into the brain, an important place undoubtedly belongs to different parts of the neocortex, first of all to the temporal and frontal cortex, which are the main substrate of memory.

Circulation of excitation along neuronal circuits while learning, as well as consolidation, and storage of the memory trace are provided as a result of chemical coding when synaptic contacts are switched on. Under the influence of incoming information, new synapses are formed, their size and the amount of released mediator becomes larger, and dendrites proliferate with an increase in the number of spines on them.

A very wide set of synaptic transmitters turns out to be involved in this process. They include acetylcholine, catecholamines (dopamine and noradrenaline), serotonin, glutamate, GABA and some others. Here we should also emphasize that, despite the complex and polymediatoric nature of control of neuronal activity, it can be exercised in a rather differentiated way. Thus, whereas the enhancement of noradrenergic transmission accelerates learning in animals under negative reinforcement, the activation of serotonergic mechanisms is more important for the development and retention of skills under positive emotional reinforcement.

Intracellular biochemical reactions are essential for long-term memory processes. These reactions are aimed at the launch of the genome of nuclear apparatus which culminates in increased synthesis of RNA, and neuro-specific protein on ribosomes. The latter migrates to the area of synaptic transmission, which is subject to repeated stimulation by conditioned signals. Here protein is involved in the formation of postsynaptic membranes and specific receptors. The previously ineffective synapse is transformed into an actively functioning one.

Various peptides (opioids, hormone-like compounds, cholecystokinin, neuropeptide Y, etc.) also contribute to the process of synaptic plasticity. Activation of the genome and synthesis of specific proteins during the period of learning leads to the emergence of neuronal associations that represent the memory engram.

According to current data, a rather trivial scenario of events in the process of organization of long-term memory can be considerably supplemented by the enhancement of new formation of neurons. This is the basis of the original hypothesis (Sokolov E.N., Nezlina N.I., 2003), which deserves a more detailed description. Its general meaning can be reduced to several statements. First of all, an impulse for the activation of long-term memory is provided by the formation of neurons which are capable of fixing new information from stem cells. Secondly, newly formed functional elements migrate to specific areas of the brain, where they ultimately differentiate. Thirdly, they must integrate into neuronal networks, consolidating the memory trace for an extended period of time.

New neurons emerge from subependymal tissue of cerebral ventricles, where self-repairing progenitor cells are produced, and they actively migrate to various brain structures. Their form and destination depend on the age of the animal and on how much they are needed in this or that cerebral structure. In young primates, newly formed neurons mainly migrate to the gyrus dentatus of the hippocampus, and to prefrontal, and temporal areas of the neocortex.

Once in the target structure, the poly-potent stem cell during differentiation undergoes the phase of transformation into a specialized neuron. This is largely determined by novelty signals and the environment in which the cell finds itself. The presence of axonal ends, a set of

mediator substances, in such a micro-locus determines the formation of various receptor apparatuses on the cell membrane, which contributes to incorporation of an already differentiated cell into necessary neuronal networks. Those elements which failed (did not have time) to form synaptic contacts with their neighbors are eliminated by apoptosis.

It has now been proven that in the adult brain, the formation and survival of new cells follow the same patterns as in the developing brain. An important role is played by sensory influx, repetition of significant signals in the process of learning. According to some observations, neurogenesis in the gyrus dentatus of the hippocampus significantly increased in rats and mice, for example, immersed in the information-enriched environment, which coincided with more successful learning ability in water maze.

Interestingly, brain aging is clearly slowed down by information load. Those who are intellectually engaged turn out to have a lower risk of developing neurodegenerative diseases such as Alzheimer's or Parkinson's disease. Increased amount of new information weakens spontaneous apoptosis in the hippocampus and provides some sort of protective effect in seizures and stroke.

Incorporation of new neurons into functional networks is one of the conditions for system plasticity, and maintenance of stable viability of nerve cells is the key to stability of long-term memory. In order to successfully integrate into a network, such a "novelty neuron" must address its axon to a certain target cell. The latter releases neurotrophins (NT), which determine the direction of the cone of growth and its progression. Ribosomes in the body of the new cell synthesize proteins, which are delivered to nerve terminals by axoplasmic current and participate in regulation of presynaptic processes. Novelty signal in the form of action potential launches a release of nerve growth factors from the presynapse, in addition to classic mediators. Nerve growth factors additionally enhance neuronal regeneration with formation of new synaptic contacts. After the formation of a functional unit is completed, its axonal and dendritic synapses switch to operation mode, preserving memory for a long time with previous stimulation (Sokolov E.N., Nezlina N.I., 2003).

Thus, the proposed hypothesis of the formation of long-term memory takes into account current knowledge about the contribution of neurogenesis and nerve growth factors involved in it to the brain’s cognitive activity. On the whole, summarizing our answer, several fundamentally important aspects should be pointed out. These include dependence of mnestic processes on mobilization of various neuromediators, neuropeptides, and regulatory proteins, as well as connection of memory with predominant involvement of a number of specific brain structures.

2. Question: What brain structures participate in the organization of cognition?

Answer: In addition to the neocortex, the old cortex or hippocampus undoubtedly stands out among the brain structures which are very closely related to cognitive processes. Being, as Mac Lean (1955) put it, "the heart of the limbic system", it has been attributed with all kinds of functions over the long years of study. In our opinion, among them, participation in regulation of memory and learning, emotional state and temporal organization of behavior (E.B. Arushanyan, E.V. Beyer, 2001) may be considered as most significant.

Understanding of the place that the hippocampus holds in mental activity is largely determined by peculiarities of its structure and its morphofunctional connections with neighboring brain structures. Due to the distinct layered structure and wide presence of large pyramidal neurons strictly oriented in one direction, it is possible to differentiate lower and upper fields (CA3 and CA1, respectively) within the hippocampus. Their neurons are included in different anatomic circles involving many limbic nuclei, which, in turn, are endowed with various functional properties. Unique features of the structure are believed to create extraordinary abilities of hippocampal neurons to store large amounts of information and to analyze it in an orderly way in time and space.

As a result, connection of the hippocampus with processes of memory and learning, which is given special importance, has a very peculiar character. According to results of experiments with stimulation and damage of the structure, as well as with evaluation of the functional state of its cellular elements during the formation of conditioned reflexes, the hippocampal deficit does not significantly affect the rate of formation of simple reactions, as well as events which are already well fixed in memory.

However, the formation of conditioned responses that require memorizing visual and spatial environmental clues or tracking the time factor in changing circumstances is significantly impaired. In humans and animals, the ability to assess changes of conditions and flexibly adjust the program of behavior in new circumstances turns out to be impaired. Hippocamp-ectomized animals are unable to distinguish meaningful signals from secondary ones. Following the breakdown of restraining hippocampal control of information incoming to the brain, signals that lose the element of "novelty" continue to monopolize attention, steadily filling information channels. That is why the main feature of the mnestic role of the hippocampus is sometimes seen in providing comparison of current knowledge with traces stored in memory.

Based on the given data, organic lesions of the hippocampus of various genesis (trauma, deterioration of hemodynamics, neuro-intoxication) that disorganize intrahippocampal relations and interaction with neighboring brain structures may have various consequences for cognitive processes. Depending on the focus localization and the degree of diffusion of the lesion, the result can be both hyper- and hypoactivity of the hippocampus. In the first case this adds to the clinical pattern of the psychopathology in people a feeling of insecurity, a tendency to neurotization and development of depressive state. The latter is rather typical of senile changes in the psyche or of residual phenomena after a past craniocerebral trauma.

In the case of hippocampal deficiency, on the contrary, impoverishment in the emotional sphere, and a tendency towards self-isolation and autism may occur. Perhaps due to additional defects in the perceptual field, animals stop reacting to a threatening situation like they used to, and start acting more "decisively". When Alzheimer's disease is modeled, for example, in rats by bilateral intrahippocampal injections of beta-amyloid peptide with brain tissue damage, the passive avoidance response and orientation in space are clearly affected. A combined impairment of memory and emotional reactivity is apparently the underlying cause for that.

Two kinds of shifts in cognitive activity can probably also result from disturbances in the chronotropic role of the hippocampus. As the analysis of our own materials and literature has shown, it can be rightly attributed to a group of brain formations that possess the so-called secondary oscillatory properties (E.B. Arushanyan, E.V. Beyer, 2001). Oversimplified

modification of hippocampal chronotropic activity is another possible source of cognitive pathology, if we recognize the importance of the chronobiological factor for the stability of normal cognitive processes.

Increased anxiety because of the hippocampal hyperfunction should inevitably stipulate destabilization of biological rhythms and vital circadian periodism, in particular. According to the results of our studies, prolonged electric stimulation of the structure in free-moving rats, which suppressed locomotion, which is usually elevated in the dark phase of the day, significantly smoothed circadian rhythm. In humans, manifestation of such a defect appears to be disturbances in night sleep. At the same time, local electrolytic damage of the dorsal hippocampus led to a characteristic restructuring of animals' mobility with more frequent movements in the dark and high-amplitude fluctuations in circadian activity. Hippocamp-ectomized animals behaved more "decisively," which was manifested in a sharp increase of locomotion immediately after turning off the light.

In addition to the neocortex and hippocampus, the striatum is obviously also involved in the regulation of cognitive functions. It is known that the striate body or striatum is composed of basal ganglia of the forebrain. Among them, the complex of the caudate nucleus and the shell (neostriatum) is phylogenetically younger and more closely related to the formation of complicated behavioral programs. Neostriatum (not precisely, but more commonly called simply the striatum), which reaches its maximum development in primates, was long considered to be a purely motor formation in the neurophysiological and neurological literature.

The change in such, as it is obvious now, too one-sided approach occurred only in the 1960s. Studies by E.B. Arushanyan et al. (1972) have proven that striatal mechanisms and, first of all, the caudate nucleus have a direct “interest” in the organization of higher nervous activity. First of all, it is shown that striatum has the closest direct and indirect connections with frontal sections of the neocortex, and forms with it a single functional unit that is aimed at organization of complicated behavioral programs. Secondly, the caudate nucleus, as part of the striatum, is actively involved in regulation of perception. This structure can simultaneously modulate the function of various afferent systems, and in particular effectively participate in the processes of integration of visual impulsation. By controlling the position of the body in space, the nucleus is inevitably involved in spatial perception. In addition, along with reticular formation of brainstem, it is probably responsible for the interanalytic interaction. And thirdly, organization of attention depends on the functional state of the striatum, if we assume it to be capable of isolating most significant moments for the current situation. Due to existence of the functional antagonism between restraining caudato-cortical and activating reticulo-cortical systems, weak excitation of the caudate nucleus, can apparently provide greater clarity to generalized attention processes by limiting the scale of impulsation ascending to the neocortex. Meanwhile, by inhibiting signals of little importance for a given situation as they approach the cortex, the nucleus is involved in regulation of selective attention as well. Presence of these properties is confirmed by high distractibility of caudate-ectomized animals, delayed extinction of their classic and instrumental conditioned reflexes, and even the formation of perseverative behavior. Motor automatisms with persistent repetition of meaningless actions after the nucleus is inactivated can also be partially considered as indicators of loss of the ability to concentrate attention.

3. Question: How does the visual system contribute to the brain's cognitive activity?

Answer: In humans and animals perception of the surrounding world depends on functional activity of various analyzers. Therefore they largely determine cognitive activity in general. However the degree to which different analyzers contribute to it is not the same.

For humans the visual system is especially important. And there are several reasons for that. First of all, it is related to an exceptional social role of vision in organization of the human brain, because through the eyes it receives the lion's share (some researchers estimate it at 90%) of afferent information. Secondly, the retina and central parts of the visual analyzer function through a variety of neurotransmitter mechanisms, which makes it possible to interfere with their activity at different levels and in different (including pharmacological) ways. Thirdly, the light perceived by the retina serves as an external time sensor, conditioning the formation of circadian periodism and non-stationarity of brain processes in time.

Dependence of effective activity of brain structures on the state of visual perception is a well-known and well-reasoned statement. It is based on several groups of quite obvious facts. In particular, visual stimulation has an activating effect on the neocortex EEG through the intensification of desynchronizing phenomena and mental processes. Vision participates in the formation of adequate adaptive behavior, facilitates formation of conditioned motor acts in animals and execution of psychophysiological tasks by humans. Conversely, the weakening of vision, limitation of external illumination and inflow of visual information leads to a decrease in the functional state of the brain, and increased drowsiness. In experiments, this is revealed in an increase of the latent period and the number of errors in the development and execution of conditioned reactions.

Connection between vision and memory is extremely important for the cognitive activity of the brain. Visual memory is an indispensable element of successful learning, and understanding its mechanisms is one of the key moments in the physiology of not only vision, but also of higher nervous activity as a whole. Complex hierarchical organization of the visual memory system is based on integrative mechanisms, which combine the work of visual and other cerebral systems into a functionally unified phenomenon. These integrative processes begin early at the level of the retina and are ultimately formed during the interaction between the neocortex and subcortical structures.

It is also necessary to note that visual perception and memory to a certain extent depend on the level of mental activity, emotional and motivational state. Light stress and alertness (vigilance) sharpen and improve these processes, whereas acute stress, and high levels of anxiety often have the opposite result. Interestingly, shifts in the emotional sphere have an effect on latency and amplitude of evoked visual potentials in corresponding cerebral formations that receive visual information; their hemodynamics also changes.

All parts - peripheral and central - of the visual analyzer are responsible for effective perception. Of course, the work of the retina and its structurally and functionally complex apparatus are of significant, sometimes crucial importance. Perceived and primarily processed visual information goes to the intermediate brain, switching in the area of external geniculate bodies. The latter have a polyneuronal organization, due to which after further processing visual impulses are directed to the primary (projection) zone of the neocortex. In humans this

zone is the occipital striatum cortex. From here visual information is addressed to premotor and motor cortical areas through secondary (associative) areas located in temporal and parietal areas of the new cortex, for the final processing and realization in the form of complete behavioral programs. It is necessary to take into account the fact that part of visual impulsation reaches the cortex by extra-genicular route, and that visual signals of both origins directly or indirectly reach the hippocampus, striatum, and a number of other subcortical formations as well.

The initial stage of perception and processing of visual information by the brain depends entirely on the eye work, more precisely, on the work of its retina. As it is known, the retina has a multilevel structure and consists of several layers of morphologically and functionally different cellular elements, which are involved in complex interrelations. The nature of these relations is determined by the properties of the involved neurotransmitter mechanisms. A significant number of transmitters (more than 20) and neuromodulators have been detected here. And in terms of their composition the retina of the vertebrates is in no way inferior to that of the brain.

While recognizing the apparent importance of the processes that occur directly in the retina for the vision, it should also be noted that the retino-cerebral interaction is reciprocal: while the work of the brain is modulated with the participation of the retina, the brain, in its turn, makes adjustments to the process of visual perception. This is evidenced, for example, by changes in vision during shifts in the psycho-emotional sphere, which, of course, may be a consequence of intra-central relations. However, we cannot exclude the possibility that direct retino-petal projections, identified functionally and morphologically, are launched from the center.

Significance of the visual apparatus for cognitive activity also includes provision of rhythm-organizing properties of the light. Since dysrhythmia and, in particular, disturbance of diurnal periodism leads to deterioration of cognitive processes, and stable biorhythms are necessary for their optimization, this aspect of the problem cannot be ignored. In this connection, we should only remind here of a special role of the chronobiological axis “eye - suprachiasmatic nuclei of the hypothalamus - epiphysis”.

Therefore, from different perspectives, the visual analyzer turns out to be necessary for the full-fledged mental and cognitive activity. Certainly, other exteroceptive mechanisms, first of all, the hearing organ, are also “interested” in this. Sense of smell and sense of touch should also be taken into consideration. However, compared to vision, other analyzers certainly contribute much less to cognitive processes and have little potential as a target for pharmacological therapy.

4. Question: Does cognition depend on the time factor?

Answer: There is no doubt about it. It is known that all indicators of brain activity, as well as any biological processes, undergo regular fluctuations in time. This also applies to the main components of cognitive activity - learning ability, memory, perception and attention. Frequency of such biorhythmic fluctuations varies widely. They can occur with periods ranging from several hours to several months or even years. Among different biorhythms, the circadian rhythm is the most important for the vital activity of any organisms (E.B. Arushanyan, 2000).

It also significantly contributes to the fluctuations of psychophysiological indices in humans and animals.

The beginning of in-depth study of the circadian rhythm of cognitive activity in healthy and mentally ill people started at the end of the 19th century with classic works of Lombard and Kraepelin. Critical analysis of these and later findings testified that different forms of intellectual activity (learning, memorizing, solving mnestic tasks, etc.), as well as physical work capacity reveal uneven intensity during morning, afternoon, and evening hours, depending on the time of testing.

Results of experimental studies fully confirmed information that had been initially obtained in humans. Not only throughout the day, but also during the whole period of awakeness animals of different species showed fluctuations in the rate of development of conditioned reflexes, and in the number of trials required to form an avoidant or passive-defensive skill, in the latency of behavioral responses and in the number of misactions.

It is necessary to emphasize that in normal healthy individuals such rhythmicity is expressed very weakly, and sometimes special efforts are required to reveal it. Probably for this reason too, there are sometimes significant inconsistencies in conclusions of some researchers about the localization of maximums of some psychophysiological parameters during a person's daytime wakefulness. According to some observations, the optimums of memorization and learning occur in morning hours. According to others, mental performance may, on the contrary, progressively improve in the evening. Of course, data obtained depend on a large number of variables of exogenous and endogenous nature, the features of the tests used, the system of obtaining and evaluating facts, etc.

Along with the period of active wakefulness, the second important component of the circadian rhythm of rest-wake is sleep. It is now generally recognized that it is not a passive state when only the energy potential of nerve cells is restored, but it is also a part of natural productive work of the brain. In addition, during sleep, mental activity does not stop, and dreams are certainly a reflection of this activity.

Without going deep into the generally complex issue of neurophysiological and neurochemical construction of sleep, which has been previously described quite comprehensively, only a few points should be noted. First of all, sleep itself is a typical fluctuating phenomenon. It consists of sequentially alternating phases of slow (according to EEG evaluations) and fast sleep. In humans, 4-6 such cycles are observed during the night. Interestingly, the same regularity, albeit in a smoother form, can also be traced in the dynamics of daytime wakefulness. Breakdown of natural night fluctuations of the brain activity inevitably leads to disorders in the psycho-emotional sphere during the daytime as well.

In the context of the problem discussed, the fact that sleep is directly related to mechanisms of memory and learning is extremely important. During sleep processes of memorizing and processing of information that comes into the brain not only during waking hours, but even during sleep itself, are carried out. That is why the method of learning during sleep was created in the past.

The rapid eye movement ("REM") phase of sleep is of particular importance for mnestic processes. Its role, as the famous Nobel laureate Francis Crick believed, consists in erasing unnecessary, secondary information and in maintaining the so-called reverse learning. The importance of this phase is evidenced by the shortening of its latent period when people

perform intensive mental work, and a direct connection with dreams. Moreover, tasks associated with concentration of attention and intensification of intellectual activity lead to an increase in REM-stage. In childhood, when cognition of the surrounding world is most intense, the percentage of REM sleep is also much higher than in middle-aged individuals (Graves L. et al., 2001).

Understanding the genesis of fluctuations of higher nervous activity in different phases of the sleep-wake cycle is necessary to picture the chronobiological nature of cognitive disorders and subsequently use this knowledge to develop an adequate pharmacotherapy for organic mental insufficiency. In a healthy organism circadian periodism is determined by a number of exogenous (first of all geophysical) and endogenous factors. Among the latter, central apparatuses of circadian rhythm control attract special attention, since a direct interference in their function opens quite realistic perspectives for combating chrono-pathological phenomena in the form of dangerous dysrhythmia. These kinds of apparatuses in the brain of highly organized animals include a pacemaker of circadian biorhythms - suprachiasmatic nuclei of the hypothalamus (Arushanyan E.B., Beyer E.V., 2000).

Not having their own access to executive organs, the nuclei execute their influence on behavior with the help of mediating brain structures. Among them epiphysis is undoubtedly the leading one. With obligatory participation of the nuclei, it receives information about the state of external illumination, which is primarily perceived by photoreceptor elements of the retina. It should be emphasized that the functional axis “eye - suprachiasmatic nuclei - epiphysis” takes a special place in the circadian rhythm. Secretory activity of the gland is organized according to its activity in time: maximum production of the main epiphyseal hormone melatonin occurs in the dark and sharply decreases in the light. On the one hand by means of the hormone, the reverse control of the pacemaker suprachiasmatic mechanism is carried out, and on the other - the formation of circadian fluctuations of functions of various endocrine glands and brain formations. The main purpose of melatonin is to synchronize diurnal periodism and at the same time protect the whole organism from unfavorable influences of exo- and endogenous origin that destabilize circadian rhythm. Through mobilization of specific melatonin receptors and with the help of various influences the hormone can act as an endogenous nootropic agent (Arushanyan E.B., Beyer E.V., 2015).

In our opinion, an important moment for conducting diurnal fluctuations of higher nervous activity, including cognitive processes, is the formation of a special kind of functional, chronobiological blocks with a number of brain structures (striatum, hippocampus, etc.). It is carried out with participation of suprachiasmatic nuclei.

Thus, various forms of behavioral activity (cognitive, in particular) exhibit nonstationary, and fluctuating nature, revealing a direct dependence on the time factor. To a large extent, this rhythmicity, which is determined by the functional state of central apparatuses of biorhythm control, guarantees the stability of cognitive processes.

5. Question: What are the aspects of the normal cerebral blood flow as a necessary condition for the optimal cognitive function?

Answer: Organization of cognitive processes in a healthy brain is determined by numerous factors, but the proper supply of blood to the brain structures is perhaps of the utmost

importance. The thing is that brain work, on the one hand, entirely depends on constant delivery of oxygen and nutrients, and, on the other hand, it needs a special hemodynamic reliability (stability). A complex, multicomponent system of autoregulatory is aimed at ensuring stable brain functioning. Without dwelling on the details, we will mention only a few provisions necessary to characterize the pharmacology of nootropic agents.

First of all, it is necessary to underline the excessive dependence of central neurons on the state of blood flow due to the exceptional intensity of oxidative metabolism in brain tissue. In humans, being only 2% of the total body mass, it utilizes 95% of all consumed oxygen. The intensity of oxygen consumption by neurons is dozens of times higher than by cells of other organs. Equally great is the cerebral tissue's need for carbohydrates. Limited reserves of glycogen make neurons highly sensitive to low glucose levels in blood. This is not the last of the reasons why there are various kinds of hormonal counterbalances to hypoglycemic insulin expansion (ACTH, corticosteroids, glucagon, etc.) in the body.

Interpretation of the role of the hemodynamic factor in cognitive processes is impossible without taking into account one more circumstance. It has been convincingly proven that every form of nervous activity is associated with dilation of blood vessels and intensification of blood flow. Almost any natural or artificial stimulus that changes the functional state of the brain or its separate areas is accompanied by hemodynamic shifts, and their extent is proportional to the level of activation. Gradual formation of conditioned and adaptive behavior and learning process takes the way of transformation of initially relatively generalized vascular reactions into a more localized hyperemia, limited by small populations of neurons.

Understanding of peculiarities of morphological organization of cerebral vascular network is of essential importance for the physiology of cerebral circulation. Compared with other organs, the mammalian brain is in more favorable conditions because it is supplied with blood by several parallel main arteries (paired carotid and vertebral) forming the so-called circle of Willis. Its existence enables easy compensation of blood circulation in case one of the main arteries bails out. Another interesting peculiarity is that there are paired vessels (anterior, middle and posterior arteries) extending from the circle of Willis, which run through the brain surface, forming here a rich pial vascular network. Unlike other organs, a unique feature of the brain is the supply of deep structures with blood through vessels located on its surface. Radial vessels extend from the central pial axes and run deep into the brain at a right angle, where they break down into small arteries, arterioles, and capillaries.

In natural activity, when groups of separate nerve cells are activated in the brain in quite a mosaic manner, expansion of pial and even radial arteries is not needed. In this case, the main burden of adequate blood supply is obviously taken by a well-developed capillary network. Specifics of its organization, including the existence of a reliable capillary shunt between arterioles and venules, allows it to ensure effective redistribution of blood flow without significant hemodynamic shifts. In addition, glial elements are quite “interested” in the system of functional relationships between capillaries and neurons. Glial elements are located along the entire length of the capillary and participate in formation of the blood-brain barrier and in regulation of neuronal metabolism.

In addition to vascular contractility, blood's rheological properties are also important for proper blood nourishment of brain formations. It is supposed to have good enough fluidity and low viscosity. In this connection, the state of hemocoagulation and fibrinolysis, their

equilibrium as well as the degree of adhesion and aggregation of platelets and erythrocytes are very important. Besides, the degree of deformability (filterability) of erythrocytes is also important for normal blood flow. Penetration of erythrocytes through the capillary network depends on it.

6. Question: Can hormones be regarded as enhancers of cognitive processes?

Answer: Undoubtedly. Among different regulatory mechanisms, they have one of the most important places in providing effective cognitive activity. And it concerns almost any hormones and is not related to their specific endocrine mission.

Basic importance of hormones in maintaining successful work of the neuron and, among other things, its optimal participation in cognitive processes, in our opinion, boils down to three main points. First, regulation of normal protein synthesis, which is necessary, inter alia, for NT formation and long-term memory formation; second, maintenance of reliability of synaptic passes into the cell through interaction with neurotransmitter mechanisms; and third, protection of neurons from various kinds of adverse influences. Different hormones are endowed with such properties to a different extent. And from this point of view the possibilities of hormones of epiphysis (melatonin) and gonads (estradiol) are covered separately given their special importance. Meanwhile here, when answering the raised question, we will touch upon the role of other hormonal compounds of pituitary, hypothalamic and adrenal origin.

A push for in-depth study of the role of the endocrine apparatus in cognitive activity was given by the observations of Dutch researchers conducted back in the 1950s and devoted to analysis of physiological properties of pituitary factors. It was found that the removal of the pituitary gland disturbs conditioned behavior of animals. Although the gland serves as a source of a large number of biologically active compounds, the behavioral defect was most easily compensated by ACTH injections. Its effect on the brain persisted even after adrenalectomy, i.e. it did not depend on production of corticosteroids. Later, it was proven that the stimulating effect of ACTH on behavior was not determined by the whole molecule, but only by a fragment containing 7 amino acid residues (ACTH 4-10). It was this small peptide, devoid of any specific hormonal activity of the whole molecule, that could interfere with processes of the higher nervous activity although it did not even have an effect on receptors of the adrenal cortex.

It turned out that ACTH 4-10 facilitates the formation of classic and instrumental conditioned reflexes, active and passive defensive reactions, and space orientation of animals. Since the hormonal fragment more successfully influenced the production of responses when injected after the training session, the idea emerged that it had a preferential effect on processes of memory trace consolidation, apparently due to stimulation of protein synthesis in central neurons. In animal experiments, it was found to have other advantages, for example, in the form of protection of the brain from ischemia.

Another pituitary hormone, vasopressin, originating from the posterior lobe of the gland, also has a distinct nootropic activity. It was shown that in rats with a genetic defect in the form of selective impairment of synthesis of this hormone, the production of conditioned reflex responses is sharply affected and their suppression may happen sooner. Hence, it was logically concluded that the substance might have mnestic properties (Sapronov N.S., Fedotova Yu. O., 2002).

As it was established later, indeed, introduction of vasopressin into brain ventricles (and even more successfully into the hippocampus) significantly improved animals' memory using the model of avoidance behavior, facilitating its consolidation. A predominantly hippocampal origin of the hormone's mnestic activity was evidenced by the ease with which the long-term potentiation increased after its introduction into the structure or its addition to hippocampal slices. The fragment of the molecule (vasopressin 4-8) turned out to be hundreds of times more active in its nootropic action than the hormone itself.

Improvement of cognitive activity with vasopressin, similar to the effect of other hormones, is largely provided through modulation of synaptic processes. An important place is given to its influence on monoaminergic transmission, including the enhancement of dopaminergic synaptic function. Meanwhile, a close and bilateral relationship with cholinergic mechanisms is detected. The hormonal fragment easily increased basal and potassium ion stimulated acetylcholine release from hippocampal slices. With that, intraventricular injections of precursor of choline mediator, which resulted in increased levels of acetylcholine in hypothalamic dialysate, made for a rise in plasma vasopressin content. This hormonal shift was due to the stimulation of H-cholinergic synaptic function, as it was suppressed by the H-cholinblocker mecamylamine, and not by the atropine.

There is no escaping the fact that as a natural nootropic agent, vasopressin is quite similar to piracetam in terms of some structural and functional criteria. There is also a rather curious fact that allows us to suspect that it is involved in the work of the epiphysis. As it was shown in experiments on rats, application of the hormone to the area of the lateral septum facilitated faster recognition of the partner in zoo-social contacts and also facilitated more stable memory retention of such an experience. Hormonal enhancement of cognitive activity in animals was suppressed by a specific vasopressin antagonist. After the epiphysis was removed, neither of the two effects was reproduced. But both effects were restored with the administration of melatonin to the epiphys-ectomized rats. It is quite possible that some part of the nootropic properties of vasopressin is fulfilled through the epiphysis by the activation of specific hormone receptors that are detected on pinealocyte membranes.

Along with pituitary hormones, hypothalamic releasing factors also make a significant contribution to cognitive activity. Among them, we should specifically mention thyrolyberine, which has a pronounced duality of functions and which interferes with brain activity in essentially two ways. On the one hand, according to a well-known principle, it stimulates the production of the pituitary thyrotropic hormone and then the secretory activity of the thyroid gland, which hormonal compounds, in turn, can increase functional activity of the brain. On the other hand, the intrinsic neuromodulatory role of thyroliberin seems to be even more considerable. Being formed in nerve cells of the brain, which are also widely represented outside the hypothalamus, it, among other things, effectively interferes with the function of various neurotransmitter systems; that is what primarily determines cognitive properties of the hormone.

The latter have already been described in sufficient detail. They comprise facilitation of the production of conditioned reactions, improvement of perception and attention, and optimization of memory and learning mechanisms. Release of these properties depends on a number of reasons, among which modulation of synaptic processes and improvement of cerebral circulation are probably the most important.

Thus, thyroliberin seems to be able to improve cholinergic transmission, because its anti-amnesic effect in mice was easily suppressed by scopolamine, while the dopamine blocker haloperidol turned out to be ineffective. Nevertheless, the hormone also has dopamine-mimetic properties. Under the influence of its analogue taltirelin, according to microdialysis definitions, increased extracellular dopamine content is found in the striatum and adjacent septal nucleus, which are the leading dopaminergic structures. Thyroliberin itself acted in a similar manner, although it was inferior to its analogue in activity. The inhibitor of prolyl endopeptidase, the main enzyme that degrades the hormone, increased stereotyped behavior in animals, which has a dopaminergic origin.

Thyrolyberine can also interact with mediator amino acids. In particular, it protects hippocampal neurons from glutamate- and NMDA-neurotoxicity, which was convincingly shown in vitro in nucleus slices. However, it selectively enhances only the NMDA-independent long-term potentiation in the CA3 field, but not in the CA1 of the hippocampus. It exhibits a synergistic relationship with GABA on cerebellum granulosa cells. Based on such data, the concept of existence of a special thyronergic system in the brain closely interacting with different neurotransmitter mechanisms was formulated.

The intrinsic neurotransmitter activity of thyroliberin in cognitive pathology is successfully complemented by the effect on cerebral hemodynamics. Taltirelin successfully eliminated insufficiency of cerebral blood flow and impaired oxygen and glucose consumption in the core of ischemic focus caused by cerebral artery compression, and prevented post-ischemic death of hippocampal neurons. Obviously, this explains the therapeutic potential of thyroliberin and its analogues in clinical practice in the treatment of cerebrovascular pathology of various genesis (traumatic brain injuries, subarachnoid hemorrhages, etc.).

Along with this, there is quite an extensive literature, which shows the influence of thyroid hormones - L-triiodothyronine and L-tetraiodothyronine - on cognitive processes. Similar to the hypothalamic releasing factor, they optimize various forms of behavior, improve learning and memory in animals, have an antidepressant effect and act as agonists of antidepressant drugs. Central properties of both hormones also depend on interference into the work of many neurotransmitter systems. In contrast, thyroidectomy and perinatal hypothyroidism in humans and animals manifest themselves in sustained deterioration of cognition.

A complex and ambiguous mission in the organization of cognitive activity is performed by the hormones produced by the adrenal cortex - corticosteroids. It is known that the endocrine axis “hypothalamus - pituitary gland - adrenal cortex” plays a special role in the development of response to stress. The latter also largely determines the peculiarity of its participation in mental activity.

Stressing may contribute to both strengthening and weakening of cognitive processes depending on a number of variables: the intensity (nature) of stressor and the duration of exposure, gender, age, individual and species features of the subject under stress. In general, there seems to be a certain pattern. Under otherwise equal conditions, "soft" stress is relieving, whereas "hard" and/or steady stress is more likely to lead to negative consequences and it poses a risk of developing a cognitive pathology.

However, regardless of the type of response to an aversive stimulus, the underlying factor is always a mobilization of corticosteroid hormones that change the function of internal organs

and directly interfere with the activity of the brain. This is evidenced by changes in a wide variety of indicators of its work following adrenalectomy or the introduction of exogenous hormones. Their central influence is executed through specific receptors identified in many brain structures outside the hypothalamus. Notably, the density of corticosteroid receptors is very high in the prefrontal cortex, hippocampus, amygdalar nuclei, and striatum. Gluco- and mineralocorticoids have their own specialized receptor apparatuses, which are unevenly distributed in the brain and are often responsible for the execution of different phenomena.

Optimization of cognitive activity due to the inclusion of glucocorticoid receptors in certain neuronal circuits manifests itself in the acceleration of production of conditioned reactions, and an increase in the efficiency of mnestic mechanisms, including facilitation of memory consolidation. And it depends on hormonal shifts in the carbohydrate and protein metabolism of nerve cells, as well as on the reorganization of the function of neurotransmitter systems of the brain.

Among other things, the improvement of memory may be partly determined by an enhanced release of acetylcholine from cholinergic terminals in the hippocampus. This is suggested by the results of in vivo and in vitro experiments with the use of methylprednisolone. The cholinomimetic effect is probably related to the stimulating effect of the substance on glucocorticoid receptors of presynaptic nerve terminals. Adrenal steroid hormones were also found to have a dopaminergic component in their action. They facilitated the reinforcement response in rats, demonstrating synergism with the psychomotor stimulant phenamine, the ability to modulate dopamine release from midbrain slices and, in contrast, behaved antagonistically with the neuroleptic sulpiride. Hence, there was even a hypothesis in which glucocorticoids were attributed the role of endogenous psychostimulant agents.

At the same time, these hormones can be a source of negative consequences for cognitive brain activity. Prolonged excitation of the hypothalamic-pituitary-adrenocortical system, severe ("hard") stress and sustained cortisol hypersecretion may cause sometimes severe maladaptive phenomena with impaired adaptive behavior, memory and learning difficulties. Among other things, this may cause increased vulnerability of hippocampal neurons and their degeneration. Hormonal neurotoxicity is aggravated by the synergistic effect of catecholamines on nerve cells.

As humans and animals age, the level of cortisol (corticosterone) in the blood may increase. This process is accompanied by widely known morphological shifts and cognitive decline. In particular, elderly people with higher plasma concentration of the hormone have been found to have more severe memory abnormalities compared to their peers with lower levels of the hormone. The differences in hormonal reactivity are also impacted by gender: women appear to be more resistant to corticosteroid imbalance than men.

However, not only and sometimes not so much the absolute increase in plasma concentration of hormones as the change in the dynamics of their daily production may be of importance. The flattening of the secretion curve alone can cause unfavorable functional and even morphological changes in the hippocampal neurons. Similar pattern is also found in people with Alzheimer's disease. Patients with higher rates of hypercorticism and/or more dramatically impaired dynamics of hormone production throughout the diurnal cycle had much more pronounced dementia manifestations. Administration of the glucocorticoid receptor antagonist mifepristone prescribed to such patients simultaneously alleviated both mnestic and

hormonal disturbances.

It is quite essential that a negative effect of hypercorticism on cognitive activity goes hand in hand with deterioration of the function of cholinergic mechanisms in the brain. Their damage by the selective neurotoxin aziridine is accompanied by an increase in corticosterone and ACTH levels in blood, and an increase in adrenal weight. Administration of glucocorticoids to such animals further aggravated functional and neurodegenerative shifts and more significantly impaired cognitive processes.

Corticosteroid secretion is controlled by the hypothalamic corticotropin-releasing factor (CRF) through adenohypophysis. CRF has also been shown to have independent neuromodulatory properties, which, of course, largely coincide with the activity profile of adrenocortical hormones, and, therefore, it can also influence brain activity in a mixed way. That said, two circumstances, in our opinion, deserve special attention. First, several types of receptors outside the hypothalamus have been found in the brain for CRF. They are unequally distributed in brain structures and, more importantly, sometimes play different functional roles. Stimulation of receptors localized in the hippocampus facilitates the learning process, while stimulation of those in the septum area, on the contrary, impairs it. Secondly, the CRF is co-localized with vasopressin in the same neurons of the paraventricular nuclei, which are similarly responsible for behavior, memory, and stress response.

Thus, corticosteroid hormones are undoubtedly interested in the formation of both normal and pathologically altered cognitive activity. And therefore, it is quite obvious that their significance and that of the other hormonal compounds described above cannot be ignored when discussing the genesis of cognitive pathology, as well as when solving pharmacological problems. In particular, we have to ask the following question: “Can adrenal hormones participate in the specific activity of traditional nootropic drugs?”

There are certain grounds for an affirmative answer to this question. Indeed, a stimulating effect of some racetams (piracetam, oxiracetam, aniracetam) on memory was sharply weakened in adrenal-ectomized animals or in case of the chemical blockade of the gland by aminoglutetemide, and corticosterone injections were able to potentiate the mnestic properties of piracetam.

7. Question: Does the epiphyseal hormone melatonin have an effect on memory processes?

Answer: We may apriori indirectly assume memory condition depends on the activity of the epiphysis, because memory deterioration in old age occurs in parallel with the decay of the secretory activity of the gland. Experimental and clinical observations generally confirm this assumption.

Even though MT administration has no pronounced effect on memory in healthy animals and humans, probably, even in this situation its mnemotropic properties cannot be ignored completely. It was found in our laboratory that daily (for 2 weeks) administration of a low dose of MT (0.75 mg) did not cause significant changes in visual and auditory memory in healthy volunteers compared with placebo. If the absence of the effect of the substance in such a situation was quite predictable, another result turned unexpected. When both of the studied

types of memory were tested again two weeks after the end of the MT intake, it turned out that they continued to improve, and the resulting shift became statistically significant.

According to the results of our experiments on rats, repeated administration of MT (1 mg/kg) to rats facilitated the acquisition of the avoidance skill through improved memory, judging by the acceleration of orientation in the Morris water maze. The rats spent less time searching for a safe place and they made fewer mistakes compared with the control group that received saline injections. The opposite data were obtained in experiments on rats with removed epiphysis. Compared with the sham-operated animals, epiphys-ectomized rats showed an increase in the latency of responses and in the number of misactions. The hormone in the same dose had a similar effect in case of memory impairment by scopolamine administration, and in higher dose (5 mg/kg) it weakened the amnesic effect of phosphamidon.

The given facts combined with the data from literature permitted to formulate an original hypothesis about the legitimacy of MT inclusion in the list of traditional nootropic drugs (E.B. Arushanyan, 2005). It is confirmed by the results of observations on various experimental models of brain lesions, as well as data on the clinical potential of MT in some types of organic cerebral pathology (stroke, traumatic brain injury, neurodegenerative diseases of the brain).

Thus, a protective, anti-amnesic effect of MT has been convincingly demonstrated in neuro-intoxication models. For example, mice that received D-galactose showed amnesia in the form of impaired active avoidance and spatial memory in the water maze. Similar defects were caused by streptozotocin and aluminum chloride when administered intraventricularly or intracerebrally in rats. Chronic MT injections in both situations alleviated mnestic disturbances and associated biochemical shifts in the brain tissue.

According to our observations, the amnesic effect of atropine was manifested in rats in the form of shortening of the latent period of the conditioned avoidance response in the shuttle box. Removal of the epiphysis potentiated amnesia, while the administration of MT (0.1 mg/kg), on the contrary, was accompanied by its restraint.

Obvious anti-amnesic properties of MT correlate with changes in the activity of the hippocamp, which, on the one hand, is a common target for the action of specific nootropic agents and, on the other hand, its dysfunction determines the origin of many mnestic disturbances. In particular, acute global or partial chronic cerebral ischemia, which causes deterioration of learning and working memory in rodents, is accompanied by the death of a large number of hippocampal pyramidal neurons in the CA1 field. Against the background of pre-administration of MT, behavioral and morphological shifts turn out to be less significant. On the contrary, epiphys-ectomy enhances the effect of ischemia by almost doubling the number of dead cells. Similarly, when ischemic cerebral edema was induced in rats, the occlusion of the middle cerebral artery, according to nuclear magnetic resonance data, changed the functional state of the hippocampus and neighboring brain entities much more weakly in the case of preventive MT use.

The fact that improvement of the mnestic processes can be a consequence of a direct change in the hippocampal activity is also confirmed by other observations. The clear “interest” of the structure is also supported by the results of some of our observations too. Limited hippocampal destruction prevented, for example, the influence of MT on the behavior of rats in a conflict situation. Specific theta-activity on the hippocampal EEG changed in the opposite way when MT was administered and when the epiphysis was removed, and with a clear

dependence on the time of day. According to the histochemical and morphometric data of the functional state of pyramidal neurons of the CA1 and CA3 hippocampus fields, MT did not change their normal state, but distinctly modulated the activity of cells under stressful conditions (E.B. Arushanyan, E.V. Beyer, N.A. Loktev, 2001; P. Botvev, E.B. Arushanyan, T.A. Voronina, 1992).

As for the clinical evidence of MT involvement in the regulation of memory processes, it is most widely demonstrated in the study of the hormone action in patients with various forms of organic cerebral pathology (stroke, traumatic brain injury, neurodegenerative diseases such as Parkinsonism and Alzheimer's disease).

Thus, according to our observations, MT increased the volume of visual and auditory memory in individuals with a history of traumatic brain injury, which was accompanied by optimization of visual perception. According to campimetry assessment of the light-perceptive function of the retina, the threshold of response to light and color signals decreased more sharply against the background of the past trauma. Compared with MT, the traditional herbal nootropic preparation bilobil was even less effective with respect to this indicator.

In recent years, there have been attempts to use MT for the treatment of Alzheimer's disease. If we summarize the data obtained, it can be concluded that the use of the hormonal preparation due to its chronotropic properties can be of use since there is an evident optimization of nighttime sleep, and a weakening of elevated depression. However, noticeable improvements in cognitive functions are not always present.

This may depend on a number of reasons, and first of all, apparently, on the dose and duration of MT administration. In the studies that we had access to, relatively low doses of MT were used (3 or 4 mg of the substance daily) for 3 to 4 weeks. In addition, the studies included quite a limited (7-10 people) number of patients with dementia of varying severity. If higher daily doses of MT were used (up to 10 mg) and the therapy was continued longer (2-3 years), the treatment efficacy also turned out higher.

Even though the clinical data do not coincide with the therapeutic potential of MT that was expected based on experimental findings, we believe that this shall not be a discouragement and become an obstacle to further research in the same direction. A peculiar clinical experiment conducted by D. Cardinali and his colleagues allows us to refrain from excessive skepticism. Two men, who were homozygous twins and who suffered from genetically determined AD of similar severity, were under observation. Both patients received identical conventional pharmacotherapy, however, one of them was also prescribed MT (6 mg per day) for an extended period of time (36 months!). Eventually, after completing the course of treatment, this patient was found to have a moderate improvement in memory and a milder version of the disease compared to his sibling (Brusco et al., 2000; Cardinali et al., 2002).

Thus, based on the given facts, we can say that the epiphyseal hormone melatonin shows distinct mnemotropic properties.

8. Question: To what extent can the immune system be interested in the organization of cognitive processes?

Answer: Despite the fact that this question is not very common, it is hardly accidental. The immune mechanisms in a healthy body are involved in the modulation of mental activity.

However in pathological conditions their “interest” in these processes increases immensely, turning the interaction of the nervous and immune systems into an object of psychopharmacological treatment, in particular with the use of nootropic agents. This relationship has come into the focus of researchers' attention only recently because of two circumstances - proof of the absence of a special "immune privilege" of the brain and the surprising similarity of both systems.

In the past, there was a strong belief that the nervous structures were reliably protected by the blood-brain barrier from all peripheral immunological events due to a special structure of the cerebral capillaries. In addition, the existence of antigen-presenting cells in the central nervous system was neglected. However, later it was discovered that the brain has a reliable internal immunological "protection" represented by macrophages and microglia capable of expressing the antigens of the main histocompatibility complex.

The functional similarity of two most important systems - nervous and immune - upon closer examination turned out to be absolutely striking. Both consist of a large number of phenotypically different cells united in highly complex networks. Individual elements as a part of such networks are similarly interconnected by direct and response-correcting feedbacks. The only difference is that cells in the nervous system are rigidly fixed in space, whereas in the immune system they are continuously moving. Same modes of communication are identified in both systems: similar connections of mediator, peptide and polypeptide nature and identical receptor apparatuses. Immunoglobulins, and cytokines (different types of interleukins, interferons) are found in the brain. In turn, cerebral hormones (vasopressin, oxytocin, corticotropin-releasing factor, etc.) and transmitters (acetylcholine, serotonin, noradrenaline) are involved in the modulation of activity of immune-competent cells.

It is especially important to emphasize a surprising similarity in the organization of the processes of memory and memory trace reproduction in the brain and the processes of immune cells functioning, and in providing the two with identical neurochemical mechanisms. Moreover, the brain-specific calcium-binding protein S-100 is detected in lymphocytes, and it is actively involved in the formation of memory and goal-seeking behavior in animals due to regulation of synaptic and intracellular phenomena in neurons.

Participation of immunological factors in the organization of normal brain activity is shown in a number of observations. First of all, it is shown in the results of systemic administration of immunomodulatory agents that trigger an immune response, which noticeably impacts the behavior of experimental animals, their emotional state, sensitivity to pain, etc.

In this connection, there is quite an indicative data that is obtained from the study of the activity of neurotrophin, which is a mixture of natural polysaccharides with immunomodulatory properties and a wide spectrum of action, which is especially pronounced when it is necessary to compensate for impaired functions. It turned out that neurotrophin in the rat model of the active-defensive skill was able to notably increase the efficiency of the animals' actions and reduce the number of errors against the background of the general strengthening of orientation-exploratory behavior. In rabbits, it accelerated the learning process with positive reinforcement, improving the reproduction of the new skill. It is believed that the main source of these shifts is a change in the activity of neurons of the sensorimotor cortex and hippocampus, as evidenced by the restructuring of their rhythm. Since polysaccharides similar

to this preparation do not themselves penetrate into the brain, the described effects can be explained by a change in the secretory activity of the peripheral blood T- and B-lymphocytes.

It is quite obvious that the psychotropic properties of peptide immunomodulators such as the clinically known thymalin and thymogen have a secondary origin. They have the same stimulating effect on the behavior of rats in the open field as typical nootropic agents (piracetam, cerebrolysin). It is necessary to point out the fact that they prevented the fading of orientational-exploratory behavior for a longer period of time in comparison with the latter.

Various cytokines also exhibit a stimulating effect on behavior when administered not only intracerebrally but also systemically. For example, injections of reoferon (an interferon alpha preparation) in mice revitalized spontaneous motor activity even more significantly than the psychomotor stimulator sydnocarb. Interleukin-6 can eliminate scopolamine-induced amnesia, and its intrahippocampal injections significantly shortened the latent period of the passive avoidance reflex in rats. Interestingly, genetic lines of mice deprived of the interleukin-2 gene have dramatically impaired memory and spatial learning in the water maze. Finally, we shall also mention the observations showing a clear inverse correlation between the latency of the passive-defensive avoidance response in rats and the immunological reactivity, as judged by the level of the antibody formation.

The above stated data definitely point to the participation of immune mechanisms in the organization of the higher nervous activity. Their contribution to the mental processes can be determined by direct or mediated changes in the activity of nerve cells, and modulation of neuronal development and differentiation.

According to numerous data, the influence of immune-competent cells on the brain function is carried out through mediators of the immune system - cytokines. Specific cytokine receptors that exhibit reactions on cytokines are detected in various cerebral formations, but their density is most significant in the new cortex, most of the hippocampus, and the cerebellum, i.e., in highly plastic structures associated with the organization of adaptive behavior and cognitive processes. Such receptors are designed not so much for the cytokines formed in the periphery and somehow penetrating into the brain but for those compounds that are secreted locally, because the neurons of the mentioned formations have apparatuses for their synthesis and for the expression of relevant receptors.

The functional role of immunological factors in the normal brain function is important and controversial. First of all, various cytokines (interleukin-1 beta, interleukin-6, and interferons) are involved in the differentiation of neurons of the developing brain and in the neuroprotection of cells in adult animals, including by stimulating the production of proteins with neurotrophic properties. Second of all, certain interleukins can control the synaptic transmission by regulating the release of mediators (noradrenaline, serotonin, GABA) and the effectiveness of their receptors, especially in the structures where the cytokine synthesis is most intense. Besides, interleukin-1 facilitates the differentiation of stem cells from the subependymal zone of the brain into dopamine-containing neurons, while alpha-interferon is shown to have a sensibilizing effect on opiate receptors. Due to such facts some researchers confidently classify cytokines, such as interleukin-2 or interferon alpha, as typical neuromodulators.

In addition to the described control of the function, primarily of the neocortex and limbic nuclei, immunomodulatory compounds can be “interested” in shaping various behavioral acts

through the change of the functional state of endocrine centers. Due to the achievements of a new integrative science - neuro-immune endocrinology, it is now obvious that another link, the endocrine system, is also actively involved in the interaction between the nervous and immune mechanisms. Hypothalamic nuclei and pituitary gland become targets for cytokines action, which is reflected in the production of vasopressin and tropic hormones of adenohypophysis, and therefore secondarily, in the higher nervous activity. The fact that cytokine receptors are found on the rhythm-organizing neurons of the hypothalamic suprachiasmatic nuclei is essential for the organization of behavior in time.

Summarizing the presented experimental results, it is necessary to state that the functions of the nervous and immune systems are interconnected very closely. This suggests the existence of a single neuro-immunomodulatory mechanism. It is also important that the main interaction between the two systems is played out in the neocortex and hippocampus - the structures that, among other things, play an exceptional role in the processes of learning and memory.

CHAPTER II. PATHOPHYSIOLOGICAL AND PATHOCHEMICAL ASPECTS OF COGNITIVE DISORDERS

9. Question: What are the special features of the origin and development of amnestic disorders in people?

Answer: Memory impairment is a common feature in a wide variety of brain diseases and it is attributed to most of the cognitive disorders. Memory impairments vary considerably in etiology and clinical manifestations and have been quite extensively described in literature.

There are many types of amnesia which can be divided into: temporary amnesias of the functional origin and persistent ones, often progressive, of organic origin. The former can be provoked by psychogenic factors (increased anxiety, neurotic states, depression), neuro intoxication (long-term therapy with anxiolytics, alcoholism), and epileptic seizures. The second ones occur in cerebrovascular pathology (stroke, senile and vascular dementia), neurodegenerative diseases (Alzheimer's and Parkinson's disease, Huntington's chorea), traumatic brain injury, tumor lesions, infectious and organic pathology, etc.

Types of memory impairments also differ significantly depending on their manifestations and genesis. A distinction is made between the so-called modality-specific and modality-nonspecific amnesias. Here, the term “modality” refers to the scale of the mnestic defect. In the case of specific impairments only one modality is usually affected, i.e. one, strictly specific type of memory (visual, auditory, motor); if all modalities are affected, we refer to nonspecific impairments (E.N. Sokolov, N.I. Nezlin, 2003).

As a rule, modality-specific amnesia occurs in focal, local damages of the large hemisphere cortex and is manifested in difficulties with the processing of various specific information because of the limited organic defect in the cortical representation of a particular analyzer. If it is located in the occipital area, then the visual memory is selectively affected; if it is in the temporal lobe - audio-verbal memory, etc. Stroke, brain tumors, and local traumatic brain lesions are some of the most frequent reasons that may lead to modality-specific disorders.

The basis of modality-nonspecific mnestic disorders usually stems from a more generalized defect in the work of brain structures, which affects the processes of perception, consolidation of the memory trace, storage and reproduction of any information. Besides depending on the nature and location of the organic pathology, memory mechanisms are affected in different ways. Age-related memory changes are, undoubtedly, among the most widespread versions of modality-nonspecific impairments.

Gradually increasing memory deterioration accompanies normal aging of the brain as well. After 45-60 years old people often begin to complain about forgetfulness. However, negative mnestic shifts tend to be subtle and weakly progressive, and they usually do not lead to significant difficulties in daily life. The main causes of such amnesia are increasing cerebral vascular sclerosis and limitations of the cerebral hemodynamics.

Unlike in normal aging, much more serious disturbances of mental activity in general

and of memory, in particular, are observed in senile and vascular dementia of such forms of age-related pathology as Alzheimer's disease and Parkinsonism.

Senile dementia, or dotage, is a disease of the elderly with progressive atrophic changes, primarily in the neocortex. Even though it begins subtly, it often becomes the result of a failure of compensation of brain processes against the background of a previous disease (infectious, cardiovascular, etc.). Clinical picture of dementia has a certain progression: complex, creative forms of activity are the first to suffer, and as the disease develops, severe memory impairments with the so-called amnesic disorientation take the central place in the development of dementia.

In amnesic disorientation time orientation is disturbed first, then space orientation, and later - that of one's own personality. Characteristically, patients not only lose the ability to date events chronologically, but they also completely lose the "sense of time". Besides it is important to note that as dementia progresses, a person's active attention is sharply impaired and distractibility increases. Adequate perception of the surrounding world is so gravely affected that external stimuli provoke only the old, most habitual and automated reactions.

Amnesic disorders of the so-called Korsakoff syndrome look different. It is characterized by selective impairment of intermediate memory connected with transformation of short-term into long-term. Meanwhile the short-term memory itself is usually preserved. Patients are able to store a considerable amount of information for a short period of time. Reproduction of knowledge and performance of automated motor skills (procedural memory) appear to be relatively preserved as well. The mnestic defect is so isolated that Korsakoff amnesia is sometimes referred to as a "pure" one given that it is not accompanied by severe behavioral disorders. It is believed that Korsakoff syndrome is based on the pathology of the hippocampus and its interaction with the associated limbic structures, primarily the amygdala nuclei. Alcoholism, tumors and traumatic injuries of the hippocampus itself or hippocampal circle formations and stroke in the posterior cerebral artery region are frequent causes of Korsakoff amnesia.

In addition to senile dementia, another and more common cause of dementia in old and senile age is considered to be Alzheimer's disease, which, according to some estimates, is diagnosed in 60% of patients with dementia manifestations, and it is ten times more frequent in women than in men. The main symptoms and dynamics of the pathological process of this disease are well known. Its typical form is characterized by relatively rapid development and early onset of neurological symptoms.

The decay of memory takes the central place in the clinical picture of Alzheimer's disease, but unlike in senile dementia, there is a greater rate of memory reserves depletion and a faster onset of amnestic disorientation. Eventually, it ends up with complete depletion of the gained life experience and deep amnesia. In parallel with the progression of amnesia, attention and perception defects and problems with comprehension of surrounding events develop rather quickly. Advancing dementia is also characterized by an early onset of weakness, instability of the visual system and optical-agnostic disorders of the neurological nature. From a pathogenetic perspective, Alzheimer's disease appears to be a complex phenomenon that depends on neurodegenerative changes in the neocortex and subcortical structures with the leading role of the deficiency of upward cholinergic projections coming from the forebrain base to the frontal cortex.

In general, a complex mnestic insufficiency when various memory mechanisms are

deeply affected, occurs in all types of dementia, not only Alzheimer's. Therefore, in contrast to age-related changes in memory, dementia patients do not respond to help in memorization and reproduction of information. Large-scale and complex nature of the defect is also emphasized by the fact that all types of memory are subject to deterioration: memory of life events (episodic), skills memory (procedural), and perception of the world (semantic).

Therefore, memory disorders in humans have different genesis and different depths of impairments. Depending on the degree of a brain damage, the range of cerebral structures involved in the pathological process varies considerably. On the one hand, this means that it is necessary to apply a differentiated approach to the treatment of amnesia when choosing medications (nootropics, in particular). On the other hand, in very advanced cases, in severe dementia that is based on widespread degenerative neuronal lesions, one can apriori expect low efficacy of almost any type of pharmacotherapy.

10. Question: How does the disruption of the functionality of the corpus striatum affect cognition?

Answer: Based on the physiological role of the striatum and its direct involvement in the organization of mental activity, disturbances in striatal mechanisms must inevitably lead to cognitive disorders. It is important to note that they can equally come from both striatal hypo- and hyperactivity. Moreover, despite the fact that sometimes the pathogenetic and pathochemical nature of the basal ganglia lesions may be exactly opposite, the changes in the mental sphere turn out to be similar, if not identical, in many respects.

Indeed, experimental simulation of increased functional activity of the nucleus by its prolonged chemical or electrical irritation, or, on the contrary, its hypofunction caused by brain tissue damage leads to similar defects in the higher nervous activity of animals. It is expressed in the difficulty of perception of sensory signals and spatial orientation, deterioration of memory and attention. Various neuro intoxications, including poisoning with amphetamine-type psychostimulants, end up with the same consequences.

In essence, the same is true for people with neurodegenerative and mental diseases, the origin of which depends on lesions of the striatum which differ from morphological and functional points of view. In particular, the so-called subcortical dementias or encephalopathies stand out among various clinical types of dementia. Parkinsonism (Parkinson's disease) and Huntington's chorea are among them. Despite the fact that both pathologies are of striatal origin, they differ dramatically in genesis and motor accompaniment. Nevertheless, in both cases mental disorders look similar, with peculiar personality changes.

A gradual and steady decline of memory is typical of patients with Parkinsonism and chorea. Mnestic disorders are modal-nonspecific, i.e., they equally affect verbal, visual and motor memory, attention is almost constantly affected as well. In general, intellectual disorders are diffusive in nature and manifest themselves in different forms of psychopathological shifts. While Huntington's chorea often ends up with severe dementia, in the case of Parkinsonism the decrease of memory and cognition does not always reach the degree of deep dementia.

Along with that, both disorders are distinctly different in their pathogenesis and external motor manifestations. Parkinsonism is characterized by the well-known clinical trio: slowed movement, rigidity, and tremor. Chorea, on the other hand, is characterized by hyperkinesia.

This is due to unequal breakdowns in the inter-mediator relationships, which develop primarily in the territory of striatum.

Today the dopaminergic concept of Parkinsonism still dominates in neurology. Its foundations were laid in the middle 1960s, when almost simultaneously several independent groups of researchers identified neurons in the brain that operate via dopamine; its highest concentration was shown in the basal ganglia, and its own synaptic mission as a mediator was postulated.

According to the main idea of this concept in organic Parkinsonism there is a degeneration of cells of substantia nigra and nigrostriatal axons ascending from it; while in a medically induced (neuroleptic) version of the pathology nigrostriatal dopaminergic transmission is affected because of the blockade of postsynaptic dopamine receptors directly in the striatum. In the past it was believed that the weakening of purely inhibitory nigral control results in the development of striatal hyperactivity (disinhibition phenomenon). Since it was already assumed that intrastriatal intercalary cells in contact with dopaminergic afferents produce acetylcholine, then an inadequate increase in the function of cholinergic mechanisms was considered to be another neurotransmitter defect in Parkinson's disease.

This understanding of the pathogenesis of Parkinsonism was also the basis of the pharmacotherapy which was very encouraging at first and which applied both dopaminergic transmission stimulants and central cholinoblockers. Since dopaminomimetics similar to L-DOPA or the psychostimulant phenamine (d, l - amphetamine) relieve parallel cognitive disturbances while eliminating motor disorders, then in our opinion, they could be conditionally classified as nootropic agents.

Later it turned out that the situation with the mediator defect in Parkinsonism is more complicated than previously assumed. Given the close intersection of neurotransmitter systems at the striatum level, of course, the case could not be limited to a selective breakdown of the dopamine-acetylcholine interaction alone. GABA-, serotonin-, noradren-, histamine-, and peptidergic mechanisms also get involved in the disturbance of intermediator balance. Nevertheless, the role of a trigger factor in the development of motor and cognitive disorders that accompany Parkinsonism is still attributed to the primary insufficiency of nigrostriatal dopaminergic transmission.

Things have to be quite the opposite in the context of nigrostriatal hyperfunction. In humans it underlies various psychoses, including schizophrenic ones. The understanding of the therapeutic antipsychotic capabilities of neuroleptics is based on their dopamine-blocking activity. In experiment, the model condition for studying psychoses is stereotyped animal behavior in the form of monotonous (automated), meaningless actions. Abnormal behavior occurs under the influence of high, neurotoxic doses of dopamine agonists, in particular, phenamine (amphetamine), which gave rise to the name of such behavioral disorders - phenamine stereotypy. In addition to motor automatisms, it is characterized by a specific disorder of mental activity. Poisoned animals stop reacting to any adequate stimuli, their conditioned reflex activity is roughly disrupted. It is curious to observe stereotyping cats as they can perform monotonous turns of the head from side to side without any distractions for a long time while staring blankly into vacancy. This detachment is very reminiscent of autism in mentally impaired people, and cognitive impairment is very typical of the clinical picture of schizophrenia.

Stereotyped behavior, apparently of human psychopathology as well, is also based on a breakdown of the dopamine-acetylcholine neurotransmitter "axis" but only with the opposite sign: nigrostriatal dopaminergic hyperactivity is combined with functional insufficiency of intrastriatal cholinergic mechanisms. For this reason, disorganization of phenaminic stereotypy and alleviation of schizophrenic symptoms can be obtained by limiting dopaminergic transmission via neuroleptics or by enhancing the activity of cholinergic cells with, for example, anticholinesterase agents. Meanwhile, as in the case of Parkinsonism, other neurotransmitter systems (serotonin-, noradren-, GABA-ergic, etc.) are inevitably involved in the formation of these conditions.

To summarize, it is necessary to note that the nigrostriatal system serves as a pin on which Parkinsonism-psychopathology is "swinging" back and forth: while one form of the pathology strengthens - the other weakens, and vice versa. However, despite the possibility of changing the striatal function by means of antagonistic mechanisms, it ends up with similar disturbances for the cognitive activity.

This statement is fully applicable to Huntington's chorea which has similar psychopathological manifestations but a different origin. Hyperactivity of the corticostriatal glutamatergic pathways seems to play the leading role here. Addressed predominantly to spiny striatal neurons, these pathways can perform a dual mission - both provoke the death of neurons and provide a neuroprotective effect. This is most likely achieved via two types of metabotropic glutamate receptors, activating (type I) and inhibiting (type II) postsynaptic elements respectively.

In recent years it has been established that in Huntington's chorea, the formation of a pathological mutant gene involved in the expression of a special protein called huntingtin can occur in the nerve cells of the striatum and its controlling corticostriatal projections. It turns out to be toxic for the nervous tissue because of the intensification of apoptosis processes, including via increased production of reactive oxygen radicals. Mutant huntingtin increases the activity of certain subunits of glutamate NMDA-receptors expressed predominantly on spiny striatal neurons, which causes their subsequent death. Meanwhile, accumulation of N-terminal fragments of huntingtin in the cytoplasm of cortical cells in early stages of Huntington's chorea can lead to degeneration of corticostriatal pathways.

Dangerous hyperactivity of corticostriatal glutamatergic projections primarily leads to the death of cholinergic cells of the striatum. Postmortem analysis of choline acetyltransferase activity and choline levels in the striatum and hippocampus in chorea patients revealed a dramatic decrease in both. Meanwhile, insufficiency of cholinergic mechanisms is an important cause of mnestic disorders. Striatal dopamine obviously makes a certain contribution to the degeneration of intrastriatal elements. Its level increases as a compensatory means, most likely, to neutralize glutamate aggression, but because of its own neurotoxicity it results in further exacerbation of destructive processes.

Thus, diverse and, what is essential, oppositely directed disorders of the striatum often lead to the same result in the form of severe cognitive disorders. However modern understanding of the pathochemical nature of these disorders undoubtedly opens up new perspectives for the search for polymodal ways of their drug treatment, including with the help of nootropic agents.

11. Question: Is cognitive pathology connected with vision deterioration?

Answer: Deterioration of vision is essentially an indispensable associate of organic mental insufficiency of different origin. Given this, it is necessary to distinguish what is the primary - a visual defect or a brain lesion. A clear understanding of the cause-and-effect relationship seems important in order to decipher the pathogenesis of the disease and to select adequate pharmacotherapy.

As previously noted, healthy vision is an essential condition for the proper functioning of the brain. Its deterioration leads to the weakening of information inflow to the brain structures and simultaneously disorganization of oscillatory processes in the body.

In mentally healthy people a decrease of ambient illumination causes lower mental and physical performance, and a decrease in the accuracy of operations. Prolonged work in poorly lit places and even more so an acute loss of vision pose risks of developing mental disorders. In the mild form they are manifested as increased anxiety, neurotic status, and if severe, they take the form of major psychic depression and even psychosis. Neurotization is also promoted by shift work and the need to work night shifts. In elderly people and persons with sight loss this coincides with the disturbance of circadian frequency of many indicators, including the dynamics of natural secretion of various hormones.

Along with that, prolongation of the light period due to phototherapy is accompanied by an improvement in the mental status of depressed patients and positive shifts in the clinical picture in patients suffering from various forms of somatic pathology. Normalization of night sleep and even a relief of symptoms of neurodegenerative diseases like Parkinsonism are also noted. According to some reports, a whole range of retinal lesions and vision defects revealed in psychophysiological tests are, among other things, determined by retinal dopamine deficiency. It can develop in various pathological conditions, including aging. Based on this background, agonists of peripheral dopamine receptors were used for the therapy of various kinds of cerebral disorders, and not without success.

Weakened or changed regime of ambient illumination significantly affects the behavior of animals as well. They show difficulty in developing conditioned reflexes and higher frequency of misactions in the labyrinth. Constant exposure to light or darkness increases anxiety and stress readiness in rodents, accompanied by disorganization of daily locomotion, which takes the form of a free-flowing rhythm. In fact, the circadian periodicity of any physiological indices can be manipulated by means of changing the photoperiod length.

Vision deprivation does not simply cause the restructuring of the cerebral electrical activity and functional state of cerebral structures. In case of prolonged afferentation restriction in the central neurons, neurochemical shifts in the form of changes in the rate of formation and release of transmitters and the number of specific receptors are replaced by morphological disorders. Naturally, their most pronounced atrophic pattern occurs in the primary projection areas of the neocortex.

Thus, the restriction of visual perception leads to quite predictable deterioration of the brain activity including cognitive functions. But the opposite statement is also true: primary cerebral pathology (organic or functional), as a rule, is accompanied by visual impairments. There is a lot of convincing evidence in support of this statement.

As it was already noted, with age due to progressive weakening of the function of the central neurotransmitter mechanisms and increasing rate of neurodegeneration, the work of many brain formations is affected, which is combined with decreased efficiency of sensory and perceptual factors, including visual and hearing impairment. A decrease in light- and color sensitivity of the retina in the elderly because of the defects in processing of visual information in the central apparatuses is joined by local dystrophic processes in the eye and deterioration of the retinal blood circulation. Meanwhile, it is interesting that the amplitude of the evoked visual potentials in the cortex increases noticeably in old age as compared to young people. The reason is seen in the weakening of cortical inhibitory mechanisms (Scialfa C.T., 2002).

Deterioration of visual function also accompanies tumor and traumatic lesions of the brain. According to observations of clinicians, tumors in almost half of cases, regardless of their localization, are combined with changes in visual acuity and the appearance of scotomas on the retina. A picture of retinal pathological shifts allows us to make a niveau diagnosis and specify the location of the process. If compression and atrophy of an optic nerve or tract are excluded, then the connection of visual perception defects with tumor lesions of frontal, temporal or occipital lobes shall be recognized as essential.

Visual disorders also accompany traumatic brain injuries. Of course, the severity and stability of the disorders is determined by the localization and degree of brain damage. Nevertheless, even a hydrodynamic effect alone, irrespective of the presence or absence of hemorrhage, can probably be the cause of quite persistent changes in visual functions.

The results of studies performed in our laboratory to assess retinal reactivity using the method of campimetry show that young people who have a history of brain trauma of different severity show negative shifts in the state of retina even many months after the incident and in the absence of subjective complaints. Similar to what is registered in elderly subjects, they show higher threshold of the luminous sensitivity in different, especially peripheral visual fields, and more significant latent periods of sensorimotor response, in addition scotomas are often detected. This is supported by experimental data showing that local neurotoxic damage to a restricted area at the base of the forebrain in monkeys (with degeneration of ascending cholinergic pathways) significantly impairs their performance of visual tasks.

The clinical picture of Alzheimer's disease is an example of connection between visual defects and organic cerebral insufficiency against the background of the neurodegenerative pathology. In addition to purely neurological symptoms, patients show widespread visual disturbances in the form of deterioration of not only light- but also color perception. There are reasons to say that this disease is a systemic lesion of cholinergic mechanisms. According to some observations, cholinergic retinal ganglion cells are also involved in the pathological process. Therefore, dementia and cognitive (visual) disorders are two sides of the same disease. A direct involvement of the peripheral visual apparatus is evidenced by changes in electroretinogram parameters and, according to tomography, by thinning of the optic nerve in patients. Gross abnormalities in the acquisition and exercise of visual-spatial skills are so typical of Alzheimer's disease that such shifts are even suggested for consideration as predictors of the cognitive impairment in the early stages of the disease.

Changes in the sensory sphere in cerebral neurodegenerative pathology are not isolated; they not only affect the visual system, but are often associated with abnormalities in the functioning of other analyzers as well. In Alzheimer's disease, for example, hearing is also

affected. Deterioration of audio as well as visual memory obviously depends on cholinergic deficiency. Hearing impairment also accompanies Huntington's chorea and Parkinsonism, and the latter is also characterized by olfactory defects in the form of microsomia.

The above information clearly demonstrates that there is a close connection between organic lesions of the brain and sensory, first of all, visual disturbances. If they develop primarily, as in aging, they facilitate the formation of cognitive disorders, but when they have a secondary nature, being an associate of any cerebral pathology, they inevitably aggravate its course. Hence, in our opinion, the fight against sensory (visual) defects shall be an indispensable element of the complex therapy of cognitive disorders of any origin.

12. Question: Does cognitive pathology depend on chronobiological disorders?

Answer: There are several quite axiomatic postulates in chronobiology. One implies the oscillatory nature of any physiological processes, and the other proceeds from the fact that any form of pathology is invariably accompanied by disorganization of biological rhythms. The latter fully applies to cognitive disorders. This problem, in turn, has two aspects: a chronobiological defect can arise from initial organic brain pathology with subsequent disorders of cognitive activity, but they can also be secondary and result from primary disorganization of behavioral biorhythms.

According to these indisputable statements, any forms of organic lesions of the brain are necessarily accompanied by chronobiological disorders. A convincing proof here is a breakdown of the basal sleep-wake cycle which accompanies cerebral pathology. Although it manifests itself in different ways, it occurs necessarily and more commonly as a sleep disorganization.

Among other things, deterioration of qualitative and quantitative indicators of night sleep is very typical of an aging brain with its inherent vascular atherosclerosis. In addition, it is noted that total sleep time becomes shorter, and its depth decreases with frequent awakenings. Shortened duration of REM sleep and modification of its components are also quite typical. A similar picture is observed in patients who have suffered traumatic brain injury, stroke, or other cerebrovascular disorders.

Sleep disorders are also constant companions of organic neurodegenerative diseases like Alzheimer's disease and Parkinsonism. These disorders are so specific that the beginning of the study of Parkinson's disease and cerebral sleep apparatuses, for example, coincides in time. A stimulus to the study of both phenomena is in fact the classic work by Economo published back in 1918, which described an epidemic of "encephalitis lethargica" in Austria. Difficulty falling asleep, frequent spontaneous awakenings combined with daytime somnolence, as well as decreased REM phase, and a drop in the amplitude of "sleep spindles" on the EEG are typical of the above mentioned diseases. Interestingly, successful therapy of Parkinsonism with central dopamine agonists (DOPA drugs) in the form of limiting motor disorders coincides with the normalization of sleep and its electrographic correlates and the weakening of amnesia.

A chronobiological defect in the form of sleep disorders, which appears on the basis of primary organic brain pathology that is accompanied by cognitive disturbances, becomes the source of its further deterioration with aggravation of the clinical picture of the disease. As a

result, a vicious circle is created, and one of the ways to eliminate it is the use of various rhythm-stabilizing influences.

If dysrhythmia is an indispensable companion of cerebral pathology, the structure of which includes deterioration of cognitive processes, then the opposite is also true when the primary breakdown of biorhythms can lead to secondary disorders in the psycho-emotional sphere.

A number of social factors contribute to the primary disorganization of biorhythms. These include regular stress, night shift work, transmeridian flights in the latitudinal direction, and space flights. In all cases, there is an initial breakdown in the work of the biological clock, primarily in the dynamic functional complex "suprachiasmatic nuclei of the hypothalamus - epiphysis" with the formation of deviations of circadian biorhythms of various stability. This corresponds to a quite typical set of behavioral disorders. It necessarily includes deterioration of night sleep, memory, concentration and visual perception. In other words, all signs of cognitive pathology are present. Added by dysphoria, asthenia, and unfavorable shifts of vegetative status, they result in a complex of symptoms characteristic of desynchronosis.

Another form of artificial exogenous dysrhythmia is sleep deprivation. Total sleep deprivation or selective elimination of its REM stage in relatively healthy people is fraught with negative shifts in the psycho-emotional sphere. Disturbances of attention and memory, increased fatigue, and increased errors in solving intellectual tasks are noted. In this connection sleep deprivation is sometimes used to simulate amnesia in the study of nootropic activity of substances. However, in patients with mental depression even partial repeated sleep deprivation causes the weakening of the depth of affectus and it has been used for therapeutic purposes as a reliable antidepressant procedure since the 1960s.

It is particularly important to point out a possible correlation of mental depression and cognitive dysfunction. As it is known this form of psychopathology is accompanied, among other things, by memory and learning impairments, which are successfully eliminated by antidepressant drugs. This has allowed some researchers to assume that comorbidity of depressive and dementive manifestations is not a simple coincidence, but it is based on their pathogenetic similarity. Such a formulation of the question correlates with our position, according to which it is justified to look for a single chronobiological basis here. The fact is that mental depression can be viewed as a special kind of chronobiological defect, caused by the phase mismatch of separate circadian rhythms among themselves. The resulting desynchronosis in its functional sense is close, if not identical, to the latitudinal one which is characterized by cognitive dysfunction.

Cognitive deterioration due to primary or secondary dysrhythmia depends on the changes in the rhythmicity of synaptic transmission and the work of oscillatory brain structures. It is known that various central neurotransmitter mechanisms detect rhythmic fluctuations, including in the circadian mode. The synthesis and release of transmitters into synaptic cleft, the number and sensitivity of postsynaptic receptors change with this frequency. And different exogenous and endogenous destabilizing influences can change such rhythmicity, rough disturbance of which through disorganization of the function of brain formations ultimately results in a pathology of the higher nervous activity.

The special importance of central cholinergic mechanisms for cognitive activity has already been emphasized earlier. By their example, it is easily confirmed that there is a direct

interest of a particular neurotransmitter system in the formation of the circadian periodism of behavior. Thus, selective damage of cholinergic neurons by a specific neurotoxin aziridine injected into the lateral ventricles of rat brains simultaneously with deterioration of cognitive processes also destabilized the dynamics of circadian rhythms of motility and body temperature in the form of a drop in the amplitude of fluctuations and their phase shift. Acetylcholine deficiency noticeably affects sleep and its rhythmic structure. The lack of choline mediator precursor in the food of animals provokes an increase in the duration of wakefulness and shortening of the REM phase of sleep because of a decrease in the activity of stem cholinergic neurons involved in its generation. On the other hand, acetylcholine release in the frontal cortex of freely moving animals occurs in a circadian rhythm and depends on the functional state of the brain oscillatory structures.

Of course, direct responsibility for pathological fluctuations of cerebral functions primarily belongs to failures in the regular work of central apparatuses of biorhythm control. Morphological or functional insufficiency of the leading rhythm-organizing formation, the suprachiasmatic nuclei of the hypothalamus, undoubtedly belongs to the main causes of dysrhythmia. Their damage in experimental animals provokes not only behavioral arrhythmia but also sleep disorders. A sharp decrease in the volume of the nuclei and progressive death of their cellular elements are detected postmortem in the aged human brain. There is a reason to believe that degeneration of suprachiasmatic neurons also occurs in people who suffer from Alzheimer's disease. At least, a bilateral injection of beta-amyloid peptide into hamster nuclei causes cognitive disorders, which are characteristic of this disease, and simultaneous breakdown of circadian periodism.

Another important source of chronopathology of cognitive processes and behavior in general could be the deficient functioning of the epiphysis. With age, for example, its natural involution and progressive decrease in the secretion of the main hormone melatonin takes place (plasma concentration of the hormone in 45-year-old subjects is only half of that produced during puberty). And this entails impaired cognitive performance and impaired nighttime sleep because of the lack of a natural nootropic with increased lipid peroxidation, neurodegeneration, immune deficits, etc. Restriction of melatonin control of the function of the leading pacemaker also contributes to the pathology.

Interestingly, in healthy middle-aged individuals desynchronosis due to shift work, flights, or artificial prolongation of the waking period is almost always accompanied by changes in the scale and dynamics of the daily melatonin secretion. Such shifts apparently largely determine many of the components of behavioral dysrhythmia, including amnesia. Dysrhythmic manifestations undoubtedly have a complex nature, but special attention, we believe, shall be paid to the restructuring of the work of the functional "axis": retina - suprachiasmatic nuclei - epiphysis.

Along with primary oscillatory formations of the brain, disorganization of the normal circadian dynamics of the higher nervous activity can be caused by disturbances in the activity of secondary oscillators, such as the hippocampus and the striatum. A hypo- and hyperfunction of both formations predispose to the development of dysrhythmia in the form of desynchronosis, including the one that underlies mental depression. In particular, disorders in emotional and motivational spheres and in cognitive processes that accompany this pathology, as well as the breakdown of rhythmostasis, in our opinion, can be reasonably regarded as

consequences of inadequate amplification of the function of the hippocampus which controls both.

Thus, the disturbance of natural fluctuation processes that accompanies any form of cerebral organic pathology inevitably becomes a source of cognitive activity impairment. Therefore it seems obvious that for its normalization, besides traditional approaches it is necessary to resort to the help of different kinds of influences aimed at stabilization of circadian periodism and elimination of dysrhythmia.

13. Question: What is the genesis of cognitive impairments and of the mechanism of injury of neurons in the brain blood flow dysfunction?

Answer: Cerebrovascular pathology is the main source of deterioration of cognitive activity, manifested as a standard set of symptoms in the form of weakening of perception and attention, amnesia, and difficulties in the educational process. The depth and scale of such disorders and the degree (possibility) of their compensation depend on the form of pathology, localization and volume of brain damage. In severe cases it all comes down to dementia (Neri D., 2000).

Brain diseases, which are based on a primary hemodynamic defect and which combine similar disorders in the cognitive sphere, are characterized by pathogenetic diversity. Therefore, the international classification proposed for their description is rather complicated.

Making the task simpler, all types of cerebrovascular pathology can be subdivided into chronic and slowly progressing disorders, and acute disorders of cerebral circulation. The former include various types of the so-called discirculatory encephalopathy (atherosclerotic, hypertensive, neurotoxic genesis), and the latter are represented by temporary, transient disorders of hemodynamics, accompanied by reversible focal and general cerebral symptoms, as well as stroke with stable lesion of brain functions.

In-depth study of the nature of ischemic brain lesions and the search for the ways of their effective pharmacotherapy has become of particular medical and social importance in recent years. In the developed countries one and the same unfavorable tendency is observed, which is an increasing frequency of such diseases with a sharp rise in mortality rate, outpacing even that of malignant tumors.

This, among other things, explains the interest in creating adequate experimental models of vascular pathology that are close in origin and pathogenetic sense to the corresponding diseases in humans. Most of them are based on occlusion of the main or regional vessels and are reviewed in detail separately. Here we will only emphasize the similarity of cognitive and behavioral disorders in different simulations of cerebrovascular pathology.

Due to numerous clinical studies, today we have come closer to understanding the genesis of a number of chronic forms of ischemic brain lesions. In particular, a direct correlation between the cerebral hemodynamic state, the severity of cognitive deterioration in old age and inclination to psychic depression has been shown. This statement appears to be important based on the chronobiological identity of mental disorders. The leading pathogenetic role of the vascular factor in triggering Alzheimer's disease is now well substantiated. With the help of emission computed tomography and nuclear magnetic resonance the nature of the second most common (after Alzheimer's disease) so-called vascular dementia is thoroughly described. The

range of risk factors that may facilitate the triggering of chronic cerebrovascular insufficiency is also clarified, including, besides the well-known causes (atherosclerosis, hypertension, hypodynamia, diabetes, etc.), a wide range of ecological and social factors (De la Torre J.C., 2002).

But the clear progress in deciphering the cellular and systemic organization of acute vascular incidents, such as stroke, deserves to be recognized as particularly significant. Among other forms of vascular pathology, this severe phenomenon has recently been frequently ranked as a primary cause of mortality and serious disability in people. Its comprehensive study is extremely important for our country, turning into a state task since Russia, unfortunately, occupies almost the leading place in the world in terms of stroke mortality rate.

Two main types of strokes are known: hemorrhagic and ischemic, which differ in their etiology and therapeutic approaches. In hemorrhagic stroke, blood bursts from a pathologically altered vessel, negatively affecting the surrounding brain tissue. In the case of ischemic stroke, hypoxia with subsequent formation of the infarction zone dominates the case. According to modern epidemiological data, unlike in the past, ischemic stroke is now much more frequent than hemorrhagic one.

In both types of the pathology the progressive death of neurons as a result of increased apoptosis and necrosis is observed in the ischemic focus. The dynamics of the preceding pathochemical shifts and processes around the infarction zone have already been studied and characterized in detail.

In ischemic stroke the area of the brain surrounding the infarction called the "penumbra" attracts most of the attention of researchers and clinicians. The phenomena occurring here largely determine the future of the incident regarding whether the ischemic necrosis is going to progress or terminate. The "penumbra" is a functionally labile zone, where reparative processes and successful pharmacological treatment are both possible.

A complex cascade of biochemical reactions triggered by primary ischemia shows a certain sequence. The initial, triggering moment of the cascade is undoubtedly the energy deficit due to the limitation of oxygen and carbohydrate delivery, which quickly causes deterioration of protein synthesis. A fall in the level of macroergic compounds in turn involves anaerobic glycolysis with lactic acid accumulation and disturbed acid-base balance. The resulting metabolic acidosis combined with hypoxia causes defects in electrolyte metabolism in the form of increased intracellular content of first of all calcium and sodium ions. This and accumulation of certain neurotransmitters facilitate edema and cytotoxic processes.

Excitatory amino acids (EAA) - aspartate and glutamate - significantly promote ischemia and nerve cell death in the early stage. Ischemic hypoxia is accompanied not only by an increase in their release from presynaptic terminals, but also by a complication of reuptake. An increase in concentration of primarily glutamic acid ("glutamate shock") is an initial link in the glutamate-calcium cascade associated with neurotoxic (excitotoxic) neuronal damage. Excessive activation of predominantly ionotropic NMDA-receptors increases additional penetration of calcium ions into the cell, an excessive accumulation of which is the main factor of aggression. Calcium ions stimulate phospholipases, causing increased decay of membrane phospholipids, increased formation of pro-inflammatory prostaglandins and free oxygen radicals. The former facilitate vasoconstriction and simultaneously increase their permeability and perivascular edema, while free radicals support the branching stage of lipid peroxidation

chain. The excitation of NMDA-receptors and the rise of intracellular concentration of calcium ions also lead to increased apoptosis as a result of induction of genes that trigger this process.

NO (nitrogen oxide) also contributes to ischemic cell damage. Under normal conditions, it provokes vasodilation, but its excessive formation in pathology causes inhibition of mitochondrial oxidative phosphorylation. The formed peroxynitrate inactivates superoxide dismutase, facilitating free-radical reactions.

Glial cell elements are equally involved in ischemia. Microglia actively participates in mechanisms of delayed neuronal death because of the production of the whole complex of neurotoxic factors. These include proinflammatory cytokines (IL-1alpha, IL-6, IL-8, tumor necrosis factor-alpha, etc.). In response to acute focal ischemia they can stimulate the production of C-reactive protein and complement factors.

The described shifts are aimed at damaging neurons and forming ischemic edema in brain tissue. Vascular insufficiency is aggravated by primary or secondary disorders of the rheological properties of blood. Its viscosity builds up because of increased hemocoagulation and limited fibrinolysis, adhesion and aggregation of formed elements of blood (erythrocytes and platelets) grows, and filtration of erythrocytes and monocytes becomes weaker. As a result of impaired permeability of the microcirculatory stream in the ischemic area oxygenation decreases further.

Understanding of the complex of diverse mechanisms involved in cerebral ischemia opens up prospects for targeted and simultaneously polyvalent drug treatment of the cerebrovascular pathology. Protection of neurons from damage and restoration of blood circulation (reperfusion) in emergency situations shall be performed as quickly as possible. This is also motivated by the fact that rostral neurons of the brain (first of all, neocortex), which are most actively interested in the formation of cognitive activity, are particularly sensitive and vulnerable to ischemia.

14. Question: How and by what does cerebral hypoxia affect cognitive processes?

Answer: Since the functional state of cerebral neurons, even in comparison with other nerve cells, reveals extraordinary dependence on oxygen consumption, naturally, hypoxia strongly affects their activity and related cognitive processes. Cerebral hypoxia is caused by a variety of reasons (insufficient oxygen in the external environment, pathology of internal organs, etc.), but probably the most common one is circular ischemia caused by impaired cerebral circulation. In turn, ischemic phenomena depend on age-related vascular atherosclerosis, stroke, and traumatic brain injury. Regardless of genesis, in any case there is an imbalance between the need of the brain tissue for oxygen and its actual delivery. Hypoxia is accompanied by a complex of behavioral shifts and morphofunctional disorders at the cellular level. Their severity depends on the depth and duration of oxygen deficiency.

In experimental animals acute hypoxic or dosed normobaric hypoxia is accompanied by defects in conditioned reflex behavior, when passive and active forms of avoidance and labyrinth reactions are affected, and, in general, the production and execution of conditioned responses is impaired. Similar consequences are noted in regional ischemia caused by vascular occlusion or traumatic brain injury. Even after short-term hypoxia the recovery of previous

behavioral parameters does not occur immediately, at times only after many weeks. Similar phenomena are shown in the elderly, and in patients who had a stroke or a cerebral injury. All parameters of cognitive activity are affected in the form of a decline in perception and attention, impairment of memory and learning ability, and a sharp decrease in physical and mental activity.

Biochemical changes caused by hypoxia are quite diverse at the cellular level, but the leading factor is undoubtedly an impaired function of mitochondrial enzyme complexes, which leads to suppression of aerobic synthesis of energy. Oxygen entering neurons is involved in oxidative phosphorylation reactions, because it is a substrate of cytochrome oxidase - a terminal enzyme of the mitochondrial respiratory chain. Eventually, the intracellular level of macroergic compounds (ATP and creatine phosphate) decreases. Reduction of ATP, in turn, disrupts phosphorylation of membrane proteins and lipids, on which neuronal integrity depends. This results in a decay and loss of membrane phospholipids, and increased membrane permeability and fluidity. It should be noted that cells attempt to compensate for the defective respiratory chain and energy starvation by activation of succinate dehydrogenase and enhancement of amber acid oxidation. Utilization of succinate, which is not a product of glucose oxidation, is a reserve pathway for energy generation under hypoxia.

Concurrently, oxygen deficiency causes deterioration of synaptic transmission because of the special dependence of the processes of mediator synthesis and release, and receptor function on the level of energy metabolism. This relationship is of reciprocal nature. Among other things, succinate, for example, stimulates metabolism of catecholamines, and those control its oxidation. The relationship between stress activation of hypothalamic-pituitary-adrenocortical mechanisms under hypoxia and compensatory enhancement of the succinate oxidase system has also been shown. Thus, under oxygen deficiency, synaptic and hormonal mechanisms are directly interested in the enhancement of metabolic reactions aimed at maintaining the energy stability of neurons.

Another negative feature of hypoxia is the fact that it leads to increased formation of highly toxic free-radical compounds. Their production (in particular, NO) is necessary for the regulation of normal respiration. However, their excessive accumulation under oxygen starvation is a source of destructive consequences for neurons. A convincing argument for the significance of increased activity of free-radical processes is the weakening of abnormalities in cell energy induced by ischemic hypoxia through substances with antioxidant properties.

Generally described biochemical shifts in oxygen deficiency are clarified by the results of morphological studies. Light and especially electron microscopy of nervous tissue allows us to estimate the pattern of intracellular structural changes and unequal vulnerability of different types of neurons in different parts of the brain (Borodkin Y.S., Shabanov P.D., 1986).

An indicator of initial defects in oxidative and energy metabolism of neurons are morphological changes in mitochondria, in the cristae of which many respiratory enzymes are concentrated. Their swelling with the destruction of cristae and inner membranes has been established, and the extent of such shifts can be seen in the degree of reversibility of hypoxic disturbances. A clear destruction of mitochondrial membranes is regarded as a criterion of irreversibility of the processes occurring in response to hypoxia. These organelles are most easily affected in synaptic processes of cells, since synapses are characterized by high intensity of energy metabolism. Meanwhile, the swelling of mitochondria can also be interpreted as an

indicator of compensatory phenomena aimed at alleviating oxygen starvation, since some of the swollen mitochondria are capable of restoration during the brain experience.

Severe disturbances of oxidative processes and neuronal energy cause further secondary shifts and serious damage to other types of metabolism, primarily protein and lipid. The protein synthesizing apparatus of cells includes nucleolus, granular and agranular reticulum, polysomes, and ribosomes. An increase in protein synthesis is usually expressed in hypertrophy and proliferation of these ultrastructures, whereas its decrease is expressed in their destruction. Deep hypoxia is accompanied by the decay of cytoplasmic lipoproteids and changes in the morphology of the nucleolus and polysomes as the evidence of deterioration of repair processes. This is also confirmed by biochemical data on the inhibition of nucleic acid metabolism, especially RNA, associated with an intensification of their decay and deterioration of synthesis. Even in newborn animals, which are more resistant to hypoxia, it causes a significant decrease in DNA and protein levels in neurons. Along with that, within certain limits, oxygen deficiency can have a stimulating effect on the metabolism of certain lipids and proteins.

Morphological evidence of a special interest of synaptic transmissions in hypoxia is presented. Depending on the depth of oxygen deficiency, changes in the size of presynaptic terminals and/or a decrease in the number of synaptic vesicles are observed. This is often accompanied by modification of astrocytic processes. A decrease in the number of synaptic vesicles and the appearance of emptied granules present obvious evidence of impaired processes of neurotransmitter synthesis and reservation. However, the swelling of nerve terminals is sometimes accompanied by an increase in the number of granules, most likely as an element of compensatory reaction.

Inter-neuronal contacts, which differ in function and localization, show different sensitivity to hypoxia and are therefore damaged at different rates. For example, synapses of nonspecific pathways react more to oxygen starvation than those of specific pathways. In case of excessive severity of oxygen deficiency, deformation and complete destruction of synaptic structures are recorded.

Interestingly, in case of senile hypoxia in the dendrite area this process progresses in a certain sequence: first, the synapses at the apical dendrite spines are affected; later, as ischemia aggravates, the damage shifts more towards the dendrite tree base, up to complete loss of spines and then a decay of the bare dendrite itself. There is an opinion that the degree of neuronal response to ischemic hypoxia directly depends on the area of the dendrite tree.

In addition to neurons, satellite glia is actively involved in reactions to hypoxia. In the initial stage of hypoxia it is characterized by progressive reaction in the form of closer contact of the bodies and processes of glial cells with the bodies of neurons. Fused with them, the swollen oligodendrogliocytes then get involved in the process of neuronal death. The number of microgliocytes, which normally constitute a small percentage of the total number of glial elements, rapidly increases in brain regions that suffer before the rest during aggravation of hypoxia (neocortex, hippocampus, amygdala, thalamic nuclei). They play an important role in phagocytosis of decaying nerve cells. At first, the shifts of astrocytes and oligodendrocytes are compensatory in nature and aimed at weakening the metabolic disturbances in neurons, but later their reserve capacities become exhausted.

Thus, hypoxia, causing ultrastructural changes in neurons, also affects glia. Meanwhile, not all brain formations show the same sensitivity to oxygen starvation. The majority of phylogenetically young sections are more severely damaged compared to phylogenetically older ones. The cells of the cortex and cerebellum are the first to be affected, less than subcortical structures, but also to a different extent. We shall keep in mind that cellular elements of the same part of the brain are involved differently in the hypoxic effect. The upper layers of the neocortex, for example, are more sensitive than the lower ones; when carotid and vertebral arteries are ligated, neurons of layers IV-V incur more damage. Structural features of neurons are also important, since small intercalary cells more often show reduced resistance to oxygen deficiency compared to large effector elements.

Summarizing the given data, we have to state that hypoxia, which causes primary disorders of oxygen and energy metabolism in nerve cells, can further provoke secondary changes in protein and lipid metabolism. Once emerged, the latter surface in the form of suppression of synthesis and axonal transport of mediators, changes in ionic permeability, and then destruction of cell membranes. At the ultrastructural level, the hypoxic pathology of cells is staged with an initial increase in reactive shifts aimed at mobilizing the reserve capacities of neurons; and while the severity of the process gets worse, the disruption of intracellular homeostasis leads to irreversible changes and cell death.

Thus, given the adverse effects of hypoxia on the cerebral activity in general and cognitive processes in particular, combating it appears to be an extremely urgent task. From the pharmacological point of view, to ensure successful antihypoxic protection of cerebral neurons, urgent reoxygenation, normalization of energy metabolism and/or inclusion of reserve mechanisms of cells still capable of recovery are required first of all.

Also, it is necessary to keep in mind the possibility (and sometimes necessity) of neuroprotection through a reverse method - not enhancement, but restriction of neurons' respiratory function. This can be achieved via various interventions aimed at restricting their activity by hyperpolarization of cell membranes. It is possible to reduce the need of nerve cells for oxygen and thereby increase tolerance to hypoxia by including various inhibitory receptors (GABA, adenosine A1 type, alpha2-adrenoreceptors, etc.). This method allows to increase the experience of neurons in the zone of "penumbra" in case of focal ischemia and even in case of global violation of the cerebral circulation.

15. Question: What is the role of free radical processes in the organic pathology of the brain?

Answer: None of the acute and chronic cerebral lesions can manage without them, although in essence free-radical processes have a protective mission in the body. Excessive production of free radicals, their cytotoxic effects are aimed at protection against various adverse factors of internal and external environment, including by destroying microbes and their own defective cells. However, when uncontrolled, this process in the form of oxidative stress becomes a serious threat to any, not only cerebral, cell elements causing their damage and resulting in various diseases.

In normal tissue respiration various metabolites (intermediates) of molecular oxygen are formed. They include its active forms such as superoxide and hydroxyl radicals, hydrogen

peroxide, and singlet oxygen forms. It is necessary to single out a free radical compound, which is of particular interest now - nitric oxide (Question 21). All of them under certain circumstances take on the toxic properties and are directly responsible for cell death in brain ischemia of different genesis (stroke, trauma, vascular atherosclerosis) or neurodegenerative pathology.

After L. McCord and J. Fridovich discovered the dismutation reaction involving the superoxide dismutase enzyme, the so-called superoxide theory of cellular toxicity was formulated. Even then it was clear that increased production of free radicals caused many problems for neurons: blocking of sulfhydryl groups of thiol enzymes, hydroxylation of DNA bases, and its fragmentation. Lipid molecules, in particular phospholipids of the neuronal membrane are damaged in the form peroxidation reaction (LPO) of them and their proteins, which destabilizes membrane structures and disturbs the structure of the intercellular matrix.

Brain formations are particularly vulnerable to the toxic effects of oxygen metabolites because the brain utilizes most (95%, according to some estimates) of the oxygen consumed by the body. Meanwhile, the brain contains a huge amount of lipids. Their unsaturated compounds are a substrate for active LPO reactions. Initial consequences of the developing oxidative stress include the appearance of lipofuscin granules in neurons, which are formed as a result of interaction of malondialdehyde with amino groups of proteins. Increased lipofuscin formation regularly accompanies brain ischemia, aging, and neurodegenerative diseases such as Alzheimer's disease.

Any living systems which actively consume oxygen, obviously the brain in the first place, need protection from free radical aggression. For the normal functioning of cells the growth of pro-oxidant compounds which are formed in them needs to be balanced by deactivation with the help of antioxidants. Various kinds of enzymatic and non-enzymatic antioxidants are aimed at this. Superoxide dismutase and catalase are the enzyme representatives of the latter. Healthy cells also contain a significant amount of glutathione, which as a coenzyme is a part of glutathione peroxidase and glutathione reductase with high antioxidant activity, and in addition it serves as an acceptor of hydroxyl ions and singlet oxygen. Antioxidant properties have recently been shown in some hormones (e.g., epiphyseal melatonin), and the anti-apoptosis protein Bcl-2. Along with these, well-known antioxidants include vitamins A, tocopherol, ascorbic acid, and certain carotenoids.

It is suggested to distinguish three levels of antioxidant protection of cells, which are engaged in a certain sequence. Initially, the formation of toxic hydroxyl radicals is prevented by superoxide dismutase and catalase. The second line of defense comes into play if the formed hydroxyl radicals have already triggered LPO reactions. To neutralize them natural antioxidants of vitamin origin are involved - tocopherol and ascorbic acid, bioflavonoids, and carotene derivatives which are interested in its regeneration. The third line of defense against free-radical processes, represented by glutathione peroxidase and enzymes that ensure the restoration of oxidized glutathione appears to be the most effective. By utilizing hydrogen peroxide, glutathione peroxidase can probably participate in the first stage of antioxidant defense too.

An imbalance between pro- and antioxidant compounds leads to the development of oxidative stress, which can provoke typical stress disorders in the body. Once again, the brain turns out to be in a hot spot, showing increased sensitivity to such stress, since the activity of

its antioxidant protection enzymes (catalase, glutathione peroxidase) is significantly lower than that of other tissues. This is also the reason why free radicals turn out to be much more aggressive here. Ultimately, this results in a host of negative consequences for the central neurons in the form of triggering the glutamate-calcium cascade, enhancement of neurotoxic properties of nitric oxide, and activation of apoptosis and immune system activity.

For these reasons oxidative stress is most directly related to neuronal damage in aging, cerebral ischemia, and severe forms of neurodegenerative pathology, such as Alzheimer's disease, Parkinsonism, or multiple sclerosis. In any case, defects in mitochondrial oxidative phosphorylation are prerequisites for their development. In neurodegenerative diseases, this leads to the formation of intracellular toxic compounds, including those of peptide nature, which in turn potentiate the activity of the glutamate-calcium cascade. In particular, the formation of the toxic peptide beta-amyloid protein is recognized as a pathogenetic factor of Alzheimer's disease, and in the case of Parkinsonism it is methyl-4-phenylpyridine. Parkinsonism is also characterized by decreased levels of glutathione and glutathione peroxidase activity in substantia nigra neurons.

Intensified accumulation of intracellular toxins initiated by oxidative stress subsequently aggravates it further, which culminates in progressive death of nerve cells. As it is shown by the example of the beta-amyloid analogue - Abeta compound - the neurodegeneration that it causes when administered intracerebrally is characterized by a sharp decrease in memory and learning impairment in animals, correlating with the extent of damage to the cortical and hippocampal neurons.

The development of oxidative stress is promoted not only by the activation of free-radical processes, but also by the primary suppression or defectiveness of the antioxidant defense system. For example, age-related involution of the epiphysis brain gland is accompanied by a sharp decrease in melatonin production, which has distinct antioxidant activity, and this is one of the reasons for the increased production of free radicals in brain tissue and associated deterioration of cognitive activity in elderly people.

Thus, a shift in the normal balance between pro- and antioxidant reactions in favor of the former may be an important cause of nerve cell damage in various types of organic cerebral pathology. On the contrary, a direct or mediated shift of this type of balance in the opposite direction appears to be an equally important condition for achieving a therapeutic effect.

16. Question: What is the role of nitric oxide in the normal and pathologically deteriorated cognition?

Answer: Among universal endogenous regulators of intracellular processes nitric oxide (NO) is now increasingly attracting the attention of researchers. Water-soluble NO molecules play a dual role, both positive and negative, in the activity of the nervous system. When they pass freely through undamaged cytoplasmic membranes, under normal conditions they control the tone of the cerebral vessels and participate in the regulation of synaptic transmission. Conversely, when produced in excess as a free radical, NO poses a threat to the cells, promoting neurodegenerative processes.

In the body NO is formed from L-arginine under the influence of the synthase enzyme (NOS), which occurs in several isoforms. One of them (eNOS) is found in the vascular

endothelium, others (nNOS and iNOS) are localized in blood cells (macrophages, neutrophils) as well as micro- and astroglia. Induction of NOS, but only within certain limits, optimizes the brain activity in different ways.

Through mobilization of eNOS the guanylate cyclase - cGMP system is activated, followed by the dilation of cerebral vessels and improvement of the regional cerebral blood flow. Simultaneously, rheological properties of blood improve in the form of weakened adhesion and aggregation of platelets. This in combination with vasodilatation inevitably leads to an increase in the functional activity of the brain structures involved, among other things, in the organization of cognitive processes.

There are two ways through which NO optimizes the cell function directly at the neuronal level - through its antihypoxic and synaptotropic properties. Blocking of NOS significantly reduces the resistance of neurons to oxygen deficiency in various brain formations and, above all, in the cortex and hippocampus. Although the mechanism of protective effect of NO in hypoxia remains unclear, there are reasons to assume its connection with the restriction of apoptosis. Along with that, NO can interfere with synaptic transmission by modulating the state of postsynaptic receptors and processes of mediator release and reuptake, as in glutamatergic and dopaminergic synapses. Among other things, this leads to an enhancement of the long-term synaptic potentiation (LTP). Inhibition of NOS results in the shortening of LTP, which correlates with memory impairment.

Clearly, the significant physiological role of NO takes a back seat if this compound is accumulated in cells in increased concentrations. This phenomenon occurs in a variety of pathological situations: in cerebral ischemia, brain injuries, neuronal damage by toxic substances, etc., when the neurotoxic properties of NO come to the fore. Excessive increase in EAA levels (primarily glutamate) and excitation of NMDA receptors leads to the launch of intracellular metabolic cascades, of which the glutamate-calcium cascade is especially important. The subsequent activation of calcium-dependent enzymes causes a sharp increase in the synthesis of NO (due to NOS activation) and production of other free radicals (hydroxyl, hydrogen peroxide, etc.). Together, they act as performers of the final act of intracellular tragedy and neuronal death via the mechanism of necrosis and apoptosis.

NO has a very high diffusion potential and spreads easily over relatively long distances in the brain, even though the time span is quite short (within a second). As a free radical with one unpaired electron, NO reacts with most biological molecules that it encounters. However, the oxidative potential of NO is noticeably lower than that of free radicals of other origin. It becomes particularly aggressive only after its transformation into secondary oxidants.

The main cytotoxic factor is peroxynitrate, which is formed due to the interaction of NO with the superoxidation radical. In contrast to NO itself, peroxynitrate molecules are much more stable and are highly toxic, which can be seen in the oxidation of sulfhydryl groups of enzymes and proteins, and DNA damage. By reacting with metal ions in superoxide dismutases, peroxynitrate causes the formation of an even more toxic nitrozonium ion and subsequent formation of nitrofurans. It is believed that such oxidants play an essential role in ischemic neuronal death, being the leading factors of oxidative stress. However, we cannot ignore the fact that some of the damaged neurons can regenerate, when hemodynamics is restored in the ischemic brain tissue and not without the help of the vasodilatory effect of NO.

The noted duality is also inherent in the control of apoptosis. In the form of peroxynitrate NO is involved in the initiation of apoptotic mechanisms. As demonstrated by the example of nerve cell culture under hypoxia simulation, NOS inhibitors significantly reduce the severity of apoptosis and increase the number of surviving neurons. And the proapoptotic effect of NO is apparently connected with the mobilization of enzymes of the caspase family. Meanwhile, while hyperproduction of NO under severe hypoxia potentiates apoptosis, a different picture is observed under moderate oxygen deficiency and adaptation to hypoxia. In this situation, the free radical compound reveals anti-apoptotic properties.

The neurotoxic effect of NO primarily extends to the cerebral cortex, hippocampus, hypothalamus, and striatum - the brain formations where the NOS activity is particularly high. Since the majority of neurons do not contain NOS, their damage depends on the exogenous pool of NO originating mainly from activated astrocytes, endothelial and blood cells (macrophages, neutrophils). The number of such producers is increased in the aging, ischemic, and infected brain.

Inadequately enhanced synthase induction is an important source of lesions in brain structures responsible for cognitive activity. Modern researchers believe that this is one of the causes of age-related and neurodegenerative pathologies such as Alzheimer's disease. In fact, senile deterioration of cognitive processes is aggravated by NOS activation in the epiphysis, which results in increased death of pinealocytes and a decrease in melatonin secretion.

At first glance, the above represented information suggests that inhibition of NO production is supposed to provide a neuroprotective effect and improve cognitive function, thereby serving as part of the therapeutic action of nootropic agents. Indeed, there are some indications that NOS inhibitors can be used therapeutically in Alzheimer's disease, inter alia by limiting the activity of the enzyme with melatonin.

However, the problem of controlling the destiny of NO and thus that of neurodegenerative processes, unfortunately, does not have an unambiguous solution. It turned out that large doses of NOS blockers sometimes fail to provide a protective effect and may even worsen the course of brain ischemia. In addition, despite limiting the death of cortical or hippocampal neurons, some nootropic drugs (representatives of racetams and vasodilators) activated NOS instead of inhibiting it.

Thus, while attributing significant importance to hyperproduction of NO as a trigger of nerve cell damage in the brain, we must refrain from oversimplifying the approach to treating psychoneurological diseases by solely suppressing the production of this compound. As it was demonstrated above, NO is capable of showing a dual behavior depending on the circumstances, and probably not least because of the existence of functionally different isoforms of the synthase enzyme. Therefore, in our opinion, the task shall come down not to complete inhibition of NO production, but to the reduction of its content to some optimal level, so as not to affect physiologically valuable properties of the endogenous regulator.

17. Question: How does the lack of cholinergic mechanisms in the brain affect cognitive dysfunction?

Answer: Such connection is very easy to trace, taking into account an extremely important role of the latter in the normal organization of cognitive activity. Not surprisingly,

there is an impressive number of experimental and clinical observations proving the dependence of severe cognitive disorders on the dysfunction of central cholinergic synapses.

Two types of experimental evidence are presented - with simulation of functional and organic cholinergic insufficiency. The former includes the results of numerous studies on the effects of M- and H-choline blocking agents on memory and learning, which have already been cited. Since psychoneurological diseases with cholinergic deficits are predominantly organic in nature, methods that provide morphological damage to cholinergic neurons by mechanical means or by specific neurotoxins may be more appropriate for their simulation.

A selective choline-derived AF64A neurotoxic agent - ethylcholine mustard aziridine ion or aziridine has been most frequently used for this purpose in recent years. Its intracerebral administration to rodents causes cholinergic dysfunction with behavioral, neurochemical, and morphological abnormalities very similar to the common neurodegenerative Alzheimer's disease in humans. In particular, after an injection of aziridine into the lateral ventricles of the rat brain, cholinergic deficiency in the form of a drop in acetylcholine levels and a decrease in choline acetyltransferase activity develops most easily in the neocortex and hippocampus. This is accompanied by the formation of severe amnesia and deterioration of the production of avoidance skills. Interestingly, the implantation of fetally derived cholinergic neurons in either structure eliminates the neurochemical defect and behavioral disorders. In the case of intrastriatal application of the neurotoxin, it is described that there is a simultaneous drop in extracellular level of acetylcholine and GABA in the striatum, but not of dopamine.

Alzheimer's disease is certainly a clinical version of the typical cholinergic insufficiency, leading to severe cognitive impairment. It is characterized by a reduced number of cholinergic synapses in the cortex and hippocampus, degeneration of cholinergic neurons of the forebrain base with reduced extracellular concentration of mediator, and limited choline acetyltransferase activity. The severity of cholinergic disorders correlates with the degree of mental dementia and the rate of an increase of senile plaques and neurofibrillary tangles in neurons, which are viewed as the main morphological indicators of the disease. Meanwhile, there is an interesting viewpoint, according to which cholinergic deficiency enhances the formation of the specific beta-amyloid peptide with neurotoxic properties in cells.

The neuronal amyloidosis that initially occurs on the basis of cholinergic insufficiency, apparently, aggravates histopathological and mnestic defects, first of all, because of the anticholinergic activity of beta-amyloid itself. As it is shown in experiments on rats, the latter (in the form of the artificially produced Abeta compound) when administered intracerebrally demonstrates a neurotoxic effect as a trigger of oxidative stress at the neuronal level, and disturbance of the permeability of membrane ion channels with a simultaneous decrease in choline acetyltransferase activity in the cortex and hippocampus. Such cellular shifts correlate with impaired memory and impaired learning of passive avoidance and spatial orientation in animals. Similar to Alzheimer's disease, cholinergic processes in the cortex and hippocampus are particularly sensitive to the damaging effect of Abeta, but they are not significantly affected in the striatum. Judging by electrophysiological data, deterioration of attention and memory is accompanied by the disturbance of cholinergic transmission in the hippocampus in the case of traumatic brain injury as well.

Cholinergic insufficiency is also evidenced in other organic brain lesions accompanied by cognitive disorders. Huntington's chorea is among them. However, unlike Alzheimer's type

of pathology, it is characterized more by the lesion of cholinergic neurons of the striatum. A decrease in choline acetyltransferase activity here coincides with the degeneration of intrastriatal interneurons. As it is shown in the studies on transgenic mice with simulated Huntington's chorea, they are characterized by extremely low choline acetyltransferase activity and limited choline uptake by synaptosomes of the striatum with no changes in the function of nigrostriatal dopaminergic mechanisms.

As for another form of neurodegenerative pathology, Parkinson's disease, it is characterized more by abnormal hyperactivity of cholinergic neurons rather than by their weakening, at least at the striatum level. Central M-cholinoblocking agents are known to be used for elimination of motor manifestations of the disease. Consequently, serious difficulties in improving mnestic processes arise in such patients, and it becomes difficult to prescribe to them anticholinesterase drugs that would be universal and effective enough to combat cognitive impairment.

Age-related pathology can be reasonably regarded from the same standpoint. The leading position of cholinergic dysfunction in the origin of memory and learning impairments in old people and animals can now be universally recognized. However, it has been established that even though old age is accompanied by pathological rearrangement of cholinergic processes, the resulting shifts are different from those occurring in neurodegenerative diseases. As we age, not only does the function of cholinergic neurons of the cortex and hippocampus decrease, but the permeability of the blood-brain barrier for choline and its consumption by neurons during acetylcholine synthesis also become restricted. However, judging by the results of experiments on old rats and mice, their acetylcholinesterase and choline acetyltransferase activity, as well as the response of cholinergic neurons to presynaptic action of oxotremorine remain high enough. Thus, in natural aging there is less severe damage to cholinergic mechanisms in the brain than in Alzheimer's disease and other forms of neurodegenerative pathology.

18. Question: What are the consequences of an excessive increase in the activity of excitatory amino acids for the brain function?

Answer: As it was noted earlier, mediator excitatory amino acids (EAA), above all - glutamate, are actively involved in the function of the healthy brain; in particular, they are necessary for the normal performance of cognitive processes. However, according to the current data, hyperactivity of glutamatergic synaptic transmission may lead to serious problems, and it is considered to be an important and sometimes the leading factor in the genesis of a variety of severe brain dysfunctions. Neurodegenerative, ischemic, and convulsive forms of pathology which are invariably accompanied by cognitive disorders, stand out among them. One of the factors that can lead to this is an increase of neurotoxic properties of glutamic acid.

The possibility of a toxic damage to nerve cells by glutamate was first demonstrated in 1957 in a study of its effect on the structures of inner retinal layers of mice. The significance of this observation was appreciated only two decades later, when Olney et al. formulated a hypothesis of the so-called "excitotoxic death" of neurons. It is based on experimental evidence of cytotoxic activity of glutamate and aspartate shown in various neuronal elements.

Subsequently, the hypothesis, which turned out to be very productive, gained wide popularity among not only researchers, but also clinicians.

In brief, the origin of toxic effects of EAA looks as follows. Under the influence of adverse factors, a significant amount of the mediator accumulates in glutamatergic synapses. This occurs due to an increased release of the amino acid from presynaptic terminals or a disruption of inactivation mechanisms in the synaptic cleft, including weaker reuptake by astrocytes. However, overexcitation of postsynaptic receptors, especially of NMDA-type, may also be the cause. Whatever it is, eventually postsynaptic neurons are hit by the so-called "glutamate shock" with dramatic consequences for these neurons, up to necrotic death.

Two types of neurotoxic glutamate effects have been described in the cellular elements of the neocortex, hippocampus, striatum, and cerebellum: an urgent one with a short latent period and a delayed calcium-dependent response. The latter in the form of a glutamate-calcium cascade acts as a source of severe neuronal damage. Glutamate overexcitation of NMDA receptors leads to an urgent opening of calcium channels in the cell membrane and a sudden, sharp increase in its concentration in neurons. A massive release of calcium ions into the cell triggers further cascade reactions, which manifest themselves in uncoupling of conjugated oxidative phosphorylation with a drop in energy resources, intensification of catabolic processes, activation of intracellular enzymes that damage membrane structures, and accumulation of lipid peroxidation products.

At the terminal stage, nitric oxide (NO) actively engages in cell death, and its interest in the toxic effect of glutamate is now regarded as particularly important. Intracellular calcium ions bind to calmodulin and mobilize NO synthase. The interaction of created NO with reactive oxygen forms causes an appearance of highly toxic products such as peroxynitrate and further irreversible cell damage. Along with that, various chemical compounds with synthase inhibitor properties distinctly weaken neuronal death caused, for example, by NMDA.

As evidenced by the results of neuroanatomical analysis, dendrosomatic contacts of nerve cells are most sensitive to the damaging effect of local applications of glutamate or systemic administration of large doses of the amino acid. Therefore, their areas where the density of glutamate receptors is particularly high suffer the most, as shown by the example of the hippocampus. Prolonged electro excitation of the perforant pathway, which is the main afferent glutamatergic input to the structure, leads to significant degeneration of cellular elements, primarily in the CA1 field.

Excessive excitation of EAA-ergic synapses is among the leading causes of severe psychoneurological disorders, including neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Even though the results of certain clinical studies in such patients differ markedly, there are clear indications of the pathogenetic significance of such a neurotransmitter defect. This is evidenced by a certain correlation between the level of glutamate or a glutamate/aspartate imbalance in the cerebrospinal fluid in Alzheimer's disease and Parkinsonism and the severity of memory and learning impairments. Postmortem examination of the brains of individuals affected by these diseases sometimes reveals enhanced glutamate binding by neurons of the caudate nucleus.

Increased glutamate activity and toxicity towards the nerve cells of highly plastic brain formations (new cortex, hippocampus, striatum, cerebellum) in degenerative diseases may be a consequence of synergy between the amino acid and other neurotransmitter systems. The

objects of such interaction are often cholinergic and dopaminergic mechanisms that can, as it was indicated, under certain circumstances potentiate the excitatory effects of EAA and thereby enhance their neurotoxic properties. For example, such relationships in the striatum appear to be formed at the level of dopaminergic nigrostriatal axons and simultaneously at the intrastriatal cholinergic intercalary cells.

The role of EAA hyperactivity is also great in the development of ischemic phenomena that accompany functional or organic disorders of cerebral circulation, stroke. As it was first shown by Kemp et al., the triggering of morphological changes in cerebral ischemia may be associated with excessive accumulation of glutamate and aspartate. The fact that preventive administration of the noncompetitive NMDA-receptor antagonist dizocilpine prevented cerebral tissue damage during short-term bilateral carotid artery clamping in animals confirmed the validity of this statement. Based on these and latter findings, a key, trigger position of excess glutamic acid in the death of nerve cells in the ischemic zone is now recognized by many researchers.

Ligation of one of the carotid arteries in rats causes a typical morphological picture of ischemic stroke with lesions of the new cortex, hippocampus, striatum, and amygdala. Interestingly, according to the topography and structural characteristics, the resulting disturbances are almost identical to those developing under the influence of toxic doses of glutamate. As it turned out, dizocilpine prevented ischemic necrosis primarily in the CA1 zone of the hippocampus, where the highest density of NMDA-receptors is concentrated. Along with this, the content of glutamate and aspartate in cerebrospinal fluid increases sharply in people during the first hours of ischemic stroke. The degree and duration of the amino acid shift are of predictive value in determining the course and outcome of stroke and the dynamics of the recovery process.

Under the gross restriction of cerebral hemodynamics, ischemic neurons become the direct source of EAA accumulation; large portions of glutamate and aspartate enter the extracellular space from their terminals. This triggers the glutamate-calcium cascade with the above described negative consequences for the activity and life of neurons. Deep cerebral anoxia leading to the accumulation of intracellular calcium, among other things, contributes to the triggering of the phosphoinositide regulatory system, which culminates in the suppression of excitatory postsynaptic processes. As for an inevitable increase of NO production in response to NMDA receptor hyperactivity, it has a dual importance for the course of ischemia. On the one hand, enhanced NO production leads to the synthesis of neurotoxic products; on the other hand, through the dilation of cerebral vessels NO improves blood flow and simultaneously contributes to the retrograde blockade of NMDA receptors.

Glutamate hyperactivity also poses a risk of impairments to other brain functions, including seizures and psychotic manifestations. Proconvulsive properties of EAA have been known since the early 1950s, when the application of glutamic or asparaginic acid to the cortical surface in dogs and monkeys caused clonic convulsions. By now, the convulsive effects of various EAA receptor agonists and, conversely, the anticonvulsant properties of their antagonists have been described extensively. When applied to the problem of cognitive disorders, this issue has an indirect bearing, since they develop only as a consequence of past seizures.

Taking into account the involvement of EAA in the genesis of different forms of psychoneurological pathology, we must admit that the understanding of mechanisms that can counteract the mediator hyperactivity is extremely important for their successful therapy. In natural conditions, the first place among them, apparently, shall be given to antagonistic effects of inhibitory amino acids like GABA. The hyperpolarization of cell membranes caused by them regularly prevents glutamate aggression for example. Among other reasons, the unleashing of the latter is undoubtedly promoted by the disturbance of the normal functional equilibrium between the two polar types of mediator amino acids. Other transmitters with inhibitory properties, including adenosine (A1) receptor agonists, shall also participate in the formation of the anti glutamate defense system. If we view exogenous interventions from a neuroprotective point of view, of course, glutamate receptor blockers like dizocilpine come first among them. However, despite its long history of study, neither this compound nor its close analogues, for a number of reasons, have reached clinical practice yet.

While placing another emphasis on the need to limit the hyperactivity of EAA-ergic transmission in the pathological conditions described above, one more circumstance shall not be left out of consideration. As it was already mentioned, the other extreme can also contribute to cognitive impairment; that is a restriction of the function of EAA-ergic synapses; this fact is evidenced by the existence of amnesic activity in NMDA-receptor antagonists. Besides, it was found that animals of different species and humans with age show a progressive decrease in NMDA-receptor density in the frontal cortex, hippocampus, and striatum. Therefore, in the conditions of age-related deterioration of cognitive activity, it is necessary to rely not on restriction but, on the contrary, on enhancement of EAA-ergic transmission.

19. Question: Can dysfunctions in the immune system affect cognition?

Answer: They can directly, and today there is no doubt about it. As G.N. Kryzhanovsky (1999) fairly believes an immune defect can be found in all forms of neurological and mental diseases. And this problem, in our opinion, shall be regarded from two perspectives: on the one hand, a defeat of the cells of the central nervous system provokes an immune pathology that further aggravates psychoneurological disorders; on the other hand, primary disorders of the immune regulation on periphery may be a secondary cause of the failure of brain functions (E.B. Arushanyan, E.V. Beyer, 2002).

If we discuss the first aspect of this problem, the main accent shall be put on those forms of cerebral pathology for which deterioration of cognitive activity is especially typical. Here we refer to neurodegenerative brain diseases, traumatic brain injury, cerebrovascular disorders, age-related diseases, i.e. everything that becomes the object of the pharmacotherapy with nootropic agents.

The presence of the immunological defect in diseases accompanied by central neuronal degeneration (Alzheimer's, Parkinson's, Huntington's, multiple sclerosis and others) is a long-standing and well-reasoned statement. For example, a high titer of antibodies to neurospecific proteins is found in the peripheral blood and cerebrospinal fluid of patients suffering from Alzheimer's disease. The main target of autoimmune aggression are cells affected by the toxic beta-amyloid peptide, which level in the brain tissue directly correlates with the severity of the pathology. Increased proliferative activity of T-lymphocytes and production of a number of

cytokines (primarily, interleukin-1) also coincides with this, aggravated by the inflammatory process around the so-called senile plaques in neurons and apoptosis, and leading to the subsequent necrotic cell death. When toxic Parkinson's disease is simulated in animals, there is an increased production of antibodies against dopaminergic neurons, which further potentiates a disruption of nigrostriatal relations. The severity of both forms of the pathology, according to clinical and immunological studies, directly correlates with the severity of dementia. Increased permeability of the blood-brain barrier for autoantibodies apparently also plays an important role. In the case of Alzheimer's disease, this is probably because of the neurotoxicity of beta-amyloid.

Similarly, the severity of the course of traumatic brain injury and resulting cerebral circulation disorders largely depend on sensibilization of the organism to brain-specific antigens. Proposed hypothesis suggests that the cause of a traumatic disease in the form of a progressive course of the consequences of traumatization, as well as a paralleled inflammatory syndrome associated with deterioration of cerebral hemodynamics, is an unusually pronounced immune response. The most frequent expression of anti-brain antibodies occurs in order to eliminate specific proteins of the nervous tissue such as S-100 protein, basic myelin protein, glial fibrous protein, etc. Appearance of these antigen-proteins, their antibodies, and increased release of cytokines, in particular interleukin-10, in blood directly characterize the severity of the brain damage.

An ischemic stroke, arterial hypertension, deterioration of cerebral hemodynamics of atherosclerotic origin are invariably accompanied by an increase in autoantibodies, including antibodies to certain types of mediator receptors. This is so closely related to the genesis of the pathology that based on the dynamics of the antibody titers in the first day of stroke, for example, it is possible to predict its course; and their high background level may indicate that the brain is preconditioned for stroke. A variety of neurochemical shifts develop in the periphery of the ischemia center, including the activation of proinflammatory (TNF, interleukin-1 beta) and vasoactive (interleukin-6) cytokines. Interestingly, along with the processes aimed at cell destruction and apoptosis enhancement, the reparative mechanisms that trigger the expression of neuronal growth factors and plasticity proteins (BDNF, NGF) are concurrently activated in the ischemic zone.

The production of cytokines (interleukin-2, interleukin-12, TNF, etc.) turns out to be that unified immunological "ground" on which the whole complex of senile diseases is based. An increased activity of cytokine-induced proteins predetermines nervous, psycho-emotional, cardiovascular, and other disorders. In particular, it is now beyond dispute that atherosclerotic vascular lesions are of the autoimmune nature, when the content of Th-1 lymphocytes and activated macrophages with enhanced expression of interleukin-6 and TNF increases in the vascular intima during the acute stage.

It is known that the above listed types of cerebral pathology are accompanied by mental disorders of varying severity. Anxiety (neurosis) and mood deterioration (depressive syndrome) are the most common ones. Meanwhile, these and other forms of psychopathology are accompanied by disorders of the immune status, which in turn support the course of psychopathology. Coexistence of depression and dementia is caused by a particularly close causal relationship.

An immunological defect turns out to be not only a pathogenetic factor in a number of psycho-neurological diseases accompanied by cognitive deterioration, but cognition, as noted, can also suffer in a secondary way because of the immune pathology of the peripheral origin that occurred first.

In the acute phase of bacterial infection, in fever the patient's malaise is associated with depressive symptoms, drowsiness, and also with cognitive deterioration. Similar phenomena are shown in autoimmune diseases of the locomotor system, when antigens (lipopolysaccharide or salmonellosis endotoxin) are administered to healthy people. This coincides with a plasma increase in the levels of TNF, interleukin-1 beta, interleukin-6 and their soluble receptors. Mouse strain with genetically determined immune system abnormalities in the form of damaged macrophages, T- and B-lymphocytes, antibody production, and inadequate cytokine production exhibit markedly reduced ability to learn passive and active defensive skills, and morphological changes are detected in their neocortex and hippocampus.

Peripheral blood cytokines can exert their central properties in two ways: they either reach the brain directly, or some afferent channels of information transmission get involved. Most cytokines represent rather large molecules, which cannot cross the blood-brain barrier, since this requires special conditions (its increased permeability, presence of special transport mechanisms). At the same time, irritation of afferent nerves by proinflammatory cytokines is quite possible, among them afferents of vagus can play a notable role as long as its transection significantly weakens their central effects.

Thus, there is a certain correlation between the launch of the immune response in the center or in the periphery and disorganization of higher nervous activity including defects in memory and learning. What mechanisms underlie this? Apparently, they are quite varied.

Indeed, proinflammatory cytokines (interleukin-1-beta, interleukin-6, TNF and some others), whether generated inside or outside the brain, can directly induce neurodegeneration and disruption of synaptic transmission, especially in ischemic and toxic lesions. The specificity of such shifts is evidenced by the possibility of their elimination by antagonists of corresponding receptors, anti-inflammatory cytokines, and glucocorticoids. In response to systemic or intracerebral administration of interleukin-1-beta, the level of synaptic transmitters (monoamines) in the hypothalamus changed simultaneously with impaired eating and social behavior of animals, and lipopolysaccharide increased serotonin and dopamine metabolism in the new cortex and hippocampus through the mobilization of interleukin receptors. Incidentally, this antigen markedly increased mRNA expression for interleukin-1-beta and TNF in various brain structures.

Key proinflammatory cytokines show the ability to inhibit microsomal oxidation by increasing the content of free radicals. The production of interleukins and their receptors is not just increased in the brain in Alzheimer's disease, but it is particularly elevated in the hippocampus. Repeated injections to rats of autoantibodies derived from the blood of such patients reduced hippocampal acetylcholine levels, causing a dysfunction of cholinergic mechanisms which is so characteristic of the disease. A special interest of the hippocampus in the action of cytokines on the brain is also evidenced by the fact that the addition of interleukin-2 to the medium containing its slices dose-dependently inhibited short- and long-term post tetanic potentiation there.

However, cytokines in the brain can perform both negative and, so to speak, creative missions. Being a product of the primary pathological process, they can also contribute positively by enhancing nerve cell regeneration. For example, in multiple sclerosis macrophages, microglia, and astrocytes, on the one hand, express antigens that trigger the immune response and, on the other hand, by means of increased production of neurotrophic factors they provide a distinctive protection of neurons from damage. Inclusion of T-lymphocytes by various antigens in the brain injury increased mRNA expression for a number of neurotrophins (NGF, BDNF, NT-3) and for their tyrosine kinase receptors. One of the cytokines - interleukin-6 also has its own neurotrophic properties.

Hence, the collected evidence definitely demonstrates the dependence of cognitive disorders in various organic brain diseases on the functional state of the immune system. Some mechanisms of the immune-cerebral relations are also known today. Yet, it is necessary to point out their ambiguous nature. Immunological hyperactivity can be a source of multidirectional influences on the function of central neurons: immunocompetent cells themselves and their mediators, cytokines, can both worsen and improve neuronal activity.

20. Question: What is apoptosis and what are the consequences of its exacerbation for cognition?

Answer: Apoptosis is a genetically programmed death ("suicide") of cellular structures of different types, including cerebral neurons. From a general biological standpoint, it appears to be a natural biochemical mechanism aimed at maintaining the cellular composition of tissues at a certain qualitative level by liquidation of morphological elements that have become functionally unnecessary or harmful. With all its obvious necessity for the normal activity of the healthy organism, apoptosis is supposed to be kept within strictly defined boundaries. Otherwise, its excessive activation or restriction can pose a risk of the development of a pathology. Therefore, a cascade of factors that trigger apoptosis is counteracted by anti-apoptotic processes.

To understand the nature of cognitive disorders and develop methods to combat them, it is necessary to keep in mind that biochemical and morphological signs of increased apoptosis are regularly detected in many neurodegenerative diseases (Alzheimer's, Parkinson's, Huntington's, multiple sclerosis), cerebral ischemia of different etiology, stroke, and traumatic brain injury. Meanwhile, inadequate inhibition of apoptosis leads to the development of brain tumors. All these factors make apoptosis an important target for a directed drug therapy, including with the use of nootropic agents.

It shall be noted that apoptosis consists of two stages - the initial, reversible stage, when it is possible to stop the process, and when there is still an opportunity and time for a pharmacological maneuver. Then apoptosis enters into an irreversible stage, which culminates in fragmentation of DNA molecules, appearance of signs of cell disintegration and utilization of its parts with the help of macrophages.

From the point of view of clinicians, of course, it is necessary to understand the biochemical sequence of phenomena underlying apoptosis and those factors that favor an excessive launch of the process of cell degradation, and especially its weakening. There are many reasons that can modulate apoptosis, and they can be determined by a direct effect on the

neuron genome and intracellular metabolism, and can depend on external influences, including mediators, neurotoxins, and hormones. According to modern concepts, there is a certain sequence of apoptotic process development, which is initiated by mitochondrial dysfunction.

The resulting disturbances in the energy supply of nerve cells certainly serve as a trigger mechanism of apoptosis. NO which includes the formation of super oxidative radicals is indirectly involved in this process. Acute ischemia, hypoxia potentiate apoptosis by, among other things, weakening the protective role of oligodendrocytes and by enhancing the toxic properties of beta-amyloid protein. The formation of active oxygen forms, which cause increased synthesis of pro-inflammatory cytokines, as well as increased production of excitatory amino acids combined further aggravate the initiated process.

In addition to the aforementioned, there are other things that clearly contribute to apoptosis. These include a synthesis of specific pro-apoptotic proteins and neurotrophins. In neurodegenerative diseases (Alzheimer's disease, Parkinsonism) an increased expression of proteins - apoptosis stimulators - is found; these include Bax, Bad, APO-1, hypoxic protein-alpha, etc., which, by the way, are opposed by peptides with reverse, anti-apoptotic function - Bcl, Bcl-x. A similar situation is observed regarding nerve growth factors, some of which, like tumor necrosis factor (TNF) trigger apoptosis, while others (BDNF, NGF) counteract it. Interestingly, the neurotoxic effect of alcohol in chronic administration can be partially determined by the inhibition of type 2 NF induction.

At the final stage of apoptosis when it becomes irreversible, a whole group of enzymes from 1-beta-interleukin-converting proteases called caspases takes the leading role. Their pronounced activation, observed in brain injury and Alzheimer's disease, leads to nuclear matrix cleavage, destabilization of chromatin structure, DNA decay and final death.

Given the described phenomena, what are the natural mechanisms of prevention of excessive apoptosis from turning into a pathogenetic link in the disease? Similar to the initiating factors, there are obviously several of them. Stating this, cholinergic mechanisms deserve a special display. In the cortical and hippocampal cell cultures of newborn rats, for example, choline deficiency provokes widespread apoptosis with decreased levels of phosphocholine and phosphatidylcholine in neuronal membranes. While choline injections improved spatial memory in labyrinthine rats, a lack of the precursor acetylcholine caused its impairment. The anticholinesterase drug tacrine distinctly attenuated ischemia-induced apoptosis in the primary culture of mouse astrocytes and inhibited the expression of pro-apoptotic genes.

Other natural ways to counteract apoptosis have also been studied. These include anti-apoptotic NFs. For example, application of glial neurotrophic factor (GDNF) to the surface of the rat cortex attenuated cell death in the zone of "penumbra" of ischemic lesion with occlusion of the median cerebral artery. Interference in the function of excitatory amino acids also leads to a protective effect. While NMDA prevented apoptotic death of pyramidal neurons in CA1 and CA3 areas of rat hippocampus, a non-selective blocker of NMDA receptors dizocilpine weakened such neuroprotection. The latter is also supported by adenosine receptor agonists of type A1 due to hyperpolarization of neuronal membranes.

The understanding of hormonal protection from apoptosis seems very promising. Ovarian estrogenic hormones, in particular, have similar properties. Among other things, they were found to have the ability to limit the toxic effect of beta-amyloid protein on cortical neurons by the activation of protein kinase C, which plays a key role in apoptosis. Repeated

injection of estradiol into the cell culture of hippocampus and septum clearly prevented their apoptotic death. In the system of such neuroprotection the attention of researchers is increasingly attracted by the hormone of the brain epiphysis gland - melatonin that is actively interested in brain protection from any unfavorable factors, including age-related ones. Its effect on the apoptosis processes can be defined as restriction of cytotoxic properties of excitatory amino acids (glutamate, aspartate), prevention of fragmentation of hippocampal DNA neurons in the ischemic zone and attenuation of amyloid-induced cell degeneration in Alzheimer's disease.

Thus, the deciphering of the nature of "programmed death" of nerve cells - apoptosis - and natural ways of its restriction open up new prospects for the therapy of severe forms of cerebral pathology, including those accompanied by cognitive disorders.